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EDITORIAL

Geometry and models in chemistry

István Hargittai

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Abstract Geometry is an important ingredient in the chemical sciences and especially in structural chemistry. It is closely related to modeling, which is a favorite epistemological tool in chemistry. In the history of chemistry, simple geometrical models have often preceded sound experimental elucidation of structures. A series of examples are presented that include gas-phase electron diffraction; the origin of molecular mechanics; estimation of experimental error in quantum chemical computations; qualitative models of molecular structures; symmetry-lowering effects; biological macromolecules; and chirality.

Keywords Geometry · Modeling · Molecular mechanics · Experimental error in computation · Precision and accuracy · Molecular packing · Biomolecular structures · Enantiomers

Ubi material, ibi geometria.
Johannes Kepler (1571–1630)

Geometry is the daughter of property.
Bernard Le Bouyer (Bovier) (1657–1757),
Conversations on the Plurality of Worlds
(1686, translated by H. A. Hargreaves, 1990)

We could present spatially an atomic fact which contradicted the laws of physics, but not one which contradicted the laws of geometry.
Ludwig Wittgenstein (1889–1951),
Tractatus Logico–Philosophicus 1961
(London: Routledge & Kegan Paul)

I have been influenced by Eugene P. Wigner's characterization of scientific research. He expressed it eloquently in his Nobel lecture when he quoted his teacher, Michael Polanyi in that "…science begins when a body of phenomena is available which shows some coherence and regularities, [that] science consists in assimilating these regularities and in creating concepts which permit expressing these regularities in a natural way." Wigner (and Polanyi) saw in this the real transferability of the scientific approach, and more so than in transferring concepts, such as energy, for example, "to other fields of learning" [1].

The beginning of my interactions with Wigner dated back to 1964 when he wrote me a long letter in response to an article I had published in a Hungarian literary magazine in reference to his essay on the limits of science. This article was my first ever publication and it was in my senior year of university studies. Our interactions culminated in our meeting in person and extended conversations in 1969 at the University of Texas at Austin (Fig. 1). On this occasion, he introduced me to the intricacies and broad applications of the symmetry concept [2]. We then remained in on-and-off correspondence throughout the years. The utilization of the symmetry concept has become

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I. Hargittai (✉)
Materials Structure and Modeling Research Group of the Hungarian Academy of Sciences, Department of Inorganic and Analytical Chemistry, Budapest University of Technology and Economics, PO Box 91, 1521 Budapest, Hungary
e-mail: istvan.hargittai@gmail.com

Fig. 1 Eugene P Wigner and the author on the campus of the University of Texas at Austin in 1969 (by unknown photographer, © I Hargittai)

an all-embracing feature of our work in structural chemistry throughout the decades [3].

Gas-phase electron diffraction

Of the uses of models in my research in structural chemistry, my first example is the electron diffraction determination of molecular structure [4, 5]. It is amazing how much information may be extracted from the diffraction pattern of a gaseous sample—a set of diffuse concentric rings (Fig. 2). However, the primary information obtainable from an electron diffraction pattern is scarce; it may be just about the magnitude of the principal internuclear distances in the molecule and about the relative rigidity of the molecule. The same is true for the visual inspection of the intensity distribution that comes directly from the experimental pattern. In contrast, the sine Fourier transform of the intensity distribution is related to the probability density distribution of the internuclear distances in the molecule (called the radial distribution—a misnomer), and thus it provides a considerable amount of information graphically, in a visually perceivable way. However, since the radial distribution is obtained via certain mathematical manipulations, it is used for general orientation rather than for quantitative elucidation of parameters.

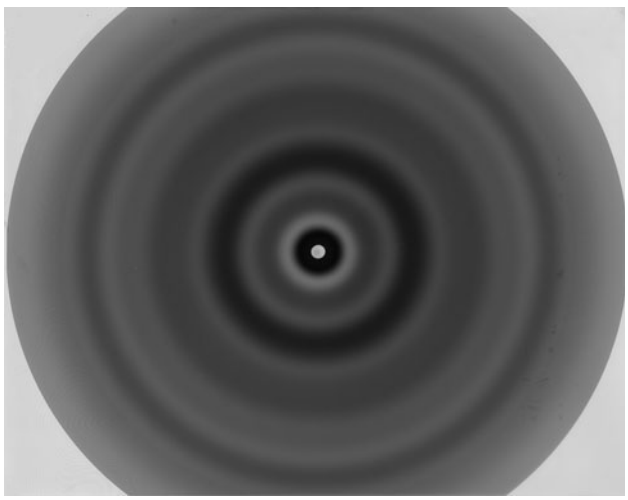

Fig. 2 Gas-phase electron diffraction pattern of adamantane recorded by Kenneth Hedberg and the author in 1969 in Corvallis, Oregon

It is the intensity distribution, referred to above, that is subjected to rigorous analysis and is the primary source of the reliable quantitative structural information. More often than not, the analysis utilizes a least-squares procedure for the refinement of parameters. Such a procedure, however—it being based on a non-linear relationship—necessitates suitable initial sets of parameters for best results. Here is where model building comes into the structure analysis for which the sources include already existing structural information, intuition, and information directly read off from the Fourier transform of the intensity data. A poor initial model may result in reaching a local minimum in the structure refinement yielding a false structure for which there have been plenty of examples in the literature. The situation may be remedied by careful compilation of the model, by testing the results against all other available evidence, and by employing more than one technique simultaneously in the structure determination that would complement each other.

Roots of molecular mechanics

Concerning modeling in the computational determination of molecular structure, a pioneering step was made in the 1940s by Frank Westheimer [6] who initiated a new technique, molecular mechanics. He had participated in the American defense efforts and, when the war had ended, he had returned to the University of Chicago to resume his teaching and research. He had to start anew and had time to think about basic problems. This is how half a century later he described the birth of molecular mechanics [7]:

> I thought through the idea of calculating the energy of steric effects from first principles and classical physics, relying on known values of force constants for bond stretching and bending, and known values of van der Waals constants for interatomic repulsion. I applied this idea to the calculation of the energy of activation for the racemization of optically active biphenyls. Minimizing the energy of a model for the transition state leads to a set of n equations in n unknowns, one for each stretch or bend of a bond in the molecule. It seemed to me that, to solve these

equations, one needed to solve a huge $n \times n$ determinant. Fortunately for me, Joe Mayer came to the University of Chicago at the end of WWII. Joe was an outstanding physical chemist; he and his wife Maria [Goeppert Mayer] wrote the outstanding text in statistical mechanics. During the war, he had been working at Aberdeen, Maryland, using the world's first digital computer to calculate artillery trajectories. Perhaps Joe could have access to that computer, and could show me how to solve my determinant on it. So I went to him and asked him to help me. He didn't know about optically active biphenyls, so I made some molecular models and explained the stereochemistry to him, and showed him my mathematical development, up to the determinant. Then, in something like half an hour, he found a mathematical trick that we used to solve my equations without needing the determinant. That's how the solution of real problems in molecular mechanics got started. It has become big business since. Furthermore, it turns out that my instinct for computerizing was correct, since that is the way in which the field has since been developed.

The history of molecular mechanics must include—in fact perhaps begins with—a publication by Terrell Hill that presented the same general method I had invented for expressing the energy of molecules in terms of bond stretching, bond bending, and van der Waals interactions, and then minimizing that energy. Hill published the method [8], but with no application, no "reduction to practice." I hadn't known that we had a competitor, or that one could publish a bare research idea. After Hill published, I immediately wrote up the work that Mayer and I had already done, theory *and* successful application to determining the activation energy for the racemization of an optically active biphenyl, and submitted it for publication [9].

"Experimental errors" in quantum chemical calculations

Tremendous progress has been made in computational chemistry and in particular in ab initio determination of molecular structures. This is another area where modeling has fundamental role, but here only one aspect is singled out, viz., the consideration of "experimental error," in quantum chemical computational work. One of the pioneers of the field, John Pople described the estimation of "experimental error" [10]:

> The way I like to do this is to set up a theoretical model. You apply one theoretical model essentially to all molecules. This model is one level of approximation. Then you apply this one level of calculation to a very large number of different molecules. In fact, one level of approximation is applied to all molecules, giving you an entire chemistry corresponding to that approximation. That chemistry, of course, would not be the same as real chemistry but it would approach that chemistry and if it is a good model, it will approach real chemistry well. What I try to do is to take a given model and then to use that model to try to reproduce a lot of well-known facts of experimental chemistry. For example you try to reproduce the bond lengths in a large number of simple organic molecules, or the heats of formation for that set of molecules, in a situation where the experiment is beyond question. Then you can actually do statistics and say that this theory reproduces all known heats of formation to the root-mean-square accuracy of 2 kcal/mol. When you've done that you build some confidence in the level of theory. If you then apply the same theory in a situation where experiment may not exist, you know the level of confidence of your calculations.

Qualitative models

Even in today's world of sophisticated quantum chemical calculations, qualitative models continue to play an important role in chemical research. As is known, successful models select one or a few of the properties of the system or systems they intend to describe and ignore the rest. A model is successful if it can be used for predictions of properties of systems not yet studied and, on occasion, not yet even existing. The systems used for testing the model should be within the scope of applicability of the model. One of the most successful qualitative models in predicting molecular shapes, geometries, and even structural variations in series of substances has been the Valence Shell Electron Pair Repulsion (VSEPR) Model [11]. It assumes that the valence shell of the central atom in the molecule is spherically symmetrical and the interactions among the electron pairs in this valence shell—taking into account all electron pairs regardless whether they are bonding pairs or lone pairs—are described by the potential energy expression $V_{ij} = \mathrm{k}/r_{ij}^{n}$. Here, k is a constant, r_{ij} is the distance between the points i and j, and the exponent n is large for strong and small for weak repulsions, but they are generally stronger than simple electrostatic coulomb interactions.

The task is to look for the molecular shape for which the potential energy reaches its minimum. The exponent n is not known, but this is not an impediment to the application of the

model, because as soon as it is larger than three, the results become insensitive to the choice of n. This insensitivity of the results to n is the secret of the wide applicability of the model. The resulting shapes of the arrangements of the electron pairs for two, three, four, five and six electron pairs in the valence shell will be linear, equilateral triangular, tetrahedral, trigonal bipyramidal, and octahedral, respectively. A set of sub-rules extends the model toward more subtle variations of molecular geometry. The applicability of the model has limits, of course. Thus, for example, it is gradually less applicable with increasing ligand sizes relative to the size of the central atom, because for such structures non-bonded repulsions become gradually the dominating interactions [12]. The popularity of the VSEPR model has been greatly enhanced by its successful application for predicting and explaining structures that initially appeared to be counter-intuitive. A rich collection of examples discussed in a systematic way has appeared [13].

Precision and accuracy

An important feature of any model aiming at a realistic representation of structures is the inclusion of motion. The low-frequency, large-amplitude, so-called deformation motions may lead to some of the experimental techniques yielding lower symmetry molecular shapes than the equilibrium structure that would correspond to the minimum position of the potential energy function [14, 15]. The relationship between average structures and the equilibrium structure has become a cornerstone consideration with increasing precision of the experimental determination of molecular geometry and the enhanced sophistication of quantum chemical calculations. Beyond certain precisions, for example, the computed bond lengths and their experimentally determined counterparts cannot be the same, and any demanding comparison of such information and their meaningful discussion requires considerations of the accuracy of structural information [16]. The experimental results also depend on the way averaging over molecular motion takes place in the interactions any given technique utilizes in the experiments [17]. The impact of motion, however, may only be one of the possible origins of changes in molecular symmetry. Various other effects have been uncovered and taken into account with the expanding scope of reliable structure determinations, including the Jahn–Teller effect [18], and other effects [19].

Molecular packing

When molecules aggregate and build crystal structures, their geometries undergo changes to smaller or larger extents. Again, with improving precision, such changes have come increasingly to the attention of structural chemists. First of all, the symmetries of extended structures can be described by space groups and this approach also points to certain limitations in the classification of crystal structures within classical crystallography. Even within the framework of classical crystallography, the interesting question arises whether or not some of the modes of molecular packing are more advantageous than others. Both questions will be touched upon briefly in our following discussion.

Starting with the second question, as early as two millennia ago, already Lucretius noted that "Things whose fabrics show opposites that match, one concave where the other is convex, and vice versa, will form the closest union" [20]. With this statement Lucretius annunciated a fundamental principle of the best packing arrangement for arbitrary shapes. Packing considerations can be studied in a simplified way using two-dimensional space group patterns,

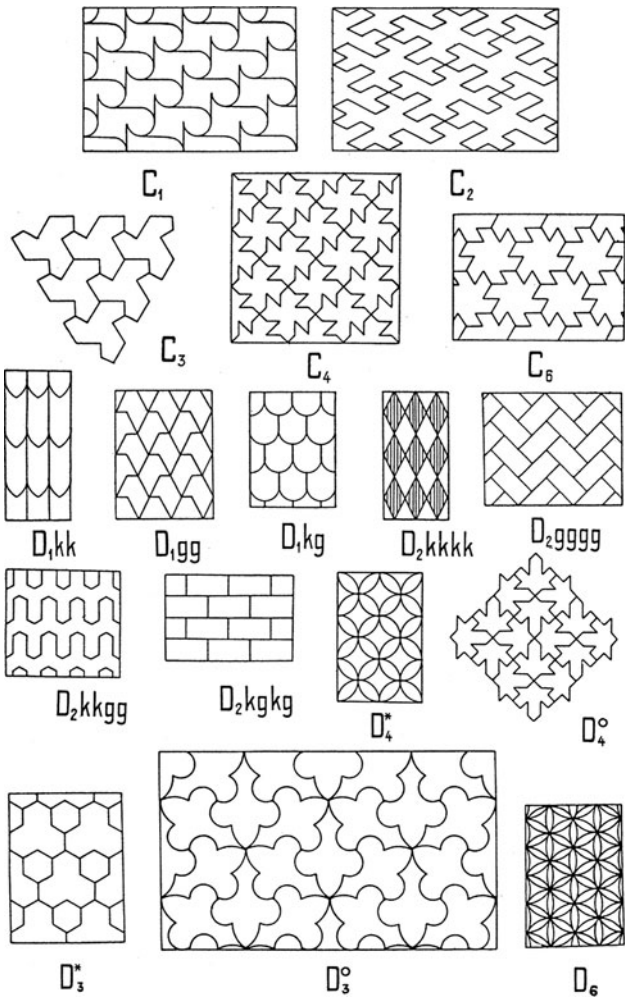

Fig. 3 George Polya's two-dimensional space group patterns in which the basic motives cover the surface without gaps or overlaps [21]

as was done by the mathematician George Polya [21]. His 17 groups were distinguished by the property that the repeating motives covered the surface without gaps or overlaps (Fig. 3). His conceptual approach was well augmented by Aleksandr I. Kitaigorodskii's (Fig. 4) empirical approach in which he designed a rudimentary structure-seeker (Fig. 5). With this device, he tested virtually all 230 three-dimensional space group possibilities on arbitrary-shaped wooden molecular models for most efficient packing.

Fig. 4 Aleksandr I Kitaigorodskii in the 1960s in Moscow (courtesy of Laszlo Breier, Budapest)

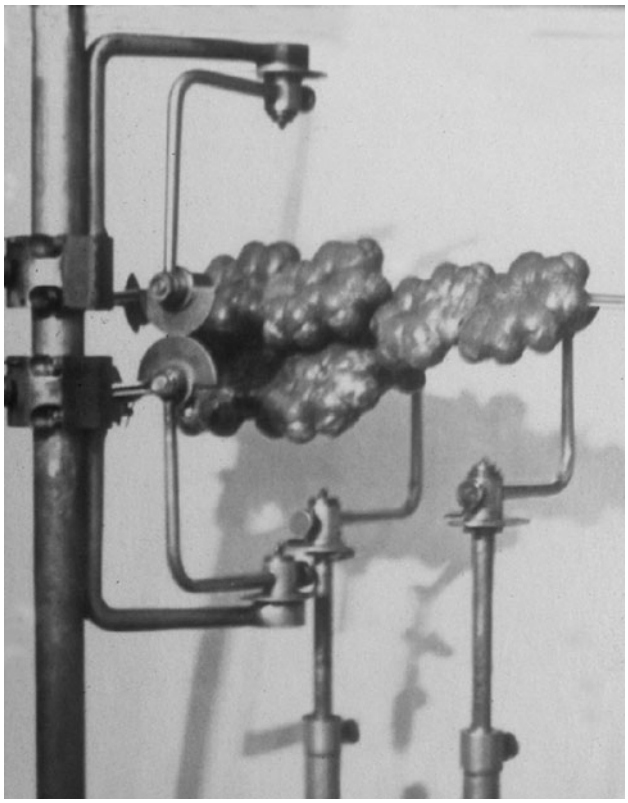

Fig. 5 Kitaigorodskii's "structure-seeker" with wooden molecular models

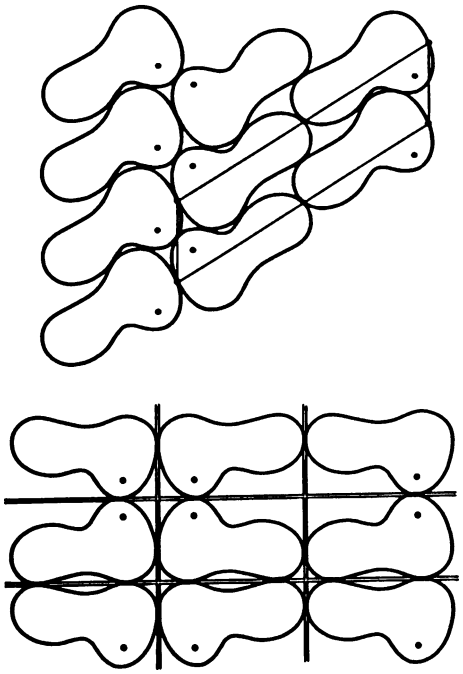

Fig. 6 Packing of the same arbitrary shapes with twofold symmetry (*top*) and mirror planes (*bottom*) after Ref. [3]

Kitaigorodskii showed the preeminence of twofold symmetry and the disadvantage of mirror symmetry for most efficient space utilization (Fig. 6). For a more detailed discussion, see, e.g., Ref. [3].

As to the first question, the importance of modeling appeared conspicuously in two recent discoveries of new materials, quasicrystals [22] and fullerenes [23], but they are not discussed here at any lengths.

Biomolecules

Modeling was also decisive in the discovery of the alpha-helix structure of proteins by Linus Pauling [24] as well as in the discovery of the double-helix structure of nucleic acids by James D Watson and Francis Crick. In addition to physical modeling, Watson and Crick utilized Rosalind Franklin's X-ray diffraction information and Erwin Chargaff's data on the quantitative equivalence of purine and pyrimidine bases in the DNAs of diverse organisms along with other sources of knowledge.

In this connection, and with the benefit of hindsight, the reverse question might also be asked concerning modeling, viz., Why did not Franklin and Chargaff use modeling in their respective investigations? In case of Franklin, this would have been most straightforward, given the similarity of her research and those of Linus Pauling, on the one hand, and Watson's and Crick's, on the other. It has been suggested that Franklin was close to the solution, but,

lacking modeling, the results of her DNA structure would have emerged in steps rather than in one big splash as did Watson's and Crick's.

The situation with Chargaff's research is fuzzier. His careful measurements established not only that the molar ratio of total purines to total pyrimidines was close to one, but also that the molar ratios of adenine to thymine and of guanine to cytosine, respectively, were not far from one [25]. This was the kind of regularity that Wigner and Polanyi considered to be the gist of science. The data Chargaff collected scattered quite a bit, and the pattern did not emerge unambiguously as we think of it today. Yet Chargaff did notice it and was brave enough to annunciate it. Alas, he stopped short of asking the crucial question of Why? If the regularity was a real phenomenon, there must have been a reason for it; it must have occurred as a consequence of something. Today we know that it was base-pairing between the two strands in DNA, and Chargaff might or might not have arrived at the concept of the double helix had he attempted to model what he had observed. The sad truth is, he never tried. His missing this may have been the reason for his ubiquitous bitterness to the end of his long life in connection with the whole field of molecular biology.

An interesting example of helical structure is shown by the tobacco mosaic virus (TMV) as depicted in Fig. 7. It has a simple rod shape with a regular helical array of proteins and there is a single-stranded ribonucleic acid molecule embedded within this protein coat. When this structure was to be modeled for the Brussels world exhibition in 1958, the builders of the large-scale model ran into the problem of identifying the initial point in building this model. The structure had been worked out originally by Rosalind Franklin and Aaron Klug with the participation of Kenneth Holmes and John Finch at Birkbeck College in London. By the time of the preparation of the physical model, Franklin had become ill and died in March 1958. It fell on Klug to recognize that to build the structure physically, there must be an initial point—in nature, it is a specific nucleation event. This realization led Klug to formulate the "difference between ordinary polymers and biological macromolecules. The key to biological specificity is a set of weak interactions. A polymer chemist could start building the model in the middle or at any other point. But for us, it was important to find the special sequence for initiating nucleation" [26].

At this point it is perhaps prudent to issue a caveat that not all model-building leads to the solution of all problems, especially if it is done remotely from experiment. Watson's and Crick's triumph in their quest for the DNA structure could easily mislead some who thought otherwise, because Watson and Crick did not carry out experiments. That did not mean though to rely on model building alone; on the

Fig. 7 Aaron Klug with the tobacco mosaic virus model at the Laboratory of Molecular Biology of the Medical Research Council in Cambridge, UK, in 2000 (photograph and © by the author)

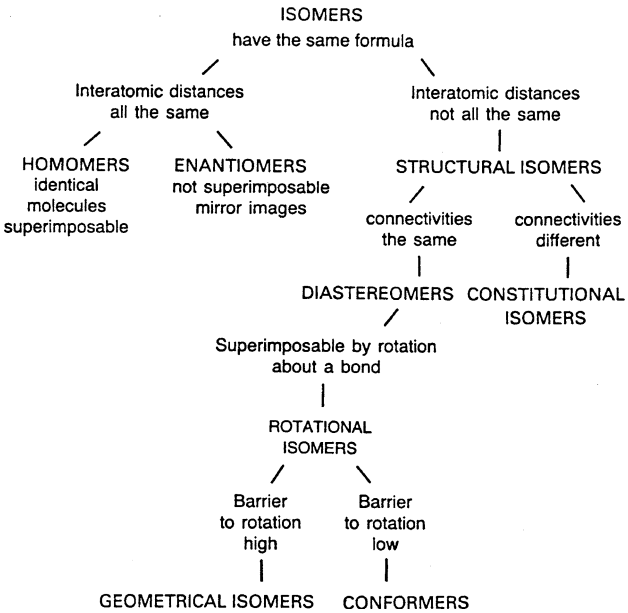

Fig. 8 Classification of chemical isomerism after Ref. [13]

Fig. 9 Two sets of Louis Pasteur's models demonstrating enantiomers at the Institut Pasteur in Paris (photographs and © by the author)

contrary, they relied on experiment and the best one at that, except that it was not their own experiment. Even then, Watson's and Crick's initial model necessitated a large amount of experimental work in Maurice Wilkins's laboratory before the original model could be considered established unambiguously. Quite a few other proposed structures for fibrous polynucleotide systems that were based on model building did not survive the test of eventual experimental studies [27].

Isomers

An important historical example of modeling involved the classification of isomers in chemistry as illustrated in Fig. 8. Of the kinds of isomerisms, the enantiomers—not superimposable mirror images—stand out in that they have no differences in distance geometry, i.e., in the interatomic distances, between the isomers. Yet even for relatively simple molecules the enantiomers may be vastly different in biological function. This isomerism may be described as differing in handedness, hence the name often used for the phenomenon—chirality. Louis Pasteur was the first who suggested that molecules may be chiral and he made macroscopic models of chiral objects to improve their perception. He may have been motivated to make these large-scale models because he wanted to demonstrate them to Jean Baptiste Biot, the discoverer of optical activity, and by the time of Pasteur's discovery, Biot's vision had considerably deteriorated. Pasteur's models have been preserved at Institut Pasteur in Paris (Fig. 9).

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