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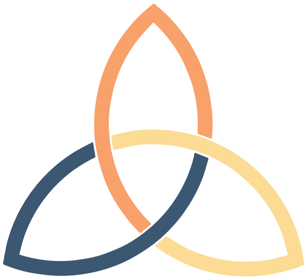

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An International Journal of the History of Chemistry

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Editorial

What Would I Have Done Had I Known

Pierandrea Lo Nostro

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Richard Weiss, a distinguished Member of our Scientific Committee and one of the founding fathers of *Substantia*, suddenly passed away on December 28, 2023.

He leaves a terrible empty space in our minds and hearts.

Richard promoted our Journal in the scientific community with great fervor, we will always miss his advices and support.

In our website, at <https://riviste.fupress.net/index.php/subs/about> we show the video that he recorded in 2017 at Georgetown, when we launched the Journal. No one else could have better communicated our intentions and hopes for a new way of doing scientific publishing than him! Today, after seven years, his words still reflect the sense of our work with the Journal, a challenge full of satisfaction.

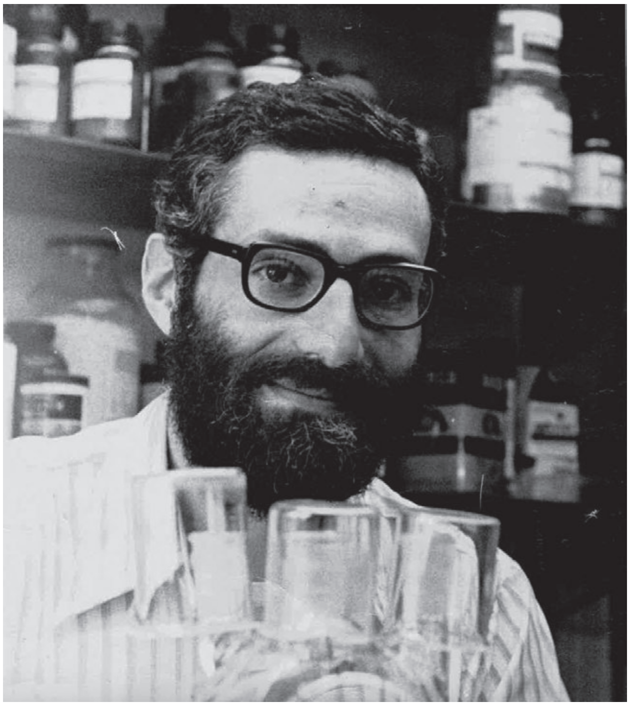
The very first time I had a chance to interact with him was in 2005-2006, when he edited two papers of mine submitted to *Langmuir*. I remember his dedication, help and care in evaluating the papers for that journal.

Then we had other chances to meet and discuss topics of common interest.

We will miss his friendly dedication and long-term outlook.

We will do our best to make the most of his wisdom.

Now we believe that the best way to commemorate Richard and his participation in cultural and societal activities is to publish the last contribution he sent us in June 2023, on the anniversary of "Juneteenth", the liberation of African American slaves in the US.



Richard G. Weiss (1942-2023).

> *It may be presumptuous of me, a white man whose 'ancestors' arrived in the US on ships from Eastern Europe during the 19th century, to write about Juneteenth. Still, that will not stop me. Please keep in mind that what I write is one person's opinion, without claiming that it is factual or even useful to anyone besides the author. Also, that 'utility' is only for his experience.*
>
> *Until a very few years ago, Juneteenth had little meaning to me. And even now, that meaning cannot and should not be extrapolated to others. It does resonate with me because shared oppression, subjugation, and mistreatment are things which I recognize were a part of what it was and is to be black in America today. When my family and I were living in Brazil, many of our white and mixed-race neighbors refused to recognize that the same racism I saw in my youth was rampant there. The nuances were different, but*

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the basic societal issues were the same—lighter skin translated intrinsically to higher social standing.

Today, in my neighborhood, almost all are 'white' because of economic and social inequities, many of which can be traced to before and after the Civil War. To place this in a more local perspective, my parents were clearly racist, and some of their ideas did creep into the way that I looked at African Americans (and how they looked at me!!). Endemic prejudices, introduced in one's youth are very difficult to erase. When I think about the injustices perpetrated by Georgetown University, my employer for more than 50 years, I ask myself: "What would I have done had I known the misdeeds of Rev. Thomas Mulledy, the former president of Georgetown, who sold 272 human beings to pay off the university's debts, and separated the families without regard for relationships? Even more vexing is the question, "What would I have done had I been a member of the faculty in 1838 that sold the slaves?" I cannot answer either of these questions honestly.

I only hope that I would have respected the human dignity of and fought for the enslaved people involved. But I don't know…

Richard G. Weiss

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Research Article

The Discovery and Analysis of PFAS ('Forever Chemicals') in Human Blood and Biological Materials

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Abstract. This paper reviews the development of analytical techniques used prior to the early 1980s in the identification of organofluorine compounds in human blood. The compounds of interest are industrial products, the so-called Forever Chemicals, which are stable long-chain per- and polyfluoroalkyl substances (PFAS) that are highly resistant to breakdown. Because of their special properties they have been used since the 1950s in a wide range of commercial and domestic products. Academic research in the 1960s and 1970s that originally focused on fluoride in dentistry and human health led to the finding that PFAS were present in the blood of residents of several cities in the United States. This, and concerns over their toxic properties, encouraged industrial research into analytical methods for their detection. Notably, and because long-chain PFAS are non-volatile, special techniques were developed for analysis by gas chromatography.

Keywords: Forever Chemicals, organic fluorine in biological materials, PFAS, PFOA, PFOS, exposure to PFAS.

INTRODUCTION

The concern over widespread contamination of water, and as a result of human blood, with so-called Forever Chemicals is a growing global issue, as reflected in recent years both in the media and scientific journals.[1] It is related to the uses and environmental releases of extremely stable long-chain per- and polyfluoroalkylated compounds containing multiple carbon-fluorine bonds, and is mainly associated with the first, and main, manufacturers, Minnesota Mining and Manufacturing (3M), and DuPont, in the United States. Other sites of manufacture include several European countries, Japan, and Israel. These compounds are industrial substances, collectively referred to by the acronym PFAS. Perfluoroalkylated substances are fully fluorinated. Polyfluoroalkylated substances are not fully fluorinated. Those compounds discussed here are amphiphilic in nature: At the end of the carbon chain is a

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[1] Krafft and Riess, "Per- and polyfluorinated"; Brunn, et al., "PFAS: forever chemicals."

functional group, such as a carboxylic acid (-COOH), or carboxylate, or a sulfonic acid (-SO_3H), or sulfonate.

PAFS persist in the environment, resisting degradation. They bioaccumulate, impacting on soil and water, and enter the food chain. Public exposure of the outcomes includes the 2019 film "Dark Waters" based on an article published in *The New York Times* during January 2016.[2] This focused on toxic releases from DuPont's manufacturing operations and subsequent litigation. More recently 3M internal documents made available during litigation have been reviewed.[3] In this litigation evidence for the ubiquitous presence of PFAS in human blood and sources of potable water, in addition to matters of toxicology, were prominent.[4] Other accounts in the media go back to the start of the present century. Thus in May 2000, the *Washington Post/Los Angeles Times* included an article based on a 3M announcement which stated that as a result of contamination of blood in the general population the corporation would discontinue some of its stain-repellant products. According to 3M's senior vice president for research and development: "We have tested it [PFAS, in human blood] pretty widely – not only in this country but in other countries, as well – it's found in very low levels everywhere we test." These fluorinated compounds had been made and used since the 1950s, and 3M health officers had measured their total concentrations in the blood of its workers since the late 1970s, and subsequently of communities at some distance from sites of manufacture. 3M observed: "The surprise wasn't that it was in our workers – that's something we've known for a long time … It was a complete surprise that it was in the blood bank supplies."[5] The general concern has moved way beyond the United States. In the UK for example these compounds, along with microplastics, are investigated as emerging contaminants in potable water supplies. Widespread environmental exposure, occupational and otherwise, with particular reference to blood levels and threats posed to health by PFAS released into water, and present in industrial products, has stimulated major research campaigns. A significant source of water contamination are PFAS surfactants used in the formulation of tough, resilient aqueous film-forming foam (AFFF), manufactured by 3M. They have been widely employed at military bases and airport facilities for extinguishing fuel fires, and especially following aviation accidents.

The main advance in gathering knowledge about the exceptional scale and prevalence of PFAS in the environment came about at the turn of the twenty-first century through the use of electronic instruments with advanced analytical capabilities. These instruments enabled detection of PFAS in low parts per trillion (ppt). As a result of ongoing health concerns, in 2009 the US Environmental Protection Agency (EPA) drew up a short term health advisory, and published its first validated method for PFAS compounds in drinking water, with detection limits of less than 2 ppt. How knowledge of these contaminants first came about, as described here, arose from experiments conducted in the 1970s by academic investigators.

PER- AND POLYFLUOROALKYL SUBSTANCES (PFAS)

The most important per- and polyfluoroalkyl substances contain, as manufactured, linear or branched chains of generally eight carbons. In the case of eight-carbon linear chains they are derivatives of perfluorooctane. PFAS are extremely stable, a property that has been exploited in their applications, including for protection of household items and carpets, in addition to the fire-fighting materials.[6]

Because these compounds are characterized by strong fluorine-carbon bonds, the organic fluorine has been referred to as "fixed" fluorine, and also as "non-exchangeable" fluorine.

The first important commercial fluorinated alkyl substances were the chlorofluorocarbons, or CFCs, and hydrofluorocarbons, including the halocarbon refrigerants trademarked as Freon by Du Pont in 1931. CFCs were followed by organic compounds in which all the hydrogens attached to carbon were substituted by fluorine. They included the tough, nonflammable, and "non stick" polymeric material Teflon (PTFE), or polytetrafluoroethylene, invented by Roy J. Plunkett at Du Pont (later known as DuPont) in 1938.

By 1950, Du Pont was marketing organic fluorine compounds for other uses. For example, in 1950, a report appeared in *Chemical Industries* headed "Fluorineophyte: New Company in New Jersey Turns Out Polytrifluorochloroethylene Oils, Greases and Waxes." This new company purchased the monomer "from Du Pont which reportedly makes it by dechlorination with zinc of Freon… and polymerize it to various degrees for [its]

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[2] Rich, "The lawyer"; see also Bilott, *Exposure: Poisoned Water*.

[3] Lerner, "3M knew about the dangers"; Williams, "Toxic: 3M knew." See also, Nadi, et al., "The devil they knew."

[4] See, for example, *Reuters*, "3Ms $10.3 billion PFAS settlement."

[5] Mayer and Brown, "3M to discontinue."

[6] Naturally occurring organic fluorine compounds are extremely rare. Some are present in volcanic and geothermal emissions. See, for biosynthesis of fluoroacetate and 4-fluorothreonin, O'Hagan and Harper, "Fluorine-containing natural products."

basic products."[7] Also in 1950, *Chemical Industries* made known the availability of Du Pont perfluoroalkyl compounds, with 12 to 41 carbon atoms.[8]

To synthesize the eight-carbon chain perfluoro compounds of interest here, Du Pont used, from 1970, the process of telomerization, involving a telogen (organoiodine compound) and a taxogen (tetrafluoroethylene), that participate in a series of addition reactions, to bring about radical polymerization.

The 3M method of manufacture, which began in around 1950, was based on the process of electrochemical fluorination invented by Joseph H. Simons at Pennsylvania State University in the 1930s. The organic substance to be fluorinated is placed in a cell containing liquid, anhydrous hydrofluoric acid. Fluorine is adsorbed on nickel fluoride at the anode, and hydrogen is evolved at the cathode. Fluorination is believed to take place by a free radical mechanism.[9] In the case of the starting material octanesulfonyl fluoride, one product is perfluorooctane sulfonyl fluoride (POSF), which is converted to perfluorooctane sulfonic acid (PFOS). The electrochemical process favours formation of both straight and (to a lesser degree) branched chains. 3M investigated PFAS and their derivatives for properties that could be applied in commercial products, and synthesized novel compounds in which various functional groups were introduced. Research on certain of these compounds showed that they strongly repelled water and oil. This led to the introduction in 1956 of 3M's Scotchgard and a variety of textile finishes. Certain PFAS were found to act as efficient surfactants, concentrating in the surface of liquids or on the surface of solids. Industrial surfactants serve as anti-foaming agents, as foam builders, as wetting agents, as emulsifiers, as dispersants, and as detergents.[10] From the mid-1960s, 3M PFOS was used extensively in the already mentioned firefighting foams, performance products formulated as complex systems of perfluorochemical surfactants containing emulsifiers. When formulated with polyisocyanates, perfluoroalkyl compounds gave urethane (polyurethane) coatings. By the late 1970s, these and other per- and polyfluoro products were, as surface treatments, applied to a variety of other uses, mainly products that involved regular human exposure, including for treatment and protection of carpets (urethane adipates), as well as for paper and packaging products. The finishing products were surface coatings that resisted adhesion: they are anti-adhesive coatings. Low surface free energies as imparted by fluorine were favoured, and the industrial materials were designed to incorporate the required physical properties. Certain polymers, as functionalized fluorinated precursors, contain both fluorine and hydroxyl groups (-OH) to confer reactivity and adhesion.

This broad activity continued until the end of the twentieth century, by which time many thousands of per- and polyfluoroalky compounds had been synthesized.

ANALYSIS

The analysis and quantitation of PFAS in biological materials and water is nowadays undertaken with sophisticated instrumental techniques, especially high pressure liquid chromatography (HPLC, today "pressure" is replaced by "performance") hyphenated with tandem mass spectrometry (MS), referred to as HPLC-MS/MS. The modern methods, with sensitivities of parts per trillion, came into widespread use during the last decade of the twentieth century. Before then, the presence and quantitation of PFAS in biological material was achieved by indirect techniques that were originally closely identified with fluoride research in dentistry. This is the purview of this paper which describes the early development of analytical methods for detection and quantitation of fluorine in industrial perfluoro compounds containing various terminal functional groups as discovered in blood and serum. Because of their prevalence, the main focus is on the eight-carbon chain perfluorooctanoic acid (PFOA), and perfluorooctanates, and PFOS and perfluorooctane sulfonates (Figure 1). PFOA and PFOS were manufacture by 3M. Du Pont purchased PFOA from 3M prior to its startup of the telomerization process. Du Pont never made PFOS.

The goal of the analytical research was the ability to isolate, identify, and quantitate the PFAS in blood, serum, and biological materials. The key early technique was based on the release of ionic fluorine (fluoride) by decomposition of organic fluorine compounds. The first methods involved controlled burning, either by ashing in air in a furnace, or combustion using a suitable closed flame apparatus, a "bomb," in order to break the chemical bonds between organic carbon and fluorine (C-F) in alkyl chains (in terminal groups, $-CF_3$; and in chain groups, $-CF_2-$), thereby releasing the fluoride ion (F^-).

Following the decomposition, all the released fixed fluorine, along with previously unbound fluoride, in biological materials and blood, was determined as the fluoride ion. The fluoride ion concentration, without release of the bound fluorine as fluoride, was determined sepa-

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[7] "Fluorineophyte."

[8] *Chemical Industries*, August 1950, p. 266.

[9] Simons, "Fluorochemicals"; Kissa, *Fluorinated Surfactants*, pp. 31-36.

[10] Kissa, Ref. 9, pp. 1-12.

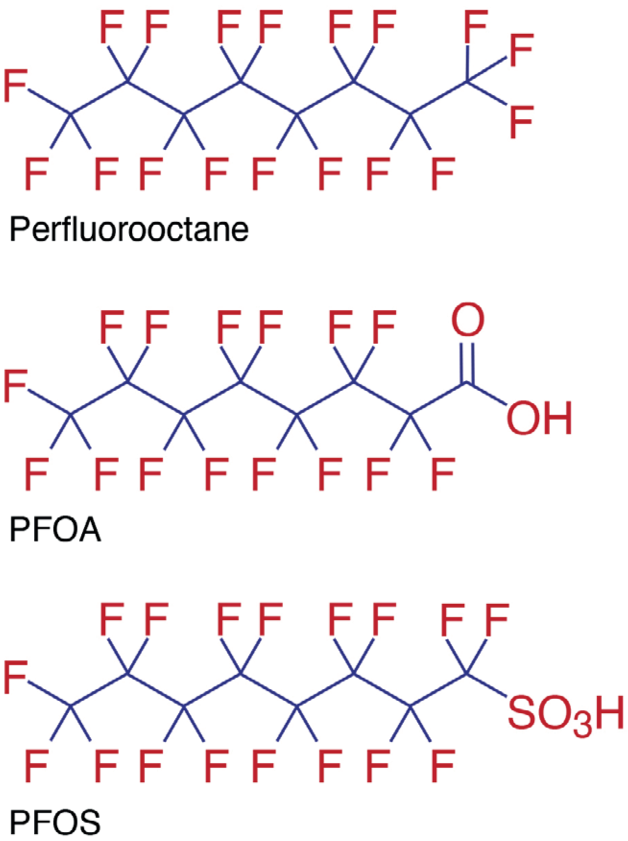

Figure 1. Perfluorooctane, PFOA (perfluorooctanic acid), and PFOS (perfluorooctane sulfonic acid).

rately. The difference, that is total fluoride less the fluoride measured before decomposition, represented the organic fluorine, as present in PFAS. Other techniques discussed here include the use of fluorine-specific electrodes, derivatization of PFAS to afford products suited to gas chromatography (GC), and decomposition with sodium biphenyl. Significantly, as mentioned here, there was also a diffusion method not involving ashing which though giving erroneous results acted as the stimulus for more fruitful investigations. By the late 1970s the methods of analysis had been refined to the extent that quantitation at low parts per billion (ppb) of total PFAS in blood was achieved. This survey is of special interest to the history of chemical analysis because the 1970s represented a major changeover period from "wet and dry" methods of analysis to instrumental methods of analysis; skills in manipulation on the bench would give way to skills in interpreting spectral data.[11] Here, as we shall see, both techniques were harnessed to great effect in the trace analysis of organic fluorine in biological materials. Moreover, this is an excellent example of the adaptation of techniques to the special needs brought on by concerns over specific contaminants.[12]

RELEASE OF FLUORINE AS FLUORIDE FROM PFAS

The development of methods for the analysis of fluoride followed concerns in the 1930s relating to levels of the ion in potable water and the impact on dental health. Trace measurements of fluoride at the low parts per million (ppm) level were undertaken, and standard methods were developed for measurement of fluoride in water. Analysts combined titrimetry with colorimetry, and other readily available techniques, to quantitate the fluoride. Novel techniques were developed in which the intensity of a colour from a complex produced by reacting the fluoride with a standard indicator colorant was proportional to the concentration of fluoride. In the 1940s, the Scott-Sanchis method, based on the use of Alizarin red S as indicator (an aqueous solution of sodium alizarin sulfonate), was used to determine fluoride in water.[13] By the mid-1950s this method had been improved considerably, particularly for removal of interfering ions. Rapid quantitative analysis was achieved with benchtop instruments, the colorimeters, and also with the spectrophotometers introduced around 1940. These techniques had achieved a high level of sophistication by the late 1950s.[14] Greater specificity was in general obtained with colorimetry. The interest in the relationship between fluoride and cancer encouraged international research into trace analysis of fluoride during the 1950s and 1960s.

Refinements in combustion included decomposition in the closed Parr oxygen bomb. In 1956, P. B. Sweetser of Du Pont's Chemical Department employed a version of the combustion method to determine quantitatively the fluorine in a number of fluorine-containing organic compounds, including Teflon and the sodium salt of trifluoroacetic acid. Sweetser used R. Wickbold's oxyhydrogen combustion method to decompose the organic fluorine to carbon dioxide and hydrogen fluoride (HF). The fluoride was absorbed in sodium hydroxide solution, and titrated with thorium nitrate, using Alizarin red S

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[11] Morris, *The Matter factory*.

[12] Homburg and Vaupel, eds, *Hazardous Chemicals*.

[13] In 1945, the concentration of fluoride ion in potable waters in the United States was adjusted to 1 ppm. This followed the discovery in the early 1930s that fluoride ion at higher concentrations caused dental fluorosis. Dickinson, *The Chemical Analysis*, pp. 109-111; See also *Standard Methods*, pp. 98-107; and *Methods of Analysis*, pp. 311-317.

[14] They included analysis of fluoride based on its reaction with zirconium ions and 2-(parasulfophenylazo)-1,8-dihydroxy-3,6-naphthalene-disulfonate (SPADNS).

as indicator.[15] Sweetser preferred the Wickbold method because, he explained, with the alternative Parr bomb method, "in the case of highly volatile compounds and compounds with high fluorine content there has been difficulty in the decomposition step." The method was found suitable for "compounds notorious for their stubbornness in resisting decomposition."[16] Chemists at 3M later achieved greater success in the use of the Parr bomb to determine organic fluorine in serum.[17] In general, however, the Wickbold method was preferred. These, as we shall see, were important observations.

The introduction of fluoridation for dental purposes stimulated research into new methods for determination of the presence of fluoride in different media. Ashing of biological material for the microdetermination of fluoride at the low ppm using titrimetric techniques had been adopted by analytical chemists from the late 1930s. They included Wallace David Armstrong (1905-1984) at the Department of Physiological Chemistry, University of Minnesota.[18] In the 1950s, Armstrong, then with the Department of Biochemistry, The Medical School, was a senior figure in fluoride analysis. With Leon Singer (1918-1988), the latter at Minnesota's School of Dentistry, he undertook investigations using a diffusion technique, namely electron transfer catalysis. The work was published in 1954. It did not involve ashing or combustion.[19]

Armstrong assisted the Indian researchers Pothapragada Venkateswarlu and D. Narayana Rao, at the Department of Biochemistry, the Government Medical College, Trivandrum (in the state then known as Travancore-Cochin). They published on the estimation of fluorine (actually fluoride) in biological materials, also in 1954.[20] Venkateswarlu (1926-2015), who plays a role here, studied for his undergraduate degree in biochemistry at Andhrra University during 1946-1948. It was probably in the late 1950s that he joined Armstrong at Minnesota in order to study for his doctorate in physiological chemistry and microbiology, which was awarded in 1962. Over the following years Venkateswarlu studied fluoride analysis in biological materials and later contributed to methods used in trace determinations of fluorine in organic perfluoro compounds.

In 1959, Singer and Armstrong had used ashing to determine the presence of fluoride in blood serum. The presence of organic fluorine in blood was almost certainly not then appreciated, nor even a consideration, in this work. It was enough to release fluoride quantitatively from biological material. The sample was ashed with magnesium oxide, as fixative, and total fluoride was determined by colorimetric analysis, using the fading in colour of a zirconium-Eriochrome Cyanine R lake. They observed that "absorbance of the solutions can be measured with commonly available spectrophotometers."[21] Around this time specific-ion electrode coulometric titration for halogens had come into general use, and thus was applicable to fluoride. The end point was determined by a silver-saturated calomel combination.

THE DONALD R. TAVES VERSUS ARMSTRONG AND SINGER CONTROVERSY

The introduction of several new commercial products containing the organofluorine compounds stimulated the further application of analytical techniques, particularly in industry, for determining fluorine when bound to carbon. However it had little or no impact on the trace determination of organic fluorine in biological materials. That would change with Singer and Armstrong's studies after their results were questioned by Donald R. Taves, at the University of Rochester, New York. Taves, subsequently with his doctoral student Warren S. Guy (b. 1942), and in collaboration with NMR expert Wallace Siegfried Brey (1922-2023), at the University of Florida (Gainsville), would in the mid-1970s provide unequivocal evidence for the ubiquitous presence of PAFS in human blood.

Donald Taves (b. 1926) requires a brief introduction. He received his BS degree in 1949 and his MD in 1953, both from the University of Washington. In 1954 he was appointed a public health resident with Washington's Clark-Skamania Health Department. He was awarded the MPH (Masters in Public Health) in 1957 from the University of California. In 1960, when he was still a public health officer, he enrolled on a PhD programme to study bone mineralization, under William F. Neuman, joint head of the Department of Radiation Biology and Biophysics at the University of Rochester. However, his main interest was in the impact of fluoridation, a topic in which he would later become a leading expert.

Taves' recent reminiscences inform us on his first interactions with Armstrong and Singer and his intro-

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[15] Matuszak and Brown, "Thorium nitrate." See also McClure, "Microdetermination."

[16] Sweetser, "Decomposition," p. 1768; and Wickbold, "Die quantitative,"

[17] Belisle and Hagen, "Method for the determination of the total."

[18] For Armstrong, see Singer and Posner, "Wallace D. Armstrong (1905-1984)."

[19] Singer and Armstrong, "Fluoride determination by electron transfer catalysis."

[20] Venkateswarlu and Rao, "Estimation of fluorine." Venkateswarlu also published under V. Pothapragada. From 1956, Travancore-Cochin was known as Kerala.

[21] Singer and Armstrong, "Determination of fluoride in blood serum," p. 106. See also Singer and Armstrong, "Regulation of human plasma."

duction to trace fluorine analysis in biological materials.[22] According to Taves, since the late 1950s he had been interested in the impact of sodium fluoride introduced to the body by fluoridation on renal disease, and in methods for measuring serum fluoride at the levels required to perform the proper renal clearance studies. In 1959, he applied in writing to Harold Hodge, head of the new Department of Pharmacology at Rochester, for a doctoral post in order to continue this work, but Hodge did not respond, perhaps, because as a proponent of fluoridation, he opposed Taves' questioning of the 1950s fluoridation policy of the California Department of Public Health. That was the reason for his joining Neuman. Taves first met with Armstrong and Singer around 1960 at a scientific meeting held in San Francisco. "I made a trip to San Francisco to meet with Armstrong and learn about the new method that he and Singer were developing for measuring serum fluoride." This method was based on diffusion of the fluoride. Taves:

> I was hoping that I could use their method to study the effects of renal disease on serum fluoride. Wallace, better known as Wally, was one of the few MDs who belonged to the American Dental Association (ADA), and the ADA's journal published many of the early biochemical studies. I knew he was going to talk about their new method of analysis and outline the preliminary results of using it on serums from fluoridated and non-fluoridated cities at a meeting in San Francisco. I was particularly interested in their finding that there was no difference in serum fluoride due to fluoridation and at the same time finding a big difference in terms of dental caries. I found that worrisome because I hypothesized that serum levels should correlate with the amount that was ingested. We exchanged our viewpoints for about an hour in the hallway outside of the meeting without convincing the other…[23]

Following completion of his PhD dissertation in 1963 on "Factors Controlling Calcification," Taves received a post as assistant professor with Neuman's department. He was now "free to pursue the fluoride analysis question," and visited Singer's lab "where they [Armstrong and Singer] were still working on their new [diffusion] method," but were facing difficulties. Taves remembers: "As we were talking, his lab technician interrupted to say that the values she was obtaining were still too low relative to their earlier methods. His response was to increase the length of time of diffusion." Taves, in retrospect, observes: "Rather than extending the time, they should have checked to see if all the fluoride had diffused. If they had done that, they would have known that they were dealing with a contaminant rather than fluoride and, with more diffusion time, they would obtain higher values due to the contamination." There were certainly problems of both identity and quantitation.

In 1965, Armstrong and Singer published details of a modified diffusion method which "eliminated the requirement for ashing biological materials with magnesium oxide as fixative."[24] However, Taves, now an expert in fluoride analysis, was unable to accept their results. The reported fluoride level was far too high. Taves drew attention in *Nature* to the fact that, as compared with his method, which involved ashing, the reported Singer and Armstrong determinations of "fluoride from serum indicate that the generally accepted value for normal humans is too high by as much as a factor of ten."[25]

Singer and Armstrong responded to Taves after undertaking ashing by the method that they had used in 1959. They claimed that from the two methods of analysis, diffusion and ashing, they obtained similar results, using human plasma (sera that has had clotting agents removed), reporting, in June 1967, in *Nature*:

> Taves has indicated that our method for estimation of serum fluoride content based on diffusion of hydrogen fluoride gives results which are about ten times too large, but our values of human plasma fluoride content, which he quotes, were not obtained by the diffusion method but by an entirely different procedure which requires ashing of the sample with magnesium oxide followed by separation of the fluoride by distillation from perchloric acid. The agreement of the results for fluoride analyses of urine, bovine plasma, dentine, liver and muscle obtained by the two procedures [of Singer and Armstrong], which are quite different in principle, furnishes mutual support of the reliability and accuracy of both methods. Nevertheless, we have carried out further experiments, some of which are like those reported by Taves, and our evidence is that both of our methods give results for plasma fluoride content which are not markedly in error.[26]

Taves was quick to reply, in September 1967, again in the columns of *Nature*: "In 1966 I published results showing that the normal concentration of fluoride in human serum is about one-tenth the generally accepted value – that of Singer and Armstrong."[27] That was from

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[22] Taves, "Fluoride: From nutrient."

[23] Ref. 22.

[24] Singer and Armstrong, "Determination of fluoride: Procedure."

[25] Taves, "Normal human serum."

[26] Singer and Armstrong, "Normal human serum fluoride."

[27] Taves, "Use of urine to serum fluoride." "Part of the evidence supporting my results was the 'at least five-fold discrepancy' that could be shown in their [Singer and Armstrong] data which is most easily explained by an error in the measurement of the serum fluoride. The discrepancy involves the ratio of urine to plasma fluoride concentrations when determined by fluorine-18 as compared with stable fluoride analyses. Because the concentration of fluoride in urine is well estab-

their diffusion method. Taves, however, could not fault their ashing method. It was to his credit that he could now explain the unexpectedly high results obtained by Singer and Armstrong using ashing.

Taves established that Singer and Armstrong had, by resorting to complete ashing, measured both the free fluoride ion normally present and the far greater amount of fluoride ion that had been released from a hitherto unexpected organic fluorine-containing compound. Taves' own results, following his modification of the ashing procedure, to ensure complete ashing, were now in good agreement with those of Singer and Armstrong. Here it should be pointed out that because of the extremely strong fluorine-carbon bonds, earlier ashing experiments were not always carried out to the point where all the carbon-fluorine bonds were broken. This had been noted by Sweetser at Du Pont in 1956. Armstrong had, unwittingly, brought about release of most or all of the fluorine as fluoride.

It is also important to emphasize here that this led to the clearest early experimental evidence for the presence of industrial per- and polyfluoro compounds in blood and biological materials.

In March 1968, Taves, now an associate professor at Hodge's Department of Pharmacology, associated with Rochester's School of Medicine and Dentistry, explained:

> It has been assumed that there is only one form of fluoride in serum, the inorganic F ion. It would therefore seem that either the value for serum fluoride which I found (1 μM) … or that found by Singer and Armstrong (7.5 μM) … must be in error. While the diffusion method of Singer and Armstrong has been shown to produce erroneous values, the same cannot be said for their ashing and distillation procedure. The evidence that the serum fluoride is about 1 μM in a fluoridated community does not rule out the possibility that more fluoride could be made available from serum by ashing... [28]

Taves investigated the available methods for analysis of fluoride at low levels of detection, including use of the fluorescence of a morin-thorium complex, and a fluoride ion-specific electrode. The latter was used to establish, following ashing, the presence of perfluoroalkyl compounds in blood plasma. Taves found "excellent agreement between the findings with the fluoride electrode and those employing the morin-thorium reagent." Moreover,

> These results are consistent with the hypothesis that there are two forms of fluoride in serum, exchangeable [fluoride] and non-exchangeable [fluorine]…. In 1950, Smith, Gardner, and Hodge found normal values ... for serum fluoride in a fluoridated community, implying that they were measuring only exchangeable fluoride [the fluoride ion]. They distilled fluoride from blood… and then ashed the distillate. *If in fact there is a non-exchangeable fluoride in serum, it did not break down or diffuse under these conditions, implying a large stable molecule. These findings are consistent with the presence of a fluorocarbon molecule* (emphasis added).[29]

Having validated the method of Armstrong and Singer when they used ashing, Taves continued to refine his experimental techniques to establish, also with ashing as the first step, the presence of perfluoroalkyl compounds in blood plasma. In one case, hexamethyldisoloxane, which accelerated the release of fluoride, was used in the next step, diffusion separation with electrophoresis, which was highly sensitive to the presence of the fluoride ion.[30] According to Taves, he had eliminated interference from contaminants that had caused the Armstrong and Singer diffusion method to give high readings. In his November 1968 paper in *Nature*, Taves reported "Evidence has been given that there are two types of fluoride in human serum. The observation that 80-90 per cent of the fluoride is not made available as exchangeable fluoride until after ashing suggests that it might be bound in some fashion to the serum proteins. I have therefore determined the distribution of exchangeable and non-exchangeable fluoride relative to the serum proteins, after electrophoresis…. Free-flow curtain electrophoresis was used because the concentration of fluoride in serum is very low, making it necessary to use large volumes of serum. The serum was obtained from a normal human who obtained his water from a fluoridized supply."[31] The "normal human" was Taves himself. He now interpreted his result: It provided unequivocal evidence for the presence of a perfluorocarbon compound, likely of industrial origin, in serum. Shortly after, Taves assigned the further investigation of fluorine in serum to Warren S. Guy.

By 1975, Guy and Taves had isolated the fluorine in human blood obtained from blood banks in five districts, three in New York State and two in Texas. Taves and Guy released fluoride by ashing, and the total fluoride was determined with the fluoride electrode. For analysis of the unashed serum they used preparative silicic acid chromatography. This revealed a dominant

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lished in contrast to that in serum where analysis is much more difficult, it is reasonable to question the latter when there is a discrepancy. Singer and Armstrong, however, in their recent rebuttal, think that I came to erroneous conclusions because I directed attention to only two of their analyses, which they now consider aberrant."

[28] Taves, "Evidence,' 1968a.

[29] Ref. 28.

[30] Taves, "Separation of fluoride," 1968b.

[31] Taves, "Electrophoretic mobility," 1968c.

peak. Following four separations, the same fractions that gave this peak were combined and re-chromatographed as a cleanup step. The NMR expert Wallace Brey was asked to undertake fluorine NMR (^{19}F-NMR) analysis of the material that gave the sharp peak. This indicated the presence of one or more organic perfluoro compounds. Brey's ^{19}F-NMR suggested a chain of atomic groupings of the type $-CF_2-$; a $-CF_2-$ grouping located next to a terminal $-CF_3$ grouping; and the terminal grouping itself $-CF_3$. Apart from the $-CF_2-X$ grouping where X was an unknown functional group (perhaps = COOY, a carboxylic acid, where Y= H, or another atom or atomic grouping), this was consistent with a perfluoro carboxylic acid or derivative: $CF_3-(CF_2)_n-CF_2-COO-Y$. There was also the suggestion of the presence of branched isomers. A structure such as $CF_3-(CF_2)_n-CF_2-COO-Y$ ruled out other perfluoro compounds of commerce consisting of smaller molecules. Thus whereas Taves had identified a perfluorocarbon compound(s) in his 1968 paper in *Nature*, Guy, Taves, and Brey had in 1975 more specific evidence of a long-chain perfluorocarbon compound, or compounds, of six or seven carbons, which, they speculated, was a perfluoro carboxylic acid or some other closely related compound.[32]

Certain of the chemical shifts in the NMR spectrum were in close agreement with the spectra obtained from linear perfluorooctanic acid used as standard. However, there was one notable difference. The chemical shift for the $-CH_2-$ grouping next to the $-COOH$ in perflurooctanic acid, run as the standard, was -120.2 ppm, whereas in the sample it was -114.3 ppm. Could the 3M corporation assist with complete identification?

KNOWLEDGE TRANSFER TO 3M

With their results to hand, Guy, Taves, and Brey made preparations to give a joint presentation on organic fluorocompounds in human tissues on 25 August 1975 at the Chicago meeting of the American Chemical Society. Anxious to establish, prior to the meeting, the exact nature of the compound isolated from human blood, Guy made two phone calls to 3M for assistance in identification. On 14 August 1975, Guy made his second phone call, to G. H. Crawford of 3Ms Photographic Products Division. A few days later, Crawford summarized his version of the phone conversation. "I got John Pendergrass [of 3M's Medical Department] on the line and Guy brought in a Dr Tays [sic.]." Brey's interpretation from his NMR data indicated that the compound

> is fluorocarbon carboxylic acid with a C_6 or C_7 fluoroalkyl group. Dr Brey suspects a branched end on the chain, e.g. perfluoro t-butyl … The discussion involved Dr Guy's speculative questions as to where such a 'universal' presence of such compounds in human blood could come from…. Somewhere he got the information that 3M's fluorocarbon carboxylic acids are used as surfactants and wanted to know if they were present in 'Scotchgard' or other items in general use by the public… We plead ignorance but advised him that 'Scotchgard' was a polymeric material not a F.C. [fluorocarbon] … They have done experiments involving water boiled in Teflon cookware with negative results. We suggested obtaining plasma specimens from uncivilized areas, e.g. New Guinea where they don't use too much 'Teflon' cookware or 'Scotchgard'.

Crawford and Pendergrass

> adopted a position of scientific curiosity and desire to assist in any way possible and suggested that our own analytical people might be able to clarify Dr Brey's NMR findings (I know Wallace Brey from way back. He is highly respected, conservative and not given to frivolous speculations)…My recommendation … is to get Richard [Newmark, at 3M Central Research Analytical] in touch with Brey, obtain spectra for his own interpretation perhaps samples to run on our equipment, etc., in other words, keep scientists talking to scientists in the spirit of cooperative scientific enquiry. On the positive side—if it is confirmed to our satisfaction that everybody is going around with fluorocarbon surfactants in their bloodstreams with no apparent ill-effects, are there some medical possibilities that would bear looking into?[33]

A copy of the paper given by Taves, Guy, and Brey at the August ACS meeting was sent to 3M, no doubt in the hope that the corporation would assist with identification. The document included the NMR information, which was acted upon at 3M.

According to an internal 3M chronology, during 17 to 21 September 1975, Newmark at Central Research Analytical compared the ^{19}F-NMR spectra of PFOA, PFOS, and related compounds, with that obtained by Brey. After further NMR studies, Newmark advised his colleagues on November 6: "$C_8F_{17}SO_3H$ spectra matches that presented by Guy, et al." The 114.3 ppm peak that had confounded the academic workers was close to a peak of 114.2 ppm from PFOS. Thus, Newmark, on the basis of instrumental evidence, was of the opinion that Guy and Taves likely had isolated PFOS as the main component of the fraction. As it turned out, he was cor-

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[32] Spectral data was reproduced in Guy, Taves, and Brey, "Organic fluorocompounds."

[33] Environmental Working Group. G. H. Crawford, "Record of a telephone conversation – August 14, 1975," 3M Interoffice Correspondence, 20 August 1975, pp. 270-272.

rect. However, 3M did not inform Guy and Taves of Newmark's analysis. More important, in the long term, was the fact that 3M was now alerted to the fact that populations outside the factory wall were exposed to PFAS. The outcome was that 3M immediately undertook internal investigations into techniques for measuring their presence in human blood. On 16 December 1975, 3M representatives visited Rochester to consult with Guy and Taves: "3M proposes, and Guy and Taves agree that 3M will attempt to isolate and identify organic fluorine in human blood." On 17 February 1976, 3Ms "Central Research Analytical develops an accurate analytical method for determining parts per billion quantities of organic fluorine compounds in human blood. Method tested on blood from American Red Cross and value agrees with those in literature."[34] Tests on 3M personnel conducted during April to October 1976 gave concentrations of "organic fluorine compound" from 50 to 1,000 times normal values.

The detailed account of the findings of Guy, Taves, and Brey appeared during 1976 in their chapter on "Organic Fluorocompounds in Human Plasma: Prevalence and Characteristics." This was similar to the document provided to 3M following the August 1975 ACS meeting. The paper described how, "In order to further characterize the organic fluorine fraction, it was purified from 20 liters of pooled human plasma and characterized by fluorine nmr." Figure 5 was a reproduction of Brey's ^{19}F-NMR spectra. The blood was obtained from blood banks of 106 individuals from five cities where there had been no change in fluoride in potable water for at least five years. Fluoride was obtained by ashing and determined with the fluoride electrode. The values for inorganic fluoride (F^-) and organic fluoride (R-F) "show that the average fluoride concentration in plasma is directly related to the fluoride concentration in the water supply, and that the average organic fluorine concentration in plasma is not." Moreover, "A series of compounds having a structure consistent with that found here for the predominant form of organic fluorine in human plasma is widely used commercially for their potent surfactant properties."[35]

On 25 February 1977, at the Denver meeting of the American Association for the Advancement of Science, Guy, then at the Childrens' Hospital, Cincinnati, Ohio, lectured at a Fluoride Symposium on "Perfluorooctanoic Acid in Human Plasma." The July issue of *Fluoride*, journal of the International Society of Fluoride Research, included "a special report on the symposium: Guy announced that with Taves he "had isolated in 1976 by spectroscopic analysis, perfluorooctanoic acid, a major component in pooled plasma which accounts for at least 1/3 of the organic fluoride content."[36] Moreover, "Guy and Taves again report finding $C_7F_{15}CO_2H$ in pooled plasma and attribute its presence to industrial products."[37] Among them was 3Ms Scotchgard.

However, the academic workers were not made aware of Newmark's findings. In September and October 1976, there were a number of exchanges between 3M and Taves over the analysis of PFOA, while in late October Singer requested samples of PFOA with the intention of improving on the analysis method of Taves. By this time chemists at 3M were making advances in PFAS analysis. Some years later, Taves stated: "They [3M] would come check with me periodically – they wouldn't tell me what they were doing, but they wanted to know what I knew."[38] It probably suited 3M, as almost certainly the sole manufacturer of PFOS (FC-95), for the academic workers to believe that PFOA was the major component of the material isolated by Guy and Taves during their chromatographic separation. Notwithstanding the reluctance on the part of 3M to reveal its findings in 1976, two years later its chemists started to publish their methods for PFAS. But here we must backtrack a few years for a brief summary of Venkateswarlu's research in the 1970s

Reverse Extraction

In 1971, Venkateswarlu and co-worker P. Sita, around that time affiliated, respectively, with the Department of Biochemistry at Sri Venkateswara Medical College, and the Postgraduate Institute of Medical Education and Research Chandigah, in India, published on "A New Approach to the Microdetermination of Fluoride." This was based on an adsorption-diffusion technique. Fluoride was adsorbed on calcium phosphate, and it was found "possible to concentrate traces of fluoride from a large amount of sample low in fluoride, a feature which permits more reliable determination of fluoride."[39] By late 1971, no doubt as a result of their achievements in fluoride analysis, Venkateswarlu and Sita had received posts in the United States, at, respectively, the Department of Biochemistry, The Medical School, University of Minnesota, and the University of Minnesota Hospital. With Singer and Armstrong, Venkateswarlu adapted the calcium phosphate method to "the isolation and con-

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[34] Ref. 33, pp. 276-278.

[35] Guy, Taves, and Brey, Ref. 32, pp. 118, 125, 131.

[36] Waldbott and Yiamouyiannis, "Special Report."

[37] Ref. 36.

[38] Bryson, *The Fluoride Deception*, pp. 234 and 352-353 (notes 11 and 12).

[39] Venkateswarlu and Sita, "A new approach," 1971a, p. 760.

centration of ionic and ionizable fluoride from interfering substances in biological fluids and [it] eliminates the requirements of ashing and diffusion." They speculated that in plasma the ionic fluoride is "in equilibrium with a loosely bound fluoride [ionizable fluoride]… furnishing additional ionic fluoride."[40]

Notwithstanding this suggestion, in 1974, Venkateswarlu published what would become his first significant contribution to trace PFAS analysis, a reverse extraction technique for increasing the availability of released fluoride. The total fluoride, following extraction as a fluorosilane, according to the 1968 method of J. A. Fresen, F. H. Cox, and M. J. Witter, at the University of Groningen, was determined with the hanging drop fluoride electrode.[41] The method enabled detection in serum, with "a two- to threefold gain in the concentration of fluoride compared with that in the original sample."[42]

In 1974 Venkateswarlu, as a result of his skills in fluoride analysis, joined the 3M Commercial Chemicals Division, where he continued with research into improvements in trace analysis. In 1977 published a comprehensive review of methods for analysis of fluorine in biological materials.[43] His chapter was completed before Guy, Taves, and Brey published their findings in 1976. In 1979, Guy published a chapter on "Inorganic and Organic Fluorine in Human Blood," in which he surveyed methods for analysis of fluorine, and especially misleading information from diffusion-colorimetry. Guy agreed with Venkateswarlu, who had opined: "The values so obtained reflect ionic fluoride plus interfering substances, the latter masquerading as nonionic fluorine … in unashed body fluids… this practice should be discontinued." Of the organic fluorine compounds present in human plasma, Guy, still ignorant of 3Ms findings, concluded that "The major type is probably a derivative of perfluoro-octanic acid, presumably a synthetic environmental contaminant."[44]

GAS CHROMATOGRAPHY AND DERIVATIZATION

The main analytical work on PFAS at 3M was carried out from around October 1975 by chemists Jon Belisle and Donald F. Hagen at Central Research. In this, they had a special interest in the application of gas chromatography to the determination of PFAS, and of PFOA and its derivatives.

From the time of its introduction in the early 1950s, gas chromatography (GC) became the method of choice for separating volatile organic compounds. Early instruments were built inhouse in industrial and academic laboratories. From the mid-1950s, they became available from mainly American manufacturers of electronic instruments.[45] In the 1960s, two highly sensitive detectors were introduced into GC, the flame ionization detector (FID) and the electron capture detector (ECD); both were ideal for analysis of halogens. Narrow capillary gas chromatography columns improved resolution and were preferred in organic trace analysis of pesticides, water, and contaminants in the atmosphere. Identification was achieved with mass spectrometry (MS).[46]

Interestingly, in 1971, using GC, there was further evidence of the stability and environmental presence of chlorofluorocarbon compounds. James Lovelock, at the University of Reading, UK, used his invention, the ECD, to measure "Atmospheric Fluorine Compounds as Indicators of Air Movements." Lovelock worked with volatile organofluorines the great stability of which was such that he suggested the use of these "industrial stable compounds as indicators of air movements and wind indicators."[47]

GC is suited to the analysis of volatile, as well as stable, organic compounds. PFAS compounds are not volatile enough and are thus unsuited to GC. Derivatization in which organic fluorine is first converted into fluoride was found to provide a route to volatile products that could be readily detected by GC. In 1967, a method for quantitative measurement of a volatile fluorosilane, was published by R. Bock and H. J. Semmler at the University of Mainz.[48] It involved conversion of organic fluorine to inorganic fluoride, followed by quantitative measurement of the volatile, stable fluorosilane. It was similar to the method of Fresen, Cox and Witter, which Venkateswarlu had used in 1974.[49] In 1978, Belisle

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[40] Venkateswarlu, Singer, and Armstrong, "Determination of ionic (plus ionizable)," 1971b, p. 356.

[41] Fresen, Cox, and Witter treated trimethylchlorosilane with water, to release the corresponding silanol (R_3SiOH, where R = methyl), which reacted selectively with fluoride ion to form the stable, volatile trimethylfluorosilane (CH_3SiF), suited to GC analysis. Fresen, Cox, and Witter, "The determination of fluoride."

[42] Venkateswarlu, "Reverse extraction technique," on p. 880.

[43] Venkateswarlu, "Determination of fluorine in biological materials," 1977, on pp. 93-201.

[44] Guy, "Inorganic and organic fluorine in human blood," on pp. 136-137 and 141. Guy quoted from Venkateswarlu, "Fallacies in the determination." Later reviews by Venkateswarlu include "Determination of fluorine," 1994.

[45] Ettre, "American instrument companies."

[46] In MS unknown molecules are subjected to fragmentation. The recorded fragmentation patterns, by use of special "atlases," with tables showing peaks corresponding to structural features of groups of atoms (fragments), enables the determination of complete structures.

[47] Lovelock, "Atmospheric fluorine."

[48] Bock and Semmler, "Abtrennung und Bestimmung."

[49] Ref. 41.

and Hagan at 3M were of the opinion that the Bock and Semmler procedure "presented a new approach for the separation and determination of fluoride."[50]

Using the Bock and Semmler procedure, the two 3M chemists undertook research to determine the total organic fluorine content in blood, and serum/plasma. They employed oxygen bomb combustion, and reaction of the released fluoride with the extractant triethylsilanol to afford the triethylfluorosilane, which was then analyzed by GC. As applied to perfluorooctanoic acid (PFOA), the total fluoride was determined with a flame ionization detector. Using an internal standard, they determined less than 1 ppm, and as low as 0.010 ppm. "The application of this method to a sample (both with and without combustion), allows one to determine the concentration of both organic (bound fluorine) and inorganic (ionic fluoride) in the sample." [51]

According to Belise and Hagen: "It should be possible to increase the lower limits of detectability for fluoride by concentration techniques such as reverse extraction," the method published in 1974 by their colleague Venkateswarlu, who, they noted, had demonstrated that "perfluorooctanoic acid would be a good compound to use in evaluating the new method for the decomposition and recovery of fluoride." With the oxygen bomb procedure and the use of whole blood, 95 ± 5% at the microgram level of added perfluorooctanoic acid was recovered. Similar results were obtained with *p*-fluorobenzoic acid.

Belisle and Hagen concluded: "The determination of total fluoride in biological samples requires the more vigorous oxygen bomb decomposition technique for quantitative results. Gas chromatographic measurement of the fluoride ion level via the resultant fluorosilane reaction is accurate, dependable, specific, and applicable over a wide dynamic range. This combination appears to provide the most ideal method yet developed for the determination of organic and inorganic fluoride contents."[52]

In 1980, 3M medical director F. A. Ubel and colleagues published a preliminary report on the exposure to PFAS of its plant workers using analysis of a triethylsilane derivative. It was limited to detection of total organic fluorine from the blood stream at 0.5 ppm. Higher than normal levels were found in the ambient air. "No ill health effects attributable to exposure" to ammonium perfluorooctanate, 3M's FC-143, "were found among these workers…. Through certain modifications in the process steps and improvements in engineering controls, a substantial reduction in the airborne fluorochemical levels within the plant was achieved."[53] This lack of ill health effects would be the corporation's standpoint, at least in the public domain, for the next two decades, and, as detection limits were lowered, would include individuals without occupational exposure.

In 1980, also, derivatization of PFOA to give a volatile product was achieved by esterification, in which, for example, the acid group, -COOH was changed to the methyl ester, $-COCH_3$. The methyl esters were prepared by *N*,*N*-dimethylformamide dimethyl acetal derivatization. The method was first described in 1977 by Donald E. Elliott, at National Foam System, Inc. (Lionville, Pennsylvania). The methyl esters, were, for comparative purposes, analyzed by GC with a FID and a thermal conductivity detector (TCD). The samples analyzed covered the C-5 to C-12 range.[54]

A similar method of derivatization was used by Hagen and Belisle for detection of PFOA and other free acids of 3M compounds at the low parts per billion. They determined PFOA in blood and other biological samples by conversion to the volatile methyl ester (via the diazomethane). The ester was analyzed at 3M using GC, this time with the electron capture detector (ECD).[55]

In 1981, Hagen, Belisle, Venkateswarlu, and James D. Johnson, a drug metabolism expert at Riker Laboratories, reported that that they had developed a quantitative microanalytical method based on this methylation route using a sensitive microwave plasma detector, specifically for perfluorooctoanate in blood. At that time, "only a few public donor samples were analyzed."[56] Blood samples were taken from 3M plant workers and other employees. In the mid-1980s, hyphenated GC-MS was used to quantitatively determine perfluorooctanic acid, as its benzyl ester, in plasma and urine.[57]

However, it should be emphasized, esterification of was not suited to the perfluorosulfonates, which included PFOS.

SODIUM BIPHENYL DECOMPOSITION

Another technique for measuring organic fluorine involved sodium biphenyl reductive decomposition, as originally described by L. M. Liggett, of Wyandotte

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[50] Belisle and Hagen, Ref. 17, p. 545.

[51] Ref. 17.

[52] Ref. 17.

[53] Ubel, Sorenson, and Roach, "Health status."

[54] Elliott, "Anomalous response."

[55] Belisle and Hagen, "A method for the determination."

[56] Hagen, et al., "Characterization of fluorinated metabolites," p. 336.

[57] Ylinen, et al. "Quantitative gas chromatographic."

Chemicals Corporation in 1954.[58] Only in the 1970s was the sodium biphenyl reagent found suitable for trace determination of fluorine in blood. T. P. Stein and colleagues at Pennsylvania School of Medicine, and Herbert W. Wallace, at Exxon Research and Engineering Company, Linden, New Jersey, undertook determination of fluorocarbon compounds in blood as part of a programme for using fluorocarbon emulsions as artificial oxygen carriers. One product they used was FC-47, perfluorotributylamine. Their publication described the use of a method which they claimed had wide applicability. This involved sodium biphenyl decomposition, and fluoride specific ion electrode coulometric titration.[59]

Venkateswarlu, while continuing with development of his reverse extraction technique for the determination of fluorine in biological materials, introduced reductive cleavage of the C-F bonds using the sodium biphenyl reagent and determined the resulting fluoride ions with the hanging drop fluoride electrode. The fluoride specific (selective) ion electrode was suggested as an alternative to GC analysis; Venkateswarlu had earlier made the valid point that the method involving reverse extraction was simpler and cheaper than GC or MS.[60]

According to Venkateswarlu in 1982, the use of the sodium biphenyl reagent for determination of fluorine in organic compounds in blood serum had to await “the present availability of sodium biphenyl reagent having an adequately low fluoride blank.”[61] Sodium biphenyl featured in another paper, coauthored by Venkateswarlu, “Automated Molecular Absorption Spectrometry for Determination of Fluorine in Biological Samples.” It described a method for “rapid screening of blood serum samples from plant workers for organic fluorine.” The 3M authors of this paper reductively cleaved the C-F bonds at room temperature with the sodium biphenyl reagent, extracted the fluoride with diphenylsilanediol, and quantitatively determined total fluorine by aluminum monofluoride molecular absorption spectrometry. However, the method “has not, so far, been used by us to determine organic fluorine in normal human or animal blood sera, in which the organic fluorine levels would be relatively lower than those in the samples from plant workers exposed to organic fluorochemicals.”[62]

3M’s somewhat sarcastic remark to Guy suggesting that he should obtain blood samples from the inhabitants of New Guinea would soon backfire. By 1980, 3M needed a better understanding of the pervasiveness of PFAS, and with the help of the People’s Republic of China obtained serum from inhabitants of a rural district in China where 3Ms products were unlikely to be found. In 1981, Belisle published on fluorine determination in serum obtained from these donors. His conclusion: “It is clear that nearly everyone (greater than 98 percent) has both forms of fluorine in his blood and that the reported values are somewhat dependent on the method of analysis.” However, in his published opinion: “As yet, we have no conclusive evidence to indicate that the prevalence of trace amounts of organic fluorine in human blood is primarily the result of industrial fluorochemicals.”[63]

TOTAL ORGANIC FLUORINE, STANDARDS, AND LIMITS OF DETECTION

As has been described in the foregoing, the early investigations into organic fluorochemicals in blood and biological materials presented many challenges and required some innovative thinking. In 1968, Donald Taves determined using an ashing method what he believed to be an organofluorine typical of products made in industry. In 1975, Taves and Guy isolated the major fraction of PFAS present in pooled samples of blood and tentatively identified it, with the help of the NMR expert Wallace Brey, with PFAS compounds, perhaps PFOA or a similar compound manufactured by 3M. At that point, chemists at 3M took up the story and established, on the basis of NMR comparisons with the data of Brey, the likely presence of PFOS in the pooled blood of city dwellers. 3M developed techniques using pure samples for determination of the limits of detection of PFOA. Methods of standardization were validated. By around, 1980 derivatization followed by gas chromatography enabled quantitation of PFOA and other perfluorocarboxylic acids. For comparative purposes, studies were made with different GC detectors. The detection limit of PFOA in a 10 ml sample of blood plasma was 0.015 ppm. However, PFOS was not amenable to methyl ester derivatization. By 1981, following concerns raised by environmental releases of PFAS from finishing processes, Du Pont had developed derivatization - gas chromatographic techniques for measuring trace amounts of PFOA in blood and, significantly, water. Most activities at this time were concerned with standardization.

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[58] Liggett, “Determination of organic halogen.”

[59] Stein, et al, “Determination of fluorocarbon,” pp. 480, 483.

[60] Venkateswarlu, Ref. 42, p. 878.

[61] Venkateswarlu, “Sodium biphenyl,” p. 1132.

[62] Venkateswarlu, et al., “Automated molecular absorption,” p. 2236.

[63] Belisle, “Organic fluorine in human serum.”

Table 1. Timeline for techniques of trace PFAS analysis until 1983. TOF = Total Organic Fluorine; LOD = Limit of Detection.

Year	Reference	Matrix	Technique	Result
1968	Taves, *Nature* 217 (1968, March 16):1050-1051; and Taves, *Nature* 220 (1968, November 9):582-583.	Blood	Ashing, electrophoresis	Evidence of PFAS (covalent fluorine) in serum
1974	Venkateswarlu, *Anal. Chem.* 46(7) (June 1974):878-882		Reverse extraction, fluoride specific electrode	Threefold increase in trace fluoride recovery
1976	Guy, Taves, and Brey, in Filler, ed., *Biochemistry Involving Carbon-Fluorine Bonds* (1976):117-134.	Blood banks	Isolation of a PFAS from human blood, and ^{19}F-NMR	Tentative evidence for PFOA or similar compound(s) in blood
1977	Elliott, *J. Chromatogr. Sc.* 15 (10) (1977):475-477	Standards	*N*,*N*-dimethylformamide-dimethyl acetyl derivatization, GC	0.5 mg in 0.5 mL. No quantification
1978	Belisle and Hagen, *Anal. Biochem.* 87(2) (July 1978):545-555	Standards	Combustion, silane derivatization, GC	For PFAS. LOD: Less than 1 ppm, and as low as 0.010 ppm
1980	Belisle and Hagen, *Anal. Biochem.* 101(2) (1980):369-376	Plasma, urine, liver	Diazomethane derivatization, GC	For PFOA. LOD: 0.02 ppm in 10 ml sample; 0.015 ppm for plasma; 0.0015 ppm for urine; 0.06 ppm for liver tissue.
1981	Belisle, *Science* 212 (4502) (1981):1509-1510.	Blood of Chinese donors		For TOF. Blank of 0.002 ppm in a 10 ml serum sample
1981	Hagen, Belisle, Johnson, and Venkateswarlu, *Anal. Biochem.* 118 (1981):336-343.		Methylation, GC, with microwave plasma detector	For perfluorooctanate
1982	Venkateswarlu, *Anal. Chem.* 54(14) (1982):1132-1137; and Venkateswarlu, et al., *Anal. Chem.* 55(14) (1983):2232-2236.	Blood of 3M plant workers	Decomposition with sodium biphenyl, automated molecular absorption spectrometry	For TOF

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There was little further progress in techniques until the 1990s, when for analysis of PFAS this decade saw a tremendous leap forward with the application of high pressure liquid chromatography (HPLC) for separation, combined with tandem mass spectrometry (MS/MS) for detection.[64] Quantitative measurement of PFOA, POSF and other PFAS was achieved without the need for decomposition and derivatization. The hyphenation of HPLC with MS required a means for overcoming the large pressure difference between the HPLC apparatus and the high vacuum MS spectrometer. This involved the introduction of new devices, and ultimately electrospray ionization, the value of which was appreciated at 3M around 1990.[65] Though problems remained with selectivity and sensitivity the combined techniques provided evidence of widespread environmental exposure.[66] Specific PFAS compounds in small volumes of blood were identified in the early 1990s. Improvements were made in the accuracy of measurements. By 1997, the detection limit for PFOS was down to 50 ppb.

In 2009, when there was sufficient evidence of public health threats created by trace PFAS, the US Environmental Protection Agency (EPA) drew up a short term health advisory for exposure of 200 ng/L for POSF, and 400 ng/L for PFOA, and published its first validated method (537) for fourteen PFAS compounds in drinking water, with detection limits for POSF of 1.4 ppt, and for PFOA of 1.7 ppt.[67] Increasing knowledge of PFAS toxicity, increasingly stringent regulatory activities, and increasingly lowering thresholds of concern, especially in the United States, led to a change from C-8 PFAS to less toxic products based on C-6 and other compounds in reformulation of fluorinated surfactants. This in particular applied to the fluorinated surfactants used in aqueous film-forming foams AFFF that were found in groundwater near military bases and airports from the late 1990s.[68] Nevertheless, there were concerns

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[64] MacDonald, "Waters Corporation."

[65] Fenn, "Electrospray ionization."

[66] The literature on PFAS analysis since around 2000 is extensive. See for example Villagrasa, de Alda, and Barcelo, "Environmental analysis," and Yahnke and U. Berger, "Trace analysis." For concerns from within the scientific community see for example, Blum, et al., "The Madrid Statement."

[67] US EPA "Determination of selected perfluorinated."

[68] Moody and Field, "Perfluorinated surfactants," and, more recently, Dubocq, et al., "Characterization of the chemical contents."

that the new products were not without risks to the environment

All analytical methods introduced since the early 2000s are refinements of HPLC-MS/MS hyphenation. Inter-laboratory studies, new standards, and updated validated EPA methods evolved in attempts to tackle the environmental legacy of Forever Chemicals. By the second decade of the twenty first century individual contaminants present in trace amounts could be identified and quantified.[69] Further EPA promulgations and advisories led to a landmark ruling on 8 January 2024, aimed at preventing companies from starting or resuming the manufacture or processing of 329 PFAS "that have not been made or used for many years without a complete EPA review and risk determination."[70]

SUMMARY AND CONCLUSION

This account suggests itself as a useful example of the roles of error and failure in the development of scientific knowledge, and of puzzle solving providing a heuristic cue.

The main stimulus in the investigation of PFAS in human blood and biological materials arose from the publication of what appeared to be erroneous results arising from fluoride analysis by a diffusion technique.

The diffusion technique was developed around 1960 by Armstrong and Singer who were interested in measuring fluoride in biological materials. However, their published results were questioned by Taves, who believed that the fluoride content was far less. The interactions between Armstrong and Singer, on the one side, and Taves, on the other, took place in the columns of *Nature*. Armstrong and Singer resorted to ashing, which appeared to support their findings. Unlike most previous workers, however, they, wisely as it turned out, extended the time of combustion. They did not realise it at the time but they had brought about quantitative release of organic fluorine in biological material by its decomposition, that is, the conversion of organic fluorine into the ionic form, fluoride (F^-). They measured quantitatively the total fluoride. It was Taves who, through repeating the ashing method, in 1968 explained the apparent anomalous results when he established that two forms of fluorine, fixed (organic) and exchangeable (ionic), existed in blood, and could be clearly distinguished. The organic fluorine was calculated by subtracting fluoride, as analyzed quantitatively in the compound *without* ashing, from total fluoride. Taves considered that the source of the organic compound(s) he had isolated was a large molecule, with a high fluorine content, not unlike the industrial perfluorocarbon compounds. It was a promising explanation.

In 1975, Taves and his associate Guy amassed sufficient evidence, following chromatographic separation of a major fraction, to confirm that there were perfluorocarbon compounds in the blood of communities located beyond manufacturing sites. They decided tentatively on the basis of ^{19}F-NMR data supplied by NMR expert Brey that what they had isolated was a perfluoro acid, or a closely related compound.

Guy made contact with 3M requesting assistance in identification. This was not forthcoming. However, based on internal NMR analysis, 3M decided that the substance isolated by Taves and Guy was PFOS. This was a matter of considerable concern because 3M was the primary manufacturer of PFOS. It was this definitive evidence for the presence of PFAS compounds in human blood that led 3M to undertake intensive research into trace PFAS analysis by a number of techniques. These included conversion of perfluoroalkanoic acids into volatile derivatives that were suited to analysis by GC. This work benefited from earlier studies in organic fluorine analysis, and newly available instrumental techniques, in particular fluorine-specific electrodes, NMR, and GC detectors suited to trace analysis of halogens.

The novel applications of methods described here enabled analysis for trace organic fluorine in blood and water. Derivatization without decomposition was useful for PFOA, but not suited to PFOS. This was the situation until the 1990s, when quantitation of PFAS and of its individual components was achieved following hyphenation of HPLC with MS. It brought about a complete transformation in methods of analysis. During the first decade of the twenty first century HPLC-MS/MS, aided by successive improvements, would become the method of choice in rapid, trace PFAS analysis, including compound identification, particularly in water, which is a key concern today. In the United States and parts of Europe the pervasiveness of PFAS contamination has increasingly attracted public attention, and action, but, it seems, not to the same levels elsewhere. However, testing and research into methods for the removal of these persistent organic pollutants from water and waste is an ongoing international effort.

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[69] See for example, on particle-induced gamma-ray emission (PIGE), Ritter, et al., "PIGE as a screening tool."

[70] EPA press office, "Biden-Harris administration." For the situation in Europe, see Brunn, et al., Ref. 1.

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Research Article

Synthesis, Structural Characterization, and Biological Evaluation of (*E*)-*N*-(4-Bromobenzylidene)-3-Methoxybenzohydrazide Monohydrate

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Abstract. Synthesis and structural elucidation of a new type of hydrazone Schiff base *(E)-N'*-(4-Bromobenzylidene)-3-Methoxybenzohydrazide Monohydrate, and its structure were characterized by FT-IR, ^{1}H, ^{13}C NMR and mass spectroscopic analysis. The single crystals of (4-BRMBH) were grown from the DMSO solvent, orthorhombic system with $P2_12_12_1$ space group through single-crystal X-ray diffraction analysis. DFT calculations were performed to understand the electronic properties including frontier molecular orbitals (FMO), molecular electrostatic potentials, and global chemical reactivity descriptors. Intermolecular interactions in the crystal structures were obtained using the Hirshfeld surface analysis. The majority contribution to the Hirshfeld surface is H···H (39.5%) contacts. The molecular docking study were carried out by *in silico* method to analyse their anti-tuberculosis aspect against InhA, the enoyl acyl carrier protein reductase from *Mycobacterium tuberculosis.* Finally, chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties were determined.

Keywords: hybrid crystals, π···π interactions, molecular docking, Hirshfeld surface, ADMET.

INTRODUCTION

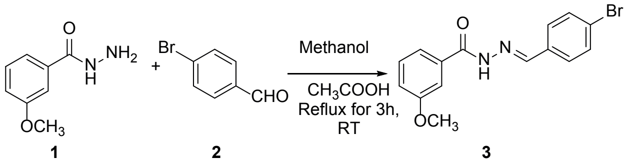
The compounds having azomethine functional group –C=N– are recognized as Schiff bases [1]. Schiff bases are a class of mixes that can be effortlessly set up from the buildup of essential amines or amino alcohols with carbonyl mixes [2,3]. The presence of various substituents on both the amine and carbonyl-containing moieties could change their underlying and electronic properties of the compound. A little change in either moiety may affect in a sizeable modification of their structural and functional behavior [1,4]. Such properties have energized researchers of various fields, for example, precious stone specialists, material researchers, organic chemists, and so forth to center their considerations on Schiff bases [5–17]. The Schiff base hydrazone core has additionally pulled in much consideration in the fields of drug and restorative science [18, 19] due to hydrazide subsidiary was recently announced as a powerful and specific inhibitor for antibacterial-antifungal [20], calming [21], antimalarial [22], *Entamoebahistolyica* [23], against tuberculosis exercises [24]. For every one of these reasons underlying conduct of the Schiff bases has been accounted.

In the present study, we report the synthesis of compound $C_{15}H_{15}BrN_2O_3$ derived from benzohydrazide *via* Schiff base route, bromophenyl ring attached to benzo hydrazidee complex has effective inhibitory activity against various antibacterial activities. Benzohydrazide heterocycles are very good bio isosteres of esters and aldehydes, which has a pharmacological activity by hydrogen-bonding interactions with receptors. In view with the above importance of compound, we have done the structural confirmation by single crystal X-ray crystallography. Since, X-ray diffraction has become indispensable tool in crystal chemistry as it helps in solving the molecular structure, magnitudes and directional characteristics. In view of these, in the present work the XRD analysis of title compound is reported to understand its molecular interactions, conformation and packing modes along with studying configuration. Single crystal studies for the synthesized compound and the results are depicted here. The compounds were characterized by IR, ^{1}H, ^{13}C and mass spectroscopy. DFT studies have been employed to explain the electronic properties of molecules as a dipolarophile. We report the spectral, structural and biological properties of the compounds. Molecular docking and the Hirshfeld surface analysis with d_{norm} and 2D fingerprint plots were performed and their results are discussed.

2. RESULTS AND DISCUSSION

2.1. Spectral data

The IR spectrum of the compound is showed that the IR (KBr, cm^{-1}): (C=O amide, 1652), (NH, 3206), (CH aliphatic, 2837–3079), (C=N, 1580), (C–H aromatic, 3079). The ^{1}H and ^{13}C NMR spectra are the amide proton signal at 11.8 ppm, CH=N– signal at 8.4 ppm singlet (azomethine proton), the proton couplings between 7.81 and 7.16 ppm indicate the presence of aromatic protons in ^{1}H NMR spectrum. The OCH_3 proton was indicated by a singlet at 3.84 ppm. In ^{13}C NMR spectrum is carbonyl (NH–C=O) signal was observed at 163 ppm, aromatic and CH=N– signals at 120–150 ppm, methoxy carbon signal at 55.8 ppm. The crystal structure supports the mass spectral data as well as the m/z = 333.10 [M$^+$].



Scheme 1. General produce of (E)-N¢-(4-bromobenzylidene)-3-methoxybenzohydrazide.

2.2. Single crystal XRD

The crystals of single crystal X-ray diffraction analysis revealed that the title compoundwas crystallized in the Orthorhombic crystal system, with $P2_12_12_1$ space group. The unit cell parameters for the compound are a = 4.7974(3) Å, b = 12.5672(9) Å, c = 25.3675(16) Å, b = 90.77° and Z = 4, 1529.40(17) Å^3, and the symmetry code of the molecule in the crystal unit is (i) x–1/2, –y+1/2; (ii) x+1/2, –y+1/2, z–1/2; (iii) x+1, y, z–1; (iv) x–1, y, z+1. The bond parameter such as bond length (Å), bond angle (°), dihedral angle (°) and hydrogen interactions are shown in Tables 2, 3 and 4 were measured. In this water also involved in the hydrogen bonding interaction, but it does not change symmetry, there was observed a negligible influence due to the water present. The structure parameters were calculated and compared with X-ray diffraction bond parameters, for example, the carbonyl (C=O) bond length was observed as about 1.229 Å, were as the calculated value was about 1.228 Å. Similarly, the observed C=N (1.262 Å), C–N (1.337 Å), C–O (1.375 Å), and C–C in ring (1.44–1.35 Å) bond lengths are matches well with the computed parameters. The hydrogen bonding (HB) interactions have been observed like D–H, H···A, D···A and D–H···A among the closest molecule, the donor nitrogen makes the intermolecular hydrogen bonding with the closest neighboring oxygen (O3) atom in the hydroxybenzylidene, its D···A hydrogen bonding distance is about 0.85 Å, similarly O(3)–H(3B)···O(1)#1, O(3)–H(3A)···O(1)#2 (Table 4) shows the intermolecular hydrogen bonding value 0.84 and 0.83.

The determined structure was optimized by density functional theory (DFT) calculation (Fig. 1). The ORTEP diagram of 4-BRMBH with displacement ellipsoids drawn at 50% probability level is shown in Fig. 2. The

Table 1. Crystal data and structure refinement for 4-BRMBH crystal.

Identification code	4-BRMBH
Empirical formula	$C_{15}H_{15}BrN_2O_3$
Formula weight	351.20
Temperature (K)	296(2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	*a* = 4.7974(3) Å a = 90° *b* = 12.5672(9) Å b = 90° *c* = 25.3675(16) Å g = 90°
Volume (Å^3)	1529.40(17)
Z	4
Density (calculated) (g cm^{-3})	1.525
Absorption coefficient (mm^{-1})	2.699
F(000)	712
Crystal size (mm^3)	0.150 ´ 0.100 ´ 0.100
q Range for data collection (°)	2.281 to 25.019
Index ranges	–4 £*h* £5, –14 £*k* £14, –30 £*l* £29
Reflections collected	19553
Independent reflections	2690 [R(int) = 0.0505]
Completeness to q =25.019°	99.7%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7451 and 0.5892
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2690/4/201
Goodness-of-fit on F^2	1.006
Final *R* indices [*I*> 2s(*I*)]	R_1 = 0.0403, wR_2 = 0.0895
R indices (all data)	R_1 = 0.0822, wR_2 = 0.1070
Absolute structure parameter	0.004(7)
Extinction coefficient	*n*/*a*
Largest diff. peak and hole (e Å^{-3})	0.520 and –0.587
CCDC	1839157

details of the crystal data and structure refinement are given in Table 1. The title compound exists in the amido form with a C8–O1 bond length of 1.228(7) Å. The molecule has an E conformation with respect to the azomethine bond, which is confirmed by the torsion angle C4–C7–N1 of 179.1(6)°. The two aromatic rings (C1–C6 and C9–C13), are almost planar hydrazone moiety. There is an intramolecular O–HN, O–H, C–H hydrogen bonding present in the molecule as N2–H(2A)–O3, O3–H(3A)–O1,O3–H(3B)–O1, C7–H7–O3. In this compound both intermolecular and intramolecular hydrogen bonding were occurs shown in Fig. 3a.

This compound is an example of a system where a single atom acts both as donor and acceptor. There are also C–HO (water) contacts present enclosing ring motifs (Fig. 3b). Finally, sheets are formed lying parallel. There are weak-interactions within the sheets involving the bromine-bearing aromatic ring of the molecule. A supramolecular network is built in the lattice by means of intermolecular N–H···O and two O···H–O interactions together with non-classical C–H···O interactions involving the lattice water molecule stacking the molecules along the b-axis direction shown in Fig. 3c.

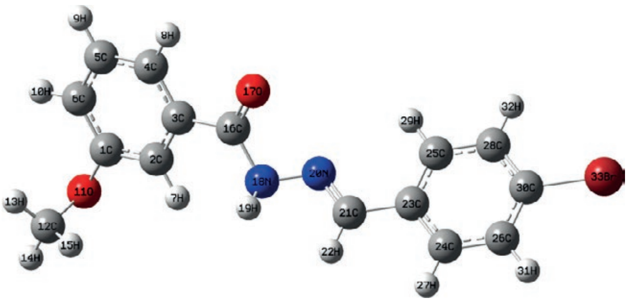


Figure 1. Optimized molecular structure of 4-BRMBH crystal.

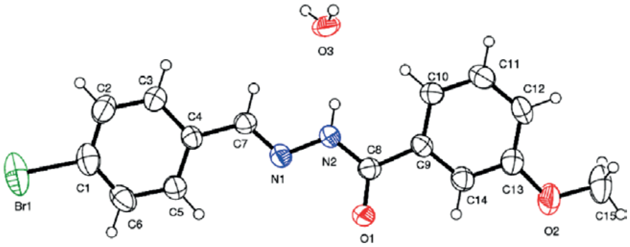


Figure 2. ORTEP of 4-BRMBH crystal.

The resulted bond lengths and bond angles are in good agreement with the standard values, and the list of all the bond lengths, bond angles and torsional angles are presented in Tables. 2 and 3. Both intermolecular and intramolecular hydrogen bonding details for compound 4-BRMBH listed in Table 4.

2.3. Hirshfeld surface analysis

Three-dimensional (3D) molecular Hirshfeld surfaces and the two-dimensional (2D) fingerprint plots represent a new way of visualizing and analyzing intermolecular interactions in molecular crystals. The molecular Hirshfeld surface [33] of a crystal is created by dividing space in the crystal into regions where the electron distribution of sum of atoms for the molecule dominates the corresponding sum over the crystal. Hirshfeld surfaces and their related fingerprint plots are generated using the program Crystal Explorer 3.0 [34]. The crystallographic information file (cif) is given as input to the Crystal Explorer program. The Hirshfeld surface

Table 2. Bond lengths (Å) and bond angles (°) for 4-BRMBH crystal.

Bond lengths (Å)					
C(1)–C(6)	1.354(10)	C(7)–N(1)	1.262(7)	C(12)–H(12)	0.9300
C(1)–C(2)	1.371(10)	C(7)–H(7)	0.9300	C(13)–C(14)	1.374(9)
C(1)–Br(1)	1.898(7)	C(8)–O(1)	1.228(7)	C(13)–O(2)	1.375(8)
C(2)–C(3)	1.363(9)	C(8)–N(2)	1.334(8)	C(14)–H(14)	0.9300
C(2)–H(2)	0.9300	C(8)–C(9)	1.494(8)	C(15)–O(2)	1.398(9)
C(3)–C(4)	1.384(8)	C(9)–C(14)	1.378(8)	C(15)–H(15A)	0.9600
C(3)–H(3)	0.9300	C(9)–C(10)	1.380(8)	C(15)–H(15B)	0.9600
C(4)–C(5)	1.378(8)	C(10)–C(11)	1.373(10)	C(15)–H(15C)	0.9600
C(4)–C(7)	1.448(8)	C(10)–H(10)	0.9300	N(1)–N(2)	1.379(7)
C(5)–C(6)	1.387(9)	C(11)–C(12)	1.365(10)	N(2)–H(2A)	0.85(3)
C(5)–H(5)	0.9300	C(11)–H(11)	0.9300	O(3)–H(3A)	0.83(2)
C(6)–H(6)	0.9300	C(12)–C(13)	1.370(9)	O(3)–H(3B)	0.84(2)

Bond angles (°)					
C(6)–C(1)–C(2)	121.4(6)	N(1)–C(7)–C(4)	122.5(6)	C(12)–C(13)–C(14)	119.8(6)
C(6)–C(1)–Br(1)	120.0(6)	N(1)–C(7)–H(7)	118.7	C(12)–C(13)–O(2)	124.7(6)
C(2)–C(1)–Br(1)	118.6(6)	C(4)–C(7)–H(7)	118.7	C(14)–C(13)–O(2)	115.5(6)
C(3)–C(2)–C(1)	118.3(7)	O(1)–C(8)–N(2)	122.1(6)	C(13)–C(14)–C(9)	121.2(6)
C(3)–C(2)–H(2)	120.8	O(1)–C(8)–C(9)	120.9(6)	C(13)–C(14)–H(14)	119.4
C(1)–C(2)–H(2)	120.8	N(2)–C(8)–C(9)	117.1(5)	C(9)–C(14)–H(14)	119.4
C(2)–C(3)–C(4)	122.2(6)	C(14)–C(9)–C(10)	118.7(6)	O(2)–C(15)–H(15A)	109.5
C(2)–C(3)–H(3)	118.9	C(14)–C(9)–C(8)	116.7(5)	O(2)–C(15)–H(15B)	109.5
C(4)–C(3)–H(3)	118.9	C(10)–C(9)–C(8)	124.6(6)	H(15A)–C(15)–H(15B)	109.5
C(5)–C(4)–C(3)	118.1(6)	C(11)–C(10)–C(9)	119.4(6)	O(2)–C(15)–H(15C)	109.5
C(5)–C(4)–C(7)	123.2(6)	C(11)–C(10)–H(10)	120.3	H(15A)–C(15)–H(15C)	109.5
C(3)–C(4)–C(7)	118.6(6)	C(9)–C(10)–H(10)	120.3	H(15B)–C(15)–H(15C)	109.5
C(4)–C(5)–C(6)	119.9(6)	C(12)–C(11)–C(10)	121.7(7)	C(7)–N(1)–N(2)	116.0(5)
C(4)–C(5)–H(5)	120.0	C(12)–C(11)–H(11)	119.2	C(8)–N(2)–N(1)	119.3(5)
C(6)–C(5)–H(5)	120.0	C(10)–C(11)–H(11)	119.2	C(8)–N(2)–H(2A)	120(5)
C(1)–C(6)–C(5)	120.0(6)	C(11)–C(12)–C(13)	119.1(6)	N(1)–N(2)–H(2A)	120(5)
C(1)–C(6)–H(6)	120.0	C(11)–C(12)–H(12)	120.4	C(13)–O(2)–C(15)	119.2(6)
C(5)–C(6)–H(6)	120.0	C(13)–C(12)–H(12)	120.4	H(3A)–O(3)–H(3B)	113(4)

was obtained using the CIF file data from single crystal XRD analysis. The contact distances d_{norm} is based on d_e express the distances of the nearest nucleus external and d_i is the internal to the surface respectively. The shape index in the molecule structure indicates the shape of the electron density, surface around the molecular interactions. In Fig. 3 (a–d), the deep in red circular indicates hydrogen bonding contacts, whereas the bright red areas in the surface plot indicate H···O and O···H dominant interactions. The light color range area represents longer and weaker contacts [35].

The intercontact in the crystal packing of the title compound 4-BRMBH are quantized using Hirshfeld surface computational analyses. The red-colored spots over the Hirshfeld surface indicate the intercontacts involved in the intermolecular interactions [33,34]

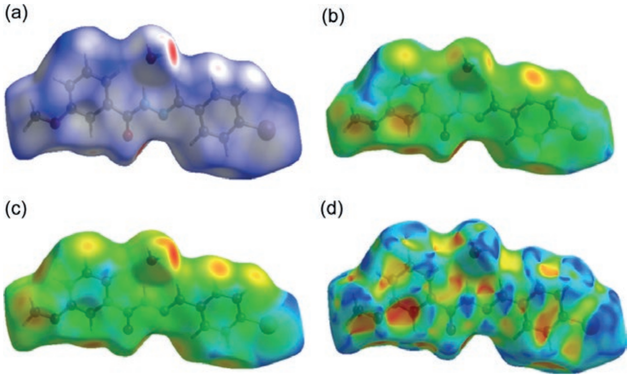


Figure 3. Hirshfeld surfaces of 4-BRMBH crystal: a) d_{norm}, b) d_e, c) d_i and d) shape index.

Table 3. Torsional angles (°) for 4-BRMBH crystal.

C(6)–C(1)–C(2)–C(3)	–1.4(11)	C(14)–C(9)–C(10)–C(11)	0.1(10)
Br(1)–C(1)–C(2)–C(3)	177.6(5)	C(8)–C(9)–C(10)–C(11)	179.2(6)
C(1)–C(2)–C(3)–C(4)	0.2(10)	C(9)–C(10)–C(11)–C(12)	2.0(11)
C(2)–C(3)–C(4)–C(5)	0.8(10)	C(10)–C(11)–C(12)–C(13)	–2.5(12)
C(2)–C(3)–C(4)–C(7)	–178.6(6)	C(11)–C(12)–C(13)–C(14)	0.9(11)
C(3)–C(4)–C(5)–C(6)	–0.6(10)	C(11)–C(12)–C(13)–O(2)	–179.2(7)
C(7)–C(4)–C(5)–C(6)	178.7(6)	C(12)–C(13)–C(14)–C(9)	1.2(10)
C(2)–C(1)–C(6)–C(5)	1.6(11)	O(2)–C(13)–C(14)–C(9)	–178.7(6)
Br(1)–C(1)–C(6)–C(5)	–177.5(5)	C(10)–C(9)–C(14)–C(13)	–1.7(10)
C(4)–C(5)–C(6)–C(1)	–0.5(11)	C(8)–C(9)–C(14)–C(13)	179.1(6)
C(5)–C(4)–C(7)–N(1)	–0.2(9)	C(4)–C(7)–N(1)–N(2)	–179.6(5)
C(3)–C(4)–C(7)–N(1)	179.1(6)	O(1)–C(8)–N(2)–N(1)	0.1(9)
O(1)–C(8)–C(9)–C(14)	7.3(8)	C(9)–C(8)–N(2)–N(1)	–178.8(5)
N(2)–C(8)–C(9)–C(14)	–173.8(5)	C(7)–N(1)–N(2)–C(8)	176.4(5)
O(1)–C(8)–C(9)–C(10)	–171.8(6)	C(12)–C(13)–O(2)–C(15)	–1.5(11)
N(2)–C(8)–C(9)–C(10)	7.1(9)	C(14)–C(13)–O(2)–C(15)	178.3(6)

Table 4. Hydrogen bonds (Å and °) for 4-BRMBH crystal.

D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
C(7)–H(7)···O(3)	0.93	2.50	3.304(8)	144.6
O(3)–H(3B)···O(1)$^{\#1}$	0.84(2)	1.99(3)	2.812(7)	169(8)
O(3)–H(3A)···O(1)$^{\#2}$	0.83(2)	2.08(4)	2.884(7)	161(8)
N(2)–H(2A)···O(3)	0.85(3)	2.06(3)	2.885(7)	163(7)

Symmetry transformations used to generate equivalent atoms:
$^{\#1}$ –x+1, y–1/2, –z+1/2; $^{\#2}$ –x,y–1/2, –z+1/2.

[36–39]. The dark-red spots on the d_{norm} surface arise as a result of the short interatomic contacts, *i.e.,* strong hydrogen bonds, while the other intermolecular interactions appear as light-red spots. The 2D-fingerprint plots are used to plot intercontacts with respect to d_i and d_e (Fig. 4b).

The intercontacts (quantification) were done using visualization of the Hirshfeld surfaces and 2D fingerprint plots in Fig. 4. The strong interactions in crystal intercontacts were found to be H···O (15.3%), H···H (39.5%), C···H (12.5%) and weak interactions N···H (1.9%), C···C (5.7%), N···C (5.5%), O···C (0.8%) are present. The 2D fingerprint plots of these intercontacts are shown in Fig. 5b. The major contributions are from H···H, C···H, and O···H when compared to other intercontacts. The C···C and C···H intercontacts are involved in C–H···O, N–H···O and C–O···p interactions. The dominant interactions particularly H···O, O···H are mainly responsible for maintaining charge transfer leading to nonlinearity at the micro level.

2.4. Optimization of (E)-N-(4-bromobenzylidene)-3-methoxybenzohydrazide 3

Molecular geometry, optimization of compound 4-BRMBH 3 structures, and numbering of atoms molecules are shown graphically in Fig. 1 obtained at B3LYP/6-31G* method. Table 5 shows their geometrical characteristics, including computed total energies, moments of dipoles, RMS, and maximum Cartesian force. The global minimum energies are found to be 1326.0352 a.u (36083 eV) respectively. The RMS Cartesian force value is 0.01578. It is discovered that their maximal Cartesian forces are 0.05705. A molecule's dipole moment, which represents the molecular charge distribution, is expressed as a three-dimensional vector. As a result, it may be used as a descriptor to clarify the movement of charges inside molecules. As a result of DFT/B3LYP/6-31G* calculations, the smallest dipole moment was observed for compound 3 (3.315386 Debye) Of course, the addition of other atoms has an influence on their stability. Moreover, it promotes the formation of hydrogen bonds.

2.5. Frontier orbitals and quantum chemical calculations (FMO)

In molecular systems, frontier molecular orbitals (FMOs) frequently take the lead in molecular systems. The HOMO and LUMO are employed in the chemical stability of the molecule. Electronic transitions and their energies difference Eg energy gap and chemical reactivity descriptors are given in (Table 5). The HOMO, LUMO

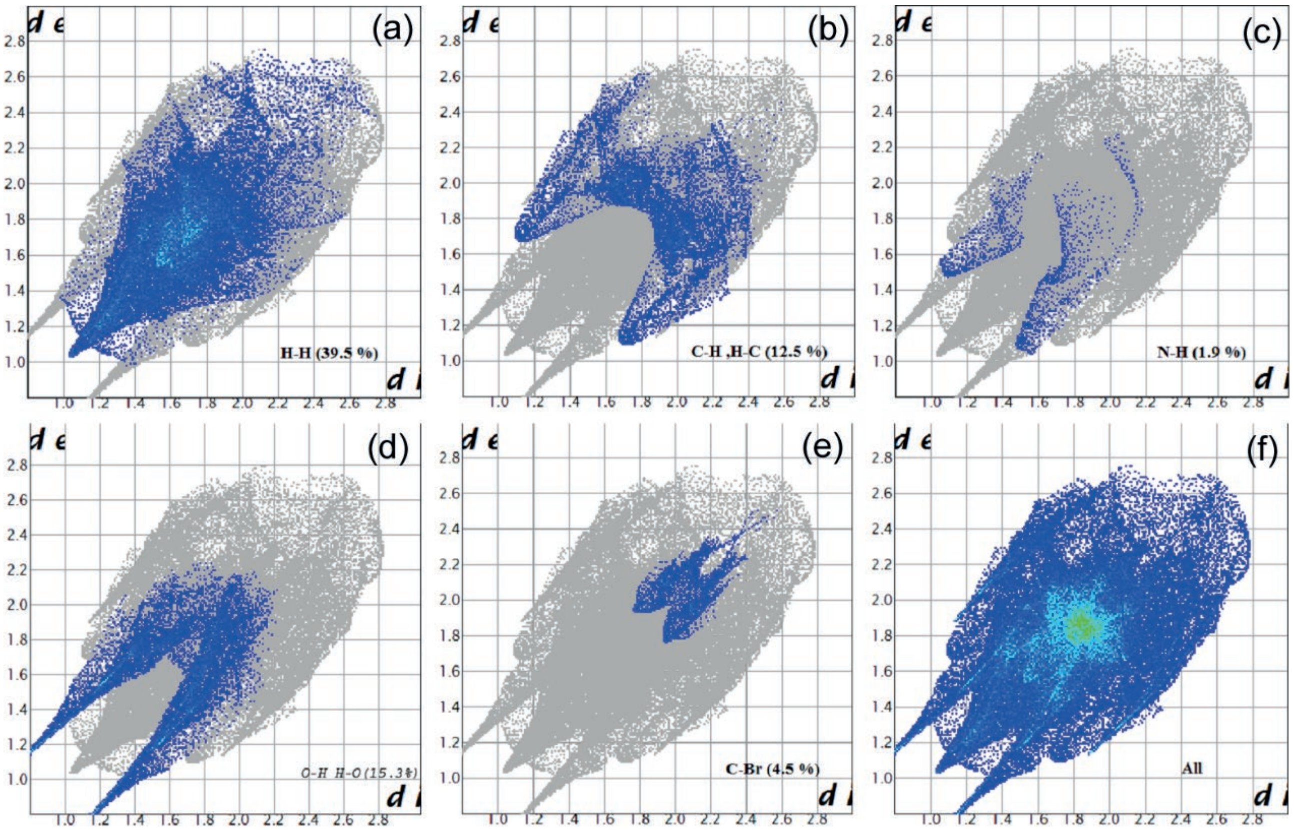


Figure 4. Fingerprint plots of 4-BRMBH crystal. All; showing reciprocal contacts and resolved into **(i)** H...H, (ii) C...H, (iii) N...H, (iv) O...H, (v) C…Br, showing the percentage contact contributing to the total Hirshfeld surface of the molecule. Black arrows are show spikes for different interactions.

energies, and band gap of present compounds are depicted in (Fig. 5).

In the present investigations, the energy gap of compound 4-BRMBH is - 4.28 eV. A small energy gap of HOMO-LUMO means more chemical activity. this decrease in gap low shows that the compound can easily flow electrons, favoring the biological activity of the compound. EHOMO illustrates the capacity for electron donation, while ELUMO illustrates the capacity for accepting electrons. The resulting tittle compound global reactivity indexes are calculated and summarized in Table 6. The electronic chemical potential of 6.12 eV. The analysis of the global electrophilicity and nucleophilicity indexes helps in describing the biological activity of the molecule, shows that compound 3 acts as a strong electrophile (ω = 1.86 eV) and a strong nucleophile (N = 3.65 eV). Analysis of the global CDFT indices confirms that 3 has a higher electrophilic and nucleophilic character which does allow it participation in polar processes. Their 3D plots are illustrated in Fig. 5. It is clear from the figure of the acridine molecule that the HOMO and LUMO orbitals are localized essentially on the acridine and substituted systems. The density of states makes it clear that the green colour denotes the negative phase and the red colour, which corresponds to the positive phase.

Using the energies of FMOs, we calculated the reactivity descriptors of (*E*)-*N*¢-(4-bromobenzylidene)-3-methoxybenzohydrazide monohydrate molecules. A = - E_{LUMO}: represent the electron affinity; I = - E_{HOMO} represent the ionization potential and l = ½ (I + A) is the electronic chemical potential. The chemical hardness (η) is found to be 2.170 eV for compound 3, respectively. Based on the value found of the electrophilicity index, we can conclude that the (*E*)-*N*¢-(4-bromobenzylidene)-3-methoxybenzohydrazide monohydrate is a good electrophile. Therefore, it is able to accept an electron doublet in order to form bonds with another reagent which is necessarily a nucleophile. Electronegativity is also determined (χ = (I + A)/2) and it is found to be χ) = 3.980 eV.

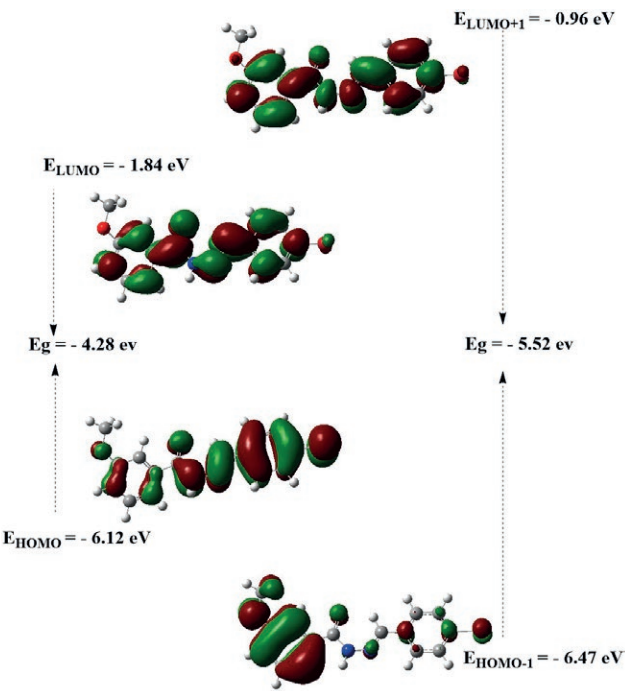


Figure 5. Energy level of EHOMO, ELUMO and Egap for the synthesized compounds **3** computed by B3LYP/6-31 G (d,p) method.

Table 6. Global Electronic Proprieties and Reactivity Indexes at 4 Compounds (in eV).

E LUMO	= - 1.84
E HOMO	= - 6.12
E HOMO -E LUMO (Eg)	= - 4.28
E LUMO +1	= - 0.96
E HOMO-1	= - 6.47
E HOMO-1 - E LUMO +1	= - 5.52
Reactivity descriptors	
Ionization potential (I)	= 6.12
Electron affinity (A)	= 1.84
Chemical hardness (η)	= 2.170
Chemical softness (x) = 1.070	
electronic chemical potential (μ)	= - 3.980
Electronegativity (χ)	= 3.980
global electrophilicity (ω)	= 3.650
Maximum charge transfer index D N Max = 1.86	

2.6. Molecular electrostatic potential surface

The molecular electrostatic potential (MEP) is an elucidation tool the complete information of molecular properties and intermolecular interactions, it allows us to electrophilic and nucleophilic sites in the molecular system reactive biological activities, these sites provide electrophilic site indicates a strong attraction, while the nucleophilic site indicates a strong repulsion and polar and nonpolar sites of the molecule in color variations as shown in a pictorial form (Fig. 6). The regions of the molecule with positive values of the electrostatic potential are indicated by blue color, the red color characterizes electrophilic reactivity (most negative). The green and gray colors correspond to an intermediate potential situated between the two extremes (red and dark blue). The yellow and light blue colors split the difference between the medium color (green) and the extremes (red/dark blue). As a result, MEP surfaces area between -7.623e-2 a.u (deepest red) to 7.623e-2 a.u (deepest blue) molecule (Fig. 5), a maximum positive region is localized on the nitrogen N and hydrogen H atoms indicating a possible site for positive potential (blue and light blue) sites are found in the benzene and pyridine rings (electrophilic reactivity). From the MEP plots, it was concluded that the oxygen of hydroxy possessed high electropositive potential (red) and the activated possessed slightly low electropositive region (blue).

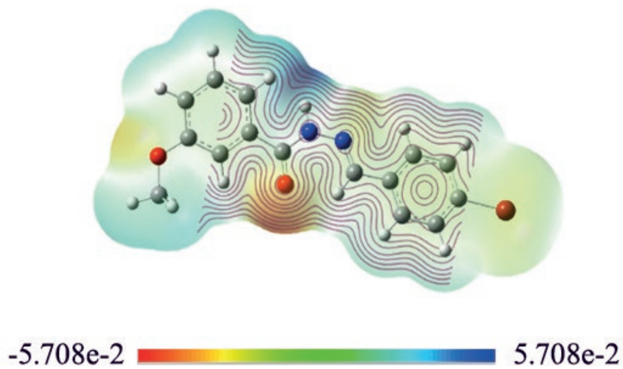


Figure 6. MEP formed by mapping of total density over electrostatic potential in gas phase for the synthesized compounds **3**

(DOS) spectrum (Fig. 7) characterizes the energy levels per unit energy increment and its composition in energy. The green and red lines in these graphs, corresponding to the displaying study per orbital, describe the HOMO and LUMO energy levels, respectively. As a result, the energy level of the HOMO orbital is about - 6.162eV, and the energy level of the LUMO orbital is about -1.84 eV. The HOMO-LUMO gap energy (Eg) of compound 3 is equal to 4.28 eV. This low energy value promotes the transfer of electrons in the acridine molecule. These values are compatible with those obtained by the DOS spectrum. The state HOMO-1 form another set of degenerate orbitals - 6.47 eV and +LUMO orbital lying at -0.96 eV, located on all the atoms of the rings. Eg close to - 5.52 eV in solution involves an expected high reactivity for compound 4-BRMBH.

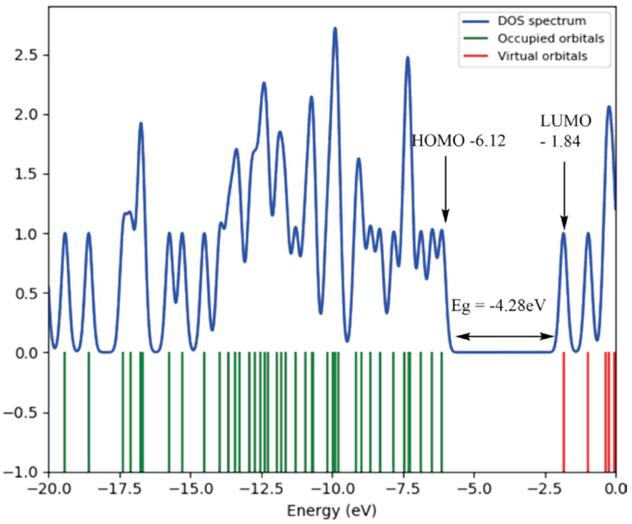


Figure 7. DOS spectrum of (E)-N¢-(4-bromobenzylidene)-3-methoxybenzohydrazide 3.

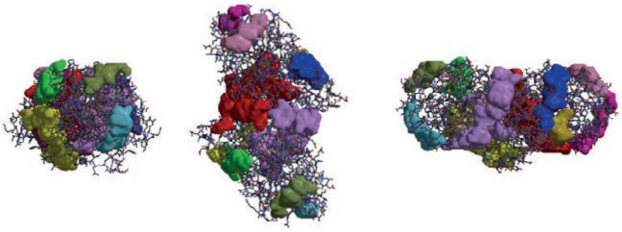


Figure 8. The docked ligand compound **3** at the same catalytic site receptor.

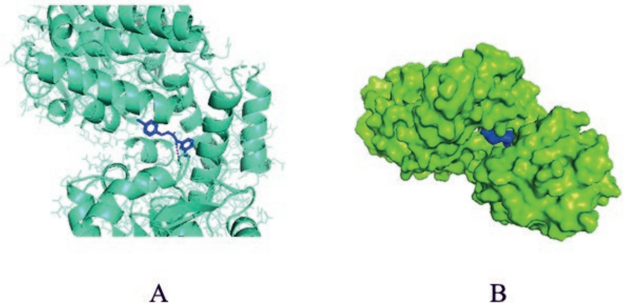


Figure 9. A) Orientation of compound 4-BRMBH in the active sites of tuberculosis proteins PDB ID: 7vjt B) The docking poses of 3 in the binding site with Surface area.

Computational results related to ^{1}H NMR spectrum of H atom camB3LYP/6-311+g(d) (ppm) Experimental (ppm) Calculated and experimental FT-IR spectra. In this work, the B3LYP/6- 311 G (d,p) theoretical model was used to obtain the ground state geometries of selected compound 3 in vacuo. Frequency calculations showed that there were no imaginary frequencies, which indicates that the stationary points correspond to the equilibrium geometries. The calculated molecular geometry was used as an input structure for further calculations IR for better understanding of electronic properties, the theoretical spectra have been calculated by TDDFT/B3LYP method.

2.7. Molecular docking

Docking studies were carried out to find the potential binding affinity and the interaction between the compounds for receptor protein as shown in Figs. 8-10. Compound 4-BRMBH has van der Waals interactions with surrounding hydrophobic residues Try1637, Phe1670, Met1669, Asp1666, Thr1589, Lys1588, Ser1636 and Phe1585. In compound Asn1640 is bridged through H_2O forming hydrogen bonds through hydrazide group. The study also revealed that the benzohydrazide scaffolds are the key residues at the active site of prostate cancer, anti-tuberculosis etc. Moreover, compounds have minimum binding energy, which could be considered as a good inhibitor. The synthesized compounds were found to display good binding affinity to the receptor with minimum binding energy equal to −9.70 kcal/mol. From docking studies, we found that the compound showed highest glide score −9.27 kcal/mol and glide energy of −42.126 kcal/mol respective and their docking scores are shown in Table 7. These *in silico* results

Table 7. Molecular docking results showing CDock score and types of interactions.

Compound id	CDocker Energy	Type and number of interactions	Residues involved
4-BRMBH	−27.28	van der Waals interaction-1	Between $-OCH_3$ of methoxy benzo hydrazide and of amino acid residue: LYS: 165
		van der Waals interaction-1	Between −C=O of methoxy benzo hydrazide and of amino acid residue: ILE: 194
Iisoniazid (Standard)	−22.1896	Electrostatic interaction-2	Between −C=O of benzo hydrazide and of amino acid residue LYS A: 165
		van der Waals interaction-1	Between hydrogen of benzohdrazide and LYS A: 165 of amino acid residue. Between hydrogen of benzohydrazide and of amino acid residue ASP: 148

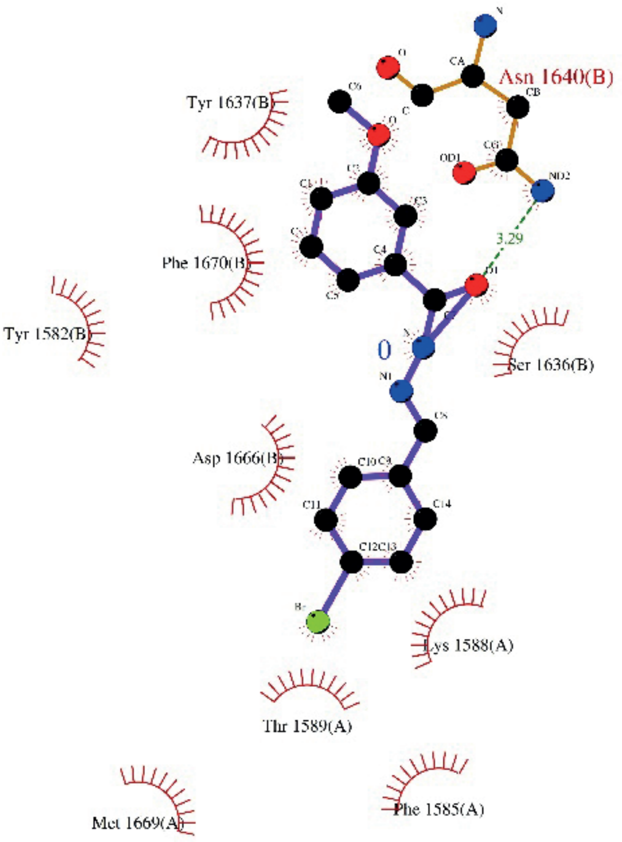


Figure 10. LigPlot+ Interaction of compound 4-BRMBH with 7vjt.

revealed that the synthesized benzohydrazide compounds may be an effective drug candidate for antituberculosis.

The 3D crystal structure of the enzyme reported in this work was downloaded from the Protein Data Bank (PDB id: 7vjt) and was processed by the addition of hydrogen, assigning the bond order, identifying overlaps, creating zero order bonds to metals and creating disulfide bonds. The 2D structures of the synthesized ligands were drawn from Chem Draw and saved as mol format and was examined so as to generate the best pose by analyzing the binding interactions. After the generation of the grid, the ligands synthesized were docked to identify the interaction with the active site of the protein. The scoring functions and hydrogen bonds formed with the surrounding amino acids were used to predict their binding modes, their binding affinities and orientation of these compounds at the active site of *Mycobacterium tuberculosis* InhA protein.

In order to find suitable inhibitor for *M. tuberculosis* docking studies was carried out for InhA protein. The enoyl-ACP reductase from *M. tuberculosis*, known as InhA, was a member of an unusual FAS-II system that prefers longer chain fatty acyl substrates for the purpose of synthesizing mycolic acids, a major component of mycobacterial cell walls. Mycolic acids, which were essential building blocks of the waxy cell wall of mycobacteria. Inhibition of InhA blocks mycolic acid biosynthesis, thereby impairing the integrity of the cell wall and eventually leading to cell death [40 - 42]. New compounds that directly target InhA and dodge the activation step are promising candidates for combating multidrug-resistant strains of *M. tuberculosis*. There was a structural similarity between the synthesized compound and isoniazid, one of the standard antimycobacterial references. Therefore, the docking results of 4-BRMBH were compared with that of isoniazid and were tabulated in Table 7. It was observed that the CDocker score of 4-BRMBH was comparable with that of standard isoniazid. Therefore compound 4-BRMBH may be suitable to overcome the drug resistance of *M. tuberculosis*. The protein–ligand interaction study was accomplished using LigPlot. the identification of such residues leads to support the observed activity *M. tuberculosis* exhibited by the studied compounds.

2.8. ADMET analysis

In-silico prediction of pharmacokinetics and drug-likeness pro*f*iles. *Clinical trials of* newly investigated drugs are known to be read are the absorption, distribution, metabolism, excretion, and toxicity (ADMET) belongings of the compound (Table 8). The drug-likeness of the compound is accessed based on the Lipinski's rule of five (RO5) and the result shows no violation of the rule. Many parameters are studied using virtual screening methods, such as human intestinal absorption HIA, partition coefficient (log p), drug solubility (S), topological polar surface area (TPSA), cell permeability, and drug-likeness score. An available oral drug is chosen in accordance with Lipinski's rule of + ve if the molecular weight < 500, the number of hydrogen bond donors < 5, the number of hydrogen bond acceptors < 10, and Log P is <5.41 The number of rotatable bonds is used to reflect molecular flexibility, which is important for oral bioavailability. Lipinski's rule RO5 of result 0 violation showed that compound 4, possess good molecular weight (g/mol), two Hydrogen Bond Accepted and Hydrogen Bond Donor values two log P 2.45 which are significantly justified if their drug-likeness behavior were justifiable with the standard values. The RO5 deviation (Mol. Wt≥500 g/mol; HBD≥ 5; HBA > 10; and logP≥ 5). drug-likeness score is an amalgam of complex balance of several molecular properties and structure features that

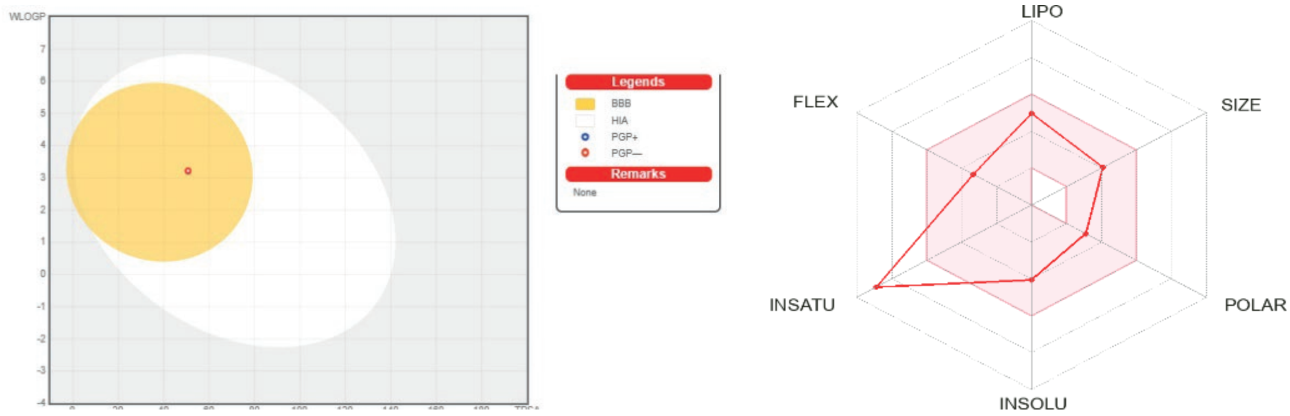


Figure 11. BOILED-Egg models and Swiss ADME bioavailability radar reports of 4-BRMBH.

determine the behaviour of molecules drug. 0.55 good drug score values, which depicted their wonderful drug-like behaviour to be suitable drug candidates against cancer protein. The results got from the Swiss ADME and Molinspiration search engine are listed in Table 8.

The same observed in the BOILED-egg diagram (Fig. 11) analysis shows that the compound is strong within the permissible range of standard drugs, where the dot in the yellow zone demonstrates blue dot indicates cannot be affected by the P-glycoprotein of the CNS system by P-glycoprotein, point locate in Boiled Eggs yolk is a molecule passively permeate through the blood–brain barrier (BBB) the red color region demonstrates the ability to stay in the brain. In the current study, the synthesized ligand and its complexes were initiated to be in a good pact with the criteria and can be said to possess good bioavailability the result proves that the compound is safe and unable to cause allergies on the skin. The drug scores of compounds, are remark clever and could be mentioned as moderate drug scores [43].

2.9. Target prediction

Nowadays, the probable targets of small molecules can be provided by established bio-/chemo-informatics approaches. Ligand-based target prediction has shown high-quality performance and the ability to quickly predict correct protein targets of compounds in drug discovery context. Predictions made using the Swiss Target web tool aim to predict the most probable protein targets of small molecules. The current analysis was restricted to the top 15 Homo sapiens targets. Molecule 3 was estimated to have a 27.7 % probability of binding enzyme receptors.

3. EXPERIMENTAL

3.1. Materials and methods

The reagents, solvents were obtained from commercial sources like Sigma-Aldrich, Spectrochem, etc. and used without further purification. The reactions were monitored by Merck silica gel 60 thin layer chromatography (TLC) and visualized in UV light chamber.

3.2. Characterization techniques

A Bruker AXS (Kappa Apex II) X-ray diffraction meter was used for single crystal XRD studies with graphite-monochromated MoKa radiation (l = 0.71073Å) at room temperature. The data collection, data reduction, and absorption correction were performed by

Table 8. Physicochemical descriptors and ADME parameters[a].

M.W g/mol	RB	H-A	H-D	TPSA	MR	*W log P (lipophilicity)*	ESOL log S	BBB Permeant	log Kp cms^{-1}	Lipinski Violations	PAINS alerts	GI absorption	Synthetic Accessibility
255.27	1	4	3	73.58 Å^2	75.09	2.73	-4.30	Yes	-5.15	0	0	High	1.74

[a] R bond =Rotatable bond, H-A = Hydrogen bond acceptor, H-D =hydrogen bond donor, TPSA = topological polar surface area, BBB = blood brain-barrier, log P = lipophilicity, log S = water solubility, log Kp = permeability coefficient, PAINS = pan-assay interference structure.

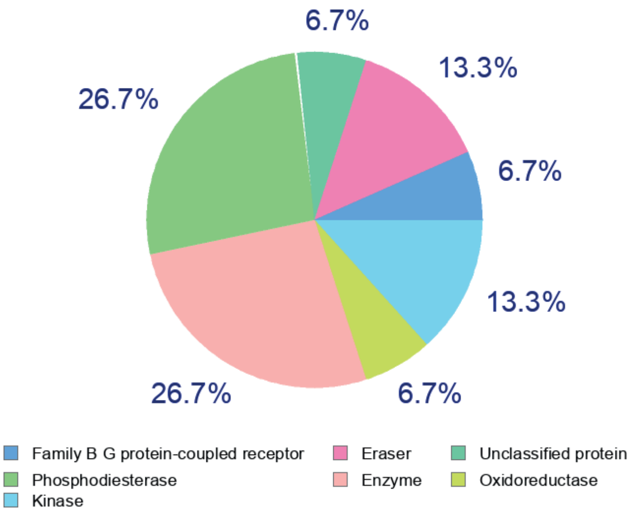


Figure 12. Swiss Ligand-based target prediction of 4-BRMBH.

APEX2. The structure was solved by the direct method procedure and the non-hydrogen atoms were subjected to anisotropic refinement by full-matrix least squares on F^2 using SHELXL-2016 [4]. The ^{1}H and ^{13}C NMR spectra were recorded in Bruker AVANCE II at 400 MHz respectively using DMSO-d_6 solvent at room temperature. The morphology of the crystals was examined with a JEOL JSM-5610 scanning electron microscope (SEM) is outfitted with BE detector [12]. Thermo gravimetric and differential thermal analysis (TG-DTA) was carried out using a NETZSCH STA 449 F3 thermal analyzer in the nitrogen atmosphere.

3.3. *Computational studies*

The theoretical calculations were carried out using the Gaussian 09W program package [13]. The geometry using density functional group theory (DFT) B3LYP method with LANL2MB as the basis set. Using the GaussView 09 molecular visualization program [14,15], the optimized structure of the molecules have been visualized. Polarizability and first-order molecular hyperpolarizability were premeditated by using finite field method as default with DFT method 6-311G (d, p) as basis set [16–19]. The density of states (DOS) plots was obtained by using Gauss-Sum software. Global electronic proprieties, HOMO and LUMO, energy gap (DE), electronegativity (c) and reactivity indexes, including electronic chemical potential (μ), chemical hardness (η), softness (s), ionization potential (I), electron charge transfer (DN) global electrophilicity (ω), and global nucleophilicity N were computed by the following expressions: $\mu = (EHOMO + ELUMO)/2$ and $\eta = (ELUMO - EHOMO)$, $\omega = \mu 2/2\eta$, and $N = EH - EH(TCE)$. The Parr functions were used to calculate the local reactivity indexes, namely, local electrophilic (Pk+), and nucleophilic (Pk–), via the analysis of the Mulliken atomic spin density (ASD) all these global molecular reactivity descriptors are estimated from the optimized structures.

Hirshfeld surfaces and fingerprint plots were generated from the CIF files of the desired compounds using the Crystal Explorer (Version 3.1). Intermolecular distance information on the surface can be shown in a two-dimensional histogram of d_e and d_i, which is a unique identifier for molecules in a crystal structure, and is known as a fingerprint plot [20, 21].

3.4. In-silico *molecular docking*

Molecular docking studies were carried out by using Schrodinger software [22]. The protein structure of the androgen receptor (PDB:7vjt) were obtained from RCSB Protein Data Bank with the resolution of 1.70 Å and prepared using Protein Preparation Wizard in Maestro 11.2. OPLS-2005 was used for the optimization and minimization until root mean square deviation reached 0.3 Å [23]. Further grid was formed in the protein using Receptor grid generation. The ligands 4-BRMBH were prepared using ligand preparation wizard and optimized the structures. The docking was carried out using the ligand docking module with an extra precession method using GLIDE XP [24–26].

3.5. General procedure for synthesis of (E)-N'-(4-bromobenzylidene)-3-methoxybenzohydrazide

The hydrazone derivative used in the present work (Scheme 1). The 4-BRMBH single crystals were grown at room temperature. A mixture of 3-methoxybenzohydrazide (2.20g, 2 mmol), and 4-bromobenzaldehyde (3.66g, 2 mmol), and 1 ml of aceticacid in methanol (50 ml) were developed and the solution was blended to create a homogenous solution at room temperature for 3 h. TLC verified the completion of the reaction. The solution was filtered, slightly warmed and allowed to evaporate very slowly. The crystallization took place within a period of 4–5 days and the grown yellow color crystals were harvested. Under reduced pressure, excess solvent was evaporated and the material (I) remaining was under reduced pressure, excess solvent was evaporated and the left material (I) recrystallized from methanol.

3.6. *X-ray crystallography*

Data collection of $C_{15}H_{15}BrN_2O_3$ was performed using STOE IPDS 2 diffractometer equipped graphite monochromatic MoKa radiation 296 K [27]. The structure solution was solved by means of SHELXT [28] and refinement were carried out on F^2 by full matrix least square technique. For obtaining the visualization, Mercury Window [29] was used. The other two programs employed in preparation for publication are WinGX [30] and pubCIF [31]. A riding model was used for refinement of all hydrogen atoms C–H and NH atoms. Also PLATON [32] software was used to investigate the hydrogen bond in the crystal. The experimental details for $C_{15}H_{15}BrN_2O_3$ were summarized in Table 1.

3.7. DFT calculations

The GaussView program was applied to model the initial structures of (*E*)-*N*¢-(4-bromobenzylidene)-3-methoxybenzohydrazide monohydrate **3**. Then, their molecular optimizations of geometries were carried out in the gas phase with the density functional theory (DFT) with the Gaussian 09 software package [23]. All the quantum-chemical calculations have been performed using the hybrid B3LYP Becke's Three Parameter Hybrid Functional using the Lee Yang-Parr correlation functional at 6-31G (d, p) basis set [24, 25]. Furthermore, several electronic properties for instance the frontier molecular orbitals, gap energies, and reactivity descriptors.

The density of states (DOS) plots was found by using Gauss-Sum software programm. Global electronic proprieties, HOMO and LUMO, energy gap (DE), electronegativity (c) and reactivity indexes, including electronic chemical potential (μ), chemical hardness (η), softness (s), ionization potential (I), electron charge transfer (DN) global electrophilicity (ω), and global nucleophilicity N were computed by the following expressions: μ = (EHOMO + ELUMO)/2 and η = (ELUMO − EHOMO), ω = μ2/2η, and N = EH − EH(TCE). The Parr functions were used to calculate the local reactivity indexes, namely, local electrophilic (Pk+), and nucleophilic (Pk–), via the analysis of the Mulliken atomic spin density (ASD) all these optimized structures are utilized to estimate these global molecular reactivity characteristics.

3.8. ADME/Tox profile

ADME/Tox is used to predict important capacity to properties evaluate necessary Lipinski's rule. The rule is beneficial for developing a prospective therapeutic molecule and designing drugs. SWISS ADME and molinsperation predictor web server tool to describe, molecular weight, Rotatable bonds, hydrogen bond acceptor, hydrogen bond donor (HBDs), absorption, distribution, molar refractivity, topological polar surface area (TPSA), water solubility (log S), lipophilicity, blood brain-barrier, skin permeability (log Kp), synthetic accessibility score (SA), percentage absorption, pharmacokinetics, drug- lead likeness. The use of these representations has specifically been contributive to drug optimization and avoiding late-stage failures.

CONCLUSION

In this present work, we have synthesized 4-BRMBH crystal and successfully grown from the solvent's methanol by slow evaporation technique. The structure of small molecules was determined by NMR and single crystal XRD analysis. The crystal structure is elucidated by with a $P2_12_12_1$ space group. Theoretical calculations by DFT clearly support the experimental observations. The intermolecular interactions in the crystal structures were quantified using the Hirshfeld surface analysis, and the molecular docking studies, results showed that the compounds had very good binding affinity to receptor protein (7VJT) which can be a potent molecule for anti-tuberculosis. ADMET prediction indicated that drug-likeness outlines of the compound. As a result, it is possible to say that compound 3 as suitable applicant for the development of the new *M. tuberculosis* agent. The above remarkable considerations and pharmaceutical applications prompted us to give vital information for further development.

AUTHORS CONTRIBUTIONS

All authors (K Ananthi, H Anandalakshmi, A Nepolraj and S Akshaya) have contributed equally to writing and reviewing the manuscript.

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Historical Article

The Wonderful and the Useful: Experiments In Samuel Parkes' *Chemical Catechism*

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Abstract. This article aims to present an overview of the experiments contained in Samuel Parkes' book, *Chemical Catechism*. In a context of great interest towards science in Britain, many popular chemistry books were published in the early 19th century. Among them, *Chemical Catechism* was a highly successful work, receiving several editions and translations into other languages. Its chemical content is presented in the form of short questions and answers, complemented by extensive footnotes that serve various purposes. One of these purposes was to guide the tutor in conducting demonstrations and experiments for the pupils, and to convince them of the practical nature of science. The experiments could have sensory, scientific, or industrial appeal, or could be integrated into discussions about theoretical aspects of chemistry. Analysis of the experiments reveals some of Parkes' conceptions about chemistry and its popularization. Once the pupils' attention had been captured by the experiments with great sensory appeal, the presentation of theoretical explanations would lead to an understanding of how chemists work and how chemistry could be useful for personal prosperity and the benefit of the nation.

Keywords: Samuel Parkes, Chemical Catechism, 19th-century chemistry, popularization of chemistry, chemical experiments.

INTRODUCTION

In the beginning of the 19th century, Britain was going through a period marked by conflicts and the increasing renewal of manufacturing processes in the context of the Industrial Revolution. Considering the growing need to follow the advances experienced by the Kingdom, and strongly driven by the technological adventures of the time, natural philosophy found in the United Kingdom a favourable place and time for its development and dissemination. The Royal Institution can be highlighted as an example among the various societies created in this period with the aim of spreading useful knowledge through lectures and demonstrative experiments. In addition to being appealing in terms of their usefulness in the development of crafts and manufacturing, the wonders of science were also attractive to audiences looking for an interesting and fun entertainment.[1]

Alongside the lectures, introductory chemistry books also received attention from individuals with a keen interest in science. Although some of these books presented technical concepts that could be difficult for beginners to understand, they played the role of promoting the communication of scientific knowledge to the public, without the ambition of training science specialists with their content.[2]

An introductory work that achieved sizeable prominence in the beginning of the 19th century was the *Chemical Catechism*, by Samuel Parkes (1761–1825), originally published in Britain in 1806 and later translated into several languages.[3] The book consists of a series of questions and answers, followed by extensive footnotes that complement the catechetical part of the text. A relevant feature is that, with each new edition of the *Catechism*, Parkes updated some of the topics covered according to the developments of chemistry, intending to keep his book up to date and close to the progression of science itself. This shows the proximity between the science produced at the time and the general public, who could follow the advances in science according to the updates of works dedicated to science popularization.[4]

One of the alluring aspects of Parkes' work is the inclusion of experiments, which are presented in both footnotes and a dedicated chapter at the end of the book. Some of them were personally referred to Parkes by Humphry Davy (1778–1829), one of the most celebrated chemists and science popularisers of the period. In Parkes' conception, the *Chemical Catechism* experiments were presented with the objective of establishing a way of accessing the truth that only experimentation and analysis of the facts could demonstrate.[5]

Considering the context of early-19th-century chemistry popularization books, this article aims to investigate the way in which experimentation and chemical demonstrations figure in Parkes' *Chemical Catechism*. The study of this theme aims to contribute to the reflection on how important experiments were in the scope of science popularization books, and what were their objectives in a time of great fervour for science itself – a time when important experiments and chemical works, such as those of Davy and Michael Faraday (1791–1867), took place.

This paper analyses the experiments and demonstrations included in the *Chemical Catechism*, focusing on Parkes' objectives and on his opinion about the issue of experimentation, either explicit or implicitly present in the book. In order to contextualize it, scientific popularization in late 18th century and early 19th century is discussed, the period in which the *Chemical Catechism* was written and published.

The different editions of Parkes' book, found in digital format on Google Books, Internet Archive and Hathi Trust databases, were used as sources for this article. Research sources also include reviews made at the time of the publication of the *Chemical Catechism* in British journals (also found in the abovementioned digital databases) such as *The Monthly Review*, and the works of historians of science such as David Knight, Frank James, Frederick Kurzer, Jonathan R. Topham, Jean-Luc Chappey, Jan Golinski and Bernard Lightman.[6]

BRITAIN'S ENTHUSIASM TOWARDS SCIENCE IN EARLY 19TH CENTURY

During the second half of the 18th century and the first half of the 19th century, science was regarded with intense enthusiasm and popularity in Britain. In particular, chemistry was responsible for much of this fascination which, according to Knight, found the height of its notoriety at that time.[7] Chemistry was seen not only as a fun curiosity with great sensory appeal, but also as a necessity and a considerable concern for society.[8]

At the end of the 18th century, France was in a period of intense political and social upheaval, and was also experiencing an intensive scientific euphoria. Being involved in internal and external conflicts, it depended on science to perfect goods and processes related to military purposes, while Britain needed scientific improvements to advance techniques aimed at its self-sufficiency.[9] Especially because of conflicts with France (which, after the furore of the French Revolution, were later involved in the Revolutionary Wars and the subsequent Napoleonic Wars), Britain had its access to Continental trade reduced and restricted. The Kingdom was then driven to make the most of its own resources for the subsistence of its manufactures, which, at the time, were increasingly demanding due to the advance of industrialization.[10] Therefore, according to Knight, "France around 1800 led the world in science, but Britain led the world in technology".[11]

Following the Industrial Revolution, significant changes were brought about in Britain. With the advancement of manufacturing techniques, growth of trade and accumulation of capital, a social class of wealthy manufacturers, traders and bankers rose. Such class was also gradually convinced of the usefulness of scientific advancement to foster their economic objectives.[12]

In the midst of this historical and social context, while representing a promising path for the technological development necessary for British manufacturing, science also lured large audiences with explosions, colour changes and odours. The public flocked increasingly to auditoriums to have a first-hand view of the wonders that science could present.[13] One of the institutions that stood out in the introduction of science to the public was the Royal Institution, founded in 1799 with the aim of "diffusing the Knowledge, and facilitating the general Introduction, of Useful Mechanical Inventions and Improvements; and for teaching, by Courses of Philosophical Lectures and Experiments, the application of Science to the common Purposes of Life".[14]

The American chemist Benjamin Silliman (1779–1864) noted that science lectures attracted audiences of different ages and of both sexes, interested in the wonders that science, especially chemistry, could perform.[15] This can also be seen in the diary of the young French traveller Louis Simond, who documented his visit to London in the years of 1810 and 1811. In his journal, Simond wrote that, although many were the subjects covered by the lectures at the Royal Institution, such as astronomy, mechanics and natural history, these sciences were not as "fashionable" as chemistry. According to Simond, the reason was that they were not "susceptible of any brilliant exhibitions; there is no noise, no fire, – and the amphitheatre never fills, but for Mr. Davy".[16]

Although the lectures represented the main course of action of the Royal Institution, soon its members realized that they alone were not enough, and the institution needed to expand its appeal to the public. Thus, it didn't take long for the great scientific experiments performed to the public to become a popular featuring, in which the execution was often dangerous by our current safety standards.[17] This effort to bring science to a large audience and show it in an fascinating way, aiming at practical learning, was one of the aspects that marked the popularization of chemistry during this period.[18]

Golinski[19] described two lines of thought on how science popularization should be, quite different in their purposes. The first, which comprised a minority of authors, was prompted by a more radical ideal, being driven mainly by Enlightenment goals. This group included authors such as Joseph Priestley (1733–1804) and Thomas Beddoes (1760–1808), who supported a useful natural philosophy, linked to political aspects. For them, if natural philosophy was used by the population, it would be a powerful tool to understand the Universe, something that could put an end to the undue authority usurped by the nobility. Following this line of thought, Priestley was one of the leaders of the movement which called for a reformation of the British Parliament, but ended up being forced into exile in the United States in the 1790s. The second group was formed by the vast majority of natural philosophers from industrialized regions in Britain, who sought to keep radicals away from national scientific institutions and fought the so-called "Jacobin" ideals.[20] For this group the popularization of science aimed to entertain and empower workers so that they could exercise their functions even better, but maintaining the established hierarchical system.[21]

SCIENTIFIC POPULARIZATION IN BOOKS

Along with the growing enthusiasm for science which encouraged institutions to offer more and more scientific lectures and demonstrations to their audiences, there was also a significant increase in the number of scientific publications during the 19th century. Among the reasons leading to this gradual expansion were the technological advances that took place, mainly, during the first half of the century. The very improvement of printing techniques allowed books to become more accessible. Publishers then targeted new audiences, including the middle and working classes in their markets.[22] Consecutive reprints of books designed to popularize chemistry attest to the widespread allure this genre held at the time.

Until the beginning of the 19th century, books were considered to be luxury items, as they were printed on manually-controlled presses and illustrated with metal engravings, which made them really expensive. It was only after 1820 that literature, whether philosophically based or not, gained considerable impetus, thanks to advances such as the steam-powered printing press, and the improvement of techniques which made paper production cheaper and more accessible.[23] During the 1840s, the production of books had already improved to the point that their circulation was four times bigger than at the beginning of the century. With the advent of the new techniques, journals became more popular and numerous, making Britain one of the pioneers in the mass production of printed publications.[24]

According to Knight, another element to consider is that even though a good part of the population was still illiterate, there was an increasing demand for literary works from the minimally educated layer of the population, which also tended to see science as a considerably interesting subject and helped to boost the publication of scientific popularization books.[25]

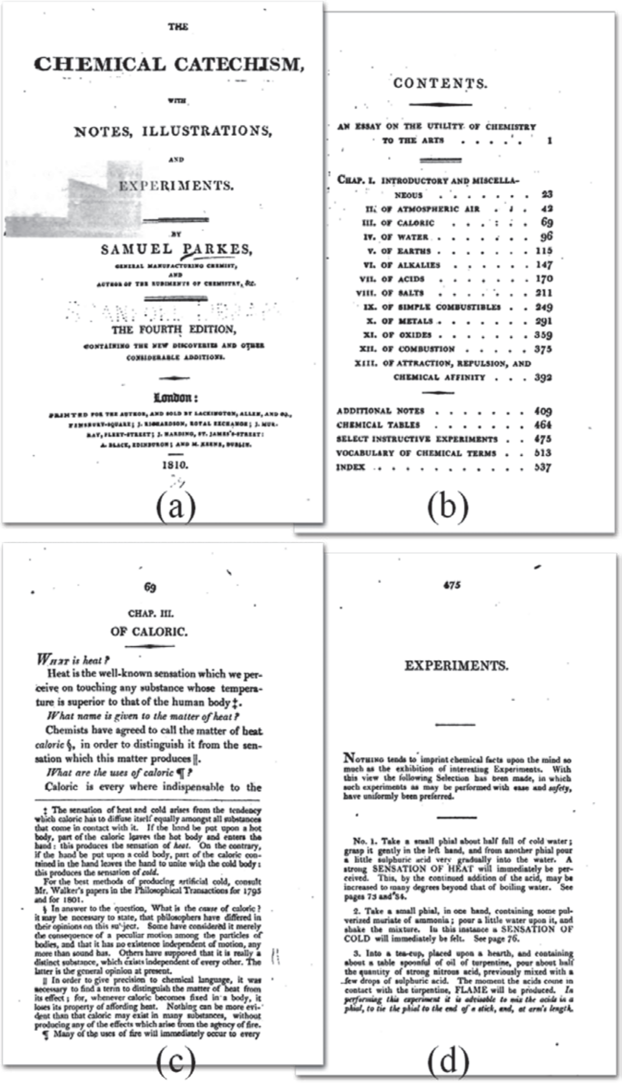
Several branches of natural philosophy were covered in popular works during the period. One can cite Margaret Bryan (1750-1816) with her *Compendious System of Astronomy* (1797) and *Lectures on Natural Philosophy*

(1806); Jeremiah Joyce with his *Scientific Dialogues* [on mechanics, astronomy, hydrostatics, pneumatics, optics, magnetism, electricity and galvanism] (1800-1803) and *The Wonders of the Microscope* (1812); Jane Marcet (1769-1858) with *Conversations on Natural Philosophy* (1819) and *Conversations on Vegetable Physiology* (1839); and Mary Somerville (1780-1872) with *The Mechanism of the Heavens* (1831) and *The Connexion of the Physical Sciences* (1834).[26] However, in a context of industrial rise associated with tensions with France and the Continental Blockade, chemistry emerged as an eminently useful and necessary science. Its image was connected to an idea of progress in industry and crafts, exactly as it would be explored by Parkes in his life and work.[27]

Among the books published at that time, *Conversations on Chemistry*, by Jane Marcet, and the *Chemical Catechism*, by Parkes, both published for the first time in 1806, are noteworthy. Their objective was to introduce basic concepts of chemistry to those who knew nothing, or just a little, about it, mainly children and young people. Although Marcet made it clear in the preface that she targeted the female audience when writing *Conversations on Chemistry*, contemporary reports revealed that her book reached a much broader audience than the one to which it was allegedly directed. Parkes, in turn, claimed to have the education of his only daughter as the initial reason for writing the *Chemical Catechism*. However, when he realized that his work reached a much larger dimension than initially expected, and encouraged by friends, Parkes decided to publish his book to help to educate children, who could use chemical knowledge to boost and improve any activities they came to dedicate themselves to in the future.[28]

The way Marcet and Parkes introduced chemistry in their works was quite different from previous chemistry books, and their approaches were also different from each other, even though their formats had already been used in publications from other areas. According to Lightman, the new formats adopted for popularization probably had the objective of attracting new readers to the subject by making chemistry as attractive as prose fiction, which was quite popular at the time.[29]

While Marcet wrote her text in the form of dialogues, introducing three characters – two girls, Caroline and Emily, and their tutor, Mrs B. –, Parkes used the catechism form, with short assertive questions and answers, fostering the pupils to know and repeat it by heart. In his preface to the third edition of the *Chemical Catechism*, Parkes explained that this form was chosen because it had "[...] at least all the advantages that any other mode of instructing youth in chemistry can claim". In this way, pupils' learning would be guaranteed, as "if the author's original intention be followed, the progressive improvement of the student will be pleasant, rapid and correct".[30] Figure 1 illustrates the overall layout of the book.



THE

CHEMICAL CATECHISM,

WITH

NOTES, ILLUSTRATIONS,

AND

EXPERIMENTS.

BY

SAMUEL PARKES,

GENERAL MANUFACTURING CHEMIST,

AND

AUTHOR OF THE RUDIMENTS OF CHEMISTRY, &c.

THE FOURTH EDITION,

CONTAINING THE NEW DISCOVERIES AND OTHER

CONSIDERABLE ADDITIONS.

London:

PRINTED FOR THE AUTHOR, AND SOLD BY LACKINGTON, ALLEN, AND CO.,

FINSBURY-SQUARE; J. RICHARDSON, ROYAL EXCHANGE; J. MUR-

RAY, FLEET-STREET; J. HARDING, ST. JAMES'S-STREET:

A. BLACK, EDINBURGH; AND M. KEENE, DUBLIN.

1810.

(a)

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CHAP. III.

OF CALORIC.

What is heat?

Heat is the well-known sensation which we perceive on touching any substance whose temperature is superior to that of the human body ‡.

What name is given to the matter of heat?

Chemists have agreed to call the matter of heat *caloric* §, in order to distinguish it from the sensation which this matter produces ‖.

What are the uses of caloric ¶ ?

Caloric is every where indispensable to the

‡ The sensation of heat and cold arises from the tendency which caloric has to diffuse itself equally amongst all substances that come in contact with it. If the hand be put upon a hot body, part of the caloric leaves the hot body and enters the hand: this produces the sensation of *heat*. On the contrary, if the hand be put upon a cold body, part of the caloric contained in the hand leaves the hand to unite with the cold body: this produces the sensation of *cold*.

For the best methods of producing artificial cold, consult Mr. Walker's papers in the Philosophical Transactions for 1795 and for 1801.

§ In answer to the question, What is the *cause of caloric*? it may be necessary to state, that philosophers have differed in their opinions on this subject. Some have considered it merely the consequence of a peculiar motion among the particles of bodies, and that it has no existence independent of motion, any more than sound has. Others have supposed that it is really a distinct substance, which exists independent of every other. The latter is the general opinion at present.

‖ In order to give precision to chemical language, it was necessary to find a term to distinguish the matter of heat from its effect; for, whenever caloric becomes fixed in a body, it loses its property of affording heat. Nothing can be more evident than that caloric may exist in many substances, without producing any of the effects which arise from the agency of fire.

¶ Many of the uses of fire will immediately occur to every

(c)

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EXPERIMENTS.

Nothing tends to imprint chemical facts upon the mind so much as the exhibition of interesting Experiments. With this view the following Selection has been made, in which such experiments as may be performed with ease and *safety*, have uniformly been preferred.

No. 1. Take a small phial about half full of cold water; grasp it gently in the left hand, and from another phial pour a little sulphuric acid very gradually into the water. A strong SENSATION OF HEAT will immediately be perceived. This, by the continued addition of the acid, may be increased to many degrees beyond that of boiling water. See pages 73 and 84.

2. Take a small phial, in one hand, containing some pulverized muriate of ammonia; pour a little water upon it, and shake the mixture. In this instance a SENSATION OF COLD will immediately be felt. See page 76.

3. Into a tea-cup, placed upon a hearth, and containing about a table spoonful of oil of turpentine, pour about half the quantity of strong nitrous acid, previously mixed with a few drops of sulphuric acid. The moment the acids come in contact with the turpentine, FLAME will be produced. *In performing this experiment it is advisable to mix the acids in a phial, to tie the phial to the end of a stick, and, at arm's length.*

(d)

Figure 1. Overall layout of Parkes' *Chemical Catechism*. (a) Title page; (b) Table of contents; (c) Example of a page showing the main text in catechism form and the footnotes; (d) First page of the numbered "select instructive experiments".

In the next section, some of Parkes' biographical data that may help to understand the context and content of the *Chemical Catechism* are presented.

SAMUEL PARKES – BIOGRAPHICAL SKETCH

Samuel Parkes was born in Stourbridge, Worcestershire, on May 26, 1761. At the age of five, he began to attend a children's school in his town. At ten he became a pupil of the independent minister, Dr. Stephen Addington (1729–1796), remaining under his guardianship until the age of fourteen. After passing through the brief tutelage of a blacksmith in Ross-on-Wye, Parkes returned to Stourbridge, where he joined his father in the family's grocery business for the next 18 years. Parkes was an avid reader from an early age and collected many books in his personal library along his life. This was an important feature of Parkes' self-taught education, as he did not attend a university. Around 1790 Parkes helped set up a public library in Stourbridge, of which he himself acted as administrator for some years. At the same time, Parkes helped create a chapel for Unitarian worship in his city.[31]

In 1793, Parkes moved to Stoke-on-Trent, where he started a soap-making business and married Sarah Twamley (1766–1813). In 1797 their only child, Sarah Mayo, was born. According to Kurzer (1997), his interest in controlling the soap manufacturing process in a more effective way led Parkes to the study of chemistry, which soon became his main professional interest.[32]

Financial problems led Parkes to move with his family to London in 1803. With a loan from a friend and a small amount of his own, he settled in the city and began his career as a chemical manufacturer. After just three years in London, Parkes managed to settle all the debts incurred, which indicates the success of his new trade. However, although the activity as a manufacturer of chemical products required him intense attention and dedication, it did not prevent Parkes from continuing other personal projects. In 1806, he published the first edition of *Chemical Catechism*; in 1809, the volume entitled *Rudiments of Chemistry*; and, in 1815, his third book, *Chemical Essays*.[33]

In addition to the abovementioned works, Parkes also published short texts, which often dealt with chemistry and its usefulness in issues of economic interest to the United Kingdom, such as *Thoughts on the Salt Laws* (1817) and *Letter to Farmers and Graziers on the Use of Salt in Agriculture* (1819). Furthermore, due to his knowledge in practical chemistry matters, Parkes also participated in legal and parliamentary hearings as a witness or expert consultant on several occasions.[34]

After the unexpected death of his wife in 1813, Parkes's daughter helped him to run the household and accompanied him on some travels. In June 1825, a year after his daughter's marriage to Joseph Wainwright Hodgetts (1797–1851), Parkes fell seriously ill during a journey to Edinburgh and, as soon as it was deemed prudent, was taken back to London by his son-in-law. After months of illness Parkes died on December 23, 1825.[35]

THE *CHEMICAL CATECHISM*

Entitled *A Chemical Catechism for the use of Young people*, the first edition of Parkes' most popular work was released in May 1806, with a print run of fifteen hundred copies – the smallest compared to the print runs of subsequent editions. The *Chemical Catechism* had a total of thirteen editions, twelve of which were released between the years 1806 and 1826. The thirteenth edition was released posthumously in 1834, after revision and adaptation by Edward William Brayley of the London Institution.[36]

Parkes relied on a number of publishers and many editions of his *Catechism* were translated into Spanish, French and German, also circulating in the United States and Russia.[37] It is difficult, therefore, to estimate the popularity of the book, as well as its financial return, even in comparative terms with other scientific popularization books of the period. Kurzer suggests measuring the social ascension experienced by Parkes by observing the title pages of successive editions of the catechism.[38] While in the first edition, from 1806, the author is briefly introduced as "Chemist of preparations", in the fifth, from 1812, the presentation changes to "Author of *Rudiments of Chemistry* and one of the Owners of the Haggerstone Chemical Works". In the author's last edition, in 1826, Parkes devotes no less than nineteen lines to listing his affiliation with the various philosophical and literary societies to which he was associated, or from which he received honours, in England and abroad, including Portugal, France, the United States, Scotland and Russia.[39]

Although originally designed as a book for his daughter, the final audience Parkes addressed the *Chemical Catechism* to was a male audience. In the first essay of the book, he directs arguments to parents about the use of chemistry to benefit the development of their children's future profession. Parkes argues that the content of the book had the objective of teaching chemistry to young people, so that, if they were land owners, they could apply chemistry for its better use and exploitation; or, if the young man intended to be a physician, he might understand the principles of chemistry and use them in his profession; or even, for those who wanted to venture into industry, chemical knowledge would definitely be of enormous value for the execution of their functions.[40]

The main part of the text is explicitly aimed at learners and adopts the catechetical style, consisting of short, direct questions and equally short answers. The text also includes a large number of footnotes. Unlike the main text, the notes bring larger and more elaborate paragraphs, which discuss the most diverse issues – including, for example, suggestions of experiments to be carried out by the tutor together with the young learner, or even details of industrial processes involved in obtaining compounds cited in the main text. Also in the footnotes, the author makes several exaltations to divine wisdom and goodness, in allusion to natural theology[41], and makes comments on contemporary chemistry, mentioning studies and scholars – in most cases, authors affiliated to the "new chemistry" disseminated by Antoine Lavoisier (1743–1794) and his collaborators[42]. The footnotes offer not only a reference to how science was presented at the time, but also cover aspects of history, culture and even the morality prevailing among the British aristocracy in early 19th century.

CHEMISTRY *AD OCULI*: THE EXPERIMENTS IN THE *CHEMICAL CATECHISM*

Being a professional of chemical preparations, Parkes emphasized the use of experiments by young people to improve their chemical knowledge. According to him, "Nothing tends to imprint chymical facts upon the mind so much as the exhibition of interesting experiments".[43] To help tutors to perform experiments, the *Chemical Catechism* included illustrative figures of laboratory equipment, as well as descriptions of chemical utensils.

The experiments suggested by Parkes can be found in two different sections of the book. The catechetical part of the text, due to its question-and-answer format, was not designed to include experiments, although there are some brief mentions of them. Experiments are described and explained in the footnotes and in an additional section at the end of the work, entitled "Select Instructive Experiments", which constitutes an entire chapter dedicated only to experiments and chemical demonstrations.[44]

The main goal of the footnote experiments is to illustrate, explain or even "prove" the theories presented in the several chapters. In the footnotes, the discussion of the experiment would start from the observation of the procedure performed by the tutor and contemplation of the results by the pupil.[45] The following example was extracted from a chapter on the composition and properties of atmospheric air. The footnote presents an experiment designed to illustrate combustion, one of the properties of oxygen gas:

> The necessity of oxygen for supporting combustion may be shown by the following simple experiment. Pour a little water on a flat dish, place two or three lighted wax tapers of different lengths in the water, and invert a tall glass jar over them. The flame of the different tapers will soon be seen to grow smaller, and at length will be extinguished in succession. That which is highest will be extinguished first, and the shortest taper the last, owing to the purer air occupying the lower part of the jar.[46]

It can be seen, in this example, that not only instructions are given for carrying out the experiment, but a brief explanation about the relation between tapers sizes and the order in which they go out is also introduced. Another example is an experiment designed to show the role of caloric in expansion and condensation of fluids:

> Put a little ether into a small retort, tie a bladder to the beak of it, and hold the retort over a lamp. The ether will quickly boil, and the gas which arises from it will soon occupy the bladder and distend it to its full size. If the bladder be then held in water, the gas will be condensed by the loss of its heat, and the bladder will collapse. In order for this experiment to succeed, it is necessary previously to warm the bladder to 80 or 90 degrees [*F*], to prevent the gas from being condensed in the first instance.[47]

Here Parkes uses simple instruments and materials, such as an animal's bladder, a retort, a little ether, water, and a lamp, to demonstrate the phenomenon and provides instructions to guarantee the expected effects.

While visual appeal was prevalent in the designed demonstrations, it was not the sole sensory aspect explored by Parkes in the footnotes. Some experiments also engaged the sense of smell, as seen in the production of ammonia described in the chapter entitled "Of Alkalies":

> By the following process ammonia may be formed, so as to become evident to the senses in a short time. Take some filings of tin or zinc, pour on them some moderately dilute nitrous acid. After a short time stir into the mixture some quick-lime [*i.e., calcium oxide*], or caustic alkali[48], and a very strong pungent smell of ammonia will be produced.[49]

The so-called "select instructive experiments" had a different objective from the experiments that figure in the footnotes. In the introduction to this chapter, Parkes points out that its original intent was to explain the reason for each experimental result and the concepts that the experiments illustrate to the pupil. However, he claims, such approach could undermine the inquisitive spirit that must be cultivated in youth; therefore, Parkes decided that he would only present the way of conducting the experiments and that it would be up to the student to seek the explanation of the causes and effects as presented in the previous chapters of the *Chemical Catechism*. At the end of each experiment, Parkes mentions the pages which refer to the respective concepts, so that the pupil would be able to consult them when trying to understand the observed phenomenon. Parkes also points out that one should not proceed to the next experiment if not completely satisfied with the self-elaborated explanation for the previous one.[50]

The "select instructive experiments" were presented in a numbered list which grew from one edition to another. The first edition of the *Chemical Catechism* lists 154 experiments, a number greatly increased in the following edition, with the addition of 91 experiments. Later editions had further additions, including nine experiments recommended by Humphry Davy, to whom Parkes thanked in a note: "For the following Experiments I am indebted to the polite communication of Professor Davy".[51] The latest editions featured 255 experiments in all.[52]

As mentioned above, explanations for the phenomena are not given with the description of the procedure of the "select instructive experiments", but should be found in the body of the preceding chapters. In the upcoming example, Parkes describes a mixture that produces heat and directs the reader to previous pages discussing the generation of caloric from mixtures (p. 73) and its role in maintaining bodies in a fluid state (p. 84):

> No. 1 . Take a small phial about half full of cold water; grasp it gently in the left hand, and from another phial pour a little sulphuric acid very gradually into the water. A strong SENSATION OF HEAT will immediately be perceived. This, by the continued addition of the acid, may be increased to many degrees beyond that of boiling water. See pages 73 and 84.[53]

In this instance, perceiving the phenomenon involves the sense of touch. Furthermore, other senses could also come into play. Experiments designed to engage sight, hearing, and smell are also described, as exemplified below:

> 33. Fix a small piece of solid phosphorus in a quill, and write with it upon paper. If the paper be now carried into a dark room, the writing will be BEAUTIFULLY LUMINOUS. See page 262 [*on the properties of phosphorus*].
> (...)
> 36. Take about six grains of oxymuriate of potass [*i.e., potassium chlorate*], and three grains of flour sulphur; rub them together in a mortar, and a smart DETONATING NOISE will be produced. (...) If the same mixture be wrapped in paper, laid on an anvil, and smartly struck with a hammer, the report will be as loud as what is usually produced by a pistol. See page 221 [*on chlorates (then called oxymuriates or hyperoxymuriates) and their explosive properties*].[54]
> 159. Take a small piece of phosphuret of lime [*i.e., calcium phosphide*], a little moistened by the air, and let a single drop of concentrated muriatic acid fall upon it. In this case phosphuretted hydrogen will also be evolved, accompanied by SMALL BALLS OF FIRE darting from the mixture, and the most intolerable fetid smell that can be conceived. See page 256 [*on the production and properties of hydrogen phosphide*].[55]

In this last example, the appeal is related to both smell and vision, and several other experiments jointly appeal to more than one sense. The only sense that is not explored is taste, although there are very few mentions of the taste of compounds produced in an experiment. The production of ammonium chloride, also known as *sal-ammoniac*, is illustrative:

> 24. Take carbonate of ammonia (the common volatile *smelling* salt), and pour upon it muriatic acid so long as any effervescence continues. The produce will be a SOLID SALT, perfectly *inodorous*, and of little taste. See page 165 [*on the production and properties of ammonium chloride*].[56]

The brief mention of the taste of ammonium chloride is neither part of the experiment's attractiveness nor of the analysis in discussion, but rather a passing description of an evidence that a new substance was produced in the chemical reaction.

The sensorial appeal was not only for Parkes, but for most of the popularisers of science at the time, a powerful asset to amaze the public, exciting curiosity for the scientific phenomena by means of explosions, colours, odours and lights. Such breath-taking experiments gained popularity and aimed the public of chemical lectures and demonstrations, as well as the readers of the introductory chemistry books. In the first half of 19th century, the public image of chemistry was that of "a science of the secondary qualities (colours, tastes, and smells), where thinking had to be done with fingers, nose, and eyes".[57]

Although Parkes stated that the experiments in his book were chosen because they could be carried out with "ease and *safety*",[58] many of them involve the handling of dangerous, toxic, easily flammable or potentially explosive substances, such as potassium chlorate (explosive), phosphorus (flammable), mercury and ammonia gas (toxic). In spite of the danger, Parkes not only teaches how to obtain such substances, but also suggests several experiments which require their manipulation. An example may be seen in the chapter on hydrogen, in which Parkes explains in a footnote how to obtain gaseous hydrogen sulphide:

> To obtain sulphuretted hydrogen gas [*i.e., hydrogen sulphide*], melt together in a crucible three parts by weight of iron filings and one of sulphur; reduce the mass to powder, and put it with a little water into a glass vessel with two mouths: lute one end of a crooked glass tube into one of these mouths, and let the extremity of the tube pass under a glass jar in a pneumatic trough, the jar being inverted and full of water. Then pour diluted muriatic acid through the other mouth of the vessel, which must immediately be closed up. Sulphuretted hydrogen gas will now be disengaged in abundance and flow into the glass jar, displacing the water.[59]

In addition to the seemingly light-hearted description of how to obtain dangerous substances, Parkes also suggests various experiments with explosive effects intended to amaze learners, some of them with the added risk of resulting in toxic products. Hence, the main criticism Parkes received in periodicals at the time was about the dangerousness of some of his experiments, which were certainly not recommended for beginners, much less for young people. According to an anonymous article published in *The Monthly Review*:

> The 'select instructive experiments' (...) are judiciously chosen. The only objection that we shall make to them is, that several of them appear of a hazardous nature. Desirous, probably, of exciting curiosity as much as possible, Mr. Parkes has too frequently introduced explosive or detonating substances, the management of which requires the greatest caution, and the most experienced dexterity. We should not deem it safe for a tyro in chemistry, even of advanced age, to repeat all the processes described by Mr. Parkes; much less would we trust such substances as phosphorus and the fulminating powder in the hands of 'young people'.[60]

However, Parkes is not completely reckless. In a few selected experiments, he gives safety warnings and explains how the demonstration could be done in a more cautious way, as in one of the experiments from the chapter on combustion:

> If one ounce of strong nitrous acid be mixed with about half its weight of concentrated sulphuric acid, and poured into a little oil of turpentine, the whole will immediately burst into flame. In this experiment it is the oxygen of the nitric acid which produces the combustion. The phial from whence the mixed acid is poured, should be tied to the end of a long stick, to preserve the operator from being injured by the splashing of the materials.[61]

The warning clearly seeks to protect the demonstrator from a possible projection of reagents due to the violence of the chemical reaction. Despite this caveat, however, the demonstration is still highly dangerous and possibly disastrous. Furthermore, warnings like these in the *Chemical Catechism* are much less frequent than desired or even necessary.

Sometimes the dangerousness of experiments is indicated by acknowledging the risks instead of an explicit warning. An example may be found in the chapter on metals, in which Parkes describes the combustion of metallic arsenic as a spectacular experiment: "If metallic arsenic be previously inflamed in oxygen gas, it will burn till the whole is consumed. The combustion is very brilliant, and forms a striking experiment".[62] In fact, Parkes acknowledges elsewhere that arsenic is poisonous, and that if a grain of white arsenic were administered all at once to a person, the result could even be death. Still, Parkes gives no instructions on how to manipulate the experiment's product, or on how to make the procedure more cautious. He just adds that if any amount is ingested on purpose or by mistake, "the best medicine is sulphuret of potash" (*i.e.*, potassium sulphide) dissolved in water.[63]

As editions went by, some security warnings were added, as one can see in the experiment that received the number 55 in the first edition and 60 in the second.

> 55. Take three parts of nitre [*i.e., potassium nitrate*], two of potash [*i.e., potassium carbonate*], and one of sulphur; make them thoroughly dry, and then mix them by rubbing them together in a warm mortar. The resulting compound is called *fulminating powder*. If a little of this powder be placed upon a fire-shovel over a hot fire, it gradually blackens, and at last melts. At that instant it EXPLODES WITH A VIOLENT REPORT.[64]

In the second edition, the same text is followed by a warning in italics: "60. (...) *Note, This mixture is not dangerous, like the metallic fulminating powders; none of the which should be entrusted in the hands of young people*."[65] However, even with the additions, such alerts are very few compared to the number of dangerous experiments.

Parkes also adds in the footnotes of the *Chemical Catechism* many recommendations of other works with interesting experiments related to the topics discussed in his book, so the tutor could look for more demonstrations if he considered it necessary. Among these recommendations are works by Lavoisier, John Roebuck (1718–1794), Richard Chenevix (ca. 1774–1830) and Joseph Priestley.

EXPERIMENTAL CHEMISTRY: THE WONDERFUL AND THE USEFUL

In our analysis, the experiments presented in the *Chemical Catechism* were classified into six categories, according to their different objectives: (1) proof of statements; (2) attractive or curious phenomena; (3) demonstration of specific chemical phenomena; (4) laboratory procedures; (5) production of substances in laboratory; (6) processes related to industrial or large-scale production.

The first category (proof of statements) predominantly appears in the footnotes and encompasses the objective of articulating the main text with supporting experiments to validate the given scientific claims. Such experiments were proposed from a dogmatic perspective: Parkes presents them as a safe way to reach the truths of Nature, because, according to him, the rationalization of investigation and experiment would lead the young mind away from sophistry, fanaticism and superstition, which could deceive the unprepared mind.[66] An example is the way Parkes describes an experiment after stating that liquid substances are solid substances that have been converted into fluid by heat:

> The following experiment will *prove* that it is caloric which converts solids to fluids: – Expose a pound of water and a pound of ice, both at 32° [*F*], in a room the temperature of which is above the freezing point. The water will arrive at the temperature of the room several hours before the ice is melted. The caloric, therefore, which has all the time been entering into the ice, but is not to be found in it by the thermometer, must have become *chemically* combined with it in order to give it fluidity.[67]

Parkes' emphasis on the word "prove", together with the choice of terms when introducing other experiments in the footnotes – such as: "The operation of this principle may be made apparent by the following experiment";[68] "[*The pressure of the atmosphere*] may be shown by a simple experiment";[69] "This may be made evident by the following striking experiments";[70] "In order to be convinced that...";[71] and "[*That ice contains a large portion of air*] may be seen by the following experiment"[72] – show Parkes popularizing an image of science in which experimentation has a validation role. In these experiments, practice was a means of proving the theory that had previously been explained to the learner.

The second category (attractive or curious phenomena) includes experiments intended to fascinate the pupil to the point of provoking his mind to unravel the concepts behind the experiment. An example is the experiment to produce combustion under water:

> 39. Put a little oxymuriate of potass [*i.e., potassium perchlorate*] and a bit of phosphorus into an ale-glass, pour some cold water upon them cautiously, so as not to displace the salt. Now take a small glass tube, and plunge it into some sulphuric acid: then place the thumb upon the upper orifice, and in this state withdraw the tube, which must be instantly immersed in the glass, so that, on removing the thumb, the acid may be immediately conveyed upon the ingredients. This experiment is an example of a very singular phenomenon, COMBUSTION UNDER WATER.[73]

Other examples of this category are the abovementioned experiments numbered 1 and 36.

The third category (demonstration of specific chemical phenomena) consists of a selection of experiments in which Parkes gives an example of a concept or phenomenon. In their very statement Parkes makes it clear that the given experiment is an example, using expressions such as "This experiment will afford an example of...",[74] "This shows how...",[75] "This is illustrative of...",[76] as one can see in the example below:

> 118. Put a little alcohol in a tea-cup, set it on fire, and invert a large bell glass over it. In a short time an aqueous vapour will be seen to condense upon the inside of the bell, which, by means of a dry sponge, may be collected, and its quantity ascertained. This may be adduced as an example of the formation of WATER BY COMBUSTION.[77]

The fourth category (laboratory procedures) is characterized by the objective of teaching aspects of scientific methodology, general techniques – such as a test for analysing the components of a mixture – or even operations commonly used in the laboratory and in industry. In this category, there are experiments to which Parkes explicitly relates a given laboratory process as well as experiments whose application is implicit – such as when a precipitation is used to detect a substance. As examples, we quote below the experiment which teaches how to detect volatile acids and muriates (*i.e.*, chlorides) using ammonia, and also the description of the crystallization technique:

> 61. Whenever uncombined muriatic, or any volatile acid is suspected to be present in any chemical mixture, it may be detected by ammonia. A single drop of ammonia on a feather, or small slip of paper, held over the mixture, will immediately render the VAPOUR VISIBLE.[78]
> Take a portion of sulphate of soda (Glauber's salt) and dry it over a common fire, which will reduce it to less than half its weight. Dissolve this dried salt in three times its weight of boiling water, set the liquor aside, and, when cold, beautiful crystals resembling the original crystals will be found in the liquor. By an attentive examination

> of the liquor, the crystals may be seen to form as the liquor cools. This is a cheap and easy experiment, and may be exhibited to the pupil as an example of crystallization in general.[79]

The fifth category (production of substances in laboratory) covers the objective of teaching tutor and pupil how to produce some of the compounds mentioned in the main text, or how to obtain compounds necessary for the execution of other experiments. Unlike the demonstrations included in the previous categories, such experiments were neither intended to appeal to the senses nor to prove a concept, but only to produce something. In the following example, Parkes describes in a footnote to the chapter on acids how to obtain chlorine gas for experimental use:

> Oxymuriatic acid [*i.e., chlorine gas*] gas may be obtained for chemical experiments by the following method: Put into a retort a little black oxide of manganese in powder; and pour upon this double its weight of strong muriatic acid; connect the retort with the pneumatic trough, and receive the gas over water. When the ascension of the gas slackens, apply the heat of a lamp, and it will be disengaged in abundance.[80]

The sixth category (processes related to industrial or large-scale production) built in this analysis gathers experiments related to manufacturing processes found in British industries. Some of such industrial processes were of great economic interest at the time, such as dyeing and bleaching fabrics, or the application of prints on calico, silk and linen.[81] This category promptly refers to one of the first objectives presented by Parkes for writing and publishing the *Chemical Catechism*: to instruct young people so that they could better apply chemistry to improve their future professional activities.[82] One example is the experiment which describes printing on calico:

> 90. Dip a piece of white calico in a strong solution of acetate of iron; dry it by the fire, and lay it aside for three or four days. After this, wash it well in hot water, and then dye it black, by boiling it for ten minutes in a strong decoction of Brazil wood. If the cloth be now dried, any figures printed upon it with a *colourless* solution of muriate of tin, will appear of a BEAUTIFUL SCARLET, although the ground will remain a permanent BLACK.[83]

The analysis of the experiments reveals some of Parkes' conceptions about chemistry and its popularization. In the first place, it was necessary to attract the attention of the pupils, so that they would be interested in what chemists had to say – for this, nothing better than to amaze them with experiments and demonstrations that appealed to the senses by means of explosions, flames, colours, odours, unusual phenomena, which should also create emotional impact. Once their attention had been gained, it was necessary to make sense of such observations and explain what chemistry is all about. Hence the importance of experiments demonstrating phenomena or "proving" theoretical explanations. It was also necessary for pupils to understand how chemists work, what their devices and procedures are, so that they could also perform the same tasks – if not while young, perhaps in the exercise of their future professional activities. To make it possible, many experiments described laboratory techniques and processes. Experiments dedicated to the preparation of substances had a similar goal, providing chemicals which could be used in different manufactures and industrial processes.

Thus, the experiments that demonstrated processes related to the manufacture of useful things justified and served as a crowning achievement for learning chemistry, as it leads to the benefit of the nation and personal prosperity. One can imagine that, in a sense, Parkes projected his own personal trajectory into these experiments: he saved himself from bankruptcy, amassed fortune and fame by producing and selling chemicals.

FINAL REMARKS

In this paper, we aimed to analyse the different types of experiments described in the *Chemical Catechism*, considering their form and objectives. The experiments had different objectives, which determined their place in the text and the way they were described. Experiments could offer sensory, scientific and industrial appeal or be part of discussions of theoretical aspects of chemistry.

The experimental dimension of science can be singled out as one of Parkes' major concerns in writing the *Chemical Catechism*. Besides suggesting experiments in the footnotes throughout the main chapters, Parkes also devoted an entire section of his book to them.

One can observe that Parkes presented experiments with different objectives in mind: amazing pupils with attractive or curious phenomena; validating or demonstrating the main points of the chemical concepts presented in the catechetical part of the text; introducing laboratory processes; producing substances; and introducing processes related to manufacturing. The success of the *Chemical Catechism* may be seen as an index of the popularity of chemistry in a period in which this science was teeming with conceptual novelties and possibilities of applications to feed industrial development.

Given the variety of experiments proposed by Parkes, the contemporary reader may wonder whether they could still be used today to teach or promote chemistry to students or the general public. Many of the described demonstrations are ingenious and could serve as good starting points for discussions on chemical concepts. However, as seen in this article, current safety standards are much more stringent than in Parkes' time. Therefore, any of his experiments need to be carefully assessed for safety in order to evaluate their feasibility for use in the current context.

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Historical Article

Lavoisier's *Traité élémentaire de chimie*: At the Intersection of Chemistry and French

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Abstract. Communication through language is crucial to properly disseminate knowledge and new discoveries in all disciplines. *Traité élémentaire de chimie* by Antoine Lavoisier is regarded as the first modern chemistry textbook and can be utilized as a teaching tool for interdisciplinary studies within the fields of chemistry and French. A contemporary rereading of Lavoisier's text offers insight into the chemistry being performed in the eighteenth century which was recorded and shared using eighteenth century French language. A reexamination of this historical text provides a variety of pedagogical exercises that can be used across the two disciplines. From chemical principles to unit conversions to shifts in French orthography, *Traité élémentaire de chimie* possesses a wealth of knowledge that can be enjoyed by a wide audience within the humanities and natural sciences. Lavoisier's *Traité élémentaire de chimie* can be employed in several different courses providing chemical principles for science courses while serving as a historical French writing sample for advanced French composition courses.

Keywords: chemical education, eighteenth century studies, pedagogical tools, interdisciplinary chemistry-French studies

Antoine Lavoisier is often regarded as a key figure in chemistry given his significant contributions to the field in the late eighteenth century and his text, *Traité élémentaire de chimie (Traité)*, is regarded to be the first modern chemistry textbook.[1-5] In 1789, the original text was published in French and has since been translated to several languages, including English in 1790. The historical text *Traité* not only serves as a record of the chemistry that was being performed at the time but also provides a glimpse into the evolution of the French language as we know it today. This article seeks to present a concise introduction of how the traditional text can be used as a tool for the interdisciplinary study of chemistry and French through the evaluation of both chemical and French language concepts. An anachronistic reexamination of this text through multiple lenses offers readers more avenues to incorporate *Traité* as a teaching tool in a given course. *Traité* can be used as a pedagogical tool to teach some of the fundamental concepts of chemistry and the orthographical shift used for the *imparfait* (imperfect) tense in the French language. A contemporary rereading of *Traité* offers a number of

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teaching exercises that can be easily incorporated into the curriculum of a General Chemistry course or an upper-division French Composition course.

A petit background of Lavoisier's text is presented to provide insight into the enormity of the project that sought to reorganize chemical knowledge in the eighteenth century. *Traité élémentaire de chimie* was conceived as a teaching textbook, originally published in two volumes. The first volume (Tome Premier) is divided up into two parts: Part One (Première Partie) primarily discusses the formation and decomposition of aeriform fluids (gases), the combustion of simple bodies, and the formation of acids across 17 chapters. Part Two (Seconde Partie) primarily consists of tables and observations concerning the combination of acids with bases and the formation of neutral salts. While the first volume often attracts more attention given its quest to present chemical information is an orderly manner, the second volume (Tome Second) contains Part Three (Troisième Partie) which describes the instrumentation and operations of chemistry during the eighteenth century. Lavoisier specifically included Part Three at the end of *Traité* to provide readers information on how the experiments and measurements were carried out after an appropriate foundation of chemistry had been presented. In addition to the tables of data presented in this part, an appendix containing terms and definitions is provided as reference. Part Three concludes with illustrations of labware and experimental setups which provide reference as to how the experiments were performed during the time period. Of notable interest, the illustrations found in *Traité* were composed by Lavoisier's wife, Marie-Anne Paulze.[6]

From a pedagogical standpoint, Lavoisier's chapter on combustion (*Chapitre IX. – De la quantité de Calorique qui se dégage des différentes espèces de combustion*) is suitable for the presentation of important concepts in chemistry and the French language. We will explore this chapter as a tool to teach about the foundations of the Law of Conservation of Mass, traditional French units of mass, and the orthography used during the time period (eighteenth century). For flexibility, it should be noted that Lavoisier's text will be used as a reference when discussing key principles in modern chemistry and will not be based on the complete historical timeline for the Law of Conservation of Mass. This afforded liberty will allow the concepts to be rationally connected to one another while retaining its historical essence. At the introductory level, a combustion is a type of chemical reaction in which a substance combines with oxygen to form one or more oxygen-containing compounds; the reaction often causes the evolution of heat and light in the form of a flame.[7] Lavoisier explored the combustion of several substances which included *le phosphore* (phosphorus), *le carbone* (carbon), *l'hydrogène* (hydrogen), *la cire* (wax), et *l'huile d'olives* (olive oil) which confirmed the results of earlier experiments leading to the proposal of the Law of Conservation of Mass. The Law of Conservation of Mass states that matter is neither created nor destroyed in a chemical reaction (*e.g.,* combustion reaction).[7] Lavoisier was able to carefully measure the mass of each reactant before the reaction occurred and the mass of products obtained after the reaction completed. In each instance, Lavoisier obtained a mass of products which was equal to the mass of the starting reactants. Although never specifically written, "matter is neither created nor destroyed during a chemical reaction"; these observations led Lavoisier to include this underlying principle as a central theme in his text. This phenomenon was termed the Law of Conservation of Mass and this law helped contribute to the particulate nature of matter that scientists accept today. In fact, Lavoisier's results in *Traité* were cited by John Dalton as he proposed Atomic Theory in the early nineteenth century which states that each element is composed of tiny indestructible particles called atoms, that all atoms of a given element have the same mass and other properties, and that atoms combine in simple, whole-number ratios to form compounds.[8] To further illustrate the significance of Lavoisier's observations, consider the reaction between hydrogen (H_2) and oxygen (O_2) yielding water (H_2O) as shown in Scheme 1. For clarity, this reaction is described using a balanced chemical equation (Scheme 1) which was not included in Lavoisier's original text. The large numbers found in front of hydrogen and water are called coefficients and tell the reader that there are two equivalents of each substance. The absence of a coefficient is understood to be one equivalent. The balanced chemical equation displays the same number of atoms on each side of the reaction arrow, reminiscent of Lavoisier's observations that matter is neither created nor destroyed during a chemical reaction.

The pictorial representation of the combustion of hydrogen using Lewis Dot Structures is shown in Figure 1. This representation shows that all the atoms in the starting materials that constitute hydrogen gas and oxygen gas at the beginning of the reaction can be found in the resulting water products. Similar to the previ-

$$2\,H_{2\,(g)} + O_{2\,(g)} \longrightarrow 2\,H_2O_{\,(g)}$$

Scheme 1. Balanced chemical equation of hydrogen combustion.

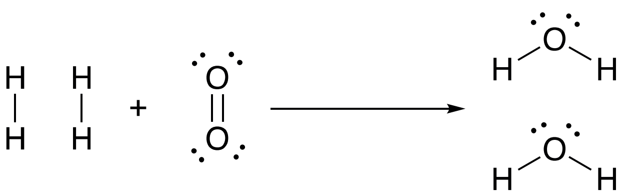

Figure 1. Pictorial representation of hydrogen undergoing combustion.

Table 1. Lavoisier's table of data describing the recorded masses of reactants and products of hydrogen combustion.

	livres	onces	gros	grains
Quantité de gaz hydrogène brûlé[a]	1	–	–	–
Quantité de gaz oxygène employé pour la combustion[b]	5	10	5	24
Quantité d'eau formée[c]	6	10	5	24

[a]Amount of hydrogen burned [b]Amount of oxygen gas used for the combustion [c]Amount of water formed.

ous example, Lavoisier's observation can be paired with another related concept (Lewis Dot Structures) discovered later, to reaffirm that matter is neither created nor destroyed. The results from various combustion reactions performed by Lavoisier helped lay the foundation for Atomic Theory.

Taking a more quantitative approach, the masses of the reactants and products were reported using the, now obsolete, Traditional French Units of Measurement (based on the Apothecaries' System), more specifically units of mass.[9] A subsection of Lavoisier's data table for the combustion of hydrogen is provided in Table 1 with English translations provided in the footnotes**.**

The table reports that Lavoisier reacted 1 *livre* of hydrogen gas in the presence of 5 *livres* 10 *onces* 5 *gros* and 24 *grains* of oxygen gas. The resulting mass of water, 6 *livres* 10 *onces* 5 *gros* 24 *grains*, is equal to the sum of the masses of hydrogen and oxygen consumed during the combustion. This observation was used to establish the foundation of the Law of Conservation of Mass.

From a historical standpoint, the Traditional French Units of Mass offer students the opportunity to learn about mass units used during the eighteenth century, well before the introduction of the International System of Units (SI Units). Historically, the mass units used during the eighteenth century varied from region to region giving rise to several different mass systems. In fact, in the 1790 English translation of *Traité*, *Elements of Chemistry* by Robert Kerr, a conversion table between the *livre* and the English troy weights is presented.[10]

$$1\ livre \bullet \frac{16\ onces}{1\ livre} \bullet \frac{8\ gros}{1\ once} \bullet \frac{72\ grains}{1\ gros} = 9216\ grains$$

Equation 1. Use of dimensional analysis for the conversion of one *livre* to *grains.*

Mathematical exercises using traditional French units can be employed to assist students in further developing their math skills and recognizing the interconversion of units. This can be accomplished by using another chemistry concept, dimensional analysis which is a method for unit conversions. For example, the *livre* can be divided into 16 *onces* where one *once* can further be divided into 8 *gros.* One *gros* can be further divided into 72 *grains.* Equation 1 shows the mathematical conversion of one *livre* to grains based on the historical conversions used by Lavoisier.

Not only can Lavoisier's text provide information about the science being performed and how it was recorded, but it can also serve as a historical record of French language evolution. Among the impactful information Lavoisier presented throughout his chapter on combustion, an "unusual" spelling motif seems to recur in Lavoisier's writing. An excerpt of *Chapitre IX* is presented with the unusual spellings underlined:

> *Mais quand on voudroit supposer que l'acide phosphorique retient encore une quantité considérable de calorique, comme le phosphore en contenoit aussi une portion avant la combustion, l'erreur ne pourroit jamais être que de la différence, & par conséquent de peu d'importance.*
>
> But when one wanted to suppose that phosphoric acid still retains a considerable caloric quantity, as phosphorus also contained a portion of it before the combustion, the error could never be anything but the difference, and consequently of little importance.

Upon reading the language used by Lavoisier in the excerpt above, the "unusual" spelling occurs when he uses the *imparfait* (imperfect) tense describing the retention of heat by phosphoric acid. The verbs conjugated in the *imparfait* tense are "incorrect" by today's standards but are spelled correctly for that time period. Each of the words are conjugated in the third person subject pronoun *imparfait* tense, referring to ongoing past events without reference to a time of starting or finishing.[11-13] Table 2 provides information about the words and their conjugations.

There is a distinct difference in spelling between the historical *imparfait* conjugation and the conjugation of today's age. Before the release of *la sixième édition du Dictionnaire de l'Académie Française* (sixth edition of

Table 2. Table of words and their third person subject pronoun *imparfait* conjugations.

Infinitif (infinitive)	English Definition	*Imparfait* Conjugation (historical)	*Imparfait* Conjugation (modern)
Vouloir	want	*vouloit*	*voulait*
Contenir	contain	*contenoit*	*contenait*
Pouvoir	can, to be able to	*pouvoit*	*pouvait*

the French Academy's Dictionary) in 1835, the *imparfait* tenses were spelled with –*oi*–, a digraph corresponding to the phoneme /ɛ/.[14] With the release of *le Dictionnaire*, words spelled with the digraph –*oi*– were respelled using the digraph –*ai*– which effectively changed the spelling of numerous words including all the *imparfait* conjugations.[15] The change was proposed by *l'Académie Française* to better match the sound the of the spoken word and its spelling.[16,17] *L'Académie Française* is the governing body of the French language and its origins can be traced back to the seventeenth century when it was established by Cardinal Richelieu under the rule of King Louis XIII.[18]

In summary, Antoine Lavoisier's *Traité élémentaire de chimie* can be utilized as an interdisciplinary teaching tool to bridge chemistry and the French language together as it provides ~~a~~ historical perspective of chemistry while highlighting the orthographical changes within the French language. The text can serve as a reference for teaching fundamental scientific concepts, historical aspects of French society, and how the French language is an ever-evolving language. This article seeks to encourage others to explore crossovers between the physical sciences and humanities which can inspire students to broaden their breadth of studies. Lavoisier has had a tremendous impact on modern chemistry and his text provides a glimpse into the history of, not only science, but of the French language as well. Given the availability across the internet, at no charge, *Traité* is a valuable resource for students of both chemistry and French and those who have an interest in interdisciplinary studies.

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Historical Article

Professor Shin Sato, a Physical Chemist and Teacher for 50 Years

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Abstract. This article presents a portrait of the scientific work of the Japanese physical chemist Shin Sato[1] (1928-2022) at Tokyo Institute of Technology from the mid-1950s until 2019. His work included studies in both photochemistry and radiation chemistry with a special emphasis on small molecules, attention given to analogies with the behavior of small molecules under atmospheric condition. Noteworthy is his contribution to a new intuitive semi-empirical method of drawing the Potential Energy Surface of the collisions between an atom and a diatomic molecule, now known as the LEPS Method. He published more on the following: photosensitization reactions of mercury, cadmium, zinc and benzene; insertion of NH radical into the C-H bond of carboxylic acid to form amino acids; the isotope effects of deuterium on the reaction of the hydrogen atom with the hydrogen molecule; ESR studies and calculations of tunneling in bimolecular reactions; developing temperature dependent rate formula for the reactions at temperatures lower than 10 K, lower than the Arrhenius equation that is applicable to temperatures higher than room temperature. Sato published a textbook on quantum chemistry, co-authored a book on photochemistry and radiation chemistry and translated from English two chemistry books. As a teacher he supervised about one hundred students in his laboratories. By his research and teaching he became a bridge between the Eastern and Western scientific and cultural worlds. He had a major impact on intercultural dialogue.

Keywords: Shin Sato, physical chemistry, LEPS method, photochemistry, radiation chemistry, Tokyo Institute of Technology.

INTRODUCTION

During 1972-1973 the author, a recent graduate from the chemistry department, The Hebrew University of Jerusalem, held a UNESCO and Japanese government fellowship in chemistry and chemical engineering course. I arrived at the Tokyo Institute of Technology (T.I.T.) in Tokyo with twelve other UNESCO fellows. Following introductory conversations with several professors, Shin Sato was chosen to be the mentor for my research in his laboratory. This article is based upon our many years of correspondence, meetings during visits to Japan and T.I.T., and his assistance with my recent research about the history of chemistry in Japan. There are contributions from George C. Schatz, Toshiyuki Takayanagi, and Kazutaka Nakamura all of whom collaborated with Sato. The main aim here is to describe the physical chemistry research of Shin Sato, and the recognition which he received.

The paper consists of two sections:

The first section covers "Shin Sato's Biography and Scientific Career."

The second section is somewhat personal in that it discusses how "Sato Followed my Career, and my Literary Writing, and Mentored my Japanese Studies." Sato followed my progress in other scientific directions. I returned to the T.I.T. Japan (2008) and to the International Research Center for Japanese Studies in Kyoto (2009-2010), in order to study the history of chemistry, and Sato graciously helped me in research, the language, and the culture and history of Japan. I emphasize the importance and extracurricular benefits of students' exchange programs, and research grants to visit foreign countries.

1. SHIN SATO'S BIOGRAPHY AND SCIENTIFIC CAREER

Sato's Biography

Shin Sato was born in Yokohama in 1928 (his birth year is 辰 *tatsu*, dragon in the Japanese calendar). He was the second son of four siblings: an elder brother, a younger brother, and a younger sister. In 1954 he married a childhood friend who was a pianist. He had two daughters. His elder daughter became a musician and his younger daughter studied physics and worked for an electronics company.[2]

Sato's Professional Curriculum Vitae

Shin Sato's academic career was mainly at the Tokyo Institute of Technology in Tokyo: He graduated in 1951; was Assistant professor, Department of Chemistry, 1956 -1960. He was appointed Doctor of Engineering (D.Sc.) in 1960; Associate professor, Department of Chemistry, 1961-1963; Associate professor, Department of Applied Physics, 1964-1981; Professor, Research Laboratory Nuclear Reactors, 1981-1988.

In according with the regulations of the governing body of academic institutes, at age 60 years, in April 1989 he retired from T.I.T. to become professor emeritus at T.I.T. He then became a professor at the College of Arts and Science, Chiba University 1988-1993. He then taught chemistry at a private university.

Figure 1. Shin Sato's photo taken by M. Kaji, at K. Shibuya's house, 2008.

Sato spent two periods out of Japan: as a postdoc fellow, 1956 Sep.-1958 Dec., and as a visiting scientist, 1965-1966., both at the National Research Council (NRC), in Ottawa, Canada.

In 1975, he received the Teshima Award, which was given to an instructor at T.I.T.

He served as President, of the Japan Society of Radiation Chemistry during 1987-1989.[3]

What was the scientific context in which Shin Sato developed his chemistry knowledge, worked at the T.I.T. and who was his teacher? Before presenting Sato's research, a short paragraph on Tokyo Institute of Technology is called for.

Tokyo Institute of Technology

Tokyo Institute of Technology (東京工業大学), *Tōkyō Kōgyō Daigaku* (now Tokyo Tech) is a national research university located in the Greater Tokyo Area. Tokyo Tech is an institute for higher education in Japan dedicated to science and technology, one of the first five Designated National University Corporation started in 2017: (Tokyo University of Tokyo (founded 1887); Kyoto University (1892); Tohoku University (1907); Nagoya University (1939) designated in 2018); Tokyo Institute of Technology (designated in 2018). It is one of the most prestigious universities in Japan. Since 1924, Tokyo Tech's main campus has been located at Ōokayama, on the boundary of Meguro and Ota, with its main entrance facing the Ōokayama railway station. Its history goes back to 1881 when the government of Japan founded a Vocational School, 13 years after the Meiji Restoration (1868). During the years it went through several changes of name and size; its name was changed to Tokyo Technical School in 1890, Tokyo Higher Technical School in 1901, and Tokyo Institute of Technology around 1946. Currently it has two other campuses.[4] The alumni of T.I.T. share a kindred brotherhood, especially when they happen to meet, even if they did not know each other before.

Physical Chemistry and Sato

Progress in Japanese chemistry and physical chemistry was outlined by Furukawa (2017) and Kikuchi and Siderer (2021). In the case of Shin Sato, he followed in the footsteps of "Professor Shōji Shida (1912-2001), who graduated from Kyoto University, and arrived at the Laboratory of Physical Chemistry, Tokyo Institute of Technology in 1952. Shin Sato was one of Shida's students. They published several articles and a book together."[5] (Kikuchi and Siderer (2021)).

Sato's Main Fields of Research

In a letter by Sato to the author on 16 July 2017 he wrote:

> I am still alive, writing the history of my research work over 65 years.
> LEPS method, Reaction of oxygen atoms with olefins, Benzene photosensitized reaction, Theoretical calculation of G-values, Radiation chemical reactions in liquid carbon dioxide and in liquid nitrogen, Empirical rate formula for low temperature reactions and ion-molecule reactions, and so on.

The following is Sato's summary, an adapted translation into English by Kazutaka Nakamura, his former student. It includes the relevant article numbers from Sato's list of publications (Appen.1.), including some of his, and others' comments on his articles.

> Sato: "If we divide the world of physical chemistry into three fields: structure, physical properties, and reaction, the field I have been involved in belongs to the reaction category."

After becoming a special research student, Sato participated in research on "recombination reactions of hydrogen atoms on metal surfaces," which is the basis of solid catalytic reactions. Therefore, his study was exclusively on reaction kinetics. He read books such as "The Theory of Rate Processes" by H. Eyring. Sato wrote:

> At that time, I proposed a new method for drawing potential energy surface, now known as the LEPS (London-Eyring-Polanyi-Sato) method. It was widely used in the kinetics and dynamics of chemical reactions and still often appears in papers. In the 38 years since then, there are more than 200 articles including books and commentaries, but not one paper has been cited by overseas researchers to the same extent as this letter.[6]

Sato published his first letter to the editor of the International *Journal of Chemical Physics* "On a New Method of Drawing the Potential Energy Surface" in March 1955 (received December 1954). He extended that letter into "A New Method of Drawing the Potential Energy Surface" in the *Bulletin of the Chemical Society of Japan*, in Sept. 1955. His third letter on this topic was published in the *Journal of Chemical Physics* in December of the same year.

In those letters he addressed the Energy Potential curve that was started by Morse, writing a semi-empirical equation for the anti-bonding energy for a reaction of molecule-atom collision, for which, he wrote, there was not an approximation function. "For the potential energy of the system of three atoms London derived an equation which has been used by Eyring *et al.*" Sato made some slightly different assumptions and derived a new equation for energy. He calculated and showed a figure of the Potential Energy Surface of H_3. The result obtained differs essentially from Eyring's one which has two saddle points and one basin; Sato's result coincided with that of a nonempirical calculation. (Glasstone et al. (1941) and Ref. 3 therein: Hirschfelder, (1937)).

In the introduction to the second letter Sato explained the need for an approximate function for the anti-bonding states of two atoms:

> When two atoms approach each other, there appear two energy states generally: the one is bonding and the other anti-bonding. The potential energy for the bonding state can be obtained experimentally as a function of the distance between two atoms. As is well known, the curves for many diatomic molecules are conveniently approximated by the Morse function (P.M. Morse, (1929)). For the anti-bonding state, however the curve cannot be obtained experimentally and the function is not yet proposed. The present author researched the function and found that the equation [of a modified Morse equation] is in good agree-

> ment with results previously calculated by other authors (Appen.1. no. 4 (1955), Refs. 3 and 4 therein: H.M. James (1937) and J. O. Hirschfelder (1950)) The applicability of that function for the anti-bonding states of other diatomic molecules cannot be ascertained because of no existing data…." (Appen.1. no. 4 (1955)).

The third letter on this topic that dealt with "Potential Energy Surface of the System of Three Atom." Different reagents were used, e.g., H+HX→H_2+X, whereas X=H, Cl, Br, I, and F+H_2 →HF+H). Sato showed the validity of his semi-empirical equation in these cases (Appen.1. no. 5 (1955), Table 1).

Early Scientific Recognition of "A New Method of Drawing the Potential Energy Surface (1955) LEPS Method"

Sato's work on Potential Energy Surface of the System of Three Atoms (1955), led to the modified LEP term into LEPS (London-Eyring-Polanyi-Sato Method), (H. S. Johnston (1966)).

H. S. Johnston wrote:

> This equation is based purely on intuition… Thus Sato's potential-energy surface for H_3 is a complete potential-energy surface that appears to be qualitatively correct…
> …This Semiempirical method does not predict activation energy. Its evaluation of other properties of the saddle point will be compared with other methods in a later section, where it will be referred to as the LEPS (London-Polanyi-Eyring-Sato) method (Johnston (1966) p. 179).

The LEPS method and Modified LEPS method calculations were further studied and published by Sato's group in 1988 and 1990.[7]

Recollections of Shin Sato by George C. Schatz[8]

Schatz recalls:

> I was a graduate student at Caltech in the early 1970s, at a time when it first became possible to describe the dynamics of the simplest possible chemical reactions using computational methods to solve the Schrödinger equation for the motion of the nuclei. To do these studies it was necessary to have a potential energy surface (PES) that describes the forces between the nuclei while the reaction occurs. Potential surfaces were extremely difficult to determine in those days, but one way to do it was to solve the electronic Schrodinger equation using semiempirical theory, in which the complex parts of this equation were replaced by approximate functions that were based on a combination of physical intuition and guessing. It turns out that for reactions involving an atom colliding with a diatomic molecule, this was first done in the late 1920s and 1930s by the famous scientists London, Eyring and Polanyi, leading to a function called the LEP potential. However it was subsequently demonstrated that this function had unphysical features, so it wasn't useful for studying reactions. However in 1955, Shin Sato published a paper (J. Chem. Phys. 23, 592 (1955)) that modified the LEP expression in a way that fixed the most serious problems with LEP, leading to what was known as the LEPS potential surface. I used this function in some of my studies in the 1970s, and as a result I was aware of Shin Sato, but I never thought I would meet him.

Sato's Experience in Canada

In September 1956, Sato went to Canada to study at the National Research Council of Canada in Ottawa. At that time, his mentor was Prof. R. J. Cvetanović, who was forming oxygen atoms by photochemical methods and studying their reactions with olefins. Cvetanović was one of the leaders in photochemistry at that time and Sato was attracted to his line of work. Under his supervision, Sato photolysed NO_2 with ultraviolet light (high-pressure mercury lamp) to form oxygen atoms and investigated their reactions with various olefins.[9]

> Sato: "This was around the time that photochemical smog began to become a problem. Cvetanović's work on the reaction of oxygen atoms with hydrocarbons has now become a classic, but it is very famous in this field. Since that time, I had wanted to work on reactions involving nitrogen atoms."

Sato joined Cvetanović laboratory for a second time (1965-1966), when he worked on "Intersystem Crossing of the Electronically Excited Dideuteroethylene Molecules Formed in Benzene Photosensitization." This was collaboration between the research carried out at T.I.T. by Terumi Terao and Shun-ichi Hirokami of Sato's group, and the work he carried out in NRC Ottawa. (Appen.1. no. 29 (1966). In the introduction the authors explain:

> Electronically excited states of olefins are formed when olefin molecules absorb ultraviolet light either directly or from photosensitizers. The chemical behavior of the excited states depends both on the amount of energy transferred and on the nature of the sensitizer employed. With ethylene the following reactions are observed: (i) *cis-trans* isomerization (in the reaction of *cis-* and *trans*-1,2-dideuteroethylene), (ii) internal H-atom scrambling (formation of 1,1- from 1,2-dideterroethylene), (iii) molecular decomposition into H_2 and acetylene, and (iv) decomposition into H-atoms and vinyl radicals.
> Studies of these chemicals processes present an interesting opportunity to gain insight into the nature and behavior of the excited states involved.

A previous article by Cvetanović is referred to (Cvetanović 1964).They present the results of the benzene-photosensitized isomerization of dideuteroethylene at room temperature.

They showed experimental evidence for a rapidly occurring intersystem crossing of the electronically excited dideuteroethylene molecules initially formed in the benzene-photosensitized reaction at 2537 Å and 25°C to another excited state which is responsible for the internal H-atom scrambling. They concluded that the mechanism is entirely analogous to that previously postulated for the photoexcited states sensitized by $Hg(^3P_1)$ atoms but the rate constants for intersystem crossing and molecular decomposition are drastically decreased as a result of the smaller amount of energy available for the excitation (Appen.1 no. 29 (1966)).

Back In Japan

After returning to Japan in December 1959, Sato found that radiation chemistry had become the main research subject in Shida's laboratory at T.I.T. He participated in radiation chemistry research, starting with "Radiolysis of Cyclohexane." His Doctoral Dissertation (D.Sc.) was "Research on the reaction between oxygen atoms and olefins" Tokyo Institute of Technology Academic Bulletin, (1960) first issue; 酸素原子とオレフィンの反応の研究、東京工業大学学報、１９６０年　第一号。博士論文.

Sato summarized the effect of the change in Shida's lab to radiation chemistry and later observed: "Thus, after becoming an associate professor in January 1961 and running an independent laboratory, I was engaged in research in both the fields of photochemistry and radiation chemistry. My subsequent papers have been almost equally divided between photochemistry and radiation chemistry."

Photochemistry Research

Photosensitization reactions

In a series of articles Sato's groups studied the mechanism of photosensitization by mercury, cadmium, zinc and benzene, and the combination of the photoexcited state with molecules like water, alcohols, ethers, cyclohexane and others. This method allowed them to better understand the mechanism of energy charge transfer, life time of excited state of the intermediate that was formed between the photoexcited reactant and the molecule it collided with, the emission of light from the combined intermediate excited species and/or their dissociation.

A useful introduction to this area of work can be read in Calvert and Pitts *Photochemistry* (1966), on Sensitized Fluorescence.[10] Calvert and Pitts further explained and showed relevant results and suggested mechanisms for those results.[11]

In the following, examples from Sato's laboratory of photosensitization reactions and their mechanisms are summarized.

Mercury Photosensitized in Sato's laboratory

Photosensitization by mercury in Sato's laboratory was carried out between 1960 and 1978, starting with "Mercury Photosensitized Decomposition of Cyclohexane at High Temperatures".[12]

In the mercury photosensitization experiments in 1978, in addition to demonstration of charge transfer another phenomenon of the complex emission was studied in "Phase-Shift Studies of Mercury-Photosensitized Luminescence of Ammonia" (Appen. 1. no. 103 (1978)). For an introduction to phase-shift see Note 13. This article is summarized here:

In the introduction to a 1978 article by Sato and coauthors, they surveyed seven articles in this field dating 1970-1977 (Refs. there). The introduction is followed by a detailed experimental section on the instruments and measuring methods, as well as materials purity and their sources. Two emission lines were detected at 282 nm and 350 nm, attributed to two intermediate excited complexes of the excited mercury with ammonia, labeled $HgNH_3\dagger$ and $HgNH_3{}^*$, an unstabilized and a stabilized intermediate respectively. The phase-shift between the photosensitized luminescence of each of these spectral lines and the light emitted from the excited mercury atom were measured. Fig. 2 of the article presented phase difference between the 253.7 nm fluorescence from the excited complex at 282 nm and 350 nm as a function of the ammonia pressure. Solid lines show the values calculated according to equations (9) and (10) of the proposed reaction mechanism.

Cadmium Photosensitization

The reactions of Cd photosensitization, measuring the emission from the complex between the photoexcited triplet Cd with ammonia, amines, water, ethane, and ethylene, was studied. (Appen.1 no. 81 (1975))

This research was mainly conducted with Shigeru Tsunashima (later to become professor of the Department of Applied Physics, T.I.T.), and was completed around 1980 with about 20 papers published.[14]

Two examples follow:

1. Cadmium Photosensitization of Aliphatic Amines

In Shunzo Yamamoto and Sato's article, "The Quenching of the Cadmium Resonance Radiation at 326.1 nm by some Aliphatic Amines and the Cadmium-sensitized Luminescence of These Amines." (Appen. 1. no. 78 (1975)), they described their experiments and findings as outlined in the following:

> From the pressure dependence of the intensity of the 326.1 nm resonance line, [Table 1 there], the efficiencies of the quenching of the resonance line by methylamine, ethylamine, n-propylamine, n-butylamine, *sec*-butylamine, *tert*-butylamine, diethylamine and trimethylamine were estimated to be 14.2, 36.0, 58.6, 71.2, 116.7, 434.5, 69.6, and 66.0 respectively, the efficiency of ammonia being assumed to be unity [Fig. 3 there]. The relative values of rate constants for the formation of the excited complexes between the excited cadmium atoms and the amines, and the wavelengths at the peaks of the emission bands from the complexes, were measured [Tables 2 and 4 there]. The quantum yields of luminescence were also measured by comparing the integrated intensities of the emission bands with the decrease of the intensities of the resonance line at 326.1 nm upon the addition of amines. From the relationship between these values and the structure of the amines, it is concluded that the complexes are of the charge-transfer type.

In their discussion they present a reaction mechanism similar to the mechanism they showed before that explains their findings and interpretation. (Appen. 1. no. 77 (1975)). The mechanism involves cadmium excitation by light, its collision with argon or amines to give products, and in addition, the excited cadmium atom and amines collisions that form two excited intermediates, an unstabilized and a stabilized complex between the triplet cadmium and the amines. The evolving luminescence is emitted from the stabilized complex whereas the unstabilized complex does not fluoresce.

2. Cd Photosensitized Reactions of Water, Alcohols and Ethers

In a following article in the same year: "The Cadmium-photosensitized Reaction of Water, Alcohols and Ethers – The Quenching of the Resonance Radiation at 326.1 nm and the Photosensitized Luminescence" (Appen.1 no. 81 (1975)), after summarizing their previous two related articles, Sato and his co-authors stated:

> It now seems valuable to observe the similar luminescence in the cadmium-photosensitized reactions of water, alcohols and ether, to measure the rates of the quenching of the resonance radiation and of the formation of the complex, and to determine the effects of the structure of the alcohols and ethers on the quantum yields of the luminescence and the position of the emission band, in order to gain a further understanding of the cadmium-photosensitized luminescence.

They showed the emission band contours for H_2O, methanol and ethanol in Fig. 1, including NH_3 emission graph from their 1973 article (Appen.1. no. 68 (1973)). In Table 1 they present the wavelengths at the peak of the emission band and quantum yield of the luminescence. Table 4 shows the rate constants of the quenching of the resonance radiation and of the formation of the complex for Primary-, Secondary-, and Tertiary Amines. A mechanism similar to that described in previous papers (Appen. 1. no. 77 (1975) and Appen.1. no. 78 (1975)) is presented, followed by discussion of the rate constants of the various steps in the mechanism suggested. In a final statement they mention a factor that affects some of the results which is still an open question for them.

Benzene Photosensitization[15]

For benzene photosensitization article an example is given above in the section about Sato second visit to Canada.

Zinc Photosensitization[16]

The article on "The intramultiplet mixing of $Zn(4^3P_J)$ by collision with ^4He and ^3He" employed pulsed laser techniques. Several cross sections of the collisions between the zinc triplet and the helium isotopes were assumed and calculated (Appen. 1. no. 179 (1990)).

Photochemical Reactions Research Continued

Amines Formation[17]

In a series of articles by Sato's group including Shigeru Tsunashima, they showed the insertion of the NH radical into the C-H bond of olefins and C-H bond of carboxylic acids. NH radical was formed by the photolysis of hydrogen azide HN_3, and the insertion of the NH radical to the C-H bond of olefins producing amines: ethylamine from the ethane solution, propyl amine and isopropylamine from the propane solution, and isobutyl- and t-butylamine from the isobutane solution (Appen.1. no. 108 (1979), Appen.1. no.117, (1980)).

Amino Acid Formation

In a further study they conjectured that if the singlet NH inserts into the C-H bonds of hydrocarbons, the singlet NH will insert into the C-H of carboxylic acids to form amino acids. It was considered that the formation of amino acids on the primitive earth is an interesting problem in the study of prebiotic molecular evolution. Thus, they could further show by the photolysis of hydrogen azide, NH_3, in the relevant solutions, the insertions of NH radical into C-H bonds of carboxylic acids that produced amino acids: glycine was formed from acetic acid, α- and β-alanine formed in the case of propionic acid (Appen. 1. no. 120 (1981)) and isobutyric acid, α-and β-aminoisobutyric acids are formed, which correspond to the two types of the C-H bonds involved in the carboxylic acid. They suggested the chemical mechanism for these reactions, and showed that the quantum yield of amino acids increased with an increase in the number of C-H bonds in the reactant acid. They concluded that their study suggests a new possibility of the prebiotic synthesis of amino acids on the primordial earth (Appen. 1. No. 125 (1981)).

Discussion of the Photochemistry Reactions

In *Photochemistry* by Jack G. Calvert and James N. Pitt's textbook they explained and summarized the works in photochemistry since books dated more than twenty years earlier and emphasized: "During this period the primary literature of photochemistry has progressed at a phenomenal rate." (Calvert (1966) Preface, p. vii).

Describing the content of the book, its authors wrote: "In chapter 2 the reactions of the electronically excited atoms, conceptually the simplest of the photochemical systems, are studied. In chapter 3 the photochemistry of simple molecules and in Chapters 4 and 5 the photochemistry of more complexed molecules are covered." They cited several of S. Sato articles in chapters 2 and 3.[18-20] (Calvert (1966)).

Specific discussion in a photosensitized article was presented in 1971, in an article on "Photosensitization by Cd($^3P_1$) atoms. II. Gas Phase Decomposition of Cyclohexane" by B. L. Kalra and A. R. Knight, in which they discussed Sato's group articles on mercury and cadmium photosensitization. (Appen. 1. no. 16, and Appen.1, no. 35) (B. L. Kalra and A. R. Knight, (1972)).

Radiation Chemistry Research

The Cobalt-60 source for γ-rays radiation that was used in the chemical experiments stood in the basement of the radiation laboratory building. Sato's office, the vacuum systems laboratory and measuring instruments were on the second floor.

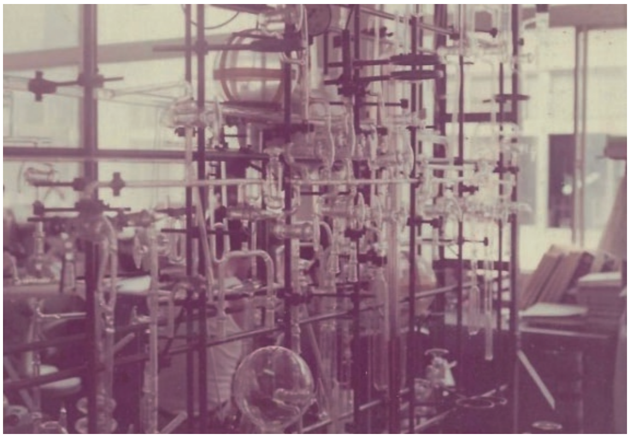

Figure 2. The vacuum system in Sato's radiation chemistry laboratory: Used by the author in 1972-73.

In the study of radiation chemistry, efforts were made to clarify the initial process of radiation chemical reactions, focusing on the γ-ray decomposition of cyclohexane.[21] Among these experiments, the study of the formation mechanism of N_2 by adding N_2O to cyclohexane and showing that electrons play a role in the initial process attracted considerable attention. Sato commented: "It is not surprising in hindsight, but in the late 1960s it was not believed that electrons could be observed as a manifest [of] chemical reaction in the radiolysis of hydrocarbons." In July 1974 Sato went to Seattle, to attend the 5th International Congress of Radiation Research and presented a paper on the reaction of CO_2.

Theoretical Calculation Method of G-values[22]

In the field of radiation chemistry Sato developed the "theoretical calculation method of G-values" with Dr. Shinichi Ohno of JAERI (Japan Atomic Energy Research Institute) and Dr. Kiyoshi Okazaki (Appen. 1. no. 73 (1974)). The study of the G-value of other reactions were further studied[23] which attracted attention from abroad. For this research Sato received The Seiichi Teshima Memorial Research Award that is designed to encourage research at the National University Corporation's Tokyo Institute of Technology, and is awarded to individuals who have achieved particularly outstanding research and writing.

This work continued, by comparing theoretical and experimental results. Sato later added: "The theoretical calculations were done by Mr. Okazaki's calculation of the G-value, and Mr. Takayanagi's trajectory calculation and my long-standing thought have come to fruition."

Sato observed in retrospect: "The next 10 years [1970s] will be the most productive time for me. The lab was poor, but the ideas were plentiful." Another frank, revealing statement that he wrote: "Experimentation is creation every day. I strengthened my imagination so as not to lose to the creativity of the students." [24]

In the 1970s, Sato's laboratory began to receive research grants and modernized its measuring instruments. The first of these is the Febetron 706 electron accelerator (pulse width: 3 nanoseconds, current: 6000A), which, in combination with a vacuum ultraviolet spectrometer, makes it possible to measure "elementary reactions involving atoms" in real time. As a result, they were able to study the reaction of hydrogen atoms, the isotope effects of H and D, the reaction of oxygen atoms, and the reaction of nitrogen atoms. Sato added: "I had been thinking about [those] for a long time. Nitrogen atoms are difficult to generate photo chemically and have not yet been fully investigated.

Around this time, Dr. Tsunashima and Dr. Hironobu Umemoto (a research associate in the Department of Applied Physics at that time) developed a method to apply the phase-shift method to photochemical reactions, making it possible to directly measure rate constants in photochemical reactions.[25]

Electron Spin Resonance (ESR) Research

Still in the 1970s, Sato was able to receive another Grant-in-Aid for Scientific Research, which enabled him to purchase an Electron Spin Resonance (ESR) absorption spectrometer and at the same time to set up research facilities at low temperatures such as liquid helium. Several works using ESR were published.[26] Thus, they were able to measure the tunneling effect that appears in the reaction of hydrogen atoms, which Sato wrote that he had dreamed of 30 years earlier, and that the tunneling effect is far greater than usually believed.

ESR Studies Discussed by K. Nakamura[27]

> In Sato's lab, both the photochemistry and radiation chemistry were studied at low temperatures using ESR. The structure of cation radicals, which are produced by radiolysis with Cobalt-60 γ-rays radiation in Freons and SF_6 matrices, has been studied at 77 K (Appen.1. no. 135 (1983), no. 142 (1985), no. 145 (1985), and no. 146 (1986)). In photochemistry, bimolecular reaction of H-atom with simple molecule such as SiH_4 has been studied in a rare-gas matrix at very low temperatures between 4.2 and 100 K. Structures of SiH_5 were found to be an intermediate with two conformers during the hydrogen abstraction reaction ($H+SiH_4 \rightarrow H_2 + SiH_3$). (Appen.1. no. 144 (1985)).[27]

G.C. Schatz's letter of 22.12.2023 continues:

> In 1985, I spent two months in Japan as a result of being granted a travel award from the Japan Society for Promotion of Science (JSPS). By then I was at Northwestern University, and my primary reason for visiting was to interact with a former office mate of mine (when I was a postdoc at MIT), Kazuo Kitahara. As a result I spent some time at Tokyo Institute of Technology, where Sato was located his entire career. It was during this time that I met Sato, who was actively involved in radiolysis studies in which radiation was used to produce deuterium atoms in matrices of solid H_2 at temperatures of 2-5K. This leads to the reaction $D + H_2 \rightarrow HD + H$, which is slightly downhill in energy due to the difference in zero point energy between H_2 and HD, and therefore has a measurable rate using electron paramagnetic resonance spectroscopy. Sato's research group had measured this rate, and was trying to interpret the results using transition state theory. By then my research had led to the determination of highly accurate rate coefficients (better than transition state theory) for $D + H_2$ and other reactions, including results at the very low temperatures that Sato was interested in, so I was able to help Sato to improve his modeling, leading to an accurate comparison of Sato's experimental results with first principles theory. The good agreement obtained suggested that even though the Sato experiments were done in a low temperature matrix, one could understand the rate based on assuming the rate was governed by a collision between D and H_2 without interacting with anything else. Moreover we were able to show that the resulting rate coefficient was largely governed by the "Wigner threshold law" of quantum mechanics, which refers to collisions that take place in the very low temperature limit (Appen. 1. no. 156 (1987)).

Quantum mechanical tunneling for the $H + H_2 \rightarrow H_2 + H$ reaction and its isotopic analogues in solid hydrogen.

Toshiyuki Takayanagi's memories follow: [28]

> My research career with Sato started in 1985. Sato was an experimentalist in physical chemistry field, but he was very familiar with theoretical chemistry. When I joined his research group, he was very interested in the experimental study performed by Prof. Tetsuo Miyazaki at Nagoya University, who found that the $D + H_2 \rightarrow HD + H$ reaction occurred in solid hydrogen at timescale from several minutes to hours at very low temperatures around $T = 4$ K. Notice that this reaction is an isotopic analogue of the $H + H_2 \rightarrow H_2 + H$ hydrogen exchange reaction, which is also

> the simplest chemical reaction consisting of only three atoms. Accurate ab initio molecular orbital calculations have already shown that the reaction barrier of this reaction was around 10 kcal/mol. This suggests that quantum mechanical tunneling should be playing an important role in order to explain the experimental result in solid hydrogen performed by Miyazaki's group. This is a primary hypothesis made by Sato. So the next project is to calculate the thermal rate coefficients for the $H + H_2 \rightarrow H_2 + H$ and its isotopic analogs at very low temperatures as accurate as possible and then to compare to the solid state experimental results performed by Prof . Miyazaki. These theoretical calculations were a part of my PhD thesis.
>
> Accurate calculations of thermal rate coefficients for the $H + H_2 \rightarrow H_2 + H$ and its isotopic analogs in the gas phase have long been very important subjects in the theoretical chemistry field. Fortunately, very accurate ab initio electronic structure calculations of the full-dimensional potential energy surfaces have been already done. Using the developed potential energy surface, quantum reactive scattering theory has been applied to calculate accurate reactive cross sections as well as thermal rate coefficients. George C Schatz and Aron Kuppermann have developed a sophisticated theory to perform accurate multi-dimensional quantum reactive scattering calculations for the first time. In 1987, Prof. Schatz was temporarily staying at Tokyo Tech for three months and Schatz and Sato have started a collaboration work on the calculations of rate coefficients for the $H + H_2 \rightarrow H_2 + H$ and its isotopic analogs at very low temperatures.
>
> Needless to say, it is a very daring conjecture that the gas phase chemical reaction rate theory is applied to the solid state reaction. However, Sato believed that the gas phase theory could be approximately applied since the molecular density is not so large in solid hydrogen. In an early stage of the computational work, a simple transition state theory including sophisticated multi-dimensional tunneling correction was used to calculate the rate coefficients at low temperatures. Later, multi-dimensional quantum reactive scattering theory was applied. Through a series of those theoretical projects, we succeeded in explaining the experimental findings by Prof. Miyazaki; i. e., it was definitely established that quantum mechanical tunneling was playing an important role for the $H + H_2 \rightarrow H_2 + H$ and its isotopic analogs at very low temperatures (Appen.1. no. 170 (1989), Appen.1. no. 173 (1989), Appen.1. no. 176 (1990)).

On 27 January 1987 Sato wrote to the author: A week ago, I was very busy because I organized a small seminar for the reaction kinetics. Nearly 50 people (all Japanese) joined the meeting and discussed for three days. I believe that the meeting was fruitful.

It is interesting that, apparently, he appears not to have discussed the relations between photochemistry and radiation chemistry despite his research on small molecules in both cases.

Sato Theoretical Work

During his last twenty year, Sato has been working on theoretical calculations. He wrote: "I would like to continue my research mainly on theoretical calculations in the future."

After his retirement during the years 2004-2019, he published six articles as a sole author (Appen.1. no. 181, (2004)[29] and Appen. 1. no. 182 (2005)). Then followed the articles (Appen. 1. no. 183, Appen.1. no. (2011), Appen.1 no. 184 (2016), Appen.1. no. 185 (2017)[30] and Appen.1. no. 186 (2019)).

In a short paper in the journal Radiation Chemistry放射線 化学 issue 80 p. 6 (2005) that Sato titled: 雀百まで (What is learned in the cradle is carried to the tomb), he discussed his two recent articles: on "Cumulative Reaction Probability N(E) as Estimated from Empirical Bimolecular Rate Constant k(T)" (Appen.1. no. 181 (2004)) and on "Tunneling in Bimolecular Reactions" (Appen.1. no. 182 (2005)).

Those two articles were written after Sato's retirement. Sato used to visit the library of Tokyo Tech to study in the morning. At lunch time, he came to visit Professor Kazuhiko Shibuya in his office at the Department of Chemistry with a lunch box that he bought in the cafeteria. He knew that Shibuya ate lunch in his office. Over lunch, they talked about a lot of things, research, friends in the academia, foreign countries, etc. They became good friends.[31] Sato mentioned discussion with Kazuhiko Shibuya[32] and acknowledged him and Dr. Mitsuhiko Takasawa in (Appen.1. no. 182 (2005)). Shibuya married Yumiko Sato (not Shin Sato's daughter) who is my good friend since she was the coordinator of the UNESCO Chemistry and Chemical Engineering Course at T.I.T. in 1972-73 (Figs, 3, 4. and 6).

In a letter to the author (9.4.2020), Sato wrote:

> I have been working for last few years to make temperature dependent rate formula for the reactions at low temperatures which are lower than room temperature reaching 10K. As you know, Arrhenius equation is applicable to the reactions at temperatures higher than room temperature. For the reaction rates at the temperatures lower than room temperature, Arrhenius equation has been modified without little success. Three papers for this problem have been published in the Journal, Chemical Physics 49 469-470 (2016); 45 487 (2017); 525 110358 (2019). If you find out interest in them, please read these papers which are written with poor English containing many mistakes in the numbers so on (Appen.1. no. 184, (2016), no. 185 (2017), no. 186 (2019)).

In those last articles he presents the equations which he developed or improved, and shows graphs containing data from his laboratory or quoting others' data, checking the agreement between the theory and the experimental results.

In 2019, in the conclusion to his last article Sato wrote:

> Conclusion
> Proposed empirical rate formula (4) was found to be able to express all experimental data of ion-molecule reactions and low-temperature-high-speed reactions taken up in this paper. Since the existence of Wigner's limits was ascertained, the rate constants could be expressed from very low temperature such as ~10 K to high temperatures ~1000 K. As a result, several comments could be revealed. (Appen.1. no. 186 (2019)).

Books Authored by Shin Sato are in Japanese[3]

In addition to the research articles listed in appendix 1, Sato published and translated several books. Their details, original Japanese titles and titles in English are listed in appendix 2. They include:

1. Text books *Photochemistry and Radiation Chemistry* (**1966**, co-author Shōji Shida, Appen. 2, no. 1).
2. *Quantum Chemistry* (**1974**, Appen.2, no.2,). In this book he included a short explanation to the LEPS method. Each of the 13 chapters is followed by questions; selected answers are given at the end of the book.
3. Co-authored *Introduction to Modern Chemistry* (**1992**, Appen.2, no.3).
4. Translated into Japanese: *"Chemical Kinetics and Dynamics"* (**1995**, Appen.2 no. 4).
5. Co-authored translation of "*Reactions in Quantum Chemistry* (**1998**, Appen. 2. no. 5), see below, Schatz telling about the effect of the translation of his book into Japanese.

Other publications, not listed in Sato's Lists of Publication and books (Appendix 1 and Appendix 2), including review article, commentary, translation, shared writing, etc. are listed in Supplementary Material of Prof. Shin Sato.

Laboratory Life: Shin Sato's Attitude to Students and Colleagues

I have counted 100 names of students and colleagues who were co-authors of Sato's articles during 1954-1991. The impact of all those former students in Japanese academy, industry and commerce, government and prefectural offices, teaching in colleges and high schools should be appreciated. Among them, co-authors that I knew in 1972-1973: I. Yasumori, S. Tsunashima, Y. Hatano, K. Hosoya, K. Okazaki, T. Toyono, K. Yamamoto, Y. Ishikawa, and laboratory assistant Ms. R. Yugeta. I met Y. Hatano a few years ago and learnt about his successful career.[33] Yo-ichi Ishikawa and his wife Sachiko who live in Kyoto are good friends of mine.

Sato had a sensitive human approach to his students and colleagues. Concerning a colleague who had just left the room after my arrival, Sato said: "He came to discuss his scientific and personal problems." Sato attended Okazaki's wedding and possibly weddings of other students.

Saturday afternoons in the radiation laboratory were dedicated to the Mahajan game.

We went for a short vacation to the beach in Ibaraki prefecture, in the Kantō region of the main island, Honshu (27-30 July 1973): Sato, his students and his daughters. We all lived in a local family house who also cooked meals for us. We walked along the beautiful vacant beach and avoided a nearby crowded one. Local fishermen treated us with food from shells that they had just gathered.

During the year I was Sato's student I was invited to Sato family's house in Yokohama three times. On 10th December 1972 Prof. Sato, his younger daughter and I traveled by train to Kamakura, where we met his student K. Yamamoto who lived there. After a day visiting the temples, the large Buddha statue, and the lovely gardens, we visited Yamamoto's parents' house. Yamamoto's mother humbly greeted her son's professor visiting their house by kneeling at the entrance door. We continued early evening by Yamamoto's car to Sato's house in Yokohama. In the house, the eldest daughter played the piano. We ate a good supper, listened to records of Israeli songs, and watched a TV movie telling of samurai war eight hundred years ago. On 7th January 1973 Professor Sato invited his present and past students to his house. Together we all went to a Chinese restaurant and returned to the house to play Mahajan. In September 1973 Sato invited his students to his house before the start of the school year and my departure. I do not know whether other professors treat their students with hospitality at home, but I appreciate very much his invitations to me and others.

In 2017 Sato advised me that Tsunashima passed away after a heart attack. Tsunashima became professor of the Applied Physics department after Sato moved to the Department Research of Nuclear Reactors. After the department's change they continued their collaboration and worked together for more than fifty years.

In the 1970s Prof. Sato had two more foreign students: L. Wojnarovits, IAEA fellow 1975-1976, originally from Institute of Isotopes of the Hungarian Academy of Sciences, Budapest, and Kim Eung-Ryul_, 1977, later Professor in Hanyang University, South Korea. Going through Sato's List of Publication there are names of four non-Japanese co-authors: Y. Siderer (Appen. 1. no. 83 (1975)). L. Wojnarovits (Appen.1. no. 92 (1976)), E. R. Kim (Appen.1. no. 95 (1977)), and G.C. Schatz (Appen.1. no. 156 (1987)), coming from four overseas countries, that is, Israel, Hungary, South Korea and the United States respectively, which seems like a nice spread of guests from around the globe. Those are in addition to his articles from Cvetanović lab in Canada.

G.C. Schatz Recollection of Sato's Translation of his Book and his Attitude to Students and Colleagues:

> I got together with Sato and his research group several times during my visit, and I recall Sato as being a gentle person, who was truly dedicated to his scientific work, and helped his students to become better scientists. He was also very kind to me, which was endearing. I was acutely aware that Sato had been a teenager during WWII and probably had a very difficult time surviving, let alone become a scientist who would make important contributions to the science that I found fascinating at that time. My research interests changed after 1985, so I did not meet Sato after that visit (occasionally we exchanged letters), however two other events brought us together from a distance. One is that Sato translated a book that I wrote with my colleague Mark Ratner, "Quantum Mechanics in Chemistry", published in 1991, into Japanese. He sent me a copy, and it sits prominently on my bookshelf. Several younger Japanese scientists that I have met since then have told me that this book was influential in their careers. The other is that the lead student on our joint paper, Toshiyuki Takayanagi, was a visitor for one year in my research group in the 1995-96. We wrote several papers together, and I have kept in touch with him since then in his position on the faculty at Saitama University. Also, I have followed the field of reaction kinetics in low temperature matrices as others have continued to study this topic. Our joint paper in 1987 now has 64 citations including several in the last 5 years, so my collaboration with Shin Sato has had lasting value to the scientific community, and I am delighted that I had the chance to meet and work with him (Appen. 2. no. 5).

Shin Sato, More on His Life

From his early history Sato told me that after the war, in 1945, there was a great scarcity of food and hunger. He went with his uncle to his mother's old family village near Matsushima, Miyagi Prefecture, north-east of Tokyo. They brought back home a sack of rice, the Japanese staple food.

He regularly took a train from Yokohama to the station near the institute, Midorigaoka station, and walked to the building in which the radiation chemistry laboratory was located. Students came to study and working with him. In the afternoon he went to the South Building in which the photochemistry laboratory was located. In the late afternoon he played Japanese table games like Go and Shogi, that is, Japanese chess, with other partners from the applied physics department. Early evening he returned to the radiation laboratory. He continued supervising students in the laboratory, in which there were glass vacuum systems and measuring instruments. Early in the evening he changed his campus brown shoes to his black commuting shoes which he left in the morning near his desk, took his thin leather bag loaded with papers to be read later, and returned to the train station to Yokohama.

Sato continued his research in the Department of Applied Physics of T.I.T. In 1983 he moved as a professor to the Research Laboratory for Nuclear Reactors.

From 1974 until 2019, Sato wrote in his letters to me about his daughters growing up, then the birth of his granddaughter and great-granddaughter. He passed away in April 2022.

2. SATO FOLLOWS MY RESEARCH CAREER, LITERARY WRITING, AND MENTORS MY JAPANESE STUDIES

UNESCO group of twelve fellows from Afghanistan (2), Bulgaria, Egypt (2), India (2), Israel, Pakistan, Poland and South Korea (2) attended several cultural events and lectures and occasionally travelled out of

Figure 3. Shin Sato teaches Yona Siderer how to play Japanese Chess. Ms. Yumiko Sato (unrelated to S. Sato), UNESCO course coordinator, is watching, 1973.

Figure 4. UNESCO Course participants visit a nuclear reactor station and a nearby park, 1973.

Figure 5. Prof. Shin Sato and Dr. Yona Siderer in front of the Main Building, Tokyo Institute of Technology, 1984. Taken when I was a summer visiting scientist in Y. Inoue laboratory at Riken, the Physical and Chemical Research Institute in Saitama.

Tokyo. In one of those travels, we were accompanied by the UNESCO office staff and Sato, standing at the end of the right hand row (Fig. 4). On another tour in May, 1973, the UNESCO fellows went to Kyoto, Kobe, Hiroshima, Nagasaki, Kumamoto, Beppu and Nara, exposing us to the beauty, geography and history of Japan.

During my Ph.D. studies at the Weizmann Institute of Science in Rehovot, Israel (1974-1979), I studied the mechanism of oxygen evolution in plant photosynthesis by observing light induced room temperature changes of manganese ESR signals in chloroplasts. In a letter on 30th September 1974 Sato reflected: "…Now, I am very glad to hear that you could start to work at the Weizmann Institute. Photosynthesis is one of the most exciting fields. I sincerely hope that you make a great progress there and grow up as an excellent researcher. I know you have a great ability for this." Sato congratulated me for receiving an EMBO fellowship to London for three months, adding in an aerogram in 1977: "Please write to me your impression of England." When I wrote to Sato that I was offered a post-doc position at Princeton University he answered on 7 December 1978: "If I were you, I won't miss the chance for a next big jump."

Between 1984 and 1994 I sent Sato my poetry book that includes my painting. He reflected on those occasions in the followings letters: On 30th January 1984: "Unfortunately my English is not good enough to appreciate the nuance of your poems, but I understand the situations and feelings which you are intending to tell us." On 29th April 1993 he observed: "Two weeks ago, I received your package which contained two Hebrew books with [the famous poet Shuntaro] Tanigawa translations of your poems. I can recognise our portrait on the cover of your book. You have done nice work." On 25th February 1994 he wrote: "Since I received your books of poems and translation and a pamphlet for your paintings and poems, I was surprised by your talent. One of the paintings entitled "interior" makes me recall Matisse." On 7th March 1973, I presented Sato with the book "The Little Prince" in Hebrew for his birthday. The book is still kept among his belongings in his house in Yokohama, together with other five books including my Ph.D. Dissertation, my poems and paintings, Natsume Sōseki's book *Kusa Makura* translation that I sent him. I saw the books in his house during a visit on 13 July 2023.

Sato Follows Siderer Research and Teaching the History of Chemistry in Japan

Early in July 2008 I arrived again at T.I.T., as a recipient of a Japan Foundation Fellowship to study "the history of chemistry in Japan" in Professor Masanori Kaji's laboratory. Masanori Kaji and Kazuhiko Shibuya encouraged me to teach a course on this topic to Master's students of chemistry at T.I.T. I taught an eight meetings course during October to December 2008. Preparing the eight session course assisted my further research.[34] Kaji was first an organic chemist, eventually a very capable historian of chemistry, who studied in Russia, and made many overseas colleagues-friends. He passed away in 2016, at the age of sixty years. (Siderer, 2016).

Sato attended my lecture on "Chaim Weizmann, a Chemist and a Statesman" which I presented at the Annual Meeting of the Japanese Society for the History of Chemistry at T.I.T. in 2008, since then, I have been a member of this society. Sato reflected on Weizmann's career, appreciating his Japanese patent.[35] The *Kagakushi*

Figure 6. In front of the Centennial Hall, Tokyo Tech 2015. From Left: Kazuhiko Shibuya, Shin Sato, Yona Siderer, and Yumiko Shibuya.[36]

Jitten that was prepared by members of that society includes my contribution on Chaim Weizmann, introducing the successful chemist and the first president of the State of Israel to the Japanese readers (Encyclopedic Dictionary 2017).

After six months at T.I.T. (2008), I went to the International Research Center for Japanese Studies (Abbreviated in Japanese: Nichibunken) in Kyoto for one year (2009-2010), holding their Visiting Scholar Fellowship. Professor Frederik Cryns was my host at Nichibunken, we continue our correspondence and discussion concerning writing and publishing my research results.

Sato meticulously and patiently answered my various naive questions, adding to my knowledge of Japanese culture and history when I studied the history of chemistry in Japan. Starting with the research of the Japanese physician and scholar Udagawa Youan (1798-1846), I needed further Japanese explanation and clarification for several topics that I encountered. Those topics included names of people, names of places, e.g. hot springs, the Japanese traditional calendars, and counting the age of Japanese people. Certain kanji characters that were changed, modified or deleted during time, Japanese chemistry nomenclature, Galvani pile, Utamaro's *Book of Insects*, Japanese 1873-74 translation of H. E. Roscoe's 1872 (Science Primer Chemistry) book, Kuroda Chika a pioneering woman chemistry career, etc. (Siderer 2017, Siderer 2021a. Siderer 2021b, Kikuchi and Siderer 2021), Siderer 2023a, Siderer 23b).

While participating in several of the annual meetings of the Japanese Society for the History of Chemistry I had the opportunities to meet T.I.T. friends and others (Fig. 6).

Sato appreciated the support from Israel after the March 2011 Tsunami-earthquake-Fukushima reactors disaster: On 30.3.2011 he wrote: "Dear Yona, Israeli medical team has opened their office at Minami-sanriku-chou in Miyagi prefecture. Their activity was reported on TV. The town was completely destroyed by the tsunami. Half of the residents have been found dead or are still missing, Shin."

CONCLUSIONS

In the foregoing I have summarized the research work of Professor Shin Sato, a physical chemist who spent his career at Tokyo Institute of Technology in Japan. Very early, in 1954-1955, he added to the already known equation of London-Eyring-Polanyi for the drawing of the Potential Energy Surface (PES) for the collision of two small molecules (LEP), and developed his intuitive semi-empirical improvement of their equation that was later called LEPS Method (S after Sato), and later highly cited. His interest in photochemistry deepened during the two periods he spent in the laboratory of R. J. Cvetanović in NRC, Ottawa, Canada (1956-1958 and in 1965-1966). On returning to Japan, and finding that the laboratory he had left had moved over to radiation chemistry, he entered into this new field. After receiving his Doctor of Engineering degree he directed two laboratories, in photochemistry and in radiation chemistry. He attracted around a hundred students to his laboratories, taught chemistry, and continued to work on understanding the dynamics of small molecules, excited states of light induced or γ-rays hit of olefins and other small molecules, reaction of photosensitization by mercury, cadmium, zinc and benzene, and the reactions of nitrogen. Through these investigations he improved the calculation of reactions rate in low temperatures that could not be calculated by the Arrhenius equations.

The year I spent in Tokyo in Sato's laboratory as a UNESCO fellowship fellow influenced the rest of my life: It gave me the opportunity to appreciate the Japanese scientific culture. I enjoyed the friendly atmosphere in the laboratory. I was taken by Japanese art and literature, and fascinated by the kanji, the Chinese-Japanese characters that deepened my research on the history of chemistry in Japan, for which so much inspiration and help was given to me by Shin Sato.

POST-SCRIPT

I invited Sato's younger daughter, and her husband to attend my lecture on Prof. Sato (*Professor Shin Sato, Physical Chemist and my Teacher for 50 Years*, (Siderer

2023b)) at the Annual Meeting of the Japanese Society for the History of Chemistry held at Hitotsubashi University in Tokyo on 8th July 2023. After my lecture we sat together with my friends Kazuhiko Shibuya and his wife Yumiko, and friends of Sato, and discussed his life. On 13th July Sato's younger daughter's husband accompanied me and a friend from Tokyo to Sato's grave in a cemetery in the outskirts of Yokohama. We put flowers and a small plant near the grayish tombstone. We continued and visited his house in Yokohama. Walking upstairs from the street to the house, we entered the living room that had somewhat changed during his illness. But the wonderful spirit, with the many books, the magazines, and the musical notes was still there. Sato's younger daughter later wrote to me, thanked me for having visited her father's grave and told me some stories about him during her childhood.

NOTES

1. Japanese names are written with the family name follows the first name, as they appear in publications titles in English, contrary to the traditional Japanese order of family name first.
2. Information contributed by Sato's family, 28 December 2023.
3. Correspondence with K. Nakamura during 2023.
4. T.I.T. website 17.1.2024, and Wikipedia, 17.1.2024.
5. Shida. (Appendix, hence Appen. 1. no. 7 (1955), Appen. 1. no. 8 (1955), Appen. 1. no. 38, (1968), Appen. 1. no. 39 (1968), Appen. 1. no. 40 (1968)) (Kikuchi and Siderer (2021)) (Appen. 2. no. 1. Shōji Shida and Shin Sato (1966)).
6. Sato LEPS Method (Appen. 1. no. 3 (1954), Appen. 1. no. 4 (1955), Appen.1. no. 5 (1955), Appen 1. no. 10 (1956)).
7. LEPS Method and Modified LEPS method (Appen. 1. no. 161 (1988)), Appen.1. no. 176 (1990), Appen.1. no. 178 (1990)).
8. George C. Schatz to Siderer on 22nd December 2023: Morrison Professor of Chemistry at Northwestern University. He specializes in theoretical and computational chemistry, and has worked in many subdisciplines over the years (nanoscience, materials modeling, light-matter interactions, electronic structure, rate processes). Early in his career (1971-2000) he studied processes important in chemical reaction dynamics that overlapped with Shin Sato.
9. NO_2 Photolysis (Appen.1. no. 11 (1958), Appen. 1. no. 12 (1958), Appen. 1. no. 13 (1958), Appen. 1. no. 14 (1959), Appen. 1. no. 15 (1959)). Articles nos. 11 and 13 in appendix 1 were cited in a leading photochemistry book by Calvert and Pitts, (1966).
10. Sensitized Fluorescence. "Franck predicted in 1922 that a transfer of electronic energy could occur between excited atoms and atoms of a different species in their ground states (Ref. 60). He further stated that the efficiency of the transfer should increase for various systems as the difference in electronic energy levels of the excited donor atom D* approached the difference in energy levels of the non-excited atom A (i.e., approached resonance). This prediction was soon verified by Cario and Franck, who irradiated mixtures of mercury and thallium vapors with the Hg 2537 Å line, to which the thallium was transparent. The observed sensitized fluorescence from the excited states of thallium which lie near or below the 4.86 ev of $^3P_1$ mercury (Ref. 61)." Calvert, chapter 2-9D p. 84.
11. Calvert, (1966), pp. 83-105.
12. Mercury Photosensitization. (Appen. 1. no. 17 (1960), Appen. 1, no. 23 (1964), Appen. 1, no. 35 (also Cd) (1968), Appen. 1. No. 55 also Cd and benzene (1970), Appen. 1. no. 82 (1975), Appen. 1. no. 97 (1978), and Appen. 1. no. 103, (1978)).
13. Phase-shift method for emission lifetime determination. Fluorescence may be excited with light of intensity modulated at a high frequency (5-12 Mc/sec). Because of the finite lifetime of the excited state of an absorbing molecule, there is a delay before the emission of fluorescence by the excited molecule; this results in a difference in the phase of the modulated fluorescence emission and the modulated exciting light. The difference in the phase angle ϕ can be measured experimentally, and the mean fluorescence lifetime can be calculated from its relation to ϕ: $\tan \phi = r2\pi\nu$ (7-31), where ν is the frequency of the modulation of the light. (*Photochemistry* (1966) on phase shift. p. 806; After Lord and Rees (Ref. 120 there).
14. Cd Photosensitization. (Appen.1. no. 33 (1967), Appen.1. no. 34 (1968), Appen.1. no. 35 also Hg(1968), Appen.1. no. 37 also Hg(1968), Appen.1. no. 42 (1968), Appen.1. no. 44 (1969), Appen.1. no. 48 (1969), Appen.1. no. 53(1970), Appen.1. no. 68 (1973), Appen.1. no. 69 (1973), Appen.1. no. 70 (1974), Appen.1. no. 75 (1975), Appen.1. no. 77 (1975), Appen.1. no. 78 (1975), Appen.1. no. 81 (1975), Appen.1. no. 90 (1976), Appen.1. no. 96 (1977), Appen.1. no. 100 (1978), phase-shift), Appen.1. no. 105 (1979), Appen.1. no. 109, (1979) phase shift, Appen.1. no. 112 (1980), Appen.1. no. 113 (1980), Appen.1. no. 119 (1980)).

15. Benzene Photosensitization. (Appen.1. no. 22 (1963), Appen.1. no. 26 (1965), Appen.1. no. 28 (1966), Appen.1. no. 29 (1966) Appen. 1. no. 46 (1969) in Japanese), Appen.1. no. 63 (1972), Appen.1. no. 64 (1972)).
16. Zinc Photosensitization. (Appen. 1. no. 41 (1968), Appen. 1. no. 172 (1989), Appen. 1. no. 179 (1990)).
17. Amine formation. (Appen. 1. no. (108 (1979), no. 115 (1980), no. 117 (1980), no. 120 (1981), no. 125 (1981), no. 128 (1982), no. 129 (1982), no. 132 (1983), no. 134 (1983), no. 136 (1984), no. 139 (1984), no. 148 (1986 Phase-shift), no.149 (1986 phase shift), no. 163 (1988), no. 165 (1988), no. 167 (1988)).
18. Calvert p. 102. In chapter 2 on "The Interaction of Light with Atoms", they cite the article by Arai, Sato and Shida, in *Nippon Kagaku Zassi*, **81**, 1790, (1960), ref. 110, p. 102) (Appen.1. no. 6, in Japanese). On cycloalkanes, "in Studies of $Hg(^3P_1)$-cyclohexane mixtures over the range of 60-400°C, they found that below 200°C the major products are hydrogen, bicyclohexyl, and cyclohexene, in accord with Gunning et al.(ref. 107 therein) Above 300°C the ring ruptures, and products include propylene, methane, ethylene, ethane, butadiene, propane and butane, presumably arising from the decomposition of the cyclohexyl radical formed in the primary act. The quenching cross section of cyclohexane was estimated to 1.9 $Å^2$. (Calvert and Pitts, *Photochemistry* (1966) p. 102).
19. Calvert p. 218. In chapter 3, "The Interaction of Light with simple molecules" section 3-3B-2 "The Oxides of Sulfur and Nitrogen: SO_2, SO_3, N_2O, NO, and NO_2" the following article is cited. "Sato and Cvetanović, however, in studying the Photooxidation of 1-butene by nitrogen dioxide, found that the same addition products, α-butene oxide and butanal, were formed at several ultraviolet wavelengths, including 4047A. Furthermore, the ratio of their yields was the same at all these wavelengths. They found no reaction at 4358 Å. They point out that this would be difficult to understand if free oxygen atoms were not involved at all wavelengths used, including 4047 A but not 4358 Å." (Calvert 1966. p. 218. Ref. 168 (p. 237)).
20. Calvert p. 221. Chapter 3 section 3-3B-2 "The Oxides of Sulfur and Nitrogen: SO_2, SO_3, N_2O, NO, and $NO_{2,}$ as the previous section … "Sato and Cvetanović (ref. 173: (Appen.1. no.13 (1958))) have found a change in the electronic state of oxygen on photolysis at the shorter wavelengths. 1-butene was photooxidized, using NO_2 photolysis at 3261, 2537, and 2288 Å. Between 2537, and 2288 Å a change in the mechanism of oxygen atom attack occurred, and it is likely that the primary reaction for these conditions is NO_2+hv > NO (X^2II) + O(^{1}D). As in all cases discussed in this book we have restricted our attention to those directly concerned with the nature of the primary photochemical processes." (Calvert (1966)).
21. Cyclohexane. (Appen.1. no. 16 (1960), Appen.1. no. 17 (1960), Appen. 1. no. 19 (1962), Appen. 1. no. 20 (1962), Appen. 1. no. 21 (1963), Appen. 1. no. 24 (1964), Appen. 1. no. 30 (1967), Appen. 1. no. 31 (1967), Appen. 1. no. 36 (1968), Appen. 1. no. 43 (1968), Appen. 1. no. 58 (1971), Appen. 1. no. 59 (1971), Appen. 1. no. 92 (1976), Appen. 1. no. 104 (1979)).
22. G-Values. (Appen. 1. no. 67 (1973), Appen. 1. no. 72 (1974), Appen. 1. no. 79 (1975)).
23. G-Values. (Appen. 1. no. 80 (1975), Appen. 1. no. 82 (1975), Appen. 1. no. 86 (1975), Appen. 1. no. 87 (1976), Appen. 1. no. 89 (1976), Appen. 1. no. 91 (1976), Appen. 1. no. 94 (1977), Appen. 1. no. 102 (1978)).
24. Citation of the original sentence in Japanese: 『どの論文にも夢があった。実験とは毎日毎日が創造である。 学生の創造に負けないように想像力を逞しくした』。
25. Phase Shift Method. (Appen.1. no. 97 (1978), Appen.1. no. 100 (1978), Appen.1. no. 103 (1978), Appen.1. no. 113 (1980), Appen.1. no. 149 (1986)).
26. ESR experiments. (Appen.1. no. 135 (1983), Appen.1. no. 140 (1984), Appen.1. no. 144 (1985), Appen.1. no. 145 (1985), Appen.1. no. 146 (1986), Appen.1. no. 150 (1986), Appen.1. no. 153 (1987), Appen.1. no. 155 (1987), Appen.1. no. 164 (1988), Appen.1. no. 171 (1989), Appen.1. no. 175 (1989)).
27. Kazutaka Nakamura is an Associate Professor at Tokyo Institute of Technology. He was a student in Sato's lab officially in 1984-1986. Nakamura recalled ESR experiments in which he was involved. (Email, 12.2023).
28. A short introduction: Toshiyuki Takayanagi was a student of Sato since 1985; he is now a professor at Saitama University, Department of Chemistry. Takayanagi wrote his reflection about their scientific research in the 1980s, his acquaintance with Schatz in Sato's lab and his work at Schatz's laboratory as a result of that acquaintance and a co-authored article: T. Takayanagi, N. Masaki, K. Nakamura, M. Okamoto, S. Sato and G. T. Schatz (Appen. 1. No. 156 (1987)).
29. Abstract of Sato's 2004 article. Approximate cumulative reaction probabilities have been calculat-

ed from two empirical rate equations: one is the 3-parameter rate equation, $AT^n\exp(-E/k_BT)$, and the other is the modified Arrhenius equation proposed in Chem. Phys. Lett. 160 (1989) 295, for expressing the rate constants at low temperatures. Numerical calculations were made for the $D + H_2 \rightarrow DH + H$ reaction. It is shown that this reaction occurs mainly through tunneling at 200 K, and that the 3-parameter rate equation involves the tunneling effect along with the correction at high temperatures (Apenn.1. no. 181 (2004)).

30. Abstract of Sato's 2017 article. On "Empirical rate formula for ion-dipolar molecule reactions": New empirical rate formula for the low temperature reactions is proposed. The formula proposed previously has been simplified by using incomplete gamma function. A few examples of temperature dependence of rate constants for the reactions of ions with dipolar molecules and that for the reaction $F+H_2 \rightarrow HF +H$ are demonstrated by using new rate formula (Appen. 1. no. 185 (2017)).
31. Mrs. Y. Shibuya conversation with the author on 1 August 2023.
32. K. Shibuya, discussion, in the above mentioned journal Radiation Chemistry 放射線 化学 issue 80 p. 6 (2005).
33. I met Y. Hatano with his friend T. Yamaguchi and their friend in a restaurant near Tokyo Station in 2016.
34. History of Chemistry in Japan: From Cotton Dyeing to Nobel Laureates. Monthly reports I sent to Japan Foundation in Tokyo, 2008.
35. Chaim Charles Weizmann Letter patent no. 33502, English translation 1924 001. A copy of Chaim (Charles) Weizmann patent: "Improvement of relating to the carrying out of bacteriological process", in Japanese Patent Bureau, in 1918 (Taisho 7), and reregistered in 1924 (Taisho 13). A copy is kept at the Weizmann Archive at the Weizmann Institute of Science, Rehovot.
36. On 8 November 2015 Sato congratulated me for becoming a member of the Directorate of the Israeli Association for Japanese studies (IAJS). S. Sato, Tatsumasa Dōke and Mrs. Yumiko Shibuya attended my seminar at T.I.T. in July 2018. I keep twenty five New Year greeting cards that he had annually sent; the last one is for 2022 showing snow on top of Mount Fuji, flowers and flying cranes, one of Japanese symbols of longevity.

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APPENDIX 1. SHIN SATO LIST OF PUBLICATION IN JOURNALS

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3. S. Sato, On a New Method of Drawing the Potential Energy Surface, J. Chem. Phys., 23, 592 (**1954**).
4. S. Sato, A New Method of Drawing the Potential Energy Surface, Bull. Chem. Soc. Jpn., 28, 450 (**1955**).
5. S. Sato, Potential Energy Surface of the System of Three Atoms, J. Chem. Phys., 23, 2465 (**1955**).
6. 佐藤 伸, 金属表面上における水素原子再結合反応（第 2 報）白金表面上における再結 合反応の機構, 日化誌, 76, 1308 (**1955**).
7. 中田和夫, 佐藤 伸, 志田正二, 金属表面上における水素原子再結合反応（第 3 報） 銅単結晶表面上の再結合, 日化誌, 76, 1313 (**1955**).
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18. 佐藤 伸, 寺尾光身, 志田正二, シクロヘキサンの放射線分解, 日化誌, 81, 555 (**1960**).
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SUPPLEMENTARY MATERIAL OF PROF. SHIN SATO

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Historical Article

For a Dialogue Between the Teaching of Chemistry and the History and Philosophy of Chemistry: the Case of the Concept of 'Chemical Element'

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Abstract. The concept of 'element' is one of the most important concepts in the chemical sciences. It plays a key role to explain the chemical reactions and the basis of the periodic table. It is also central to the modern philosophy of chemistry because of its role in discussions about the nature of the periodic system and natural classes. In the field of chemistry teaching it is a paradigmatic case of alternative conceptions. In general, two definitions of 'chemical element' coexist. The first, due to Lavoisier, conceptualizes an 'element' in a macroscopic ontology and the second, usually considered the 'modern' definition, conceptualizes an element in an ontology of particle. Some authors state that it is time to consider the former conceptualization as merely 'historical' and focus teaching on the basis of the most recent definition. The present paper aims to address this problem from a pluralist perspective by highlighting the pedagogical relevance of incorporating historical-philosophical analyses in the explanation of scientific concepts.

Keywords: chemical element, Lavoisier, Mendeleev, Paneth, history and philosophy of chemistry.

INTRODUCTION

The concept of 'element' is one of the main categories of the chemical world. It plays a central role both in chemical reactions and in the periodic table, and it is of the utmost importance for the philosophy of chemistry because of its role in discussions about the nature of the periodic system and the problem of natural kinds. With the revival of the philosophy of chemistry in the middle of the 1990s, some chemists, philosophers of chemistry, and historians of chemistry sought to clarify this concept. But at present the disagreements are deep: while there is a broad consensus about the *extension* of the concept of 'element' (its coverage), there is no agreement about its *intension* (what a predicate 'says': its sense), nor even about the terminology to be used.

The notion of ‘element’ has evolved from a philosophical domain to the scientific-philosophical one. The question ‘what is an element?’ has been a long-standing debate since the dawn of ancient Greek philosophy to the present day. Recently, the philosopher of chemistry Eric Scerri coordinated the publication of *What is a Chemical Element?* which brings together a variety of approaches that aim to provide an update on the current state of the debate about chemical elements. The book welcomes contributions from different perspectives, such as those of historians, philosophers, and chemists with ontological, epistemological, and educational concerns.[1]

In general, two definitions of ‘chemical element’ coexist in chemistry teaching. The first, due to Lavoisier, defines an ‘element’ in a macroscopic ontology (simple substance), and the second, usually considered the modern definition, conceptualizes an element in an ontology of particle. In the light of this situation, some authors state that it is time to consider the former conceptualization as merely ‘historical’ and focus teaching on the basis of the most recent definition.

The aim of this paper is to address this problem from a pluralist perspective by highlighting the pedagogical relevance of incorporating historical-philosophical analyses in the explanation of scientific concepts. To this end, we will begin by recalling the first reflections on the need to distinguish between the concepts of ‘element’ and ‘atom’ in Classical Antiquity in Section 2. The first challenge to the doctrine of four elements by Boyle is reviewed in Section 3. Lavoisier’s conception of element as ‘simple substance’ will be discussed in Section 4. The conceptual distinction between ‘chemical element’ and ‘simple substance’ given by Mendeleev is discussed in Section 5 and then we will analyze Paneth’s treatment of the subject in Section 6. Finally, we will investigate the problem from a new perspective, no longer centred on the assumed dilemma of choosing between the two main definitions, but based on a pluralist approach by highlighting the relevance of historical-philosophical analyses in the explanation of scientific concepts.

ANCIENT TIMES: ‘ELEMENTS’ AND ‘ATOMS’

The dialogue between chemistry teaching and philosophy about ‘elementarity’ can begin by reflecting on the difference between the concepts of ‘element’ and ‘atom’ inherited from classical Greek philosophy. Both concepts are rational abstractions used to account for the existence of material things, their differences and transformations. However, these concepts are linked to distinct philosophical traditions and will influence the theories of matter of future alchemists and chemists. The theory of physical atoms began with Leucippus and Democritus, while the main theory of the elements was developed by Aristotle.

Democritus introduced the term ‘atom’ (indivisible, though whether theoretically or physically is a matter of dispute) to denote entities that were immutable in form, solid, and of different sizes and weights. These atoms joined together to form compounds that gave rise to different kinds of things in the world, but they retained their identity because they were only juxtaposed to one another, like the letters of an alphabet, which may form different words but themselves remain identical. Democritus’ universe is made up of infinite atoms with various geometrical shapes that move in the vacuum without obeying any necessity. [2]

Aristotle’s theory of matter was called hilemorphism, because he considered that all material elements had as basic metaphysical constituents form and matter (hyle), which did not exist separately except by abstraction. This theory was based on the acceptance of the existence of four elementary principles (earth, water, air, and fire), themselves products of the association between two essential qualities (earth- dry and cold; water - cold and humid; air - humid and hot; fire - hot and dry) with the homogeneous and inert material substratum, so that the existence of a vacuum was impossible. The four elements were also substances in a philosophical sense. The substance is what underlies properties, which inhere in it. The properties may change, but the substance remains, subsists. Water was the bearer of macroscopic properties such as liquidity, mobility, wetness, and coldness. This is the first sense in which ‘element’ was conceived: an abstract entity which not only underneath all the other substances but also is the bearer of macroscopic properties. The doctrine of the four elements exerted great influence in Antiquity and, though with some modifications, also in the Middle Ages, when it was common to add ether as the ‘fifth element’ or quintessence, as postulated by Aristotle. [3]

Although Aristotle and his commentators rejected the existence of indivisible material particles, their doctrine of the continuum did not exclude the idea that combination occurred from minimal particles of matter. Even modern critics of Aristotle, such as Bacon and Boyle, re-signified the concept of minima naturalia in their respective theories of matter, which rejected both atomism and Aristotle’s quality-bearing elements, because they resulted from empirical investigations guided by rigorous experimental control. [4]

ROBERT BOYLE: THE CHALLENGE TO THE DOCTRINE OF FOUR ELEMENTS

The doctrine of four elements survives until the Middle Ages, when it slowly began to show some problems. The first step was given by Robert Boyle (1627-1691). In 1661 Boyle published *The Sceptical Chymist* in which the ancient four-element formulation was challenged by demonstrating that the entities called 'elements' were not in fact elemental:

> […] to prevent mistakes, I must advertise you, that I now mean by elements, as those chemists, that speak plainest, do by their principles, certain primitive and simple, or perfectly unmingled bodies; which not being made of any other bodies, or of one another, are the ingredients, of which all those called perfectly mixt bodies are immediately compounded, and into which they are ultimately resolved: now whether there be any one such body to be constantly met with in all, and each, of those, that are said to be elemental bodies, is the thing I now question. [5]

Nonetheless, Boyle traditionally appears in chemistry textbooks and even in some histories of chemistry as the 'inventor' of the modern notion of element: it is said that he defined the elements. He is said to have defined the elements as the indecomposable bodies that make up mixed bodies and into which the latter can decompose. This reference to Boyle's 'revolutionary' definition is now cited by historians as an example of a historical error that consists in abstracting from its context a statement that statement that appears 'true', that is to say, at-present acceptable. [6, 7]

In other words, Boyle was not substituting a modern notion of the element to the Aristotelian definition, but questioned the function of the element in the practice of chemists, that is, the idea of finding units beyond diversity, both principles of genesis and principles of intelligibility of this diversity. The experimental evidence seemed to suggest that those supposedly 'elements' could be broken down in smaller parts. Boyle introduced thus new methods and new tools for the knowledge of matter and the concept of minima naturalia (combination occurred from minimal particles of matter). In fact, Boyle's corpuscles are rather different from Democritus's and Epicurus's atoms and resembling the minima naturalia adopted by chemists in the early part of the seventeenth century. Even as a critic of Aristotle, Boyle resigned the concept of 'minima naturalia', rejecting both atomism and Aristotle's quality-bearing elements. The importance that Boyle attached to chemical experiments in order to prove the existence of corpuscles clearly shows that his chemical theories and corpuscular philosophy were in fact already strictly linked at the outset of his career. His theory of matter is corpuscular, not strictly mechanical, as it includes agents endowed with formative power. According to Clericuzio, "Boyle's chemical and medical works clearly show that he did not subordinate chemistry to the principles of mechanical philosophy. He explained chemical processes in terms of corpuscles endowed with chemical, not just mechanical properties". [8]

But what is the nature of these corpuscles? Boyle separates the hierarchy of materiality into three distinct levels. In *Origine of Forms and Qualities* (1666), he describes what he understands by minima naturalia; then he moves on to describe the second hierarchical level, what he calls second-order agglomerates, formed by the extreme adhesion of the minimal particles. At this moment, a fundamental property for his theory of matter emerges: the texture. And, finally, we have the bodies of the manifest world. Boyle does not resort to the last blocks of matter, but to corpuscles of higher orders of composition. In fact, it is these corpuscular clusters with their respective textures that are responsible for the different natures and properties of matter. [4, 8]

LAVOISIER: ELEMENT AS 'SIMPLE SUBSTANCE'

In the last three decades of the 18th century, chemistry was the scenario of theoretical controversies, experimental innovations, and the establishment of some long-lasting consensuses. One of these controversies concerned with the role of air in combustion, which also engendered the question of the composition of metals (Were they mixtures or simple bodies/elements?), and one of the consensuses reached was the establishment of a nomenclature technique. The history of this period has produced a variety of narratives, coming from different historiographies, as well as diverse ontological, epistemological, and methodological interpretations. Antoine-Laurent de Lavoisier (1743-1794) is the name that occupies the collective memory when it comes to the chemistry practiced in the last three decades of the century.

Following a trend among the chemists of the second half of the eighteenth century, well represented by Pierre-Joseph Macquer (1718-1784), Lavoisier was one of the first to conceive an element as the final stage of chemical decomposition. In the preface of his *Traité Elémentaire de Chimie* published in 1789, he presented his operational or empirical definition of 'element' using as a synonym terms like 'simple body' or 'principle'. According to him,

> If we apply the term *elements*, or *principles* of *bodies*, to express our idea of the last point which analysis is capa-

> ble of reaching, we must admit, as elements, all the substances into which we are capable, by any means, to reduce bodies by decomposition. Not that we are entitled to affirm, that these substances we consider as simple may not be compounded of two, or even of a greater number of principles; but, since these principles cannot be separated, or rather since we have not hitherto discovered the means of separating them, they act with regard to us as simple substances, and we ought never to suppose them compounded until experiment and observation has proved them to be so. [9]

Lavoisier and his collaborators –among them his wife Marie Anne Pierrette Paulze– published the well-known list of 33 elements as 'simple bodies' or 'simple substances'. The term 'element' finds then its reference in the macroscopic domain: observable and tangible simple substances that can be isolated (oxygen, lead, gold, and so on). This operational definition of 'element' is commonly found in several textbooks at the university level. In addition to material 'simple bodies', Lavoisier also grouped among the 'elements', the 'principles' bearing qualities such as the 'caloric principle' and the 'oxygen principle' which attests to its connection with a common conception in the eighteen century, that is, those that considered the 'principles' or 'elements' as 'carriers of material qualities'. [10, 11]

Thus, after many centuries, the notion of 'element' moved from the philosophical domain to the scientific one in Lavoisier's time. An element was no longer conceived as an abstract (unobservable) entity but as an entity that could be isolated and whose properties could be observed experimentally. Lavoisier invites us to think about whether it is possible to experimentally obtain simple corpus or elements (principles).

MENDELEEV: THE CONCEPTUAL DISTINCTION BETWEEN 'CHEMICAL ELEMENT' AND 'SIMPLE SUBSTANCE'

As is known, in the early nineteenth century the English physicist-meteorologist John Dalton (1766-1844) proposed a hypothesis that made it possible to know the relative values of the mass of the 'simple bodies' that combined during a chemical transformation, so that the new concept had no relation with the atomistic philosophy of the Ancients (Democritus, Epicurus, Lucretius). For Dalton, the term 'atom' was associated with the material units that entered into the chemical combinations predicted by the laws of equivalences, simple proportions, and multiple proportions, and received a graphical representation that allowed writing their compounds through formulas. [12]

For the emergence of a new concept of chemical element, the distinction between 'atoms' and 'molecules' proposed by the physicist Amedeo Avogadro (1776-1856) was relevant. This distinction was important for the Russian chemist Dmitri Mendeleev (1834-1907) to point out the difference between 'simple bodies' and 'chemical elements'. Thus, Mendeleev no longer considered these expressions as synonymous, as Lavoisier had done, and the abstract sense of 'element' was gradually replaced by a concept based on the results of experimental work. Mendeleev argued that his periodic classification of the elements had to do with the elements conceived as 'abstract elements' and not with the elements considered as 'simple substances'. According to Mendeleev, the elements in an abstract sense had an essential property: its atomic weight. This property allowed him to order them in a unique sequence.

In the Introduction of his *Principles of Chemistry*, Mendeleev points out that it is important to make a clear distinction between the notion of 'simple substance', understood as isolated homogeneous substance or as an invisible part of the material of a compound body, of the notion of 'chemical element'. Hence, Mendeleev claims:

> The red oxide of mercury does not contain two simple bodies, mercury and oxygen. It is neither the mercury as a metal nor the oxygen in the gaseous form that is contained in the oxide in question, but only the substance of these simple bodies. The elements do not undergo any modification, they are immutable. For example, we find in nature carbon in the form of charcoal, graphite and diamond, which are simple bodies, but made up of a single element, carbon. [13]

The abstract concept of the element proposed by Mendeleev originated from the concept of allotropy. Thereby, the term 'chemical element' no longer denoted the final product of a chemical analysis process, but came to refer to a relational and abstract measure, that is, the atomic masses obtained by experimental techniques. According to Mendeleev,

> […] the elements have an exactly measurable property, that of their atomic weights. The weight of the atom expresses its relative mass or, in other words, an abstraction made from the notion of the atom, this greatness shows the relation that exists between the constituent masses of the independent chemical units, that is, of the elements. [14]

The concept of 'chemical element' denotes a purely abstract entity that does not have an isolated existence, given that it was only possible to identify by its relations of mass with other chemical elements. Mendeleev considered the abstract individuality of the chemical elements as one of the three fundamental laws that govern the Universe. [15] According to him,

> Kant thought that there existed in the Universe two objects that provoked the admiration and veneration of men: the moral law within us and the starry sky above us. Deepening the nature of the elements and the periodic law it is necessary to add a third object: the nature of the elemental individuals who express themselves around us.[16]

PANETH: 'SIMPLE SUBSTANCE' AND 'BASIC SUBSTANCE'

If the existence of allotropes was one of the reasons that led Mendeleev to propose the distinction between 'simple bodies' and 'chemical elements', the discovery of the non-radioactive isotopes by Francis Aston in the 1910s brought considerable difficulties not only to the concept of elementarity, based on the atomic weights, but also to the simplicity of the periodic table that grouped elements into chemically similar families.

The discovery of isotopy posed a threat to the periodic table, as the number of elements as 'simple substances' seemed to increase very rapidly. As the elements were ordered according to their growing atomic weights, it was legitimate to question if these new atoms were manifestations of the same element or, on the contrary, they corresponded to different chemical elements. This episode was known as the 'isotopes crisis' and in the 1920s implied the end of both a 'chemical' way of defining the nature of the elements and the periodic classification that had hitherto been known.

The Austrian Friedrich 'Fritz' Paneth (1887-1958), a pioneer of radiochemistry with a deep philosophical background, solved the crisis by recalling Mendeleev's philosophical distinction between 'simple substance' and 'basic substance'. The discovery of isotopes concerned with new elements conceived as 'simple substances', but the primary criterion of periodic classification involved the element in a more fundamental sense of the term. Experimental evidence in support of that conceptual distinction was provided by Paneth and the radiochemist George Hevesy (1885-1966), which showed that isotopes belonged to the same chemical species in the sense that they exhibited complete replaceability. They based their conception of replaceability or chemical identity on electrochemical experiments in 1913-1914, which showed that the chemical behavior of beta-radioactive lead (Pb-210) was indistinguishable from that of naturally occurring lead (which they believed was just another lead isotope). [17]

The solution proposed by Paneth was based on the observation that the chemical elements with identical chemical properties, but with different atomic masses, had a common physical identity: the atomic number. In fact, since 1916 Paneth suggested associating the number of protons in the nucleus of atoms with the concept of chemical element. [18] After adopting this criterion in 1923 by the newly created IUPAC [19], Georges Urbain (1872-1938) analyzed the chemical and physical reasons for that choice. For him, "this definition has the advantage of solving the isotope question, so that different isotopes of the same chemical element are integral parts of this same element" [20]. This gave rise to what some authors considered the 'modern' conception of an element, which identifies it with its nuclear charge, i.e., with the number of protons in its nucleus.

In 1931, in a conference held in Königsberg, Paneth presented a philosophical analysis of the historical evolution of the concept of 'element', which became a reference for some current debates among chemists and philosophers of chemistry concerning the meaning of 'chemical element'. Paneth suggested a dual interpretation of the concept of 'chemical element' by appealing to Mendeleev's distinction between 'element' and 'simple body'. According to him, it is necessary to distinguish between 'basic substance' and 'simple substance' as different aspects of the chemical element. The latter concept prioritizes the empirical sense with observable magnitudes, whereas the former referred to entities that do not change during chemical reactions. In Paneth's words, the term 'basic substance' denotes "…the indestructible substance present in compounds and simple substances…", whereas the term 'simple substance' refers to "that form of occurrence was meant in which an isolated basic substance uncombined with any other appears to our senses". [21] He emphasized that the most fundamental meaning of the concept of 'element' was its manifestation as 'basic substance'.

Paneth resolved thus the 'isotope crisis' by recalling the ordering of the elements in the periodic system as 'basic substances' and not as 'simple substances, recovering the dual sense of the concept formulated by Mendeleev. If the chemists had focused only on the simple substances, they would have been forced to recognize new 'elements' in each new isotope discovered. Paneth argued then that the periodic table of chemical elements could be retained on the basis that the chemical properties of isotopes of the same element are indistinguishable. [15]

THE TEACHING OF THE CONCEPT ‘CHEMICAL ELEMENT’: BUILDING BRIDGES WITH THE HISTORY AND THE PHILOSOPHY OF CHEMISTRY

We have briefly reviewed the road from ‘element’ to ‘chemical element’. In general, two definitions coexist in teaching: the first, due to Lavoisier, defines an element in a macrochemical ontology, and the second defines an element in an ontology of particle and was established in 1923 as stated above. A survey of conceptualizations in some of the main textbooks at the university-level allow to appreciate that several definitions are consistent with the operational definition proposed by Lavoisier in 1789. Let’s see some examples:

- “An element is a fundamental substance that can’t be chemically changed or broken down into anything simpler”. [22]
- “Elements are substances that cannot be decomposed into simpler substances by chemical or physical means”. [23]
- “A substance that cannot be decomposed into simpler substances by chemical means”. [24, 25]
- “Elements are substances that cannot be decomposed into two or more simpler substances by ordinary physical or chemical means”. [26]

At the same time, the modern or physicalist definition of ‘element’ which finds its referent in the atom, is presented in some other textbooks. A couple of examples:

- “A substance whose atoms are all chemically the same, containing a definite number of protons”. [27]
- “An element is a substance composed of only one kind of atom”. [28]

Ghibaudi *et al.* correctly point out that both conceptualizations are plausible from critics. In the case of the operationalist definition of Lavoisier, the element as ‘simple substance’ leaves unsolved the persistence of the elements in compounds, probably the greatest mystery in the chemical sciences. On the other side, to identify elements with atoms gives a wrong idea about the existence of the elements within substances. Further, it is possible to claim that from the individuation criterion of an element (that is, its atomic number) solely, it is not possible to determine macroscopic properties like its melting point, its boiling point or its flammability limit.[29]

The concept of ‘element’ is probably the paradigmatic case of alternative conceptions in chemistry due to its relevance. [30, 31, 32] In the light of this apparent dilemma, some authors suggested that the conception of ‘element’ in terms of Lavoisier should be considered as purely historical [33,34] whereas Ghibaudi et al. [29] state that it is necessary to take a stand between the two definitions bearing in mind the progress of chemistry. But in another such textbook an element is conceptualized as: “[…] the simplest type of matter with unique physical and chemical properties. It consists of only one kind of atom, and, therefore, cannot be broken down into a simpler type of matter by any physical or chemical methods”. [35]

The particularity of this definition lies in the fact that involves the two ontologies implied in the discussion, which would seem to complicate even more a possible solution to this problem. In the light of this situation, we consider that this topic gives the opportunity to recall that a problem of interpretation in science is not just a scientific problem (as is generally assumed) but a philosophical-scientific one. This means that a philosophical standpoint is always present in its interpretation. In turn, this implies that there is not a single ‘true’ solution to the problem but, on the contrary, there are different possible interpretations.

In line with the reductionist approach that prevails in science at present-day, some authors have proposed an interpretation of an ‘element’ which finds its reference, again, in the atom. For instance, Roundy says: “Each element is defined by its atomic number (or number of protons in the nuclei)” [36] and more recently William Jensen who claims: “…the term element refers to a specific type of nuclei or, more accurately, to a class of nuclei with the same atomic number” [37], definition with which Ghibaudi and coworkers agree.

These physicalist definitions are not without problems. One of them concerns to the conceptual identification between ‘element’ and ‘atom’. As Alex Johnstone has explained, this goes against the psychology of learning. [38] In the case of beginners, it is better to taught progressively, starting with observations at the macroscopic level. We consider that Johnstone’s observation is relevant because he remembers us the origin of chemistry as an experimental discipline. In this sense, Lavoisier’s and Boyle’s definitions of the ‘element’ are resulting from the experimental work, a constitutive feature of chemical sciences.

Taking this into account, Nelson suggests to define an ‘element’ as a “substance that does not undergo chemical decomposition into, and cannot be made by chemical combination of, other substances”. [39] In a later work, this author formally distinguishes ‘element’ from ‘elementary substance’ where the former is defined as “basic type of matter existing as elementary substances that can be interconverted without change in mass”, and the latter denotes his previous definition of ‘element’. [40]

In the same line, the definition of ‘chemical element’ given by IUPAC (International Union of Pure and Applied Chemistry) does not seem to illuminate precisely the problem at hand:

1. A species of atoms; all atoms with the same number of protons in the atomic nucleus.
2. A pure chemical substance composed of atoms with the same number of protons in the atomic nucleus. Sometimes this concept is called the elementary substance as distinct from the chemical element as defined under 1, but mostly the term chemical element is used for both concepts. [41]

Although the two definitions are proposed for the same term, they do not cancel the conceptual identification, again, between 'element', 'atom', and 'pure substance'. At the same time, they do not account for the abstract nature of the concept. As we saw above, the abstract sense allows to explain the different allotropes and isotopes of an element from an abstract entity that underlies all of them. Whereas this interpretation has been supported by some authors [18], others adopt a physicalist view of the abstractness leaving aside any metaphysical connotation of the term. [42]

An interesting and little-known definition provided by Robert Luft (1997) appeals to the old sense:

> Element is an immaterial entity without physical or chemical properties, root of a specific chemical species and common feature to his atoms, molecules, ions and isotopes. It is characterized by two data: a symbol and an order number, the atomic number, that indicates the position of the chemical species within the Periodic Table.[43]

According to Scerri [15], this characterisation is used in the French system of chemical education. Having reviewed the two main definitions of the concept of 'element' that can be found in university textbooks, we have seen that both present advantages and difficulties. The situation looks as a dilemma. However, if we admit that neither candidate definition has explanatory priority, that is, if they do not provide a conceptualization absent of problems, it is then reasonable to ask why a single definition should be privileged. The priority of an ontology of particle over a macrochemical ontology is based on the reductionist assumption widely accepted, in general, by chemistry educators and most of philosophers of chemistry.

In the light of the above considerations, we believe that this problem needs to be addressed carefully when teaching. Even though pedagogical recommendation do not fall within our competences, we consider that some philosophical reflections can be valuable to this problem. First, it is important to remember that scientific practice implies a continuous construction of knowledge. If this is accepted, it would seem appropriate to explain to future scientists the interstices, the problems, and the empty spaces faced by scientific knowledge.

We consider that, at advanced level of teaching, the two classical definitions of 'element' reviewed here along with the Luft's definition and, at the same time, the scientific and philosophical problems associated (the historical development of the concept, the different definitions proposed and the limitations of each conceptualization, the domains of reality implied) would allow students to appreciate the very nature of the problems and the different tools and arguments that science and philosophy provides to address them. On the contrary, the teaching of a 'mummified' chemistry, free of conceptual problems and the associated debates, does not reflect the own scientific practice and, from our viewpoint, it should not be replicated when teaching chemistry to the extent possible. [44]

In this regard, we believe that scientific monism, according to which there is only one scientific story about the world that can be told, should be avoided as far as possible as well. There is a vast philosophical literature and a scientific practice that supports this perspective. As Hasok Chang claims in "Is Water H_2O", objective and univocal truth is not an aim of scientific practice. Pluralism must engage in cultivating multiple scientific systems and lines of inquiry, as science is a multi-aim enterprise, not the search of literal truth:

> But why is it better to be pluralistic? Why keep multiple systems of knowledge alive? The immediate reason for this is the sense that we are not likely to arrive at the one perfect theory or viewpoint that will satisfy all our needs […] If we are not likely to find the one perfect system, it makes sense to keep multiple ones. [45]

This topic presents a very important particularity that is necessary to consider in the light of its teaching. Indeed, there are several definitions of 'element' built on two domains of reality coexisting in the teaching praxis. The key point here is to highlight that, in this case, plurality does not imply incompatibility among the definitions. As a result, the alternative conceptions give different images of the notion of 'element'. Thus, instead of choosing only one definition, we do believe that it is richer to introduce the students to the historical-philosophical aspects associated to the notion of 'element' and the problems closely associated to their possible interpretations. This historical and philosophical analysis contributes to the process of emphasizing the discursive dimension of teaching-learning processes of science twin in real classroom situations. At the same time, this approach also contributes to develop argumentative abilities in chemistry students. [46, 47, 48]

Likewise, we consider that at least some of the following questions would deserve to be discuss in the teaching of this subject matter: Is the individuation criterion of an element based on its atomic number enough to explain its properties and the position of a chemical element in the periodic system? Is its complementation with quantum mechanics fully satisfactory to explain the properties of a group in the periodic table? Let take one case that have led chemists and philosophers to heated debates at times. What are the best positions of hydrogen (H) and of helium (He) in the chart? According to their chemical properties or according to their electronic configurations? [49]

In a recent work, Helge Kragh poses an interesting question concerning the ontological status of the super-heavy elements, that is, those whose atomic numbers are greater than 102. [50] It is known that the isotopes of those elements have very short life-times and they are detected at nuclear processes. So, in strict sense, they exist just at the time of detection. But in what sense is it possible to claim that they have existence like the ordinary elements?

CONCLUSIONS

The concept of 'element' is a paradigmatic case of alternative conceptions in chemistry teaching. In this paper we have addressed this problem from a pluralist perspective by highlighting the pedagogical relevance of incorporating historical-philosophical analyses in the explanation of scientific concepts. In this regard, after a survey of the different conceptions of the element from antiquity to the present day, it is possible to assert that pluralism is a consequence of a historical and philosophical study of the concept. Thus, this approach makes it possible to overcome the assumed dilemma of choosing between the two main definitions of 'element', which involve two ontologies.

This topic gives us a rather unique opportunity to introduce the history and the philosophy of chemistry at the science classroom. These metadisciplines give a more real picture of science by revealing, explicating or elucidating different aspects of science. In this sense, the analysis reveals that reality implies more than one domain and a wide variety and diversity of scientific constructs. The metascientific studies can also help us to understand the kind of knowledge built by science and, as a consequence, the kind of teaching that should be encouraged to impart to future scientists.

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In Memoriam

Remembering Dr. Ernst Kenndler: A Pioneer in Capillary Electrophoresis and Its Basic Principles

Andreas Rizzi[1], Bohuslav Gaš[2], Marja-Liisa Riekkola[3], Norberto A. Guzman[4,*]

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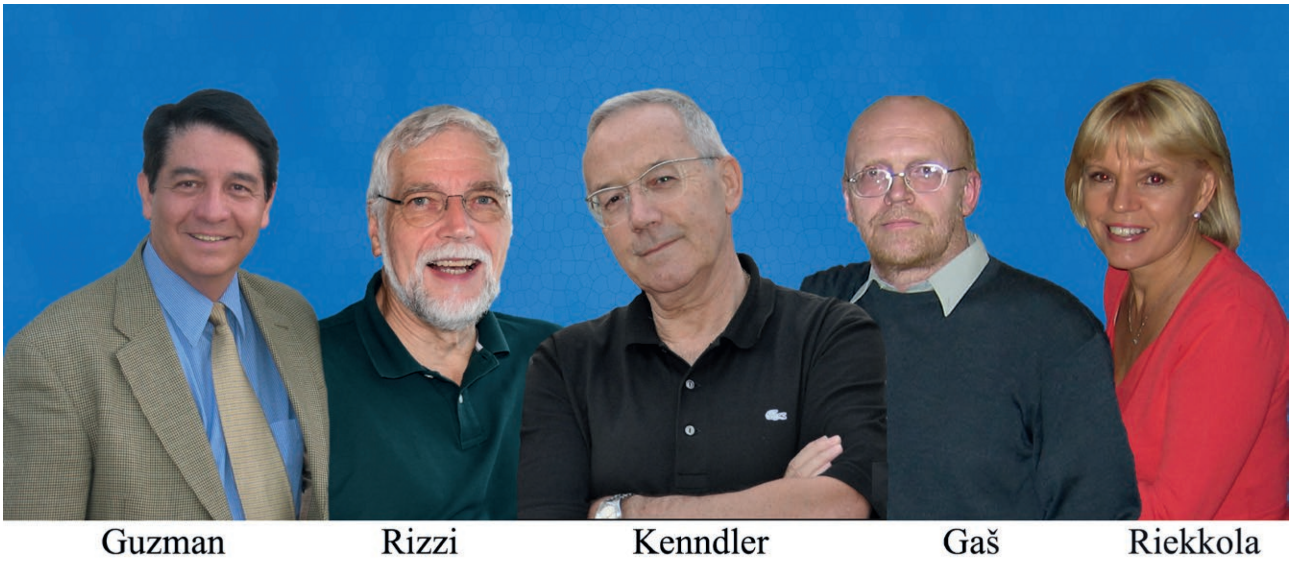
Great orators have has the remarkable ability to captivate their audiences and keep their attention. They can break down complex topics into understandable concepts that educate and inspire. Dr. Ernst Kenndler had this natural gift and could transform the challenging subject of electrophoresis into brilliantly memorable lectures, delivering serious content with humor, imagination, and flair. A kind of a storyteller that motivated, educated, and ignited our inner fire.

Ernst Kenndler was born on July 9, 1943, in Linz, Austria. In 2023, it could have been his 80th birthday anniversary. It was in this stunning city, decorated with ornate buildings and grand churches that he began his early education and received an Abitur Diploma to qualify for college entry. Ernst Kenndler enrolled at the University of Vienna in 1961 to pursue studies in chemistry and physics. He worked at the Institute of Analytical Chemistry, where radiochemistry was the primary focus of research at this academy. After receiving his Ph.D. degree in Analytical Chemistry, he joined the group of renowned Professor J.F.K Huber as a postdoctoral student.

In 1975, Dr. Kenndler shifted his investigation to gas chromatography, eventually leading him to focus on isotachophoresis and capillary zone electrophoresis. He soon became a distinguished member of the international analytical chemistry community, playing a significant role in understanding the principles of separation science, especially in the field of electrophoresis. Dr. Kenndler served as a Professor of the Institute for Analytical Chemistry, Faculty of Sciences at University of Vienna in Austria, from 1990 until his retirement in 2008. The University of Helsinki, Finland, granted Ernst Kenndler in 2004 the title of Docent in Analytical Chemistry, in recognition of his scientific and teaching merits. Additionally, he was a lecturer at the Academy of Fine Arts, Vienna, from 1986 to 1999. Yet perhaps his most noteworthy professional achievement, was authoring nearly 250 scientific papers.

During his last years in academia, Dr. Kenndler became interested in bioanalysis, specifically, the macromolecular assembly of viruses. Additionally, he worked on theoretical aspects of capillary electrophoresis with organic solvents, and their implications for separation. Despite retiring, he continued to be very active in his vocation, writing papers, serving as a mentor for younger scientists, as well as a member of the Editorial Board for many separations science journals. Over the decades, he collaborated with countless professors and students throughout Europe and Latin America, establishing an incredibly vast network and inspired nearly everyone he worked with.

Dr. Ernst Kenndler was a connoisseur of many things, including arts, history, and food – so much so, that we called him a "walking library." He was so affable; you could immediately engage into a conversation with him and feel as if you had known him for years. Ernst Kenndler was always compassionate, empathetic, and positive with his pupils and although he could be strict, he was an exceptional lecturer who forged deep and lasting bonds with his students. As a scientist, he was indelible, leaving behind a legacy of scholarly work related to the basic principles of electrophoresis and its history. Without a doubt, Dr. Kenndler was an inspirational professor, a dedicated mentor, and an innovative scientist that will never be forgotten. He will be greatly missed.



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