

Computing optical rotation via an N -body approach

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Abstract Properties of four chiral compounds—(*S*)-methyloxirane, (*S*)-methylthiirane, (*S*)-2-chloropropionitrile, and (*M*)-dimethylallene—centered in a solvation shell of six to seven water molecules have been computed using time-dependent density functional theory at several wavelengths using a many-body expansion. Interaction energies, total system dipole moments, and dynamic dipole polarizabilities converge rapidly and smoothly, exhibiting only minor oscillations with higher-body contributions. At three-body truncation of the expansion, errors in such properties as compared to the full cluster typically fall to less than 1 % (and much smaller in most cases). Specific optical rotations, however, are found to converge much more slowly and erratically, requiring five-body contributions to obtain errors less than 5 % in three of four test cases, and six-body terms for (*S*)-methylthiirane. The source of this behavior is found to be the wide variation of both magnitude and sign of the specific rotation with changes in the configuration of individual solute/solvent clusters. Thus, unlike simpler properties such as energies or dipole moments, where each fragment makes a small, same-sign contribution to the total property, specific rotations typically involve much larger contributions that partly cancel in the many-body expansion. Thus, the

computational costs of molecular dynamics simulations of explicit solvation, for example, will be only partially alleviated by such expansions.

Keywords Many-body expansion · Optical rotation · Solvation · Response properties

1 Introduction

Over the last two decades, the quality with which optical properties of chiral molecules [1–8] can be computed has increased dramatically, including optical rotation [3, 9–14], electronic [15–25], and vibrational [26–33] circular dichroism, and Raman optical activity [34–44]. In the 16 years, since Polavarapu [9] published the first *ab initio* calculations of optical rotation, for example, comparison with *vapor phase* experimental measurements [45–51] has revealed that such response properties often require high levels of electron correlation [13, 52–55], large one-electron basis sets (including diffuse functions), [10, 56–59] and, in some cases, vibrational corrections [52–55, 58, 60–66]. As a result of this effort, the number of remaining discrepancies between theory and experiment for gas-phase measurements of optical rotation has been significantly reduced [14, 45, 67].

However, the vast majority of experimental measurements of such properties are made in condensed phases, either in solvent or in the neat state, and attempts to simulate such environments accurately for chiroptical properties have seen only limited success. Continuum-based solvent models [68–71], for example, have been reported to reproduce experimental trends (as opposed to absolute values) only for those systems in which electrostatic solute–solvent interactions are dominant [54, 55, 64, 72, 73].

Dedicated to Professor Thom Dunning and published as part of the special collection of articles celebrating his career upon his retirement.

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However, in cases where molecule-specific interactions are significant, implicit solvent models are not reliable. Microsolvation studies by Xu et al. [74, 75] on the paradigmatic chiral compound methyloxirane have revealed that both the magnitude and sign of the computed optical rotation can vary substantially depending on the number and configuration of solvent molecules in the region closest to the solute. In addition, combined molecular dynamics and density functional studies by Beratan et al. [76, 77] on the same compound in water and benzene have demonstrated that the solute can produce a surprisingly strong transfer of chirality to the solvent.

Clearly, a careful accounting of explicit solute–solvent interactions—at least in the cybotactic region—is vital to the accurate simulation of the exquisitely sensitive chiroptical response. However, the cost of such calculations is prohibitively expensive at present. Given the high-degree polynomial scaling of conventional quantum chemical methods— $\mathcal{O}(N^3)$ for Kohn–Sham density functional theory (DFT) [78] and $\mathcal{O}(N^5)$ for coupled cluster theory [79, 80]—inclusion of even a few water molecules, much less larger solvents such as benzene or cyclohexane, is far beyond the current state of the art. The cost of such computations is further exacerbated by the need to average properties of large numbers of snapshots of solute–solvent configurations along dynamical trajectories. While reduced- or even linear-scaling density functional and coupled cluster methods exist [81–86], their prefactors—and thus their algorithmic crossover points—lie too far out in terms of system size for them to provide any significant advantage for such computations.

One possible means of reducing the computational cost of explicit solvation models is to apply a many-body expansion to the (relatively) weak interactions of the solute and solvent components. This approach involves decomposition of the total energy, E , of the complete solute–solvent system into N -body contributions, *viz.*

$$E = \sum_I E_I + \sum_{I<J} V_{IJ} + \sum_{I<J<K} V_{IJK} + \cdots \quad (1)$$

where

$$V_{IJ} = E_{IJ} - E_I - E_J \quad (2)$$

and

$$V_{IJK} = E_{IJK} - V_{IJ} - V_{IK} - V_{JK} - E_I - E_J - E_K, \quad (3)$$

etc. In the above equations, E_I is the energy of fragment/monomer I , E_{IJ} is the energy of the dimer composed of fragments I and J , etc. Thus, the $V_{IJ,\dots}$ represent N -body corrections, and truncation of the expansion at a particular term may yield a cost-effective approximation to a computation on the complete system, provided that the concomitant loss of accuracy is sufficiently small. Such expansions have

been widely used in quantum chemistry for decades, and we particularly note numerous applications of such an approach to water and other molecular clusters [87–92]. Often the scheme is enhanced by embedding the cluster in an electrostatic (or other simple) potential [90, 93], or making use of theory and/or basis-set hierarchies that treat higher-body terms using less expensive quantum chemical methods [91, 94]. Furthermore, while most applications of Eq. (1) have focused on (interaction) energies, extensions to first-order properties such as dipole moments [90] and energy gradients [91] have also been recently reported. For the properties investigated thus far, the many-body expansion is found to converge rapidly, with truncation at three-body terms yielding small errors—often a fraction of a percent—relative to the much more expensive computation performed on the aggregate system [90, 91].

The goal of the present work is to examine the convergence of the many-body expansion for higher-order solute properties such as frequency-dependent dipole polarizabilities and optical rotations. As test cases, we have chosen several small chiral compounds whose chiroptical response has been well studied, both in vapor and in condensed phases. However, our purpose here is not to reproduce experimental measurements, but instead to determine if truncation of Eq. (1) is still effective for properties that are much more sensitive to the quality of the wave function than are energies or first derivatives.

2 Computational details

The molecular dynamics program Gromacs [95] was used to place each of the four test solutes—(*S*)-methyloxirane, (*S*)-methylthiirane, (*S*)-2-chloropropionitrile, and (*M*)-dimethylallene—in a fixed configuration of water molecules. From these snapshots, only those solvent molecules lying completely within a sphere of radius of 5.5 Å from the solute's geometric center were retained, yielding clusters of six or seven water molecules surrounding the solute. (See the supporting information for coordinates of each cluster.) For each test case, interaction energies, dipole moments, dipole polarizabilities, and specific optical rotations were computed using the many-body expansion of Eq. (1).

The specific rotation of a chiral compound may be computed using the Rosenfeld optical activity tensor [1, 96],

$$\mathbf{G}'(\omega) = -\frac{2\omega}{\hbar} \sum_{j \neq 0} \frac{\text{Im}(\langle \psi_0 | \boldsymbol{\mu} | \psi_j \rangle \langle \psi_j | \mathbf{m} | \psi_0 \rangle)}{\omega_{j0}^2 - \omega^2}, \quad (4)$$

where $\boldsymbol{\mu}$ and \mathbf{m} are the electric and magnetic dipole operators, respectively, and ω is the frequency of plane-polarized light. The summation in Eq. (4) runs over the excited electronic (unperturbed) wave functions, ψ_j , each

associated with an excitation frequency, ω_{j0} . The Rosenfeld tensor was computed at four wavelengths—355, 436, 589, and 633 nm—using time-dependent density functional theory (TD-DFT) with the B3LYP [97, 98] functional in Gaussian 09 [99]. Gauge-including atomic orbitals (GIAOs) [100, 101] were employed with the length representation of the electric dipole operator to ensure origin independence of the computed rotations. All computations were performed with the aug-cc-pVDZ basis set of Dunning and co-workers based on previous studies of its efficacy, especially for DFT [56, 59].

The specific rotation is related to the trace of the \mathbf{G}' tensor [4],

$$[\alpha]_{\omega} = \frac{(72.0 \times 10^6) \hbar^2 N_A \omega}{c^2 m_e M} \times \left[\frac{1}{3} \text{Tr}(\mathbf{G}') \right] \quad (5)$$

where \mathbf{G}' and ω are given in atomic units, N_A is Avogadro's number, c is the speed of light (m/s), m_e is the electron rest mass (kg), and M is the molecular mass (amu). In order to obtain the specific rotation of the solute within the solvent cluster, the many-body expansion of Eq. (1) was used to obtain the \mathbf{G}' tensor for the complete solute-solvent system at a selected truncation level. The coordinate system of the full molecular cluster was held fixed for all fragment computations to ensure that the separate tensors could be combined. The final specific rotation was obtained from this composite \mathbf{G}' tensor, with the mass M taken to be only that of the solute.

In order to automate use of the many-body expansion of Eq. (1), a local version of the PSI4 [102] program was modified to generate separate calculations automatically for all required fragment combinations based on a master input file containing the coordinates of the complete solvent-solute system. The individual fragment computations can then be carried out independently and in parallel fashion. The Python front end of PSI4 was modified to monitor the status of these automatically generated jobs, compiling the results as the various tasks complete. When all data required for a particular truncation level have been collected, the corrections are automatically computed by Python functions tied into the PSI4 driver. Furthermore, these functions are completely general, enabling easy extension to other properties of interest or higher levels of theory or approximation.

3 Results and discussion

3.1 (S)-2-Chloropropionitrile

The interaction energy of (S)-2-chloropropionitrile (Table 1) with seven water molecules in a configuration

Table 1 Absolute percent errors for (S)-2-chloropropionitrile in a cluster of water molecules relative to the full eight-body calculation

| N-body truncation | Interaction energy | Dipole moment | Polarizability (633 nm) | Specific rotation (633 nm) |
|-------------------|--------------------|---------------|-------------------------|----------------------------|
| 1 | – | 8.46 | 2.47 | 106.66 |
| 2 | 11.75 | 2.55 | 2.90 | 26.91 |
| 3 | 1.06 | 0.11 | 0.34 | 13.05 |
| 4 | 0.10 | 0.01 | 0.41 | 13.27 |
| 5 | 0.15 | 0.01 | 0.30 | 4.18 |
| 6 | 0.07 | 0.01 | 0.06 | 1.88 |
| 7 | 0.02 | 0.00 | 0.01 | 0.80 |

extracted from a molecular dynamics simulation is well represented by the truncated many-body expansion of Eq. (1). Limiting the expansion to only two-body terms yields an error of nearly 12 % as compared to a computation on the full cluster. However, extension to three-body contributions reduces the error to ca. 1 %, and four-body terms are accurate to 0.10 %, comparable to the convergence observed for water clusters by Tschumper [103].

For dipole moments, the convergence of the many-body expansion is somewhat faster, with two-body truncation yielding percent errors of less than 3 % relative to the full cluster. Three-body truncation of the dipole moment is accurate to within 0.11 %, and higher-order terms are essentially negligible. These results for dipole moments are consistent with trends observed by Truhlar et al. [90] for dipole moments of chloride or hydrogen fluoride in aqueous solution, as well as for pure hydrogen fluoride clusters. For solvated chloride, for example, they observed errors of under 3 % at the two-body truncation (referred to as pairwise additive in Ref. [90]) without employing electrostatic embedding.

The convergence of the expansion for frequency-dependent polarizabilities (evaluated at 633 nm) starts even better than interaction energies and dipole moments, with a simple sum of monomer polarizabilities giving an error of only 2.5 %. However, extension of the sum to pairwise contributions actually increases the error slightly to ca. 3 %. While three-body components quickly reduce the error to under 0.5 %, subsequent corrections are somewhat larger than observed for interaction energies and dipole moments.

Experimental and computational studies of the chiroptical properties of (S)-2-chloropropionitrile have been reported before by Wiberg et al. [50] and by Kowalczyk et al. [57]. The latter reported modest basis-set dependence of both DFT (B3LYP) and coupled cluster methods. The specific rotation of the (S)-2-chloropropionitrile plus water cluster is found to be significantly larger and of opposite sign than that of the isolated solute molecule (+156.4 vs.

$-12.3 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$ at 633 nm; see Ref. [57]). Although the cluster is not energetically optimum, the large perturbation introduced by the solvent cage is additional evidence of the importance of molecule-specific interactions on this property.

Unfortunately, convergence of the specific rotation of the solvated chloropropionitrile with many-body contribution (Table 2) is substantially slower than observed for the other properties. Employing solely monomers yields the incorrect sign of the rotation (e.g., -10.4 vs. $+156.4 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$ at 633 nm). Incorporation of dimers in the expansion produces a qualitatively correct specific rotation, but with a quantitative error of 27–33 % for the wavelengths considered here. Extension to trimers cuts this error roughly in half, with the computed rotations still smaller in magnitude than those obtained for the full cluster. However, inclusion of four-body terms overshoots the correct value yielding the same percent error of approximately 13 %. Only when five-body terms are employed does the error finally decrease to under 5 % for the specific rotation and then to under 2 % at the six-body truncation.

3.2 (S)-Methyloxirane

The many-body expansion converges for the interaction energy of (S)-methyloxirane (Table 3) with a surrounding cluster of water molecules slightly faster than for (S)-2-chloropropionitrile, with the pairwise truncation of Eq. (1) giving an error of less than 7 %, as shown in Table 3. The errors are slightly oscillatory for (S)-methyloxirane, however, with that arising from the four-body expansion (0.14 %) slightly higher than from the three-body components (0.09 %). Nevertheless, the errors beyond trimers are negligible for the interaction energy.

The dipole moment of the (S)-methyloxirane plus water cluster requires dimers to reproduce that of the full cluster to within 2 %, and, unlike the interaction energy, the errors

decay smoothly with the many-body expansion. In addition, just as for (S)-2-chloropropionitrile, the 633-nm dipole polarizability of (S)-methyloxirane converges more slowly than either the dipole moment or interaction energy expansions, and it exhibits an oscillatory pattern similar to that observed for the interaction energy.

(S)-methyloxirane has long served as a challenging test case for quantum chemical models of optical activity [52–54, 76, 77, 104]. Its vapor-phase specific rotation is small and bisignate ($+7.49 \pm 0.30 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$ at 355 nm and $-8.39 \pm 0.20 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$ at 633 nm; see Ref. 49) and thus exceedingly sensitive not only to the choice of theoretical method and basis set, but also to the inclusion of molecular vibrational corrections, which were found to be necessary to reproduce experimental results. In addition, the optical activity of (S)-methyloxirane exhibits strong solvent dependence, such that even the sign of its liquid-phase specific rotation varies with the choice of solvent [105].

Like its (S)-2-chloropropionitrile counterpart, the specific rotation of (S)-methyloxirane contained within a cluster of seven water molecules ($270.7 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$ at 633 nm) is larger than that of the isolated molecule. Furthermore, the rotation is monosignate (positive) at all wavelengths down to 355 nm, unlike the gas-phase property. The specific rotation of (S)-methyloxirane converges much more slowly in the many-body expansion (Table 4) than the other properties considered here, though the convergence is slightly better relative to (S)-2-chloropropionitrile. Monomer, dimer, and trimer truncations approach the full value from below with the last yielding a fortuitously small error (as small as 0.08 % at 589 nm). However, like (S)-2-chloropropionitrile, the series is not converged at this point: the four-body truncation overshoots and the error increases to 5–8 %, depending on the wavelength. Expansion to six-body terms is necessary to converge the error relative to the full cluster down to around 1 %.

Table 2 Specific rotations [$\text{deg dm}^{-1} (\text{g/mL})^{-1}$] and absolute percent errors (APE) relative to the full eight-body calculation for (S)-2-chloropropionitrile in water

| N-body truncation | 355 nm | | 436 nm | | 589 nm | | 633 nm | |
|-------------------|---------------------|--------|---------------------|--------|---------------------|--------|---------------------|--------|
| | $[\alpha]_{\omega}$ | APE | $(\alpha)_{\omega}$ | APE | $(\alpha)_{\omega}$ | APE | $(\alpha)_{\omega}$ | APE |
| 1 | -52.4 | 109.23 | -27.5 | 107.88 | -12.4 | 106.81 | -10.4 | 106.66 |
| 2 | 380.6 | 32.95 | 246.2 | 29.35 | 132.4 | 27.22 | 114.3 | 26.91 |
| 3 | 488.6 | 13.92 | 302.2 | 13.29 | 158.0 | 13.19 | 136.0 | 13.05 |
| 4 | 642.8 | 13.24 | 394.4 | 13.15 | 206.2 | 13.31 | 177.1 | 13.27 |
| 5 | 547.4 | 3.55 | 336.1 | 3.58 | 174.8 | 3.96 | 149.9 | 4.18 |
| 6 | 577.2 | 1.70 | 355.1 | 1.88 | 184.5 | 1.41 | 159.3 | 1.88 |
| 7 | 572.2 | 0.81 | 351.4 | 0.82 | 183.7 | 0.95 | 157.6 | 0.80 |
| 8 | 567.6 | – | 348.5 | – | 182.0 | – | 156.4 | – |

Table 3 Absolute percent errors for (*S*)-methyloxirane in a cluster of water molecules relative to the full eight-body calculation

| <i>N</i> -body truncation | Interaction energy | Dipole moment | Polarizability (633 nm) | Specific rotation (633 nm) |
|---------------------------|--------------------|---------------|-------------------------|----------------------------|
| 1 | – | 12.34 | 2.06 | 69.88 |
| 2 | 6.57 | 1.80 | 2.94 | 19.35 |
| 3 | 0.09 | 0.22 | 0.24 | 0.36 |
| 4 | 0.14 | 0.09 | 0.60 | 7.52 |
| 5 | 0.07 | 0.04 | 0.52 | 3.81 |
| 6 | 0.05 | 0.01 | 0.18 | 1.12 |
| 7 | 0.01 | 0.00 | 0.00 | 0.00 |

3.3 (*M*)-Dimethylallene

The convergence of the many-body expansion for the interaction energy, dipole moment, and dipole polarizability of (*M*)-dimethylallene in a cluster of water molecules (Figs. 1, 2; Table 5) is very similar to that observed for (*S*)-2-chloropropionitrile and (*S*)-methyloxirane. Indeed, for all three properties, the series converges slightly faster, and the three-body truncation already provides errors of less than 1% as compared to the full cluster. The series oscillates only slightly for the interaction energy and polarizability with a slight increase in the error between three- and four-body contributions, but the errors remain small enough to be negligible.

(*M*)-Dimethylallene is unique among the chiral molecules considered here in that it exhibits a stereogenic axis rather than a stereogenic center. Its specific rotation was the subject of a detailed investigation in 2008 by Wiberg et al. [51] who reported a surprisingly large difference between its measured values in the neat liquid and vapor. At long wavelengths (633 and 589 nm), the specific rotation of the isolated molecule (-108.4 and -125.1 deg dm $^{-1}$ (g/mL) $^{-1}$; see Ref. [51]) is approximately the same as that of the solute plus water snapshot

extracted from the dynamical simulation. For the shorter wavelengths, however, the rotation is much larger for the cluster, suggesting that the lowest excited state shifts to lower energy due to the interaction with the nearby water molecules.

The specific rotation of (*M*)-dimethylallene, on the other hand, converges more slowly than either (*S*)-2-chloropropionitrile or (*S*)-methyloxirane, though the qualitative behavior is essentially the same (Table 6). At long wavelengths, the specific rotation of the cluster is approached from below (i.e., from more negative values), with increasing many-body truncation, and the four-body expansion overshoots as before. The behavior is somewhat different at shorter wavelengths, however, with the many-body expansion approaching the full value from above and exhibiting greater oscillation. This is a result of the fact that the Rosenfeld tensor diverges in the vicinity of a resonance, and the lowest excitation energy is clearly also sensitive to the truncation of the series. In the case of (*M*)-dimethylallene, errors as large as 20 % (corresponding to -21 deg dm $^{-1}$ (g/mL) $^{-1}$ at 633 nm) remain even at the five-body truncation level.

3.4 (*S*)-Methylthiirane

The many-body expansion for the interaction energy, dipole moment, and dipole polarizability of (*S*)-methylthiirane in a cluster of six water molecules (Table 7) converges more smoothly than for (*S*)-methyloxirane and (*M*)-dimethylallene, with no oscillation apparent with increasing truncation level. The specific rotation of (*S*)-methylthiirane plus water, on the other hand, is much more difficult to model accurately. Vapor-phase specific rotations were measured in 2005 by Wilson et al. [49] who reported $+36.5 \pm 1.7$ deg dm $^{-1}$ (g/mL) $^{-1}$ at 633 nm and $+64.7 \pm 2.3$ deg dm $^{-1}$ (g/mL) $^{-1}$ at 355 nm for the (*R*) enantiomer. Crawford et al. [61] reported DFT and coupled cluster specific rotations as well as electronic

Table 4 Specific rotations (deg dm $^{-1}$ (g/mL) $^{-1}$) and absolute percent errors (APE) relative to the full eight-body calculation for (*S*)-methyloxirane in water

| <i>N</i> -body truncation | 355 nm | | 436 nm | | 589 nm | | 633 nm | |
|---------------------------|--------------------------|-------|--------------------------|-------|--------------------------|-------|--------------------------|-------|
| | (α) $_{\omega}$ | APE | (α) $_{\omega}$ | APE | (α) $_{\omega}$ | APE | (α) $_{\omega}$ | APE |
| 1 | 408.3 | 65.08 | 215.0 | 67.42 | 97.1 | 69.55 | 81.5 | 69.88 |
| 2 | 928.0 | 20.63 | 528.6 | 19.89 | 256.9 | 19.44 | 218.3 | 19.35 |
| 3 | 1,185.3 | 1.38 | 666.6 | 1.02 | 318.6 | 0.08 | 269.7 | 0.36 |
| 4 | 1,235.2 | 5.65 | 696.7 | 5.59 | 340.0 | 6.65 | 291.0 | 7.52 |
| 5 | 1,156.0 | 1.12 | 647.4 | 1.89 | 311.0 | 2.47 | 260.4 | 3.81 |
| 6 | 1,163.6 | 0.48 | 662.5 | 0.40 | 318.4 | 0.14 | 273.7 | 1.12 |
| 7 | 1,174.7 | 0.48 | 661.0 | 0.18 | 320.4 | 0.48 | 270.7 | 0.00 |
| 8 | 1,169.1 | – | 659.8 | – | 318.8 | – | 270.7 | – |

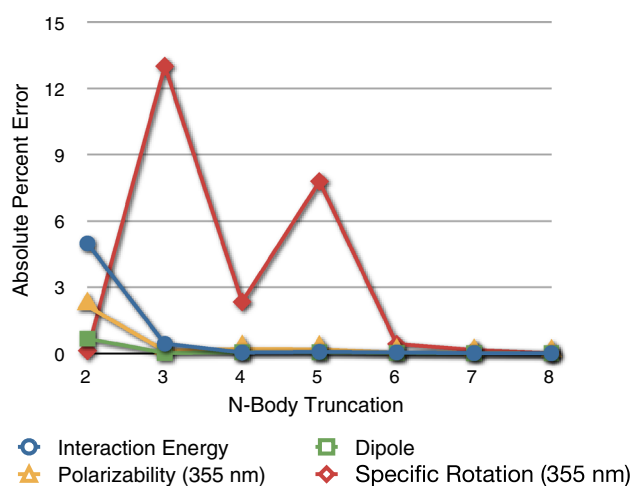


Fig. 1 Absolute percent error in the interaction energy, dipole moment, polarizability (355 nm), and optical rotation (355 nm) for (*M*)-dimethylallene solvated by seven water molecules as a function of *N*-body approximation level. The monomer approximation is excluded due to its large error

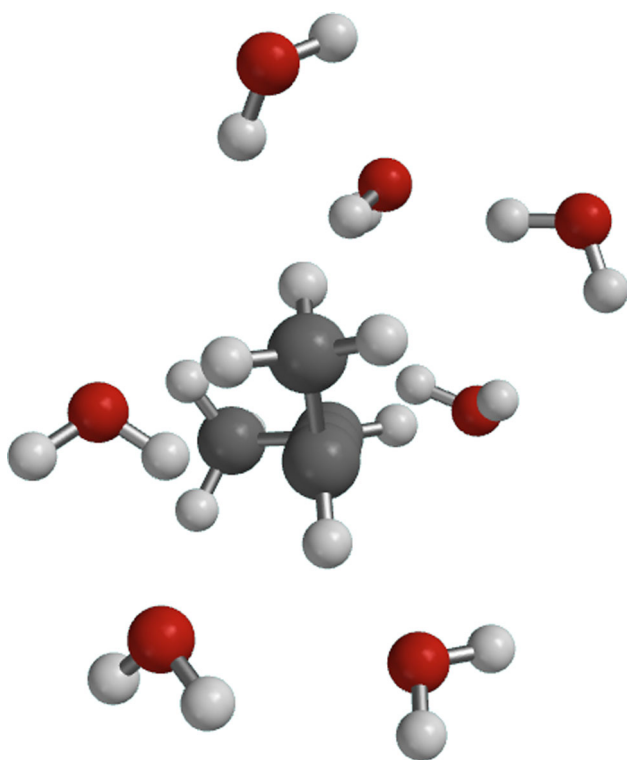


Fig. 2 (*M*)-Dimethylallene solvated by seven water molecules within a 5.5 Å radius of the solute's geometric center. Coordinates of the structure are found in the supporting information

circular dichroism spectra for (*S*)-methylthiirane in 2007 and found that vibrational corrections were necessary to produce reasonable comparison with experiment in the long wavelength regime, but the same corrections distorted the comparison for shorter wavelengths.

Table 5 Absolute percent errors for (*M*)-dimethylallene in a cluster of water molecules relative to the full eight-body calculation

| <i>N</i> -body truncation | Interaction energy | Dipole moment | Polarizability (355 nm) | Specific rotation (355 nm) |
|---------------------------|--------------------|---------------|-------------------------|----------------------------|
| 1 | – | 11.27 | 2.68 | 75.66 |
| 2 | 4.97 | 0.66 | 2.13 | 0.12 |
| 3 | 0.43 | 0.01 | 0.11 | 12.99 |
| 4 | 0.03 | 0.04 | 0.19 | 2.33 |
| 5 | 0.06 | 0.04 | 0.17 | 7.78 |
| 6 | 0.04 | 0.01 | 0.03 | 0.42 |
| 7 | 0.01 | 0.00 | 0.02 | 0.15 |

The specific rotation of (*S*)-methylthiirane in the cluster of six water molecules modeled here is bisignate, with a strong positive Cotton pole as the wavelength of the polarized field becomes shorter. The specific rotation of the isolated molecule, [61] however, is monosignate according to both experiment and coupled cluster theory, though the B3LYP functional finds a bisignate dispersion due to its underestimation of the energy of lowest excited state. The convergence of the many-body expansion of the specific rotation of the (*S*)-methylthiirane plus water cluster is more erratic than that of the other species investigated here. At 633 nm, for example, the rotation shifts from $-42.5 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$ using only monomers to $+83.9 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$ using dimers, and then back to $-23.1 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$ with trimers. At 355 nm, on the other hand, the variation is even more pronounced (though without concomitant sign changes), with a one-body truncation of $+74.0 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$, two-body truncation of $+665.2 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$, three-body $+1.1 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$, and four-body $+138.4 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$, before the series finally begins to approach the untruncated result. The relatively small total rotations at long wavelengths produce very large corresponding percent errors—more than 2,000 % for the pairwise expansion at 589 nm, for example.

4 Conclusions

When describing the interactions between solute and solvent, the venerable many-body expansion converges rapidly and smoothly for energies, dipole moments, and dipole polarizabilities—that is, properties that are strongly localized and/or easily partitioned into local contributions. On the other hand, for properties such as optical rotations, whose values (both magnitude and sign) depend strongly on more distant interactions as well as basis-set effects, Eq. (1) converges much more slowly. We have demonstrated that for four paradigmatic chiral compounds—(*S*)-methyloxirane, (*S*)-methylthiirane, (*S*)-2-chloropropionitrile, and

Table 6 Specific rotations [$\text{deg dm}^{-1} (\text{g/mL})^{-1}$] and absolute percent errors (APE) relative to the full eight-body calculation for (*M*)-dimethylallene in water

| <i>N</i> -body truncation | 355 nm | | 436 nm | | 589 nm | | 633 nm | |
|---------------------------|-------------------|-------|-------------------|-------|-------------------|-------|-------------------|-------|
| | $(\alpha)_\omega$ | APE | $(\alpha)_\omega$ | APE | $(\alpha)_\omega$ | APE | $(\alpha)_\omega$ | APE |
| 1 | −190.5 | 75.66 | −253.6 | 25.53 | −163.9 | 23.65 | −143.8 | 32.16 |
| 2 | −783.4 | 0.12 | −422.7 | 24.15 | −187.6 | 41.56 | −157.0 | 44.33 |
| 3 | −884.1 | 12.99 | −394.8 | 15.96 | −156.6 | 18.17 | −129.6 | 19.15 |
| 4 | −800.7 | 2.33 | −323.2 | 5.09 | −123.7 | 6.67 | −99.9 | 8.16 |
| 5 | −843.4 | 7.78 | −392.6 | 15.31 | −155.5 | 17.28 | −129.8 | 19.27 |
| 6 | −785.7 | 0.42 | −334.2 | 1.86 | −133.4 | 0.67 | −108.9 | 0.13 |
| 7 | −781.4 | 0.15 | −341.6 | 0.32 | −131.9 | 0.52 | −108.2 | 0.55 |
| 8 | −782.5 | — | −340.5 | — | −132.5 | — | −108.8 | — |

Table 7 Absolute percent errors for (*S*) in a cluster of water molecules relative to the full seven-body calculation

| <i>N</i> -body truncation | Interaction energy | Dipole moment | Polarizability (589 nm) | Specific rotation (589 nm) |
|---------------------------|--------------------|---------------|-------------------------|----------------------------|
| 1 | — | 11.51 | 3.37 | 797.96 |
| 2 | 8.31 | 1.68 | 1.98 | 2,028.61 |
| 3 | 0.37 | 0.08 | 0.36 | 393.10 |
| 4 | 0.10 | 0.01 | 0.07 | 119.60 |
| 5 | 0.03 | 0.00 | 0.02 | 20.76 |
| 6 | 0.01 | 0.00 | 0.01 | 26.76 |

Table 8 Specific rotations ($\text{deg dm}^{-1} (\text{g/mL})^{-1}$) and absolute percent errors (APE) relative to the full seven-body calculation for (*S*) in water

| <i>N</i> -body truncation | 355 nm | | 436 nm | | 589 nm | | 633 nm | |
|---------------------------|-------------------|--------|-------------------|----------|-------------------|----------|-------------------|----------|
| | $(\alpha)_\omega$ | APE | $(\alpha)_\omega$ | APE | $(\alpha)_\omega$ | APE | $(\alpha)_\omega$ | APE |
| 1 | 74.0 | 41.23 | −50.7 | 464.48 | −47.3 | 797.96 | −42.5 | 647.85 |
| 2 | 665.2 | 428.46 | 262.0 | 1,785.14 | 101.5 | 2,028.61 | 83.9 | 1,574.83 |
| 3 | 1.1 | 99.12 | −35.7 | 356.77 | −26.0 | 393.10 | −23.1 | 306.56 |
| 4 | 138.4 | 9.93 | 7.5 | 45.71 | −11.6 | 119.60 | −10.9 | 91.30 |
| 5 | 114.4 | 9.10 | 14.2 | 1.83 | −4.2 | 20.76 | −4.8 | 15.05 |
| 6 | 125.5 | 0.30 | 12.4 | 11.11 | −6.7 | 26.76 | −6.7 | 17.24 |
| 7 | 125.9 | — | 13.9 | — | −5.3 | — | −5.7 | — |

(*M*)-dimethylallene—each contained in a small cluster of water molecules, the expansion is highly oscillatory and erratically convergent. Admittedly, the appearance of (relatively) strong hydrogen bonding interactions between the solute and solvent (and between solvent molecules themselves) makes the choice of water a worst-case scenario, and Eq. (1) may exhibit better behavior for more weakly interacting solvents such as cyclohexane. However, even in such cases, the transfer of chirality from the solute to the solvent (e.g., through the chiral hole analyzed by Beratan et al. [77]) yields widely disparate optical rotations among the various *N*-body fragments. As a result, the many-body expansion will still be exceedingly sensitive to truncation.

It may be possible to relieve at least some of the computational burden of explicit solvation models

through, e.g., multi-theory QM/MM schemes [91, 93, 106] or distance-based criteria to eliminate minor contributions to the many-body expansion [107]. However, the non-locality of chiroptical properties on which such schemes rely is still poorly understood. This work suggests that the “chiral imprint” onto the solvent extends sufficiently far out from the solute as to require models of condensed phase dynamics that are much more robust—and potentially much more costly—than previously hoped. This is particularly discouraging considering the large number of molecular dynamics snapshots that must be averaged in the case of optical rotation to achieve a balanced representation of the opposing sign contributions from different molecular configurations [108].

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