The Molecule as an Epistemic Object: An Ontosemiotic Perspective on Its Historical Emergence

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Abstract. This article presents an epistemological and historical analysis of the emergence and evolution of the concept of molecule, using the Ontosemiotic Approach to knowledge and instruction as its theoretical framework. From this perspective, the meaning of the term 'molecule' is understood not as a fixed definition but pragmatically: as a system of operative and discursive practices directed towards solving specific problems in historically situated contexts. Through a diachronic study, the paper identifies and characterizes a series of partial meanings of the concept, from Dalton's compound particles and the Avogadro–Cannizzaro distinction between atoms and molecules to the structural representations of organic chemistry and contemporary quantum-mechanical treatments, together with the hybrid configurations that connect the last two. It then examines how these partial meanings are articulated into a holistic meaning of the concept, bringing out the discontinuities, semiotic mediations and shifts in ontological commitments that have shaped its development. The study thus shows how the Ontosemiotic Approach can be used to analyse the plurality of meanings of chemical concepts and their coexistence in practice, and it suggests hypotheses for teaching the concept of molecule that remain to be tested empirically.

Keywords: Ontosemiotic approach; concept of molecule; holistic meaning; history of chemistry; epistemology.

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1. INTRODUCTION

The concept of molecule constitutes a cornerstone of the intellectual architecture of modern chemistry. While the atom is commonly presented as the fundamental unit of the elements, it is the molecule that functions as the unit with which the composition and structure of a large class of substances are characterized, although not of all: ionic, metallic and network solids are not molecular. Its historical emergence was not a mere empirical discovery, but involved changes in what chemists were prepared to assume

about the constitution of substances. Nevertheless, the ontological status of molecules remains a central problem in the philosophy of chemistry. The difficulty does not stem from a lack of empirical evidence, but from the fact that what counts as a molecule appears to depend on the level of theoretical approximation adopted[1] and on the models and representational systems employed[2]. Fundamental chemical concepts do not always carry univocal ontological commitments. The concept of chemical element, for instance, has been used to denote both a simple substance and a basic substance that persists in its compounds, a duality examined from several perspectives in the essays edited by Scerri and Ghibaudi[3].

This tension is usually framed as a contrast between a naïve realism, which conceives molecules as discrete physical entities existing independently of any description, and an instrumentalism that treats the molecule as an operational construct. Yet this opposition is too schematic. Many nineteenth-century chemists used atoms and molecules without deciding whether they were real entities, useful fictions or operational devices[4], and the same reticence affected the interpretation of bonds and structural formulae (Section 4.3). The history of molecular concepts is thus also a history of how chemists suspended, negotiated or selectively adopted ontological commitments. For its part, this study adopts what Lombardi calls a Kantian-rooted pluralist realism: ontological commitments regarding molecules are neither read off a ready-made reality nor reduced to instruments, but constituted through chemical practices under the constraints that an independent reality imposes (Section 2.2).

In order to address this complexity, the present study adopts the theoretical architecture of the Ontosemiotic Approach (OSA) to mathematical and scientific knowledge[5, 6] in order to carry out a historical and epistemological reconstruction of the genesis and evolution of the concept of molecule. From this perspective, the meaning of a term or concept is not understood as an abstract definition, but pragmatically: as a system of operative and discursive practices oriented towards solving problem situations within historically situated contexts. The central aim is to identify and characterize the partial meanings of the concept of molecule that have emerged, from Dalton's "compound particles" to contemporary quantum-mechanical treatments, and to analyse how they are articulated into a holistic and systemic meaning. The expression 'epistemic object' in the title is taken from Rheinberger, for whom epistemic things "are material entities or processes—physical structures, chemical reactions, biological functions—that constitute the objects of inquiry. As epistemic objects, they present themselves in a characteristic, irreducible vagueness" (p. 28)[7]. This vagueness is what drives research, and it distinguishes epistemic objects from technical objects, which are stable enough to serve as tools for investigating other things. The molecule has played both roles: it was an epistemic object while its constitution and structure were under investigation, and it became a technical object as stabilized representations of it came into routine use in analysis and synthesis. It continues to play both roles today, since the molecule remains an object of research in quantum chemistry (Section 4.4). By situating this evolution within the history and philosophy of chemistry, the study shows how the OSA can be used to analyse the plurality of meanings of chemical concepts and suggests some hypotheses for chemistry education.

Section 2 presents the Ontosemiotic Approach and its ontological stance as a tool for historical and epistemological analysis, which conceives scientific constructs as emerging from systems of practices and their holistic meaning as a systemic network that integrates and coordinates partial meanings. Section 3 describes the methodology, a diachronic analysis of epistemic configurations, and proposes, as a working hypothesis, the historical periods that mark turning points in the systems of practices associated with the four partial

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meanings identified. Section 4, the core of the paper, analyses these partial meanings (protomolecular, physicochemical, structural and quantum) together with the hybrid configurations that connect the last two. Section 5 discusses how they are articulated into a holistic meaning and compares this conception with other perspectives in the history and philosophy of chemistry. Finally, Section 6 presents the conclusions, the implications of the study for the philosophy of chemistry and some prospective hypotheses for chemistry education.

2. THE ONTOSEMIOTIC APPROACH AS A TOOL FOR HISTORICAL AND EPISTEMOLOGICAL ANALYSIS

Within the Ontosemiotic Approach (OSA), practice is the elementary unit of analysis: any action or expression, linguistic or otherwise, performed by an agent to solve a problem, communicate a solution, or validate a result[8]. In OSA terminology, the 'meaning of an object' is the system of operative and discursive practices that a person or an institution carries out to solve the problems in which the object intervenes, 'object' being any entity (problem, language, concept, proposition, procedure, argument) that takes part in such practices[5]. The expression is a shorthand: strictly speaking, meaning is a property of the terms and concepts that designate the object, not of physical entities. Accordingly, this article speaks of the meaning of the term or concept 'molecule' and reserves the unqualified word 'molecule' for the chemical entity. From this standpoint, the meaning of 'molecule' is determined not by an *a priori* definition but by what chemists do with the concept in their practice.

2.1. The OSA and the Nature of Knowledge

The Ontosemiotic Approach to knowledge and instruction originated in the field of mathematics education; however, its ontological, semiotic and epistemological tools can be applied, with the adaptations discussed in Section 5, to the analysis of scientific concepts, particularly in chemistry. This theoretical framework distances itself from Platonic or purely idealist conceptions of knowledge, proposing instead a pragmatic[9] and anthropological paradigm[10]. On this view, scientific knowledge is not understood as access to pre-existing entities in a *noumenal* world, but as the outcome of human problem-solving activity. This view converges with Laudan's thesis that science is essentially a problem-solving activity, whose progress depends on its effectiveness in solving empirical problems and in removing conceptual ones, such as inconsistencies between theories[11]. In OSA terms, both kinds of problem are problem situations that drive systems of practices, and conceptual problems correspond to what the OSA calls semiotic conflicts (Section 4). Accordingly, the meaning of a concept such as that of molecule is defined by the system of operative and discursive practices enacted by a scientific community when confronting a specific problem situation. This perspective enables the historian of science to trace not only the "discovery" of an object, but also the evolution of the languages and modes of reasoning that endowed it with functional existence[12].

2.2. Ontological Stance

The anthropological view of knowledge outlined above entails a specific use of the term 'ontology'. Here it does not denote an inventory of a ready-made reality, independent of any description, to which chemical concepts would correspond one to one. In line with the Kantian tradition revisited by Putnam's internal realism[13], it denotes the domain of

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objects constituted when knowing subjects organize experience through their conceptual schemes and practices. As Torretti argues, objective situations "are not given but constituted […]"; in short, "objectivity is an achievement" (p. 81)[14]. Lombardi has developed this position into a pluralist realism. For her, an ontic domain "is not a mere creation of the mind, but arises from the synthesis between the noumenal realm and our framework" (p. 91)[15], and the frameworks involved are "shaped and stabilized through social practices, not only linguistic but also material practices of manipulation and transformation" (p. 87)[15]. Different frameworks thus constitute different ontic domains, "equally objective in different contexts and in function of certain interests and purposes" (p. 86)[15]. This thesis has been used to defend the ontological autonomy of the chemical world with respect to physics.

This stance fits the OSA notion of objects emerging from systems of practices[12]. OSA objects are neither mental entities nor ready-made things: they emerge from the practices with which a community solves problems. Accordingly, the ontological commitments regarding molecules are relative to the system of practices in which the term 'molecule' functions: molecules are real not as entities given independently of chemical practice, but as objects constituted by that practice under the constraints imposed by experimental results. Each partial meaning identified in Section 4 thus presupposes its own ontological commitments. Finally, the prefix 'onto-' in 'ontosemiotic' refers to the typology of objects that intervene in practices, described below, not to a metaphysical inventory of the world.

The analysis distinguishes five levels: (i) the molecular entity; (ii) the molecule as represented or conceptualized in a given period; (iii) the signs and models through which it is represented, such as formulae, structural graphs, ball-and-stick models or orbital diagrams; (iv) the practices in which these representations are produced and interpreted; and (v) the ontological commitments licensed by the success of these practices. Peirce's distinction between the immediate object, "the Object as the Sign itself represents it", and the dynamical object, "the Reality which by some means contrives to determine the Sign to its Representation", makes the difference between levels (i) and (ii) precise (CP 4.536) [9]. Each historically situated molecular object is an immediate object, an object-as-represented that emerges from a system of practices, while inquiry remains constrained by a dynamical object that no representation exhausts. In OSA terms, level (ii) corresponds to the object emerging from each configuration, level (iii) to its languages and level (iv) to its system of practices. The partial meanings analysed below are reconstructed at levels (ii) to (iv), together with the ontological commitments (v) that each presupposes. Claims about representations are therefore not converted directly into claims about the molecular entity (i): any such claim is mediated by the commitments that the practices license, which are discussed in Sections 5.2, 5.3 and 6.

2.3. The Ontosemiotic Configuration of the Concept

To understand the evolution of a construct such as the molecule, the OSA identifies a configuration of primary objects[5] involved in scientific practices. These objects do not operate in isolation, but are interwoven within a complex semiotic network. First, one considers the languages—terms, expressions, notations, and graphical representations—that allow the chemical entity to be represented on paper or in the laboratory. These are accompanied by the problems that drive chemical activity, and by the definitions (conceptualizations) that seek to delimit the identity of the object. The configuration also includes the propositions, procedures and arguments that serve to validate scientific conclusions. In the transition from classical to quantum chemistry, for example, one can observe how changes in computational procedures and validation arguments reconfigured

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the ontological commitments regarding molecules, which came to be represented as systems of nuclei and electrons described by electron densities and probability distributions.

The languages of a configuration are signs in Peirce's sense: a sign stands in a triadic relation to an object and to an interpretant, the effect it produces in an interpreter (CP 2.274; 4.536)[9]. The OSA notion of semiotic function, the correspondence that a subject establishes between an expression and a content according to a rule[16], is therefore triadic rather than binary: the rule, as used by a person or an institution, plays the role of the interpretant. Peirce's classes of signs allow the languages of chemistry to be differentiated, as Weininger has shown for chemical visual representations[17]. A sign may represent its object by likeness (icon), by being really affected by it (index) or by virtue of a law or habit of interpretation (symbol) (CP 2.247–2.249); among hypoicons, images partake of simple qualities of their object, whereas diagrams represent the relations among its parts by analogous relations among their own (CP 2.277). Icons, and diagrams in particular, have a further epistemic value: by observing them, truths about the object can be discovered beyond those used to construct them (CP 2.279). These distinctions are applied in the historical analysis of Section 4.

2.4. Dualities and Meanings: From Partial to Holistic Meaning

This framework pays particular attention to epistemic and cognitive dualities, particularly the dialectic between the unitary and the systemic. The OSA makes it possible to understand that a concept is not an indivisible unit, but rather a system composed of multiple partial meanings that have emerged at different historical moments. Each of these partial meanings corresponds to a specific ontosemiotic configuration: the molecule as a unit of volume in gases is distinct from, though related to, the molecule as a three-dimensional stereochemical structure. Historical and epistemological analysis is most informative when it identifies how these partial meanings are articulated, and at times come into tension, to give rise to what the OSA calls the holistic meaning of the concept[5].

2.5. An Example from Mathematics Education: The Concept of Function

The kind of analysis proposed here can be illustrated with the concept of function, studied within the OSA by Godino, Burgos and Wilhelmi[16]. Rather than tracing a succession of definitions, the analysis starts from the types of problems in which functional relations intervene and from the practices developed to solve them. Six partial meanings are identified, each with its own configuration of problems, languages, procedures, propositions and arguments: operative-tabular (Babylonian tables used to interpolate and predict quantities), operative-graphic (Oresme's graphical representation of the intensity of qualities), geometric-algebraic (curves expressed by equations in Descartes and Fermat), analytic (the function as an analytical expression in Johann Bernoulli and Euler), arbitrary correspondence between numerical sets (Dirichlet, prompted by the problem of representing functions by Fourier series), and mapping between arbitrary sets (Dedekind and the set-theoretic definition). In the first stages, the function is only implicit in practices; it becomes an explicit object, with its own types and properties, when problems require operating with functions themselves, as in eighteenth-century analysis.

This analysis yields three results that a purely historical narrative does not provide. First, transitions between meanings are explained by problems that previous practices could not solve, such as functions that can be neither drawn nor written as a formula,

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rather than by the refinement of a definition. Second, meanings are distinguished by explicit criteria: the degree of generality of the objects involved and the languages used to express them. Third, the holistic meaning is not the latest definition but a network of meanings linked by family resemblances: dependence and covariation connect the first meanings, whereas the set-theoretic one retains only the idea of correspondence. Earlier meanings remain in use, since calculus works with formulae relating variables while topology requires the set-theoretic definition. The same three questions guide the analysis of the concept of molecule below: which problems drive each configuration, which criteria distinguish configurations, and how they coexist.

3. METHODOLOGY: DIACHRONIC ANALYSIS OF EPISTEMIC CONFIGURATIONS

The methodology is a diachronic ontosemiotic analysis. Rather than offering a narrative of discoveries, it reconstructs the systems of practices that chemists mobilized to solve specific problems and the configuration of objects (problems, languages, concepts, propositions, procedures and arguments) involved in each of them[12]. Attention is also paid to the unitary–systemic duality: how the molecule is treated as a unit for some purposes and represented as a system of relations for others.

The historical corpus consists of the primary texts in which the main configurations were formulated: Dalton (1808), Avogadro (1811), Cannizzaro (1858), Kekulé and Couper (1858), Butlerov (1861), van 't Hoff and Le Bel (1874), Lewis (1916)[18], Heitler and London (1927)[19], and Mulliken (1932)[20], together with the works of Ingold and of Woodward and Hoffmann for the hybrid configurations[21, 22]. Nineteenth-century texts were consulted in the translations collected by Leicester and Klickstein[23], except those of Couper and Butlerov, which are known here through the historiography[24, 25]; twentieth-century texts are cited directly. Primary sources were used to identify the elements of each configuration, and the historiography of chemistry to situate them in their controversies and reception[24–28].

The periodization is a working hypothesis, not a claim about sharp boundaries: dates are indicative, periods overlap, and transitions often give rise to hybrid configurations (Section 4.5). A new period is delimited when three changes converge: in the dominant problem (combining weights; atomic and molecular weights and formulae; isomerism and spatial arrangement; bonding and stability), in the procedures and arguments used to validate claims about molecules, and in the representational register. These criteria yield four configurations; finer divisions, such as separating stereochemistry from structural theory, are possible and are treated here as developments within a configuration.

The OSA categories (problems, languages, concepts, procedures, propositions, arguments) were fixed in advance, as part of the theoretical framework, but their contents were taken from the sources: each cell of Table 1 summarizes what the texts of the corresponding period document. This reduces, though it does not eliminate, the risk of circularity: the categories organize the material, but they do not decide which problems, signs or arguments appear in each period.

The reconstruction also makes three claims that the historical record could refute: (i) each period has its own configuration, which would fail if changes in problems, procedures and representations did not occur at the same time; (ii) transitions are driven by problems that existing practices could not solve, which would fail if meanings changed without such problems; and (iii) earlier configurations persist alongside later ones, which would fail if an earlier configuration fell out of use once a later one appeared.

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4. ANALYSIS OF THE PARTIAL MEANINGS OF THE MOLECULE

4.1. The Protomolecular Meaning: "Compound Particles" (1803–1811)

The first partial meaning of the concept of molecule emerged with early nineteenth-century chemical atomism, in the context of the law of definite proportions and of the law of multiple proportions that Dalton's theory itself predicted[26]. In this period, the meaning we term protomolecular manifests itself in the practices of Dalton. Although he occasionally used 'molecule' as a synonym of 'ultimate particle' (p. 57)[29], he did not use it in its modern sense. His aim was to ascertain "the relative weights of the ultimate particles, both of simple and compound bodies, the number of simple elementary particles which constitute one compound particle, and the number of less compound particles which enter into the formation of one more compound particle" (p. 163)[29]. In OSA terms, this configuration rests on a duality between the macroscopic and the microscopic: the problems of the time were essentially gravimetric, concerning the determination of combining weights, yet solving them required the postulation of discrete particles endowed with specific relative weights.

Semiotic mediation at this stage was rudimentary but innovative. Dalton's notation combined three semiotic modes. Simple atoms were "denoted by a small circle, with some distinctive mark; and the combinations consist in the juxtaposition of two or more of these" (p. 168)[29]. The circular form had an iconic basis, suggesting a spherical particle; the association of each mark with a particular element was conventional and therefore symbolic; and the juxtaposition of marks operated diagrammatically, displaying relations among constituent parts (CP 2.277)[9]. This practice was constrained by the rule that "when only one combination of two bodies can be obtained, it must be presumed to be a binary one, unless some cause appear to the contrary", from which Dalton concluded that water was "a binary compound of hydrogen and oxygen" (p. 167)[29].

From the standpoint of the OSA categories of analysis, the Daltonian "compound particle" is not yet a molecule in the structural sense, but rather a mass point endowed with the capacity for chemical combination. The system of practices of this period focused on elemental composition and weight, omitting any consideration of the internal arrangement of components. Despite these limitations, this protomolecular meaning was fundamental to the establishment of chemistry as a quantitative science, providing the first rules of correspondence between the world of substances and that of microscopic entities—rules on which later configurations would build.

4.2. The Physicochemical Meaning: The Avogadro–Cannizzaro Distinction (1811–1860)

The transition toward what we term the physicochemical meaning of the molecule began with a conceptual problem, in Laudan's sense (Section 2.1), within the system of practices of early atomism. Gay-Lussac's law of combining volumes (1809) suggested a simple relation between volumes and numbers of particles, whereas Dalton had held that "the number of ultimate particles or molecules in a given weight or volume of one gas is not the same as in another" (p. 57)[29]. In 1811 Avogadro proposed that "the number of integral molecules in any gases is always the same for equal volumes" (p. 232)[30]. In his terminology, 'integral', 'constituent' and 'elementary' molecules correspond roughly to what are now called the molecules of compounds, the molecules of elements and atoms[26]. To reconcile this hypothesis with the observed volumes, he supposed that the constituent molecules of simple gases "are not formed of a solitary elementary molecule, but are made up of a certain number of these molecules united by attraction", and that they split in combination, usually into two, although "it is possible that in other cases the division

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might be into four, eight, &c." (pp. 234–235)[30]. From an ontosemiotic standpoint, this proposal was both a physical hypothesis and a semiotic reconfiguration, since it introduced a new rule of correspondence between the macroscopic behaviour of gases and the microscopic constitution of matter.

For nearly half a century Avogadro's proposal was not adopted by most chemists, and for reasons that were not mere confusion. Accepting it required the molecules of elements to be composed of two or more identical atoms, which conflicted with Berzelius's electrochemical dualism, and vapour densities gave anomalous results for substances such as mercury, phosphorus and sulphur[26]. Many chemists, notably in France, preferred equivalents, which seemed to avoid speculative commitments: Dumas renounced atoms in 1836 after finding discrepancies between vapour-density and other determinations, and Berthelot still rejected Avogadro's hypothesis against Wurtz in 1877[4].

During these decades, the lack of consensus on atomic weights meant that the same substance could be assigned different formulae by different chemists and schools[26]. Cannizzaro's Sunto (1858) offered a coherent system for determining atomic weights and molecular formulae by recovering Avogadro's hypothesis with a decisive qualification: equal volumes of gases "contain an equal number of molecules, not however an equal number of atoms, since the molecules of the different substances […] may contain a different number of atoms" (pp. 407–408)[31]. Combining vapour densities with the law of Dulong and Petit, he made atomic and molecular weights mutually consistent. The distribution of the Sunto at the Karlsruhe Congress of 1860 made it influential, but the reform of atomic weights was a gradual process, largely prepared before 1860 and completed unevenly afterwards[26].

In OSA terms, this configuration marked a qualitative change: the molecule ceased to be conceived as a Daltonian "compound particle" and came to be conceived as a unit defined by its behaviour in the gaseous phase and by its molecular weight. The configuration integrated languages (formulae based on consistent atomic weights), procedures (vapour-density determinations) and arguments (the distinction between atomic and molecular weights and the consistency of independent determinations). Two developments must, however, be distinguished: the standardization of atomic and molecular weights, which spread gradually after 1860, and the acceptance of molecules as physically real entities. The atomic hypothesis was deemed by many chemists "metaphysical rather than physical", and at Karlsruhe they debated "whether the physical atom and the chemical atom were one and the same" (pp. 110–111); physical atomism was still contested in the early twentieth century, when Ostwald claimed that the laws of chemical combination could be deduced from energetics without atomic hypotheses[27].

4.3. The Structural Meaning: Three-Dimensional Architecture (1860–1920)

The structural meaning emerged from the problem of the constitution of organic compounds, and isomerism, the existence of substances with identical composition but different properties, soon became its decisive test. It is not a single homogeneous configuration. In 1858 Kekulé and Couper independently proposed that carbon atoms combine with four units of affinity and can link with one another to form chains[24]. For Kekulé, "carbon is tetratomic", and in compounds with several carbon atoms "the carbon atoms themselves are joined together" (p. 419)[32]; Couper introduced dotted lines to represent these links. In 1861 Butlerov coined the term 'chemical structure' for the manner in which atoms are mutually bound, as known through their reactions. These contributions concerned chemical constitution, that is, connectivity, and were articulated through what would later be called the concept of valence[25].

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Three-dimensional configuration is a distinct development. In 1874 van 't Hoff and Le Bel independently related optical activity to the spatial arrangement of groups around a carbon atom. Van 't Hoff found that the theory "is brought into accord with the facts if we consider the affinities of the carbon atom directed toward the corners of a tetrahedron of which the carbon atom itself occupies the center" (p. 446)[33]; Le Bel reached a more general argument from molecular asymmetry, treating atoms and radicals as "spheres or material points" and admitting the regular tetrahedron only as a particular case (p. 460)[34]. Physical models and spatial diagrams thus became tools of inference, which allowed chemists to reason about entities that could not be directly observed[35], and late nineteenth-century textbooks progressively adopted three-dimensional representations[36].

In OSA terms, the structural meaning links chemical reactivity to molecular form. The molecule, previously represented as a point, came to be represented as an object with shape and bonds, allowing classical organic chemistry to predict and synthesize millions of new compounds on the basis of geometrical combination rules. This stage consolidated a fundamental duality: the molecule as a discrete unit for physics and, simultaneously, as a complex system of spatial relations for chemistry. It did not, however, produce a single interpretation of structural formulae. Some of their early proponents denied that they depicted physical arrangements. Crum Brown held that his graphic formulae indicated the chemical, not the physical, position of atoms[25]; Frankland stated that by 'bond' he did not "intend to convey the idea of any material connection between the elements of a compound" (pp. 96–97)[27]; and for Kekulé rational formulae were "reaction formulas" (p. 99)[24]. Chemical constitution, spatial configuration and physical molecular structure were differentiated only gradually and controversially. Van 't Hoff's directed valences began to endow bonds with a spatial meaning[28], against the opposition of chemists such as Kolbe, who dismissed this as "pencil and paper chemistry" (p. 69)[27]. Far from being supplanted by quantum mechanics, structural formulae continued to provide the working language of organic chemists, and practitioners of quantum chemistry combined the visual imagery of Kekulé and Crum Brown with the abstract symbolism of Dirac and Schrödinger[27].

4.4. The Quantum Meaning: Molecules as Systems of Nuclei and Electrons (from the late 1920s)

The development of quantum mechanics in the 1920s entailed a profound revision of the ontological status attributed to molecules. Building on the electron theory of valence (Section 4.5), Heitler and London explained the bond in the hydrogen molecule through electron-pair exchange[19], and Mulliken introduced molecular orbitals extending over the whole molecule[20]. The molecule came to be described as a system of nuclei and electrons whose stationary states are solutions of the Schrödinger equation, usually within the approximation of fixed nuclei[1]. This configuration introduced new semiotic mediations, such as molecular orbitals and potential-energy surfaces, which did not replace structural formulae but have coexisted with them, performing different inferential functions: structural formulae support reasoning about connectivity and synthesis, whereas orbitals and energy surfaces support reasoning about stability, spectra and reaction paths. For Coulson, electron densities gave "flesh and blood to cover the bare bones that Couper and Frankland and Kekulé and Crum Brown had represented by a line" (p. 259)[27].

This shift posed a fundamental epistemological challenge: the tension between molecular structure, heir to the nineteenth-century structural meaning, and quantum formalism. Whereas structural chemistry assigned fixed relative positions to atoms,

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quantum mechanics, in its strictest formulation, dissolves the notion of shape into probability distributions. In practice, this tension is handled through the Born–Oppenheimer approximation, which allows nuclei to be treated as fixed in order to recover molecular geometry. However, as Sutcliffe and Woolley have argued, molecular structure is not derivable from the full quantum-mechanical treatment of an isolated system of nuclei and electrons: the clamped-nuclei Hamiltonian introduces nuclear positions as fixed parameters, an assumption in tension with the treatment of nuclei as quantum particles[1, 37, 38]. Thus, the quantum meaning does not annul previous meanings, but neither does it simply subsume them: the notion of structure is imported from classical chemistry into the quantum system of practices. Nor does quantum chemistry supply a single conception of the chemical bond: structural conceptions, which identify bonds with localized features of the electron distribution, coexist with energetic ones, which treat bonding as a stabilization of the whole system[39].

In OSA terms, the quantum configuration is, to date, the most complex of those identified here, in the degree of abstraction of its languages and procedures. It does not complete the holistic meaning of the concept of molecule but enriches it, adding the predictive power of quantum mechanics to the heuristic strength of classical structure, and it remains open to further reconfiguration. As a result, the molecule is represented today in multiple ways: as a graph for the synthetic chemist, as a potential-energy surface for the computational chemist and as an electron-density map for the crystallographer. Several authors argue that the concept of molecular structure requires assumptions incompatible with quantum mechanics, without this undermining its theoretical or practical legitimacy[38, 40, 41]. The thesis defended here is therefore not that these meanings are free of contradiction, but that they coexist legitimately in chemical practice despite formal incompatibilities, each within its own domain of validity.

4.5. Hybrid Configurations: The Electronic Theory of Organic Chemistry and Frontier Orbitals

The transition between the structural and quantum meanings was not a clean break. Between the 1910s and the 1950s, organic chemists developed an electronic theory of organic reactions that, as Nye has shown, combined nineteenth-century structural chemistry with Lewis's identification of the bond with a shared electron pair[18, 27]. Building on Lewis's theory, Robinson and Ingold introduced a new language (curved arrows, partial charges, inductive and mesomeric effects, nucleophiles and electrophiles) to solve a new type of problem: explaining reaction mechanisms and predicting where and how molecules react[21]. The procedures and arguments of this theory were largely qualitative and were not derived from quantum mechanics. Frontier orbital theory, developed by Fukui and closely related to the orbital-symmetry rules of Woodward and Hoffmann, is a later hybrid of a different kind: it uses the language of molecular orbitals, notably the interaction between the highest occupied and the lowest unoccupied orbitals, but applies it to problems of the structural meaning, such as predicting the course of reactions in which specific bonds are formed or broken[22, 42].

From the ontosemiotic perspective, both theories are hybrid configurations: they articulate objects from two partial meanings within a single system of practices. Both presuppose the chemical bond as a unit of the structural meaning, and their validity is restricted to problems of bond formation and cleavage[42]. They show that the boundary between the structural and quantum periods is porous, and they provide the clearest evidence of the model alternation discussed in Section 5.1.

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5. DISCUSSION: ARTICULATION OF THE HOLISTIC MEANING

In contemporary chemistry, the transition between the partial meanings described above does not occur through hierarchical replacement, but rather through what the Ontosemiotic Approach terms the *articulation of meanings*. The professional chemist does not rely on a single definition of the molecule, but instead mobilizes a "toolbox" of models, each with its own ontological commitments, which is activated according to the problem situation at hand. Table 1 synthesizes the constitutive elements of the holistic meaning of the concept of molecule as reconstructed from the Ontosemiotic Approach. Its purpose is to show, in a comparative manner, how the different partial meanings—protomolecular, physicochemical, structural, and quantum— are configured as differentiated systems of practices, each with its own problems, languages, concepts, propositions, procedures and arguments. The table thus shows the ontosemiotic plurality of the concept and the relations of dependence, complementarity, reorganization and tension among its partial meanings.

Table 1. Elements of the partial meanings of the concept of molecule

	Protomolecular	**Physicochemical**	**Structural**	**Quantum**
Actors' characterizations	Dalton (1808): "compound particles" formed by a definite number of "simple elementary particles"	Avogadro (1811): *molécules intégrantes*, *constituantes* and *élémentaires*. Cannizzaro (1858): molecular weights from vapour densities	Kekulé, Couper (1858): tetratomic, self-linking carbon; Butlerov (1861): 'chemical structure'; van 't Hoff, Le Bel (1874): spatial arrangement	Heitler–London (1927): bond from electron-pair exchange; Mulliken (1932): molecular orbitals extending over the molecule
Problems	Explaining definite and multiple proportions	Reconciling combining volumes with atomic theory; atomic and molecular weights	Constitution of organic compounds; isomerism; later, optical activity	Explaining bonding, stability and spectra
Practices	Gravimetric analysis; tables of relative weights	Vapour-density and specific-heat determinations	Synthesis and degradation; isomer counting; polarimetry	Spectroscopy; X-ray diffraction; quantum-chemical computation
Languages	Dalton's symbols	Formulae based on consistent atomic weights (e.g., Cannizzaro)	Graphic and constitutional formulae; stereoformulae; ball-and-stick models	Wave functions; orbital diagrams; potential-energy surfaces
Propositions	Laws of definite and multiple proportions; rule of greatest simplicity	Avogadro's hypothesis; law of combining volumes; Dulong–Petit law	Tetravalence of carbon; tetrahedral carbon	Schrödinger equation; Pauli principle; Born–Oppenheimer approximation
Procedures	Relative weights from combining masses	Molecular weights from vapour densities; Cannizzaro's method	Structure determination from reactions, isomer number and optical activity	Approximate solution of the Schrödinger equation; geometry optimization
Arguments	From fixed ratios to discrete particles	Consistency of independent	From isomer counts and optical activity	Agreement between calculated

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	determinations of atomic weights	to constitution and configuration	and experimental data

Note: The first row corresponds to the OSA category of concepts and records characterizations documented in historical sources, in the actors' own terms; the remaining rows are retrospective analytical reconstructions within the OSA categories. Hybrid configurations (Section 4.5) are not shown.

5.1. Model Alternation as Semiotic Competence

The diachronic analysis developed in the preceding sections reveals that the evolution of the concept of molecule does not follow a linear replacement of obsolete theories by more accurate ones, but rather a process of coexistence, reorganization and occasional abandonment of partial meanings. In contemporary chemical practice, the ability to move between Kekulé's structural meaning and the quantum meaning of molecular orbitals is not experienced as an obstacle, despite the formal incompatibilities noted in Section 4, but as a fundamental form of semiotic competence: knowing which meaning is valid for which problem. The clearest evidence of this competence is provided by the hybrid configurations described in Section 4.5. The organic chemist who draws curved arrows on a structural formula and reasons about frontier orbitals is not switching arbitrarily between models, but coordinating objects from two partial meanings within a single system of practices.

In OSA terms, model alternation is a pragmatic use of different epistemic configurations, in which the subject selects the system of practices—and, consequently, the meaning of the term 'molecule'—that proves most effective for solving a given problem situation. This capacity to keep theoretical and experimental perspectives simultaneously in view, without merging them, is a characteristic form of chemical expertise.

The ability to move between models has, however, a restricted domain, as the hybrid theories show (Section 4.5): according to Ochiai, they succeed because they deal only with bond formation and cleavage, where the classical concept of the molecule remains consistent with quantum calculations. He relates these theories to the Kantian *Anschauung*, the intuition through mental pictures that guided nineteenth-century chemists, and describes the curly arrow and the orbital lobe as a semiotic coding rather than a visualization of mathematically derived orbitals[42]. In OSA terms, the success of these theories depends on the diagrammatic languages of the structural meaning, which remain operative within the quantum one. As Meinel emphasizes, molecular models function as operative tools mediating between theory and experimentation; their value lies not exclusively in their fidelity to an underlying physical reality, but in their heuristic power[35]. In Peirce's sense, abduction is the inference from a surprising fact to a hypothesis that would render it "a matter of course" (CP 5.189)[9]. Molecular images take part in such inferences because, as diagrams, they allow relations to be read off by observation[43]. Kekulé's benzene ring is an example: from the composition and substitution behaviour of aromatic compounds he inferred that all of them share a common nucleus of six carbon atoms, which he then represented as a closed chain[24]. Within the OSA framework, the chemist handles a unitary–systemic duality: the molecule is treated as a simplified functional unit in certain contexts and as a complex quantum system in others, which suggests that disciplinary expertise entails mastery of these semiotic translations[6].

Consequently, chemical expertise does not consist in adopting the quantum model as the only correct one, but in the capacity to manage this plurality of meanings. The articulation of the holistic meaning of the concept of molecule lies in recognizing that each partial meaning has its own domain of validity, and that the tensions among them are managed in practice rather than resolved in theory. As Cartwright argues even for

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physics, success does not require unification: "Many of its brilliant successes come from constructing crafty models that incorporate theories that are not unified" (pp. 109–110)[41]. This competence in moving between semiotic registers and ontosemiotic configurations is part of chemical expertise, and it supports the autonomy of chemistry from physical reductionism[15], preserving models that, although simplified, retain an indispensable operative validity in the laboratory.

5.2. Semiotic Discontinuities and Shifts in Ontological Commitments

The evolution of the concept of molecule is also marked by semiotic discontinuities that reconfigured the ontology presupposed by chemical practice. In OSA terms, these ruptures are not mere changes in nomenclature, but shifts in ontological commitments prompted by new problem situations that previous languages and procedures could not resolve. The transition from Dalton's compound particles to Avogadro's molecules is an example: the conflict was not resolved through the accumulation of experimental data, but through a new conceptual distinction between elementary and constituent molecules, which, once recovered by Cannizzaro, restored coherence to the system of physicochemical practices (Section 4.2). These shifts should not, however, be read as a sequence of commitments adopted successively by the whole community. Within each period, chemists followed different strategies: French equivalentists avoided atoms altogether; Dumas held a corpuscular view of matter while rejecting atomic weights as undeterminable; and Gerhardt and Kekulé used atoms and rational formulae while declaring the question of their existence a metaphysical one[4]. The partial meanings identified here are therefore reconstructions of dominant configurations, not uniform stages of belief.

These discontinuities are particularly evident in the transition from structural to quantum chemistry, although it was mediated by hybrid configurations (Section 4.5). Whereas the structural meaning relied on a mechanical and visual semiotic mediation (graphs and three-dimensional models), the quantum meaning shifted the focus from the relative positions of atoms to electron densities and probability distributions. In OSA terms, this entailed a transformation in the meaning of the concept: the molecule ceased to be conceived as a body with a fixed form and came to be represented as a system of nuclei and electrons whose properties are calculated rather than read off from an image.

Nevertheless, these ruptures do not imply a complete break. Ontosemiotic analysis reveals the persistence of a practical role across theoretical frameworks: in many, though not all, chemical practices, the molecule functions as the operative unit with which substances are characterized, synthesized and transformed. This continuity should not be read as a microessentialist thesis, according to which the identity of a substance is given by its molecular microstructure. That thesis has been contested: Weisberg and Needham argue that chemists also individuate substances by macroscopic and thermodynamic criteria, so that water is not simply a collection of H_2O molecules; Bursten, that microstructure can guide classification without functioning as an essence; and Havstad, that many chemical kinds resist any single microstructural criterion[44-48]. Taken together, these discontinuities and continuities suggest that chemical progress is not a mere accumulation of knowledge, but a series of transformations in the systems of representation and argumentation that define, in each period, what counts as a real chemical entity.

5.3. From the Molecule as a Thing to an Increasingly Relational and Processual Conception

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The diachronic trajectory also shows a change in the ontological commitments presupposed by molecular practices. In the early stages of structural chemistry, some chemists interpreted the molecule within a mechanical framework, in which atoms were spheres connected by rigid bonds, while others regarded structural formulae merely as summaries of chemical reactions (Section 4.3). Quantum and computational chemistry have displaced this picture: molecular properties are represented as features of a system of interacting nuclei and electrons, whose geometry is recovered only by fixing the nuclei (Section 4.4), and which, in molecular simulations, appears as a pattern of fluctuating configurations rather than as a rigid architecture.

The thesis defended here is therefore a modest one: contemporary molecular ontology has become increasingly relational and processual. It is relational because properties such as shape, bonding or polarity are attributed relative to models, approximations and scales of observation; it is processual because these properties are increasingly represented as stable patterns of dynamic interactions rather than as fixed attributes of a thing. This claim concerns the representations and practices of quantum and computational chemistry, that is, the immediate object in the sense of Section 2, and the commitments they license. It does not establish that molecules are processes in the technical sense of process ontology: dynamic systems, mathematical models and probability distributions belong to different categories, and a process ontology of molecules, such as Seibt's account of dynamic entities[49], would require criteria of individuation and persistence that lie beyond the scope of this paper. In OSA terms, this shift corresponds to the passage from iconic and diagrammatic to symbolic and computational mediations (Sections 4.4 and 5.2), and reinforces the systemic and context-dependent character of the holistic meaning of the concept.

5.4. The OSA in Dialogue with the History and Philosophy of Chemistry

The reconstruction proposed here can be compared with several positions in the history and philosophy of chemistry, considering what each contributes that the OSA lacks, what the OSA adds, and where it reaches its limits.

Hoffmann's reflections on chemical identity, built on the tension expressed in the title of his book *The Same and Not the Same*[50], capture a dimension that the OSA leaves in the background: chemistry makes many of its own objects, so that synthesis, and not only representation, shapes what a molecule is taken to be. Bensaude-Vincent shows that molecular entities are stabilized through instruments and material operations, and that chemists often suspended or negotiated their ontological commitments[4, 51]; the OSA, developed for mathematics, where the ostensive objects of practice are mainly notations, has no explicit place for these material mediations. Nye's history of the formation of theoretical chemistry[27] explains how disciplinary boundaries, schools and controversies shaped the configurations analysed here, a social dimension that the OSA, centred on institutional meanings, tends to treat as homogeneous. Chang's "active normative pluralism" (p. 269)[52] holds that several systems of practice should be cultivated rather than merely tolerated; the OSA describes the coexistence of meanings but does not by itself justify it.

What the OSA adds is an explicit configuration of problems, languages, procedures, propositions and arguments for each meaning (Table 1), which allows meanings to be compared element by element and helps to explain why they coexist: each is tied to a type of problem with its own domain of validity. It also clarifies how meanings are articulated within a single system of practices, as in the hybrid theories of Section 4.5. A reductive

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alternative, which seeks to ground molecular identity in quantum mechanics alone, would explain the success of quantum chemistry, but not why formally incompatible models remain jointly indispensable[38, 40, 41].

The OSA also has limits. It does not by itself settle ontological questions, which require the stance made explicit in Section 2, and its categories organize, but cannot replace, historical evidence. Conversely, the chemical case extends the framework: instruments and ontological commitments must be included as components of configurations, and articulation must be understood not only as the coordination of meanings across contexts but also as their combination within hybrid configurations.

6. CONCLUSIONS AND PERSPECTIVES

The diachronic reconstruction presented in this study shows that the concept of molecule has not followed a linear trajectory of refinement towards an absolute truth, but has instead evolved through a series of epistemic configurations responding to specific operative needs. From the perspective of the Ontosemiotic Approach, the emergence of the molecule can be understood as the result of successive reconfigurations of scientific practices and of the interactions among their primary objects. The OSA shows that later configurations do not simply erase earlier ones: some partial meanings remain functional in specific contexts. Reorganizations also involved losses and abandoned alternatives, such as the ontological prudence of equivalentism, Brodie's algebraic calculus of chemical operations[4] or Ostwald's energetics; and the quantum treatment weakened the direct link between structural formula and reactivity that hybrid theories later had to restore (Section 4.5). Moreover, the evolution of the concept is marked by the resolution of semiotic conflicts, such as those over the atom–molecule distinction or the nature of the chemical bond, in which new languages and arguments proved decisive.

Thus, the ontosemiotic lens supports the claim that the concept of molecule is a holistic construct: a network of meanings that enables the chemists to operate with equal competence when weighing a substance (physicochemical meaning), predicting a reaction (structural meaning), or simulating an electronic property (quantum meaning). The history of the concept of molecule is thus also a history of the changing capacities for representation and action of chemical practice.

The ontosemiotic analysis can contribute to the debate on realism in contemporary philosophy of chemistry. The diachronic trajectory of the concept suggests that chemical practice is better described by the Kantian-rooted pluralist realism outlined in Section 2 than by a naïve realism seeking a one-to-one correspondence between the term 'molecule' and an immutable physical entity. From this standpoint, the reality of the molecule does not reside in its ultimate *substantiality*, but in the effectiveness of the systems of practices that allow it to be manipulated and transformed. As the OSA framework maintains, the ontological status attributed to a scientific object is inseparable from the network of semiotic functions that constitute it in a given context[5]; accordingly, the commitment to the reality of molecules is licensed insofar as epistemic configurations—whether structural or quantum—enable the prediction of phenomena and the synthesis of new substances.

This approach offers a way to mediate the tension between structural realism and instrumentalism. While structural realism holds that what persists across theoretical change are the mathematical and structural relations among entities, the ontosemiotic analysis suggests that what persists is a holistic meaning composed of the articulation of partial meanings. In this view, molecular form is neither an intrinsic property derivable from quantum mechanics nor one invalidated by it, but a property constituted within a

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specific system of practices that retains its operative validity. Philosophy of chemistry thus benefits from understanding the ontology presupposed by chemical practice as dynamic and relational, which supports the autonomy of chemistry from physical reductionism (Section 5.1).

The distinction between the molecular entity and the models through which it is represented reinforces the idea that chemistry is a science of mediations: instruments, languages and representations do not merely describe chemical phenomena but contribute to configuring them. As Harré has argued, laboratory instruments form "apparatus–world complexes" (p. 20)[53] whose phenomena are not simply found in nature, and the grammars of chemical discourse, such as the mereologies with which chemists speak of molecules and their parts, shape what counts as a chemical entity[54]. By understanding the meaning of the concept of molecule as a system of practices, philosophy of chemistry can better account for how the discipline maintains its coherence across theoretical discontinuities and across scales, from the laboratory bench to mathematical formalism.

Finally, these results suggest some hypotheses for chemistry education. Presenting atomic and molecular models as a sequence of superseded errors may contribute to students' difficulties in reconciling apparently contradictory representations. An alternative would be to make explicit the partial meanings of 'molecule', the problems for which each is suited and the semiotic discontinuities between them, so that the ball-and-stick molecule and the electron-density molecule are understood as tools with distinct domains of validity[55,56]. As in the case of function[16], where the most general meaning cannot be the starting point of instruction, the meanings reconstructed here could serve as a reference for selecting and sequencing those appropriate to each educational level.

A pluralist presentation could also help overcome the "scientific monism" (p. 87) that Mocellin and Labarca identify in chemistry classrooms, presenting chemistry as a field with historical tensions and open questions rather than as a catalogue of finished truths[57]. Whether teaching sequences based on the plurality of meanings actually improve students' understanding of models and of the nature of chemistry cannot be settled by a historical and epistemological analysis; it is a question for future research in chemistry education.

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REFERENCES

1. R. G. Woolley, Is There a Quantum Definition of a Molecule?, *J. Math. Chem.* **1998**, *23*, 3–12.
2. J. Hunger, How Classical Models of Explanation Fail to Cope with Chemistry—The Case of Molecular Modeling, in *Philosophy of Chemistry: Synthesis of a New Discipline* (Eds.: D. Baird, E. Scerri, L. McIntyre), Springer, Dordrecht, **2006**, pp. 129–155.
3. E. Scerri, E. Ghibaudi (Eds.), *What Is a Chemical Element? A Collection of Essays by Chemists, Philosophers, Historians, and Educators*, Oxford University Press, New York, **2020**.

4. B. Bensaude-Vincent, Atomism and Positivism: A Legend about French Chemistry, *Ann. Sci.* **1999**, *56*, 81–94.
5. J. D. Godino, *Ontosemiotic Approach in Mathematics Education: Foundations, Tools, and Applications*, Author edition (DIGIBUG, Universidad de Granada), Granada, **2024**. https://hdl.handle.net/10481/93738
6. J. D. Godino, C. Batanero, V. Font, The Onto-semiotic Approach to Research in Mathematics Education, *ZDM Int. J. Math. Educ.* **2007**, *39*, 127–135. https://doi.org/10.1007/s11858-006-0004-1
7. H.-J. Rheinberger, *Toward a History of Epistemic Things: Synthesizing Proteins in the Test Tube*, Stanford University Press, Stanford, **1997**.
8. J. D. Godino, C. Batanero, Clarifying the Meaning of Mathematical Objects as a Priority Area of Research in Mathematics Education, in *Mathematics Education as a Research Domain: A Search for Identity* (Eds.: A. Sierpinska, J. Kilpatrick), Kluwer, Dordrecht, **1998**, pp. 177–195.
9. C. S. Peirce, *Collected Papers of Charles Sanders Peirce*, Vols. 1–8 (Eds.: C. Hartshorne, P. Weiss, A. W. Burks), Harvard University Press, Cambridge, MA, **1931–1958**. Cited as CP followed by volume and paragraph number.
10. L. Wittgenstein, *Philosophical Investigations*, Basil Blackwell, Oxford, **1953**.
11. L. Laudan, *Progress and Its Problems: Towards a Theory of Scientific Growth*, University of California Press, Berkeley, **1977**.
12. V. Font, J. D. Godino, J. Gallardo, The Emergence of Objects from Mathematical Practices, *Educ. Stud. Math.* **2013**, *82*, 97–124. https://doi.org/10.1007/s10649-012-9411-0
13. H. Putnam, *Reason, Truth and History*, Cambridge University Press, Cambridge, **1981**.
14. R. Torretti, Objectivity: A Kantian Perspective, in *Kant and Philosophy of Science Today* (Ed.: M. Massimi), Cambridge University Press, Cambridge, **2008**, pp. 81–95.
15. O. Lombardi, A Kantian-Rooted Pluralist Realism for Science, in *Current Debates in Philosophy of Science* (Ed.: C. Soto), Springer, Cham, **2023**, pp. 81–101.
16. J. D. Godino, M. Burgos, M. R. Wilhelmi, Onto-semiotic Analysis of the Emergence and Evolution of Functional Reasoning, *Revista de Investigación en Matemática y su Enseñanza (RIME)* **2024**, *1*, 9–37. https://doi.org/10.32735/S2810-7187202400013181
17. S. J. Weininger, Contemplating the Finger: Visuality and the Semiotics of Chemistry, *HYLE* **1998**, *4*, 3–27. https://www.hyle.org/journal/issues/4/weinin.htm
18. G. N. Lewis, The Atom and the Molecule, *J. Am. Chem. Soc.* **1916**, *38*, 762–785.
19. W. Heitler, F. London, Wechselwirkung neutraler Atome und homöopolare Bindung nach der Quantenmechanik, *Z. Phys.* **1927**, *44*, 455–472.
20. R. S. Mulliken, Electronic Structures of Polyatomic Molecules and Valence, *Phys. Rev.* **1932**, *40*, 55–62.
21. C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, **1953**.
22. R. B. Woodward, R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie/Academic Press, Weinheim/New York, **1970**.
23. H. M. Leicester, H. S. Klickstein (Eds.), *A Source Book in Chemistry, 1400–1900*, Harvard University Press, Cambridge, MA, **1952**.

Accepted Manuscript

24. A. J. Rocke, *Image and Reality: Kekulé, Kopp, and the Scientific Imagination*, University of Chicago Press, Chicago, **2010**.

25. C. A. Russell, *The History of Valency*, Leicester University Press, Leicester, **1971**.

26. A. J. Rocke, *Chemical Atomism in the Nineteenth Century: From Dalton to Cannizzaro*, Ohio State University Press, Columbus, **1984**.

27. M. J. Nye, *From Chemical Philosophy to Theoretical Chemistry: Dynamics of Matter and Dynamics of Disciplines, 1800–1950*, University of California Press, Berkeley, **1993**.

28. P. J. Ramberg, *Chemical Structure, Spatial Arrangement: The Early History of Stereochemistry, 1874–1914*, Ashgate, Aldershot, **2003**.

29. J. Dalton, *A New System of Chemical Philosophy*, Part I, R. Bickerstaff, Manchester, **1808**; reprint: Citadel Press, New York, 1964 (page numbers refer to the reprint).

30. A. Avogadro, Essai d'une manière de déterminer les masses relatives des molécules élémentaires des corps, et les proportions selon lesquelles elles entrent dans ces combinaisons, *J. Phys. Chim. Hist. Nat.* **1811**, *73*, 58–76; Engl. transl. (Alembic Club Reprints, No. 4) in ref. 23, pp. 231–238.

31. S. Cannizzaro, Sunto di un corso di filosofia chimica fatto nella Reale Università di Genova, *Il Nuovo Cimento* **1858**, *7*, 321–366; Engl. transl. (Alembic Club Reprints, No. 18) in ref. 23, pp. 407–417.

32. A. Kekulé, Ueber die Constitution und die Metamorphosen der chemischen Verbindungen und über die chemische Natur des Kohlenstoffs, *Ann. Chem. Pharm.* **1858**, *106*, 129–159; partial Engl. transl. in ref. 23, pp. 418–420.

33. J. H. van 't Hoff, Sur les formules de structure dans l'espace, *Arch. Néerl. Sci. Exactes Nat.* **1874**, *9*, 445–454; Engl. transl. in ref. 23, pp. 445–452.

34. J. A. Le Bel, Sur les relations qui existent entre les formules atomiques des corps organiques et le pouvoir rotatoire de leurs dissolutions, *Bull. Soc. Chim. Paris* **1874**, *22*, 337–347; Engl. transl. in ref. 23, pp. 459–462.

35. C. Meinel, Molecules and Croquet Balls, in *Models: The Third Dimension of Science* (Eds.: S. de Chadarevian, N. Hopwood), Stanford University Press, Stanford, **2004**, pp. 242–275.

36. M. Chioccioli, An Investigation into the Role and Importance of Three-Dimensional Representations through an Analysis of Late 19th and Early 20th Century Chemistry Textbooks, *Substantia* **2025**, *9*, 99–109. https://doi.org/10.36253/Substantia-3430

37. B. T. Sutcliffe, R. G. Woolley, On the Quantum Theory of Molecules, *J. Chem. Phys.* **2012**, *137*, 22A544.

38. B. T. Sutcliffe, R. G. Woolley, Is Chemistry Really Founded in Quantum Mechanics?, in *Quantum Chemistry: Philosophical Perspectives in Modern Chemistry* (Eds.: O. Lombardi, J. C. Martínez González, S. Fortin), Springer, Cham, **2022**, pp. 173–202.

39. R. F. Hendry, Two Conceptions of the Chemical Bond, *Philos. Sci.* **2008**, *75*, 909–920.

40. H. Chang, Reductionism and the Relation between Chemistry and Physics, in *Relocating the History of Science: Essays in Honor of Kostas Gavroglu* (Eds.: T. Arabatzis, J. Renn, A. Simões), Springer, Cham, **2015**, pp. 193–209.

41. N. Cartwright, *A Philosopher Looks at Science*, Cambridge University Press, Cambridge, **2022**.

Accepted Manuscript

42. H. Ochiai, Why Do Prima Facie Intuitive Theories Work in Organic Chemistry?, *Found. Chem.* **2023**, *25*, 359–367. https://doi.org/10.1007/s10698-023-09470-1

43. E. M. Ghibaudi, An Exercise of Applied Epistemology: Peirce's Semiosis Implemented in the Representation of Protein Molecules, *Substantia* **2024**, *8*, 45–56. https://doi.org/10.36253/substantia-2558

44. M. Weisberg, Water Is Not H_2O, in *Philosophy of Chemistry: Synthesis of a New Discipline* (Eds.: D. Baird, E. Scerri, L. McIntyre), Springer, Dordrecht, **2006**, pp. 337–345.

45. P. Needham, Microessentialism: What Is the Argument?, *Noûs* **2011**, *45*, 1–21.

46. P. Needham, Determining Sameness of Substance, *Br. J. Philos. Sci.* **2017**, *68*, 953–979.

47. J. Bursten, Microstructure without Essentialism: A New Perspective on Chemical Classification, *Philos. Sci.* **2014**, *81*, 633–653.

48. J. C. Havstad, Messy Chemical Kinds, *Br. J. Philos. Sci.* **2018**, *69*, 719–743.

49. J. Seibt, Forms of Emergent Interaction in General Process Theory, *Synthese* **2009**, *166*, 479–512.

50. R. Hoffmann, *The Same and Not the Same*, Columbia University Press, New York, **1995**.

51. B. Bensaude-Vincent, *Matière à penser: Essais d'histoire et de philosophie de la chimie*, Presses universitaires de Paris Ouest, Nanterre, **2008**.

52. H. Chang, *Is Water H2O? Evidence, Realism and Pluralism*, Springer, Dordrecht, **2012**.

53. R. Harré, The Materiality of Instruments in a Metaphysics for Experiments, in *The Philosophy of Scientific Experimentation* (Ed.: H. Radder), University of Pittsburgh Press, Pittsburgh, **2003**, pp. 19–38.

54. R. Harré, J.-P. Llored, Mereologies as the Grammars of Chemical Discourses, *Found. Chem.* **2011**, *13*, 63–76.

55. M. Izquierdo-Aymerich, A. Adúriz-Bravo, Epistemological Foundations of School Science, *Sci. Educ.* **2003**, *12*, 27–43. https://doi.org/10.1023/A:1022698205904

56. J. K. Gilbert, D. F. Treagust (Eds.), *Multiple Representations in Chemical Education*, Springer, Dordrecht, **2009**.

57. R. C. Mocellin, M. Labarca, For a Dialogue between the Teaching of Chemistry and the History and Philosophy of Chemistry: The Case of the Concept of 'Chemical Element', *Substantia* **2024**, *8*, 81–89. https://doi.org/10.36253/substantia-2324

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