



Kurt Mislow centennial—he changed the way people think about stereochemistry

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Abstract

Kurt Mislow (1923–2017) and his family were refugees from Nazi Germany. He studied at Tulane University and at Caltech and spent most of his career at Princeton University as Hugh Stott Taylor Professor of Chemistry (from 1988, Emeritus). He excelled in his research and his pedagogy of stereochemistry, introduced the term “chirality” into the chemical textbook literature, and delineated some of the theoretical underpinning of modern stereochemistry. He showed that shape, form, and symmetry play a central role in organic chemistry. He authored an introductory text on stereochemistry that has served generations. His pupils and those who learned from him through his publications carry on his legacy.

Keywords Kurt Mislow · Molecular structure · Symmetry · Chirality · Stereochemistry

Kurt Mislow (1923–2017, Figs. 1 and 2) was Hugh Stott Taylor Professor of Chemistry, Emeritus, at Princeton University at the time of his death. He was born in Berlin, Germany, and in 1936, together with his parents, became a refugee from Nazi Germany. In 1997, we recorded a long, leisurely conversation, and he told me more about his life [1] than in the various obituaries or elsewhere appeared. Kurt’s father was in business, and because he had to move around, so did the family. Kurt spent his formative years in Düsseldorf, a German industrial city. It was a violent time when he was growing up; there were street fights, especially between the Communists and the Nazis even before Hitler came to power in 1933. Then, following the Nazi takeover, the Communists disappeared, and the Nazi violence was directed against the Jews. First, it was mostly humiliation and intimidation. Then came the infamous pogrom of *Kristallnacht* in 1938, but by then, the Mislow family had

emigrated. Kurt had the Nazi slogans and songs imprinted in his mind, such as “The Jews are our misfortune” or “When Jewish blood spurts from the knife, it’s going even better.” At the time of our recorded conversation [1], Mislow still had his old brown German passport used for leaving Germany. It had the spread eagle on its cover holding the swastika in its claws with a big red capital letter J printed over it. This conspicuous J was there at the request of the head of the Swiss Federal Police who wanted to be sure to keep Switzerland closed before Jewish refugees from Germany. Kurt’s grandfather had a business in electric equipment with close connections in Italy, so they left for Italy in 1936. The grandfather though stayed and was later murdered in Germany.

Kurt attended an Italian high school with emphasis on humanistic subjects, so parallel to learning Italian, he had to study Greek and Latin. Italian Fascism was far less threatening than German National Socialism though it much worsened when Italy drew closer to Germany toward the end of the 1930s and introduced harsh anti-Jewish legislation. By then, in 1938, the Mislows moved to England and Kurt attended a grammar school. He was in a boarding school about whose horrors he did not wish to speak. It was also in that school that he was exposed for the first time to serious physics and mathematics. When he read a chemistry book in his senior year, J. R. Partington’s *Textbook of Inorganic Chemistry*, it sealed his professional path in chemistry. Kurt and his father were considered enemy aliens upon the beginning of World War II and were

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Fig. 1 Kurt Mislow, 1997, at the Department of Chemistry, Princeton University (photograph by Istvan Hargittai)

interned on the Isle of Man. When they were released, and Kurt was about to begin his studies at Cambridge University, an affidavit arrived from a New York uncle, and the family sailed to the USA.

First, they lived with relatives in New York, and Kurt earned some money as a page boy in the Columbia Main Library. Then, he moved to New Orleans, Louisiana, with a generous scholarship from Tulane University. He was happy to study but had open eyes on the rest of his surroundings as well. He observed racism, and it shocked him, because it was something he had thought he left behind in Europe. He took a streetcar twice a day, so he saw segregation daily. There were movable shields on the back of the seats, saying that they were for whites. When there were no more empty seats for whites and more whites came, the conductor moved the shields, and some of the black seats became white seats. If the black seats were occupied, those passengers had to give up their seats. Mislow spoke about this with emotion and, of course, we know that this was the arrangement that originated a historic impulse in the civil rights movement. In 1955, in a bus in Montgomery, Alabama, a young African-American woman, Rosa Parks, refused to yield her seat when the bus driver ordered her to vacate it for a white passenger.



Fig. 2 Kurt Mislow and Istvan Hargittai, 1986, at a symmetry meeting in Darmstadt, Germany (by unknown photographer)

Even if not in such drastic ways, there was also anti-Semitism—Mislow remembered. The local chapter of Alpha Chi Sigma, the national chemical honor society for undergraduates, did not take Jewish students, Blacks, and women. Many years later, Mislow checked when the exclusivity of white, Christian, and male membership ended. He thought it was a chronology of progress that in 1948 Jewish chemists, in 1954, black chemists, and in 1970, women chemists became eligible.

Mislow's career in chemistry took off in 1944 when after he got his B.S. degree at Tulane University, he became Linus Pauling's graduate student at Caltech. Mislow especially enjoyed Pauling's course in quantum mechanics in which he used Pauling and Wilson's text [2]. Mislow obtained his PhD in 1947. Although he had plans to do postdoctoral work with Melvin Calvin at Berkeley, Pauling got him a job at New York University (NYU), so he started at NYU. It was a teaching job, but right at the start, Mislow became acquainted with a book that had profound influence on his entire scientific career. At the time, it was not even a book, only a collection of mimeographed lecture notes of George W. Wheland (1907–1962) at the University of Chicago [3]. Wheland had been a doctoral student of James B. Conant at Harvard University and a post-doctoral fellow at Caltech and worked with Pauling on the theory of resonance. Following a tour in Europe, in the mid-1930s, he became a Professor of Chemistry at the University of Chicago and stayed there for the rest of his career.

Wheland's teaching introduced Mislow to the power of symmetry in discussing stereochemistry that, in Mislow's words, "symmetry and chirality were at the heart of stereochemistry" [1]. Wheland's teaching inspired Mislow throughout his entire career and, directly, the first paper Mislow published at NYU. It was titled "The Concept of Internal Compensation" [4]. It looked into the intricacies of the optical activity of meso-tartaric acid. This brief paper offered an experimental solution to the puzzle of "internal compensation." There are conformations with a plane of symmetry and conformations with a center of symmetry of meso-tartaric acid and many asymmetric ones in between. The question was the cause of the optical inactivity of the substance. Some suggested that one half of the molecule causes an optical rotation that is compensated by the optical rotation of the other half, and this is independent of the conformation. This is what they called internal compensation. Wheland found this unacceptable since once there is a chiral conformation, it should be optically active, and Mislow in this paper proposed an experiment to settle the issue. Meso-tartaric acid is achiral, but it is a diastereomer of D-tartaric acid and L-tartaric acid, and they both are chiral. This was to become Mislow's typical approach, to go after puzzles relentlessly and solve them.

He was advancing and advocating symmetry arguments, which was a straightforward way of predicting structural characteristics without detailed structural information. Examples included the asymmetric molecules of the type Cabcd (a carbon atom with four different ligands) to have six different bond angles, the carbenium ions in asymmetric molecules to be non-planar, or that the NMR signals of symmetry-nonequivalent nuclei should be shifted relative to one another. For Mislow, these were straightforward consequences of Louis Pasteur's discoveries, whereas when people found them experimentally, they considered these observations a novelty. Eventually, Mislow's approach became accepted and generally followed, but it took a long time, a great deal of efforts, and often much frustration on the way. He wrote his *Introduction to Stereochemistry* [5] to introduce the organic chemists into the concepts Wheland and Mislow popularized. The book appeared in 1965 and has stayed in print ever since, going through many reprints. Today, all modern organic chemistry textbooks carry on these ideas, but it was Mislow who introduced symmetry and chirality into the organic chemistry textbook literature.

It is then an interesting question whether there is any difference between structural chemistry and stereochemistry. The question may sound to concern semantics, but to Mislow, the difference had a deeper meaning. He thought chemical structure to be an invention of chemists because, at least in quantum mechanics, it is an undefined concept. Still, he gave a succinct definition of what he considered to be molecular structure at the very beginning of his *Introduction*

to *Stereochemistry* [5]: "Molecular structure is a description of the arrangement or distribution of particles in a molecule." This is not only acceptable to any structural chemist; it is quite comprehensive and helpful. Mislow emphasized that the Born–Oppenheimer approximation is necessary to consider the nuclei in the molecule to behave like particles sitting inside the clouds of electrons. To him, stereochemistry is based on this powerful classical model. There has been general agreement concerning this relationship. Where Mislow differed from many was the relationship of stereochemistry and constitution: he did not consider stereochemistry secondary to constitution. In his scheme, symmetry comes first and constitution takes second place to it [6].

To illustrate, we quote the scheme of the hierarchy of isomers (Fig. 3) from our own book on symmetry ([7], by Magdolna Hargittai and Istvan Hargittai). The relevant chapters in this book, of its first edition, had gone through Mislow's critical and constructive review, and quoting this figure is in some way an expression of tribute to him. This scheme reflects Mislow's ideas, and he enthusiastically reviewed the initial manuscript of *Symmetry through the Eyes of a Chemist*, probably because he saw that it was on a common wavelength with his teachings in considering the relationship among isomers. Our (Magdolna Hargittai and Istvan Hargittai's) interactions with him started by correspondence; later, there were personal meetings, several, over the years, always uplifting and instructive, always friendly and stimulating.

Although Mislow never updated his *Introduction to Stereochemistry*, his research over the decades could be considered as its updates. Soon following its publication, he and his graduate student, Morton Raban, published a seminal review on stereoisomeric relationships. They described local

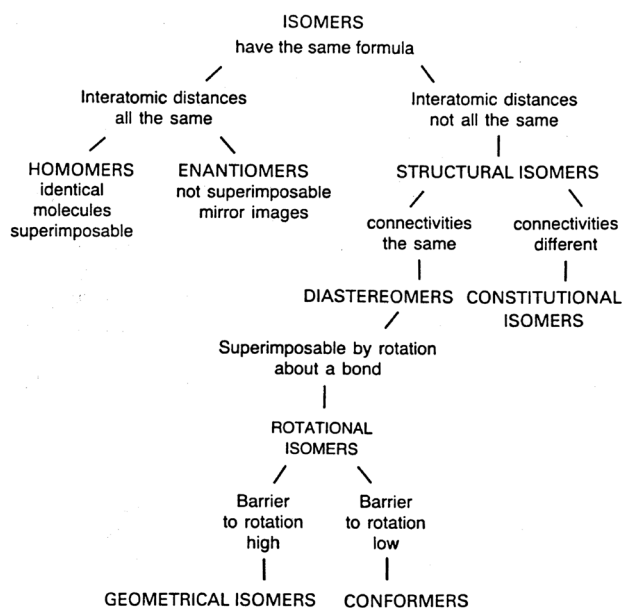


Fig. 3 Hierarchy of isomers (Ref. [7], p 100, Fig. 3–1)

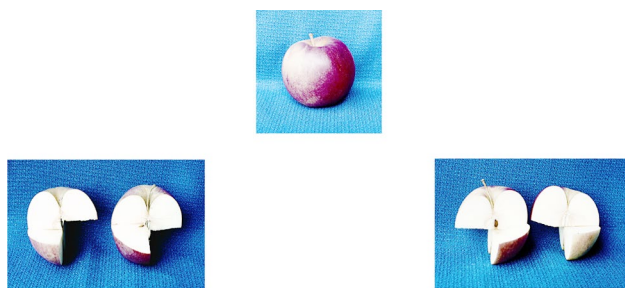


Fig. 4 *La coupe du roi*: An apple can be cut into two homochiral halves in two ways, which are enantiomorphous to each other, i.e., the two homochiral segments on the left are enantiomorphs of the two homochiral segments on the right (Ref. [7], pp 75–76, Fig. 2–46)

symmetry relationships and the enantiotopic and diastereotopic groups [8]. Morton Raban (1942–2020) devoted his research career at Wayne State University to further develop what he learned from Mislow in stereochemistry.

Another example along the lines of furthering the ideas introduced in his 1965 book, Mislow and Jay S. Siegel in 1984 presented the concept of chirotopic groups with a discussion of cases of such groups with local symmetry [9]. They clarified a number of classical concepts to assist the determination of the presence or absence of chirality in a variety of structures. At the time, Siegel was a graduate student. He has had a distinguished career including appointments in Switzerland, France, at the University of California, San Diego, and lately in China.

The 1984 Mislow–Siegel publication could be considered to be a derivative of a paper in 1983 by Anet et al. [10]. They produced a reaction related to the French parlor trick called “*la coupe du roi*” (the royal section). The trick is about cutting an apple into homochiral halves as shown in Fig. 4.

Cinquini et al. [11] demonstrated the first chemical analog of *la coupe du roi* by bisecting the achiral molecule *cis*-3,7-dimethyl-1,5-cyclooctandione into homochiral halves: two 2-methyl-1,4-butandiol molecules. What Mislow and his

associates demonstrated was a chemical analog of a *reverse la coupe du roi*: it was the formation of the achiral dimer from two chiral 4-(bromomethyl)-6-(mercaptomethyl) [2.2]metacyclophane molecules [10] as illustrated in Fig. 5.

Our eclectic presentation of Mislow’s research interests attempts to give a cross section of his works. He characterized his opus as “made up of lots of individual contributions that fit together, sort of like a jigsaw puzzle.” [1]. The extended stereochemical application of nuclear magnetic resonance spectroscopy occupied an important place in this jigsaw puzzle. Again, with Raban, he published some trail-blazer studies [12, 13]. For the first time, he established the absolute configuration for a variety of optically active biphenyl molecules [14]. He found the stereochemistry of internally mobile molecules to be a challenge and he developed a whole set of studies on correlated rotation, molecular propellers, and molecular gears [15].

An intriguing question was the quantitative characterization of chirality, just as it is that of symmetry. He did not shy away from such puzzles even though it is not possible to provide simple and unambiguous solutions to them: there is no unique function for doing this. Mislow kept returning to this challenge over the years [16, 17]. He was not too kind with respect to the exploitation of chirality for business. He called it “Huge and profitable. That growth has been fueled by the pharmaceutical companies, which are under pressure to produce enantiopure drugs.” He noted the proliferation of special chirality-related journals at the time of our conversation (1997), such as *Chirality*, *Tetrahedron Asymmetry*, and *Enantiomer* [1].

Above, we have already alluded to Mislow’s involvement in epistemology. He wondered about the start of interest in chirality and found that the great German philosopher Immanuel Kant (1724–1804) was the first who considered the meaning of chirality and noted its paradoxical nature [18]. Kant recognized the paradox in that the idealized left and right hands have the same metric properties: they are isometric. In that sense, they are congruent, yet they cannot

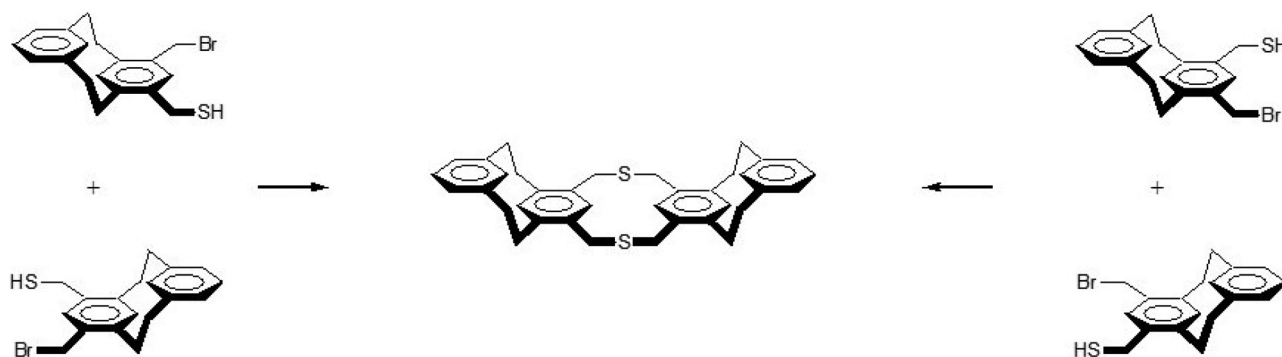


Fig. 5 Formation of the dimer of two homochiral 4-(bromomethyl)-6-(mercaptomethyl) [2.2]metacyclophane molecules: A *reverse la coupe du roi* (after Ref. [10])

be superposed, so they cannot be congruent. Kant found at least a semantic solution as he called the nonsuperposable mirror images “inkongruente Gegenstücke” (incongruent counterparts). As Mislow was moving increasingly into chemical topology, he recognized that the mathematician Johann Listing (1808–1882) at the University of Göttingen was the first who looked into topological chirality. Listing described the mirror-image relationship between enantiomorphous knots in a paper in 1848. It was the same year when Louis Pasteur (1822–1895) published his paper about optically active tartarates. Lord Kelvin (1824–1907) of the University of Glasgow is considered to be the one who first defined chiral and chirality. He wrote early on [19]: “I call any geometrical figure, or group of points, chiral, and say that it has chirality if its image in a plane mirror, ideally realized, cannot be brought to coincidence with itself.” Mislow’s own commentary on the subject of chemical chirality was a modern exposure of the subject [20].

Mislow received much recognition during his life much of which expressed the appreciation of his peers, making it especially valuable. He was a Sloan Fellow, 1959–1963. He spent visiting stints at the ETH Zurich in 1956 and at Cambridge University in 1974 as a Guggenheim Fellow. He received the Solvay Medal in 1972, the Prelog Medal in 1986, the Chirality Gold Medal in 1993, and the Arthur C. Cope Scholar Award in 1995. He was a member of the National Academy of Sciences (1972), the American Academy of Arts and Sciences (1974), and a Fellow of the American Association for the Advancement of Science (1980). In 1988, he taught a course titled “Social Responsibilities of Scientists” designed for graduate students at Princeton University. Above we mentioned Kant, Listing, Pasteur, and Kelvin, who are among the greats of past chirality studies and Kurt Mislow belongs to that list. This remembrance is our tribute to this exceptional contributor to twentieth-century science.

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