

macroscopic label, as in (*S*)(+) and (*R*)(–)-CHFCIBr in Figure 1. Here, *R* (for *rectus*) and *S* (for *sinister*) are the absolute configurations in the standard nomenclature³.

Optical rotation and circular dichroism (a small difference in the absorption of right- and left-circularly polarized light) at visible and ultraviolet wavelengths measure natural optical activity in the electronic spectrum of a molecule. It had long been appreciated that extending natural optical activity into the vibrational spectrum could provide more detailed and reliable stereochemical information, because a vibrational spectrum contains many more bands sensitive to the details of the molecular structure⁴. This was finally achieved in the early 1970s, when vibrational optical activity was first observed in small chiral molecules in fluid media using two complementary techniques: a circular-polarization dependence of vibrational Raman scattering of visible laser light⁶, and circular dichroism of infrared radiation⁷. These are now known as Raman optical activity (ROA) and vibrational circular dichroism (VCD), respectively.

Haesler *et al.*¹ tested the limits of a new ROA instrument developed in their laboratory by applying it to a chiral molecule for which it would be very difficult, if not impossible, to determine the absolute configuration using any other existing physical technique. They chose (*R*)-[²H₁,²H₂,²H₃]-neopentane, which is C(CH₃)₄ rendered chiral through isotopic substitution — deuteration — of three of the four methyl groups (Fig. 2). In other words, chirality was induced by replacing ordinary hydrogen (¹H) in three of the four CH₃ groups with deuterium (²H, or D), producing one each of CH₃, CH₂D, CHD₂ and CD₃.

Haesler and colleagues' synthesis¹ of (*R*)-[²H₁,²H₂,²H₃]-neopentane with high enantiomeric purity was itself an achievement, and was attempted only after calculations⁸ suggested that the ROA might be measurable. It is a gas at room temperature, but was collected as a

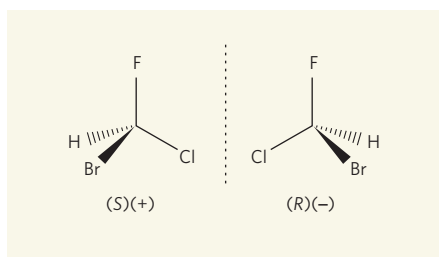


Figure 1 | Chiral archetype. Lord Kelvin's classic definition of chirality² emphasizes the non-superposability of a chiral object and its mirror image, exemplified here by the enantiomers of bromochlorofluoromethane, CHFCIBr.

liquid for ROA measurements by distilling into a cooled capillary tube that was subsequently sealed. Three distinct orientations of each of the CH₂D and CHD₂ groups are possible, generating nine distinct rotational 'conformers' that all contribute to chiroptical observable properties and tend to cancel.

The ROA turned out to be just detectable at the limit of sensitivity of the authors' new instrument, which measures tiny circularly polarized components in the vibrational Raman bands down to a few parts in 10^{–5} of the total band intensity (Fig. 2). This instrument separates the right- and left-circularly polarized components of the backscattered light and collects them into the ends of two fibre-optic strands. This allows separate Raman spectra for the right- and left-circularly polarized components of the scattered light to be dispersed simultaneously, one above the other, onto a multichannel detector. Subtraction then provides the required ROA spectrum. Because the right- and left-circularly polarized Raman spectra are measured during the same acquisition period, the 'flicker noise' arising from dust particles, density fluctuations, fluctuations in laser power and so on cancels out, resulting in greatly superior signal-to-noise characteristics compared with earlier designs of the instrument. Other novel features provide a high

degree of suppression of the spurious signals that can plague this type of delicate polarization measurement.

Haesler *et al.*¹ simulated the ROA spectrum of the chiral neopentane using *ab initio* quantum-chemical protocols⁸. They summed the partially cancelling ROA spectra computed for each of the nine possible rotational conformers present at thermal equilibrium. The resulting theoretical spectrum was close enough to the observed spectrum with respect to the signs and magnitudes of the ROA bands for the *R* absolute configuration to be assigned unequivocally to their neopentane sample. This highlights the power of vibrational optical activity generally — VCD (ref. 9) as well as ROA — for determining absolute configuration: as there are numerous bands, a calculation that reproduces the signs of most, if not all, of them correctly will provide an absolute configuration on which one might stake one's life.

As well as probing the most delicate sources of chirality in small molecules, ROA provides valuable information about very large chiral molecular structures, such as proteins, sugars and nucleic acids¹⁰. Even intact viruses are accessible to ROA measurements, and from these, for instance, details about the folds of coat proteins and the nucleic-acid structure may be deduced. The power of chiroptical spectroscopic techniques for biomolecular applications derives from their ability to cut through the complexity of conventional spectra (which are 'blind' to chirality), to reveal three-dimensional information about the most rigid, twisted chiral parts of the structure. These are usually found within the backbone in large biomolecules, and generate the largest chiroptical signals. The decisive advances in ROA instrumentation reported by Haesler *et al.*¹, backed up by powerful theoretical simulation techniques, should facilitate widespread exploitation of vibrational optical activity in chemical and biomolecular science. ■

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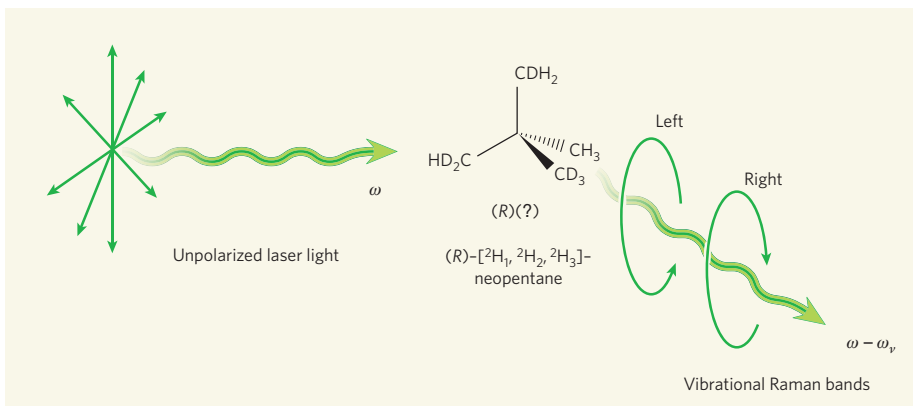


Figure 2 | Determination of the absolute configuration of (*R*)-[²H₁,²H₂,²H₃]-neopentane. Unpolarized laser light incident on the deuterated molecule produces tiny but measurable right- or left-circularly polarized components in the bands of the resulting vibrational Raman spectrum. ω is the angular frequency of the incident visible laser beam and $\omega - \omega_v$ that of one of the many vibrational Raman bands. By comparing these measurements with the expectations of *ab initio* simulations, Haesler *et al.*¹ could assign the *R* absolute configuration to their sample. No (+) or (–) sign is associated with the *R* absolute configuration because there was insufficient material to measure the corresponding optical rotation.

1. Haesler, J., Schindelhof, I., Riguet, E., Bochet, C. G. & Hug, W. *Nature* **446**, 526–529 (2007).
2. Lord Kelvin Baltimore Lectures (Clay, London, 1904).
3. Eliel, E. L. & Wilen, S. H. *Stereochemistry of Organic Compounds* (Wiley, New York, 1994).
4. Barron, L. D. *Molecular Light Scattering and Optical Activity* 2nd edn (Cambridge Univ. Press, 2004).
5. Bijvoet, J. M. *et al.* *Nature* **168**, 271–272 (1951).
6. Barron, L. D., Bogaard, M. P. & Buckingham, A. D. *J. Am. Chem. Soc.* **95**, 603–605 (1973).
7. Holzwarth, G. *et al.* *J. Am. Chem. Soc.* **96**, 251–252 (1974).
8. Hug, W. & Haesler, J. *Int. J. Quantum Chem.* **104**, 695–715 (2005).
9. Stephens, P. J. & Devlin, F. J. *Chirality* **12**, 172–179 (2000).
10. Barron, L. D. *Curr. Opin. Struct. Biol.* **16**, 638–643 (2006).

Correction

In the News & Views Q&A article "Organometallic chemistry: C–H activation" by Robert G. Bergman (*Nature* **446**, 391–393; 2007), the e-mail address given for the author was incorrect. The correct address is rbergman@berkeley.edu