Solvent Ordering

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Contribution of a Solute's Chiral Solvent Imprint to Optical Rotation**

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A long-standing challenge in molecular stereochemistry is to assess the "chiral imprint" of a chiral solute on the surrounding solvent. The solute's influence on ordering the solvation sphere should contribute to the optical rotatory dispersion (ORD). The magnitude of this contribution, however, has never been determined. We now show that for (*S*)-methyloxirane in benzene, the chiral imprint in the solvent sphere dominates the optical rotation (OR). To the best of our knowledge, this is the first evidence in support of a chiroptical property dominated by the dissymmetry induced in the solvent.

The observed specific OR angles and ORD of chiral molecules in solution are well known to be strongly influenced by solvent–solute interactions. For example, (*S*)-methyloxirane has a positive OR in water and a negative OR in benzene.[1] Thus, theoretical modeling to understand both the sign and magnitude of OR is of interest. Access to experimental gas- and solution-phase OR data[2] and to modern linear-response OR calculations[3] provides the tools needed to dissect solute and solvent contributions to OR. Recently, we showed that water–methyloxirane interactions in an aqueous solution dominate the observed ORD;[4] in contrast, for methyloxirane in benzene, we show here that the chiral solvent ordering is the dissymmetry that dominates the ORD.

The solvent dependence of OR for chiral molecules has been computed recently using coupled-cluster (CC) and time-dependent density functional theory (TD-DFT) using implicit continuum solvent methods.[5] Kongsted et al. used CC combined with a continuum solvent description to calculate the influence of solvent on the OR of (*S*)-methyloxirane.[6] The authors concluded that continuum models: 1) do not reproduce the experimentally observed solvent shifts of the ORD spectra as a function of solvent; and 2) cannot describe the contribution of the chiral solvent structure induced by the chiral solute to the observed OR. Explicit solvent models capture solvent/sign anomalies in the OR and allow attribution of contributions to OR arising from a solute's chiral imprint on its environment as shown below.

In our study, Monte Carlo (MC) simulation of solute and solvent combined with TD-DFT methods were used to compute the OR of (*S*)- and (*R*)-methyloxirane. Thus, the off-resonance ORD of methyloxirane in benzene was calculated using an explicit solvent model. MC simulations of (*S*)- and (*R*)-methyloxirane in an equilibrated box of benzene were performed in a NPT ensemble, using BOSS.[7] The all-atom OPLS-AA[8] force field was used in the MC simulations. OR values were computed using TD-DFT implemented in Turbomole 5.6[9] with different combinations of the BP86/BLYP correlation-exchange functionals and SV/SVP/aug-cc-pVDZ basis sets at four wavelengths. All calculations were performed with the resolution of identity approximation (RI-J).[10] Grimme et al. showed that accurate TD-DFT predictions of frequency-dependent OR for large molecules can be achieved efficiently with the RI-J approximation;[11] structures used in the TD-DFT analysis were taken from the MC simulations. Each structure had benzene molecules within a cut-off distance of 0.5 nm from the center-of-mass of methyloxirane. The total number of benzene molecules within the cut-off distance was eight to ten. The specific rotation was averaged over an ensemble of 1000 structures at each wavelength to generate the ORD of (*S*)- and (*R*)-methyloxirane in benzene. The error estimate of the average OR was calculated using a renormalization group blocking method.[12] A more detailed description of the MC simulation setup, the TD-DFT calculations, and the ORD measurement appears in the Supporting Information.

Figure 1 shows the computed ORD spectra of (*S*)- and (*R*)-methyloxirane in benzene using explicit and implicit solvent models. The ORD spectra were calculated using the BP86 functional with the SVP basis set. Calculations using a dielectric continuum based on the COSMO model[13] (an implicit solvent model) with a benzene dielectric constant of 2.0 do not provide the correct sign of the OR approaching resonance from long wavelengths. Explicit solvent, however, correctly predicts the sign of the OR at these wavelengths.

The computed ORD spectra of (*S*)- and (*R*)-methyloxirane based on explicit solvent models are related by a simple reversal of sign, as expected. Interestingly, in the methyloxirane–benzene system, the OR of the solvent imprint (benzene cluster without the chiral solute) is comparable to the total OR of the system (solute+benzene) at all wavelengths (Figure 1). Thus, the chiral solvent ordering of benzene, or the chiral imprint, dominates the ORD. Chiral solutes are known to induce chiral solvent ordering. Fidler et al., for example, showed that dissymmetric solvent organization around a chiral solute accounts for 10–20% of the total circular dichroism intensity attributable to an optically active chromophore.[14] Our ORD calculations for methylox-

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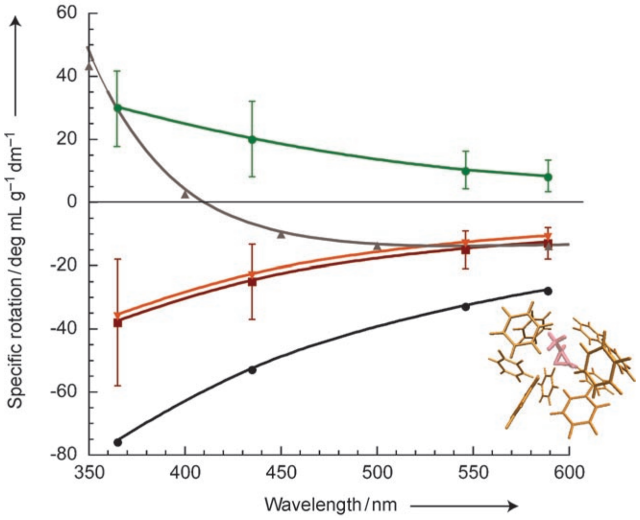

Figure 1. Optical rotatory dispersion (ORD) of methyloxirane–benzene clusters (shown in the MC structure snapshot) (*S* solute: ■, *R* solute: ●), and the solvent imprint (▼) for the *S* enantiomer computed using explicit solvent models. Calculations used TD-DFT/BP86 functional and SVP basis set, and *S* solute in an implicit solvent (▲) based on the COSMO model. The error bars are calculated using the blocking method.[12] For comparison experimental values with the *S* solute (●) are also given (see the experimental procedure in the Supporting Information for details).

irane in benzene attribute the chiroptical signature to the dissymmetric benzene cluster around the methyloxirane (see the MC structure snapshot in Figure 1). Morimoto et al. recently showed that the attractive interactions between benzene rings results in the formation of a cyclic trimeric dissymmetric benzene cluster in solution, which is reminiscent of the assembles seen in our MC simulations.[15]

Computed OR values are very sensitive to molecular conformation.[3g,h] Thus, the difference in the computed and experimental OR values (Figure 1) might arise from the approximations in the description of molecular interactions in the MC simulation of methyloxirane in benzene arising from the force field limitations as well as approximations in the quantum mechanical calculations.

The ORD spectra of the chiral solvent imprint were also computed using different combinations of BP86/BLYP correlation exchange functionals and SV/SVP/aug-cc-pVDZ basis sets (see Figure 1 S in the Supporting Information). We found no significant variation in the computed ORD spectra with the choice of functional or basis set. Previous theoretical studies suggested that TD-DFT methods with the B3LYP functional and (at least) an aug-cc-pVDZ basis set are required to produce reliable gas-phase OR predictions.[16] We emphasize that using a nonhybrid DFT functional, such as BP86/BLYP, permits use of the RI-J approximation implemented in Turbomole 5.6 to reduce the computational time by six orders of magnitude compared to calculations with hybrid functionals such as B3LYP; this is especially important for performing 20000 OR calculations of benzene–methyloxirane clusters (with 106–130 atoms) using varied functionals and basis sets. Ensemble-averaged calculation of OR for chiral molecules in solution gives similar results with pure and hybrid functionals, as previously shown for ORD calculations of methyloxirane in aqueous solution.[4] Recently, Hassey et al. used single-molecule spectroscopy to show that the chiroptical response of molecules spans a range of large positive and negative values, and hence they suggested that, in the solution phase, the measured chiroptical response represents an ensemble average of orientations and solvent interactions.[17]

In order to show that the predicted chiral solvent structure in methyloxirane–benzene solution is not an artifact of the methodology, we also computed the OR of an achiral ethylene oxide–benzene solution (see Figure 2S in the Supporting Information). The ORD was calculated using MC simulation and TD-DFT (with BP86/aug-cc-pVDZ), as described above for the methyloxirane–benzene system. Each ethylene oxide–benzene structure snapshot from the MC simulation is dissymmetric, with a nonzero contribution to the OR: the ensemble-averaged OR value, however, is close to zero, as expected.

Our results indicate that the contribution to OR of a dissymmetric solvent imprint can exceed the OR contribution of the solute itself. Implicit solvent models are not sufficient to describe the imprint effects because they lack explicit inclusion of the solvent electronic structure. A judicious choice of solvent modeling is essential to describe the chiroptical signature of molecules in solution.

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