

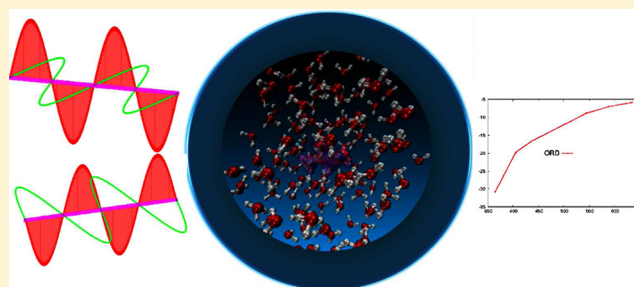
The Optical Rotation of Methyloxirane in Aqueous Solution: A Never Ending Story?

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ABSTRACT: The long-standing problem of the calculation of the optical rotation (OR) of (R)-methyloxirane in aqueous solution at different wavelengths is solved by means of a novel gauge-invariant computational protocol able to take into account at the same time for intramolecular averaging specific and bulk solvent effects, leading for the first time to a quantitative agreement (both sign and absolute value) between computed and experimental OR values at several frequencies.



INTRODUCTION

The inclusion of solvent effects in the calculation of chiroptical properties and spectroscopies can be crucial to gaining accurate descriptions.^{1,2} In fact, solvent effects can be huge, due both to polarization effects and to supramolecular clustering patterns which cannot be neglected whenever strong interactions, such as hydrogen bonding, dominate the solute–solvent interaction.

Methyloxirane is a well-known example of such a behavior^{3–13} and has been studied in the literature with particular attention to both solvent effects^{3–8} and vibrational corrections.^{3,8–12} Quantum Mechanical (QM) computations have been performed both at the coupled cluster and DFT levels of theory, and it has been shown^{10–14} that for an incident light frequency of 589 nm, the DFT level, using the popular B3LYP exchange correlation functional in combination with the augmented, double- ζ quality aug-cc-pVDZ basis set, provides accurate results, comparable to CCSD with very extended basis sets.¹⁴ The long-range corrected CAM-B3LYP functional has also been employed in the perspective of exploring a wider spectral range.¹⁵

A thorough study on solvent effects employing continuum solvation approaches within the Polarizable Continuum Model (PCM)¹⁶ formalism has been recently performed by some of the present authors:³ such a study underlines how continuum solvation is a viable tool to describe OR when solvent effects are dominated by bulk contributions, i.e., specific solute–solvent interactions can be neglected. However, in order to obtain reliable results, the basic PCM formulation was shown not to be adequate, because local field effects should be included in the modeling of the electronic property.^{3,17} In addition, vibrational corrections calculated with the inclusion of anharmonic terms give a substantial contribution to the final computed property, and therefore a reliable modeling of such terms in solution with the possible inclusion of nonequilibrium effects¹⁸ has to be achieved in order to finally recover the

experimental findings. However, in cases dominated by specific solute–solvent interactions, this refined model is not able to correctly reproduce solvent effects, which can be large enough to change the sign of methyloxirane OR. This is the case for benzene, where the so-called chiral imprint⁶ has been shown to be the dominating effect, and for water. A previous study by Mukhopadhyay et al.^{4,5} focused on the evaluation of the role of hydrogen bonding in the calculation of the OR of methyloxirane. This study employed a cluster model, where the solute molecule was redefined in terms of a large number of clusters including only a limited number of solvent molecules, and the full clusters were then treated quantum-mechanically in the evaluation of the OR.^{4,6} These authors then demonstrated a large effect of specific solute–solvent interactions in determining the sign of the calculated OR. A quantitative agreement with the experiments was however not achieved, that due presumably to the neglecting of intramolecular vibrational averaging effects, as well as solvent bulk effects. On the basis of the previous studies, which indicate that any of the terms of the solute–solvent interaction contribute to a similar extent to determine the calculated OR of (R)-methyloxirane, in this letter we will report on a computational protocol able to take into account all of these effects, and for the first time we will gain a quantitative agreement (both sign and absolute value) between computed and experimental OR values at several frequencies.

The protocol which we will exploit is based on an integrated QM/MM/PCM model that we have recently introduced, named QM/FQ/PCM, which is able to provide a more balanced and complete treatment of all the main effects playing a role in tuning the overall spectroscopic outcome.^{19–22} In particular, the QM core is treated by hybrid density functionals (here, B3LYP and CAM-B3LYP) which, coupled to a proper

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basis set (here the aug-cc-pVDZ), provide quantitative results. Next, the MM layer is treated by a polarizable force field (described in terms of fluctuating charges, FQ)²³ and coupled to PCM in order to have a proper description of bulk effects (QM/FQ/PCM).^{19–22} Thanks to the implementation of a fully variational treatment, of analytical first and second derivatives, and due to the extension to calculate magnetic response properties with GIAOs,²⁴ our methodology can be exploited to perform a fully consistent study of semirigid chiral solvents in condensed phases, with the further account of vibrational effects. To the best of our knowledge, the present study represents the first attempt to calculate mixed electric-magnetic response properties of chiral solutes with a full QM/polarizable MM/PCM approach. In this respect, we note that the extension of the QM/FQ/PCM approach to treat magnetic properties is far from trivial: in fact, the extension of the model to GIAOs requires the formulation and implementation of explicit additional terms, similarly to what is needed to extend the PCM to GIAOs.^{8,9} This topic will be the subject of a future publication.²⁴

Coming back to the topic of the present letter, the strategy which is here proposed is based on a few crucial assumptions: (1) Vibrational contributions are considered by adding to the electronic property computed at the equilibrium geometry a correction pertaining to the nuclear wave function, calculated by including anharmonic and solvent effects. (2) Following what has already been reported by some of the present authors,³ the contribution arising from the first normal mode, which corresponds to the rotation of the methyl group around the C–C bond, is discarded. We are in fact interested in modeling the OR in a solvating environment, where such a motion is poorly described within a normal mode picture and is physically a hindered rotation, which cannot be treated as a free motion as if the molecule were isolated. As reported in a previous paper by some of us,³ the values obtained in this way are in quantitative agreement with previous ones obtained by Ruud and Zanasi¹⁰ on the same system. (3) The motions of the solvent are treated classically by means of MD simulations, from which several snapshots are extracted and used to compute the OR. Vibrational corrections are assumed to be independent of the solvent configurations, and therefore the MD simulation is performed by freezing the (R)-methyloxirane geometry.³

On the basis of such assumptions, the following computational protocol is identified: (1) geometry optimization of (R)-methyloxirane, accounting for the effects of the aqueous environment by means of the PCM; (2) calculation of vibrational corrections with the inclusion of PCM terms as reported in ref 3; (3) generation of 2000 snapshots on the basis of a MD simulation performed by using a fixed methyloxirane geometry as obtained at step 1; (4) for each snapshot, cutting a spherical cluster centered on the solute and using it to calculate the OR at the QM/FQ/PCM level; (5) averaging the calculated OR over the snapshots and adding the vibrational corrections to the average value.

COMPUTATIONAL DETAILS

The geometry of (R)-methyloxirane was optimized with analytical gradients using the DFT/aug-cc-pVDZ level of theory and the C-PCM^{27,28} to represent the aqueous environment ($\epsilon = 78.3553$), employing both the B3LYP and the CAM-B3LYP functionals. The same level of theory was

used to calculate vibrational corrections according to the VPT2 scheme.²⁹

A 25 ns MD simulation of (R)-methyloxirane in a pre-equilibrated box of 2175 SPC water molecules was performed in the NPT ensemble using GROMACS.^{30–33} The leapfrog integrator was used with a 1 fs time step. All bonds were kept rigid using the settle algorithm³⁴ for water; the geometry of the solute was kept rigid through all the simulation. For electrostatic interactions, the particle-mesh Ewald summation method was used.³⁵ The pressure was held at 1 bar using the weak-coupling scheme³⁶ with a coupling constant of 10 ps and an isotherm compressibility of $5 \times 10^{-5} \text{ bar}^{-1}$. Each component of the system (i.e., methyloxirane and water) was coupled separately to a temperature bath at 300 K, using the Berendsen thermostat,³⁶ with a coupling constant of 0.5 ps. The all-atom OPLS-AA³⁷ force field was used for the solute.

A total of 2000 snapshots were extracted from the last 20 ns of the MD simulation (one snapshot every 10 ps). For each snapshot, a sphere centered in the solute's geometrical center was cut. Three different cutting radii were employed: 12 Å, 14 Å, and 16 Å. A 1.5 Å larger radius was used for the PCM spherical cavity. For each snapshot, the OR of methyloxirane at different wavelengths was calculated with the QM/FQ/PCM model, using either the B3LYP or the CAM-B3LYP DFT functional with the aug-cc-pVDZ basis set for the solute, the SPC FQ parameters given by Rick et al.,²³ and the C-PCM, by imposing a dielectric constant of 78.3553 for bulk water. All the DFT calculations were done by using a locally modified version of the Gaussian package.³⁸

RESULTS

OR values at 589 nm obtained in vacuo and with the addition of solvent effects by means of the PCM or by the strategy just outlined are depicted in Figure 1, which also reports the

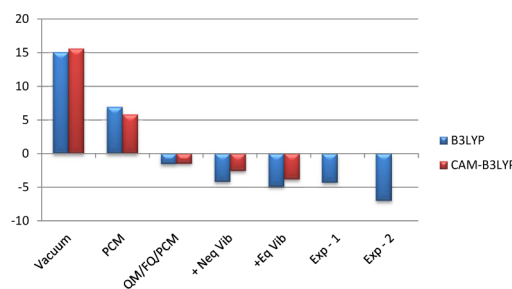


Figure 1. Calculated OR at 589 nm of (R)-methyloxirane OR in vacuo and aqueous solution, as obtained with the B3LYP and CAM-B3LYP functionals and by exploiting different approaches to model the environment (see text). Experimental data labeled Exp-1 are taken from ref 39 and Exp-2 from ref 4.

experimental value, taken from refs 39 and 4. Both the B3LYP and CAM-B3LYP results are reported. Notice that the gas-phase OR of methyloxirane has been measured by means of cavity ring-down polarimetry by Wiberg et al.⁴⁰ at two discrete wavelengths; the authors also compared their measured values to DFT calculations (without vibrational corrections), which showed a fairly good agreement.

The calculation in vacuo completely fails at reproducing the experimental data in solution, and in particular, not only the absolute value is wrong but especially the sign. The inclusion of the continuum dielectric (PCM) goes in the right direction, i.e., lowers the absolute value of the property; however, the

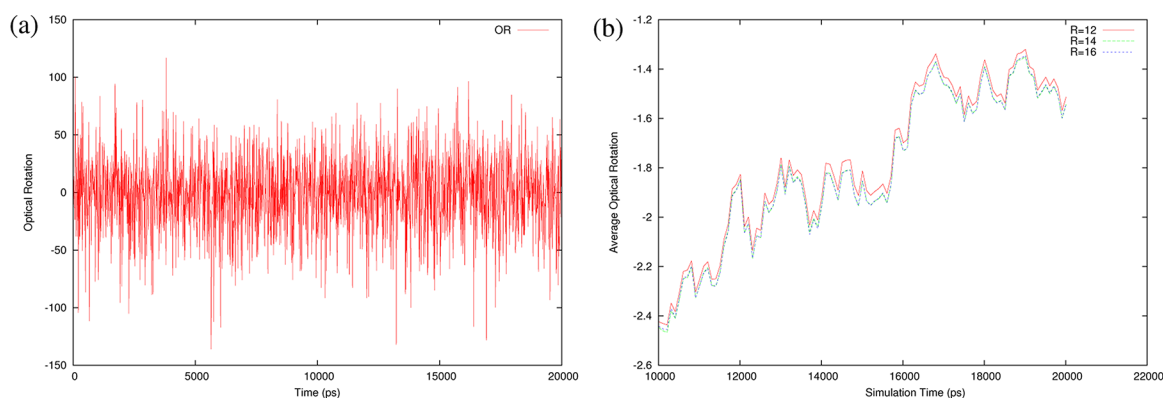


Figure 2. Instantaneous and average values of (R)-methyloxirane OR calculated at 589 nm. (a) OR instantaneous values (the 16 Å cutting radius is considered). (b) Average values as a function of the simulation time for three different cutting radius values.

computed sign remains incorrect. The correct sign is instead recovered by exploiting the QM/FQ/PCM approach: the absolute value is slightly underestimated, but when vibrational corrections are included in the average value, a quantitative agreement with the experiments is obtained. This is a success for our QM/FQ/PCM model, which is able to compute an extremely sensitive-to-the-environment property, in a complex, structured environment dominated by hydrogen bonding interactions. Notice that two different experimental data are reported in Figure 1, obtained by different sources;^{4,39} they can provide a qualitative estimate of the error bar of the experiment, and in any case our calculated values are within such an error bar. Finally, the effect of the choice of a different density functional is small, as B3LYP and CAM-B3LYP give substantially the same agreement with the experiment at this wavelength.

As a further comment on the data reported in Figure 1, it is worthy to notice that, as reported in previous papers by some of us,^{3,18} vibrational contributions can be calculated by resorting to the standard equilibrium PCM regime or to the most physically sound vibrational nonequilibrium regime. The values obtained for the vibrational corrections to the OR of methyloxirane with the B3LYP functional are -3.34 and -2.64 within the equilibrium or nonequilibrium regime, respectively (for CAM-B3LYP the same data are -2.33 and -1.37). Since a clear definition of which of the two regimes occurs in our mixed explicit/implicit model is far from being trivial, and an intermediate regime is also possibly occurring, the total OR values (electronic+vibrational) of -4.88 and -4.18 for B3LYP (-3.81 and -2.55 for CAM-B3LYP) can be considered as upper and lower bounds to the computed property for the given level of theory.

The values obtained by following the procedure reported above depend upon the cutting radius employed to define the snapshots to be exploited in the QM/FQ/PCM calculation of the OR. This is immediately noticeable from what is reported in Figure 2, which shows that the solvent has a major effect on the OR: along the simulation, the property varies wildly by 2 orders of magnitude. However, the average value converges after a long enough simulation (at least 18 ns) to the value of -1.54° . For cutting radii above 12 Å, the results are already fully converged.

In order to evaluate the effect of the electron correlation on our computed data, we show in Table 1 calculated data obtained by resorting to gas phase calculations obtained by Mach and Crawford¹⁴ by using the CCSD level and the

Table 1. Calculated OR of (R)-Methyloxirane in Aqueous Solution at 589 nm As Obtained at Different Levels of Calculation

| | gas phase | aq |
|-------------------|--------------------|-----------|
| B3LYP/aDZ | 15.1 | -4.18 |
| CAM-B3LYP/aDZ | 15.6 | -2.55 |
| CCSD/LPol-fl(456) | 16.5 ¹⁴ | -2.75^a |
| | | -1.65^b |

^aSolvent effects (FQ/PCM) and vibrational corrections calculated at the B3LYP/aDZ level. ^bSolvent effects (FQ/PCM) and vibrational corrections calculated at the CAM-B3LYP/aDZ level.

extended Lpol-fl(456) basis set,⁴¹ and adding to them solvent effects and vibrational corrections calculated at the DFT level by means of the FQ/PCM model. Such an approach is somehow approximated, since neither the direct solvent effect on the correlated wave function nor the indirect effect on the molecular structure are included: however, it can give a first-order idea of the final outcome of a correlated FQ/PCM calculation.

The results obtained with the hybrid CCSD/DFT approach are quite similar to their DFT counterparts, assessing once again the reliability of DFT in the prediction of the OR of methyloxirane at 589 nm. Notice that a hybrid computational protocol consisting of adding DFT vibrational corrections to high order coupled-cluster property values has been amply assessed in the literature by some of us.⁴²

Encouraged by the good results obtained at a single wavelength, we simulated the full optical rotatory dispersion (ORD) spectrum of aqueous (R)-methyloxirane between 350 and 650 nm, using the aug-cc-pVDZ basis set and both the B3LYP and the long-range corrected CAM-B3LYP functionals, the latter being expected to be more adequate to reproduce near resonance regions of the ORD spectrum at low wavelengths. The calculated data are reported in Figure 3 (see also Table 2) together with the experimental curve taken from ref 4.

The agreement between calculations and experiments is very good at each wavelength, with the B3LYP and the CAM-B3LYP functionals performing better at longer and shorter wavelengths, respectively (as expected). These results confirm that our QM/FQ/PCM approach, coupled to the computational protocol described above, offers a reliable way to compute challenging molecular properties in aqueous solution. Notice that the hybrid CCSD/DFT approach (see above) gives

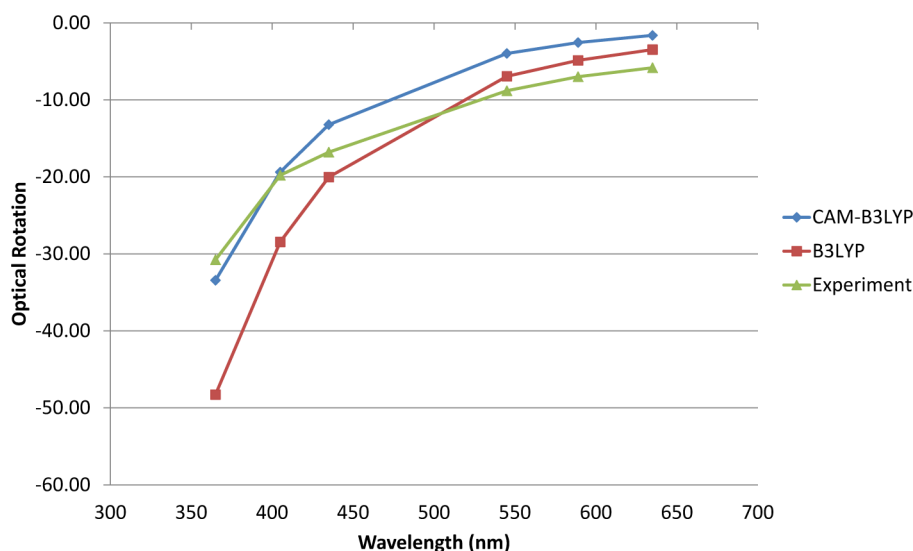


Figure 3. ORD spectrum of (R)-methyloxirane.

Table 2. ORD Spectrum Data for (R)-Methyloxirane in Water (Calculated vs Experimental)^a

| λ (nm) | nonequilibrium | | equilibrium | | |
|----------------|----------------|--------|-------------|--------|------------|
| | CAM-B3LYP | B3LYP | CAM-B3LYP | B3LYP | experiment |
| 635 | -1.62 | -2.84 | -2.71 | -3.46 | -5.82 |
| 589 | -2.55 | -4.16 | -3.81 | -4.86 | -6.98 |
| 545 | -3.96 | -6.11 | -5.45 | -6.93 | -8.81 |
| 435 | -13.21 | -18.78 | -15.69 | -20.02 | -16.79 |
| 405 | -19.37 | -27.04 | -22.23 | -28.43 | -19.79 |
| 365 | -33.43 | -46.64 | -37.04 | -48.27 | -30.76 |

^aBoth data including equilibrium and nonequilibrium vibrational corrections are reported.

very good results at reproducing the whole ORD curve, and the CAM-B3LYP is more similar to CCSD at low wavelengths, as expected.

To conclude this discussion, we stress once again how internal motions play a fundamental role in determining the OR and how their magnitude, which is related to the effect of geometrical distortion on the property, depends on the frequency (see Table 3). Vibrational corrections are in fact very important whenever the electronic contribution to the property is small: in such a case in fact, vibrational corrections can crucially determine the overall sign of the computed

Table 3. Relative Weight of Vibrational Contributions (%) to (R)-Methyloxirane Optical Rotation at Different Frequencies, Calculated with the B3LYP and CAM-B3LYP Functionals^a

| λ (nm) | nonequilibrium | | equilibrium | |
|----------------|----------------|-------|-------------|-------|
| | CAM-B3LYP | B3LYP | CAM-B3LYP | B3LYP |
| 635 | 53 | 77 | 72 | 81 |
| 589 | 42 | 64 | 61 | 69 |
| 545 | 35 | 53 | 52 | 59 |
| 435 | 23 | 33 | 35 | 38 |
| 405 | 21 | 29 | 31 | 33 |
| 365 | 18 | 25 | 26 | 28 |

^aBoth the vibrational equilibrium or nonequilibrium regimes are considered.

property. However, they are also relevant to determining the property over the whole range of frequencies (Table 3) and therefore the account of both the internal and the solvent dynamics is critical in order to gain an accurate modeling of such a sensitive property. The inclusion of vibrational corrections is, however, not sufficient to gain an accurate description of the OR of methyloxirane in aqueous solution: solvent effects have to be considered, and a reliable modeling of both specific and bulk effects is compulsory to gain a quantitative agreement between theory and experiment. In addition to that, the analysis of the snapshots of our simulations did not evidence any dominant solute–solvent configurations. This is probably the reason for the slow convergence of the property with respect to the simulation time. Furthermore, such an absence of predominant patterns explains the failure of cluster approaches to describe the OR of methyloxirane in water, and the necessity of a more refined sampling of solvent configurations to correctly describe environmental effects.

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Notes

The authors declare no competing financial interest.

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