OF MINDS AND MOLECULES

New Philosophical Perspectives on Chemistry

Edited by
Nalini Bhushan
Stuart Rosenfeld

OXFORD
UNIVERSITY PRESS
2000

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How Symbolic and Iconic Languages Bridge the Two Worlds of the Chemist

A Case Study from Contemporary Bioorganic Chemistry

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Chemists move habitually and with credible success—if sometimes unreflectively—between two worlds. One is the laboratory, with its macroscopic powders, crystals, solutions, and intractable sludge, as well as the things that are smelly or odorless, toxic or beneficial, pure or impure, colored, or white. The other is the invisible world of molecules, each with its characteristic composition and structure, its internal dynamics and its ways of reacting with the other molecules around it. Perhaps because they are so used to it, chemists rarely explain how they are able to hold two seemingly disparate worlds together in thought and practice. And contemporary philosophy of science has had little to say about how chemists are able to pose and solve problems, and, in particular, to posit and construct molecules, while simultaneously entertaining two apparently incompatible strata of reality. Yet chemistry continues to generate highly reliable knowledge, and indeed to add to the furniture of the universe, with a registry of over ten million well-characterized new compounds.

The philosophy of science has long been dominated by logical positivism, and the assumptions attendant on its use of predicate logic to examine science, as well as its choice of physics as the archetype of a science. Positivism thus tends to think of science in terms of an axiomatized theory describing an already given reality and cast in a uniform symbolic language, the language of predicate logic. (See especially the locus classicus of this position, Carnap, 1937.)

We here wish to question certain positivist assumptions about scientific rationality, based on an alternative view brought into focus by the reflective examination of a case study drawn from contemporary chemistry. Our reflections owe something to Leibniz (1686, 1695, 1714), Husserl (1922), Kuhn (1970), and Polanyi (1960, 1966), and draw on the earlier writings of both of us—Hoffmann (1995; Hoffmann & Laszlo, 1991) and Grosholz (1991; Grosholz & Yakira, 1998). We will offer a nonreductionist account of methods of analysis and synthesis in chemistry. In our view, reality is allowed to include different kinds of things existing in different kinds of ways, levels held in intelligible relation by both theory and experiment, and couched in a multiplicity of languages, both symbolic and iconic.

We argue that there is no single correct analysis of the complex entities of chemistry expressed in a single adequate language, as various reductionist scripts require; and yet the multiplicity and multivocality of the sciences, and their complex "horizontal" interrelations, do not preclude but in many ways enhance their reasonableness and success. Nor is this view at odds with our realism; we want to distinguish ourselves quite strongly from philosophers engaged in the social construction of reality (see, e.g., Pickering, 1992; Shapin, 1992; Fuller, 1994; for a balanced analysis of the problem, see Labinger, 1995). We understand the reality whose independence we honor as requiring scientific methods that are not univocal and reductionist precisely because reality is multifarious, surprising, and infinitely rich.

Formulating the Problem

The article drawn from the current literature in chemistry that we shall consider is "A Calixarene with Four Peptide Loops: An Antibody Mimic for Recognition of Protein Surfaces," authored by Yoshitomo Hamuro, with Andrew Hamilton, Mercedes Crego Calama, Hyung Soon Park, and published in December 1997 in the international journal *Angewandte Chemie* (Hamuro et al., 1997. We will refer to this article as Hamuro et al.) The subfield of the article could be called bioorganic chemistry. One way to look at biology is to examine its underlying chemistry, in a well-developed program that is both one of the most successful intellectual achievements of the twentieth-century, and a locus of dispute for biologists. For many years, organic chemists had let molecular and biochemistry "get away" from chemistry; recently, there has been a definite movement to break down the imagined fences and reintegrate modern organic chemistry and biology. The article we examine is part of such an enterprise.

We have learned something about the structure of the large, enigmatic, selectively potent molecules of biology. But describing their structure and measuring their functions do not really answer the question of how or why these molecules act as they do. Here, organic chemistry can play an important role by constructing and studying molecules smaller than the biological ones, but which model or mimic the activities of the speedy molecular behemoths of the biological world.

The article opens by stating one such problem of mimicry, important to medical science and any person who has ever caught a cold. The human immune system has flexible molecules called antibodies, proteins of some complexity that recognize a wide variety of molecules including other proteins.

> The design of synthetic hosts that can recognize protein surfaces and disrupt biologically important protein–protein interactions remains a major unsolved problem in bioorganic chemistry. In contrast, the immune system offers numerous antibodies that show high sequence and structural selectivity in binding to a wide range of protein surfaces. (Hamuro et al., 1997, p. 2680)

The problem is thus to mimic the structure and action of an antibody; but antibodies in general are very large and complicated. Hamuro et al. ask the question, Can we assemble a molecule with some of the structural features of an antibody, simplified

and scaled down, and, if so, will it act like an antibody? But what are the essential structural features in this case?

Prior investigation has revealed that an antibody at the microscopic level is a protein molecule that typically has a common central region with six "hypervariable" loops that exploit the flexibility and versatility of the amino acids that make up the loops to recognize (on the molecular level) the near infinity of molecules that wander about a human body. The article remarks that "this diversity of recognition is even more remarkable, because all antibody fragment antigen binding (FAB) regions share a common structural motif of six hypervariable loops held in place by the closely packed constant and variable regions of the light and heavy chains" (p. 2680).

What is recognition at the microscopic level? It is generally not the strong covalent bonding that makes molecules so persistent, but is rather a congeries of weak interactions between molecules that may include bonding types that chemists call hydrogen bonding, van der Waals or dispersion forces, electrostatic interactions (concatenations of regions of opposite charge attracting or like charge repelling), and hydrophobic interactions (concatenations of like regions attracting, as oil with oil, water with water). These bonding types are the subject of much dispute, for they are not as distinct as scientists would like them to be. (For an introduction to chemistry and molecular interactions, see Joesten et al., 1991). In any case, the interactions between molecules are weak and manifold. Recognition occurs as binding, but it is essentially more dynamic than static. At body temperature, recognition is the outcome of many thermodynamically reversible interactions: the antibody can pick up a molecule, assess it, and then perhaps let it go. In the dance of holding on and letting go, some things are held on to more dearly.

Whatever happens has sufficient cause, in the geometry of the molecule, and in the physics of the microscopic attractions and repulsions between atoms or regions of a molecule. The article remarks,

> Four of these loops . . . generally take up a hairpin conformation and the remaining two form more extended loops. X-ray analyses of protein–antibody complexes show that strong binding is achieved by the formation of a large and open interfacial surface (>600 Å) composed primarily of residues that are capable of mutual hydrophobic, electrostatic, and hydrogen bonding interactions.* The majority of antibody complementary determining regions (CDRs) contact the antigen with four to six of the hypervariable loops.* (pp. 2680–81)[1]

The foregoing passage is a theory about the structure and function of antibodies, but it is asserted with confidence and in precise detail. Standing in the background, linking the world of the laboratory—where small (but still tangible) samples of antibodies and proteins are purified, analyzed, combined, and measured—and the world of molecules are theories, instrumentation, and languages. There is no shortage of theories here; indeed, we are faced with an overlapping, interpenetrating network of theories backed up by instrumentation. These include the quantum mechanics of the atom along with a multitude of quantum mechanically defined spectroscopies, chemistry's highly refined means for destructively or nondestructively plucking the strings of molecules and letting the "sounds" tell us about their features (Hoffmann & Torrence, 1993, pp. 144–147). Three are equally ingenious techniques for separating and purifying molecules, that we will loosely term chromatographies. They proceed at a larger scale and, when traced, are also the outcome of a sequence of holding on and letting go, like antibody recognition.

Further, statistical mechanics and thermodynamics serve to relate the microscopic to the macroscopic. These theories are probabilistic, but they have no exceptions because of the immensity of the number of molecules—10^{23} in a sip of water—and the rapidity of molecular motion at ambient temperatures. Thus, the average speed of molecules "scales up" to temperature, their puny interactions with light waves into color, the resistance of their crystals to being squeezed to hardness, their multitudinous and frequent collisions into a reaction that is over in a second or a millennium (Atkins, 1984, 1987, 1991; Joesten et al., 1991; Hoffmann, 1995).

These theories are silent partners in the experiments described in the article, taken for granted and embodied, one might say, in the instruments. But a further dimension of the linkage between the two worlds is the languages employed by the chemists, and that is what we now propose to examine at length.

Solving the Problem

The construction of "a calixarene with four peptide loops" serves two functions in this article. It serves as a simplified substitute for an antibody, though we doubt that the intent of the authors is the design of potential therapeutic agents. More important, the calixarene serves to test the theory of antibody function sketched in the preceding discussion: Is this really the way that antibodies work? The authors note that earlier attempts to mimic antibodies have been unsuccessful, and they propose the alternative strategy, which is the heart of the article: The search for antibody mimics has not yet yielded compact and robust frameworks that reproduce the essential features of the CDRs.* Our strategy is to use a macrocyclic scaffold to which multiple peptide loops in stable hairpin-turn conformations can be attached (p. 2681).

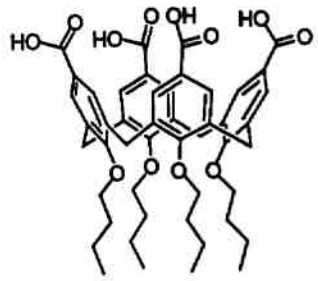
Stage 1a: The Core Scaffold

The experiment has two stages. The first is to build the antibody mimic, by adding peptide loops to the scaffolding of a calix[4]arene—a cone-shaped concatenation of four benzene rings, strengthened and locked into one orientation by the addition of small-length chains of carbon and hydrogen (an alkylation), with COOH groups on top to serve as "handles" for subsequent reaction. (The benzene ring of six carbons is a molecule with a venerable history, whose structure has proved especially problematic for the languages of chemistry, as we point out later in this chapter.) The authors write,

> In this paper we report the synthesis of an antibody mimic based on calix[4]arene linked to four constrained peptide loops. . . . Calix[4]arene was chosen as the core scaffold, as it is readily available* and can be locked into the semirigid cone conformation by alkylation of the phenol groups. This results in a projection of the para-substituents onto the same side of the ring to form a potential binding domain.* (p. 2681)

Diagram 1 is given to illustrate this description, as well as the following "recipe:" "The required tetracarboxylic acid 1 was prepared by alkylation of calix[4]arene* (*n*-butyl bromide, NaH) followed by formylation (Cl_2CHOCH_3, $TiCl_4$) and oxidation ($NaClO_2$, H_2NSO_3H)*" (p. 2681).

The iconic representation offered is of a microscopic molecule, but the language is all about macroscopic matter, and it is symbolic. The symbolic language of chemistry is the language of formulas employed in the laboratory recipe. It lends itself to the chemist's bridging of the macroscopic and the microscopic because it is thoroughly equivocal, at once a precise description of the ingredients of the experiment (e.g., *n*-butyl bromide is a colorless liquid, with a boiling point of 101.6°C, and is immiscible with water), and a description of the composition of the relevant molecules. For example, *n*-butyl bromide is construed by the chemist as $CH_3CH_2CH_2CH_2Br$; it has the formula C_4H_9Br, a determi-



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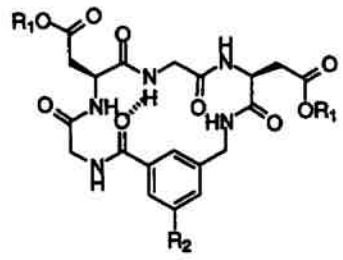
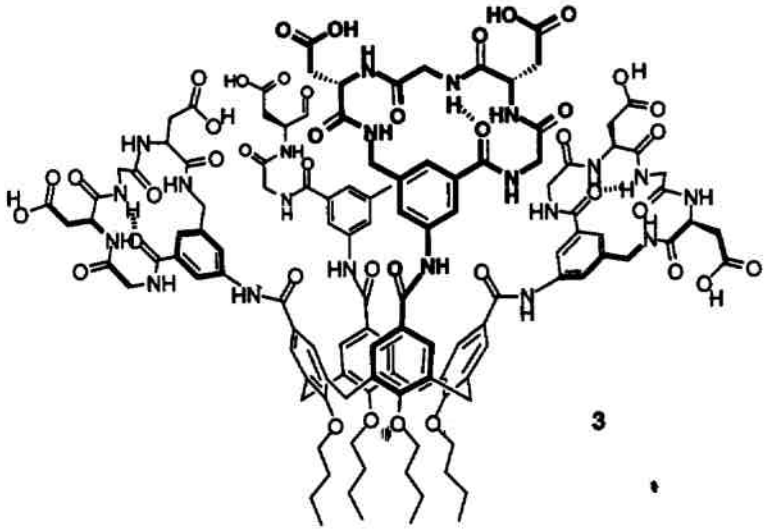


2. $R_1 = Bu^t$, $R_2 = NH_2$,
4. $R_1 = H$, $R_2 = NO_2$,



3

nate mass relationship among the three atomic constituents, a preferred geometry, certain barriers to rotation around the carbon–carbon bonds it contains, certain angles at the carbons, and so forth (Atkins 1987; Joesten et al., 1991; Hoffmann, 1995).

The laboratory recipe is thus both the description of a process carried out by a scientist, and the description of a molecule under construction: a molecule generic in its significance, because the description is intended to apply to all similar molecules, but particular in its unity and reality. There are parallels in other fields of knowledge. Thus, in mathematics, the algebraic formula of a function applies equally to an infinite set of number pairs and to a geometric curve; its controlled and precise equivocity is the instrument that allows resources of number theory and of geometry to be combined in the service of problem solving (Grosholz, 1991, chaps. 1 and 2). Likewise, here the algebra of chemistry allows the wisdom of experience gained in the laboratory to be combined with the (classical and quantum) theory of the molecule, knowledge of its fine structure, energetics, and spectra.

But the symbolic language of chemistry is not complete, for there are many aspects of the chemical substance/molecule that it leaves unexpressed: (1) We cannot deduce from it how the molecule will react with the enormous variety of other molecules with which it may come in contact; (2) We cannot even deduce from it the internal statics, kinematics, and dynamics of the molecule in space.[2] Molecules identical in composition can differ from each other because they differ in constitution, the manner and sequence of bonding of atoms (tautomers), in spatial configuration (optical or geometrical isomers), and in conformation (conformers). (See Joesten et al., 1991; Zeidler & Hoffmann, 1995; and Sobczynska, 1995/6.) An adequate description of the molecule must invoke the background of an explanatory theory, but to do so it must also employ iconic languages. Thus, the very definition of the calixarene core scaffold involves a diagram. (It was also necessary for the authors to identify C_4H_9Br as *n*-butyl bromide, a nomenclature that implies a specific connectivity of atoms.)

This diagram of calixarene is worth careful inspection, as well as careful comparison with its counterparts in the more complex molecules (for which it serves as core scaffold) furnished to us, the readers, by means of computer-generated images. First, it leaves out most of the component hydrogens and carbons in the molecule; they are understood, a kind of tacit knowledge shared even by undergraduate chemistry majors. The hexagons are benzene rings, and the chemist knows that the valence of (the number of bonds formed by) carbon is typically four and so automatically supplies the missing hydrogens. But this omission points to an important feature of iconic languages: they must always leave something out, because they are only pictures, not the thing itself, and because the furnishing of too much information is actually an impoverishment. In a poor diagram, one cannot see the forest for the trees. Not only must some things remain tacit in diagrams, but also the wisdom of experience that lets the scientist know how much to put in and how much to leave out—wisdom gleaned by years of translating experimental results into diagrams for various kinds of audience—is itself often tacit. It can be articulated now and then but cannot be translated into a complete set of fixed rules.

Second, the diagram uses certain conventions for representing configurations in three-dimensional space on the two-dimensional page, like breaking the outlines of molecules which are supposed to be behind other molecules whose delineation is

unbroken. (In other diagrams, wedges are used to represent projection outward from the plane of the page, and heavy lines are used to represent molecules that stand in front of other molecules depicted by ordinary lines.) Sometimes, although not in the context of a journal article, chemists show three-dimensional representation, such as "ball-and-stick" models. But then, in addition, one may want to see more precise angles and interatomic distances in correct proportion and so resort to the images produced by X-ray crystallography. Or one may want some indication of the motion of the molecules, because all atoms vibrate and rotate. Arrows and other iconographies of dynamic motion are used in such diagrams. The cloudy, false-color, yet informative photographs of scanning tunneling microscopy come in here, as well as assorted computer images of the distribution of electrons in the molecule.[3]

Finally, the convention of a hexagon with a perimeter composed of three single lines alternating with three double lines to represent a benzene ring deserves a chapter in itself. This molecule has played a central role in the development of organic chemistry. No single classical valence structure was consistent with the stability of the molecule. Kekulé solved the problem by postulating the coexistence of two valence structures in one molecule. In time, practitioners of quantum mechanics took up the benzene problem, and to this day it has served them as an equally fecund source of inspiration and disagreement. The electrons in benzene are delocalized, that much people agree on; but the description of its electronic structure continues to be a problem for the languages of chemistry (Brush, 1998).

An Interlude on Symbolic and Iconic Languages

Philosophers of science working in the logical positivist tradition have had little to say about iconic languages. Symbolic languages typically lend themselves to logical regimentation, but pictures tend to be multiform and hard to codify; thus, if they proved to be indispensable to human knowledge, the logical positivist would be quite vexed. As any student of chemistry will tell you, conventions for producing "well-formed icons" of molecules exist and must be learned, or else your audience will misread them. But no single iconic language is the correct one or enjoys anything as precisely determined as a "wff" in logic. The symbolic language of chemistry is, to be sure, a precisely defined international nomenclature that specifies in impressive detail a written sequence of symbols so as to allow the unique specification of a molecule. But, significantly, the iconic representations of a molecule are governed only by widely accepted conventions, and a good bit of latitude is allowed in practice, especially a propos what may be omitted from such representations. Symbolic languages lend themselves to codification in a way that iconic languages don't.[4]

Symbolic languages, precisely because they are symbolic, lend themselves best to displaying relational structure. Like algebra, they are tolerant or relativistic in their ontological import: it doesn't so much matter what they pertain to, as long as their objects stand in the appropriate relations to each other. But iconic languages point, more or less directly, to objects; they are not ontologically neutral but, on the contrary, are ontologically insistent. They display the unity of objects, a unity that might metaphysically be called the unity of existence. But there is no way to give an exhaustive

summary of the ways of portraying the unity of existence; it is too infinitely rich, and thought has too many ways of engaging it. We should, therefore, not jump to the conclusion that knowledge via an iconic language is impossible or incoherent: iconic languages despite being multiform employ intelligible conventions, they are constrained by the object itself, and they are made orderly by their association with symbolic language. An inference cannot be constructed from icons alone, but icons may play an essential role in inference.[5]

How does the iconic form of the chemical structure expressed as a diagram that displays atom connectivities and suggests the three-dimensionality of the molecule, bridge the two worlds of the chemist? The most obvious answer is that it makes the invisible visible, and does so, within limits, reliably. But there is a deeper answer. It seems at first as if the chemical structure diagram refers only to the level of the microscopic since, after all, it depicts a molecule. But in conjunction with symbolic formulas, the diagram takes on an inherent ambiguity that gives it an important bridging function. In its display of unified existence, it stands for a single particular molecule. Yet we understand molecules of the same composition and structure to be equivalent to each other, internally indistinguishable. (In this, the objects of physics and chemistry are like the objects of mathematics.)

Thus, the icon (hexagonal benzene ring) also stands for all possible benzene rings, or for all the benzene rings (moles or millimoles of them!) in the experiment, depending on the way in which it is associated with the symbolic formula for benzene. The logical positivist in search of univocality might call this obfuscating ambiguity, a degeneracy in what ought to be a precise scientific language that carries with it undesirable ontological baggage. And yet, the iconic language is powerfully efficient and fertile in the hands of the chemist.

Now we can better understand why the kind of world-bridging involved in posing a problem/construction in chemistry requires both symbolic and iconic languages for its formulation. On the one hand, the symbolic language of chemistry captures the composition of molecules, but not their structure (constitution, configuration, and conformation), aspects that are dealt with better, though fragmentarily, by the many iconic idioms available to chemists. Moreover, the symbolic language of chemistry fails to convey the ontological import, the realism, intended by practitioners in the field. Hamuro et al. are not reporting on a social construction or a mere computation, but a useful reality: the diagram confidently posits its existence. On the other hand, icons are too manifold and singular to be the sole vehicle of scientific discourse. Their use along with symbolic language embeds them in demonstrations and gives to their particularity a representative and well-defined generality, sometimes even a universality.

We return to our reading of the Hamuro et al. article.

Stage 1b: The Peptide Loops

Hamuro et al. chose cyclic hexapeptides to mimic the "arms" of the antibody because they can be modified so as to link up easily with the core scaffold, and because they form hairpin loops: "The peptide loop was based on a cyclic hexapeptide in which two residues were replaced by a 3-aminomethylbenzoyl (3amb) dipeptide analogue* containing a 5-amino substituent for facile linkage to the scaffold" (p. 2681). The recipe for

constructing the peptide loops is then given; the way in which it couples the macroscopic and the microscopic is striking, for it describes a laboratory procedure and then announces that the outcome of the procedure is a molecule, pictured in diagram 2.

> The 5-nitro substituted dipeptide analogue was formed by selective reduction (BH_3) of methyl 3-amidocarbonyl1-5-nitrobenzoate, followed by deesterification (LiOH in THF) and reaction sequentially with Fmoc-Asp-(tBu)-OH and H-Gly-Asp(tBu)-Gly-OH (dicyclohexyl carbodiimide (DCC), N-hydroxysuccinimide) to yield Fmoc-Asp(tBu)-5$NO_2$3 amb-Gly-Asp (tBu)-GlyOH. Cyclization with 4-dimethylaminopyridine (DMAP) and 2-1H-benzotriazole-1-yl-1,1,3,3,-tetramethyluronium tetrafluoroborate (TBTU) was achieved in 70% yield, followed by reduction (H_2, Pd/C) to give the amino-substituted peptide loop 2. (p. 2681)

Working in the lab, the chemist has constructed a molecule, at least a dizzying 20 orders of magnitude "below" or "inward." To be sure, what was made was a visible, tangible material—likely less than a gram of it—but the interest of what was made lies in the geometry and reactivity of the molecule, not the properties of the macroscopic substance. So it is not by accident that the leap to the level of the molecule is accompanied by iconic language. Such language also accompanies the final step in the assembly of the antibody mimic.

Stage 1c: The Antibody Mimic

Four of the peptide loops are attached to the core scaffold; the laboratory procedure begins and ends with a pictured molecule. But this time the resultant new molecule is pictured twice in complementary iconic idioms.

> Amine 2 was coupled to the tetraacid chloride derivative of 1 ($(COCl)_2$, DMF) and deprotected with trifluoroacetic acid (TFA) to give the tetraloop structure 3. The molecular structure of this host (Fig [13.]1) resembles that of the antigen binding region of an antibody but is based on four loops rather than six.* (p. 2681)

To someone who understands chemical semiotics, the iconic conventions in diagram 3 (the tetraloop molecule called structure 3 in the quote above) do allow a mental reconstruction of the molecule. But the shape of the molecule is so important that the authors decide to give it again, in another view, in figure 13.1. The figure is even printed in color in the original!

Why should the reader be offered another iconic representation? In part, it is part of a rhetorical strategy to persuade the audience of the cogency of a research program that involves mimicry. The computer-generated image of figure 13.1 is actually the result of a theoretical calculation in which the various molecular components are allowed to wiggle around any bonds that allow rotation and to reach a geometry that is presumably the most stable. In that image, the general shape of the molecule (in particular, the loopiness of the loops) is beautifully exhibited, emphasizing its resemblance to an antibody. Note that the experimentalist trusts the ability of a theoretical computer program to yield the shape of a molecule sufficiently to insert it—in color—in an article; that would not have been the case 20 years ago.

Diagram 3 and figure 13.1 are meant to be seen in tandem; they complement each other. Both representations are iconic, though perhaps figure 13.1 is more so. Diagram 3 has a symbolic dimension due to the labels, and thus serves to link figure 13.1 to the

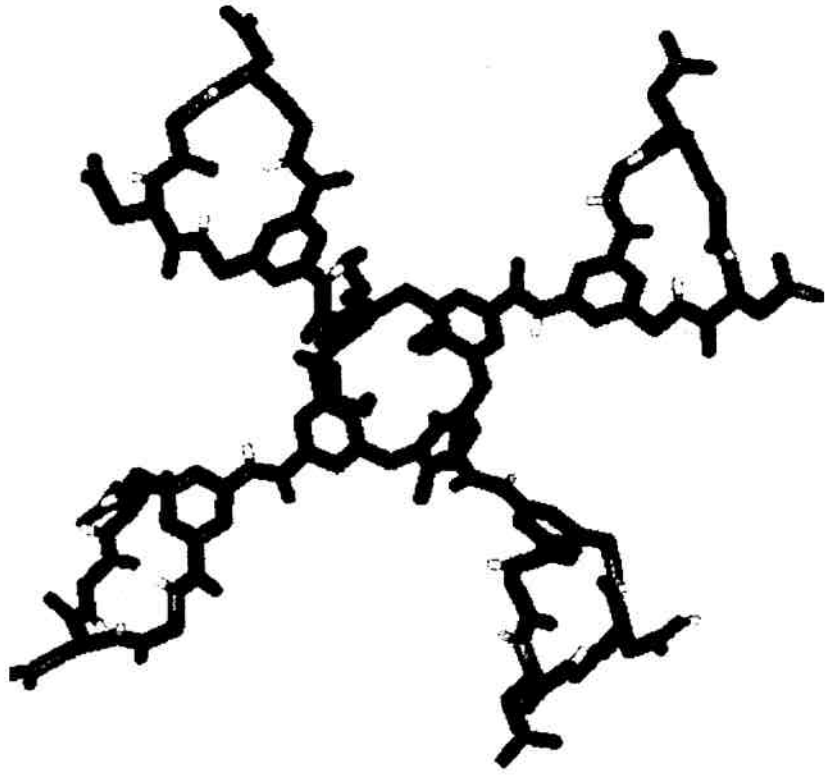


Figure 13.1 Figure 1 of Hamuro et al. article. See explanation in text.

symbolic discourse of the prose argument. Together with the reproducible laboratory procedure—given in more detail at the end of the article—Hamuro et al. give a convincing picture of this new addition to the furniture of the universe. There it stands: Ecce.

Stage 2

Once the antibody mimic has been assembled, it can be tested to see whether it in fact behaves like an antibody, a test which, if successful, in turn provides evidence supporting the theory of the action of antibodies invoked by Hamuro et al. Note the usefully—as opposed to viciously—circular reasoning here (Hoffmann, 1988): the antibody mimic correctly mimics an antibody if it behaves like an antibody; but how an antibody behaves is still a postulate, which stipulates what counts as the correctness of the antibody mimic's mimicry. To see if the antibody mimic—the base scaffold of calixarene with four peptide loops—will bind with and impair the function of a protein (the essence of what an antibody does), Hamuro et al. chose the protein

cytochrome, an important molecule that plays a critical role in energy production and electron transport in every cell, and has thus been thoroughly investigated. Moreover, it has a positively charged surface region that would likely bond well with the negatively charged peptide loops.

> We chose cytochrome *c* as the initial protein target, since it is structurally well-characterized and contains a positively charged surface made up of several lysine and arginine residues.* In this study the negatively charged GlyAspGlyAsp sequence was used in the loops of **3*** to complement the charge distribution on the protein. (p. 2681)

Note that the antibody mimic is referred to by means of the diagram **3**. In a sense this is because the diagram is a shorthand, but its perspicuity is not trivial or accidental: as a picture that can be taken in at a glance, it offers schematically the whole configuration of the molecule in space. Its visual unity stands for, and does not misrepresent, the unity of the molecule's existence.

Does the antibody mimic, in fact, bind with the cytochrome? The affinity of the two is tested by an experiment that is neither analytic nor synthetic, but, rather, a matter of careful physical measurement—an aspect of chemical practice central to the science since the time of Lavoisier. The "affinity chromatography" involves a column filled with some inert cellulose-like particles and cytochrome *c* linked to those particles (for a description of chromatography, see Laszlo, 1997). The concentration of NaCl, simple salt, controls the degree of binding of various other molecules to the cytochrome *c* that is in that column. If the binding is substantially through ionic forces (as one thinks it is for the antibody mimic), then only a substantial concentration of ionic salt solution will disrupt that binding. At the top of the column one first adds a control molecule (diagram **4**). It is eluted easily, with no salt. But the antibody mimic **3** turns out to be bound much more tightly—it takes a lot of salt to flush it out.

A second kind of chromatography, "gel permeation chromatography," gives more graphic evidence for the binding of cytochrome *c* to **3**. In this ingenious chromatography, the column is packed with another cellulose-like and porous fiber, called Sephadex G-50. The "G-50" is not just a trade name; it indicates that molecules of a certain size will be trapped in the column material, but molecules both larger and smaller will flow through the column quickly.

The results of this experiment are shown in figure 13.2, replete with labeled axes. The vertical axis measures the absorption of light at a certain wavelength; this is related to the concentration of a species, the bound cytochrome *c*–**3** complex. The horizontal axis is a "fraction number" that is related to the length of time that a given molecule (or compound? the equivocity here pervades chemical discourse) resides on the column. The pores in the Sephadex retard cytochrome *c*; it stays on the column longer (has a higher fraction number). The molecular complex of the mimic and cytochrome *c* comes out in a different peak, at lower fraction number. This means it is too large to be caught in the pores of the Sephadex, which in turn, constitutes evidence for some sort of binding between the cytochrome *c* and the antibody mimic, creating a larger molecular entity.

So there is binding; but does it impair the function of the cytochrome *c*? Evidence for that is provided by reacting the cytochrome *c* with ascorbate (vitamin C), with which it normally reacts quite efficiently; here, on the contrary, it doesn't.

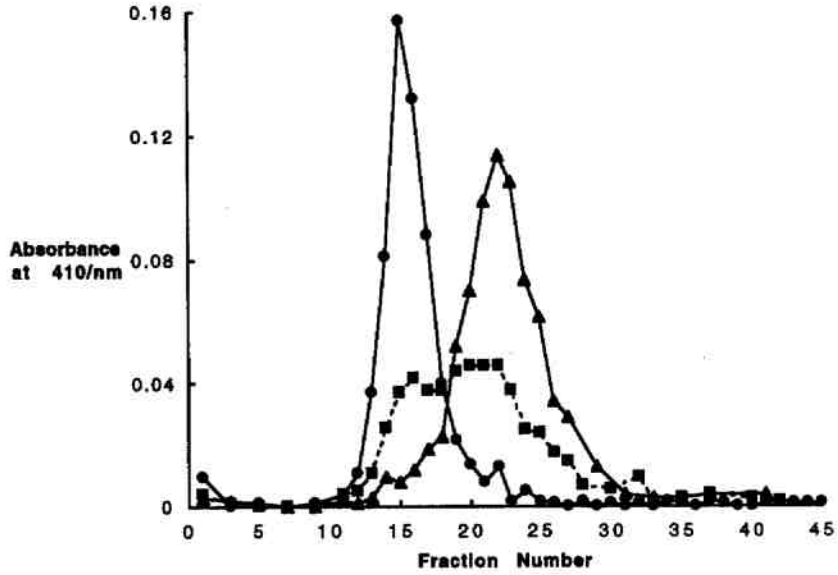


Figure 13.2 Figure 2 of Hamuro et al. article. See explanation in text.

> We have investigated the effect of complexation with **3** on the interaction of FeIII-cyt *c* with reducing agents.* In phosphate buffer Fe^{III}-cyt *c* (1.57×10^{-5}M) is rapidly reduced by excess ascorbate (2.0×10^{-3}M) with a pseudo-first-order rate constant 0.1090 ± 0.001 (Figure 4 [figure 13.3]). In the presence of **3** (1.9×10^{-5}M) the rate of cyt *c* reduction is diminished tenfold ($k_{obs} = 0.010 \pm 0.001$ s^{-1}), consistent with the calixarene derivative's binding to the protein surface and inhibiting approach of ascorbate to the heme edge (Figure 3 [figure 13.4]).

Figure 13.3 is another measurement, with the concentrations measured on the vertical axis, the time on the horizontal; it displays the outcome of an experiment on the kinetics of ascorbate reduction by cytochrome *c*, which supports the claim that the antibody mimic does impair the function of the protein, in this case its ability to react with ascorbate.

More interesting is another iconic representation, figure 13.4 which is a picture of the antibody mimic binding with cytochrome *c*. Since the authors admit, "The exact site on the surface of the cytochrome that binds with **3** has not yet been established," this image is a conjecture; and it is the outcome of the same computer program that generated figure 13.1. It "docks" "a calculated structure for **3**" at the most likely site on the cytochrome *c*, where the four peptide loops "cover a large area of the protein surface." Figure 13.4 is a remarkable overlay of several types of iconic representation. The antibody mimic (at top) is shown pretty much as it was in figure 13.1, but from the side. The atoms of cytochrome *c* are legion, and so are mostly not shown; instead, the essential helical loops of the protein are schematically indicated. But in the contact region, the atoms are again shown in great detail, not by ball-and-stick or rod representations

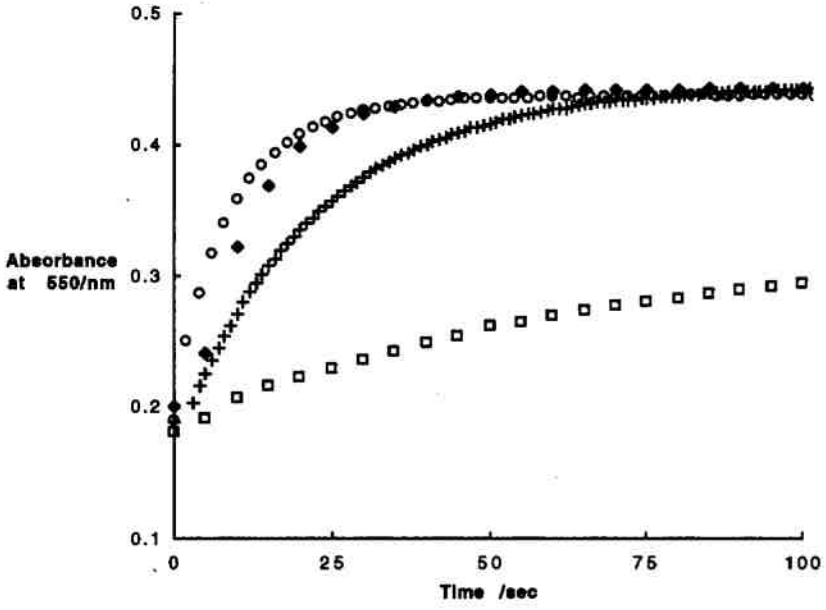


Figure 13.3 Figure 4 of Hamuro et al. article. See explanation in text.

but by tenuous spheres indicating roughly the atomic sizes or electron densities. The reader can make sense of these superimposed iconic idioms only by reference to a cognitive framework of words and symbols.

Iconic representations in chemical discourse must be related to a symbolic discourse; our access to the microscopic objects of chemistry, even our ability to picture them, is always mediated by that discourse rather than by our "natural" organs of perception. So the objects of chemistry may seem a bit ghostly, even to the practitioners for whom their existence is especially robust (see also, Laszlo, 1998). But, conversely, symbolic discourse in chemistry cannot dispense with iconic discourse as its complement, nor can it escape its own iconic dimension. The side-by-side distinction, iteration, and concatenation of letters in chemical formulas echo the spatial array of atoms in a molecule. Otherwise put, the iconic combination of symbols often articulates otherness, which is exhibited by the things of chemistry as their spatial externality and proximity. The iconic array in figure 13.3 also translates into spatial relations among symbols the temporal spread of stages of a chemical event, where otherness is priority or posteriority. Just as icons evoke existence, the unity of existence, so they evoke otherness as side-by-sideness, as externality. Identity and difference, *pace* the logicians, cannot be fully represented without the use of iconic as well as symbolic languages.

The icon in figure 13.4 stands for a molecular complex that may or may not exist. It is a possibility, a guide to future research. For the authors of the article, it is some-

Figure 13.4 Figure 3 of Hamuro et al. article. See explanation in text.

thing they very much hope does exist, a wish that can perhaps be read in the bright, imaginary colors of the image. Chemical icons work their magic of asserting and displaying the unity of existence only when the symbolic discursive context and the experimental background allow them to do so.

Whatever remains still to be worked out, the authors of the article declare a positive result, and its generalization to a broader research program.

> The new type of synthetic host 3 thus mimics antibody combining sites in having several peptide loops arrayed around a central binding region. The large surface area in the molecule allows strong binding to a complementary surface on cytochrome c and disrupts, in a similar way to cytochrome c peroxidase, the approach of reducing agents to the active site of the protein. We are currently preparing libraries of antibody mimics from different peptide loop sequences and screening their binding to a range of protein targets. (p. 2682)

Conclusions

Angewandte Chemie, where Roald Hoffmann found the article closely read in this article, is no longer especially concerned with applied chemistry; indeed, it is arguably the world's leading "pure" chemistry journal. The December 15, 1997, issue of the journal in which the Hamuro article appears contains one review, two comments or highlights, several book reviews, and 38 "communications" articles, each one to three pages in length that, in principle, present novel and important chemistry.

Without question, the Hamuro, Calama, Park, and Hamilton article is a beautiful piece of work, deserving of the company it keeps in the pages of *Angewandte Chemie*; it caught Hoffmann's attention even though the subject is not one of his fields of specialization. But is this work typical of chemistry, and sufficiently so that any close reading of it might elicit generalities valid for the field? After all, it is not clear what counts as "typical" in a science whose topics range from cytochrome *c*, to reactions occurring in femtoseconds, to inorganic superconductors. And perhaps work that strives to redefine the boundaries of a science cannot fully represent what Kuhn called "normal science."

We nonetheless believe that the Hamuro et al. article exhibits many of the important features of most work in modern chemistry, especially in the way that it moves between levels of reality. On one line the authors of the article talk of a molecular structure, and on the next of a reaction; a certain linguistic item (symbol or icon) may stand for either or both. Theory and experiment, expressed in beautifully intertwined symbolic and iconic languages, relate the world of visible, tangible substances and that of the molecule. Is this sloppiness, an ambiguity that hard science must ultimately abolish? We think not.

The intuitive may be analyzed, the tacit may be articulated, but never completely and all at once: certain indeterminacies and logical gaps always remain, even as scientists achieve a consensual understanding of complex reality. Indeed, the indeterminacy and "gappiness" of knowledge may serve a useful purpose in that it allows the double vision where creative endeavor often takes place. If, as we have claimed in this chapter, chemists habitually think at both the level of macroscopic substances and their transformations in the laboratory, and the level of the statics and dynamics of microscopic molecules, the very equivocity of the field—the way it brings physics and mathematics into the service of chemistry—may be a source of its productivity. The logical gap between the two levels of description is never closed (by some kind of reduction) but, rather, is constantly and successfully negotiated by a set of theories embodied in instruments and expressed in symbolic and iconic languages.[6]

Precisely because these languages are abstract and incomplete (in the sense of being noncategorical, not capturing all there is to say and know about the entities they describe) they are *productively* ambiguous, and can be understood in reference to both the macroscopic and microscopic. This bridging function—carried out in different but complementary ways by symbolic and iconic idioms—is the special interest of this chapter. We have tried to explain how it allows chemists to articulate and to solve problems, a task that often takes the form of imagining and then trying to put together a certain kind of molecule. Thus, our account emphasizes what happens at the frontiers of knowledge rather than retrospective codification, and the investigation and creation of objects rather than the testing of theories.

Notes

A version of this chapter was delivered under the title "Comment les langages symboliques et iconiques servent de passerelle entre les deux mondes du chimiste: une étude de cas de chimie bioorganique contemporaine," by the authors on April 19, 1998, at the Maison Rhône-Alpes des Sciences de l'Homme, Université Stendhal, Grenoble, as part of a year-long seminar on the languages of science. We thank the organizers of that seminar, especially Françoise Létoublon, for the invitation and their efforts at realizing a complex and truly interdisciplinary project. We are also grateful to Andrew Hamilton for supplying the original illustrations for the article.

The nontrivial translation of this chapter into French was masterfully accomplished by Carole Allamand. We thank her.

Emily Grosholz thanks the American Council of Learned Societies and the Pennsylvania State University for their support of her research as a Visiting Fellow at Clare Hall and a Visiting Scholar in the department of history and philosophy of science at the University of Cambridge. She thanks François De Gandt (University of Lille) and Audrey Glauert (Clare Hall) for their useful suggestions on the essay, as well as Jeremy K. M. Sanders and Darren Hamilton of the department of chemistry at the University of Cambridge for their enlightening discussion of the practice of chemistry.

Roald Hoffmann is grateful to Cornell University for a grant in support of his research, scientific and otherwise, and to Bruce Ganem for a helpful explanation of chromatography.

1. The asterisks in the quoted passages are bibliographic end notes in the original Hamuro et al. article.

2. A reductionist might argue that given great computing power and perfected quantum mechanical calculations, one could start from a chemical formula and predict observations accurately. But in practice, the number of isomers for a given formula grows very rapidly with molecular complexity, so the goal is not realistic for a molecule the size of the calixarene. Moreover, complete computability may not be equivalent to understanding. Much of what a chemist means by understanding is couched in terms of fuzzy chemical concepts—the result of horizontal and quasi-circular reasoning—for which a precise equivalent in physics cannot be found (Hoffmann, 1988, 1995; Grosholz, 1994; Scerri, 1994).

3. For an excellent account of the language of chemistry, and its parallels to linguistics, see Laszlo (1995), as well as Hoffmann and Laszlo (1991) and Weininger (1998).

4. L. Kvasz (1998) helped us think about the distinction and the interactions between symbolic and iconic languages in mathematics and chemistry, but we disagree with Kvasz about the extent to which iconic languages may be codified.

5. G. G. Granger has an interesting discussion of the languages of chemistry in his book (Granger, 1983, chap. 3), where he focuses on the distinction between natural languages and formal languages. He makes the important observation that scientific language will always be partly vernacular and partly formal. Rejecting the claim that science might someday be carried out in a pure formalism, he writes. "The linguistic process of science seems to me essentially ambiguous: for if science is not at any moment of its history a completely formalized discourse, it is not to be confused with ordinary discourse either. Insofar as it is thought in action, it can only be represented as an attempt to formalize, commented on by the interpreter in a nonformal language. Total formalization never appears as anything more than at the horizon of scientific thought, and we can say that the collaboration of the two languages is a transcendental feature of science, that is, a feature dependent on the very conditions of the apprehension of an object." (p. 33). However, Granger does not go on to consider the further linguistic aspect of chemistry, that is, its iconic aspect.

6. Laszlo (1998) has cogently argued that in their practice of analysis, modern-day chemists "dematerialize" the substances they handle, so that the transactions of the contemporary laboratory mostly involve mental representations. He goes on to argue that our age of masterly

synthesis doesn't achieve the rematerialization one might desire. Although we think Laszlo verges perilously close to denying realism, his argument nevertheless is an intriguing one, and covers some of the same representational ground that we do.

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