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Temperature Dependence of the Optical Rotation of Fenchone Calculated by Vibrational Averaging

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On the basis of vibrational averaging, the temperature dependence of the optical rotation for fenchone has been calculated using TDDFT with the B3LYP hybrid functional at three wavelengths. The results show that very good agreement is obtained between theory and experiment. It is concluded that temperature-dependent vibrational effects are likely to account for much of the observed temperature dependence in optical rotation exhibited by rigid organic molecules in case there is only a weak temperature-dependent interaction with the solvent.

The use of optical rotatory dispersion (ORD) and circular dichroism (CD) spectra for assigning absolute configurations of organic molecules has presented a unique challenge for accurate computational predictions of the linear response of chiral molecules.[1−9] Moreover, vibrational effects to chiroptical properties have been shown to be quite significant.[10−14] Therefore, including vibrational effects in the calculation of optical rotation is likely to be an important factor for reproducing experimental data.[6,7] It is further clear that vibrational corrections can be responsible for a temperature dependence of the optical rotation of rigid molecules.[15,14] For conformationally flexible molecules, one may determine a Boltzmann average of the optical rotation of each one of the contributing conformers.[16−18]

We report the calculation of the temperature dependence of the optical rotation of a rigid organic molecule and compare the results to experimental data published recently by Wiberg et al.[15] For demonstrating the vibrational effects, fenchone was selected. The CD and ORD for fenchone calculated by time-dependent density functional theory (TDDFT) have recently been shown to agree very well with experiment.[19] Knowing that the deviating effects in the quality of the calculated optical rotation due to basis set, solvent, functional, correlation effects, and so forth, in the UV−vis range are relatively small for this molecule, we are free to have a transparent view of the vibrational effects on the optical rotation. Consequently, we have selected fenchone for an initial theoretical study of the temperature dependence of optical rotation.

General techniques for calculating vibrational averages have been discussed in the literature.[10,13] The temperature dependence of optical rotation represented as a general molecular property, P, can be modeled with a convenient first-order expression:[20]

$$\langle P\rangle_T = P_\mathrm{e} + \frac{1}{4}\sum_i \coth\left(\frac{\epsilon_i}{2kT}\right)\left(\frac{\partial^2 P}{\partial q_i^2}\right) - \frac{1}{4\hbar}\sum_i \frac{1}{\omega_i}\left(\frac{\partial P}{\partial q_i}\right)\sum_j \coth\left(\frac{\epsilon_j}{2kT}\right)k_{ijj} \quad (1)$$

The term in the vibrational correction involving the second derivatives of P represents the property curvature correction. The term involving the cubic force constants k_{ijj} represents the anharmonicity correction. In eq 1, ϵ_i is the energy and ω_i is the frequency of normal mode i. P_e is the equilibrium optical rotation, T is the temperature, k is the Boltzmann constant, and q_i is the dimensionless normal coordinate number i. For $kT \gg \epsilon_i$, the coth factor increases linearly with temperature.

The calculations of the property derivatives in eq 1 have been performed via numerical differentiation. Thus, it was necessary to calculate the optical rotation for each wavelength at each one of $2(3N - 6)$ displaced geometries (where N is the number of atoms), resulting in a total of 450 computations of the optical rotation and energy gradients. Large parallel computational clusters are ideal for these types of calculations. Details of the procedure have been published previously.[13] Because accurate calculations of linear response properties can be quite time-consuming, the computation of the vibrational average of optical rotation is a rather demanding task. Due to the limit of computing resources available, we had to forego the calculation of vibrational averages for a large set of rigid organic molecules. The results of these computations will be published elsewhere.

The experimental and calculated temperature dependence for the specific optical rotation of fenchone is shown in Figure 1. We have evaluated eq 1 using the aug-cc-pVDZ basis set and the B3LYP hybrid functional. The optical rotation was obtained with the gauge-including atomic orbital (GIAO) method as implemented in Gaussian 03.[21] The experimental data are displayed in the form of least-squares linear regressions as given in the literature.[15]

From Figure 1, it can be seen that excellent qualitative and quantitative agreement exists between experiment and theory for the temperature dependence of the specific rotation. Wiberg et al. reported a linear change in the optical rotation of fenchone as a function of temperature over the range from 0 to 100 °C. We calculate the same qualitative linear dependence over this temperature range; that is, the temperature-dependent vibrational averaging procedure accurately predicts the correct magnitude and sign of the temperature effects on optical rotation. The increase in the slopes with decreasing wavelength is also in agreement with experimental observations; that is, the temper-

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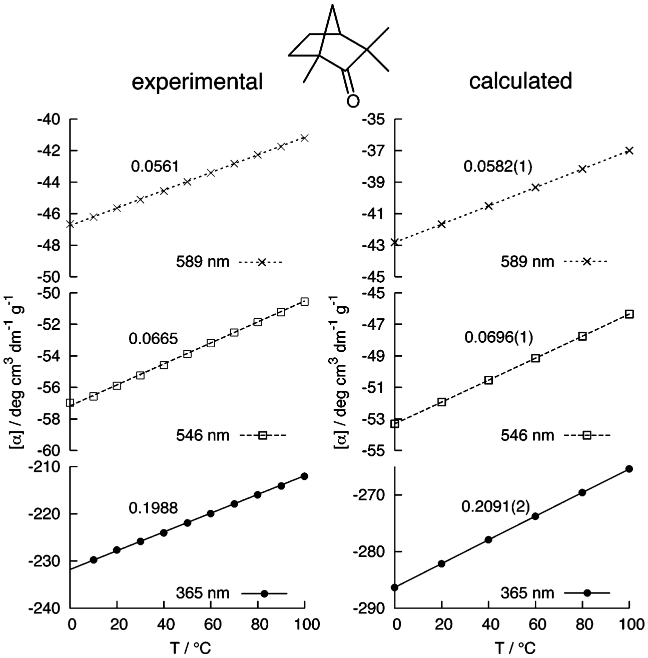

Figure 1. Experimental and calculated specific optical rotation of fenchone for three wavelengths as a function of temperature. Linear regression of experimental data points from ref 15. Slopes are indicated in units of deg·cm^3·dm^{-1}·g^{-1}/°C. Standard deviation of linear regression slopes is reported for calculated data.

TABLE 1: Comparison of Experimental and Calculated Specific Rotations for Three Wavelengths of Fenchone[a]

λ (nm)	$[\alpha]_{\text{exptl}}$	$[\alpha]_e$	$\Delta[\alpha]_a$	$\Delta[\alpha]_p$	$\langle[\alpha]\rangle_0$	$\langle[\alpha]\rangle_{273}$
365	−231.8[b]	−337.89	19.59	−5.72	−324.03	−286.32
546	−56.97	−75.51	5.18	4.75	−65.58	−53.31
589	−46.66	−61.45	4.26	4.11	−53.08	−42.82

[a] Experimental data from ref 15. The units of optical rotation are deg·cm^3·dm^{-1}·g^{-1}. $[\alpha]_{\text{exptl}}$ is the experimental optical rotation at 0 °C. $[\alpha]_e$ is the calculated equilibrium optical rotation. $\Delta[\alpha]_a$ and $\Delta[\alpha]_p$ are the zero-point vibrational contributions for the anharmonicity and property curvature terms. $\langle[\alpha]\rangle_0$ and $\langle[\alpha]\rangle_{273}$ are the vibrationally averaged optical rotations at the zero-point level and at 0 °C. [b] Calculated from the experimental linear regression.

ature dependence becomes more pronounced for shorter wavelengths. The agreement with experiment for the slopes is within about 5% for all wavelengths.

Table 1 shows the experimental and calculated optical rotations and the results of the vibrational averaging procedure for fenchone. At all three frequencies shown here, the zero-point vibrational correction (ZPVC) is positive. As the wavelength increases, the total percentage of ZPVC increases. At 365 nm, the relative zero-point correction is rather small, only about 4%, while, at 589 nm, it is much larger, that is, 14%. From analyzing the normal modes, it is concluded that there is no single vibration that stands out as an overwhelmingly strong contributor to the overall ZPVC. This finding is in agreement with our recent benchmark study of the ZPVC of optical rotation.[13] Including zero-point vibrational effects in the calculated optical rotations for fenchone yields results slightly closer to experiment. Generally, here the ZPVC contributions from the anharmonicity term (*a*) are somewhat larger in absolute value, but of about the same order of magnitude, than the property surface curvature term (*p*).

Temperature effects based on the vibrational averages for the optical rotation of fenchone provide between 12 and 19% additional correction. Here, low-frequency modes dominate the correction but we did not find one or a few obvious major contributors. As the temperature increases, there is a greater contribution from low-energy modes due to a stronger increase in the coth factor for lower vibrational frequencies. Although higher energy modes contribute to the overall vibrational correction at all temperatures examined here, an increase in temperature has a greater effect on the low-frequency modes, which consist mainly of a mixture of the bicyclic skeleton's bending and twisting modes and methyl torsions below 400 cm^{-1}. The relative temperature effects (percentages) are largest at 589 nm. For all three wavelengths, they result in closer agreement with experiment.

Time-dependent density functional theory (TDDFT), albeit being the method of choice for the present study, cannot be expected to yield perfect agreement with experiment due to inherent approximations. According to investigations by Stephens and co-workers, the B3LYP hybrid functional along with the aug-cc-pVDZ basis yields mean absolute deviations of about 25 deg·cm^3·dm^{-1}·g^{-1} between experimental and calculated specific rotations of organic molecules at 589 nm.[3,8] For this wavelength, our calculations are well within the expected deviations. It should be noted that 365 nm is not far from the trough of a negative Cotton effect.[19] An excitation with negative rotatory strength is located at about 290−295 nm. For further details of the nature of the fenchone CD spectrum and an assignment of the CD bands, we refer the reader to refs 7, 19, and 22. Our computations do not include broadening of the excited states which, however, may help to rationalize only a (perhaps small) part of the overestimation of the optical rotation at this short wavelength.

It is known that TDDFT tends to underestimate excitation energies for many organic molecules,[23] which might be a major factor contributing to observed deviations between theory and experiment in particular for the equilibrium optical rotation. Since the behavior of the temperature dependence is correctly predicted by TDDFT, one can imagine that the comparatively efficient TDDFT vibrational averaging method could be highly useful in conjunction with a high-accuracy computational model for calculating equilibrium optical rotations,[9] which should yield very close agreement with experiment. However, the computational expense of applying coupled cluster response theory to a vibrational averaging of properties for a molecule as large as fenchone by numerical differentiation is prohibitive at this time.

With the present theoretical approach, we have demonstrated that the temperature dependence of the optical rotation in fenchone is a result of temperature-dependent vibrational corrections. The magnitudes and trends of the vibrational corrections as a function of temperature coincide with experimental observations, confirming that solvent effects do not necessarily play a major role in this temperature dependence.[15] Although experimental data were obtained in the solvent ethylcyclohexane, our gas phase calculations allow us to make this conclusion because we may expect only a very limited interaction between this apolar and aprotic solvent and fenchone. These conclusions are likely to hold true for other rigid organic molecules where there is little interaction between the solute and solvent molecules. Within this realm, the computational results presented here show that theory can give qualitative and quantitative agreement of the temperature dependence of optical rotation with experimental observations. For cases where there are temperature-dependent solvent−solute interactions influencing the optical rotation, calculations as performed here may be useful to separate such solvation-induced temperature dependence from the intrinsic vibrational effects.

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Supporting Information Available: The complete citation for ref 21. This material is available free of charge via the Internet at http://pubs.acs.org.

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