Chirony of stereochemical metaphors

Franco Cozzi*[a] and Jay S. Siegel*[b]

[a] *Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, via C. Golgi 19, I-20133, Milano, Italy. E-mail: franco.cozzi@unimi.it; Fax: +390250314159*

[b] *Organisch-chemisches Institut, Universität Zürich, Winterthurerstrasse 190, CH-8057, Zürich, Switzerland. E-mail: jss@oci.unizh.ch; Fax: +4116356888*

Idioms affect the conceptualization of metaphors and models in science. The dependence of stereochemistry on molecular models makes it especially vulnerable to the use of idiomatic terms. For example, the creation and use of idiomatic terminology, based on the tetrahedral model of van't Hoff[1], caused chemists to confuse the concepts of chirality with stereoisomerism.. Twenty years ago, the distinction between chirality and stereogenicity resurfaced and chemists began to discuss this overlap and its effect on stereochemical terminology.[2] The heart of the matter is that stereogenicity[3] specifies the stereoisomeric properties of a molecular sub-unit (*e.g.* a tetrahedrally coordinated atom with four different ligands), whereas chirality[4] is an intrinsic geometric feature of the whole molecule, manifesting itself in the molecule's properties. The realization that chirality is rooted in symmetry, whereas stereogenicity stems from definitions of bonding, makes jargon such as "chiral center", "chiral axis", and "planar chirality" obsolete. Nonetheless, these and related contradictions persist, defended as colloquial idioms, even though they misrepresent the stereochemical concepts they are supposed to simplify.

Resistance to modification of jargon is anticipated, however, there are major disadvantages in retaining illogical expressions, which function by tenuous consensus rather than conceptual foundation. At best "newcomers" are led astray and experienced practitioners waste time pursuing polemics.[6] For example, the idioms mentioned above obscure the distinction between chirality and stereogenicity and their use occurs at the expense of perfectly reasonable and accepted chemical terminology. They contradict the explicit intent of stating the chirality/stereogenicity distinction, which was to dispel a conceptual confusion about the origin of certain stereochemical phenomena and to reduce the proliferation of jargon.[5]

Rather than seeing the retirement of the chiral elements, the tremendous growth of interest in stereoselective synthesis has led to a proliferation of modern idioms such as "transfer of chirality", "self-replication of chirality", "chiral discrimination", and "amplification of chirality". This proliferation of terms motivates a general discussion of the use of idioms and metaphors in stereochemistry, followed by a specific analysis of "memory of chirality" (MoC).

An *idiom* according to Webster's[7] is **1a**: the language peculiar to a people or to a district, community, or class (DIALECT), **b**: the syntactical, grammatical, or structural form peculiar to a language; or **2**: an expression in the usage of a language that is peculiar to itself either grammatically (as *synthon*) or in having a meaning that cannot be derived from the conjoined meanings of its elements (as *aromaticity*, which has nothing to do with fragrance). The same source construes *metaphor* to mean **1**: a figure of speech in which a word or phrase literally denoting one kind of object or idea is used in place of another to suggest a likeness or analogy between them (as in *synthetic arsenal*); *broadly*: figurative language, **2**: an object, activity, or idea treated as a metaphor (an analogy or model, *per se*)

These definitions show that there is a direct connection between the coinage of idioms and the development of metaphors.

In the development of a metaphor, great value is placed on the ability to convey features of an empirical phenomenon either by direct mapping of properties or by absurd contrast. For example, "ball and spring" could serve as a metaphor for the chemical bond, alluding to its oscillatory nature about an equilibrium point. This metaphor works so well that the field of molecular mechanics was built upon it and every student entering the area is aided by the simple model, despite the need ultimately to learn its limitations. In the other case, *i.e.* an absurd contrast or oxymoron, the metaphor is so blatantly unrealistic that the reader is immediately directed to change perspective, and from there, gain a better understanding of the empirical phenomenon. For example, "the alkene refuses to isomerize" would at first imply a strength of will in the alkene, but in retrospect reflects an inability of the chemist.

When idioms are used to create a metaphor, the level of sophistication rises. The student or practitioner must add a new filter in order to understand and use the model properly. If the idiom is a collection of colloquial terms without any obvious possible direct meaning, as with *aromatic*, then the filter is simply to remember the dialectical definition and apply it to the metaphor. This is more complicated when the idiom is itself an oxymoron and the metaphor is a comparison by contradiction. Not only must the definition of the term be retained, but it must be recognized that the term actually means the opposite of what one might think, so this particular metaphor is a contradiction and should revert to its original meaning after two flip-flop translations, for example a pseudo-chiral center.

We are all familiar with the game of telephone wherein multiple transfers of the same message leads to gibberish. A common joke uses the translation of "the spirit is willing but the flesh is weak" from English to Russian and back to English, and concludes that "the meat is rotten, but the vodka is good". In a similar manner, the construction of scientific models from metaphors risks leading to misunderstandings due to misconstruing the metaphor.

There are other costs of such misuse of metaphors besides mistakes and misinterpretation. For example, the exclusion of non-specialists, even highly trained practitioners in a related field, could be a particular problem for interdisciplinary research, greatly reducing the benefits of sharing expertise. We must also be mindful that these costs have a devastating impact on teaching, where clear terminology and logical metaphors are of paramount importance. For instance, a student presented with the idiom, planar chirality, does not obtain the simplifying benefit of the "ball and spring" type metaphor, and yet, the absurdity of the oxymoron does not induce any enlightening change in perspective either. Indeed, the benefit of memorizing this jargon is limited to acceptance into a clique of chemists.

Let's look specifically at evidence of this confusion arising from the phrase "memory of chirality" (MoC).[8,9] At the outset, MoC was a simple idiomatic phrase for a process in which conformational bias toward a chiral intermediate controlled the stereoselective outcome of a synthetic transformation (in particular, the base mediated alkylation of the α-carbon of

a chiral ketone).[8, 9] By using *chirality* to mean *configuration*, and *memory* in the sense of *not forgotten*, MoC describes a clever synthetic tactic, but neither embodies nor presumes any profound phenomenological underpinnings.

It is unfortunate that the quaint phrase MoC, coined by Fuji,[8b] has taken on connotations, which are illogical terminologically, through the insistence of building a metaphor on a stereochemical misconception of MoC (*i.e.* that chirality is somehow lost and remembered during the transformation). Furthermore, MoC has been extended in scope and is now associated with the stereoselective assembly of, and exchange among, supermolecular adducts.[10, 11]

In extending the MoC metaphor, the true message is obfuscated, creating an illusion of something more fantastic or paradoxical than what one finds by simple stereochemical analysis. This point is highlighted by a recent review[8a] on MoC which states that "MoC has attracted attention in part because it appears to do the impossible: how can the memory of a sole chiral center of a substrate be retained in a process that destroys that center?" Indeed, it is the misrepresentation of the term "chiral center" that brings this into question at all.

It is poor didactic procedure to use a term one knows is a contradiction in terms to establish a paradox based on this term. The closest analogy to this in logic is the *argumentum ad absurdum* in which one assumes an undesired postulate and shows that it leads to an absurdity and thereby invalidates the original hypothesis. The proponents of mixed chiralty/stereoisomeric terminologies have taken all of the logical steps except recognizing that the absurdities they have generated are proof to the contrary of their claims. In contrast, when confronted with compelling logic, they dig in their heels and insist that such terms be retained.

Evidently, in some schools misinstruction of stereochemical basics is used to support the utility of poor terminology. In the review cited above it is further claimed[8a]: "beginning students of organic chemistry learn that if an enantiopure sp[3] hybridized stereogenic center is trigonalized, any chiral products resulting from that intermediate will be racemic." If such blatantly wrong teaching is truly general, we have a more fundamental problem on our hands, but it shows the powerful connection between (mis)conception and the rise of jargon.

Let's look carefully at a couple of examples of the extended use of MoC. In the first case (Scheme 1), an enantiomerically pure carbonyl compound possessing an α-stereogenic center is treated with a base to induce enolate formation. Upon reaction with an electrophile, a new α-stereogenic center is formed with some degree of stereoselectivity, measured in terms of enantiomeric excess (ee). The fact that an enantiomerically enriched product is obtained by this transformation is ascribed to the ability of the substrate to "memorize" its original chirality throughout the process, even though it presumably becomes "achiral" upon enolization.
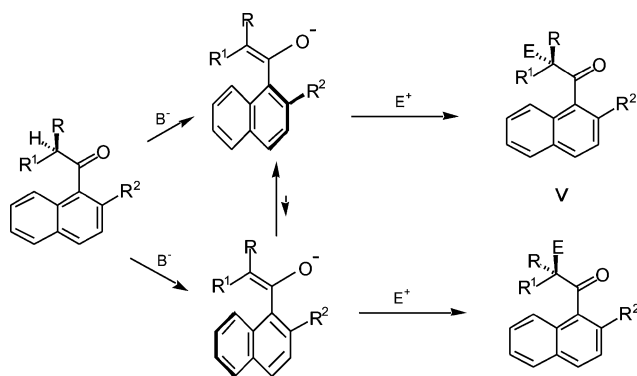
Scheme 1

Obviously, the paradox here is explained by the fact that the enolate remains chiral and does not undergo complete racemization under the reaction conditions,[12] otherwise a racemic product would have been obtained.[13] *Stereogenicity at the α-stereogenic center* is lost upon enolate formation, but the *chirality of the whole molecule* is maintained. In most of the cases examined,[9] the mechanism by which an enantiomeric imbalance is preserved involves hindered rotation around a single bond, and this imbalance manifests itself in the stereoselective course of the reaction. Thus, far from being "lost but memorized", chirality persists throughout the reaction. In other words, the problem lies with a conceptual confusion on the part of the scientists, rather than a paradox in the physical phenomena.[14]

In the second case (Scheme 2), an enantiomerically pure additive interacts in a non-covalent fashion with an achiral molecule or a racemate to form a supramolecular assembly. As a consequence of the interaction, the assembly adopts an imbalanced mixture of two chiral diastereoisomers.[15] When the additive is replaced by an achiral counterpart, an imbalanced mixture of two enantiomers of the new adduct is obtained. The last transformation is said to occur with MoC, as if the stereochemical information present in the diastereoisomers had been lost upon removal of the chiral additive, but memorized and retrieved to stereocontrol during the final step of the process.
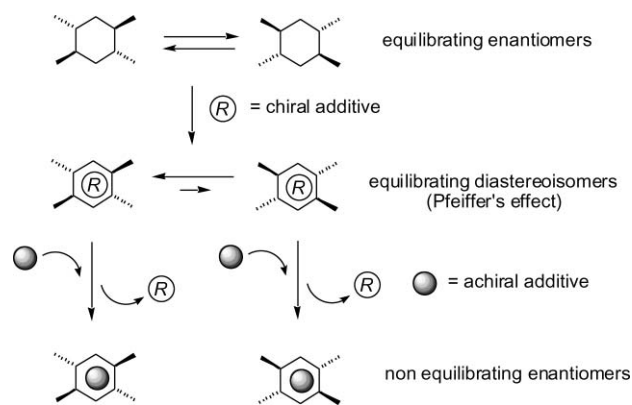
Scheme 2 An example of "memory of chirality" in supermolecular chemistry.

Although the supramolecular adduct loses the stereogenic element of the enantiopure additive upon its replacement, *the chirality of the remaining entity* is maintained throughout the sequence. It must be noted that this process does not differ from any stereoselective transformations carried out using a "chiral auxiliary", that is an enantiopure moiety introduced on the substrate to exert stereochemical control of a subsequent transformation, and then removed to release an enantiomerically enriched product. The desire to use MoC comes from a misconception of how the mechanism by which chirality is retained in a structure takes place and illustrates the way chemists have inappropriately dissected molecules into chiral and achiral parts.

Another example in which the pervasive nature of chirality in a molecule is disregarded is provided by an article suggesting that "chiral events can be regulated by achiral species".[16] In this paper, an enantiopure molecule containing two binding sites for different cations (a crown ether and two bipyridine units binding Na^{+} and Cu^{+}, respectively) is complexed first with Cu^{+} only and then with Na^{+} and Cu^{+}, sequentially. It was discovered that the ratio between two equilibrating diastereoisomeric Cu^{+} complexes changes when the complexation with Na^{+} occurs. Because the authors regard the Na^{+} cation as achiral, it is concluded that "achiral Na^{+} acts as a mediator of chiral information", overlooking the fact that, once complexed with the chiral host, Na^{+} is as chiral as any other part of the binding molecule. The folly here comes from neglect of the fact that the

complexes with and without Na$^+$ are simply different species and therefore should behave differently, independent of the chiral/achiral nature of any additive.

The present analysis of MoC is meant to encourage us not to let the metaphors of stereochemistry become more important than the molecules and chemical principles we strive to teach. Although the use of metaphors is important for the conceptualization of science, the extended use of the metaphors like "MoC" is not advisable. We all feel pressure to distinguish our work in catchy and interesting ways, however, this goal should not be pursued at the expense of logical discourse in science.

References

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2 K. Mislow and J. S. Siegel, *J. Am. Chem. Soc.*, 1984, **106**, 3319–3328.

3 Stereogenicity is defined as the property of a given structural unit to generate stereoisomers upon exchange of ligands at that unit (see ref. 1).

4 Chirality is the property of any object that is not superposable on its mirror image:K. Mislow, *Top. Stereochem.*, 1998, **22**, 1–82.

5 (*a*) A clear demonstration of how deeply this confusion has affected stereochemistry is found in the title that Cahn, Ingold, and Prelog selected for their 1966 paper on stereochemical descriptors ("Specification of Molecular Chirality"). The *R/S* and related symbols clearly describe the spatial disposition of ligands around stereogenic units rather than chirality, see: R. S. Cahn, C. K. Ingold and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, 1966, **5**, 385–415; (*b*) Perplexingly, the previous papers correctly referred to the specification of configuration, a stereogenic property; see: R. S. Cahn and C. K. Ingold, *J. Chem. Soc.*, 1951, 612–622, and; R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, 1956, **12**, 81–94.

6 One might think that this is a purist's stance in an attempt to rid chemical language of metaphor. *Au contraire*, metaphor should be welcomed into our world and used to enrich our ability to communicate. For a recent discussion of the use of metaphor in chemical communication, see:H. L. Kretzenbacher, *HYLE–Int. J. Philos. Chem.*, 2003, **9**, 191–218.

7 Merrian-Webster OnLine, see http://www.m-w.com.

8 For reviews see: (*a*) H. Zhao, D. C. Hsu and P. R. Carlier, *Synthesis*, 2005, 1–16; (*b*) T. Kawabata and K. Fuji, *Top. Stereochem.*, 2003, **23**, 175–205.

9 For specific examples see: (*a*) K. Fuji and T. Kawabata, *Chem.–Eur. J.*, 1998, **4**, 373–376; (*b*) T. Kawabata, K. Yahiro and K. Fuji, *J. Am. Chem. Soc.*, 1991, **113**, 9694–9696; (*c*) T. Kawabata, T. Wirth, K. Yahiro, H. Suzuki and K. Fuji, *J. Am. Chem. Soc.*, 1994, **116**, 10809–10810; (*d*) E. Vedejs, S. C. Fields, R. Hayashi, S. R. Hitchcock, D. R. Powell and M. R. Schrimpf, *J. Am. Chem. Soc.*, 1999, **121**, 2460–2470; (*e*) T. Kawabata, H. Suzuki, Y. Nagae and K. Fuji, *Angew. Chem., Int. Ed.*, 2000, **39**, 2155–2157; (*f*) M. A. Bonache, G. Gerona-Navarro, M. Martin-Martinez, M. T. Garcia-Lopez, P. Lopez, C. Cativiela and R. Gonzalez-Muñiz, *Synlett*, 2003, 1007–1011; (*g*) M. A. Bonache, G. Gerona-Navarro, C. Garcia-Aparicio, M. Alias, M. Martin-Martinez, M. T. Garcia-Lopez, P. Lopez, C. Cativiela and R. Gonzalez-Muñiz, *Tetrahedron: Asymmetry*, 2003, **14**, 2161–2169; (*h*) T. Kawabata, S. Kawakami and S. Majumdar, *J. Am. Chem. Soc.*, 2003, **125**, 13012–13013.

10 (*a*) Y. Furusho, T. Kimura, Y. Mizuno and T. Aida, *J. Am. Chem. Soc.*, 1997, **119**, 5267–5268; (*b*) A. Sugasaki, M. Ikeda, M. Takeuchi, A. Robertson and S. Shinkai, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3259–3264; (*c*) E. Yashima, K. Maeda and Y. Okamoto, *Nature*, 1999, **399**, 449–451; (*d*) L. J. Prins, F. De Jong, P. Timmerman and D. N. Reinhoudt, *Nature*, 2000, **408**, 181–184; (*e*) Y. Kubo, Y. Ohno, J. Yamanaka, S. Tokita, T. Iida and Y. Ishimaru, *J. Am. Chem. Soc.*, 2001, **123**, 12700–12701; (*f*) T. Ishi-i, M. Crego-Calama, P. Timmerman, D. N. Reinhoudt and S. Shinkai, *J. Am. Chem. Soc.*, 2002, **124**, 14631–14641.

11 Miscellaneous examples: (*a*) S. Sauer, A. Schumacher, F. Barbosa and B. Giese, *Tetrahedron Lett.*, 1998, **39**, 3685–3688; (*b*) M. Sakamoto, T. Iwamoto, N. Nono, M. Ando, W. Arai, T. Mino and T. Fujita, *J. Org. Chem.*, 2003, **68**, 942–946; (*c*) T. Mori, T. Sato and Y. Inoue, *Chem. Commun.*, 2003, 2302–2303.

12 Racemization does not necessarily imply formation of an achiral species: (*a*) K. Mislow, *Science*, 1954, **120**, 232–233; (*b*) K. Mislow and R. Bolstad, *J. Am. Chem. Soc.*, 1955, **77**, 6712–6713; (*c*) W. D. Hounshell, C. A. Johnson, A. Guenzi, F. Cozzi and K. Mislow, *Proc. Natl. Acad. Sci. USA*, 1980, **77**, 6961–6964; (*d*) J.-C. Chambron, J.-P. Sauvage and K. Mislow, *J. Am. Chem. Soc.*, 1997, **119**, 9558–9559. Obviously, a molecule in a racemate is as chiral as its counterpart in the enantiopure form.

13 This disregards the remote possibility of spontaneous resolution of the product.

14 Notably, this kind of result has been observed previously and fully rationalized without referring to "MoC": (*a*) M. F. Braña, M. Garrido, M. L. Lopez and A. M. Sanz, *J. Heterocycl. Chem.*, 1980, **17**, 829–830; (*b*) D. Seebach and D. Wasmuth, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 971; (*c*) B. Beagley, M. J. Betts, R. G. Pritchard, A. Schofield, R. J. Stoodley and S. Vohra, *J. Chem. Soc., Chem. Commun.*, 1991, 924–925.

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