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Determination of Absolute Configuration Using Optical Rotation Calculated Using Density Functional Theory

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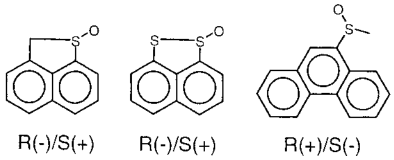
ABSTRACT



We report the first determinations of the absolute configurations (ACs) of chiral molecules using discrete frequency, transparent spectral region optical rotations calculated using density functional theory (DFT). The ACs of 2*H*-naphtho[1,8-*bc*]thiophene 1-oxide (3), naphtho[1,8-*cd*]-1,2-dithiole 1-oxide (4), and 9-phenanthryl methyl sulfoxide (5) are determined by comparison of their specific rotations to values calculated via the time-dependent DFT/gauge-invariant atomic orbital (TDDFT/GIAO) methodology using the B3LYP functional and the aug-cc-pVDZ basis set.

Enantiomers of chiral molecules exhibit specific rotations at a frequency ν, $[\alpha]_\nu$, of equal magnitude and opposite sign. In principle, therefore, the absolute configuration (AC) of a chiral molecule can be determined from its specific rotation. While the specific rotations of chiral molecules at one or a small number of discrete frequencies in the "transparent" spectral region are routinely measured following synthesis or isolation, they are rarely used to determine ACs. The determination of AC from a specific rotation requires an algorithm that reliably predicts the specific rotations of molecules of known AC. While a number of methodologies have been proposed for predicting discrete frequency, transparent spectral region specific rotations,[1] until recently none has been of sufficient accuracy and generality to permit the routine determination of ACs from experimental specific rotations. Consequently, to date very few ACs have been derived from such specific rotation data. Very recently, a new methodology for the prediction of discrete frequency, transparent spectral region specific rotations has been developed.[2] The methodology uses ab initio density functional theory (DFT). The purpose of this Letter is to report the first applications of this new methodology to the determination of AC.

The specific rotation at the frequency ν is given by

$$[\alpha]_\nu = \frac{\mathrm{ee}(\mathrm{E}_1)}{100} \sum_{i=1}^{n} x_i\, [\alpha]_\nu^i\, (\mathrm{E}_1) \qquad (1)$$

where E_1 is the enantiomer in excess, $\mathrm{ee}(\mathrm{E}_1)$ is the enantiomeric excess of E_1, n is the number of stable conformations, and x_i and $[\alpha]_\nu^i$ are the fractional population and specific

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rotation, respectively, of conformation *i*. Quantum-mechanical theory[3] relates $[\alpha]_\nu$ to a molecular parameter $\beta(\nu)$, where $\beta = {}^1/_3\mathrm{Tr}[\beta_{\alpha\beta}]$ and $\beta_{\alpha\beta}(\nu)$ is the frequency-dependent electric dipole-magnetic dipole polarizability tensor. Specifically,

$$[\alpha]_\nu = \frac{28800\pi^2 N_A \nu^2}{c^2 M}\gamma_{s,v}[\beta(\nu)]_0 \tag{2}$$

where $[\beta(\nu)]_0$ is the value of $\beta(\nu)$ at the gas-phase equilibrium geometry and $\gamma_{s,v}$ is the factor correcting for solvent and vibrational effects. The central challenge in predicting specific rotations is thus the prediction of $\beta_{\alpha\beta}(\nu)$.

The calculation of $\beta_{\alpha\beta}$ at the Hartree−Fock (HF) level of approximation has been implemented by Amos[4] for the static limit ($\nu = 0$) and by Helgaker et al.[5] for any frequency ν within the ab initio programs CADPAC and DALTON, respectively. Recently, calculations of $[\beta(\nu)]_0$ using these programs have been used to predict the specific rotations of a number of chiral organic molecules.[6] In a few cases, such calculations have been used to assign ACs.[7]

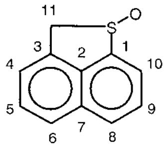
Unfortunately, our very recent studies (using a new implementation of the calculation of $\beta_{\alpha\beta}(\nu)$ at the HF level for any frequency ν within the ab initio program GAUSSIAN[8]) have clearly demonstrated that HF methods can be unreliable in predicting specific rotations.[2b−d] Results for two molecules, norbornenone (bicyclo[2.2.1]hept-5-en-2-one, **1**), and Tröger's base (2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5] diazocine, **2**), obtained using the aug-cc-pVDZ basis set (which contains diffuse functions, a sine qua non for reliable optical rotation calculations[2a]), and gauge-invariant atomic orbitals (GIAOs, otherwise known as London orbitals, which guarantee origin-independent specific rotations[2a]) given in Table 1, are illustrative. The differences between calculated and experimental $[\alpha]_D$ values are very large; in the case of **2**, the calculated $[\alpha]_D$ value is of the wrong sign. It is well-known that DFT, when state-of-the-art density functionals are used, affords more accurate predictions of molecular properties than does the HF methodology. Accordingly, we have also implemented the calculation of $\beta(\nu)$ using time-dependent DFT (TDDFT) and GIAOs.[2c,e] As seen in Table 1, $[\alpha]_D$ values predicted by the TDDFT/GIAO methodology using the B3LYP functional and the aug-cc-pVDZ basis set for **1** and **2** are dramatically superior to HF $[\alpha]_D$ values. Mean absolute deviations of aug-cc-pVDZ B3LYP and HF $[\alpha]_D$ values from experimental values for a set of 28 rigid chiral organic molecules are 23.1 and 62.7 respectively,[2c] further documenting the substantially greater accuracy of B3LYP $[\alpha]_D$ values.

Table 1. Calculated and Experimental Specific Rotations of (1*S*,4*S*)-**1** and (5*S*,11*S*)-**2**

1			**2**		
$[\alpha]_D$(calc)[a]			$[\alpha]_D$(calc)[a]		
HF	B3LYP	$[\alpha]_D$ (expt)[b]	HF	B3LYP	$[\alpha]_D$ (expt)[c]
−607	−1216	−1146	−5	+342	+287

[a] Reference 2c; $[\beta(\nu)]_0$ calculated using the Gaussian program[8] at the B3LYP/6-31G* geometry using the aug-cc-pVDZ basis set and GIAOs; $\gamma_{s,v} = 1$. [b] Reference 2c; *c* 0.17, hexane. [c] Reference 2c; *c* 0.29, hexane.

Our results lead to the conclusion that the TDDFT/GIAO methodology is the current method of choice in the determination of AC from optical rotation. In this Letter, we report the first applications of this methodology to the determination of AC, specifically for the molecules 2*H*-naphtho[1,8-*bc*]-thiophene 1-oxide (**3**), naphtho[1,8-*cd*]-1,2-dithiole 1-oxide (**4**), and 9-phenanthryl methyl sulfoxide (**5**).



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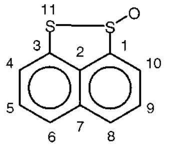

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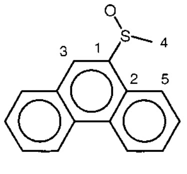

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Molecules **3** and **4** were obtained by Oxelbark et al.[9] via liquid chromatography on chiral stationary phases of racemic **3** and **4**. Specific rotations at several wavelengths were reported (Table 2). ACs were not assigned. Geometry optimization using B3LYP and the 6-31G* basis set leads to the equilibrium geometries for **3** and **4** illustrated in Figure

Table 2. Calculated and Experimental Specific Rotations of **3** and **4**

	[α] (B3LYP)[a]		
λ(nm)	R	S	[α] (expt)[b]
		Compound **3**	
589.3	−113	+113	91 (CH_3OH, *c* 0.06)
546	−138	+138	132 (CH_2Cl_2, *c* 0.06)
465	−226	+226	
436	−294	+294	265 (CH_2Cl_2, *c* 0.06)
		Compound **4**	
589.3	−1584	+1584	
546	−2074	+2074	1540 ± 50 (CH_2Cl_2, *c* 0.3) 1378 ± 48 (60% dioxane, *c* 0.4)
465	−4360	+4360	3770 ± 115 (CH_2Cl_2, *c* 0.3) 3317 ± 110 (60% dioxane, *c* 0.4)
436	−6929	+6929	

[a] $[\beta(\nu)]_0$ calculated using the Gaussian program[8] at the B3LYP/6-31G* geometry using the aug-cc-pVDZ basis set and GIAOs; $\gamma_{s,v} = 1$. [b] Reference 9.

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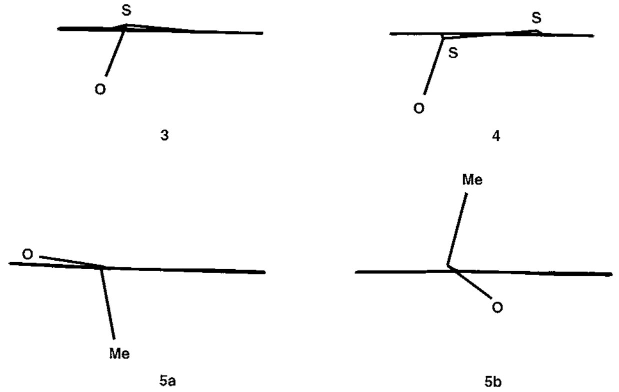

Figure 1. The B3LYP/6-31G* structures of S-**3**, S-**4**, S-**5a**, and S-**5b**. H atoms are omitted. **3** and **4** are viewed to show the degree of coplanarity of the naphthyl and bridging moieties. **5a** and **5b** are viewed to show the orientation of the SOMe moiety relative to the plane of the phenanthryl group. As viewed, the naphthyl group in **3** and **4** and the phenanthryl group in **5a** and **5b** are at the rear.

1. In both **3** and **4** the five-membered rings are close to planar; the deviation from planarity is somewhat greater in **4**. Key dihedral angles are listed in Table 1 of Supporting Information. To establish whether these structures are the only stable conformations for these molecules, B3LYP/6-31G* potential energy surface (PES) scans were carried out varying simultaneously the dihedral angles C7C2C3X11 (X = C in **3** and S in **4**) and C9C10C1S. The results, displayed in Figure 2, show that no other stable conformations exist; **3** and **4** are rigid molecules.

Specific rotations for **3** and **4** at 589.3, 546, 465, and 436 nm have been predicted using the B3LYP functional and the aug-cc-pVDZ basis set, with the results given in Table 2. In the case of **3**, B3LYP [α] values at 589.3, 546, and 436 nm are in good agreement with experimental values if the AC is R(−)/S(+); differences between experimental and calculated [α] values are 22, 6, and 29 at 589.3, 546 and 436 nm, respectively. If the AC were R(+)/S(−), the corresponding differences would be 204, 270, and 559. We conclude that, with little uncertainty, the AC of **3** is R(−)/S(+). Note that the difference between experimental and calculated $[\alpha]_D$ values, 22, is consistent with the statistical accuracy of B3LYP/aug-cc-pVDZ $[\alpha]_D$ values in our previous study.[2c] In the case of **4**, both experimental and calculated [α] values are much larger than in **3**. Experimental [α] values were reported at 546 and 465 nm in two different solvents: CH_2Cl_2 and 60% dioxane. A substantial solvent effect was observed, [α] values in CH_2Cl_2 being higher than in 60% dioxane. Much better agreement is observed between experimental and calculated [α] values if the AC is R(−)/S(+). Differences between experimental (CH_2Cl_2/60%dioxane) and B3LYP [α] values are 534/696 and 590/1043 at 546 and 465 nm respectively; if the AC were R(+)/S(−) the corresponding differences would be 3614/3452 and 8130/7677.

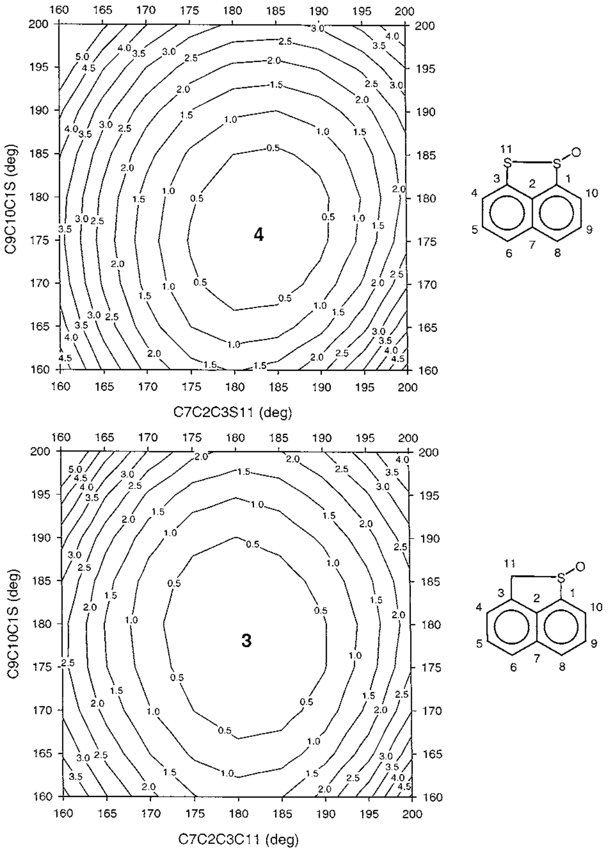

Figure 2. Potential energy surfaces of **3** and **4**. The spacing of the energy contours is 0.5 kcal/mol.

We therefore conclude that the AC of **4** is R(−)/S(+). We note that the differences between calculated and experimental [α] values are much larger than in the case of **3**. The reliability of the AC of **4** is consequently lower.

As shown in Table 3, calculated [α] values of **4** are lower, and in much better agreement with experiment, if all atoms of the molecule excepting O are constrained to be coplanar. Calculations using geometries in which only the naphthyl group or only the SS bridge are constrained to be planar show that the calculated rotation is sensitive to the bridge nonplanarity but not to the naphthyl group nonplanarity.

Table 3. Geometry Dependence of Calculated Specific Rotations of *S*-**4**

	[α] (B3LYP/aug-cc-pVDZ)[a]				
λ (nm)	**a**	**b**	**c**	**d**	[α] (expt)
589.3	1584	1376	1381	1534	
546	2074	1802	1811	2002	1540/1378
465	4360	3868	3919	4161	3770/3317
436	6929	6550	6682	6542	

[a] (**a**) B3LYP/6-31G* equilibrium geometry. (**b**) B3LYP/6-31G* geometry; all atoms coplanar excepting O. (**c**) B3LYP/6-31G* geometry; bridge atoms coplanar. (**d**) B3LYP/6-31G* geometry; naphthyl group atoms coplanar.

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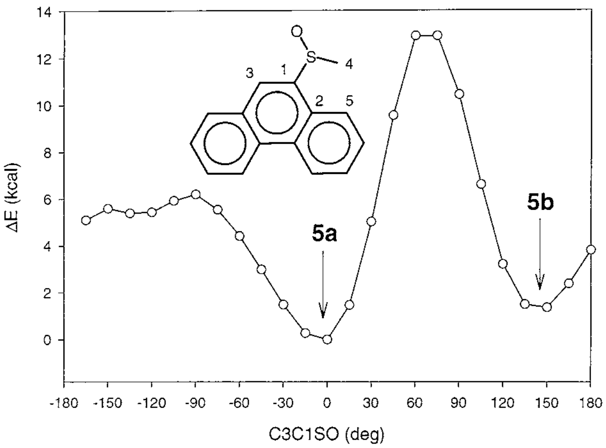

Figure 3. Potential energy surface of **5**.

Parallel calculations for **3** find a much smaller sensitivity to the nonplanarity. These results suggest that a possible explanation for the differences between calculated and experimental $[\alpha]$ values in **4** might be that the B3LYP/6-31G* geometry overestimates the degree of SS bridge nonplanarity in **4**. Alternatively, the differences may be due to solvent effects[2e] and/or vibrational effects.[10]

DFT calculations have shown that **3** and **4** exhibit only one stable conformation, i.e., they are "rigid" molecules. The prediction of optical rotation is more complex for "flexible" molecules, exhibiting more than one stable conformation. In this case, the predicted rotations of individual conformers must be averaged, weighting each by corresponding fractional populations (eq 1). By way of example, we turn now to the chiral sulfoxide 9-phenanthryl methyl sulfoxide, **5**, which was obtained by Sakuraba et al. via peracetic acid oxidation of a crystalline cyclodextrin complex of 9-phenanthryl methyl sulfide.[11] The reported $[\alpha]_D$ in $CHCl_3$ solution (*c* 0.5) was 99.5; the measured ee was 37%, leading to a value of +269 at 100% ee. The AC was not assigned. **5** is a flexible molecule; the $SOCH_3$ moiety can rotate relative to the phenanthryl group. A scan of the PES of **5** as a function of the orientation of the $SOCH_3$ group has been carried out at the B3LYP/6-31G* level, with the results shown in Figure 3. Two stable conformations are predicted. B3LYP/6-31G* geometry optimizations lead to the structures **5a** and **5b**, shown in Figure 1, which are E and Z conformations, respectively. Key dihedral angles are given in Table 2 of Supporting Information. In **5a**, the SO group is close to coplanar with the phenanthryl moiety (as in phenyl methyl sulfoxide[12]). In **5b**, the SO group is rotated significantly away from coplanarity as a result of steric hindrance by the peri-H atom of C5 (as in α-naphthyl methyl sulfoxide[12]). As a result, **5a** is lower in energy than **5b**. The B3LYP/6-31G* energy difference is 1.33 kcal/mol.

Values of $[\alpha]_D$ for **5a** and **5b** have been calculated using B3LYP and aug-cc-pVDZ, with the results given in Table 4. The predicted rotation of **5a** is much greater than that of **5b**. Fractional populations of **5a** and **5b**, calculated from the B3LYP/6-31G* energy difference using Boltzmann statistics, are 0.908 and 0.092, respectively. With these populations, the conformationally averaged $[\alpha]_D$ value is predicted to be +336° and −336° for *R*- and *S*-**5** respectively. This result is in quite good agreement with experiment if the AC of **5** is R(+)/S(−). The deviation from the experimental $[\alpha]_D$, assuming this AC, is 67°. With the opposite AC the deviation is 605°. We therefore conclude that the AC of **5** is R(+)/S(−).

Table 4. Calculated and Experimental Specific Rotations of **5**

5a $[\alpha]_D$ (B3LYP)[a]		**5b** $[\alpha]_D$ (B3LYP)[a]		**5(a + b)** $[\alpha]_D$ (B3LYP)[b]		
R	S	R	S	R	S	$[\alpha]_D$ (expt)[c]
+366	−366	+47	−47	+336	−336	+269 ($CHCl_3$, c 0.5)

[a] $[\beta(\nu)]_0$ calculated using the Gaussian program[8] at the B3LYP/6-31G* geometry using the aug-cc-pVDZ basis set and GIAOs; $\gamma_{s,v} = 1$. [b] Calculated using fractional populations 0.908 and 0.092 for **5a** and **5b** respectively. [c] Reference 11.

The calculated $[\alpha]_D$ of **5** is a function of ΔG, the free energy difference of conformations **5a** and **5b**. The variation of $[\alpha]_D$ with ΔG is shown in Figure 1 of Supporting Information. $[\alpha]_D$ decreases as ΔG decreases. The experimental value of +269 is obtained with $\Delta G \approx 0.5$ kcal/mol. Above, in the absence of an experimental value for ΔG, we have approximated ΔG by the gas-phase B3LYP/6-31G* ΔE value, 1.33 kcal/mol. The error in the value of ΔG obtained as a result is likely to be a significant contributor to the difference between the calculated and experimental $[\alpha]_D$ values.

In summary, we have shown that the ACs of molecules **3**−**5** can be confidently assigned on the basis of TDDFT/GIAO calculations of their specific rotations at discrete frequencies in transparent spectral regions, using a basis set containing diffuse functions, aug-cc-pVDZ, and a state-of-the-art functional, B3LYP. This new methodology should be of substantial utility in the determination of the ACs of chiral molecules. Exceptions to its applicability are (1) molecules whose specific rotations are comparable to or less than the intrinsic errors of the calculational methodology (ca. 20−30 for $[\alpha]_D$); (2) flexible molecules for which the calculated rotations of the multiple conformations are both positive and negative and for which the sign of the conformationally averaged rotation is sensitive to small changes in conformational free energy differences.

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Supporting Information Available: Dihedral angles of **3**−**5** and α_D of **5** as a function of ΔG. This material is available free of charge via the Internet at http://pubs.acs.org.

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