Double vision

Michelle Francl wonders if a molecule can be just a little bit chiral?

It is not, I think, an overstatement to say that chirality is the concept that gives shape to chemistry — it is chemistry's metaphorical and literal skeleton. Historically, the proposal that carbon was tetrahedral launched chemistry into three-dimensional space, shifting the field's focus from elemental ratios rooted in descriptions of bulk materials to the relationship between atomic-level structures of substances and their functions — impressive at a time when seeing a molecule was the stuff of fiction[1]. Chirality also shaped the landscape of the subject going forward, giving rise to at least a dozen Nobel prizes and continuing to feature in thousands of journal articles each year.

For the last several weeks I've been trolling colleagues with the question, 'Can a molecule be a little bit chiral?' Their answers have run the gamut from crisp 'no's to firm 'maybe's. But perhaps the most interesting answer was another question: 'why do you ask?'

The surveying of my co-workers was provoked by Andrew Zahrt and Scott Denmark's recent paper on using continuous chirality measures to drive the design of asymmetric catalysts and some of the Twitter conversations it spawned on the nature of chirality[2]. But as one colleague intuited, what I'm ultimately curious about is how chemists can have such divergent views on what is inarguably a foundational notion for the discipline of chemistry.

Physicist William Thomson (Lord Kelvin) introduced the term 'chiral' as an aside in an 1893 lecture[3] given to the Oxford Junior Scientific Club on the relationship between molecular structure, crystal packing and the overall structure of quartz crystals: 'Any geometrical figure…has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself'. The organic chemistry textbooks I pulled off the shelf behind me provided nearly identical definitions, minus Thomson's caveat about ideality. We clearly teach undergraduates that molecules are either chiral or they are not; even the latest edition of an advanced organic chemistry text I used in graduate school did not hint at chirality being anything other than a binary property of a molecule, dependent on its structure[4]. What we don't tell our students is that not every chemist agrees. Moreover, these are not new ideas: chemists and mathematicians have been exploring constructions of chirality which treat it as a continuous property for decades[5].

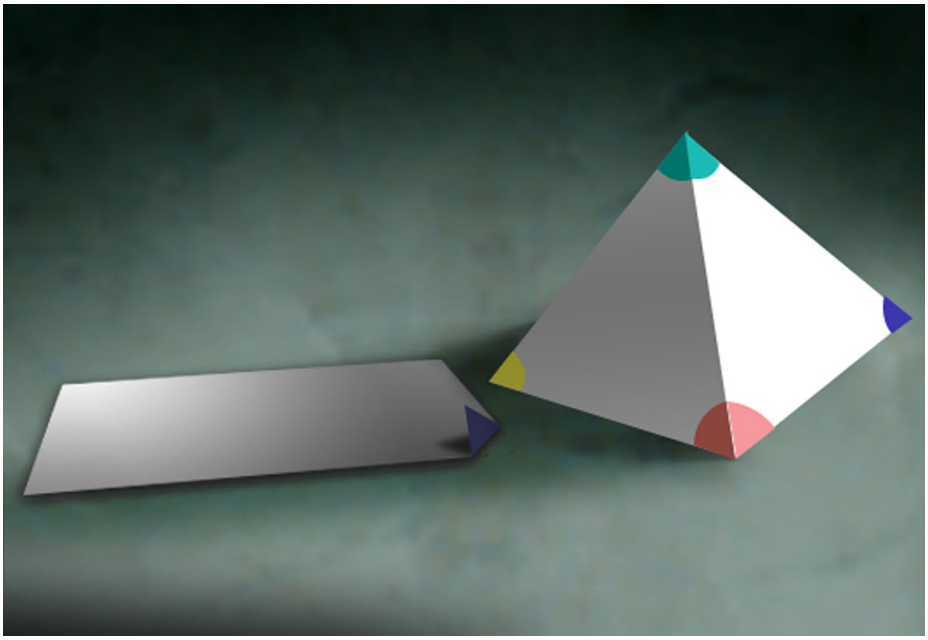

Fig. 1 | Chirality on paper. Both the sheet of paper with the bent-up corner, and the paper tetrahedron with four different vertices are not superimposable on their mirror images, but in the eyes of some beholders the sheet of paper is nearly flat, and therefore nearly achiral, while it would take a far more significant distortion of the tetrahedron to reach an achiral structure.

Underlying the desire by some chemists to create a non-binary measure of chirality is the nagging sense that a piece of paper with a small bent up corner is not as asymmetric an object as a perfect tetrahedron with four different coloured sides folded out of that same piece of paper, and so perhaps is not 'as chiral' (see Fig. 1). Others suggest that because chirality is linked with a measurable property that covers a range of values — namely optical rotation — it too should be continuously quantifiable over a range.

In his paper, *Quantification of chirality: attempting the impossible*, theoretical chemist Patrick Fowler aptly characterizes the question of whether chirality can be quantified on a continuous scale as vexing[6]. I concur and do not intend to make a case one way or the other in this essay. Fowler wonders if the core issue is, 'the well-known reluctance of chemists to adopt unfamiliar mathematical ideas'. I think not. Perhaps chemists' quarrels over whether or not chirality is strictly binary are fundamentally arguments about how we see molecules and what we imagine molecules are. But maybe we don't want to admit — neither to our students nor most of all to ourselves — that we are uncertain of the best way to represent the very objects our field works with[7]. So instead we get vexed about the nature of chirality itself.

If I asked chemists to draw a molecule, what would they draw? I will admit to having double — or more — vision when it comes to how I see molecules. All chemists do. A quick flip through any chemistry textbook will reveal that chemists routinely visualize molecules as line structures, balls and sticks, or CPK models. But beyond the representations we reach for most often in texts and articles, many of us also imagine molecules as electron-density isosurfaces, or as wispy electron-density functions extending out to infinity, or as webs of electrostatic potentials laid to entrap wary substrates. For synthetic chemists, molecules can be machines or templates with which to make other molecules. Some of us may not see molecules as mechanical objects in Euclidean space at all, but instead see them as lists, as vectors in abstract spaces, pulling up vector wavefunctions in Hilbert space, or collections of descriptors in virtual compound libraries. How we imagine molecules depends on the questions we are asking of them and the work we are expecting them to undertake. And in all of this, our focus tends to be on molecules as isolated entities, rigid and pinned to some arbitrary point in space.

How does this multiplicity of molecular representations that chemists wield inform the arguments about chirality? Kurt Mislow and Paul Bickart begin their development of a theory[8] of chirality that admits to there being degrees of chirality by reminding the reader that the representations of molecules, geometric or otherwise, are abstractions of reality and that different choices of representation may result in different answers to the question 'is this molecule chiral?'. A rigid and perfectly tetrahedral methane molecule is not geometrically chiral, but catch a vibrating methane molecule at the right moment and it is. Pushing this concept further, they argue that an ensemble of vibrating methane molecules is optically inactive, not because of the properties of a single entity, but because it is a racemic mixture of (momentarily) chiral tetrahedrons.

Mislow and Bickart do not dispute that chirality is a binary characteristic in the limit that molecules can be represented as rigid geometric objects. But, they note that if you consider a molecule to be a vector of measurable properties, such as optical activity, chirality becomes a fuzzy quantity. Consider the molecule $H(CH_2)_nCHD(CH_2)_nD$, which is geometrically chiral for all $n>0$, but at some large n, which cannot be unambiguously determined, is operationally no longer chiral. This fuzziness is true of objects as well; we would consider our two hands to be chiral, the word itself comes from the Greek for hand (as virtually every undergraduate textbook that touches on the subject points out), yet your left hand is not a perfect mirror image of your right.

The continuous chirality measure that Zahrt and Denmark developed to assess the capacity for enantioinduction relies on a conceptual framework that views molecules as templates for making other molecules, seeing chirality as a transmissible property. Just as infections can be more or less contagious, Zahrt and Denmark argue that molecules are more or less chiral depending on their ability to transmit that information to another molecule and their ability to differentiate enantiomers. Zahrt and Denmark construct their measure using Hagit Zabrodsky and David Avnir's method for determining the degree of chirality of a molecule[5], which is based on computing the minimal distance the vertices of a shape must be moved in order to reach an achiral system.

The plethora of methods for ranking molecular chirality, whether as a discriminatory function (one or zero) or as some continuous function, has parallels in the development of methods for atomic charges. There is no unique method for assigning charges to atoms in a molecule because they are not quantum mechanical observables. Similarly, Fowler notes[9] that there is no unique method for ranking molecules by their chirality, in part because there is no such thing as the 'most chiral object'. But there remains value in having such methods, even if they are at some level arbitrary, or even entirely fail in some cases.

In sketching out methods for assessing symmetry as a continuous measure, Avnir warns against clinging too closely to binary descriptions of nature. He suggests that drawing such sharp lines risks obscuring fine details of a phenomenon or object, and so we might fail to develop appropriate theoretical interpretations[10]. When chemists reach for contrived measures like atomic charges and oxidation numbers — and chirality — to help us sort through chemistry, we want to choose well. But as much as we may find one model more useful than another, or one that better matches the underlying framework we prefer for representing of molecules, there is no one right choice. Moreover, in our failure to reveal our differences over chirality to students, we are also failing to show them the multiplicity of ways chemists see molecules and perhaps depriving them of the tools they might wield to develop new theories and new frameworks. That we don't all agree on whether chirality is binary or not is a feature, not a bug!

Are some molecules more chiral than others? It obviously depends on how you define chirality, but I suspect it depends as much on what you imagine a molecule is. In any case, it's not an argument that can be won. As my students might say these days of many relationships: it's complicated. ❐

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