Amplified Vibrational Circular Dichroism

S.M. Rosa Domingos

AMPLIFIED VIBRATIONAL CIRCULAR DICHROISM

by

Sérgio Miguel Rosa Domingos

Popular Summary

Handedness is a subtle yet one of the most important properties of matter. At the molecular scale it manifests itself most prominently in chiral molecules, molecules of which the mirror image cannot be brought to coincide with itself. This apparently simple property has serious implications, most notably in the chemistry of life where the activity of two stereoisomeric forms of the same molecule can be vastly different. The development of tools to assign unambiguously the absolute configuration of chiral molecules is thus of major importance. Research conducted over the last two decades has culminated in the rise of *vibrational circular dichroism* (VCD, the differential absorption of left and right circularly polarized light) as a highly-sensitive spectroscopic technique for this purpose. VCD is capable of differentiating chiral molecules from their mirror image counterparts using vibrational signatures. However, for many biomolecules in their naturally occurring environment, VCD lacks sufficient signal intensity to be used as a standard and widely applicable analytical tool.

This thesis is concerned with the development and application of novel strategies to amplify the VCD of chiral molecules. Since its first experimental observation, it has been clear that VCD has tremendous potential as a spectroscopic tool in the investigation of molecular stereochemistry in general, and of chirality in biomolecular systems in particular. Various experimental breakthroughs as well as advances in the theoretical description of VCD and their implementation in quantum chemical programs have revolutionized the field in the last two decades, and by now VCD has become a powerful analytical tool of the pharmaceutical industry in the determination of absolute configurations of chiral drugs in early and late stages of synthesis and production. At the same time, it is generally acknowledged that the use of VCD is still far from what it potentially offers. The underlying reason is simple: VCD signals are generally very small, so it is difficult to obtain acceptable signal-to-noise ratios. There is thus much to gain if one could overcome the intrinsic small-signal limitations of VCD. This is an ambitious goal, but one that can be reached, as is demonstrated by the work in this thesis. With newly designed experiments that combine spectroscopy and electrochemistry, it is demonstrated that VCD signals can be amplified by several orders of magnitude and thus extend the applicability of VCD for a larger class of molecular systems not accessible before. At the same time, these experiments pave the way for the study of chirality in a time-resolved manner and at specific locations within a large molecular system.