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## SYMMETRY CONSIDERATIONS IN CHEMISTRY

by

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# SYMMETRY CONSIDERATIONS IN CHEMISTRY.

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ABSTRACT  The general subject will be the use (and misuse) of symmetry arguments in constructing molecular models and in the interpretation of experimental observations bearing on molecular structure.  Examples include the development of point groups and space groups for describing the external and internal symmetry of crystals, the derivation of molecular symmetry by counting isomers (the benzene structure), molecular chirality, the connection between macroscopic and molecular chirality, pseudo-rotation, the symmetry group of non-rigid molecules, and the question of "approximate symmetry".

It is difficult to place a time for the beginnings of modern chemistry, but we may start with Johannes Kepler who was one of the first to draw a connection between the symmetry of macroscopic objects and their underlying atomic structure. In his De Nive Sexangula published in 1611 he argued that the striking hexagonal symmetry of snowflakes results from the close packing of spherical, elementary particles (1).

There are two regular ways of stacking close packed nets of spheres: cubic and hexagonal close packing, as well as an infinity of irregular ways. More than forty elements, mostly metals, crystallize in one of the two regular patterns, and some in both. Thus these ridiculously simple symmetry arguments lead to mostly correct although not infallible predictions for the structure of metals.

Many of the early arguments for the particulate nature of matter came from

speculations about the beautifully symmetric shapes of crystals, not only snowflakes. By the middle of the 18th century it had been recognized that although natural crystals of a given substance may adopt different shapes, the shapes have something in common: they show the same interfacial angles. To explain this constancy Haüy (2) suggested that crystals were built by regular repetition of fundamental units — *molécules intégrantes* — which could have any arbitrary shape. Hessel (3) showed that if crystals are built by regular repetition on a lattice, their external symmetry is restricted to only 32 possible point groups — the so-called crystal classes. In particular, the only possible rotation axes are of order 2, 3, 4 and 6 — fivefold symmetry being forbidden. The next step was to enumerate all ways in which such units could be arranged in repeating patterns, a purely geometric problem that was solved by the end of the century. There are exactly 230 ways of combining elements of point symmetry and translational symmetry to form space groups, as was found independently and almost simultaneously by Federow, Schoenflies and Barlow (4). Thus, by 1912, when von Laue discovered X-ray diffraction, the mathematical theory of crystal symmetry was essentially complete, although nothing was known about the actual structure of the *molécules intégrantes*.

By now, the atomic structures of amost 200,000 crystals have been established by X-ray and neutron diffraction, providing an enormous library of information on the structures of molecules and their mutual interactions. For molecular crystals it turns out that of the 230 possible space groups, only a handful occur (Table 1) with any appreciable frequency (inorganic compounds have a different distribution but with considerable overlap). In spite of this restriction, and even when we know the chemical structure of a molecule, there is still no reliable method of predicting the way in which the molecules will self-assemble into a crystal. Model calculations involve the computation of crystal packing energy in terms of a summation over many weak interactions between the atoms, but the energy balance between different packing arrangements is often subtle and difficult to assess with confidence, except for very simple molecules. The interpretation of the results is all the more uncertain because the calculations usually ignore the contribution of

entropic factors to thermodynamic stability; moreover, besides thermodynamic stability, kinetic factors such as competitive nucleation and growth rates, may often be decisive in determining which of several nearly equi-energetic polymorphs will actually crystallize from a solvent or from the melt.

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| Space Group | Frequency | Percent |
|---|---|---|
| $P2_1/c$ | 12201 | 38.4 |
| P-1 | 6372 | 20.1 |
| $P2_12_12_1$ | 3366 | 10.6 |
| C2/c | 2351 | 7.4 |
| $P2_1$ | 1828 | 5.7 |
| Pbca | 1368 | 4.3 |

Table 1. The most frequent space groups for organic compounds, based on a sample of 31770 crystal structures from the Cambridge Structural Database. Thus, six space groups account for almost 90% of the total. Inclusion of other space groups containing only twofold operations (screw axis, glide plane, inversion center) accounts for 96.7% of the total. Other samples yield very similar results.

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Harking back to Kepler, close packing remains a necessary although not sufficient condition for a stable arrangement of molecules in a crystal. For closest packing of spheres, the packing coefficient — the proportion of the total volume actually occupied by the spheres — is 0.74, and organic crystals typically have packing coefficients quite close to this value, around 0.65 (5). In a liquid the packing coefficient is somewhat lower (around 0.58) because the molecules must have room to slide past one another. If the packing coefficient drops below about 0.5, substances become gaseous. Whereas there are only two basically different ways of close packing spheres, there are, in general, many ways of organizing a collection of identical molecules of arbitrary shape into periodic patterns with practically the same packing coefficients and energies. This is one of the factors that makes the prediction of crystal structures so difficult and it explains why polymorphism, the existence of more than one kind of crystal for the same chemical substance, is a fairly common phenomenon.

Space group theory was an invaluable aid in building and systematizing our huge reservoir of known crystal structures. It therefore came somewhat as a surprise when in 1984 certain Al/Mn alloys were found to give diffraction patterns with supposedly forbidden icosahedral symmetry — so-called quasi-crystals, based on quasi-periodic structures. These are not a "new form of matter", as was asserted in some of the earlier, more sensational accounts, but can be accommodated with minor modifications within the existing conceptual framework.

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**Counting Isomers.** But symmetry arguments also entered chemistry from a quite different direction. Well before the elucidation of molecular structure by physical methods became possible in this century, structural formulas for thousands of compounds had been inferred by purely chemical methods, that is to say, by an intricate, characteristically chemical chain of reasoning based on simple experimental facts. Substances were weighed, dissolved, allowed to react, and the products of reaction were isolated, purified and subjected to elemental analysis. The structure assigned to a compound was initially a kind of summary of the reactions that the compound could undergo. Thus, as a simple example, the formula $CH_3.CO.OH$ for acetic acid was a concise expression of the facts: (a) that one H atom behaves differently from the other three, (b) that the two oxygen atoms behave differently, e.g., one can be replaced by another atom or grouping while the other is retained, and (c) that the two carbon atoms behave differently, one being detachable as carbon dioxide, the other as methane or a methyl derivative. In this way, each compound could be associated with a formula, and each formula with a compound. Slowly, by the 1860's, such formulas began to be considered as actual atomic arrangements in which the atoms were linked by "bonds", subject to certain rules — valency rules. Each type of atom was imagined to form a definite number of bonds, e.g., four for carbon, three for nitrogen, two for oxygen, and only one for hydrogen or for chlorine. A given set of atoms could be joined into different patterns corresponding to different molecules, known as isomers, each corresponding to a different substance. Once

the molecular concept had established itself, symmetry arguments began to flower.

I mention two examples. It was known by 1860 that the benzene molecule consists of six atoms of carbon and six of hydrogen, $C_6H_6$. By standard chemical methods, these hydrogens can be replaced, one at a time, by chlorine atoms to give a quite definite number of isomers. Thus, there is only one mono-substituted compound, which, on further chlorination, yields a mixture of three di-substituted isomers. When the chlorination process is carried a stage further, one of these isomers gives a mixture of three tri-substituted compounds, one gives a mixture of two such compounds, and one gives a single pure product (Figure 1).
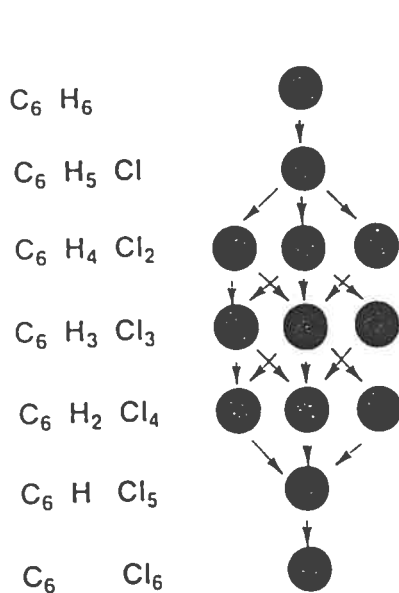
$C_6\ H_6$

$C_6\ H_5\ Cl$

$C_6\ H_4\ Cl_2$

$C_6\ H_3\ Cl_3$

$C_6\ H_2\ Cl_4$

$C_6\ H\ Cl_5$

$C_6\quad Cl_6$

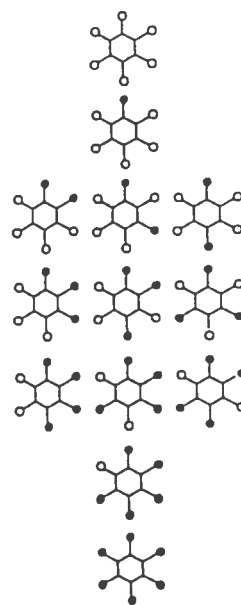FIG. 1. Relationships among the chloro-substituted benzenes. $C_6H_{6-n}Cl_n$, $n = 0-6$.

FIG. 2. Isomers of chloro-substituted benzenes, $C_6H_{6-n}Cl_n$, $n = 0-6$, based on hexagonal symmetry of the benzene molecule.

The solution of this problem was provided by Kekulé (6), who proposed a cyclic structure with sixfold symmetry for the benzene molecule. This gives the correct number of isomers of the chlorinated compounds and explains their inter-relationships (Figure 2) but it cannot be reconciled with the valency rule, four bonds per carbon atom, that had been propounded by Kekulé himself only a few years earlier. This rule would demand a less symmetric molecule, with only a threefold rather than a sixfold rotation axis (Figure 3).
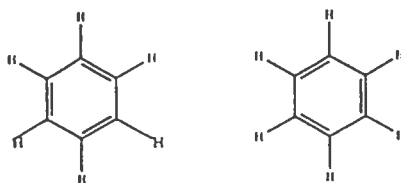
FIG. 3. Structure of benzene that satisfies the quadrivalency of carbon. Kekulé assumed that the single and double bonds interchange rapidly.

At the time there was no way of determining the atomic arrangement in molecules directly; the structures in question were purely intellectual constructions designed to explain the chemical facts, and one essential fact was that there were only three di-substituted benzenes and not four, as would be required by the lower symmetry model. Kekulé proposed to keep the cyclic formula but with the proviso that the single and double bonds change place rapidly — the molecule was imagined as a kind of hybrid of two structures that maintained the valency rules, a concept that was to recur a couple of generations later in the guise of mesomerism and resonance theory. The hexagonal structure was not the only one that was proposed at the time to explain the facts but it is the one that endured.

Extrapolation from the successful benzene formula might lead to the expectation that the molecules of the analogous eight-membered ring compound $C_8H_8$, cyclooctatetraene, would have an analogous octagonal planar hybrid structure. However, as was established many years later, the molecules of $C_8H_8$ have a non-planar structure with alternating double and single bonds. The reason why the six-membered ring molecule of benzene has its highest possible symmetry, while the eight-membered ring of cyclooctatetraene has a lower symmetry than its maximum possible became clear only with the development of quantum chemistry.

Symmetry arguments sometimes led to the right conclusion, as with benzene, but sometimes to the wrong conclusion, as in the early controversy about the molecular structure of cyclohexane, $C_6H_{12}$. As there is only a single mono-substituted isomer $C_6H_{11}Cl$, the cyclohexane molecule could be assumed to have $D_{6h}$ symmetry, with all valency rules satisfied and all hydrogen atoms equivalent (7). On the other hand, the

concept of the tetrahedral carbon atom requires a non-planar carbon ring with bond angles of around 109.5° instead of 120°, as in a planar hexagon (8). The non-planar structure ($D_{3d}$ symmetry) has two kinds of hydrogen atom (called equatorial and axial) and it should therefore give rise to two mono-substituted isomers (Figure 4). But only one compound could be isolated. For many years, therefore, the planar structure was generally accepted.
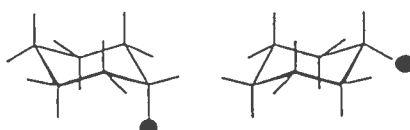


FIG. 4. Axial and equatorial isomers expected of a monosubstituted cyclohexane with a nonplanar carbon skeleton with bond angles close to the tetrahedral angle of 109.47°. Ring inversion interchanges the axial and equatorial positions.

The early investigators could not know that at room temperature the cyclohexane molecule undergoes rapid ring inversion, which interchanges the equatorial and axial substituents. This inversion process can now be followed by nuclear magnetic resonance spectroscopy. Around -90 °C there are two distinct signals from the hydrogen nuclei, corresponding to the two kinds of environment; at this temperature the inversion frequency is so slow that the two kinds of hydrogen retain their identity during the characteristic time resolution of the experiment. As the temperature is raised, however, the inversion frequency increases, the signals broaden and finally coalesce, corresponding to a set of "averaged" hydrogens. At room temperature, molecules with a substituent in an axial position and those with a substituent in an equatorial position are in rapid equilibrium, so that only the more stable of the two isomers is isolable. Rapid ring inversion was responsible for the failure to isolate more than one mono-substituted isomer.

**Molecular chirality.** Starting from observations on the morphology of ammonium sodium tartrate crystals deposited from wine, Pasteur found that tartaric acid can occur as two chemically indistinguishable compounds that differ with respect to their effect in rotating the plane of linearly polarised light — solutions of one compound rotate it to the

left, solutions of the other to the right, by equal amounts (9). Unhampered by the lack of a detailed theory of molecular structure, Pasteur postulated that the molecules of the two "optical antipodes" were related as non-superimposable mirror images. He went even further and proposed that the ability to produce substances in a single "dissymmetric" form is an intrinsic property of living systems. Today we know that achiral molecules are the exception; the vast majority of molecules are chiral, that is to say, they lack improper symmetry elements and hence are not superimposable on their mirror images. Normal laboratory syntheses based on achiral or racemic (optically inactive, containing equal amounts of the two mirror-image forms, so-called enantiomers) starting materials lead to racemic products , while the molecules involved in living systems occur almost always only as a single chiral form, as Pasteur foresaw. This means that the physiological effects of enantiomers can be very different, a matter of life and death, and one of great concern in the pharmacological industry, where considerable efforts are made to obtain products in a single chiral form, either by separation of the racemic mixture or by "chiral" synthesis leading to the desired form[1*].

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1*    Lewis Carroll's Through the Looking Glass makes several references to the left/right dichotomy ("Perhaps Looking-glass milk isn't good to drink"). It was published in 1872, at a time when chemical structural theory was being challenged by the recent finding that a substance present in muscle appeared to be identical with lactic acid obtained by fermentation of milk, except that solutions of the two substances rotated plane polarised light in opposite senses. This result was incompatible with the then current chemical formulas that showed merely which atoms were joined to which — the so-called connectedness or constitution of the molecule. It was in fact the stimulus that moved van't Hoff and Le Bel in 1874 to postulate the tetrahedral disposition of the four valencies of carbon in space and so led to the concept of stereoisomerism, the existence of isomers with the same constitution but different arrangements of the atoms in space. Looking-glass milk? Lactic acid? A coincidence? Lewis Carroll is, of course, the pseudonym of the Oxford mathematician Charles

For many years it was not known which of the two possible enantiomers for any optically active compound corresponded to the dextrorotatory isomer and which to the levorotatory. All that the then available chemical methods could do was to relate the various spatial configurations of compounds among one another — that is, to establish the configuration of a given molecule relative to some standard, usually taken as (+)-glyceraldehyde. This was arbitrarily assigned the spatial configuration I and conventionally represented by the projection formula II (Fischer projection). Within this system, for example, the configuration of (+)-tartaric acid was known to be III and that of the naturally occurring amino acids to be IV, but there was no way to establish whether the actual configuration of the reference molecule was I or its mirror image. When I was a student we were told it was impossible to answer this question, even by X-ray diffraction.
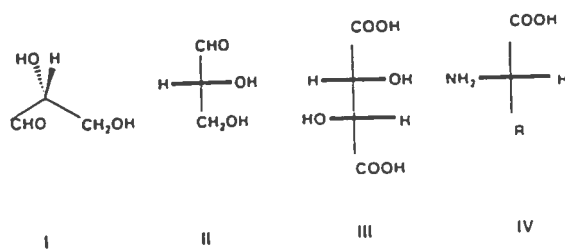


The crux of the problem lay in Friedel's Law, which stated essentially that X-ray diffraction effects are centrosymmetric, whether the diffracting crystal itself has a center of symmetry or not. In other words, the diffraction patterns from a pair of enantiomorphic crystals are indistinguishable. Friedel's Law rests on the assumption that the intrinsic phase change during the scattering of X-rays is the same for every atom. If this is true,

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Lutwidge Dodgson, and one wonders whether he had heard about the two antipodal lactic acids from his chemical colleagues. One of his closest friends, and a Fellow of the same college, was the chemist Augustus Vernon Harcourt, and another was Sir Benjamin Collins Brodie, Waynflete Professor of Chemistry in the University of Oxford from 1855 to 1873. Carroll's biographies have nothing to say on this matter, and neither do the diaries. The matter seems worth pursuing further.

then phase differences between different beams diffracted by a crystal depend only on differences in path length. For a non-centrosymmetric crystal, the structure factors F(h) and F(-h) for propagation of X-rays along two opposite directions are then related as a pair of complex conjugates, and the corresponding diffracted intensities I(h) and I(-h) are equal. In fact, as was already known by 1930 (10), Friedel's Law is not strictly true. The assumption on which it is based is only approximately valid. If the X-ray wavelength is close to an absorption edge of some of the atoms in the crystal, these atoms do not scatter exactly in phase with the others. There is a slight "phase lag". For propagation along two opposite directions, the phase differences due to the arrangement of the atoms in space are simply reversed, but the same phase lag applies to both. For non-centrosymmetric crystals, this leads to a difference between the intensities of pairs of reflections propagated in opposite directions: I(h) ≠ I(-h). In 1951 Bijvoet showed (11) that this difference could be used to make the connection between macroscopic and molecular chirality. The arbitrarily assigned spatial configuration I assigned to (+)-glyceraldehyde turned out to be correct after all.

The absolute configuration of organic compounds is usually described by means of the CIP system, so-named after the initials of its inventors (12). It consists of a series of rules for putting the four groups around a tetrahedral center into a priority sequence: $a$, $b$, $c$, $d$ where $a > b > c > d$. The first rule involves the atomic number of the directly bonded atoms; high atomic number takes precedence over low. If this is not enough to determine the sequence one proceeds to the second rule, which involves atomic mass, and if this is still not enough one proceeds outwards to the next set of atoms and applies these and other, more complicated rules. The chirality sense of the central atom is then assigned by the following convention: view the chiral center from the direction opposite to the group $d$ of lowest priority. If the sense of rotation of the other three grooups, from $a$ to $b$ to $c$ is clockwise, then the chirality sense is designated as R (rectus). If it is anti-clockwise, then the chirality sense is S (sinister) ([†2]). Thus, the central carbon atom in I

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†2    To avoid misunderstandings, note that if the directions of the bonds from the central

(and II) is R, the tartaric acid molecule in III is R, R, and the amino acid in IV is S.

We now know that the amino acids of proteins all have the S configuration (as in IV), and that the ribose units in nucleic acids all have the R configuration (as in II), and thus we know on which side of the mirror plane the molecules in all living matter on this earth exist. The proteins are built from S-amino acids, the nucleic acids from R-ribose sugar components. There is no problem in explaining the Darwinian advantage of bio-active polymers containing only one set of homochiral monomers. A polypeptide made by random condensation of R- and S- amino acids from a racemic mixture would have no chance of folding into the kind of definite pattern characteristic of an enzyme, and a polynucleotide built from a random sequence of R- and S- ribose molecules could not achieve the regular repeating helical structure required for genetic information storage and retrieval. Indeed, in a polymeric chain, a regularly repeating helical arrangement of chiral sub-units is possible only if the sub-units have the same sense of chirality, for the repetition operation is some combination of rotation and translation, operations that are incompatible with reversal of the sense of chirality. Imagine now that such a regular structure imparts some kind of advantage in the selection pressure of a primitive pre-biotic world. This could be improved stability, faster rate of formation, better autocatalytic efficiency, slower rate of hydrolyis, or faster rate of recombination from partly hydrolysed fragments. Whatever this advantage might be, mixed sequences would rapidly be eliminated. Moreover, once an evolutionally successful polymer built from a set of homochiral but constitutionally different sub-units were to appear, the chance that its exact enantiomer molecule were to appear simultaneously is virtually zero. A possible scenario for this kind of symmetry breaking by stochastic chiroselective co-oligomerization in polynucleotide systems has been recently been proposed (13).

However, this kind of argument leaves the question of the original choice of one or the other set of enantiomers open. Was it simply a matter of chance, or was there an

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atom to $a$, $b$, and $c$, are regarded as vectors $x_1$, $x_2$, $x_3$, in that order, then S corresponds to a right-handed coordinate system.

underlying physical reason for the preference? Several possibilities have been proposed over the years, such as the role of electric and magnetic fields (14) and especially that of parity non-conservation and the electroweak interaction (15). The enantiomeric energy difference due to the electroweak interaction is very small, of the order of $10^{-14}$ J mol$^{-1}$, corresponding to an excess of about $10^6$ molecules of the more stable enantiomer per mole of racemate in thermodynamic equilibrium at 300 K (note that the expected excess of R or S molecules from random "heads or tails" selection would be of the order of $10^{12}$ molecules for one mole of substance!). Inclusion of the electroweak interaction into quantum mechanical ground state energy calculations is indeed reported to show a slight preference for the R-sugars and the S-amino acids, the ones selected in the course of evolution. However, the significance of this for autocatalytic and other chemical reactions is not clear. There is still no consensus on the matter — nor is there likely to be.

**Approximate Symmetry**. For a mathematician an object either possesses a certain symmetry or it does not. For most of us, however, it seems to make sense if we say that an object is nearly but not exactly symmetric, that it possesses approximate symmetry. Can one then say that one asymmetric object is "more symmetric" than another? In the chemical context there are many molecules that are expected to possess some symmetry as isolated particles in the gas state but show significant deviations from this symmetry in a crystal, where the molecules interact with one another. For example, phosphate groups, $PO_4{}^{3-}$ almost never show exact tetrahedral symmetry in their crystalline compounds (16). Can one say that one phosphate group is more symmetric than another? One way of approaching this question is to describe the displacements from a given symmetrical reference structure in terms of symmetry coordinates (17). These are linear combinations of the original internal coordinates with special properties when transformed according to the symmetry operations of the reference point group G. In this way, the total distortion is broken down into several components, each of which preserves some of the symmetry elements of G. Another approach is in terms of the minimal distances that the vertices of a

given shape must move in order to satisfy some standard point group symmetry (18).

Recall that a figure is called chiral (handed) when it contains only symmetry elements of the first kind, i.e., those corresponding to proper operations such as rotations (and translations in case of periodic patterns). A chiral figure (hand, glove, amino acid molecule, etc.) is not superimposable with its mirror image; the presence of an improper symmetry element such as a mirror plane or inversion center in a given figure is sufficient to confer achirality (tea cup, benzene molecule, etc.). The simplest example is a scalene triangle, which is chiral in the plane. We might try to answer the question: what shape is the most chiral triangle? For a start, we need some measure of "degree of chirality". One way that looks appealing at first sight is to use a product (19) such as:

$$P = (a-b)(b-c)(c-a)$$

where a, b, c may be chosen as the lengths of the sides or as the three angles. Clearly P has the required properties in that it vanishes if any two sides (angles) are equal —to yield an isosceles triangle— and it changes sign for any non-cyclic permutation of the sides (angles). However, a detailed analysis (20) shows that according to this measure the most chiral triangle is infinitely flat and skewed; in other words it leads to the paradoxical result that the most chiral triangle is infinitely close to a straight line! We may remark that if a, b, c are chosen not as the angles but as the sines of the angles then a maximum value of P is found for a triangle with angles: 111.9°, 52.3°, 15.8°. According to another criterion, the "Hausdorff chirality measure" (20), the most chiral triangle is one with angles: 114.3°, 44.2°, 21.5°, while according to the minimal distance criterion mentioned above, it has angles 124.8°, 38.0°, 17.2° (21). Thus, even if we reject the straight line solution, three different measures yield three different answers. The respective triangles are shown in Figure 5 and the reader may decide for herself which triangle looks the most chiral. Here I might hazard the conjecture that there exists some valid measure that will make ANY chiral triangle the most chiral triangle.
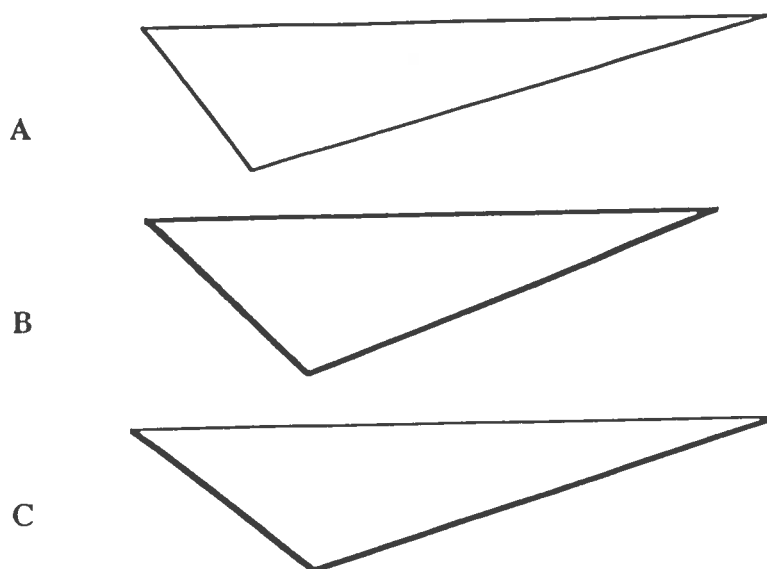
FIG 5. Three triangles that satisfy different measures of maximum "degree of chirality". From top to bottom they have angles: (A) 111.9°, 52.3°, 15.8°; (B) 114.3°, 44.2°, 21.5°; (C) 124.8°, 38.0°, 17.2°.

**Pseudorotation.** A beautiful application of the use of symmetry coordinates leads to the concept of pseudorotation (22). The carbon skeleton of the cyclopentane molecule $C_5H_{10}$ is an equilateral pentagon. If the internal angles were all exactly 108° then, of course, the pentagon would be planar, but this arrangement was known from chemical strain theory to be energetically less stable than one in which the pentagonal ring is non-planar. The relative positions of N points in space are defined by 3N-6 independent coordinates, of which 2N-3 can be chosen in an arbitrary plane, leaving N-3 coordinates to describe the deviation from planarity ; for N = 5, there are thus 2 coordinates to describe the puckering of the ring. With the use of symmetry coordinates it could be shown that: "...the ring puckering motions are: first, an ordinary vibration in which the amount of puckering oscillates about a most stable value, and second, a pseudo one-dimensional rotation in which the phase of the puckering rotates around the ring. This is not a real rotation since the actual motion of the atoms is perpendicular to the direction of rotation and there is no angular momentum about the axis of rotation." The pseudo one-dimensional path runs along a circle in the sub-space spanned by the doubly degenerate $E_2''$ symmetry displacement coordinates of the regular pentagon with $D_{5h}$ point group symmetry. It is

interesting that the angles in a non-planar equilateral pentagon cannot be equal — the pentagon is the only polygon to have this property! (23).

Other molecular processes that run along almost isoenergetic pathways involving pairs of degenerate deformation coordinates include the twist-boat conformational change of cyclohexane and several Jahn-Teller type deformations of symmetric molecular frameworks; see ref (24) for examples.

**Use of Symmetry Coordinates.** Although the vast majority of molecules occurring in nature or created by synthetic chemistry have no symmetry, point group symmetry nevertheless provides a useful classification scheme for simple molecules. For such molecules, it is convenient to use symmetry coordinates for describing small displacements of the atoms from the equilibrium structure, e.g., molecular vibrations. This is because in harmonic approximation, i.e., if the potential energy is expressed as a sum of quadratic terms in the various displacement coordinates, vibrations belonging to different irreducible representations of the molecular point group are not coupled — there are no cross-terms between them. Those that belong to the same irreducible representation are coupled and thus cannot be treated separately from one another. The symmetry classification of more-or-less rigid molecules, i.e., those where the atomic displacements are small, is fairly straightforward, but, for non-rigid molecules, the problem becomes more difficult and the choice of a reference point group may not be clear cut.

**Non-rigid molecules.** As a simple example we take the molecule of ethane, $H_3C$-$CH_3$, two methyl groups linked by a carbon-carbon bond. For our purposes, we regard the methyl groups are rigid units with threefold symmetry. An arbitrary mutual orientation of the methyl groups then corresponds to a molecule with $D_3$ symmetry, order 6 (Figure 6), so that there are six symmetry equivalent arrangements of the same figure. If we now allow rotation about the central bond, new possibilities arise. Arrangements R and $R^2$

show the result of rotating the distal methyl group by 120° and by 240° (rotation by 360° produces the initial arrangement E). Arrangements R and $R^2$ are isometric with E, and each of them also gives rise to six symmetry equivalent arrangements, making 18 in all. Moreover, since the initial arrangement E is chiral, there is another matching set of 18 isometric structures that are enantiomorphic to E. Thus the order of the isometric symmetry group of ethane is 36. Note that rotation of one methyl group with respect to the other is *not* a point group symmetry operation of the ethane molecule regarded as a rigid figure but it is a symmetry operation of the isometric group of the molecule.
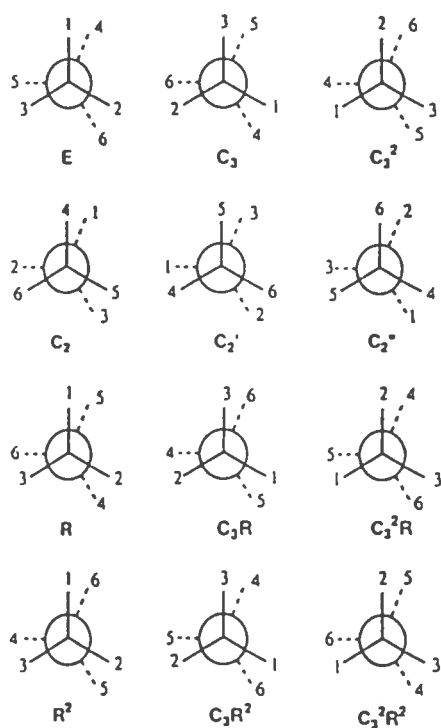


Fig. 5. A set of 18 isometric structures of the ethane molecule obtained by symmetry operations of the $D_3$ point group and by rotation of one methyl group with respect to the other. There is a matching set of 18 isometric enantiomorphic structures, so the order of the isometric group is 36.

Special conformations of the ethane molecule have higher symmetry than $D_3$; there is a set of $D_{3h}$ conformations (with the hydrogen atoms eclipsing one another) and one of $D_{3d}$ conformations (with the hydrogen atoms perfectly interposed). The latter set is the one of lowest potential energy. At normal temperature ethane molecules undergo torsional oscillation about a $D_{3d}$ conformation, and a considerable fraction accumulate sufficient

energy in the torsional mode to undergo internal rotation from one $D_{3d}$ conformation to another. In the analogous molecule dimethyl acetylene $H_3C-C\equiv C-CH_3$ the barrier is so small that internal rotation is virtually unhindered.

Problems of this type, first taken up by Longuet-Higgins (25), can be quite complex, especially when large displacements occur in several degrees of freedom, and have given rise to considerable controversy (26, 27, 28, 29). In spite of their abstract nature, they are important in determining selection rules for electric dipole type transitions and in the analysis of atomic motion in isomerization reactions.

As an alternative to thinking about such problems in terms of the feasible internal motions of a flexible molecule, one can describe the isometric group in terms of the symmetry properties of the many-dimensional energy hypersurface relevant to the dynamics of all possible molecular isomerizations (30). Every possible atomic arrangement corresponds to a representative point in the many-dimensional space, and since isometric structures must be energetically equivalent, the energy hypersurface must be invariant to all symmetry operations of the isometric group. It is difficult to visualize symmetry operations in many-dimensional space, and it is sometimes helpful to restrict the discussion to particular sub-spaces of the (3N-6)-dimensional internal coordinate space (20, 25). Note than when cyclic coordinates (torsion angles) are used as internal coordinates to describe atomic displacements in a finite molecule, the relevant sub-space corresponds to an infinite group containing elements of translational symmetry, i.e., to a space group rather than a point group.

**Teaching Symmetry Concepts.** Until about thirty years ago, the role of formal symmetry arguments in chemical thought was almost negligible. Few chemists found any use for symmetry concepts in their everyday thinking, and those few were mostly at the physical end of the science — spectroscopists, crystallographers, theoreticians. The practical chemist, engaged in making new compounds, in isolating, purifying and identifying them, in unraveling the mechanistic details of chemical reactions, was more

likely to be aware of symmetry considerations in art than in his own science And this was reflected in chemical textbooks and in the teaching of the subject. Symmetry was hardly mentioned; only, perhaps, in the explanation of "optical activity", as discussed above, but even there the emphasis was on the easily grasped concept of the "asymmetric carbon atom" rather than on the distinction between superposable and non-superposable mirror-images in terms of fundamental symmetry properties.

Today the situation is very different. Books that purport to explain group theory to chemists appear every year. Even elementary textbooks now contain mandatory chapters dealing at least with point group symmetry and often more. Along similar lines, many chemistry courses include explanations and discussions of symmetry at very early stages. In the general chemistry course that I taught in the 1980's, elementary symmetry ideas were introduced around the third week, immediately following the fundamental concept of the molecule. I must admit that some students had initial difficulty in seeing the point of learning about symmetry. While I chose highly symmetric molecules such as benzene or methane to make my point, many students were aware such molecules are quite atypical. Only a tiny fraction of the millions of known compounds are built from molecules with any symmetry whatsoever. "Learn now, understand later", was my advice, and I hope it benefited them in the end.

Why did this change in the cultural background of chemists take place? There are probably many contributory factors; the increased importance of physical methods, such as nuclear magnetic resonance (NMR) spectroscopy and X-ray crystallography in molecular structure determination, the discovery of the so-called fullerenes, the intrusion of orbital symmetry arguments (31), and probably others. For further reflections on this topic see (32)

References

1. Kepler, J. (1611) <u>De Nive Hexangula: On the Six-Cornered Snowflake</u>, translated by Hardie, C. 1966 (Clarendon Press, Oxford).

2. Haüy, R. J. (1784) <u>Essai d'une théorie sur la structure des cristaux appliqué a plusieurs genres de substances cristallines</u> (Gogué & Née de la Rochelle, Paris).

3. Hessel, J. F. C. (1830) <u>Kristallometrie oder Kristallonomie und Kristallographie</u>. Reprinted in Ostwald's Klassiker der exakten Wissenschaften, 1897 (Engelmann, Leipzig).

4. Hilton, H. (1903) <u>Mathematical Crystallography and the Theory of Groups of Movements</u> (Clarendon Press, Oxford; reprinted Dover Books, New York, NY 1963).

5. Kitaigorodski, A. I. (1973) <u>Molecular Crystals and Molecules</u> (Academic Press, New York and London).

6. Kekulé, A. (1865) <u>Liebig's Annalen</u>, 137, 129-196.

7. Baeyer, A. (1885). <u>Ber. Dtsch. Chem. Ges</u>. 18, 2269-2281.

8. Sachse, H. (1890) <u>Ber. Dtsch. Chem. Ges</u>. 23, 1363-1370.

9. Pasteur, L. (1850) <u>Ann. Chim. Physique</u> 28, 56-99.

10. Coster, D., Knol, K. S. & Prins, J. A. (1930) <u>Z. Physik</u>. 63, 345 - 369.

11. Peerdeman, A. F., van Bommel, A. J. & Bijvoet, J. M. (1951) <u>Proc. Koninkl. Ned. Akad. Wetenschap</u>. B54, 16-19.

12. Cahn, R. S., Ingold, C. K. & Prelog, V. (1956) <u>Experientia</u> 12, 81-124.

13. Bolli, M., Micura, R. & Eschenmoser, A. (1997) <u>Chemistry and Biology</u> 4, 309-320.

14. Barron, L. D. (1995) <u>Science</u> 266, 1491-1492.

15. Mason, S. F. (1991) <u>Chemical Evolution: Origin of the Elements, Molecules, and Living Systems</u>. (Clarendon Press, Oxford.)

16. Baur, W. H. (1974). Acta Crystallographica B30, 1195-1215.

17. Murray-Rust, P., Bürgi, H.-B. & Dunitz, J. D. (1979). Acta Crystallographica A35, 703-713.

18. Zabrodsky, H., Peleg, S. and Avnir, D. (1992). J. Amer. Chem. Soc. 114, 7843-7851.

19. Ruch, E. (1972). Acc. Chem. Res. 5, 49-56.

20. Buda, A. B., Auf der Heyde, T. and Mislow, K. (1992). Angew. Chem. Int. Ed. Engl. 31, 989-1007.

21. Zabrodsky, H. and Avnir, D. (1995). J. Amer. Chem. Soc. 117, 462-473.

22. Pitzer, K. S. & Donath, W. E. (1959) J. Amer. Chem. Soc. 81, 3213-3218.

23 Dunitz, J. D . & Waser, J. (1972) Elemente der Mathematik 27, 25-32.

24. Dunitz, J. D. & Bürgi, H.-B. (1994) in Structure Correlation, eds. Bürgi, H.-B. & Dunitz, J. D. (VCH, New York), Vol. 1, pp. 23--70.

25. Longuet-Higgins, H. C. (1963) Molec. Phys. 6, 445-460.

26. Altmann, S. L. (1967) Proc. Roy. Soc. London A 298, 184-203.

27. Altmann, S. L.(1971) Molec. Phys. 21, 587-607.

28. Woodman, C. M. (1970) Molec. Phys. 19, 753-780.

29 Watson, J. K. G. (1971) Molec. Phys. 21, 577-585.

30 Bauder, A., Meyer, R. & Günthard, H. H. (1974) Molec. Phys. 28, 1305-1377.

31. Woodward, R. B. & Hoffmann, R. (1970) The Conservation of Orbital Symmetry (Verlag Chemie, Weinheim, Germany).

32. Heilbronner, E. & Dunitz, J. D. (1993) Reflections on Symmetry in Chemistry....and Elsewhere (Verlag Helvetica Chimica Acta, Basel and VCH, New York).