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Comparison of Time-Dependent Density-Functional Theory and Coupled Cluster Theory for the Calculation of the Optical Rotations of Chiral Molecules

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A comparison of the abilities of time-dependent density-functional theory (TDDFT) and coupled cluster (CC) theory to reproduce experimental sodium D-line specific rotations for 13 conformationally rigid organic molecules is reported. The test set includes alkanes, alkenes, and ketones with known absolute configurations. TDDFT calculations make use of gauge-including atomic orbitals and give origin-independent specific rotations. CC rotations are computed using both the origin-independent dipole-velocity and origin-dependent dipole-length representations. The mean absolute deviations of calculated and experimental rotations are of comparable magnitudes for all three methods. The origin-independent DFT and CC methods give the same sign of $[\alpha]_D$ for every molecule except norbornanone. For every large-rotation ketone and alkene for which DFT and CC yield the incorrect sign as compared to liquid-phase experimental data, the corresponding optical rotatory dispersion (ORD) curve is bisignate, suggesting that the two models cannot reliably reproduce the relative excitation energies and antagonistic rotational strengths of multiple competing electronic states that contribute to the total long-wavelength rotation. Several potential sources of error in the theoretical treatments are considered, including basis set incompleteness, vibrational and temperature effects, electron correlation, and solvent effects.

I. Introduction

The determination of the absolute configurations of chiral molecules remains a challenging, yet critical task. For crystalline compounds, this may be accomplished using X-ray diffraction methods,[1] with the caveats that a high-quality single-crystal sample is required and that the compound must contain a sufficiently heavy atom to permit reliable anomalous dispersion measurements. For noncrystalline compounds, an alternative is asymmetric total synthesis of a selected stereoisomer followed by comparison of its chiroptical spectra to those of the original compound, an often costly and time-consuming undertaking.[2] Another possibility, however, is to use emerging quantum chemical models of optical activity to obtain theoretical predictions of the chiroptical responses of candidate stereoisomers. If such models are sufficiently accurate and reliable, they provide effective tools for the assignment of absolute configurations.

Many ab initio theoretical methods are now well established as indispensable partners to experiment for understanding and predicting chemical phenomena, such as reaction kinetics, thermochemistry, and spectroscopy.[3] Indeed, for many properties, such as molecular structure and vibrational and electronic spectra, the most advanced techniques can sometimes exceed the accuracy of even the best available experimental methods.[4−6] However, the reliable calculation of the optical properties of chiral molecules has proven to be a major challenge for electronic structure theory.[7−12] Although significant progress has been made in recent years with the development of quantum chemical models for computing properties such as optical rotation angles and electronic circular dichroism spectra,[13−24] reliable comparison to experimental data remains problematic.

Density-functional theory (DFT) has emerged in the last 20 years or so as a cost-effective approach to a wide variety of molecular properties, including optical rotation.[17,18] The scaling of DFT with molecular size is comparable to Hartree−Fock theory, and numerous calculations on organic chiral molecules containing more than 20 non-hydrogen atoms have been reported in the literature.[25−28] In several papers,[8,18,29−31] Stephens and co-workers have reported extensive statistical analyses of the performance of density-functional theory (DFT) (specifically, the B3LYP approach,[32−34] using the aug-cc-pVDZ basis set[35,36] for the optical rotation calculation at B3LYP/6-31G* optimized structures) in determining the sodium D-line specific rotations of a large number of rigid organic molecules. In one study, published in 2005, they examined 65 organic molecules, including alkanes, alkenes, ketones, and others, all with known absolute configurations and $[\alpha]_D$ values less than 100 deg dm^{-1} (g/mL)$^{-1}$.[8] The distribution of errors between theory and experiment was found to be approximately Gaussian, leading to the establishment of a 2σ range of $\pm$ 57.8 deg dm^{-1} (g/mL)$^{-1}$ within which the difference between the experimental and theoretical values of $[\alpha]_D$ for only one of the two possible enantiomers must lie in order to assign the absolute configuration with 95% confidence. Stephens et al. reported that 22 of the 65 organic molecules included in their study lie within this “zone of indeterminacy”, meaning that B3LYP calculations alone would not be sufficient to establish their absolute configurations if they were not already known. In a 2006 study, McCann and Stephens focused their analysis on 26 rigid alkenes with $[\alpha]_D$

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values ranging from 0 to 500 deg dm^{-1} (g/mL)$^{-1}$.[31] In this case, the zone of indeterminacy widened to ± 74.0 deg dm^{-1} (g/mL)$^{-1}$, but the B3LYP approach nevertheless yielded the correct sign of $[\alpha]_D$ in every case except one (β-pinene).

The coupled cluster (CC) approach, which was originally introduced into electronic structure theory in the late 1960s by Čížek and Paldus,[37−39] is now widely regarded as the most accurate and reliable wave function-based method available.[4,6,40−43] Unlike modern DFT, CC is a “convergent” model in the sense that one may systematically extend the atomic-orbital basis set and include higher levels of electron correlation to approach the exact solution to the electronic Schödinger equation. Assuming sufficient computational resources are available, this produces a natural series of diagnostics that can provide greater confidence in the computed molecular properties. However, such convergence is often difficult to achieve in practice for molecules containing more than a few heavy atoms because of the high-degree polynomial scaling of CC theory [$O(N^6)$ or worse]. Through its linear response variant,[44−48] the CC model has been extended to calculations of chiroptical properties in the last several years,[19−21] and a number of systematic studies of small- to medium-sized molecules have appeared in the literature.[10,19,20,22−24,49,50] Although the cost of the CC approach has precluded studies of large numbers of molecules, such as those studied by Stephens and co-workers, the conclusion of this work so far is that CC theory generally produces specific rotations that are closer to the experimental values, when comparing to gas-phase data.[51] However, in some cases (such as the highly problematic methyloxirane example), additional corrections such as zero-point vibrational and temperature effects must be included to obtain reasonable comparison with experiment.[10,20,23,24,52]

The purpose of this work is to compare the performance of DFT and CC methods for reproducing experimental liquid-phase values of $[\alpha]_D$ for a series of 13 rigid organic molecules containing up to ten non-hydrogen atoms, as well as experimental gas-phase values where available. The set of molecules considered here was chosen from among those studied by Stephens and co-workers and includes representative alkanes, alkenes, and ketones.[8,18,30,31] Furthermore, the set includes six molecules for which DFT gives the incorrect sign of $[\alpha]_D$.

II. Computational Methods

The specific rotation of each of the 13 test molecules was evaluated using the Rosenfeld optical activity tensor[7,53,54]

$$G'(\omega) = -\frac{2\omega}{\hbar}\sum_{j\neq 0}\frac{\mathrm{Im}[\langle\psi_0|\vec{\mu}|\psi_j\rangle\langle\psi_j|\vec{m}|\psi_0\rangle]}{{\omega_{j0}}^2-\omega^2} \qquad (1)$$

where ω is the frequency of plane-polarized light, $\vec{\mu}$ and $\vec{m}$ are the electric and magnetic dipole operators, respectively, and the summation runs over the excited electronic (unperturbed) wave functions, ψ_j, each associated with an excitation frequency, ω_{j0}. The trace of this tensor is related to the specific rotation via

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

where 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). Although eq 1 may be evaluated as written using a sum over all excited electronic states, we instead use the equivalent, but more efficient linear response approach, in which the first-order response of the ground-state wave function or density to the external electric and magnetic fields becomes the central quantity.[17−20,44] Instead of diagonalization of a large effective Hamiltonian, which would be required in the sum-over-states approach, the linear response method requires only the solution of sets of coupled linear equations, and is thus much less expensive.[55]

The structure of each of the 13 molecules was first optimized at the B3LYP/6-31G* level of theory, followed by evaluation of the $G'(\omega)$ tensor as described above using the B3LYP functional[32,33] (as implemented by Stephens et al.[34]) and the CC singles and doubles (CCSD) approach.[56] For the DFT results, the double-ζ correlation-consistent basis-set of Dunning and co-workers,[35,36] augmented with diffuse s-, p-, and d-type functions (aug-cc-pVDZ) was used to compute the specific rotations. At the CCSD level, the aug-cc-pVDZ basis set was used for all heavy atoms, while the cc-pVDZ basis was used for hydrogen, yielding basis sets ranging in size from 234 to 320 basis functions. (Studies of norbornenone indicate that this choice affects the CCSD-level specific rotation by approximately 1.4 deg dm^{-1} (g/mL)$^{-1}$ [less than 0.2%], as compared to using the full aug-cc-pVDZ basis on all atoms.) The 1*s* core orbitals of the carbon and oxygen atoms were held frozen in all CCSD-level calculations. These are the largest CC-level optical-rotation calculations reported to date.

B3LYP calculations of $G'(\omega)$ reported in this work made use of gauge-including atomic orbitals (GIAOs)[17,57−59] and are therefore coordinate-origin independent. CCSD calculations made use of the origin-dependent dipole-length gauge (LG) representation (with the molecular center-of-mass as the origin) as well as the origin-independent modified dipole-velocity gauge (MVG) representation, in which $G'(\omega)$ is shifted by its static-limit ($\omega \rightarrow 0$) value as suggested by Pedersen and co-workers.[21] For the CCSD results, we have also computed the corresponding origin-dependence vector[21] of the LG results, which serves as a diagnostic for their validity.

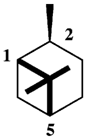
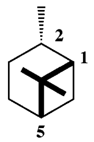
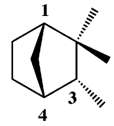
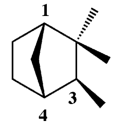
All CC-level results were carried out with the PSI3 program package,[60] and all B3LYP calculations with the Gaussian 03 package.[61]

III. Results and Discussion

Table 1 summarizes the experimental and theoretical $[\alpha]_D$ values for four alkanes: (1*R*,2*S*,5*R*)-*cis*-pinane, (1*S*,2*S*,5*S*)-*trans*-pinane, (1*S*,3*R*,4*R*)-endo-isocamphane, and (1*S*,3*S*,4*R*)-exo-isocamphane. The experimental rotations for the two pinanes were measured in the neat state, while those of the two forms of isocamphane were measured in toluene solution. We first note that all of the experimental rotations are small, less than 25 deg dm^{-1} (g/mL)$^{-1}$. For these four alkanes, the CCSD results are essentially indistinguishable from the B3LYP results, as compared to experiment. The mean absolute deviations of calculated and experimental $[\alpha]_D$ values are 13.6 for B3LYP, 14.9 for CCSD MVG, and 13.9 for CCSD LG. Both CC and DFT methods give the correct sign in only two of the four cases, *cis*-pinane and exo-isocamphane, with theory yielding essentially zero rotation for the *trans*-pinane case. The B3LYP result is closer to experiment for *cis*-pinane, while CCSD is closer for exo-isocamphane. The difference between the CCSD LG and MVG results is small in all four cases.

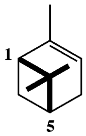
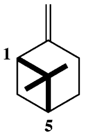
Table 2 summarizes the experimental and theoretical $[\alpha]_D$ values for two alkenes: (1*R*,5*R*)- α-pinene and (1*R*,5*R*)-β-pinene. The experimental specific rotations for both molecules were measured in the neat state. The CCSD MVG and LG

TABLE 1: Experimental and Theoretical[a] Values of $[\alpha]_D$ in deg dm^{-1} (g/mL)$^{-1}$ for Selected Alkanes

Molecule	Expt.[b]	B3LYP	CCSD (MVG)	CCSD (LG)[c]	$\|\|\Delta\|\|^d$
 (*1R,2S,5R*)-*cis*-pinane	+23.3	+17.9	+8.8	+8.8	1.4
 (*1S,2S,5S*)-*trans*-pinane	-15.9	+3.6	+0.0	-0.7	1.4
 (*1S,3R,4R*)-endo-isocamphane	+6.6	-11.1	-13.1	-9.8	0.5
 (*1S,3S,4R*)-exo-isocamphane	+15.8	+4.1	+6.5	+6.4	0.8

[a] B3LYP/aug-cc-pVDZ//B3LYP/6-31G* and CCSD/aug-cc-pVDZ(C)+cc-pVDZ(H)//B3LYP//6-31G*. [b] See refs 8 and 30 for original experimental references. [c] The center of mass was used as the coordinate-origin. [d] The norm of the CCSD(LG) origin-dependence vector in deg dm^{-1} (g/mL)$^{-1}$/a_0.

TABLE 2: Experimental and Theoretical[a] Values of $[\alpha]_D$ in deg dm^{-1} (g/mL)$^{-1}$ for Selected Alkenes

Molecule	Expt.[b]	B3LYP	CCSD (MVG)	CCSD (LG)[c]	$\|\|\Delta\|\|^d$
 (*1R,5R*)-α-pinene	+51.6	+42.4	+53.7	+44.1	8.7
 (*1R,5R*)-β-pinene	+23.1	-26.1	-2.0	-0.9	14.7

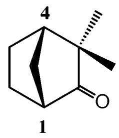
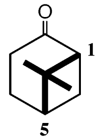
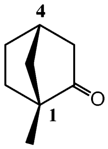
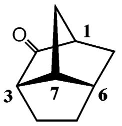
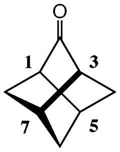
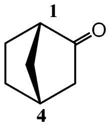
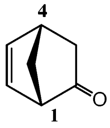
[a] B3LYP/aug-cc-pVDZ//B3LYP/6-31G* and CCSD/aug-cc-pVDZ(C)+cc-pVDZ(H)//B3LYP//6-31G*. [b] See refs 8 and 31 for original experimental references. [c] The center of mass was used as the coordinate-origin. [d] The norm of the CCSD(LG) origin-dependence vector in deg dm^{-1} (g/mL)$^{-1}$/a_0.

results are comparable for the alkenes, though the norms of the CCSD LG origin-dependence vectors are much larger than for the alkanes, indicating that the CCSD LG results are essentially arbitrary. The CCSD MVG results compare slightly more closely to experiment for the alkenes than B3LYP. The mean absolute deviations of calculated and experimental $[\alpha]_D$ values are 29.2 for B3LYP, 13.6 for CCSD MVG, and 15.8 for CCSD LG. For α-pinene CCSD MVG is nearly spot-on, whereas B3LYP undershoots by ca. 17%. Both B3LYP and CCSD (MVG and LG) give the wrong sign for β-pinene's $[\alpha]_D$, though CCSD yields essentially zero rotation in this case.

Table 3 summarizes the experimental and theoretical $[\alpha]_D$ values for seven ketones: (1*R*,4*S*)-camphenilone (measured in ethanol), (1*R*,5*S*)-nopinone (methanol), (1*R*,4*S*)-1-methylnorbornanone (chloroform), (1*R*,3*S*,6*S*,7*R*)-2-brendanone (ethanol), (1*R*,3*R*,5*R*,7*R*)-bisnoradamantan-2-one (ethanol), (1*S*,4*R*)-norbornanone (chloroform), and (1*S*,4*S*)-norbornenone (hexane). The range of values of $[\alpha]_D$ is much larger for the ketones than the alkanes or alkenes, with most between 40 and 80 deg dm^{-1} (g/mL)$^{-1}$, and one (norbornenone) much larger at −1146 deg dm^{-1} (g/mL)$^{-1}$. The mean absolute deviations of calculated and experimental $[\alpha]_D$ values are 42.7 for B3LYP, 115.2 for CCSD MVG, and 92.5 for CCSD LG. The CCSD deviations are dominated by the large-rotation norbornenone; if this case is excluded, the mean absolute deviations are 38.1 for B3LYP, 36.4 for CCSD MVG, and 40.3 for CCSD LG. The CCSD LG and MVG results vary considerably for the ketones, with large differences between the two representations for five of the eight molecules. In two cases, camphenilone and methylnorbornanone, the CCSD MVG and LG results bracket the B3LYP results. It is also noteworthy that B3LYP and CCSD LG yield the same sign in every case, and the CCSD MVG differs in sign from the other theoretical methods only for the small-rotation case of norbornanone (where it also agrees with experiment). All three methods give the correct sign for four of the seven ketones; B3LYP and CCSD LG give the wrong sign for nopinone, bisnoradamantan-2-one, and norbornanone. The failure of CCSD for (1*R*,3*R*,5*R*,7*R*)-bisnoradamantan-2-one is particularly large, with the MVG approach yielding the incorrect sign even though the total experimental rotation is nearly −80 deg dm^{-1} (g/mL)$^{-1}$.

For the 13 molecules considered above, the mean absolute deviations of calculated and experimental $[\alpha]_D$ values are 31.7 for B3LYP, 68.7 for CCSD MVG, and 56.5 for CCSD LG. If the norbornenone case is excluded, the mean absolute deviations become 28.4 for B3LYP, 25.4 for CCSD MVG, and 27.4 for CCSD LG. The CCSD MVG approach yields a different sign of $[\alpha]_D$ from B3LYP only for the case of norbornanone. Incorrect signs are obtained for the alkanes *trans*-pinane and endo-isocamphane, the ketones nopinone and bisnoradamantan-2-one, and the alkene β-pinene. It is noteworthy that, in all three cases in which the rotation is larger than 20 deg dm^{-1} (g/mL)$^{-1}$, i.e., the two ketones and β-pinene, the optical rotatory dispersion (ORD) curve is found to be bisignate in the wavelength domain of 650−355 nm,[62] indicating that at least two competing electronic states with antagonistic rotational strengths contribute significantly to the long-wavelength specific rotation. Thus, the sign errors by DFT and CC in these cases seem to correlate to the greater sensitivity of $[\alpha]_D$ to the relative excitation energies and rotational strengths of the relevant electronic states (which, in fact, may be vast in number[63]). On the other hand, the two problematic alkanes, which have relatively small $[\alpha]_D$, exhibit monosignate ORD, according to B3LYP/aug-cc-pVDZ calculations. (The ORD of exo-isocamphane, for which both CCSD

TABLE 3: Experimental and Theoretical[a] Values of [α]$_D$ in deg dm^{-1} (g/mL)$^{-1}$ for Selected Ketones

Molecule	Expt.[b]	B3LYP	CCSD (MVG)	CCSD (LG)[c]	$\|\|\Delta\|\|$[d]
 (*1R,4S*)-camphenilone	-72.3	-56.7	-69.6	-49.8	7.0
 (*1R,5S*)-nopinone	+39.9	-10.9	-8.7	-8.3	6.3
 (*1R,4S*)-1-methylnorbornanone	-45.5	-28.9	-33.3	-19.0	3.9
 (*1R,3S,6S,7R*)-2-brendanone	+46.6	+32.8	+47.8	+55.8	8.0
 (*1R,3R,5R,7R*)-bisnoradamantan-2-one	-78.4	+13.2	+50.2	+19.5	1.3
 (*1S,4R*)-norbornanone	+29.8	-10.4	+5.0	-7.6	4.3
 (*1S,4S*)-norbornenone	-1146.0[e]	-1216.5	-557.5	-740.4	7.1

[a] B3LYP/aug-cc-pVDZ//B3LYP/6-31G* and CCSD/aug-cc-pVDZ(C, O)+cc-pVDZ(H)//B3LYP//6-31G*. [b] See ref 8 for original experimental references. [c] The center of mass was used as the coordinate-origin. [d] Norm of the CCSD(LG) origin-dependence vector in deg dm^{-1} (g/mL)$^{-1}$/a_0. [e] Reference 19.

MVG and B3LYP yield the correct sign of [α]$_D$, is also bisignate, again according to B3LYP/aug-cc-pVDZ calculations.)

Several possible sources of error may account for the existing discrepancies between theory and experiment. First, the CC and DFT calculations employed here make use of relatively limited basis sets of approximately double-ζ quality. However, targeted tests with larger basis sets do not yield any significant improvement in the above results. As noted earlier, for norbornenone, the addition of diffuse functions to the hydrogen atoms at the CCSD level shifts the computed value of [α]$_D$ by 0.2%. In addition, improving the basis set for (1*R*,3*R*,5*R*,7*R*)-bisnoradamantan-2-one to aug-cc-pVTZ on the carbon and oxygen atoms while retaining the aug-cc-pVDZ basis for the hydrogen atoms (a total of 504 basis functions) shifts the B3LYP value of [α]$_D$ by only 0.8 deg dm^{-1} (g/mL)$^{-1}$ to +12.4, still far from the experimental value of −78.4 deg dm^{-1} (g/mL)$^{-1}$.

Second, the importance of triple and higher excitations on CC specific rotations has not yet been tested. To date the only study of triples to appear in the literature was reported by

TABLE 4: Gas-Phase Experimental and B3LYP/aug-cc-pVDZ//B3LYP/6-31G* and CCSD/aug-cc-pVDZ(C,O)+cc-pVDZ(H)//B3LYP//6-31G* Specific Rotations (deg dm^{-1} (g/mL)$^{-1}$) for α-Pinene, *β*-Pinene, and *cis*-Pinane at Several Wavelengths

molecule	λ/ nm	expt.[b]	B3LYP	CCSD (MVG)	CCSD (LG)[c]
	633	+46.3 ± 2.5	+36.7	+46.0	+37.7
(1*R*,5*R*)-α-pinene	589	+55.0[d]	+42.4	+53.7	+44.1
	355	+188.2 ± 2.2	+94.4	+171.6	+141.2
	633	+4.66 ± 0.6	−20.0	−0.5	+0.6
(1*R*,5*R*)-*β*-pinene[c]	589	+2.8[d]	−26.1	−2.0	−0.9
	355	−69.7 ± 3.2	−257.1	−86.6	−89.3
	633	+12.2 ± 2.6	+15.1	+7.4	+7.4
(1*R*,2*S*,5*R*)-*cis*-pinane	589	+14.2[d]	+17.9	+8.8	+8.8
	355	+61.9 ± 3.5	+68.5	+35.8	+35.4

[a] B3LYP/aug-cc-pVDZ//B3LYP/6-31G* and CCSD/aug-cc-pVDZ(C,O)+cc-pVDZ(H)//B3LYP//6-31G*. [b] Reference 51. [c] The center of mass was used as the coordinate-origin. [d] Interpolated gas-phase value. [e] Opposite-sign experimental values taken from ref 51 for (1*S*,5*S*)-*β*-pinene.

Kongsted et al. for the relatively small methyloxirane system,[24] and even in that case, the absolute contribution of triples was found to be only a few deg dm^{-1} (g/mL)$^{-1}$. Thus, it seems unlikely that large changes in $[\alpha]_D$ would be produced by higher levels of electron correlation, though for species with sensitive bisignate ORD, this remains a possibility. Furthermore, for molecules as large as those considered here, with up to ten heavy atoms, significant algorithmic advances would be required to undertake such a task. (We note that the CCSD-level calculations reported here consumed thousands of hours of computing time.)

Third, vibrational and temperature effects have been neglected in the theoretical calculations. Although several studies have demonstrated that such effects can be significant in certain cases, the molecules considered here are all conformationally rigid, with at most methyl rotations available to produce low-frequency vibrational shifts. Mort and Autschbach reported that zero-point vibrations can account for as much as 20% of the value of $[\alpha]_D$ for rigid species,[64] which would be insufficient to correct the sign errors in most of the cases in this work. On the other hand, a combination of zero-point vibrations and temperature corrections has been reported to produce changes in the sign of the specific rotation for shorter wavelengths for problematic cases such as methyloxirane[10,23,24] and methylthiirane.[65]

Fourth, the theoretical calculations reported here are limited to isolated molecules, and thus simulate only the gas-phase specific rotations, while all of the experimental data reported in Tables 1−3 were obtained for liquid-phase samples (either in solutions or neat liquids). Vaccaro, Wiberg, and co-workers have recently addressed the issue of solvation effects on optical rotation with the development of the cavity ring-down polarimetry (CRDP) technique, which has allowed the first room-temperature measurements of the specific rotation of gas-phase samples.[51,66,67] Table 4 reports theoretical and CRDP specific rotations of α-pinene, *β*-pinene, and *cis*-pinane at 633 and 355 nm (along with interpolated values at 589 nm). The shift between the gas- and liquid-phase rotations is small for α-pinene but is much more significant (and toward more negative values) for both *cis*-pinane and *β*-pinene. For *cis*-pinane, the shift from liquid- to gas-phase brings the experimental value of $[\alpha]_D$ in between the B3LYP and CCSD results, whereas for *β*-pinene, the CCSD results are much closer to the very small gas-phase value of $[\alpha]_D$ than to the neat-liquid value, though still with the wrong sign. Both B3LYP and CCSD produce the correct shape of the ORD curve for all three molecules. For α-pinene and *β*-pinene, the CCSD MVG approach compares very well to the experimentally measured dispersion, whereas B3LYP turns up too slowly for α-pinene and turns downward too quickly for *β*-pinene, resulting in large errors in the 355 nm rotations. On the other hand, the B3LYP results are excellent for *cis*-pinane at all wavelengths, whereas CCSD underestimates the ORD curve by *ca.* 40%.

The norbornenone case deserves special commentary because, although both CC and DFT methods yield the correct sign of $[\alpha]_D$, the gross underestimation of the value of the rotation by the CC methods nevertheless indicates a serious discrepancy between theory and experiment. (Another problematic case for CC methods is that of *trans*-cyclooctene, as pointed out by McCann and Stephens.[31]) As first pointed out by Ruud et al.,[19] quantum chemical calculations of the specific rotation vary dramatically in magnitude depending on the level of theory employed. While the Hartree−Fock method, which neglects electron correlation, underestimates the experimental value of $[\alpha]_D$ by nearly a factor of 2 [−607 deg dm^{-1} (g/mL)$^{-1}$], CC methods improve upon this result very little: CC2[68] shifts the Hartree−Fock value toward experiment [−1000 deg dm^{-1} (g/mL)$^{-1}$], whereas CCSD MVG shifts it away [−558 deg dm^{-1} (g/mL)$^{-1}$]. Meanwhile, the much less expensive B3LYP model [−1217 deg dm^{-1} (g/mL)$^{-1}$] compares very well with experiment in this case, differing by only a few percent. As noted above for the complete set of molecules considered here, it is unlikely that basis set, vibrational corrections, or additional electron correlation effects can account for the large difference between the CCSD and experimental $[\alpha]_D$ values. Is it possible, then, that the gas- and liquid-phase specific rotations of norbornenone may differ so substantially as to explain the apparent failure of CCSD in this case? The fact that $[\alpha]_D$ does not vary significantly in a variety of solvents, including isooctane [−1142 deg dm^{-1} (g/mL)$^{-1}$],[69] chloroform [−1236 deg dm^{-1} (g/mL)$^{-1}$],[70] and hexane [−1146 deg dm^{-1} (g/mL)$^{-1}$],[71] suggests that this may not be the case. However, similar shifts in substituted allenes have recently been observed,[72] and experimental and theoretical efforts to elucidate this problem are underway.

IV. Conclusions

We have carried out B3LYP and CCSD calculations of the sodium D-line specific rotations of a set of 13 small, conformationally rigid molecules with established absolute configurations, including a selection of problematic alkenes, alkanes, and ketones, for comparison to available experimental data. We find no substantial difference in the abilities of DFT and CC models to reproduce liquid-phase experimental results. For the systems considered here, origin-independent B3LYP and CCSD models give the same sign for the rotation of all but one molecule (norbornanone). For those alkenes and ketones for which both DFT and CC give incorrect signs relative to experiment, all exhibit bisignate ORD, suggesting that the models are unable to replicate the delicate balance among competing electronic states with antagonistic rotational strengths in such cases. Among the possible sources of error—basis set incompleteness, electron correlation, deficiencies in the choice of density-functional, vibrational and temperature effects, and solvation—the most significant source of error may be the comparison between theoretical gas-phase and experimental liquid-phase specific rotations, particularly given the overall agreement between the DFT and CC models.

The extension of theoretical models of optical rotation to include solvent effects may be carried out via continuum-based theories, by explicit solvation, or a combination of the two. The first approach has been considered by Mennucci et al.,[73] using the polarizable continuum model (PCM) of Tomasi and coworkers.[74] Mennucci et al. found that the PCM approach reproduced the experimental variations in $[\alpha]_D$ for a number of solvents, including cyclohexane, acetone, methanol, and acetonitrile, but not for carbon tetrachloride, benzene, and chloroform, presumably due to the PCM's lack of nonelectrostatic solvent−solute interactions. An explicit solvation approach, on the other hand, requires inclusion of a sufficient number of solvent molecules, at least within the cybotactic regime, in the specific rotation calculations.[75,76] However, this requires a molecular dynamics simulation of the resulting cluster, an approach that is both more complicated/expensive and of uncertain reliability due to the present limitation of such simulations to classical force fields. The third possibility of combining molecular dynamics simulations of limited numbers of explicit solvent molecules together with a continuum-based description of more distant interactions may eventually provide a reasonable compromise, but even this approach remains too expensive for all but the smallest systems. Clearly significant new advances are needed for the accurate, yet practical theoretical description of solvent effects on chiroptical properties.

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