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Solvent Effects on the Optical Rotation of (*S*)-(−)-α-Methylbenzylamine

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The optical rotation of (*S*)-(−)-α-methylbenzylamine at 589 nm has been measured in 39 different solvents at five different concentrations: 0.25, 0.50, 1.00, 2.00, and 3.00 M. A correlation of the intrinsic rotations (i.e., extrapolation of specific rotations to zero concentration) with Kamlet's and Taft's solvent parameters (α, β, and π^*) is established. The polarity/polarizability, π^*, and solvent acidity, α, terms are found to have a greater effect upon the optical rotation than the basicity of the solvent, β. The specific rotation for (*S*)-(−)-α-methylbenzylamine has been calculated with Gaussian03 using a PCM model (B3LYP aug-cc-pVDZ) for all 39 solvated systems. Comparisons between the experimental and calculated values show the importance of hydrogen bonding on specific rotation.

Introduction

A majority of chemical phenomena occurs in solution. Consequently, many studies have focused on environmental effects upon chemical reactions, which revolve around the role of the solvent and its interaction with the solute. A growing number of studies have considered the effects of the solvent upon reaction rates,[1] NMR,[2,3] UV−vis,[4] vibrational spectroscopy,[5,6] CD,[7−9] and ORD.[10,11] Generally, attempts are made to correlate properties of the solvent (dielectric constant, acidity, dipole moment, polarizability, etc.) to trends in experimental observations. This study will focus on the influence of solvents upon the optical rotation of (*S*)-(−)-α-methylbenzylamine (MBA).

(*S*)-(−)-α-Methylbenzylamine, shown in Figure 1, belongs to a class of medically and biochemically important amines. Several papers[12,13] have used various theoretical methods to examine the molecule's conformational behavior in solution. An understanding of the chiroptical properties of MBA in pharmaceutical environments is of paramount importance. The circular dichroism of MBA and its derivatives has been well studied.[14−18] Likewise, the optical rotatory dispersion of MBA has also been widely examined.[19−24] These studies have focused mainly upon substitutional and Cotton effects; however, none of these studies has considered how the solvent interacts with MBA to affect its optical rotation.

A wide variety of intrinsic and empirical solvent parameters exist, ranging from the dielectric constant, polarizability, acceptor and donor numbers, $E_T(30)$, to the Kamlet−Taft parameters α, β, and π^*. [25] The acceptor number[26] is an empirical quantity describing the electrophilic character of a solvent, and the donor number is a synonymous term that portrays the nucleophilicity of the solvent. The $E_T(30)$ solvent parameter[27] is a scale of solvent polarity based upon the transition energy for the longest wavelength absorption band of a pyridinium *N*-phenoxide betaine dye. The terms α, β, and π^* represent a solvent's acidity, basicity, and polarity/polarizability, respectively. Specifically, each term is based upon spectral shifts from a large catalog of UV/vis data for solvatochromic compounds.

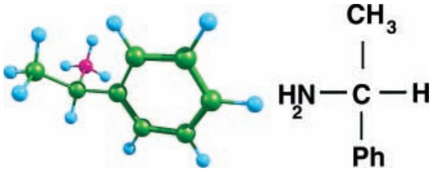

Figure 1. Structure of (*R*)-(+)-α-methylbenzylamine and (*S*)-(−)-α-methylbenzylamine, respectively.

The Kamlet−Taft parameters have been successfully applied to the description of numerous spectroscopic phenomena: NMR[28], UV−vis,[29] and IR.[30] For this study, α, β, and π^* were utilized as the solvent parameters to describe optical rotation. Unlike many previous molecules that have been studied, MBA is able to both give and accept hydrogen bonds. As a result of this behavior, selection of the Kamlet−Taft parameters for the description of the optical rotation appears to be an ideal method to describe the solvents' capabilities to give and accept hydrogen bonds from MBA. In this study, the specific rotation was fit using the solvent parameters as

$$[\alpha]_{\lambda}^{T} = a\alpha + b\beta + c\pi^* + [\alpha]_{0,\lambda}^{T} \tag{1}$$

where α, β, and π^* are the Kamlet−Taft solvent parameters, $[\alpha]_{\lambda}^{T}$ is the observed specific rotation, and $[\alpha]_{0,\lambda}^{T}$ is the optical rotation in a hypothetical noninteracting solvent at wavelength λ and temperature T.

Solvation models are typically derived from the work of Born,[31] Kirkwood,[32] and Onsager.[33] Several key features are used to differentiate types of solvation models, namely treatment of electrostatic interactions, the shape of the cavity, and the treatment of nonelectrostatic interactions. Electrostatic interactions are the result of the placement of the solute's charge distribution leading to a solvent reaction potential; examples of treatment of the electrostatic interactions are the use of the molecular dipole,[33] a multipole charge distribution in a self-consistent reaction field (SCRF),[34] and variations of the mutlipole charge distribution[35] where the charge distribution is centered on atoms and bonds. The shape of the cavity for the solute molecule has evolved from being a simple spherical cavity to either a cavity defined by interlocking van der Waals spheres or ellipsoidal shapes. The nonelectrostatic terms describe the

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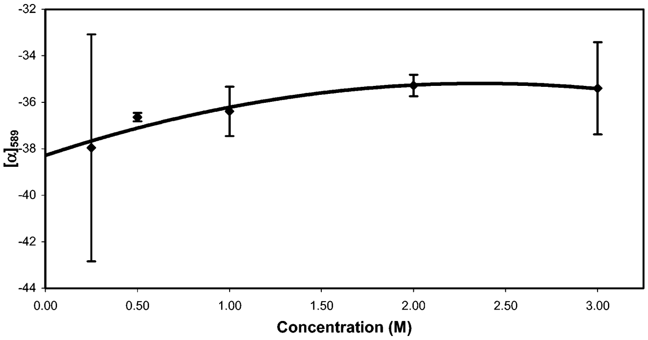

Figure 2. Example of extrapolating optical rotation to zero concentration shown in *n*-pentane. Quadratic line of best fit is shown and extrapolates to −38.29°; error bars for each data point are shown. Error bars are the result of the deviation from the three separate measurements; in general, it can be seen that the error in the lowest concentration is much larger than any other concentration recorded.

other effects that are not electrostatic in nature (dispersion, repulsion, and cavitation energies).

Briefly, the polarizable continuum model,[36] PCM, places the solute with a charge distribution $\rho(\mathbf{r})$ in a cavity which is inside of an infinitely large polarizable dielectric medium having permittivity ϵ. The molecular charge induces a reaction potential in the solvent (dielectric continuum), which in turn acts on the solute and changes the initial charge distribution, $\rho(\mathbf{r})^0$. The PCM methodology has been successfully applied to many different problems (see Tomasi[37] for a review), and among those are the geometries and energetics of hydrogen bonded systems. Recent studies[38−40] have surveyed many chemical systems and concluded that the B3LYP density functional with either the 6-311++G(2d,2p) or aug-cc-pVDZ basis set is an economic and efficient means to calculate the effects of solvation on specific rotation with reasonable accuracy. This computational approach was compared with experimental optical rotations for MBA in various solvents.

Experimental Section

(*S*)-(−)-α-Methylbenzylamine was obtained from Aldrich (>98%) and used without further purification. Solutions of (*S*)-(−)-α-methylbenzylamine and various solvents were prepared at concentrations of 0.25, 0.50, 1.00, 2.00, and 3.00 M. None of the solvents utilized in this study were purified further; a complete list of the solvents utilized is available in the supplementary information. Appropriate volumes of MBA were combined with each of the solvents to give a total volume of 2.0 mL at a molarity, M. All data points presented represent the average of 3 or more measurements for each specific concentration. Optical rotations of the prepared solutions were measured on a Perkin-Elmer 241 polarimeter at 25 °C at 589 nm in a 1 cm cell. The experimental values for each concentration were fit to a quadratic curve as suggested by Landolt[41] and Eliel,[42] and the intrinsic rotation was found by extrapolating the optical rotation to zero concentration, as shown in Figure 2. As seen in the extrapolation to zero concentration in *n*-pentane in Figure 2, the standard error in the lowest concentration data point is much larger than for the other concentrations, thus higher concentrations were utilized when a concentration profile of the optical rotation was made. The intrinsic rotation is defined as the specific rotation in an infinitely dilute solution, thus avoiding solute−solute interactions. Because calculated values of optical rotation are performed on an isolated molecule, experimental measurements must be made or inferred on isolated molecules in solution to be compared to calculated optical rotations, thus the extrapolation of optical rotation to zero concentration.[43] All optical rotation calculations were performed using the Gaussian03 program[44] with the B3LYP functional using an aug-cc-pVDZ basis set and PCM method of solvation. All necessary solvent parameters (dielectric constant, solvent radius, density, n_D^2 for dielectric constant at infinite frequency) necessary for the calculations were taken from Marcus'[45] tabulation of solvent properties. Only one minimum energy conformation (shown in Figure 1) was considered, as other conformations of MBA would be expected to be higher in energy; all geometries utilized were optimized with PCM solvation included in the system. A simple multiple variable linear regression analysis was utilized for data analysis.

TABLE 1: Intrinsic Rotations, Calculated Specific Rotations, and Kamlet and Taft Solvent Parameters for Each Set of Selected Data[a]

solvent	$[\alpha]_{int}$	$[\alpha]_{calc}$	β	α	π^*
acetone	−39.10	−33.57	0.48	0.08	0.62
carbon tetrachloride	−52.29	−48.12	0.10	0.00	0.21
toluene	−31.34	−46.05	0.11	0.00	0.49
methanol	−26.38	−32.71	0.66	0.98	0.60
cyclohexane	−40.62	−50.46	0.00	0.00	0.00
nitrobenzene	−41.97	−35.12	0.30	0.00	0.86
acetonitrile	−33.38	−33.63	0.40	0.19	0.66
1,4-dioxane	−34.17	−48.16	0.37	0.00	0.49
di-*n*-butyl ether	−33.23	−41.80	0.46	0.00	0.18
benzene	−31.86	−46.75	0.10	0.00	0.55
nitromethane	−29.34	−34.24	0.06	0.22	0.75
n-pentane	−38.29	−52.66	0.00	0.00	−0.15
benzonitrile	−29.14	−35.05	0.37	0.00	0.88

[a] Intrinsic rotations are the extrapolation of best line fit of the data to infinite dilution for comparison with calculated specific rotations.

Results and Discussion

The experimental and calculated results for a select set of solvents are shown in Table 1; the complete set of data is available in Supporting Information. Inclusion of solvent effects via PCM calculations is unable to account for concentration dependent effects; thus the concentration dependent optical rotation is fit to an appropriate form, as suggested by Landolt[41] and Eliel[42] (and recently supported by Polavarapu[43]) and the specific rotation at infinite dilution, intrinsic rotation, is used. Transformation of the experimental data to the intrinsic rotation, $[\alpha]_{int}$, allows for a comparison with calculations, which assume an isolated molecule. The results of fitting the experimental intrinsic rotation to various standard correlations (Onsager function,[33] dipole moment, $E_T(30)$ values, polarizabilities) for MBA are seen in Figure 3. The correlation between the specific rotation and the Onsager function ($\epsilon - 1/2\epsilon + 1$) is rather weak with an R^2 value of 0.172, where R^2 defines the degree of correlation. There is also no observed correlation between the specific rotation and the dipole moment, *D*, with an R^2 value of 0.057. $[\alpha]_{int}$ is seen to decrease with increasing $E_T(30)$ with an R^2 value of 0.313. No correlation was found with $[\alpha]_{int}$ and polarizability with an R^2 value of 0.058; polarizabilities were calculated using the Clausius−Mosotti equation.[46]

Previous publications have successfully utilized the Onsager function, dipole moment, and $E_T(30)$ to correlate the observed specific rotations. Rule and McLean[47] have extensively examined the effects of polar solvents on optical rotation for various chiral solutes. In this series of papers, they were able to make generalizations to the effects of highly polar solvents and associated solvents upon the optical rotation but did not consider other chemical effects. Mukhedkar[10] investigated the effects of the dipole moment of the solvent on the optical rotation of

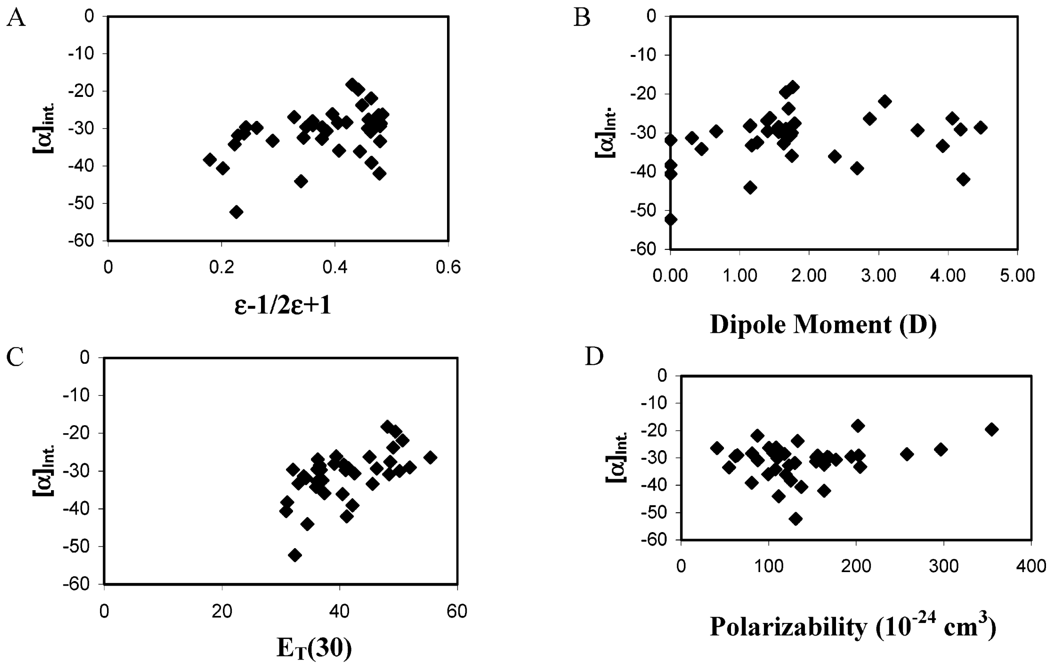

Figure 3. Plots of the intrinsic rotation of MBA at 589 nm against (A) Onsager function, (B) dipole moment, and (C) $E_T(30)$ (D) polarizability. The results for all solvents are shown.

TABLE 2: Results for Multivariable Linear Regression Analysis for Intrinsic, $[\alpha]_{int}$, Optical Rotation

	α	β	π^*	$[\alpha]_0$	*R* value
$[\alpha]_{int}$	9.84	1.02	10.40	−39.80	0.667

[a] The standard errors of each coefficient for each method are as follows: $[\alpha]_{int} = \alpha \pm 3.12$, $\beta \pm 3.48$, $\pi^* \pm 3.07$, and $[\alpha]_0 \pm 2.25$.

camphor and α-bromocamphor; a nearly linear relationship was found between the apparent dipole moment and a rotational parameter. Kumata et al.[11] attempted to correlate the rotivity, Ω, given by

$$3\Omega = \frac{3[\alpha]}{n^2 + 2} \tag{2}$$

where [α] is the specific rotation and *n* is the index of refraction of the solvent, to the chiroptical properties of propylene oxide with the Onsager function and $E_T(30)$ values. In both cases, a poor linear relationship was found. Mennucci et al.[38] correlated the optical rotations of rigid chrial organic molecules with $E_T(30)$ values and noted a modest correlation. On the other hand, Wiberg et al.[48] reported a correlation of the Onsager function with the optical rotation of 2-chloropropionitrile in a series of solvents. For these examined sets of molecules, hydrogen bonding can occur through either donation or acceptance of the hydrogen, but both processes do not occur in each of the molecules. (*S*)-(−)-α-Methylbenzylamine can donate to or accept a hydrogen bond from the solvent; therefore, a more complete means of describing the optical rotation of MBA in solution is desirable.

Table 2 shows the results for the experimental multiple variable regression analysis. The α, β, and π^* columns represent the relative importance of each solvent parameter to its contribution to the intrinsic optical rotation at 589 nm. A similar analysis was performed for light at 436 nm and yielded ratios of coefficients that were comparable to the results for 589 nm. $[\alpha]_0$ is the result of the statistical best fit to the optical rotation in a noninteracting solvent, such as cyclohexane. Statistically, there is little difference between the "goodness of fit" for the experimental and calculated values, thus allowing for direct comparison. For the multiple variable analysis, the π^* term is the dominant contributor, but the ability of the solvent to donate a hydrogen bond to the solute, the α term, is nearly equivalent. This observation indicates the importance of protonation of the amine by the solvent to the optical rotation. The ability of the solvent to accept a hydrogen bond from MBA, β, is seen to be a modest contributor to the intrinsic rotation.

An important result that will now be discussed is the profound difference in the inclusion of effects of hydrogen bonding. To demonstrate the impact of hydrogen bonding on optical rotation, an optimized B3LYP aug-cc-pVDZ PCM calculation in methanol of the fully protonated MBA (MBA^+) gave a specific rotation of −7.37°, whereas the optimized neutral geometry in methanol gave a specific rotation of −32.71°. The experimental intrinsic rotation of MBA in methanol is −26.38°, and when the effects of MBA hydrogen bonding to the methanol molecule are neglected, the percentage of hydrogen bonded MBA molecules can be calculated via

$$[\alpha] = k[a]_{MBA} + (1 - k)[a]_{MBA^+} \tag{3}$$

where [α] is the experimental intrinsic rotation in methanol, $[\alpha]_{MBA}$ is the calculated specific rotation in methanol of the neutral molecule, $[\alpha]_{MBA^+}$ is the calculated specific rotation of the cationic MBA in methanol, and *k* is the fraction of molecules that are not hydrogen bonded to methanol. Assuming that the calculated optical rotation in methanol is accurate, solving for *k* shows that approximately three-quarters of the MBA molecules are not hydrogen bonded to methanol at infinite dilution. The amount of hydrogen bonded MBA at infinite dilution in methanol is probably larger than one-fifth of all the MBA molecules. This deviation most likely reflects the inaccuracy of assuming complete protonation of MBA. It should be noted that the calculated specific rotation of the protonated MBA, MBA^+, is consistent with the prediction offered by the experimental values. The experimental intrinsic data analysis predicts that the specific rotation should be less negative upon protonation of MBA, as indicated from the α term, and this is

TABLE 3: Experimental Intrinsic and Calculated Specific Rotations for Solvents with $\epsilon < 3$ and Dipole Moment, μ, <1

solvent	$[\alpha]_{\mathrm{int}}$	$[\alpha]_{\mathrm{calc}}$	ϵ	μ (D)	$10^{-26}Q$ (esu cm^2)[a]
carbon tetrachloride	−52.29	−48.12	2.24	0.00	0.00
toluene	−31.34	−46.05	2.38	0.31	−8.00[b]
cyclohexane	−40.62	−50.46	2.02	0.00	13.20[c]
triethylamine	−29.62	−46.66	2.42	0.66	
1,4-dioxane	−34.17	−48.16	2.21	0.45	4.50[d]
benzene	−31.86	−46.75	2.27	0.00	−8.64[b]
n-pentane	−38.29	−52.66	1.84	0.00	

[a] The known quadrupole moments for solvents. [b] Perez-Casas, S.; et al. *J. Phys. Chem. B* **2003**, *107*, 4167. [c] Rebrion, C.; et al. *Chem. Phys. Lett.* **1987**, *136*, 495. [d] Reynolds, L.; et al. *J. Phys. Chem. B* **1996**, *100*, 10337.

observed qualitatively in the calculations. The explanation given above is not expected to be completely accurate but rather gives a general picture of the structure of MBA in solution utilizing the experimental and calculated data. To further address the structures of MBA in solution, we have recorded extensive FTIR and NMR data for five solvents. These results support the conclusions herein and will appear in a future publication. The quantitative results regarding the percentage of hydrogen bonded MBA molecules is intended as generalizations in the current publication and will be addressed in more detail in future work.

Comparison of the experimental and calculated values can be extended to the optimized values for $[\alpha]_0$, where MBA is not directly interacting with the solvent or itself. It should be noted that $[\alpha]_0$ corresponds to a system with no hydrogen bond donating or accepting capabilities (α and $\beta = 0$) and no polarizability/dipolarity ($\pi^* = 0$), as defined by Kamlet and Taft.[25] The noninteracting solvated optical rotation is −40.62° (obtained from cyclohexane data) whereas the calculated gas-phase optical rotation at 589 nm is −70.79°. The $[\alpha]_0$ from the experimental best fit is −39.80° whereas the calculated optical rotation in cyclohexane is −48.19°, showing a glaring difference in the two methodologies. This distinct difference between methodologies does not restrict itself exclusively to cyclohexane; Table 3 shows a comparison of intrinsic and calculated specific rotations with solvents having small dielectric constants ($\epsilon < 3$) and small dipole moments ($\mu < 1$ D). Several of the solvents in Table 3 have the capability to form or accept hydrogen bonds, which are not included in the calculation. Table 3 shows that calculated specific rotations for solvents with low dipole moments differ significantly from the experimentally observed rotations. Wiberg et al.[48] suggest that solvents with zero dipole moment but large polarizabilities and quadrupole moments (or higher order moments) give larger than expected solvent effects; this may explain the deviation that is seen between the experimentally observed intrinsic rotations, $[\alpha]_{\mathrm{int}}$, and the calculated specific rotations, $[\alpha]_{\mathrm{calc}}$, shown in Table 3.

Conclusion

The specific rotation of (*S*)-(−)-α-methylbenzylamine has been measured in a wide range of solvents in a set of concentrations such that the intrinsic rotation, $[\alpha]_{\mathrm{int}}$, can be determined and then correlated with the Kamlet and Taft solvent parameters α, β, and π^*. This first published correlation of specific rotation to the Kamlet and Taft solvent parameters is seen to be reasonably good. The data clearly show that direct interactions from hydrogen bonding are needed for a complete description of MBA in solution. The analysis further shows that the solvent protonating MBA at infinite dilution is nearly equally important as the effects of the polarity/polarizability of the solvent. To accurately determine the specific rotation of a system that can accept and donate hydrogen bonds, both chemical phenomena must be accounted for in determining the specific rotation. In accord with recent observations of Wiberg et al.,[48] solvents with small dipole moments ($\mu < 1$) but large polarizabilities and quadrupole moments give larger than expected solvent effects on optical phenomena.

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Supporting Information Available: A comprehensive table of the experimental and calculated results is available for the complete set of solvents utilized. This material is available free of charge from the Internet at http://pubs.acs.org.

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