On One Hand but Not the Other: Chirality, Quantum Chemistry, and Drug Design

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Chiral molecules are characterized in part by their lack of symmetry: specifically, their mirror images (referred to as *enantiomers*) cannot be superimposed. Such molecules play a vital role in the chemistry of life for two reasons: First, most biologically active species — sugars, enzymes, drugs, and even DNA — are not only chiral, but *homochiral*, i.e., only one of the two possible enantiomers tends to occur in nature. Second, the two enantiomers often display very different chemical behavior when reacting with other chiral molecules. A practical example is limonene [1-methyl-4-prop-1-en-2-yl-cyclohexene]: while one enantiomer smells of oranges, the other has the odor of turpentine. A more serious example is the active ingredient in the popular medicine Robitussin [3-methoxy-17-methyl-(9α,13α,14α)-morphinan]. While one enantiomer is a mild cough supressant, the opposite enantiomer is a potent halucinogenic narcotic. For such reasons, synthetic organic chemists expend considerable effort and time attempting to identify the enantiomeric composition (known as the *absolute configuration*) of a given compound.

How can one distinguish between enantiomers? X-ray crystallography is one possibility, but this requires the presence of a heavy (third-row) element and a high-quality single crystal (an unfortunately rare occurrence). In other cases, organic chemists resort to expensive asymmetric total synthesis, i.e. the generation of a selected enantiomer from simpler compounds of known chirality. After the synthesis is complete, they compare the compound's spectroscopic properties — such as optical rotation or circular dichroism spectra — to the original sample. If the properties match, the task is done; if not, try, try again. The analysis is often made more complicated by the need to distinguish not only enantiomers, but *stereoisomers* (molecules with the same connectivity, but with difference three-dimensional structures), of which there may be dozens, hundreds, or even thousands of possibilities.

An alternative approach is to use quantum mechanical models to calculate the relevant spectroscopic data. If such models are sufficiently fast, accurate, and reliable, then they may be able to identify the absolute configuration of the molecule in advance of time-consuming synthesis. This lecture will discuss the current state-of-the-art in first-principles calculations of optical rotation and circular dichroism spectra. We will examine the physical principles necessary for a realistic simulation of such properties, including their quantum mechanical foundations, and the contribution of solvent, vibrational, and temperature effects.

For additional information:

- "The Current State of *Ab initio* Calculations of Optical Rotation and Electronic Circular Dichroism Spectra," T.D. Crawford, M.C. Tam and M.L. Abrams, *J. Phys. Chem. A* **111**, 12057-12068 (2007).
- "The *Ab Initio* Calculation of Molecular Chiroptical Properties," *Theo. Chem. Acc.* **115**, 227-245 (2006).