Induced Chirality

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Induced Chirality in Achiral Media—How Theory Unravels Mysterious Solvent Effects**

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Chirality plays an important role in many branches of chemistry—from stereochemical aspects in synthetic organic and inorganic chemistry, the chemistry of peptides and sugars in biomolecular chemistry, to the implications of chiral substances in pharmaceutical chemistry. The structural investigation of chiral compounds is often based on chiroptical spectroscopic techniques such as electronic or vibrational circular dichroism (ECD or VCD), optical rotation (OR), optical rotatory dispersion (ORD), as well as Raman optical activity (ROA).[1] All of these methods give spectra in which the signals for the two enantiomeric forms of a chiral compound differ in sign, and thus allow a molecule to be distinguished from its mirror image. None of the methods are, however, able to provide the information as to which spectrum belongs to which of the two possible forms, and thus further information is necessary for assignment of the absolute configuration.

Theoretical methods can provide the missing link between chiroptical spectra and the desired structural information. They allow the calculation of the chiroptical spectra for an enantiomer with a predefined absolute configuration. If this is done for both forms of an optically active molecule, the absolute configuration of the enantiomer studied in an experiment can be assigned by comparison to the predicted spectra. In many cases an unambiguous assignment can be made (see the "ideal situation" in Figure 1). Recent studies have shown that, even with flexible molecules, a combination of several spectroscopic techniques (for example, ECD, VCD, OR) in conjunction with theoretical analysis can lead to assignments of the absolute configuration.[2] ROA spectroscopy is also a powerful technique in this context, as recently demonstrated for chiral deuterated compounds.[3] Further advances can be anticipated from ROA in regard to studies of biomolecules, since theoretical studies now make it possible to verify empirical relationships between spectral intensities and structural features.[4]

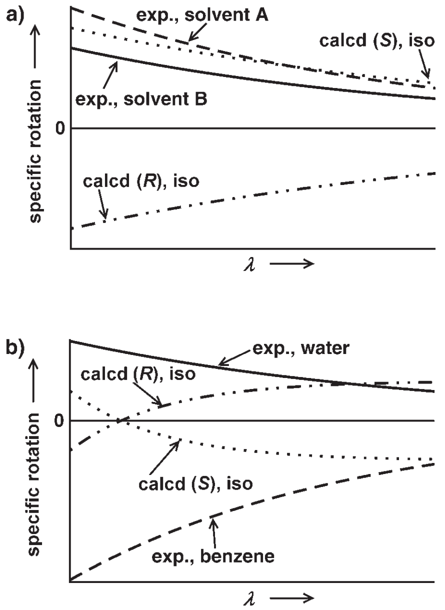

Figure 1. Schematic representation of calculated (calcd) and experimental (expt.) ORD spectra for a chiral compound. a) Ideal situation: Experimental spectra for different solvents are similar; the assignment of absolute configurations is possible by comparison with the calculated spectra of the isolated (iso) *R* and *S* enantiomers. b) Qualitative situation for methyloxirane as inferred from Refs. [9,11]: Experimental spectra differ with different solvents; spectra calculated for isolated molecules allow no conclusions to be drawn about the absolute configurations.

One of the factors that limit the applicability of theoretical methods is the influence of the environment on the molecular properties, and many unusual solvent effects[5] are known for chiroptical spectra. Besides changes in the electronic structure of the solute, a variety of structural effects can play a role; for example, the formation of optically active complexes between the solvent and solute, a different stabilization of the different conformations, and a change in the aggregation behavior of the chiral molecule.[6]

While it is often helpful to consider a solvent as just a dielectric continuum, the analysis of complex structural effects on chiroptical spectra requires that the atomistic structure of the solvent needs to be considered. Hybrid methods of quantum mechanics and molecular mechanics (QM/MM) or density-based QM/QM partitioning methods

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can be helpful in this context if an understanding in terms of the local properties of the solute is desired, as has recently been demonstrated for ECD spectroscopy.[7] The identification of important dynamic solvent effects is possible by means of either classical or first-principles-based molecular dynamics approaches.[8]

A qualitatively different type of solvent effect on a chiroptical property has now been described by Mukhopadhyay et al.[9] Their study addressed the optical rotatory dispersion of methyloxirane, which had thus far been a challenge for theoretical methods. The optical rotation of (*S*)-methyloxirane is positive in water, but in benzene it has rather large negative values, particularly at short wavelengths. The assignment of the absolute configuration by comparison with spectra computed neglecting solvent effects would not be possible in this case, since even the qualitative features of the ORD curves, which are depicted schematically in Figure 1 b, differ in different solvents.

Previous studies investigated the influence of different electronic–structure methods, vibrational corrections, and solvent effects by means of a continuum model,[10] but the change in the ORD spectrum with different solvents could not be explained. In another publication,[11] it was shown that inclusion of explicit water molecules in the spectra calculations shifts the optical rotation angles for methyloxirane close to the experimental results obtained in water. Interestingly, the solvent effect could be related to the orientation of the water molecules in the first solvation shell. This finding appears reasonable, since hydrogen bonding may lead to a preference for certain structures. The contribution of the hydration shell to the total optical rotation was shown to be negligible. The solvent effect of water on the ORD of methyloxirane can thus be traced back to specific solvent–solute interactions, which agrees with the common picture that the solvent modulates the solute properties.

Mukhopadhyay et al. could show that the solvent effect in benzene is completely different.[9] Explicit solvent molecules were employed in snapshots obtained from a Monte Carlo simulation of methyloxirane in benzene, for which ORD spectra were determined by means of time-dependent density functional theory. This simulation reproduced qualitatively the experimental ORD in benzene, in contrast to calculations based on implicit solvent models, which give a qualitatively different picture at short wavelengths.

What is more important is that methyloxirane itself apparently makes only a minor direct contribution to the recorded signal: In a computational experiment where the same snapshots were analyzed again after the solute molecule had been removed so as to decompose the total ORD signal, so that only the empty solvation shell remains (Figure 2), there was only a small change in the overall signal, and the qualitative features of the ORD spectrum remained the same. This finding means that the presence of the solute imprints a chiral structure on the inner solvation shell.

At first glance, this effect appears similar to the chiral amplification observed for some optically active dopants in liquid crystals.[12] However, as a solvent, benzene is not a mesogenic phase, and the imprinting is a dynamic and local effect. On average, the solvent cage around the chiral molecule is itself chiral, and its response to the external electromagnetic field dominates the total optical rotation in solution. The authors verified their results by a simulation with the other enantiomer and a blind test for the nonchiral solute ethylene oxide in benzene.

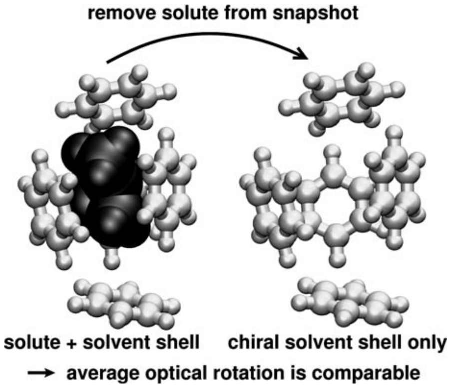

Figure 2. Illustration of the computational test carried out in Ref. [9] to decompose the optical rotation of the solute and solvent shell. The optical rotation sampled over snapshots of the solute and solvent is comparable when calculated for the full system (solute + solvent; left) or for the empty solvent shell only (solute removed from the snapshots; right). Graphics were created with the program VMD.[15]

Nevertheless, further investigation of this surprising phenomenon may be helpful to fully explore how sensitive this effect is to details of the simulation, and in particular whether the size or number of molecules in the solvent shell can lead to biased results. Since this chiral imprinting effect can be expected to be quite short-ranged, outer solvation shells, which could not be considered by Mukhopadhyay et al. in the calculation of the ORD spectra, will most probably not make a large direct contribution to chiroptical properties.

Structural aspects resulting from a molecule dissolved in a particular medium have of course been discussed and analyzed before. The debate on the iceberg effect, that is, an icelike structure around hydrophobic compounds in aqueous solution,[13] is just one example.

The possible influence of chiral structures of solvent shells around chiral solutes has also been addressed before. Fidler et al. found both theoretical and experimental evidence for this effect by comparing molecular dynamics simulations with the temperature dependence of the ECD spectrum of bromocamphor.[14] They reasoned that the change in the ECD spectrum of a rigid chiral solute with temperature must be solely attributed to the temperature effect on the structure of the solvent shell and thus provides a means to assess the solvent contribution.

However, the fact that chiroptical properties are dominated by the response of an inherently nonchiral solvent, in which locally chiral substructures are dynamically induced by a chiral solute, is indeed astonishing. It will certainly motivate further studies to determine if this is a general effect that also occurs in other chiral systems or for other chiroptical properties. However, such a direct solvent contribution is less likely to play a role in VCD and ROA spectroscopy since the solvent vibrations can often be rather easily distinguished from those of the solute.

Many types of interactions between a solvent and a solute are straightforward to understand in terms of certain solvent properties, but the results reported in Ref. [9] demonstrate that care has to be taken when solvent effects are oversimplified. It also shows that theory offers a unique possibility to uncover the mechanisms of solvent effects at a molecular level, even in cases where they may seem highly counterintuitive.

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