



Molecular Structure and Its Inverse: The Mystery of Their Origins, the Enigma of Their Detection

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The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

The origins of the molecular-chiral homogeneity that is the very basis of life remain a tantalizing mystery. Molecular chirality itself is manifest in its interaction with radiation, particularly as optical activity, although an intriguing alternative technique based in X-ray crystallography is being increasingly employed. Thus, X-ray diffraction with anomalous dispersion is currently believed to lead to the absolute configuration of a stereogenic center, the ultimate goal of structural chemistry. However, despite its apparently unerring consistency, the fundamental basis of the anomalous dispersion technique is itself enigmatic. This is because it is unclear how the technique not only distinguishes two enantiomeric lattices but also assigns the absolute configuration: all, apparently, in the absence of an external chiral influence! Indeed, as argued previously, it is highly likely that the technique succeeds because the X-rays employed are circularly polarized, itself a possible consequence of parity violation. All the same, the question of how the absolute configuration is assigned remains, as the chiral sense of the putative circular polarization of the X-rays is unknown. It is argued herein that the anomalous dispersion method is essentially based in the chirality of X-rays that must have entered—although unbeknownst as such—into the calculations leading to the absolute configuration. In fact, the enigma surrounding the anomalous dispersion method derives from uncertainties concerning the theory of X-ray diffraction itself, thus leading to the apparently inescapable conclusion that both methods are essentially empirical — but without detracting from the brilliance of the scientific achievements that led to these methods.

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1. INTRODUCTION

1.1 General Background

The molecular structural theory of chemistry evolved during the course of the 19th century apparently inspired by Dalton's atomistic ideas [1]. Although initially the structural theory essentially functioned as a codification scheme for newly discovered organic reactions, certain parallel developments conferred on the theory its sense of realism that is now taken for granted. Thus, Pasteur's discovery of optical activity and isomerism in the tartaric acids led to van't Hoff's tetrahedral carbon atom, and ultimately to the concept of molecular chirality [2]. Indeed, the structural theory hasn't looked back since!

The concept of molecular chirality led to the birth of stereochemistry [2], a testament to Pasteur's pioneering efforts. Molecular chirality, in fact, is the very basis of life itself, which depends critically on chiral homogeneity [3]: the stereo-random formation of life's infinite range of molecules would lead to diastereomeric chaos, which would hardly be conducive to the order and discipline that characterize life. (And the critical importance of molecular chirality in medicinal chemistry, as manifested in drug action, can hardly be overstated).

Molecular chirality is apparently the final imprimatur of realism on the structural theory! Yet, the structural theory is not without critique, based on the argument that it cannot be derived a priori from quantum theory [4-6]. Molecular chirality, too, is apparently caught up in this theoretical wrangling [7]. Yet again, the existence of life—not to mention the humble polarimeter—support the idea of molecular chirality in no uncertain a manner!

1.2 Origins of Molecular Chirality

The origins of the chiral homogeneity of the biosphere have been a topic of intense speculation in recent decades, with both chance and deterministic theories having been proposed [2,7-10]. Chance theories essentially center around accidental and stereoselective crystallization phenomena, particularly the second order asymmetric transformation. An intriguing deterministic theory is based in the phenomenon of parity violation, a fundamental

consequence of the weak nuclear force [8]. Parity violation, in principle, is believed to confer on the enantiomers of a chiral compound differing energy contents, termed the "parity violating energy difference" (PVED).

The PVED, however, is vanishingly small at $\sim 10^{-20}$ kJ mol⁻¹, hence not only way below conventional detection limits but also practically impossible to amplify. Yet, the philosophic allure of a "first cause" and the absence of viable alternatives have kept alive the intriguing possibility that parity violation is the origin of chiral homogeneity. This topic has been extensively debated and reviewed previously, so suffice it to state that the PVED option—however ambiguous the evidence—remains under consideration: although with what seriousness depends on individual predilections!

1.3 Detection of Molecular Chirality

Traditionally, molecular chirality has been associated with optical activity [2], so the direct detection of molecular chirality is an indicator of the most recent scientific advances. Brilliant experimental work in the early 1950's, however, laid the foundations of these developments, now enshrined as the anomalous dispersion adjunct of X-ray crystallography [11,12]. In this fascinating new technique, the classical X-ray diffraction experiment is conducted on a single crystal of a chiral compound but near its absorption edge. Under these conditions of intimate interaction between radiation and crystalline matter, Friedel's Law—a fundamental principle linking diffraction theory and chirality—breaks down [13]. Practically, this implies that enantiomeric crystalline lattices now display subtle differences in their X-ray diffraction patterns, hence can be distinguished to the point that absolute configurations of stereogenic centers can be assigned.

The theoretical basis of these advances, however, remains intriguing, as they are apparently in conflict with a fundamental tenet of stereochemistry. Thus, the detection of chirality is impossible in a wholly achiral environment [2,8], hence the breakdown of Friedel's Law is incomprehensible as is. Conversely, this apparent conflict with fundamental theory implies that—if Friedel's Law does indeed break down—there must be a chiral influence of some sort. A straightforward possibility is that the X-rays are

circularly polarized because of parity violation during their generation, so their interaction with enantiomeric crystalline lattices would be diastereomeric [8].

All the same, the assignment of the absolute configuration of stereogenic centers remains enigmatic, as the sense of the putative circular polarization of the X-rays is unknown. This apparently flies in the face of the unerring consistency of the anomalous dispersion technique in assigning configuration, but in fact indicates that the method is inherently empirical. This possibility is discussed in greater detail below, and indeed leads to intriguing insights into the basis of the X-ray diffraction method itself — not to mention philosophical questions concerning empirical science.

2. DISCUSSION

2.1 Optical Rotation and Absolute Configuration: General Considerations

Modern stereochemistry is based in the web of ideas and concepts that relate the symmetry of crystals and molecules to a measured property [2]. Historically, this exercise dates back to Pasteur, with the measured property generally being optical rotation. Typically, the rotation of plane polarized light of a certain wavelength by a solution of known concentration, is measured quantitatively in a polarimeter. Plane polarized light is itself believed to be composed equally of left and right circularly-polarized light [14], which are considered to be transmitted to differing extents by a chiral solution or medium (manifesting as the rotation of the plane of polarization).

The detection of chirality, however, does not imply that the sense of the chirality is also known. Thus, the rotation of plane polarized light by a chiral compound, observed in a polarimeter, does not necessarily yield the absolute configurations of the stereogenic centers in the compound. The absolute configuration, in fact, needs to be determined by further independent experimental studies [15].

The classical approach to assigning absolute configurations was based on chemical and structural correlations with a standard compound of assumed configuration [2]. This was typically the glyceraldehyde pair of enantiomers, the correlations being represented with the Fischer projection formulae. Thus, a compound that

could be derived from D-glyceraldehyde without affecting its stereogenic carbon center would be assigned the “D” configuration. The subsequently introduced CIP convention was essentially a rigorous system of stereochemical nomenclature, noting that the glyceraldehyde method had the advantage of correlation with a known standard.

The glyceraldehyde method, of course, assumed the absolute configuration of the C_2 stereogenic center in glyceraldehyde (as related to its optical rotation and represented in the Fischer projection). The classical method of assigning absolute configuration—despite its obvious tedium—prevailed well into the final decades of the last century. It is, however, being gradually supplanted by a purely physical technique based in X-ray crystallography, that is of intriguing sophistication and (apparently) unerring accuracy. This is the anomalous dispersion technique which, despite its obvious advantages and increasing popularity [2,11,14,15], does indeed raise fundamental questions about the nature of chirality and its detection.

The above arguments about the determination of absolute configuration are summarized below, the assignment of absolute configuration being comprised of two parts.

1. The detection of chirality: classically, this was based on optical rotation; the visual inspection of hemihedral crystals could be useful but also deceptive, as it does not ascertain molecular level chirality. (This is because chiral compounds may yield achiral crystals and vice versa.)
2. The assignment of absolute configuration: this was essentially based on correlation with a standard compound of assumed configuration (typically, glyceraldehyde in Fischer’s D,L system).

Furthermore, any system for assigning absolute configuration must be based on the above protocols, executed in some form.

2.2 Fundamental Concerns: X-ray Diffraction and Anomalous Dispersion

2.2.1 Friedel’s Law and its breakdown

The anomalous dispersion technique differs from a normal X-ray diffraction experiment in that the experiment is performed on a single crystal at the absorption edge. Thus, normal diffraction is conducted by the scattering of X-rays without their being absorbed to any significant extent by

the crystalline compound being examined. However, in the case of anomalous dispersion the scattering of X-rays occurs with discernible levels of absorption, hence implying a more intimate interaction between X-ray and the scattering electron cloud of the crystal lattice.

Under these conditions of intimate interaction, Friedel's Law apparently breaks down, with enantiomeric crystals affording differing diffraction patterns in terms of relative intensities of the observed reflections. Thus, the symmetrical diffraction pattern normally observed is altered under anomalous conditions, with the degeneracy of the "Friedel pair" reflections being lifted (in the non-centrosymmetric cases, *vide infra*).

Friedel's Law, of course, is apparently upheld during normal scattering, so enantiomeric lattices cannot be distinguished. Friedel's Law states that the moduli of the structure factors (F) for reflections that are related across a center of symmetry ("Friedel pairs") are equal (Eq. 1, h , k and l are the Miller indices):

$$|F_{(hkl)}| = |F_{(-h-k-l)}| \quad (1)$$

Thus, the observed reflection intensities being proportional to F^2 , $F_{(hkl)}$ and $F_{(-h-k-l)}$ cannot generally be distinguished. In fact, in the case of a non-centrosymmetric lattice Eq. 1 is inapplicable, although this is manifested only under the conditions of anomalous scattering. A practical consequence of this is that enantiomeric lattices yield diffraction patterns in which the Friedel pairs are distinct and lead ultimately to the absolute configuration of the stereogenic center (under anomalous scattering).

Friedel's Law itself and its breakdown under anomalous dispersion conditions are often represented in Argand diagrams, which show the various components of F , and their resultant, in vectorial fashion. There are apparently several problems with these approaches.

Firstly, the breakdown of Friedel's Law is inexplicable in the absence of a chiral directing force. Thus, the Argand diagrams merely depict the breakdown of Friedel's Law, but do not explain why. Likewise, the well-known Flack parameter is essentially a goodness-of-fit measure of the calculated and observed reflection data.

Also, the structure factors may be expressed mathematically as Fourier transforms of functions that involve atomic scattering factors and positions. Whilst this certainly infuses an element of rigor to the protocols, it has apparently led to the view that the breakdown of Friedel's Law under anomalous conditions can be explained purely mathematically. This could well be the major stumbling block in attempts to reach a satisfactory understanding of the anomalous dispersion method.

However, as has been argued previously [8], it is likely that X-rays are circularly polarized during their generation as a result of parity violation. This could explain the breakdown of Friedel's Law, along with the intimate interaction criterion obtaining under anomalous dispersion conditions. Even so, however, the assignment of absolute configuration is intriguing, as the sense of the putative circular polarization of the X-rays is unknown (i.e., left or right-handed). Thus, the anomalous dispersion experiment would only indicate whether the crystals being analyzed were chiral or not (corresponding to the rotation of plane polarized light, *vide supra*.)

Therefore, apparently, there must be another criterion that leads to the absolute configuration of stereogenic centers, as determined in the anomalous scattering experiment. In fact, this implies—in principle—that there must be a general criterion for identifying any enantiomeric lattice, before its interaction with X-rays can be explained. This is because the anomalous dispersion technique indicates that there is a consistent relationship between the (putative) circular polarization of X-rays and an aspect of the chirality of the lattice.

In other words, there must exist a general principle governing the interaction of X-rays with a chiral lattice that includes a symmetry aspect of the lattice. However, as the "hkl" notation is relative, a general principle must employ an absolute lattice symmetry aspect, either explicitly or implicitly: This indicates the importance of the unit cell, possibly the crystal orientation and the circular polarization of X-rays being unchanging.

2.2.2 Qualitative considerations

Conventional stereochemical theory, of course, requires a diastereomeric interaction for the distinction between enantiomeric lattices to be manifested. Thus, although the breakdown of Friedel's Law is to be expected—in principle—for a

chiral lattice, the breakdown becomes perceptible only under anomalous dispersion conditions!

Furthermore, a particular problem is that X-ray diffraction involves planes of scattering atoms, hence is fundamentally incapable of detecting chirality. This is because planes are essentially achiral moieties that possess a plane of symmetry (by definition). Also, the case of planar chirality [2] does not apply here as scattering may occur from either side of the plane. (In fact, even a centrosymmetric lattice may possess such chiral planes!).

Thus, the Bragg model cannot generally lead to a distinction between enantiomeric lattices. However, a scattering model that involves the unit cell as a whole can in principle detect a non-centrosymmetric lattice under appropriate conditions (e.g., the X-rays are circularly polarized).

2.2.3 Inviolable implications

The implications of the above qualitative arguments may be summarized and extended as below, noting that the success of the anomalous dispersion experiment requires that these are inviolable. The protocols of the anomalous dispersion method must submit to these implications at least in a general way, although not necessarily in a theoretically specific way.

1. There must exist a general way of designating a chiral lattice as left or right-handed. This most likely would be based on the relative orientations of chiral planes within the unit cell, the chirality of the planes themselves being designated in a certain manner, likely based on the relative orientations of atoms present in the plane.
2. There must exist a chiral influence or directing force that can distinguish between enantiomeric lattices during the anomalous dispersion experiment. The chiral influence or force is almost certainly the X-rays themselves, which are likely circularly polarized by parity violation during their generation (in a consistent chiral sense).

Alternatively, parity violation may act on the chiral lattices themselves, thus lifting their degeneracy. This may well reflect both the lattice symmetry and the diffraction patterns in a characteristic manner, thus leading to their correlation in a generally consistent way.

Of course, both the above effects may act in tandem.

3. There must exist a general principle governing the interaction of the circularly polarized X-rays with any and all chiral lattices: this must correlate the differences in the diffraction patterns afforded by an enantiomeric pair with the chirality of each lattice, the chirality being defined as in (1) above.

2.3 General Problems with Diffraction Theory: Bragg's Law to Friedel's Law

2.3.1 Limitations of the Bragg model

As noted above, the anomalous scattering technique extends X-ray crystallography to the chiral domain. In conventional X-ray diffraction theory, intensity differences are explained as arising out of phase differences present in the scattered rays. However, as has been previously argued [16,17], there are serious problems with conventional diffraction theory, as the idea of constructive and destructive interference of waves seems insupportable.

Thus, the surface on which the scattered rays are received and recorded as reflections, can never be defined to the accuracy of the wavelength of radiation. In other words, the recording surface needs to possess a smoothness of the same order as the wavelength of the impinging radiation, for the theory of interference to be valid. (In fact, both in-phase and out-of-phase waves would possess identical energies, hence cannot lead to reflections of differing intensity).

Clearly, therefore, there must be an alternative explanation for the observed "diffraction" patterns. As argued previously, again [16], a likely possibility is that scattering occurs from stacked planes in a cooperative manner, as opposed to the conventional Bragg model. This alternative absorption-emission model would explain the observed reflections without the limitations of the Bragg model indicated above.

Furthermore, in fact, this implies that the "phase problem", which is a key aspect of X-ray diffraction theory, has no basis in fact but is rather a "diversionary" artefact of an inherently dubious model [16]. The structure factor relations thus appear to represent an essentially empirical exercise: in this, the reflection intensities are apparently derived from atom scattering factors and bonding geometries, which have been

iteratively honed to high accuracy on an enormous range of structures over the decades.

Therefore, differences in the scattering efficiency of various planes—rather than phase differences—are the likely reason for the differences in the intensity of the observed reflections. The Fourier transform representations of the structure factors are thus best regarded as providing an empirical model rather than as constituting theoretical proof of the protocols. (Indeed, deviations from the model are apparently accommodated as “phase differences”).

2.3.2 The anomalous dispersion method as an empirical exercise

These arguments imply that the anomalous dispersion extension of the X-ray method also needs to be reassessed as an empirical exercise. As argued above, the conventional treatment of anomalous dispersion merely assumes the breakdown of Friedel's Law, as represented in the Argand diagrams. The fundamental requirement of a chiral influence that can discriminate between enantiomeric lattices has apparently not been recognized. Also, the protocols of the anomalous dispersion method derive from the classical Bragg model, so would be subject to the same concerns and uncertainties.

Therefore, the correlation of the observed differences in the diffraction patterns with the lattice symmetry, leading ultimately to the absolute configuration of the stereogenic centers, must also be viewed as an empirical exercise that is an extension of the more general X-ray method. Indeed, whatever the sophistication of the protocols of the anomalous dispersion method, they must conform broadly to the set of principles stated in 2.2.3 above. These principles must have entered into the calculations forming the protocols in an oblique and covert manner, as otherwise the success of the empirical method would be inexplicable.

Thus, the brilliant and pioneering studies on sodium rubidium tartrate [11,12], which laid the foundations of the anomalous dispersion method, apparently uncovered a principle governing the interaction of X-rays with a chiral lattice. Remarkably, the principle was later found to be consistent in its wide applicability, and has since stood the test of time as an empirical rationale. However, it bears stating that—as in any empirical methodology—the anomalous dispersion technique too must have a theoretical

basis, but one that remains manifestly obscure and complex!

3. CONCLUSION

Molecular chirality represents the consummation of the structural theory in both a theoretical and philosophical sense. In practical terms, however, molecular chirality is the very basis of biological life which depends critically on chiral homogeneity. Although the origins of chiral homogeneity remain unresolved, the theoretically fascinating and fundamental idea of parity violation remains an attractive possibility.

The detection of molecular chirality and the assignment of the absolute configuration of stereogenic centers are also key pursuits for both theoretical and practical reasons. Classical methods therein have gradually yielded to a fascinating new physical method that is based in X-ray crystallography, the anomalous dispersion technique. Although this leads directly and unerringly to the absolute configuration of any stereogenic center, its fundamental basis remains intriguing.

The anomalous dispersion technique is possible because of a breakdown of Friedel's Law at the absorption edge of the crystal being subjected to X radiation. Although the reasons for the breakdown of Friedel's Law are obscure, it is likely that the X-rays are circularly polarized because of parity violation. This leads to diastereomeric interactions with enantiomeric lattices, thus enabling their discrimination. (Alternatively, parity violation could act on the crystals, lifting the degeneracy of the enantiomeric pair).

The subsequent assignment of the absolute configuration, however, remains highly intriguing, although it appears to be an essentially empirical exercise. This must be based in a general principle governing the interaction of (putatively) chiral X-rays with chiral lattices, that emerged during early exploratory studies and has since been established by extensive studies on a variety of chiral structures. The empirical nature of the exercise reflects the empirical foundations of X-ray crystallography itself, which is apparently based in an unlikely model of wave interference.

These concerns, however, do not in any way detract from the brilliant ingenuity that led to these experimental methods, which have played a stellar role in the development of chemical

biology in particular and indeed science in general.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Nicolaou KC. The emergence of the structure of the molecule and the art of its synthesis. *Angew Chem Int Ed.* 2013; 52(1):131-146. DOI:10.1002/anie.201207081.
2. Eliel EL, Wilen SH, Mander LN. *Stereochemistry of organic compounds.* New York: John Wiley; 1994.
3. Davankov VA. Biological homochirality on the earth, or in the universe? A selective review. *Symmetry.* 2018;10(12):749/1-13. DOI:10.3390/sym10120749.
4. Sutcliffe B, Woolley RG. Is chemistry really founded in quantum mechanics? arXiv E-print archive, Physics. 2020;1-29. Available: <https://arxiv.org/pdf/2003.06599.pdf> Accessed 2020.
5. Sutcliffe B, Woolley RG. On the quantum theory of molecules. *J Chem Phys.* 2012;137(22):A544/1-8. DOI:10.1063/1.4755287
6. Chandrasekhar S. Controversy and complementarity in mechanistic organic chemistry. The transition state and structural theories reexamined. *Res on Chem Intermed.* 1998;24(6):625–642. DOI: <https://doi.org/10.1163/156856798X00528>
7. Quack M. How important is parity violation for molecular and biomolecular chirality? *Angew Chem Int Ed.* 2002;41(24):4618-4630. DOI: <https://doi.org/10.1002/anie.200290005>
8. Chandrasekhar S. Molecular homochirality and the parity violating energy difference. A critique with new proposals. *Chirality.* 2008;20(2):84–95. DOI: 10.1002/chir.20502
9. MacDermott AJ. Chiroptical signatures of life and fundamental physics. *Chirality.* 2012;24(9):764-769. DOI:10.1002/chir.22076.
10. Pavlov VA, Shushenachev YV, Zlotin SG. Chiral and racemic fields concept for understanding of the homochirality origin, asymmetric catalysis, chiral superstructure formation from achiral molecules, and B-Z DNA conformational transition. *Symmetry.* 2019;11(5):649. DOI: 10.3390/sym11050649
11. Le Pevelen DD. Physical and spectrometric analysis: Anomalous scattering single crystal X-ray diffraction. In: Carreira EM, Yamamoto H, Tranter GE, editors. *Comprehensive Chirality.* Amsterdam: Elsevier. 2012;8:630-647. DOI: <https://doi.org/10.1016/B978-0-08-095167-6.00852-1>.
12. Flack D, Bernardinelli G. The use of X-ray crystallography to determine absolute configuration. *Chirality.* 2008;20(5):681-690. DOI: 10.1002/chir.20473.
13. Giacovazzo C. The diffraction of X-rays by crystals. In: Giacovazzo C, Monaco HL, Artioli G, Viterbo D, Ferraris G, Gilli G, Zanotti G, Catti M, editors. *Fundamentals of Crystallography.* Oxford: Oxford University Press. 2002;180–185.
14. Atkins PW. *Physical chemistry.* 5th ed. Oxford: Oxford University Press; 1995.
15. Allenmark S, Gawronski J. Determination of absolute configuration—An overview related to this special issue. *Chirality.* 2008;20(5):606-608. DOI: 10.1002/chir.20524.
16. Chandrasekhar S. The enigma of Bragg's Law. viXra E-print archive; 2014. Available: viXra:1401.0002. Accessed 2020.
17. Chandrasekhar S. From the outside looking in at quantum theory, its dichotomies and tautologies. viXra E-print archive; 2020. Available: viXra: 2006.0238 Accessed 2020.

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