Through a Glass Darkly—Some Thoughts on Symmetry and Chemistry

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Abstract: This article reviews the development of concepts of chirality in chemistry. The story follows the parallel development of the optical properties of materials and the understanding of chemical structure until the two are fused in the recognition of the tetrahedral carbon atom in 1874. The different types of chiral molecule that have been identified since the first concept of the asymmetric carbon atom are introduced as is the notation used in various disciplines of chemistry to describe the relative or absolute configuration. In the final section, a polemical case for a unified nomenclature is presented.

Keywords: chirality; symmetry; history; molecular structure; nomenclature; optical activity

1. Introduction

Man has been fascinated by mirrors and mirror images since before the beginning of recorded history. Over 40,000 years ago, humans were making hand shapes in pigment on cave walls [1,2]. The title of this article refers to the verse in the Christian Bible “For now we see through a glass, darkly; but then face to face: now I know in part; but then shall I know even as also I am known” (Corinthians 13:12 King James Version). The cultural influence of mirrors is inestimable, from Narcissus in Greek mythology whose infatuation with his own beauty seen in reflection in a pool of water gives us the modern words narcissistic and narcissism [3] to the entire inverted world created by Lewis Carroll in his “Through the Looking-Glass, and What Alice Found There” [4]. In art, the enigmatic painting Las Meninas from 1656 CE by Diego Velázquez intrigues, fascinates and confounds us to this day.

Diastereoisomerism impinges on our daily life—not only in the difference between shaking hands (homochiral) and holding hands (heterochiral) but even to the social enantioselectivity exhibited in the tendency to shake right hands (right and right) rather than left hands (left and left) (Figure 1). This article is about the importance of such phenomena in chemistry but does not attempt to present a comprehensive history of organic stereoisomerism. This review attempts to show how the tortuous path that science has taken to reach our present state of understanding has resulted in the development of a nomenclature and jargon that are profoundly relevant to narrow areas of science but which are not generally accessible to related areas.

Methods

Standard chemical databases (Scifinder®, Web of Science) were used for identifying modern literature. Standard histories of chemistry were combined with studies of chemical textbooks and publications from the 19th century CE to identify primary literature. Wherever possible, primary literature was consulted, in particular making use of the electronic resources for monograph publications available through Google Books, Internet Archive, Haithi Trust and Biodiversity Trust.
2. Minerals Bend Light . . .

Beginnings are often difficult to identify, and this truism holds for the discussion of chirality in chemistry. However, it seems appropriate to start our story with the 1669 discovery of birefringence or double refraction by the Danish scientist Erasmus Bartholin (1625–1698, variously known as Rasmus Bartholin and Erasmus Bartholinus, Figure 2a) [7–10]. When a crystal of Iceland spar (calcite) is placed on a sheet of paper with a line drawn on it, two images of the line are visible through the crystal (Figure 2b). Although he did not use this word, Bartholin had discovered the phenomenon of birefringence which occurs in materials with a refractive index dependent on the polarization and propagation direction of light. Although Bartholin can be credited with the first experimental description of a polarization-related phenomenon, the true explanation lay 100 years in the future. Many minerals and crystals, including beryl, borax, mica, olivine, perovskite quartz, ruby, rutile, sapphire, silicon carbide, topaz, tourmaline and zircon, were subsequently shown to exhibit this phenomenon.

Christiaan Huyghens (1629–1695, variably written Christiaan Huygens, Christian Huyghens or Christian Huygens) was the first scientist to propose a wave theory of light [11] and it is not surprising that he studied the phenomenon of birefringence. He performed experiments with two calcite crystals, showing that the intensity of a beam of light passing through both depended upon the angle of rotation of the second crystal with respect to the first [11–13]. This defined a design of future polarimeters in which one optical element acts as polarizer and one as an analyzer (in this case, both roles fulfilled by the two calcite crystals) [14–18].

In contrast to the wave theory of Huyghens, Isaac Newton (1643–1727) proposed a corpuscular theory predicated upon light rays being composed of particles [19,20]. Both Huyghens and Newton developed early (and deficient) optical models to explain the phenomenon, although Newton pre-empted the concept of polarization by suggesting that the birefringence arose from “some kind of attractive virtue lodged in certain Sides both of the Rays, and of the Particles of the Crystal. For were it not for some kind of Disposition or Virtue lodged in some Sides of the Particles of the Crystal, and not in their other Sides, and which inclines and bends the Rays towards the Coast of unusual Refraction, the Rays which fall perpendicularly on the Crystal, would not be refracted towards that Coast rather than towards any other Coast” [19,20]. Similarly, Huyghens wrote “ . . . as there are two different refractions, I conceived that there are two different emanations of the waves
of light” [21]. Newton’s views on light predominated, in particular because of the tacit assumption that Huyghens’ model posited light as a longitudinal wave.

Figure 2. (a) Erasmus Bartholin first reported the phenomenon of birefringence in 1669 (public domain image from https://upload.wikimedia.org/wikipedia/commons/c/c6/Rasmus_Bartholin.jpg (accessed on 21 August 2021)); (b) when a pencil line is viewed through a crystal of calcite (calcium carbonate), two lines are visible (© 2020 Edwin Constable).

The corpuscular theory was developed further by Pierre Simon de Laplace (1749–1827), Étienne Louis Malus (1775–1812) and Jean-Baptiste Biot (1774–1862) and was at the core of late 18th-century and early 19th-century CE physics in France [22,23]. Probably the zenith of the corpuscular theory was the 1808 Prize Competition of the First Class of the Institut de France, which was won by Malus for his essay Théorie de la double refraction.

By the beginning of the 19th century CE, the wave theory was beginning to regain support, in particular as a result of the interference experiments of Thomas Young (1773–1829) [24–26]. Around the same time, Malus demonstrated that reflected light was also polarized; he stated that reflected light possessed “all the properties of an ordinary ray formed by a crystal, the principal section of which is perpendicular to the plane of reflection”—in other words, that the light is polarized perpendicular to the plane of reflection [22,27]. This can be identified as the first modern scientific explanation of polarization and he subsequently expanded both his observations and explanations.

However, it was to be a century and a half after the first observation of birefringence before Augustine-Jean Fresnel (1788–1827) published the explanation of the phenomenon and recognized that it depended on both the polarization and propagation direction of the light [28–30], which should in turn be described as a transverse wave. In developing this theory, Fresnel extended the model developed by Herschel (vide infra) to explain the rotation of plane polarized light by morphologically chiral quartz crystals. Ironically, the coup de grâce for the corpuscular theory was delivered by Fresnel in the winning essay for the Prize competition of the Academy in 1818. Even more ironic is the fact that the theme for the prize competition was formulated by the establishment with a view to obtaining the definitive explanation of polarization phenomena in terms of the corpuscular theory.

The arguments bubbled under until wave–particle duality was clarified in 1924 by Louis-Victor de Broglie (1892–1987). In one of the strange coincidences that abound in science and life, Fresnel was born in the Normandy town of Broglie.
Despite its early introduction, it is worthwhile introducing the two different types of polarized light that were used in early experiments and continue to be of importance in chemistry. The explanations use modern theory and embody the wave–particle duality of electromagnetic radiation rather than the language of the early 19th century CE. Light waves are a form of electromagnetic radiation with electric field vectors that vibrate randomly in all planes perpendicular to the direction of propagation on a time scale of $10^{-8}$ s (Figure 3a). If these light waves pass through certain materials containing a non-centrosymmetric arrangement of atoms, ions or molecules, then only the waves in a particular plane pass through. The resultant wave is described as plane or linearly polarized light. In contrast, circularly polarized light is composed of two equal-amplitude linear components that are perpendicular with a phase difference of $\pi/2$ (90°) (Figure 3b). These are the two types of polarized light which are of most relevance to chemistry, although a third form, elliptical polarization, also exists.

Figure 3. Stylized representation of the generation of (a) plane polarized light and (b) circularly polarized light. Modified from the public domain images at http://commons.wikimedia.org/wiki/User:Dave3457 (accessed on 21 August 2021).

3. . . . and so to Biomaterials

Back among the French physicists, a controversy developed between Dominique François Jean Arago (1786–1853) [31] and Biot regarding the priority of studies on polarization of light. These studies built upon the observations of Malus and the establishment eventually decided in favor of Arago [32,33]. At the same time, Arago became increasingly less convinced that the corpuscular theory could account for his observations. It fell to Biot in 1815 to show that reflected light from a mirror (using a calcite crystal as analyzer) was rotated upon passing through turpentine [34,35]. Biot was an adherent of the corpuscular theory of light and interpreted his observations in terms of this model [23]. He subsequently expanded these observations to include a number of other biological materials and naturally occurring compounds including laurel oil, lemon oil and camphor [14,36]. Biot also introduced and quantified the molecular rotatory power ($\alpha$) as a characteristic of a chemical substance or material [33]. In the first half of 19th century CE, chemists had varying opinions regarding the importance and implications of $\alpha$ as a fundamental property of a material.

Biot noted that a given quartz crystal would always rotate polarized light in a particular direction, but that different crystals could have opposite directions of rotation. Quartz crystals can exhibit a macroscopic asymmetry arising from the presence of asymmetric faces related by a left- or right-handed screw, with the left- and right-handed crystals easily being distinguished by eye. It fell to William Herschel (1738–1822, better known as an astronomer) to recognize that the left- and right-handed crystals of quartz rotated polarized light in different directions [37]. This seems to be the first association of the polarization phenomenon with the handedness of a bulk material. Herschel showed that the left-handed and right-handed crystals resulted in anticlockwise or clockwise rotation of plane polarized light propagated along the trigonal crystal axis. Nevertheless, Herschel
was led to make his observation on the basis of the identification of the phenomenon of hemihedrism in different forms of quartz by Rene-Juste Haüy (1743–1822) in 1809.

Haüy played a greater part in the history of modern chemistry than that with which he is usually credited. He postulated that crystals were composed of building blocks described as integrant molecules, defined as the smallest subdivision of the crystal which retained the chemical composition and structure. This concept is related to, but not synonymous with, the modern concepts of the crystallographic unit cell and asymmetric unit [38–41]. This story was playing itself out in the mainstream physics community and it was only the observations of Biot that brought the phenomena close to the interface between physics and chemistry. We should now see what was happening in the chemistry community at this period.

4. The Atom Arrives!

If physics was revolutionized by the developments in optics, the end of the 18th century CE and the beginning of the 19th century CE saw chemistry cautiously responding to the concept of the physical, as opposed to philosophical, atom [42–47]. The stage was set by the establishment of a number of fundamental laws.

4.1. The New Laws

4.1.1. The Law of Definite Proportion

The law of definite proportion (also known as law of constant proportion, law of definite composition or law of constant composition) is usually attributed to Joseph Louis Proust (1754–1826 CE) [48,49] although a basic acceptance of this law pervades the quantitative analysis of the time from the affinity theories onwards. The law of definite proportion is perhaps the most fundamental law in chemistry and states that a given compound, regardless of its physical state or method of preparation or origin, contains the same weight ratio of the same component elements. For example, water, ice and steam always contains a weight ratio of two parts of hydrogen to 16 parts of oxygen.

4.1.2. The Law of Multiple Proportions

The second important law is the law of multiple proportions (also called Dalton’s law), which was arguably first discovered by the Irish chemist William Higgins (1763–1825) in 1789 [50–52] but is best known in its subsequent 1804 formulation by John Dalton (1766–1844). Higgins made broad-ranging claims that he and his uncle Bryan Higgins (1741–1818) were responsible for the atomic theory attributed to Dalton [52–58] but although the Higginses postulated and made many relevant observations, they did not formulate the atomic theory in the coherent, convincing and rational manner that we associate with Dalton [59–78]. Dalton announced the law on November 12th 1802 in a presentation to Literary and Philosophical Society of Manchester [79] and subsequently republished it in his definitive works on atomic theory [80–82]. In its canonical form, the law states that if two elements form more than one compound, for example SO$_2$ and SO$_3$, then the ratio of the masses of the second element combining with a fixed mass of the first element will always be ratios of small integers.

4.1.3. The Law of Reciprocal Proportion

The law of reciprocal proportion (also known as the law of equivalent proportions or permanent ratios) dates back to the last few decades of the 18th century CE. The earliest form of this law dates to a 1777 publication by Carl Friedrich Wenzel (1740–1793) which established the concept of equivalent weight for the reactions of acids and bases [83] although the true recognition of the law belongs to Jeremias Benjamin Richter (1762–1807) [84,85]. It took the publication of *Anfängsgründe der Stöchyometrie* with its tables of equivalents of acids and bases by Richter between 1792 and 1794 to bring the concept to the attention of the broader chemical community [86]. The idea of equivalent weights was further embedded in the chemical firmament with Richter’s major work *Ueber die neueren Gegenstände*
der Chymie, published between 1791 and 1802 [87]. The correct attribution of the law to Richter was only made in 1840 by Hess [88,89]. The law played an important role in the development of the atomic theory of Dalton, as it relates the proportions in which elements combine with other elements. The simplest formulation is that if element A combines with both elements B and C, then the proportion by weight in which B and C combine is simply related to the weights of B and C which individually combine with a constant weight of A. The problem of variable valence is now easy to understand. Consider the compounds FeO, Fe$_2$O$_3$ and Fe$_3$O$_4$ in FeO, 27.92 g of iron combine with 8 g of oxygen, in Fe$_2$O$_3$, 18.61 g of iron with 8 g of oxygen and in Fe$_3$O$_4$, 20.94 g of iron with 8 g of oxygen giving three different equivalent weights of 27.92, 18.61 and 20.94, respectively.

4.2. The Atomic Theory of Dalton

The history of chemical atomism is very well documented and will not be rehearsed in detail here [79,90–92]. Dalton was not alone in thinking of the nature of matter and, as so often in scientific endeavor, by the end of the 18th century CE, the time was ripe for the “new” atomic model. The precise origins of Dalton’s atomic theory continue to be debated [93], but the novel aspect of his earliest work was to establish a method of calculating relative atomic weights. The first published work from 1805 refers to a lecture given on 28th October 1803 [79,94] but there is some evidence that the ideas date to early 1803 [95,96]. The 1805 paper comments “… I am nearly persuaded that the circumstance depends upon the weight and number of the ultimate particles of the several gases … . An enquiry into the relative weights of the ultimate particles of bodies is a subject, as far as I know, entirely new: I have lately been prosecuting this enquiry with remarkable success.” [94]. The modern canonical form of Dalton’s theory states that elements are composed of very small particles called atoms. Atoms of a given element are identical in size and mass whereas those of different elements differ in size and mass. Atoms cannot be subdivided, created or destroyed but chemical compounds are formed when atoms combine in simple whole-number ratios.

Although all of these points are found in “A New Chemical Philosophy”, they are not presented in such a concise form [80–82]. Dalton uses the word atom to describe both atoms and molecules. The classical plate at the end of Volume I, Part 1 shows inter alia atoms of ammonia, alcohol and sulfuric acid [80], although the word molecule is used freely in the text. The basics had been established … matter was composed of atoms and atoms combined to form compounds and molecules. This article is neither the place to present the conflicts in the early 19th-century CE chemical community and how these were resolved with the eventual adoption of the atomic theory, nor to show how Dalton’s proposed method of depicting elements in formulae did not meet the approval of his fellow chemists.

Even by the beginning of the 20th century CE, the atomic theory was not accepted entirely without criticism. The leading antiatomists were probably Pierre Maurice Marie Duhem (1861–1916) and Ernst Waldfried Josef Wenzel Mach (1838–1916, remembered today in the use of the Mach number to define the speed of supersonic flight), who were both skeptical of the reality of, and necessity for, the atomic model. It is claimed that after hearing a lecture by Ludwig Eduard Boltzmann (1844–1906) in 1897, Mach publicly stated “I don’t believe that atoms exist!” [43,97,98]. As an arch-conservative when it came to scientific novelty, Duhem was also an opponent of Einstein’s theory of relativity, although how much his feelings against the German physicists were motivated by French patriotism at the beginning of the First World War is open to debate [99]. It is perhaps illuminating to quote Duhem “The fact that the principle of relativity denies all instincts and common sense does not raise the suspicions of German physicists against it. Accepting it is to overthrow all of the established doctrines of space, time, and motion, all the theories of Mechanics and Physics; such chaos does not disturb the Germanic mind; in practice, it will have cleared the old doctrines and the geometrical spirit of the Germans will be delighted to reconstruct a whole new Physics with the principle of relativity as its foundation.” [99].
Although the atomists were ultimately successful in convincing the scientific community, the battle was fought hard through to the beginning of the 20th century CE [44,98,100–107]. This controversy is not forgotten even in the 21st century CE, with the rationale of the antiatomists continuing to be analyzed [107–113].

4.3. From Atoms to Molecules

We have now reached the beginning of the 19th century CE and the stage is set for the glorious growth of organic chemistry in the next three-quarters of a century, culminating in the emergence of the tetrahedral carbon atom and modern stereochemistry. This story has been told by many authors more eloquent and better qualified than I [6], and this section will identify the key developments rather than present a detailed narrative. Throughout this section, modern formulae will be used although the original (pre-Cannizarro and the Karlsruhe Conference) literature may well be at variance.

The earliest approaches to structural chemistry were based on the theories of radicals and types. Although of historical interest, these are not strictly relevant to our story and have been discussed in detail elsewhere [114,115]. In parallel, the substitution theory of Dumas was on the ascendancy and eventually displaced the earlier theories [114]. The substitution theory recognized the relationships between methane, chloromethane, dichloromethane, chloroform and tetrachloromethane in terms of successive replacement of hydrogen atoms by chlorine. Similarly, acetic acid, CH$_3$CO$_2$H, could be converted to chloroacetic acid, dichloroacetic acid and trichloroacetic acid by substitution. Inspired by these observations, Friedrich Wöhler (under the pseudonym of S.C.H. Windler) published a fictional report in which he sequentially replaced all of the atoms in manganese(II) acetate (MnO + C$_4$H$_6$O$_3$) to produce Cl$_2$Cl$_2$ + Cl$_6$Cl$_6$Cl$_6$ + H$_2$O (hydrated Cl$_{24}$) [116].

Perhaps the most remarkable observation is that the epic developments in synthetic organic chemistry and the isolation, characterization and transformation of both synthetic and natural products in the first half of the 19th century CE were made without knowledge of bonds [115]!

We stress again that the words atom and molecule were often used interchangeably at the beginning of the 19th century CE, with Dalton talking of “atoms of water” and stating that “there are only 5 atoms of sulphuric acid in a molecule of alum” [81]. The word molecule predates chemical atomism and an early use is found in a 1666 letter between Robert Boyle and D. Coxe, “These Subtilized principles meeting together may bee readily united.: which Substances thus united Constitute a little masse, or molecula of mettall, many of which are usually associated before they appeare in a visible or sensible forme” [117].

4.4. And So to Valency and Bonds

Chemical atomism brought with it the recognition that individual compounds could be described by a combination of symbols and multipliers identifying the component elements and their ratios. The graphical representation of atoms used by Dalton was replaced by the familiar alphabetical atomic symbols introduced by Jacob Berzelius (1779–1848) [118–122]. The early adoption of Dalton’s ideas by William Hyde Wollaston (1766–1828) [123] and Thomas Thomson (1773–1852) made the atomic theory readily accessible to the broader scientific community, and in 1807 Thomson was responsible for the first published version of Dalton’s model [124]. The Berzelian alphanumeric formulae were subsequently adopted by most chemists.

As early as 1808, Wollaston recognized that the depiction of molecules in terms of assemblies of atoms could also be used to describe their three-dimensional structure “I am further inclined to think . . . that we shall be obliged to acquire a geometrical conception of their relative arrangement in all the three dimensions of solid extension” [125]. Wollaston further elaborated this theme in his Bakerian lecture of 1813 [126].

Until approximately 1860, these constitutional formulae were not intended to convey information about the arrangement of the atoms within the molecule [127]. This is partly a
consequence of the Type Theory, which did not allow an easy analysis of reactivity in terms of interactions between molecular subunits. Nevertheless, it was inevitable that the lines drawn between the atoms would come to be interpreted in terms of some arrangement in space.

The concept of affinity eventually evolved into thermodynamics but also was a driver for the theory of valency in the middle of the 19th century CE and provided the basis for the use of lines to depict bonds in the modern sense. Valency originated with the 1852 observation of Edward Frankland “When the formulae of inorganic chemical compounds are considered ... it is sufficiently evident ... no matter what the character of the uniting atoms may be, the combining power of the attracting element . . . is always satisfied by the same number of these atoms” [128]. The ideas were extended to carbon compounds by Archibald Scott Couper [129–132] and August Kekulé [133,134], who recognized a valency of four for carbon, three for nitrogen, two for oxygen and one for hydrogen [6,90,91,102,127,135–139]. These pioneers also introduced a notation of depicting bonds that evolved into the sticks that we are familiar with today. Early clear descriptions of this new valency-based structural theory are seen in publications from Kekulé and Alexander Mikhailovitch Butlerov (1828–1896). Butlerov used “sausage formulae” which Kekulé condemned to footnotes on most occasions [140,141]. The structural theory became firmly embedded in organic chemistry during the 1860s as it successfully accounted for multiple bonds and some types of isomerization [6]. Even Butlerov talked of “chemical” as opposed to “physical” structure, but as early as 1863, he speculated that it would be possible in the future to determine the physical, three-dimensional, structure of molecules [142].

The chemists of the 1860s avoided claiming that their model related to the microscopic arrangement of atoms in a molecule [6,135] and they repeatedly emphasized that the bonding was based upon chemical reactivity and chemical behavior and described the “chemical position” of an atom in a molecule based on the influence it has on other atoms. This “chemical position” was not related to the physical arrangement of atoms in a molecule. Nevertheless, the success of the structural theory encouraged chemists to think that the bonding schemes they had developed to satisfy valency, might also have some physical reality.

In 1873, Johannes Wislicenus (1835–1902) came close to linking optical activity with the spatial arrangement of atoms in molecules and wrote “It only remains to describe the above-mentioned different spatial arrangement of the atoms in the same molecular structure as a strictly physical isomerism. For this, however, the term geometric isomerism would perhaps be more appropriate if, as is usual, the type of designation of the isomerism is intended to not only to express the fact of the dissimilarity of quantitatively identically molecules, but rather the inner cause of this” [143].

4.5. The Depiction of Molecules

Chemists attempted to find ways to depict the “chemical position” of functional groups within molecules. Although such structural formulae are commonplace today, it was not always so [144]! In 1857 or 1858, Archibald Couper (1831–1892) [129–131] and August Kekulé (1829–1896) [133,134,145] more or less simultaneously and independently recognized that carbon atoms with a valency of four could combine to give carbon-carbon bonds and introduced graphical methods for depicting the chemical position (Figure 4) [135,138,139]. These ideas were refined and extended by Butlerov, who, in 1861, introduced the term “chemical structure” [140,146]. Butlerov is at pains to point out that he is referring to structure in terms of “chemical position” rather than physical position of the atoms.
Johann Josef Loschmidt (1821–1895), in 1861, used circles to represent the chemical positions of atoms in molecules (Figure 4c) [147]. His depiction of ethanol (Figure 4c) looks remarkably like a modern molecular model of the compound. The chemical community did not respond to Loschmidt’s insight.

In 1864, Lothar Meyer (1830–1895) took the ideas of Couper, rationalized the double atoms and replaced the dotted lines by solid lines to give the depiction of methane shown in Figure 5a [148]. Meyer used a combination of curved “bonds” from the Type Theory and the Kekulé braces and depicted the double bond in ethene as shown in Figure 5b. His representation of ethanol (Figure 5c) is significantly less intelligible than those of Couper or Loschmidt. The book was only translated into English in 1888 in an edition that does not mention le Bel or van’t Hoff [149].

Additionally, in 1864, Alexander Crum Brown (1838–1922) introduced a notation that is used to this day. Crum Brown is exceptionally careful to state that in his constitutional formulae he is only talking about the “chemical position” of the atoms and not the physical arrangement of atoms in space. For example, he states “I do not mean to indicate the physical, but merely the chemical position of the atoms” and “This method seems to me to present advantages over the methods used by Professors KEKULÉ and ERLENMEYER; and while it is no doubt liable, when not explained, to be mistaken for a representation of the physical position of the atoms, this misunderstanding can easily be prevented” [150]. The Crum Brown notation placed the atom symbol in a circle and joined the circles according to their chemical position by lines (Figure 6). For single bonds, he used straight lines to represent the valences and for double bonds he used curved bonds. Using this graphical style, he was able to indicate double bonds as well as the chemical positions of atoms in isomeric compounds.
Figure 6. The notation introduced by Crum Brown is the genesis of that which is still used today. He placed the atomic symbol in a circle and then used the valences to indicate the atoms connected in their chemical position, with straight lines for single bonds and curved lines for double bonds. Using these graphical formulae he could distinguish between isomeric compounds such as (a) propan-1-ol and (b) propan-2-ol and clearly describe multiple-bonded species such as (c) ethanal [150].

4.6. The Importance of Models

Today, chemists think of molecules in terms of physical or virtual models. This is not a new phenomenon, but one that originated in the 19th century and it is appropriate to begin with the father of chemical atomism, John Dalton [151,152]. Dalton introduced symbols to denote atoms and combined these to give pictorial representations of molecules. In most cases, the atoms were arranged in the most symmetrical manner, although there is a hint that he might have been thinking deeper in his representation of isomeric compounds and in descriptions such as “small globular molecules of air” [80]. For Dalton, the atomic symbols and models denoted proportion rather than implying structure, although he sometimes represented atoms of water as a single sphere and sometimes as two joined spheres of hydrogen and oxygen atoms (his formula for water was HO). To demonstrate the concept of atoms in his lectures, Dalton had a set of wooden spheres made by a friend, Peter Ewart, symmetrically drilled with eight or twelve holes which could accommodate metal rods, which were used to connect other spheres (Figure 7). Wollaston also used models to demonstrate the packing of atoms and molecules of different shapes in crystals and assumed platonic arrangements (AB$_2$ was linear, AB$_3$ trigonal, AB$_4$ tetrahedral, etc.) [151,153,154].

Figure 7. Dalton’s atomic models consisted of spheres with holes drilled in them that could be connected to other balls with metal rods. Dalton probably did not imply any three-dimensional structural meaning to these representations (public domain image from the Science Museum, London, https://www.scienceandindustrymuseum.org.uk/objects-and-stories/john-dalton-atoms-eyesight-and-auroras#&gid=1&pid=1, under Creative Commons Attribution-NonCommercial-ShareAlike 4.0 Licence).
The development of graphical representations for molecules and their visualization as physical models was a phenomenon associated with the elucidation of the valence concept. We will see models reflecting these new realities in the next sections.

4.7. Do Molecules Have Shape?

The preceding sections indicate that in the first half of the 19th century CE there was little support for extending models based on chemical position to ones concerning physical arrangements of atoms in molecules. Wollaston recognized that it might be possible, indeed necessary, to make such correlations in the future, but did not embark on the task himself [125]. Two French scientists were thinking in terms of the three-dimensional structures of molecules although their contributions were largely ignored by the chemical community [155]. André-Marie Ampère (1775–1836) extended the theories of Haüy to the assembly of crystals based upon molecular shapes, similar to Wollaston [126], and developed a model in which the molecular building blocks of crystals (called particules) were composed of atoms (which he called molécules) arranged in geometric shapes [156]. Antoine Augustin Gaudin (1804–1880) developed these ideas in his 1873 book L’architecture du monde des atomes [157]. He concentrated on the symmetry of molecular arrangements, favoring linear and planar arrangements. His model reflected stoichiometry (ammonia was tetraatomic, water was triatomic) and he viewed chemical combination as involving a major reorganization of the constituent atoms. He also criticized the concepts of atomicity and valence.

Kekulé was using models with a tetrahedral carbon in the 1860s, although it is unlikely that he implied a three-dimensional physical structure—tetravalent but not necessarily tetrahedral. Nevertheless, the chemical community started to view these as models of the physical shape and structure. One of Kekulé’s co-workers was Wilhelm Koerner (1839–1925) who subsequently worked with Cannizzaro in Palermo. Koerner published on aromatic chemistry using Kekulé models and his colleague Emanuele Paternò used the tetrahedral arrangement of four equivalent bonds about carbon to develop models for a number of aliphatic compounds. Figure 8 shows Paternò’s prediction of the existence of three isomers of dibromoethane (the two structures on the right-hand side are actually conformers). Paternò only illustrated the eclipsed forms of the two tetrahedral centers. It is worth quoting Paternò at length, “This result is not without a certain importance. One of the fundamental principles of the theory of the constitution of organic compounds, based on the valency of the elements, and especially on the notion of the tetravalence of carbon, is that the four valences of the carbon atom have identical chemical functions, so that it is only possible for one type of methyl chloride, methyl alcohol, etc to exist, and that there should be only one isomer. However, the existence of isomers for compounds of the formula C₂H₅Cl cannot be explained without renouncing the idea of the equivalence of the four affinities of the carbon atom. Additionally, this was the only example hitherto known which opposed the generally adopted idea; the three isomers C₂H₄Br₂, provided they really exist, are easily explained, without the necessity of admitting a difference between the four affinities of the carbon atom, as Butlerow believes, when the four valences of the atom of this element are imagined to be arranged in the sense of the four angles of a regular tetrahedron: then the first modification would have the two atoms of bromine (or any other monovalent group) connected to the same atom of carbon; while in the two other modifications each of the two atoms of bromine would be connected to different atoms of carbon, the only difference being that in one case the two atoms of bromine would be arranged symmetrically, in the other not” [158]. This clearly indicates that Paternò and Butlerov were thinking in terms of “physical” structure before the events of 1874.
These contributions certainly helped to shape thought about the physical atom, but were outside the mainstream and by 1873 were out of date. The intellectual environment for the modern formulation of stereochemistry had been laid, although the word itself was not to be introduced until 1890 by Victor Meyer [159].

5. Introducing the Tetrahedral Carbon Atom

5.1. Back to Optical Activity

One of the optically active organic compounds that Biot had studied in 1832 (but only published in 1835) was tartaric acid (2,3-dihydroxybutanedioic acid), which is isolated from its monopotassium salt (tartar) deposited in the production of wine by the fermentation of grape juice [160]. In the 1820s, a second acid with the same formula but a different solubility was isolated. This was known variously as acide racémique, racemic acid or paratartaric acid. Biot subsequently showed that this substance was not optically active [161]. As an aside, this is the origin of the description racemic or racemate to describe a mixture of equal amounts of two different enantiomers of a compound. The name acide racémique was introduced in 1828 by Joseph Louis Gay-Lussac and refers to its natural origin in grape juice (Latin racemus = grape) [162,163].

Biot and Herschel had shown that the macroscopic asymmetry of quartz crystals (hemihedralism) was associated with the direction in which they rotated light. In 1848, Louis Pasteur (1822–1895) was following up some observations of Frédéric Hervé de la Provostaye (1812–1863) and Eilhardt Mitscherlich (1794–1863) on the crystal morphology of tartaric and racemic acid derivatives. Pasteur noted that both the sodium ammonium double salts of racemic acid and tartaric acid gave asymmetric crystals with hemihedral facets. However, all of the crystals of the tartrates possessed the same handedness, whereas those of the racemic acid salt consisted of equal numbers of right- and left-handed crystals. Pasteur separated these by hand and showed that solutions of only the left- and only the right-handed crystals were optically active. The optical inactivity of racemic acid and its salts was due to the presence of equal amounts of compounds with a different and opposite effect on polarized light [164–166]. The relationship between optical activity and asymmetry had been established for organic compounds.

By 1860, Pasteur was coming very close to a tetrahedral bonding scheme for carbon to explain the origin of optical activity: “Are the atoms of the straight acid grouped according to the turns of a right-handed helix, or placed at the vertices of an irregular tetrahedron, or arranged according to such and such a determined dissymmetrical assembly?” [167].
Pasteur had not followed the developments in atomicity and valence in the 1850s and did not make the final leap to link a tetrahedral carbon atom with optical activity.

5.2. The Year Was 1874

In 1874, the time was ripe for the correlation of ideas concerning the spatial arrangement of atoms about carbon and optical activity into a single cohesive model. Two young researchers published the same ideas almost contemporaneously [168–173]. Jacobus Henricus van’t Hoff (1852–1911) and Joseph Achile Le Bel (1847–1930) used the asymmetry of a tetrahedral carbon atom to explain the origin of optical activity. The publication by Le Bel is less general than that of van’t Hoff and is not primarily concerned with the tetrahedral carbon atom. Le Bel discusses an aspect raised by Meyer and Butlerov relating to the number of isomers of simple methane derivatives. Dichloromethane could exist as two isomers if the carbon atom were planar but only one if it were tetrahedral. Le Bel considered tartaric acid as a tetrasubstituted methane ([H][C(HO)2][C(HO)2][H][OH]) with two identically substituted carbon centers.

At this point, we introduce a third form of optically inactive tartaric acid which Pasteur obtained in 1853 and which was optically inactive (meso-tartaric acid) which he described as untwisted tartaric acid. Le Bel recognized that this form of tartaric acid contained opposite symmetry arrangements at the two carbon centers, whereas the two forms that rotated light in a right- or left-handed sense possessed two carbon atoms with the same asymmetry. However, although Le Bel was correct in all respects concerning the “asymmetric carbon atom”, his further speculation in the paper indicates that he was neither convinced by the universal tetravalency of carbon, nor its ubiquitous tetrahedral nature [154]. Kekulé had been constructing models of unsaturated compounds with double or triple bonds by combining tetrahedral centers sharing two or three valences, leading to coplanar and linear structures for alkenes and alkynes, respectively, which was not recognized by Le Bel.

van’t Hoff, like Le Bel, began with the observation that a tetrahedral carbon would only give one isomer of a C2H2Br2 compound, whereas planar carbon would give cis- and trans- isomers. He continues to the case of Cabcd compounds thus, “In case the four affinities of a carbon atom are saturated by four different univalent groups, two, but no more than two, different tetrahedra can be obtained, which are the mirror image of each other, but can never be superposed, i.e., one has to consider two isomeric structure formulae in space”. van’t Hoff continued to consider optically active molecules, including the tartaric acids (Figure 9a) and then developed a broader model for unsaturated compounds, based upon the sharing of multiple valences of tetrahedral carbon centers Figure 9b).

![Figure 9. (a) van’t Hoff’s tetrahedral CR1R2R3R4 molecules showing the mirror images and; (b) his representation of of an allene. The double bonds are represented by the sharing of the two edges of the tetrahedron representing the central carbon atom. This representation immediately shows that the vector connecting the substituents R1 and R2 is orthogonal to that connecting R3 and R4. It follows that an allene such as ClHC=CHCl can exist as two enantiomers. Figures taken from the 1894 s edition of van’t Hoff’s Die Lagerung der Atome im Raume [174]).](image-url)
The universality of the van’t Hoff notation evolved as the original 1874 pamphlets expanded into more comprehensive treatises on stereochemistry [174–178] and, for example, allowed him to predict that allenes of the type abC=C=Ccd could be resolved into two enantiomeric forms (Figure 9b) [175], although this was only experimentally confirmed in 1935 [179]. Today, organic stereochemistry is such an integral part of chemistry that we forget that it was a somewhat revolutionary concept in 1874, although the idea was embraced by Wislicenus from the beginning. Imagine the feelings of the young van’t Hoff in 1877 when he read an editorial in the "Journal für praktische Chemie" by Adolph Wilhelm Hermann Kolbe (1818–1884), one of the most influential chemists of the day, which comprehensively excoriated his work [180]. As an example of destructive and vituperous criticism, this editorial should be read by all practicing scientists (Note that for some reason the article is not available from the publisher Wiley, but can be found at gallica.bnf.fr). My favorite extract is "A Dr. J. H. van’t Hoff, employed at the School of Veterinary Medicine in Utrecht, seems to have no taste for exact chemical research. He finds it more convenient to climb upon Pegasus (obviously borrowed from the veterinary school) to make a daring flight to his chemical Parnassus and to proclaim in his La chimie dans l'espace how atoms appeared to him to be arranged in space". However, Kolbe was by no means alone in expressing doubts about the new theory [6,181,182].

The motivations and consequences of Kolbe’s intervention are analyzed in detail elsewhere [6,154,182–187].

5.3. The Cahn-Ingold-Prelog System

The basic system for the nomenclature of chiral molecules was formulated in a groundbreaking series of papers and is named the Cahn-Ingold-Prelog (or CIP) system [188–190] after the eponymous authors Christopher Kelk Ingold (1893–1970), Robert Sidney Cahn (1899–1981) and Vladimir Prelog (1906–1998). The nomenclature has been expanded and exemplified to cover a broad range of stereochemical needs by IUPAC, in particular the 1996 publication Basic terminology of stereochemistry (IUPAC Recommendations 1996) [191] and the 2013 Nomenclature of Organic Chemistry [192]. The latter work is commonly referred to as the “Blue Book”. The CIP rules can be used for all manner of stereochemical nomenclature, although we concentrate upon chiral systems.

The basics of the CIP system are simple but, as always, a veritable underworld of devils are to be found in the details. The aim is to assign a priority number to each substituent in a molecule. A substituent with a higher atomic number has a higher priority than a substituent with a lower atomic number. A lone pair is assigned the virtual atomic number of zero. Thus in CBrClFI, the priorities would be in the sequence I > Br > Cl > F, in NClFH the priority sequence would be Cl > F > H > lp and in CBrCIDH Br > Cl > D > H.

We are now in a position to use CIP to generate a stereochemical descriptor for an asymmetric tetrahedral center (Figure 10a). Draw the molecule with the lowest priority substituent facing away from you and the three remaining substituents facing towards you. Draw a curve from the highest priority substituent to the next highest. If this curve goes in a clockwise direction, the descriptor is S, if the curve is anticlockwise, the descriptor is R.

What happens if the first atoms of the substituents are the same, as in C(Me)(Et)(iPr)(Pr)? In this case, simply travel along the substituent chains until there is a point of difference. The chain with the higher priority is the one with the first point of difference involving a connection to an atom with higher priority. Thus we see that the methyl group (three H attached to the carbon) has a lower priority than ethyl (two H and one C). Similarly n-propyl has a higher priority than ethyl as at the second carbon we find a C and two H, rather than 3H. Finally, isopropyl has a higher priority than propyl as the first carbon has two C and one H attached rather than one C and two H (Figure 10b).

The final level of complexity that we introduce is the treatment of multiple bonds. A double or triple bond to an atom is treated as meaning that the atom is connected to the same atom type twice. IUPAC recommends the use of a digraph (a contraction of
“directed graph” and introduced into stereochemistry by Prelog in 1982 [193]) for the analysis of more complex systems. This is illustrated in Figure 10c for the compound C(iPr)(Pr)(CH₂CH=CH₂)(CH=CHMe). To become further acquainted with the Hades of stereochemical nomenclature, the reader is referred to the Blue Book with a request from this author to give fond greetings to the devils that he or she will encounter.

Figure 10. (a) The assignment of priority numbers using the CIP rules and obtaining a stereodescriptor after placing the lowest priority substituent away from the viewer. If the sequence 1-2-3 is clockwise, the stereodescriptor is R, if it is anticlockwise, the descriptor is S; (b) if the first atom of a substituent has the same priority, the analysis is extended along the chain until a point of difference is established, and; (c) the analysis of the compound C(iPr)(Pr)(CH₂CH=CH₂)(CH=CHMe) using a digraph with (C) denoting the duplicated atoms of the double bonds. The final priority number is shown in red in each case. Note that this is not the exact form of digraph used in the Blue Book.

6. Other Asymmetric Atoms

In this section I retain the contemporary use of “asymmetric atom” rather than the modern usage, stereogenic center.

6.1. Nitrogen

By the mid 1880s, the stereochemical theory of van’t Hoff and Le Bel had been broadly accepted by the organic chemistry community. The core of the model was the asymmetric carbon atom. It did not take long for the chemistry community to recognize that if Cabcd compounds were optically active, it might be possible to identify similar nitrogen compounds. Remembering that the electron and lone pairs belonged to the future, at the end of the 19th century CE, the general belief was that amines of the type Nabc were planar. In his doctoral thesis, under the supervision of Arthur Rudolf Hantzsch (1857–1935), Alfred Werner (1866–1919) agreed generally with this view but then speculated that “The three valences of the trivalent nitrogen atom (perhaps also the valences of other polyvalent atoms) do not lie in the plane of the nitrogen atom under all circumstances” but rather “In certain compounds, the three valences of the nitrogen atom are directed towards the corners of an irregular tetrahedron, the fourth vertex of which is occupied by the nitrogen atom itself.” He then followed this to the logical conclusion “The question arises whether derivatives of
ammonia type could not also form geometric isomers with three different radicals bound to nitrogen: \( \text{NR}_1\text{R}_2\text{R}_3 \) corresponds to the carbon compounds \( \text{CHR}_1\text{R}_2\text{R}_3 \) (Figure 11a)” [194]. Early attempts to resolve amines through the formation of salts with optically active acids were unsuccessful with a summary of the state of the art in 1927 concluding “The experiences described offer little prospect for the isolation of active forms of a compound of pure trivalent asymmetric nitrogen . . . . the absence of the [optically] active forms only mean that the energy barrier between the two forms is not high enough to prevent equilibrium between the two” [195]. The first successful resolution of a tertiary amine was in 1944 and involved the chromatographic separation of a rigid molecule, Tröger’s base (Figure 11b), in which the inversion at nitrogen is hindered [196].

![Figure 11.](image)

It is, perhaps, surprising how long it took the community to recognize that it should be possible to resolve ammonium ions of the type \([\text{Nabcd}]^+\). In part, this was because of the widespread use of addition formulae such as \(\text{NMeEtPh·RCl} \), introduced by Kekulé to rationalize the existence of such compounds, which appeared to disobey his rule that nitrogen had a fixed valency of three. Even after the models of Kekulé became redundant, it was not until the first two decades of the 20th century CE that the formulation as a salt \([\text{RNMeEtPh}]\text{Cl} \) rather than a five coordinate species \([\text{RNMeEtPhCl}] \) became accepted. This is not the place to discuss the number and type of structures proposed for these five-coordinate species, although, once again, credit goes to Alfred Werner for the correct interpretation “According to the theories developed for carbon, we assume that its valences (now better called coordination sites) are located at the vertices of a tetrahedron. Conforming to this behaviour of carbon, we can assume that for boron and nitrogen, which also have a coordination number of four, the four coordination sites will also be sited at the corners of a tetrahedron. This conclusion is of great importance for the stereoisomerism of the so-called pentavalent nitrogen, since it places it in many respects alongside carbon, as I will show later” [197]. The resolution of the ammonium salt, \([\text{N(allyl)(PhCH}_2\text{MePh}]\text{I} \) was demonstrated six years later by William Jackson Pope [198]. The first resolution of a neutral \(\text{NR}_1\text{R}_2\text{R}_3\text{R}_4 \) compound was achieved with the amine oxide \(\text{EtMePhNO} \) in 1908 [199].

6.2. Phosphorus, Antimony and Arsenic

As mentioned previously, van’t Hoff’s original pamphlet was expanded into a comprehensive overview of the state of the art in stereochemistry, not least the recognition of asymmetric centers other than carbon [174–178] and by 1898 a chapter was devoted to “The stereochemistry of nitrogen compounds”. It was inevitable that chemists would subsequently move down group 15 to search for additional chiral at phosphorus, antimony or arsenic compounds. The first compound with an asymmetric phosphorus center, \(\text{EtMePhPO} \), was resolved in 1911 [200]. Resolution of phosphanes is easier than that of amines as the barrier to inversion is higher (\(\text{NH}_3 \) ca. 25 kJ mol\(^{-1}\), \(\text{PH}_3 \) ca. 130 kJ mol\(^{-1}\)). The first resolutions of cyclic and acyclic phosphonium salts were reported in 1947 [201]
and 1959 [202], respectively, and it was only as late as 1961 that the first optically pure asymmetric phosphanes were prepared [203].

Chiral stibanes have attracted relatively little interest, although the first optically pure compounds were described in the 1940s and 1950s [204–209]. Early studies at resolving \([\text{AsR}_1\text{R}_2\text{R}_3\text{R}_4]^+\) arsanium salts were partially successful [210] although they racemized very rapidly. In 1925, the first arsane sulfide, \(\text{EtMe(HO}_2\text{CC}_6\text{H}_4)\text{AsS}\), was resolved [211]. The first optically pure “simple” arsanium salt, \([\text{EtMePh(PhCH}_2\text{)As}]^+\) and arsane \(\text{EtMePhAs}\) were only reported in 1962 [212].

6.3. Sulfur

Like amines and phosphanes, \(\text{SR}_1\text{R}_2\text{R}_3\) compounds are expected to possess an asymmetric sulfur atom on the basis of a stereochemically active lone pair. This was first demonstrated for sulfinates in 1925 [213] and sulfoxides in 1926 [214].

6.4. Other Atoms

The CIP scheme can be used to describe any compounds which are based upon a tetrahedral distribution of bonds and lone pairs, where necessary treating the lone pairs as atoms with an atomic weight of zero (i.e., the lowest priority substituent). The system is easily extended to coordination compounds such as the tetrahedral bromidochloridofluoridiodocobaltate(2–) ion.

7. Inorganic Chemistry Gets into the Act

After his doctorate, Werner turned his attention to coordination compounds. His background in stereochemistry lead him to think about the three-dimensional structure of coordination compounds. Critical to his establishment of the concept of \(\text{Hauptvalenz}\) and \(\text{Nebenvalenz}\) (oxidation number and coordination number in modern vocabulary), was his postulate that complexes of cobalt(III) and platinum(IV) were six-coordinate octahedral species [197,215].

The number of isolated isomers of coordination compounds of different stoichiometry aided Werner in discounting other coordination geometries. The observation of different optical forms of chiral coordination compounds was an essential part of the development and acceptance of the octahedral geometry of six-coordinate metal complexes [216]. In 1899, Werner started prepared complexes with ethane-1,2-diamine (en) and noted that the consequence of the chelating ligands in a compound such as \([\text{Co(en)}_2(\text{O}_2\text{CCO}_2)]^+\) was the formation of two enantiomeric forms of the complex (Figure 12): “The resultant isomeric case is not comparable to the usual asymmetry in organic molecules, which is known to cause the so-called optical isomerism, because the groupings arranged here on the right or left (two ethane-1,2-diamines) are identical; rather, the above isomerism would be comparable to that of organic double ring systems” [217].

Figure 12. In 1899, Werner identified that coordination entities such as \([\text{Co(en)}_2(\text{O}_2\text{CCO}_2)]^+\) could exist in two enantiomeric forms; reprinted from \textit{Beitrag zur Konstitution anorganischer Verbindungen. XVII. Mitteilung. Über Oxalatodithyldiaminkobaltisalze}, A. Werner, Z. Anorg. Allgem. Chem., 1899, reprinted by permission of the publisher (John Wiley and Sons, Ltd.) [217].
Werner subsequently reported the resolution of numerous salts containing complex cations such as cis-[Co(en)$_2$XY]$_2$$^{2+}$, [Co(en)$_3$]$_3$$^{2+}$, [Rh(en)$_3$]$_3$$^{3+}$ and the chiral “all-inorganic” complex cation [Co([OH]$_2$Co(NH$_3$)$_4$I)$_3$]$_6$$^{2+}$ [218–234]. The latter compound is particularly important as it dismissed the idea that the optical activity of the metal complexes was due in some mysterious way to the organic ligands: Werner wrote “The proof that the molecules of optically active compounds do not necessarily have to be carbon-containing is important because it means that the difference still existing between carbon compounds and purely inorganic compounds disappears”. [231].

An octahedral [Mabcdef] complex with six different ligands is analogous to an asymmetric carbon atom and should give rise to optical isomers. Very few people have attempted the preparation of such compounds (which have thirty stereoisomers, consisting of fifteen pairs of enantiomers) but from the 1950s onwards, some isomers of [PtBrClI(NH$_3$)(NO$_2$)(py)] (py = pyridine), very rare examples of such complexes, were prepared [235–242]. In the next section, we probe the nature of the chirality in coordination entities such as [PtBrClI(NH$_3$)(NO$_2$)(py)].

I have discussed compounds with stereogenic metal centers in detail elsewhere [216].

8. Chirality and Other Parts of the Vocabulary

8.1. An Aside on Right- and Left-Handedness

In our discussion to date, we have concentrated upon the observable of optical rotation and linked it to a sense of a right-handed or a left-handed rotation of polarized light. At the same time, by the end of the 19th century CE, the emerging stereochemistry community was drawing and talking about molecules with right-handed or left-handed properties. We need to be rather careful to distinguish between the observable (optical activity) and its fundamental origin (asymmetry or dissymmetry). The concept of the asymmetric atom embodies and encompasses the idea that optical activity should be regarded as arising from asymmetry associated with a single atomic center. In parallel, molecules were being identified in which the mirror image was not superposable on the original object but in which no single atom could be described as asymmetric [6,171,243–247]. How should species such as these be described?

A more serious problem was identified by Ruch, who recognized that chirality and handedness were not synonymous and consequently classified chiral objects into two different categories. Handed objects, such as shoes or gloves, were the first category and could be divided unambiguously into “left” and “right” objects (Figure 13a). The second class was that of non-handed objects, typified by an irregular lumpy potato (Figure 13b), which is chiral in that the mirror image is not superposable on the original, but for which there is no innate sense of “left” or “right” allowing subdivision into two sets [248–251].

![Figure 13. (a) A pair of gloves comprises a pair of mirror images which are easily identified as being right-handed or left-handed whereas (b) a potato cannot be superimposed on its mirror image because of all of the lumps and bumps on its surface, but does not have an inherent sense of right- or left-handedness.](image-url)
We clearly need to think about two different types of chiral objects—those that display a handedness and those that do not. It follows that all handed objects must be chiral, but equally that not all chiral objects must be handed. Our lumpy potatoes and many six coordinate coordination compounds fall into the category of non-handed chiral objects meeting the requirements for chirality by lacking symmetry elements [252–255].

This problem is commonly encountered in inorganic chemistry, and just as IUPAC provides the Blue Book for the nomenclature of organic compounds, the publication *Nomenclature of Inorganic Chemistry: IUPAC Recommendations 2005*, usually known as the “Red Book”, fulfills the same function for the rest of the periodic table [256].

Even the above discussion about lumpy potatoes is not the entire story, and although it has a philosophical elegance, there is a practical resolution to the problem provided by the Red Book. For coordination compounds such as $[\text{PtBrClI(NH}_3\text{)}(\text{NO}_2\text{})(\text{py})]$ there is no obvious way to assign a sense of inherent right- or left-handedness considering all six substituents and the object as a whole. However, there is a way to impose a sense of direction (if not handedness). In $[\text{PtBrClI(NH}_3\text{)}(\text{NO}_2\text{})(\text{py})]$ (Figure 14a) we can assign CIP priorities to each of the substituents on the basis of atomic weight of the bonded atom and, if necessary, travelling through the digraph to find points of divergence. Once we do this, the priorities are 1 I, 2 Br, 3 Cl, 4 NO$_2$ (N with next atom O), 5 pyridine (N with next atom C), 6 NH$_3$ (N with next atom H). Stereochemistry in coordination entities can be defined by a configuration index, with octahedral species denoted (OC-6). The spatial arrangement of the ligands is given uniquely by two additional digits using the CIP priorities; the first digit is defined as the priority number of the ligand with the lowest possible priority (highest numerical value) trans to the highest priority ligand, in this case 3. This pair then defines a reference axis for the octahedron. The second digit is the priority number of the ligand trans to the highest priority ligand in the plane perpendicular to the reference axis, in this case 4 as the nitro ligand is trans to bromide. The configuration index for this compound is, thus, (OC-6-34) (Figure 14b).

The subtlety comes when we consider the consequences of defining the principal axis, in this case defined by the I–Cl vector. The remaining four ligands define a plane (Figure 14b) and the CIP priorities are used to define the handedness. The stereodescriptor $C$ (clockwise) or $A$ (anticlockwise) is appended after the two digits and is assigned on the basis of the sequence with the lowest numerical value at the first point of difference (Figure 14c). For our pair of enantiomeric complexes the sequences are 2-5-4-6 and anticlockwise is 2-6-4-5. As 2-5 is lower than 2-6, the chirality descriptors $C$ and $A$ are given, respectively. This leads to the complete configuration index for the complexes is, thus, (OC-6-34-34-C) and (OC-6-34-A). This procedure uses the familiar CIP system to assign priority numbers to ligands and subsequently assigns a sense of handedness to our lumpy potato by defining an axis.

We have already noted that metal complexes such as $[\text{M(en)}_3]^n+$ and $[\text{M(en)}_2\text{XY}]^{n+}$ played an important role in the establishment of Werner’s coordination theory. Neither the relative nor the absolute configuration of these compounds can be established by correlation with other compounds, and the complexes were typically described using the phenomenological descriptors $d$ and $l$, $D$ and $L$ or (+) and (−) referring to the direction which light of wavelength 589 nm (i.e., the sodium D-line) was rotated. Attempts to assign the absolute configurations to tris(chelate) complexes in the 1930s using the Cotton effect [257–259] met with mixed success [260–276].

Unlike the lumpy potatoes discussed above, the tris chelates (as well as bis(chelates) such as $[\text{Co(en)}_2\text{XY}]^{n+}$) are not only chiral, but also possess an identifiable handedness (Figure 15). The first approach involved the use of skew lines to define the helical chirality of the complex [277] which was denoted with the stereodescriptors $\Delta$ and $\Lambda$ for a right-handed (clockwise) and a left-handed (anticlockwise) helix, respectively. These recommendations were incorporated into the Red Book in what I personally find one of the most difficult sections to interpret (IR-9.3.4.11–14) [256]. Figure 15 shows the application of the $\Delta$ and $\Lambda$ stereodescriptors to the $[\text{Co(en)}_3]^{3+}$ cation, where the two enantiomers are oriented with the green nitrogen atoms of each chelating ligand below the plane of the paper, and the blue
donor atoms are above the plane. The donor atoms of each en chelate ring and the metal center define the blades of a propeller. In the \(\Lambda\)-isomer an anticlockwise rotation screws the propeller into the page, whereas in the \(\Delta\)-isomer a clockwise rotation is necessary to screw the molecule away from the viewer.

![Figure 14](image1.png)

**Figure 14.** (a) The assignment of substituent priority number to the enantiomeric pair of isomers of \([\text{PtBrCl(NH}_3\text{)(NO}_2\text{)(py)}]\) using CIP rules (b) the ligands in the equatorial plane after the principal axis has been defined and (c) the definition of clockwise or anticlockwise handedness to the ligands in the equatorial plane on the basis of the CIP substituent priority numbers.

![Figure 15](image2.png)

**Figure 15.** The two enantiomers of the \([\text{Co(en)}_3]^3+\) cation. The nitrogen donor atoms closest to the viewer are shown in blue, whereas those furthest from the viewer are green. The \(\Delta\) and \(\Lambda\) stereodescriptors describe whether the molecule needs to be twisted to the left (\(\Lambda\)) or to the right (\(\Delta\)) in order to screw itself into the plane of the paper away from the viewer. A more rigorously definition is given in the Red Book (IR-9.3.4.11–14) [256].
Although the $\Delta$ and $\Lambda$ stereodescriptors are widely used, it is relevant to ask how the notation introduced in Figure 14 operates for the two enantiomers depicted in Figure 15. The difficulty is that all three ligands are identical and the six nitrogen donors all have the same priority. To differentiate the rings, a priming notation is introduced with the priority sequence $N > N' > N''$. The process is presented in Figure 16 and involves (i) identifying the three different en rings as unprimed, primed and double-primed in an arbitrary manner (ii) identifying the principal axis which yields $1''$ as the first number in the stereochemical index (iii) identifying the donor in the remaining plane trans to the highest priority donor, giving $1'$ as the second number in the stereochemical index and (iv) assigning the $A$ or $C$ stereodescriptor by looking down onto the plane from the direction of the highest priority donor on the principal axis. Thus, both $\Delta$ and $\Lambda$ enantiomers are denoted ($OC$-6-1"1''), but the full index for $\Delta$ is ($OC$-6-1"1'-A) and for $\Lambda$ is ($OC$-6-1"1'-C). Note that the descriptions clockwise and anticlockwise defined by the consideration of priority numbers does not equate to the sense of right- or left-handedness defined by the skew planes.

Figure 16. The process of deriving the full stereochemical index for the two enantiomers of $[Co(en)_3]^3+$. 

Step 1. All donor atoms have the same priority of 1
Assign primes to the ligands in an arbitrary manner.

$\Delta$

$\Lambda$

Step 2. Priority $1 > 1' > 1''$.
Principal axis is $N^1 \rightarrow N^1$.
First digit is $1''$

Step 3. The remaining plane.
Second digit is $1'$

Step 4. Looking onto the plane from the direction of $N^1$ in the principal axis allows the assignment of the $A$ or $C$ descriptor

$(OC$-6-1"1'-A) $(OC$-6-1"1'-C)
8.2. Words in and Out of Context

The vocabulary of stereochemistry uses some words with special and subtle meanings. The words asymmetry and asymmetric were used by van’t Hoff to describe the consequences of the tetrahedral arrangement of four different groups about a carbon atom. Pasteur used the word dissymmetry for the arrangement of tetrahedra in spirals. Modern usage should be dictated by the recommendations of IUPAC:

- **asymmetry**—denoting the absence of any symmetry;
- **asymmetric**—lacking all symmetry elements (other than the trivial one of a one-fold axis of symmetry), i.e., belonging to the symmetry point group $\text{C}_1$. The term has been used loosely (and incorrectly) to describe the absence of a rotation–reflection axis (alternating axis) in a molecule, i.e., as meaning chiral, and this usage persists in the traditional terms asymmetric carbon atom, asymmetric synthesis, asymmetric induction, etc.;
- **dissymmetry**—obsolescent synonym for chirality;
- **superposability**—The ability to bring two particular stereochemical formulae (or models) into coincidence (or to be exactly superposable in space, and for the corresponding molecular entities or objects to become exact replicas of each other) by no more than translation and rigid rotation [191,192,278].

Following these definitions, I have used the words chiral and chirality in cases where the original work used the terms dissymmetry or dissymmetric. Similarly, I use the terms superpose and its compound derivatives although the distinction between superpose (to place an object on or above another object, usually so that they coincide) and superimpose (to place an object on or above another object, typically so that both are still evident) is exceptionally subtle. I leave the reader to decide if there is any real difference in terms of the stereochemical operations we are describing. The study of chemical etymology [279–281] and particularly the language of stereochemistry is fascinating but outside the scope of this review [282–286].

8.3. Enter Chirality

I have already used the words chiral and chirality without comment. This is such an important concept that we need to understand its origins and consequences. By the end of the 19th century CE, it is probably fair to say that most scientists understood what a mirror image was and, even if only through reading the iconic 1871 book *Through the Looking-Glass, and What Alice Found There* by Lewis Carroll, could imagine the consequences of left-right inversion [287]. William Thomson, later Lord Kelvin (1824–1907) provided the modern definition of chirality to describe phenomena relating to the arrangement of atoms and molecules in crystals “I call any geometrical figure, or group of points, *chiral*, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself. Two equal and similar right hands are homochirally similar. Equal and similar right and left hands are heterochirally similar or ‘allochirally’ similar (but heterochirally is better). These are also ‘called ‘enantiomorphs,’ after a usage introduced, I believe, by German writers. Any chiral object and its image in a plane mirror are heterochirally similar” [288]. The earlier history of the term has been discussed in detail elsewhere [252].

The introduction of the concept of chirality was generally ignored by the chemical community, not coming into common usage until the late 1950s. The word chiral was used in two publications by Larmor in the early 1920s [289,290] and by Raman in 1950 [291]—and that is it! The word was rediscovered in the late 1950s [292,293]. Especially interesting is the complete absence of the words chiral or chirality in the first two papers describing the Cahn-Ingold-Prelog system [188,189] although they are extensively used in the third paper with the remark “This useful word [chirality] was brought to our attention by Professor K. Mislow, who referred us to Webster’s Dictionary (2nd Edition), where *chiral* is defined as Of, or pertaining to the hand, specifically turning the plane of polarisation of light to either hand” [190].

It is also appropriate to say something about the word enantiomorph, which Kelvin (vide infra) does not discuss in detail, but which IUPAC defines as “one of a pair of chiral
objects or models that are non-superposable mirror images of each other. The adjective enantiomorphic is also applied to mirror-image related groups within a molecular entity” [191, 192, 278]. The word was being used in this sense in both the United Kingdom and German chemical communities by the 1890s [294–301] having been introduced in 1856 by Naumann [302].

8.4. When the Stereochemical World Came (Slowly) Tumbling Down

As we have seen above, the transition into the 20th century CE was a comfortable time for the stereochemical world. The majority were content with the concept of asymmetric atoms to categorize whether molecules could be optically active. The concept was being extended from carbon to other atoms. Kelvin had also defined the property of chirality.

The state of the art is well described by chemistry text books of the 1890s: Ostwald’s *Outlines of General Chemistry*, 1890 [303] “whatever we may think of the assumption of the tetrahedral arrangement of the valencies—an assumption which has of late proved very useful in another field—the fact is at least very remarkable, that hitherto no optically active substance has been discovered which does not, in the above sense, possess an asymmetric carbon atom”; Mendeleef’s *Principles of Chemistry*, 1891 the effect of different isomerides on the direction of the rotation of the plane of polarization of light—this tendency promises much for chemical mechanics, but the details of the still imperfect knowledge in relation to this matter must be sought for special works devoted to organic chemistry”; Attfield’s *Chemistry*, 1894 “according to Van’t Hoff and Le Bel, all compounds that cause such rotation contain at least one atom of carbon with which is united four different atoms or radicals. Such carbon atoms are conveniently termed asymmetrical” [304]; Hinrich’s *Introduction to General Chemistry*, 1897 “a carbon atom so combined is called asymmetric by van’t Hoff (Holland, 1874) and Le Bel (France, 1874), who independently generalized this condition: No rotary polarization without at least one asymmetric carbon” [305].

9. Chiral Molecules without Asymmetric Atoms

We already noted in Section 5.2 that van’t Hoff predicted the existence of optical isomers of compounds such as allenes which do not contain an asymmetric center. In this section, I will briefly describe the types of chirality which have been introduced since 1874. Typically, modern texts on stereochemistry discuss axial chirality, planar chirality, helical chirality and topological chirality. We return to this topic later, but it is arguable whether one could regard axial chirality and planar chirality as specific cases of helical chirality. In the same way that an asymmetric atom can be identified as a stereogenic center, we now encounter the concepts of stereogenic axes and stereogenic planes. We will also see that it is sometimes an individual choice to describe chirality as arising from a stereogenic plane or axis.

9.1. Axial Chirality

Axial chirality refers to stereoisomerism resulting from the non-planar arrangement of four groups in pairs about a chirality or stereogenic axis. A chirality axis is defined by IUPAC as an axis about which a set of ligands is held so that it results in a spatial arrangement which is not superposable on its mirror image. The term stereogenic axis is synonymous with chirality axis. Allenes of the types abC=C=Ccd or abC=C=Cab exhibit axial chirality (Figure 17a). Atropisomerism is a special case of axial chirality arising from the restricted rotation about a chirality axis and exhibited by molecules such as ortho-substituted biphenyls and related biaryls (Figure 17b). The CIP system can be used to describe the configuration in molecular entities possessing axial chirality using the stereodescriptors $R_a$ and $S_a$ (Figure 17c). The assignment is relatively simple using CIP rules to determine the priority of substituents. The compounds are viewed along the axis of chirality and substituents nearest to the viewer are given the highest priority with $a > b$. The second set of substituents (most distant from the viewer) are also assigned $c > d$. 
If the direction b → c is clockwise, the compound is given the descriptor $R_a$ and if it is anticlockwise the compound is described as $S_a$.

Figure 17. (a) Allenes such as 1,3-dichloroallene are chiral and described using the stereochemical descriptors $R_a$ and $S_a$ as are (b) ortho disubstituted biaryls such as 6,6′-dinitro-[1,1′-biphenyl]-2,2′-dicarboxylic acid. (c) The assignment of $R_a$ and $S_a$ is made using the scheme shown. In each case, the molecule is viewed along the axis of chirality from the left hand side of the page. In the case of the first enantiomer of 1,3-dichloroallene, $a = \text{Cl}_1$, $b = \text{H}_1$ and $c = \text{Cl}_3$ and the direction of rotation $b \rightarrow c$ is anticlockwise and the stereodescriptor is $S_a$. In the case of the second 6,6′-dinitro-[1,1′-biphenyl]-2,2′-dicarboxylic acid enantiomer, again looking along the axis of chirality from the left hand side of the page, the priorities are easily assigned on the basis of the atomic weight of the first atom in the ortho substituents ($\text{N} > \text{C}$), giving the stereodescriptor $R_a$. (d) The chiral ligand BINAP is widely used in asymmetric synthesis.

The biaryls can also be described as atropisomers, which are conformers isolable as chemical species arising from restricted rotation about a single bond. The term was introduced by Richard Kuhn in 1933 and is derived from the Greek word ατροπος (without turn) [306]. The first biaryls to be resolved were 6,6′-dinitro-[1,1′-biphenyl]-2,2′-dicarboxylic acid (and 4,4′,6,6′-tetranitro-[1,1′-biphenyl]-2,2′-dicarboxylic acid [307] although the possibility had been predicted earlier [308–310]. Clearly, there is no fundamental difference in axial chirality associated with allenens and biaryls, although only the latter could be described in terms of atropisomerism as this term is limited to restricted rotation about a single bond. Chiral biaryls have a significant number of applications and ligands such as BINAP and derivatives find significant application in asymmetric synthesis (Figure 17d) [311,312].

9.2. Helical Chirality—An Aside?

Helical chirality is encountered in common life, whether in the turning of a screw or in the growth of climbing plants, as immortalized by Flanders and Swann in the song “Misalliance”:

The fragrant honeysuckle spirals clockwise to the sun,  
And many other creepers do the same.  
But some climb anti-clockwise, the bindweed does, for one,  
Or Convolvulus, to give her proper name. [313]

We have also seen a number of examples in earlier sections that can be described as helical chirality, most notably the direction of the screw axis in bis- and tris(chelate) octahedral complexes (Section 8.1) and the direction of rotation about the chirality axis in
axially chiral compounds (Section 9.1). The concept is visually helpful, although helical chirality can always be described in terms of a chirality or stereogenic axis.

Many biomolecules and biologically important motifs exhibit obvious helicity, ranging from the protein α-helix, through the DNA double-helix to the helical conformations associated with poly(ethylene glycol) under some conditions. It is not surprising that a subset of nomenclature has been developed to describe the helicity in these compounds which relates more to a macroscopic sense of handedness than to the book-keeping of CIP. For these compounds, the stereodescriptors $P$ and $M$ are widely used, with $P$ referring to a right-handed screw in the direction away from the viewer and $M$ to a left-handed screw in the same direction. It follows that $P$ and $M$ correlate with the descriptors $\Delta$ and $\Lambda$ used to describe bis- and tris(chelate) octahedral complexes.

An interesting group of compounds are the helicenes which are formally related to phenanthrene by the sequential addition of benzo groups to the 1,2 positions (Figure 18). The terminal rings cannot lie in the same plane as each other and the molecules twist into a helix with the chirality conveniently being described by the descriptors $P$ or $M$ recommended by IUPAC (Blue Book P92.1.2.2.1) (Figure 18b) [314]. There is no obvious or easy way to identify atoms or molecular subunits associated with the stereogenic axis identified in Figure 18b.

![Figure 18](image_url)

Figure 18. (a) The first three examples of the helicenes. The terminal benzo rings cannot lie in the same plane as each other and the molecules twist into a helical shape with (b) the chirality conveniently being described by the direction of rotation when the molecule is screwed away from the viewer (into the plane of the paper) about the chiral axis, which is shown in
red. A right-handed screw in the direction away from the viewer is labelled \( P \) whereas a left-handed screw in the same direction is described as \( M \). (c) This convention can also be used to describe compounds exhibiting axial chirality and the formalism is shown for a biaryl. This shows that for axially chiral systems \( M \) equates to \( R_a \) and \( P \) to \( S_a \).

The situation is simple with compounds in which the chirality axis coincides with a bond or bonds in the molecule. In these cases we again arrange the substituents \( a, b, c \) and \( d \) in pairs looking along the chirality axis, and the highest priority substituent in each pair identified. The descriptor is \( M \) if the path between these two is anticlockwise, and as \( P \) if it is clockwise (Figure 18c). For axially chiral systems \( M \) correlates with \( R_a \) and \( P \) to \( S_a \).

9.3. Planar Chirality

According to IUPAC, planar chirality arises from “the arrangement of out of plane groups with respect to a plane”, the latter being defined as the stereogenic or chiral plane. This is easiest to understand with the examples given in Figure 19. Figure 19a shows the compound (1E)-cyclooct-1-ene, which is the first stable cyclic alkene with a trans arrangement of the hydrogen atoms about the double bond. Two carbon atoms of the double bond and the directly attached atoms of the substituents (2 carbon and two hydrogen) define the stereogenic plane—the remaining chain can loop around the back from top right to bottom left, or from top left to bottom right. These two forms are enantiomers—remembering that our ultimate criterium for chirality is a mirror image which is not superposable on the original. The configuration of planar chirality is specified by the stereodescriptors \( R_p \) and \( S_p \) (or \( P \) and \( M \)), with IUPAC preferring the use of \( P \) or \( M \). The assignment of the \( R_p \) and \( S_p \) descriptors is on the basis of CIP priorities and the definition of both a plane and a pilot atom out of the plane, and is one of the more obscure parts of the Blue Book (P-92.1.2.1.3). Typical examples of planar chirality are shown, together with their stereochemical descriptors in Figure 19.

![Figure 19. Examples of molecules exhibiting planar chirality](image_url)
are illustrated for each enantiomer. By inspection, the right hand conformer can easily be assigned the \( P \) or \( M \) descriptor in terms of the direction of rotation to screw the molecule into the page. (c) Some molecules can be described as exhibiting either axial or planar chirality, in which case the axial and planar chirality descriptions both deliver the same helicity (\( P \) in the enantiomer selected) but with \( S_a \) and \( R_p \) descriptors.

IUPAC is uncharacteristically cautious regarding axial chirality defining it as a “term used by some authorities to refer to stereoisomerism resulting from the arrangement of out-of-plane groups with respect to a plane (chirality plane)”. The reason for this caution will now be clarified. Unfortunately, there is no general relationship between \( R \) and \( S \) and the alternative \( M \) and \( P \) descriptors and for a chirality axis \( M = R \) and \( P = S \) whereas for chirality planes, \( M = S \) and \( P = R \). This would be annoying but of no great significance if we could describe molecules unambiguously as exhibiting axial or planar chirality. Unfortunately there are systems which can be described in terms of either axial or planar chirality [315,316]. We have already seen the description of biaryls in terms of axial chirality, but it is also possible to consider them as a case of planar chirality. This is shown in Figure 19c, where both axial and planar chirality models deliver the same helicity (\( P \) in the enantiomer selected) but with \( S_a \) and \( R_p \) descriptors. There is nothing magical about this: the helicity concerns a macroscopic property of the molecule, whereas \( R/S \) descriptors are derived from the spatial arrangement of groups according to CIP priorities about different symmetry elements. This is a compelling argument for the use of helicity descriptors in such cases.

9.4. Topological Chirality

A final type of chirality that we will briefly consider is topological chirality. If we think about all of the entities that we have seen so far, they all have one property—the mirror images can be (at least in theory) interconverted without breaking bonds. Enantiomers possessing a stereogenic carbon can be interconverted through a high energy planar form, tris(chelate) complexes can be twisted about the helical axis and atropisomers can be interconverted by “forcing” the substituents past each other. Topological stereoisomers have identical bond connectivity, but they cannot be interconverted one into another by continuous deformation but only by bond-breaking and bond-making [317,318]. This is not the place to discuss molecular topology in detail. Suffice it to say that molecules possessing the topology of a trefoil knot (Figure 20a) or catenanes (Figure 20b) with an inherent sense of direction in the macrocyclic rings are topologically chiral. The chirality in these species can also be described in terms of the helicity descriptors \( P \) and \( M \).

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**Figure 20. Cont.**
chirality, but it is also possible to consider them as a case of planar chirality. This is shown in Figure 19c, where both axial and planar chirality models deliver the same helicity (P in the enantiomer selected) but with S and R descriptors. There is nothing magical about this: the helicity concerns a macroscopic property of the molecule, whereas the R/S descriptors are derived from the spatial arrangement of groups according to CIP priorities about different symmetry elements. This is a compelling argument for the use of helicity descriptors in such cases.

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Figure 20. Examples of topological chirality include (a) molecular trefoil knots and (b) directional catenands. The molecular knot is composed of 1,4-phenylene units and the brown curve represents the molecular thread. The stylized versions of the knot show the two different enantiomers [319]. The catenand contains a asymmetrically functionalized 1,10-phenanthroline metal-binding domain in each component macrocycle, resulting in a sense of direction. The stylized representations show that the mirror images are not superposable [320].

10. Order Out of Chaos—Or Chaos Out of Order?

If stereochemistry is God, then IUPAC (International Union of Pure and Applied Chemistry) is its high priest and mouthpiece! I note that when multiple different stereogenic motifs are present in a compound, IUPAC is not yet helpful in defining in what sequence or where in the name the various-descriptors should be placed. I have discussed this in detail in the context of chiral metal complexes containing both stereogenic metal centers and chiral ligands [321].

11. Polemic or Iconoclasm? The Case for More Unity in Stereochemical Notation

The description of stereochemistry in chemistry is a little bit like the curate’s egg (Figure 21) [322] or Longfellow’s little girl (When she was good, she was very good indeed, but when she was bad, she was horrid) [323]. I will attempt to justify this introductory statement!

Figure 21. Right Reverend Host: “I’m afraid you’ve got a bad Egg, Mr Jones!”; The Curate: “Oh no, my Lord, I assure you! Parts of it are excellent!” True Humility by George du Maurier, originally published in Punch, 9 November 1895.

The nomenclature and language of stereochemistry have developed in an evolutionary and highly adaptive manner. It has been modified and revised to encompass new aspects and phenomena as they were discovered. It is my opinion, that the result is not a consistent nomenclature but rather a whole series of partially overlapping (and sometimes mutually exclusive) nomenclatures which are well adapted for specific areas of interest and activity and which are often incomprehensible to the broader community. Is it iconoclasm to
wonder if there might not be a better way of doing this some 150 years after the revelations of van’t Hoff and Le Bel?

11.1. Phenomenological Descriptors

The earliest workers were restricted to phenomenological descriptions of the properties of chiral or optically active materials. Although in rare cases, optical activity could be related to the morphological appearance of crystalline materials, by the last half of the 19th century CE, the chemist was typically studying the optical properties of solutions of known weights of compounds and behaving like a lost hiker asking the questions “which direction?” and “how far?” This resulted in the phenomenological descriptors $d$, $l$ and $dl$, (+), (–) and (±). The use of $d$, $l$ and $dl$ is strongly discouraged by IUPAC and the direction of rotation should be indicated by (+) or (–) or the terms dextrorotatory and levorotatory, but dates back to the first observations by Biot “The essential oil of laurel turns the light from right to left like turpentine. The essential oil of lemon, on the other hand, and the opposite, and the dissolution of camphor in alcohol, make it turn from left to right” [35]. The optical rotation is usually quoted as the specific rotation $\alpha_{298}$ which is defined as the rotation exhibited by polarized light passing through a 10 cm long cell containing a solution at a concentration of 1 g L$^{-1}$ of the substance of interest and at 298 K, and is calculated using Equation (1)

$$\alpha_{298} = \frac{\alpha}{l \cdot c} \tag{1}$$

where $\alpha$ is the measured rotation, $l$ is the length of the experimental cell in decimetres and $c$ is the concentration in grams per litre. The same equation can be used for neat liquids replacing $c$ by the density.

However, the situation is not quite so simple as the above text might indicate. The descriptor (±) is reserved for racemic mixtures or racemates consisting of equal amounts of the (+) and (–) enantiomers of a compound, although IUPAC prefers the use of the descriptor rac. The resultant solution is optically inactive. How do you know that this is the case, rather than a solution of a compound which is fundamentally inactive, such as phenol? Before the insights of Le Bel and van’t Hoff, the only way was to fully or partially resolve the compound, by crystal picking or reaction with another optically active species. If you could not resolve it, the description (±) was not merited. Once again, think back to Pasteur—he had (+) and (–) tartaric acids, the optically inactive (but resolvable) racemic compound (±)-tartaric acid and also the optically inactive (and unresolvable) meso compound (2R,3S)-2,3-dihydroxybutane-1,4-dioic acid.

The second problem is more critical. Figure 22 shows a plot of the optical rotation of an aqueous solution of $\Lambda$-[Co(en)$_3$]Cl$_3$ (redrawn from reference [324]) against wavelength, a so-called optical rotatory dispersion spectrum. Two features are immediately apparent: (i) the sign of rotation depends on the wavelength of the light—at some wavelengths the compound is dextrorotatory and at others levorotatory and (ii) at approximately 420 and 490 nm, the chiral enantiopure solution exhibits no rotation of polarized light. In the past, the majority of polarimeters used light with a wavelength of 589 nm (the sodium D line(s)) and the specific rotation $\alpha_{298}$ and the IUPAC usage of (+) or (–) refer to this wavelength. The specific rotation may be explicitly written $\alpha_{298}^D$ or $\alpha_{298}^{589}$.

In general, the phenomenological descriptors are to be regarded as a property of the compound, but should not be relied upon to convey information about absolute or relative configuration.
Figure 22. The optical rotatory dispersion (ORD) spectrum of an aqueous solution \( \Lambda-[\text{Co(en)}_3]\text{Cl}_3 \) shows that the direction of rotation is wavelength-dependent and that at certain wavelengths this chiral species exhibits no optical rotation.

11.2. The Case of Classical “Asymmetric” Carbon Atoms

Any competent chemist should be capable of assigning a stereodescriptor \( R \) or \( S \) to a tetrahedral stereogenic carbon center. The beauty, logic and simplicity of the CIP system was commented upon earlier and we have used it extensively in this article. The IUPAC recommendations for the nomenclature of organic compounds (the Blue Book) generally recommend the use of CIP stereodescriptors [192]. However, there are a number of exceptions, especially for classes of naturally occurring compounds.

The Fischer-Rosanoff convention (D, L or DL) relates the relative configuration of a compound to an arbitrary (but ultimately correct) assignment of the absolute configuration of (+)-glyceraldehyde, which consequently was defined as D-glyceraldehyde. The absolute configuration of D-glyceraldehyde is given in the IUPAC name (2\( R \))-2,3-dihydroxypropanal. Once you have remembered this, the next hurdle is to remember that the arrangement of the groups about the stereogenic carbon is drawn with the horizontal substituents above the plane of the paper and the vertical ones below the plane (Figure 23a). Finally, you stamp on the molecule and remove the remaining stereochemical information to obtain the flat Fischer projection (Figure 23b). Remembering, of course, to place the atom defined as 1 by the IUPAC nomenclature at the top. This nomenclature is still used for sugars and amino acids, but does not find wide acceptance outside these communities (IUPAC Rule P-102.3). For sugars, the nomenclature is initially applied to the acyclic form, as shown in Figure 23b for glucose and fructose. Although these representations identify the absolute configuration at each stereogenic center, the “configurational atom” is defined as the stereogenic center with the highest numbering – if the hydroxy group projects to the right in the Fischer projection, the sugar is assigned to the ‘D’ series, if it is to the left, to the “L” series. This configurational atom is also used to define the \( \alpha \) or \( \beta \) configuration in the cyclic forms. Let us see how this works in reality. The description \( \alpha \)-D-glucopyranose uniquely defines the cyclic six-membered ring form of glucose – however, I would argue that it is deficient as a form of nomenclature. The descriptor D only gives information about one of the five stereogenic centers. Similarly, the descriptor \( \alpha \) gives information about the anomeric center by relating it to the configurational atom. To know the absolute configuration of the remaining centers one needs to remember the relative stereochemistry in each of the named sugars. As a rhetorical question, I ask if the full
IUPAC name (2S,3R,4S,5S,6R)-6-(hydroxymethyl)tetrahydro-2H-pyran-2,3,4,5-tetraol is not more informative than α-D-glucopyranose? Maybe not for glucose, but who outside the sugar community remembers the structures of compounds such as allose, idose and talose?

The stereodescriptors D and L are also retained for the nomenclature of α-amino carboxylic acids (Rule P-103.1.3.1) with the justification that the “absolute configuration at the α-carbon atom of the α-amino carboxylic acids is designated by the stereodescriptor ‘D’ or ‘L’ to indicate a formal relationship to D- or L-glyceraldehyde”. This is another example where the usage is well-established and generally understood within a specific research area but which can prove confusing to the broader chemical community.

To continue the theme of amino acids, the 2013 recommendations for nomenclature include PINs (Preferred IUPAC Names) and for the amino acids, these are the D- and L-forms. This would not be a problem if there were a general and easily remembered relationship between the stereodescriptors D and L and the descriptors R and S. However, as the Blue Book states (Rule P-103.1.3.1), the “L configuration corresponds to the S configuration of the CIP system, except that cysteine has the R configuration (and also cystine . . .)” as shown in Figure 24. If the carbon atom number 3 contains any directly attached atom with an atomic weight greater than oxygen, this inversion will occur. This is the fundamental difference between the Fischer-Rosanoff convention which relates the stereochemistry to a reference compound (glyceraldehyde) and the CIP approach which is based on the priority of substituents calculated on the basis of atomic weight. If the stereochemistry at the α-carbon is unknown, the stereodescriptor ξ is introduced, which I strongly suspect is unknown outside (and possibly within) the peptide community.

To continue the polemic, any additional stereogenic centers within an amino acid derivative are to be denoted by the appropriate CIP stereodescriptor, leading to hybrid nomenclature in the PINs such as (3S)-3-hydroxy-L-proline (Rule P-103.1.3.2.1).

Finally, the treatment of racemates of amino acids requires non-standard treatment. For other compounds, the recommendations are clear (Rule P-93.1.3): “When a racemate is described, the stereodescriptor, such as R or RS, is cited for the chirality center having the lowest locant” leading to PINs such as rac-(1R,2S)-2-chlorocyclopentane-1-carboxylic acid. This might logically lead to descriptions such as rac-D or rac-L for amino acids, but (Rule P-103.1.3.1) racemic compounds are denoted by “the stereodescriptor DL, for example DL-leucine. The stereodescriptor DL is preferred to rac, i.e., rac-leucine”.

Figure 23. (a) The Fischer-Rosanoff convention relates the absolute configuration of amino acids and sugars and their derivatives to D-glyceraldehyde ((2R)-2,3-dihydroxypropanal); (b) the convention in operation for the simple sugars L-glucose and D-fructose, where the highest priority atom is numbered 1 and placed at the top. The highest numbered stereogenic center defines the assignment to the D or L-series of sugars and is indicated with a red asterisk.
These comments are not made in criticism of IUPAC and the Blue Book, but rather to question whether the time has come for a stereochemical nomenclature that can be understood universally across the chemical community.

There is one inherent aspect of the CIP system that needs to be mentioned. It is outstandingly good at describing the absolute configuration, but does not claim to give any information about relative configuration. This is best illustrated with the pair of compounds in Figure 25a which, subjectively have the same relative stereochemistry, but have different CIP stereodescriptors. Similarly, in the $S_N2$ reaction shown in Figure 25b, which involves an inversion of stereochemistry at carbon, the CIP stereodescriptors for product and starting material are the same.

**Figure 25.** The CIP system assigns priority and consequently stereodescriptors on a precisely defined set of rules based upon atomic weight of the substituents. It must be emphasized that the CIP stereodescriptors refer to absolute not relative configuration. (a) The two compounds depicted have intuitively the same relative stereochemistry (simply replacing an OH by an SH), but this changes the priority of substituents from ($C < O < F < Cl$) to ($C < F < S < Cl$) and subsequently the two compounds have different CIP stereodescriptors and in (b) the $S_N2$ reaction involves an inversion of stereochemistry at carbon, but the CIP stereodescriptors for product and starting material are the same.

11.3. Lumpy Potatoes and Stereogenic Metal Centers

We saw in Section 8.1 how the CIP system can be used to describe both the stereochemical arrangement of ligands about six-coordinate metal centers and, by defining the principal axis (IR-9.3.5.2), can also generate stereochemical descriptors $A$ and $C$ to describe the chirality (IR-9.3.4.8). This process is relatively simple and needs little more than a knowledge of CIP rules.

Nevertheless, stereochemical descriptors such as mer and fac, as well as $\Delta$ and $\Lambda$ are a well established part of the tradition of coordination chemistry. However, this might be another case in which the intimate community is comfortable with this usage but chemists...
in other disciplines might not instantly recognize the meaning of the stereodescriptors \( \Delta \) and \( \Lambda \). Once again, there is a case to be made, or at least a question to be asked, whether a unified system based upon the stereochemical index might be more appropriate. I strongly suspect that the stereochemical index is used more outside the inorganic chemistry community than within it.

There would be little enthusiasm for encouraging the use of the descriptors (OC-6-1’1’-A) and (OC-6-1’1’-C) to replace \( \Delta \) and \( \Lambda \). In the same way that CIP does not intuitively link with relative stereochemistry, it is not simply a case of “remembering” that \( A = \Delta \) and \( C = \Lambda \) for tris(chelates). This is illustrated in Figure 26 for a compound such as bis(2-aminoethanethiolato)(oxalato)cobaltate(1–), which also serves to illustrate a number of other stereochemical nomenclature aspects. The complex has three chelating ligands, each occupying two adjacent (cis) coordination sites. There are three diastereoisomers (Figure 26a) for which descriptors such as trans are not helpful – for example, both the first and the last isomer could be described as either cis or trans on the basis of the S or N atoms. The indeces OC-6-22, OC-6-32 and OC-6-13 (Figure 26b) uniquely describe these three isomers in a way more concise and easier to understand than a verbal description of the orientation of the ligands. An interesting point is that the notation shown in Figure 26a serves to generate the unique description of the diastereoisomers, but does not suffice to describe the chirality – the OC-6-22 isomer generates the sequence 1-3-2-3 for both the clockwise and anticlockwise direction whereas for OC-6-13 it is not possible to distinguish between 2-3-3-2 and 2-2-3-3 (Figure 26c). This is illustrated for the \( \Delta \) enantiomer in Figure 26d, in which one of the two 2-aminoethanethiolato is arbitrarily denoted with primes. The introduction of the primes does not affect the notation for the diastereoisomers, but generates the sequence 1'-3-2-3' for the clockwise and 1'-3'-2-3 for the anticlockwise direction. As 3 has a higher priority than 3', the full description of the \( \Delta \) enantiomer is OC-6-22-C.

Once again, and reverting to our discussions about helicity, it is more intuitive to use the “universal” descriptors \( P \) and \( M \) which easily relate to the “screwing” of the complex into the plane of the paper.

\( \text{Figure 26. Cont.} \)
Once again, and reverting to our discussions about helicity, it is more intuitive to use the word "screwing" to describe the interaction of handedness. This has been illustrated by taking a complex such as bis(2-aminoethanethiolato)(oxalato)cobaltate(1–).

Figure 26. The assignment of A and C chirality labels in a four step process for a complex such as bis(2-aminoethanethiolato)(oxalato)cobaltate(1–).

12. Conclusions and Closing Thoughts

This article has illustrated the development of our understanding of optical activity and chirality from the earliest days of chemistry to modern times. The methods used to indicate relative and absolute stereochemical configuration have been illustrated. Many of the approaches to describing absolute configuration involve the assignment of priorities to substituent groups based upon the CIP system. The relationship of these systems to macroscopic handedness is discussed and entities which do not have an innate sense of left- or right-handedness were considered. Various origins of chirality are critically discussed, although it is to be emphasised that the final criterium for chirality should always be whether the object and its mirror image are superposable. Some of the more esoteric aspects of IUPAC recommended nomenclature are illustrated. Finally, the question of finding a balance between specialized stereochemical descriptors within specific chemical disciplines and accessibility to the broader chemical community is addressed. This latter topic is of importance for two reasons: firstly, because, generally, chemistry students come to dislike stereochemistry as they learn multiple different approaches in specific subject areas and, secondly, because chemical names, including all stereochemical indicators, should be uniquely machine readable.

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References
1. Aubert, M.; Brumm, A.; Ramli, M.; Sutikna, T.; Saptomo, E.W.; Hakim, B.; Morwood, M.J.; van den Bergh, G.D.; Kinsley, L.; Dosseto, A. Pleistocene Cave Art From Sulawesi, Indonesia. *Nature* 2014, *514*, 223–227. [CrossRef]
2. Pike, A.W.; Hoffmann, D.L.; García-Diez, M.; Pettitt, P.B.; Alcolea, J.; De Balbin, R.; González-Sainz, C.; de las Heras, C.; Lasheras, J.A.; Montes, R.; et al. U-Series Dating of Paleolithic Art in 11 Caves in Spain. *Science* 2012, *336*, 1409–1413. [CrossRef]
3. Graves, R. *The Greek Myths*; Penguin: London, UK, 2011; ISBN 9780241952740.
4. Carroll, L. *Through the Looking Glass, and What Alice Found There*; Macmillan and Co.: London, UK, 1871.
5. Mason, S.F. The Foundations of Classical Stereochemistry. *Top. Stereochem.* 1976, *9*, 1–34. [CrossRef]
6. Ramberg, P.J. *Chemical Structure, Spatial Arrangement: The Early History of Stereochemistry, 1874–1914*; Ashgate: Aldershot, UK, 2003; ISBN 0754603970.
7. Bartholini, E. *Experimenta Crystallii Islandici Disdiaclastici Quibus Mira et Insolita Refractio Detegitur*; Daniel Paulli: Copenhagen, Denmark, 1669.
164. Flack, H.D. Louis Pasteur’s Discovery of Molecular Chirality and Spontaneous Resolution in 1848, Together With a Complete Review of His Crystallographic and Chemical Work. Acta Cryst. A 2009, 65, 371–389. [CrossRef] [PubMed]
165. Pasteur, L. Researches on Molecular Asymmetry of Natural Organic Products. Alembic Club Reprints No. 14; The Alembic Club: Edinburgh, UK, 1897.
166. Pasteur, L. Researches on the Molecular Asymmetry of Natural Organic Products. Of Natural Organic Products; The Alembic Club: Edinburgh, UK, 1905.
167. Pasteur, L.; Cahours, A.; Wurtz, A.; Berthelot, M.; Barral, J.A.; Deville, S.-C.H.; Dumas. Leçons de Chimie Professés en 1860; L. Hachette et Cie: Paris, France, 1861.
168. van ’t Hoff, J.H. Sur Les Formules De Structure Dans L’espace. Arch. Neerl. Sci. Exactes Nat. 1874, 9, 445.
169. van ’t Hoff, J.H. Voorstel Tot Uitbreiding der Tegenaardigheid in de Scheikunde Gebruikte Structuurformules in de Ruimte, Beneven Een Daarmee Samenhangeende Opmerking Omtrent Het Verband Tusschen Optisch Actief Vermogen En Chemische Constitutie Van Organische Verbindi; Greven: Utrecht, The Netherlands, 1874.
170. Le Bel, J.A. Sur Les Relations Qui Existent Entre Les Formules Atomiques Des Corps Organiques Et Le Pouvoir Rotatoire De Leurs Dissolutions. Bull. Soc. Chim. Fr. 1874, 22, 337–347.
171. Riddell, F.G.; Robinson, M.J.T.; Van ’t Hoff, J.H.; Le, J.A. Bel—their Historical Context. Dix Années Dans L’histoire D’une Théorie; P.M. Bazendijk: Rotterdam, The Netherlands, 1875.
172. van’t Hoff, J.H. Dix Années Dans L’histoire D’une Théorie; P.M. Bazendijk: Rotterdam, The Netherlands, 1887.
173. van ’t Hoff, J.H. The Arrangement of Atoms in Space, 2nd ed.; Eiloart, A., Ed.; Longmans, Green and Co.: London, UK, 1898.
174. van ’t Hoff, J.H. Die Lagerung Der Atome Im Raum; Herrmann, F., Ed.; Vieweg: Braunschweig, Germany, 1877.
175. van ’t Hoff, J.H. Die Lagerung Der Atome Im Raum; Herrmann, F., Ed.; Vieweg: Braunschweig, Germany, 1877.
176. van ’t Hoff, J.H. Die Lagerung Der Atome Im Raum; Herrmann, F., Ed.; Vieweg: Braunschweig, Germany, 1877.
177. van ’t Hoff, J.H. Die Lagerung Der Atome Im Raum; Herrmann, F., Ed.; Vieweg: Braunschweig, Germany, 1877.
178. van ’t Hoff, J.H. Die Lagerung Der Atome Im Raum; Herrmann, F., Ed.; Vieweg: Braunschweig, Germany, 1877.
179. Maitland, P.; Mills, W.H. Experimental Demonstration of the Allene Asymmetry. Nature 1935, 135, 994. [CrossRef]
180. Kolbe, H. Zeichen Der Zett. J. Prakt. Chem. 1827, 15, 473–477.
181. Ramsay, O.B. Van’t Hoff-Le Bel Centennial; American Chemical Society: Washington, DC, USA, 1975.
182. Snelders, H.A.M. The Reception of J. H. Van’t Hoff’s Theory of the Asymmetric Carbon Atom. J. Chem. Educ. 1974, 51, 2.
183. Van ’t Hoff, J.H.; Springer, G.F. J. H. Van’t Hoff’s Inaugural Lecture: Imagination in Science. In Imagination in Science; Springer: Berlin, Heidelberg, 1967; pp. 6–18; ISBN 9783662377475.
184. Rocke, A.J. The Quiet Revolution; University of California Press: Berkeley, CA, USA, 1993; ISBN 9780520081109.
185. Rocke, A.J. Colbe Versus the “Transcendental Chemists”: The Emergence of Classical Organic Chemistry. Ambix 1987, 34, 156–168. [CrossRef]
186. Root-Bernstein, R.S. Visual Thinking: The Art of Imagining Reality. Trans. Am. Phil. Soc. 1985, 75, 50. [CrossRef]
187. Barthelme, D.; Maxwell, W.; Borges, J.L.; Bernstein, J.; Stewart, D. The New Yorker Magazine: University of California Press: Berkeley, CA, USA, 1969.
188. Cahn, R.S.; Ingold, C.K. Specification of Configuration About Quadrivalent Asymmetric Atoms. J. Chem. Soc. 1951, 612. [CrossRef]
189. Cahn, R.S.; Ingold, C.K.; Prelog, V. The Specification of Asymmetric Configuration in Organic Chemistry. Experientia 1956, 12, 81–94. [CrossRef]
190. Cahn, R.S.; Ingold, C.K.; Prelog, V. Specification of Molecular Chirality. Angew. Chem. Int. Ed. Engl. 1966, 5, 385–415. [CrossRef]
191. Moss, G.P. Basic Terminology of Stereochemistry (Iupac Recommendations 1996). Pure Appl. Chem. 1996, 68, 2193–2222. [CrossRef]
192. IUPAC. Nomenclature of Organic Chemistry, 2nd ed.; Eiloart, A., Ed.; Longmans, Green and Co.: London, UK, 1898.
193. IUPAC. Nomenclature of Organic Chemistry, 2nd ed.; Eiloart, A., Ed.; Longmans, Green and Co.: London, UK, 1898.
194. IUPAC. Nomenclature of Organic Chemistry, 2nd ed.; Eiloart, A., Ed.; Longmans, Green and Co.: London, UK, 1898.
195. Prelog, V.; Helmench. G. Basic Principles of the Cip-System and Proposals for a Revision. Angew. Chem. Int. Ed. 1982, 21, 567–583. [CrossRef]
196. Hantzsch, A.; Werner, A. Ueber Räumliche Anordnung Der Atome in Stickstoffhaltigen Molekülen. Ber. Dtsch. Chem. Ges. 1890, 3, 11–30. [CrossRef]
197. Wedekind, E.; Klatte, K.A. Über Die Aktivierung Einer Asymmetrischen Tertiärbase in Gestalt Von Salzen Mit Optisch-Aktiven Säuren. (54. Mitteilung Über Das Asymmetrische Stickstoffatom). Ber. Dtsch. Chem. Ges. 1927, 60, 2325–2334. [CrossRef]
198. Prelog, V.; Wieland, Ph. Über Die Spaltung Dertröger‘Schen Base in Optische Antipoden, Ein Beitrag Zur Stereochemie Des Dreiwertigen Stickstoffs. Helv. Chim. Acta 1944, 27, 1127–1134. [CrossRef]
199. Werner, A. Beitrag Zur Konstitution Anorganischer Verbindungen. Z. Anorg. Allg. Chem. 1893, 3, 267–330. [CrossRef]
200. Beecroft, W.J.; Peachey, S.J. Asymmetric Optically Active Nitrogen Compounds. Dextro- and Lavo-Azbenzyphenylallyl-methylammonium iodides and Bromides. J. Chem. Soc. Trans. 1899, 75, 1127–1131. [CrossRef]
201. Meisenheimer, J. Eine Neue Art Von Asymmetrie Beim Stickstoffatom. Ber. Dtsch. Chem. Ges. 1908, 41, 3966–3976. [CrossRef]
202. Meisenheimer, J.; Lichtenstadt, L. Über Optisch-Aktive Verbindungen Des Phosphors. Ber. Dtsch. Chem. Ges. 1911, 44, 356–359. [CrossRef]
201. Holliman, F.G.; Mann, F.G. The Stereochemistry of Organic Derivatives of Phosphorus. Part ii. The Synthesis of 2:2-Disubstituted 1:2:3:4-Tetrahydroisosophosphonium Salts and the Optical Resolution of 2-Phenyl-2-p-hydroxyphenyl-1:2:3:4-Tetrahydroisosophosphonium Bromide. J. Chem. Soc. 1947, 1634. [CrossRef]

202. Kumli, K.F.; McEwen, W.E.; Vander Werf, C.A. Resolution of a Non-Heterocyclic Quaternary Phosphonium Iodide. J. Am. Chem. Soc. 1959, 81, 248–249. [CrossRef]

203. Campbell, I.G.M. The Configuration of Heterocyclic Compounds. Part Iii. Resolution of Phenoxstibines and Resolution of 10-P-carboxyphenyl-2-methylphosphinoxstibine. J. Chem. Soc. 1947, 4–10. [CrossRef]

204. Campbell, I.G.M. The Configuration of Heterocyclic Compounds. Part Ii. Symmetric and Enantiomorphic 9-Stibiafluorenes. J. Chem. Soc. 1952, 4448. [CrossRef]

205. Campbell, I.G.M. The Configuration of Heterocyclic Compounds. Part I. Preparation of 9-Stibiafluorenes and Optical Resolution of 2-Carboxy-9-p-tolyl-9-stibiafluorene. J. Chem. Soc. 1950, 3109. [CrossRef]

206. Horner, L.; Fuchs, H. Optisch Aktive Tertiäre Arsine Aus Optisch Aktiven Quartären Arsoniumsalzen. Z. Anorg. Allg. Chem. 1911, 145–158. [CrossRef]

207. Horner, L.; Fuchs, H. Optisch Aktive Tertiäre Arsine Aus Optisch Aktiven Quartären Arsoniumsalzen. Tetrahedron Lett. 1962, 3, 203–204. [CrossRef]

208. Phillips, H. Investigations on the Dependence of Rotatory Power on Chemical Constitution. Part XXVII. The Optical Properties of N-Alkyl P-Toluenesulphinates. J. Chem. Soc. Trans. 1925, 127, 2552–2587. [CrossRef]

209. Bell, J.W.; Cranston, J. The Stereochemistry of Triarylstibines. Synthesis and Optical Resolution of P-Carboxyphenyl-2-diphenylphosphinylstibine. J. Chem. Soc. 1955, 3116. [CrossRef]

210. Bell, J.W.; Cranston, J. The Stereochemistry of Triarylstibines. Part I. Synthesis of Unsymmetrically Substituted Triarylstibines and Optical Resolution of P-Carboxyphenyl-1-naphthylphosphinylstibine. J. Chem. Soc. 1958, 1184. [CrossRef]

211. Burrows, G.J.; Turner, E.E. Experiments on the Production of Compounds Containing Arsenic as a Centre of Optical Activity. J. Chem. Soc. Trans. 1921, 119, 426–437. [CrossRef]

212. Horner, L.; Winkler, H.; Rapp, A.; Mentrup, A.; Hoffmann, H.; Beck, P. Phosphororganische Verbindungen Optisch Aktive Tertiäre Phosphine Aus Optisch Aktiven Quartären Phosphoniumsalzen. Tetrahedron Lett. 1961, 2, 161–166. [CrossRef]

213. Phillips, H. Investigations on the Dependence of Rotatory Power on Chemical Constitution. Part XXVI. The Optical Properties of Sulphoxides Into Their Optically Active Forms. J. Chem. Soc. 1958, 129, 2079–2090. [CrossRef]

214. Constable, E.C. Stereogenic Metal Centres—From Werner to Supramolecular Chemistry. Isis 1975, 66, 38–62. [CrossRef]

215. Constable, E.C.; Housecroft, C.E. Coordination Chemistry: The Scientific Legacy of Alfred Werner. Bull. Hist. Chem. 1997, 20, 50–59. [CrossRef]

216. Ernst, K.H.; Berke, H. Optical Activity and Alfred Werner’s Coordination Chemistry. Chirality 2011, 23, 187–189. [CrossRef] [PubMed]
306. Kuhn, R. Molekulare Asymmetrie. In Stereochemie: Eine zusammenfassung der Ergebnisse, Grundlagen und Probleme; Freudenberg, K., Ed.; Franz Deutike: Vienna, Austria, 1933; pp. 803–824.

307. Christie, G.H.; Kenner, J. The Molecular Configurations of Polynuclear Aromatic Compounds. Part 1. The Resolution of 1-6′-Dinitro- and 4:6′-Tetranitro-diphenic Acids Into Optically Active Components. J. Chem. Soc., Trans. 1922, 121, 614–620. [CrossRef]

308. Cain, J.C.; Coulthard, A.; Micklethwait, F.M.G. Studies in the Diphenyl Series. Part 2. The Dinitrobenzidines: A New Form of Isomerism. J. Chem. Soc. Trans. 1912, 101, 2298–2304. [CrossRef]

309. King, H. The Possibility of a New Instance of Optical Activity Without an Asymmetric Carbon Atom. Proc. Chem. Soc. 1914, 30, 250. [CrossRef]

310. Thorpe, J.F. John Cannell Cain. J. Chem. Soc. Trans. 1921, 119, 533–537.

311. Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. Modified Binap: The How and the Why. Chem. Rev. 2005, 105, 1801–1836. [CrossRef]

312. Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. Synthesis of 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (Binap), an Atropisomeric Chiral Bis(triaryl)phosphine, and Its Use in the Rhodium(I)-Catalyzed Asymmetric Hydrogenation of alpha-(acylamino)acrylic Acids. J. Am. Chem. Soc. 1980, 102, 7932–7934. [CrossRef]

313. Flanders, M.; Swann, D. At the Drop of a Hat. 1960. Available online: https://www.youtube.com/watch?v=AYr0eNtpDHs (accessed on 11 August 2021).

314. Chen, C.-F.; Shen, Y. Helicene Chemistry; Springer: Berlin, Germany, 2016; ISBN 9783662531662.

315. Lemiere, G.L.; Alderweireldt, F.C. Proposition for a New Definition of the Chiral Plane and Its Consequences for the Specification of Planar Chirality. J. Org. Chem. 1980, 45, 4175–4179. [CrossRef]

316. Hirschmann, H.; Hanson, K.R. Elements of Stereoisomerism and Prostereoisomerism. J. Org. Chem. 1971, 36, 3293–3306. [CrossRef]

317. Simon, J. Topological Chirality of Certain Molecules. Topology 1986, 25, 229–235. [CrossRef]

318. Chambron, J.-C.; Dietrich-Buchecker, C.O.; Sauvage, J.-P. From Classical Chirality to Topologically Chiral Catenands and Knots. Top. Curr. Chem. 1993, 165, 131–162. [CrossRef]

319. Segawa, Y.; Kuwayama, M.; Hijikata, Y.; Fushimi, M.; Nishihara, T.; Pirillo, J.; Shirasaki, J.; Kubota, N.; Itami, K. Topological Molecular Nanocarbons: All-Benzene Catenane and Trefoil Knot. Science 2019, 365, 272–276. [CrossRef]

320. Mitchell, D.K.; Sauvage, J.-P. A Topologically Chiral [2]catenand. Angew. Chem. Int. Ed. 1988, 27, 930–931. [CrossRef]

321. Constable, E.C.; Hartshorn, R.M.; Housecroft, C.E. 1,1′-Biisoquinolines-neglected Ligands in the Heterocyclic Diimine Family That Provoke Stereoechemical Reflections. Molecules 2021, 26, 1584. [CrossRef] [PubMed]

322. Wilkinson. Scene–Bishop’s Breakfast Table. Judy Lond. Sero-Comic J. 1895.

323. Kramer, S. There Was a Little Girl: Its First Printings · Its Authorship · Its Variants. Pap. Bibl. Soc. Am. 1946, 40, 287–310. [CrossRef]

324. Castiglioni, E.; Abbate, S.; Longhi, G. Experimental Methods for Measuring Optical Rotatory Dispersion: Survey and Outlook. Chirality 2011, 23, 711–716. [CrossRef] [PubMed]