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Prediction of optical rotation using density functional theory: 6,8-dioxabicyclo[3.2.1]octanes

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Abstract

We report calculations of the optical rotations of six 6,8-dioxabicyclo[3.2.1]octanes using ab initio density functional theory (DFT). GIAO basis sets are used to ensure origin independence of predicted rotations. Large basis sets including diffuse functions are used to minimize basis set error. The signs of $[\alpha]_D$ are correctly predicted. Magnitudes differ from experiment by 10–20 degrees [dm (g/cc)]$^{-1}$ on average. Agreement with experiment is improved by inclusion of solvent effects via the Polarized Continuum Model (PCM). The results support the conclusion that DFT/GIAO/PCM calculations of specific rotations can be useful in elucidating the absolute configurations of chiral molecules. © 2000 Elsevier Science Ltd. All rights reserved.

The optical rotation of a chiral molecule depends on its absolute configuration. In principle, absolute configurations of chiral molecules should be derivable from their optical rotations. In practice, optical rotations are rarely used for this purpose. This is attributable to the absence of practical, reliable algorithms relating optical rotation and absolute configuration. Very recently,[1] we have developed a new algorithm for this purpose based on ab initio density functional theory (DFT), a methodology increasingly used in predicting molecular properties.[2] Here, we assess the accuracy of this methodology in predicting the optical rotations of a set of six chiral 6,8-dioxabicyclo[3.2.1]octanes. Our results lead to the conclusion that the new DFT methodology should be of practical value to chemists in assigning absolute configurations of chiral molecules.

The specific rotation [α] of a chiral molecule (molecular weight M) in dilute solution measured at frequency ν is given by[3]

$$[\alpha]_\nu = \frac{28800\pi^2 N_A \nu^2}{c^2 M}\gamma_s \beta(\nu) \tag{1}$$

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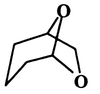
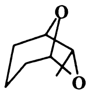
$\beta = \frac{1}{3}\mathrm{Tr}[\beta_{\alpha\beta}]$, where $\beta_{\alpha\beta}$ is the electric dipole–magnetic dipole polarisability tensor; γ_s is the condensed phase (solvent) effect. We calculate $\beta_{\alpha\beta}(\nu)$ using DFT.[1] Gauge-invariant (including) atomic orbitals (GIAOs) are used to provide origin-independent results. Calculations using a wide range of basis sets for two small molecules, methyloxirane and *trans*-2,3-dimethylthiirane, showed that, for these molecules, large basis sets including diffuse orbitals are required for accurate predictions.[1a] Accordingly, here we use the aug-cc-pVDZ and 6-311++G(2d,2p) basis sets.[1a] The solvent effect, γ_s, is calculated using the Polarized Continuum Model (PCM).[4] PCM calculations of solvent effects on the specific rotations of fenchone and α-pinene have supported the utility of this solvent model.[1b–d,1f]

We have applied our methodology to 6,8-dioxabicyclo[3.2.1]octane, **1**; *endo*-7-methyl-**1**, **2**; *exo*-7-methyl-**1**, **3**; 5,*endo*-7-dimethyl-**1**, **4**; 5,*exo*-7-dimethyl-**1**, **5**; and 1,5-dimethyl-**1**, **6**. The absolute configurations and conformations of **1**–**6** are well defined. The absolute configurations of **1**–**4** and **6** were established by chemical synthesis;[5] that of **5** was established by assuming that the sign of $[\alpha]_D$ reflects the absolute configuration of the 1,5-stereogenic centers.[5b] The absolute configurations were confirmed by mid-IR vibrational circular dichroism (VCD) studies using DFT.[6] These studies simultaneously established the dominant conformation to be 6-chair, 7-boat; no experimental evidence was obtained for the 7-chair, 6-boat conformation, consistent with the prediction that it lies >4 kcal/mol higher in energy. Literature values of the $[\alpha]_D$ for enantiomerically pure **1**–**6** are listed in Table 1.



(1R,5S)-**1**



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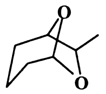

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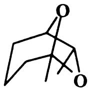

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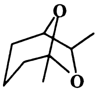
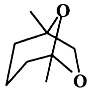


(1R,5S,7R)-**5**



(1R,5S)-**6**

Specific rotations at the sodium D line calculated for **1**–**6** using the B3LYP functional and the two basis sets aug-cc-pVDZ and 6-311++G(2d,2p) are given in Table 1. B3LYP/6-31G* geometries are used. All calculations are carried out using the Gaussian program.[7] Calculated and experimental rotations for the aug-cc-pVDZ basis set are compared in Fig. 1. We consider first the results obtained without solvent effects ($\gamma_s = 1$). The two basis sets predict very similar rotations. Calculated rotations for both basis sets are ordered: **2**>**1**>**3**>**4**>**5**>**6**. The experimental ordering is **1**>**2**>**3**>**4**>**5**>**6**. Except for **2**, calculated rotations are lower than experimental rotations. The mean absolute deviations of calculated rotations from experimental values are: aug-cc-pVDZ, 16.6; 6-311++G(2d,2p), 15.3 (units of specific rotations are degrees $[\mathrm{dm}\cdot(\mathrm{g/cc})]^{-1}$ throughout). Solvent effects have been included using the PCM for the specific solvents used in measuring $[\alpha]_D$. Calculated rotations uniformly increase. The ordering of calculated rotations for **1**–**6** is unchanged. The mean absolute deviations of calculated rotations from experimental values become: aug-cc-pVDZ, 12.6; 6-311++G(2d,2p), 11.4. Thus, on average, the agreement of calculated and experimental rotations is improved when solvent effects are included using the PCM.

Errors in calculated rotations can arise from: (i) incompleteness of the basis set; (ii) inexactitude of the functional; (iii) inaccuracy of the molecular geometry; and (iv) inadequacy of the solvent model. In order to gauge the magnitudes of errors due to (i)–(iii), in the case of **1** we have:

Table 1
Calculations of $[\alpha]_D$ for **1**–**6**[a]

		method[b]							
		B3LYP 6-311++G(2d,2p)	B3LYP aug-cc-pVDZ	B3LYP 6-311++G(2d,2p) (PCM)[c]	B3LYP aug-cc-pVDZ (PCM)[c]	B3LYP aug-cc-pVDZ (Lorentz)[d]	HF aug-cc-pVDZ		
compound	Abs. Config.							expt.[e]	solvent
1	1R,5S	93.0	94.3	101.6	104.0	122.2	67.8	115.0[f]	n-hexane
2	1R,5S,7S	118.3	118.3	127.4	128.3	162.8	61.1	108.1[g]	CCl_4
3	1R,5S,7R	86.4	83.1	94.1	90.7	114.4	72.4	94.4[g]	CCl_4
4	1R,5S,7S	80.9	80.9	83.6	83.7	110.3	46.1	86.5[g]	$CHCl_3$
5	1R,5S,7R	47.3	42.9	56.4	52.0	58.5	45.7	66.3[g]	$CHCl_3$
6	1R,5S	30.1	28.4	34.2	33.1	36.3	25.1	56.9[g]	ether
mean abs. deviation from expt.		15.3	16.6	11.4	12.6	22.4	34.8		
range of deviations from expt.		26.8 /-10.2	28.5 /-10.2	22.7 /-19.3	23.8 /-20.2	20.6 /-54.7	47.2 / 20.6		

[a] Specific rotations in degrees $[\mathrm{dm}\cdot(\mathrm{g/cc})]^{-1}$. All calculations use B3LYP/6-31G* geometries.

[b] Solvent models in parentheses. Where not otherwise indicated, all calculations are for γ_s=1.

[c] PCM calculations are carried out using the non-equilibrium Integral Equation Formalism [4c-4f]. Sphere radii were: bridgehead C, 1.7Å; methyl and methylene C, 2.0Å; O, 1.5Å; no spheres were placed on H atoms. ε_0 and ε_∞ values were: n-hexane: 1.890, 1.891; CCl_4: 2.228, 2.129; $CHCl_3$: 4.900, 2.085; ether: 4.335, 1.828. Geometries were identical to γ_s=1 calculations.

[d] n_D^{20} values used are: n-hexane, 1.375; CCl_4, 1.460; $CHCl_3$, 1.445; ether, 1.353.

[e] Normalised to 100% ee.

[f] Ref. 5a.

[g] Ref. 5b.

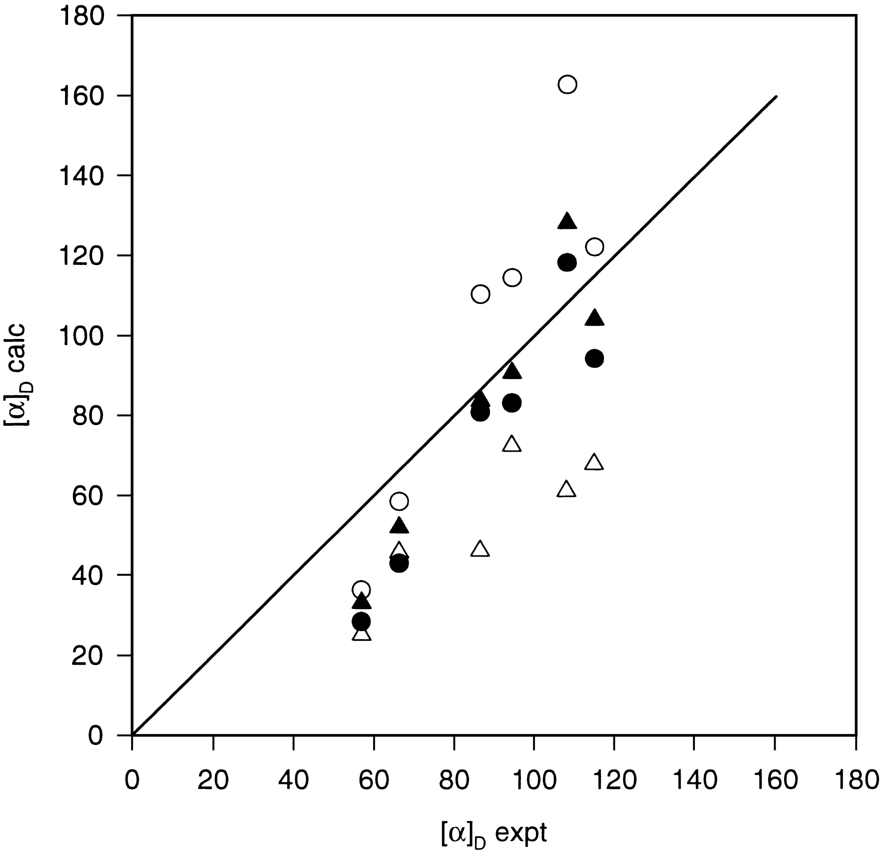


Figure 1. Comparison of calculated and experimental specific rotations $[\alpha]_D$ of **1**–**6**. ● B3LYP/aug-cc-pVDZ; $\gamma_s=1$. ▲ B3LYP/aug-cc-pVDZ; PCM γ_s; ○ B3LYP/aug-cc-pVDZ; Lorentz γ_s; △ HF/aug-cc-pVDZ; $\gamma_s=1$. All geometries are B3LYP/6-31G*. The line is of slope +1

(i) enlarged the basis set to aug-cc-pVTZ;[1a] (ii) examined three alternative functionals;[1a] (iii) examined four alternative geometries (in all cases with $\gamma_s=1$). The results are given in Table 2. The B3LYP/6-311++G(2d,2p)//, B3LYP/aug-cc-pVDZ// and B3LYP/aug-cc-pVTZ//B3LYP/6-31G* rotations vary by <4, indicating that the consequences of basis set incompleteness in the 6-311++G(2d,2p) and aug-cc-pVDZ basis sets are very small. The B3LYP/, B3PW91/, B3P86/ and PBE1PBE/aug-cc-pVDZ//B3LYP/6-31G* rotations vary by <2, indicating that calculated rotations are insensitive to the choice of functional amongst this set of hybrid functionals. B3LYP/aug-cc-pVDZ rotations calculated at five different ab initio geometries vary by ~13, indicating that calculated rotations possess significant sensitivity to the choice of molecular geometry. The variation in rotation is reduced to ~4 if the HF/TZ2P geometry is ignored. HF geometries are expected to be less accurate than DFT and MP2 geometries[2a,8] and the latter should therefore provide the more accurate rotations. These results do not identify a dominant contribution to calculational error; most probably, all factors contribute to a significant extent.

DFT includes electron correlation; HF theory does not. The importance of including correlation in calculating rotations is illuminated by comparison of HF/aug-cc-pVDZ// and B3LYP/aug-cc-pVDZ//B3LYP/6-31G* rotations of **1**–**6** (with $\gamma_s=1$) (Table 1 and Fig. 1). HF and B3LYP rotations differ substantially: the largest difference, for **2**, is 57.2; the mean absolute

Table 2
Calculations of $[\alpha]_D$ for **1**[a]

		method			
B3LYP/bs//B3LYP/6-31G*		fnal/aug-cc-pVDZ//B3LYP/6-31G*		B3LYP/aug-cc-pVDZ//geom	
bs	$[\alpha]_D$	fnal	$[\alpha]_D$	geom	$[\alpha]_D$
6-311++G(2d,2p)	93.0	B3LYP	94.3	B3LYP/6-31G*	94.3
aug-cc-pVDZ	94.3	B3PW91	95.4	B3LYP/aug-cc-pVDZ	95.4
aug-cc-pVTZ	91.1	B3P86	95.8	B3LYP/TZ2P	93.5
		PBE1PBE	94.1	HF/TZ2P	84.3
				MP2/6-31G*	97.6

[a] Specific rotations $[\alpha]_D$ in degrees $[\text{dm}\cdot(\text{g/cc})]^{-1}$. The absolute configuration of **1** is 1R,5S.

difference is 22.6. The HF rotations are significantly less accurate: the mean absolute deviation from experimental rotations is 34.8, compared to 16.6 for the B3LYP rotations.

Historically,[3b,9] solvent effects on specific rotations have most often been included using the Lorentz effective field approximation, when $\gamma_S = (n^2+2)/3$. Results obtained for **1**–**6** using this algorithm together with the B3LYP/aug-cc-pVDZ//B3LYP/6-31G* β values are given in Table 1. The mean absolute deviation of calculated rotations from experimental values is 22.4, significantly worse than the results obtained either without solvent correction ($\gamma_S = 1$) or PCM-predicted values for γ_S. This result is not surprising given prior studies of the solvent dependence of specific rotations.[10]

Calculations of specific rotation based on ab initio calculations of $\beta_{\alpha\beta}$ have been previously reported.[11,12] Calculations of $\beta_{\alpha\beta}(\nu = 0)$ have been carried out at the HF level using field-independent atomic orbitals (FIAOs) via the CADPAC program.[11a–e,12b–d] Calculations of $\beta_{\alpha\beta}(\nu)$ have been carried out at the HF level using both FIAOs and GIAOs via the Dalton program.[11d,11f,12a,12c,12d.] Solvent effects have been included using the Lorentz effective field correction.[11,12] Calculations using CADPAC neglect the frequency-dependence of $\beta_{\alpha\beta}$ and, in addition, provide origin-dependent predictions.[1a] These deficiencies are remedied by the Dalton program, which permits the frequency dependence of $\beta_{\alpha\beta}$ to be included and GIAOs to be employed, thereby affording origin-independent predictions. Our methodology improves on that of Dalton by the use of the DFT instead of the HF methodology and on the use of the Lorentz effective field correction for solvent effects by the use of the PCM. The results reported here indicate that both methodological developments increase the accuracy of predicted rotations. In addition, in this work we have used large basis sets including diffuse functions, previously shown to provide optical rotations close to the complete basis set limit.[1a] Prior studies using CADPAC and Dalton[11,12] have used small basis sets without diffuse functions, for which basis set error is substantially greater.

The DFT/PCM methodology, together with hybrid functionals and well-chosen basis sets, predicts sodium D line specific rotations of **1**–**6** with an average error close to 10. Calculations are ongoing for a much larger number and variety of molecules to assess the generality of this result. At the present time, our results support the conclusion that DFT/PCM calculations of optical rotations can provide a useful tool in elucidating the absolute configurations of chiral molecules.

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