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Determination of the absolute configuration of 1,3,5,7-tetramethyl-1,3-dihydroindol-2-one by optical rotation computation

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Abstract

The absolute configuration of 1,3,5,7-tetramethyl-1,3-dihydroindol-2-one was determined by quantum chemical calculations of specific rotation angles with coupled–perturbed Hartree–Fock methods. The computation used molecular geometries obtained from ab initio calculations as well as from molecular mechanics and semi-empirical optimization. In addition to the dependence on geometry optimization strategies, the basis set dependence of the computed rotation angle was examined. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

The quantum mechanical expression for the optical rotation angle was derived in 1928.[1,2] Since then, numerous models have been developed to predict the sign and magnitude of optical rotation angles.[3–23] Recently, ab initio coupled–perturbed Hartree–Fock methods in the off-resonance limit as well as frequency-dependent linear-response methods were used to compute quantitatively reliable optical rotation angles.[24–28] Ab initio methods combined with fragmentation strategies have been developed to assign the relative and absolute configuration of complex natural products like hennoxazole A and pitiamide A (Fig. 1).[29]

The computed specific rotation angle is derived from the electric-dipole magnetic-dipole polarizability tensor (G'), which is a measure of the overlap of electronic polarization induced by the electric and the magnetic fields of the incident radiation. Recent developments include an ability to compute this G' tensor on standard desktop workstations.[25,26,29]

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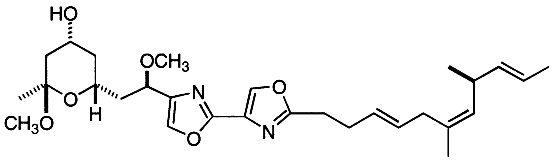
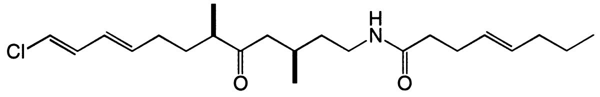


Hennoxazole A



Pitiamide A

Figure 1. Structures of hennoxazole A[30,31] and pitiamide A[32,33]

While the ab initio computation of G' tensor-derived optical rotation angles appears to be of very general scope,[21–28] much work remains to be done to establish a basic understanding of reliable protocols, sources of errors, and possible limitations of this fundamental approach for structure analysis. We now report calculations toward the elucidation of the absolute configuration of 1,3,5,7-tetramethyl-1,3-dihydroindol-2-one with ab initio coupled–perturbed Hartree–Fock methods.[34] We examined the geometry dependence of computed rotation angles in this indolinone by using optimized geometries obtained from ab initio, semi-empirical, and molecular mechanics methods. As expected, our studies show that computed optical rotation angles are very sensitive to geometry. Indeed, properly optimized geometries are essential for reliable rotation angle prediction.[25–29]

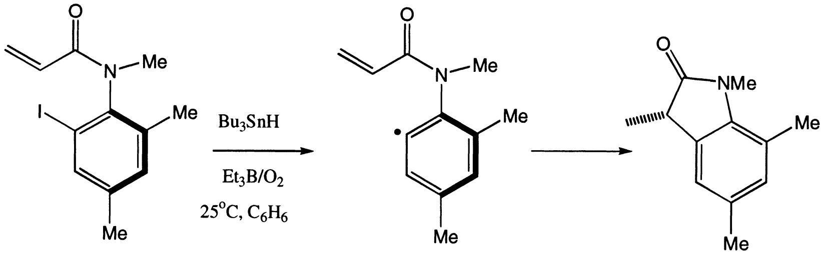
Our strategy involves the quantum mechanical computation of specific rotation angles for all enantiomeric (and diastereomeric, if applicable) isomers of the target molecule, followed by comparison of the computed with the experimental values. In general, only a single isomer is available for experimental measurement, but knowing the computed rotation values of all possible stereoisomers is essential to avoid ambiguities. In many cases, this strategy allows the direct assignment of the absolute configuration, because different stereoisomers often have significantly different $[\alpha]_D$ values even in compounds with multiple stereocenters.[35] Of course, if the experimental specific rotations are in error due to chemical degradation or impurities, the analysis may be flawed.[36–38]

2. Theoretical methodology

The configuration of indolinone **1** can be assigned based on the optical rotation angle of a single enantiomer, thus demonstrating the ease of assigning absolute configuration for this class of compounds. The numerical computations capitalize on techniques that were developed to compute G' tensor elements within the CADPAC program.[25,39] The specific rotation angle (measured at the sodium D-line), in units of degrees [dm (g/mL)]$^{-1}$, is $[\alpha]_D=1.343\times10^{-4}\ \beta\bar{\nu}^2\ (n^2+2)/3MW$ with β in units of (bohr)^4, MW the molar mass in g/mole, and $\bar{\nu}$ the frequency of the sodium D-line in cm^{-1}. The parameter β is related to the electric-dipole magnetic-dipole polarizability tensor $G'_{\alpha\alpha}$, which is computed by coupled Hartree–Fock methods. For details of the theoretical methodology see Eqs. 1–5.[40] In order to minimize origin-dependence in optical rotation calculations, we choose the origin to be at the center of mass for all optimized geometries. The DALTON program[41] uses London atomic orbitals[42,43] to avoid the origin dependence.[20] For comparison, we have also listed selected calculations with DALTON.[41,44]

3. Results and discussion

The problem of assigning the absolute configuration of **1** arose within the context of a project investigating the transfer of axial chirality in anilides like **2** via the aegis of a fast radical cyclization.[45] *o*-Iodoacrylanilide **2** was synthesized in highly enantio-enriched form and its absolute configuration was assigned as **P** by X-ray crystallography of a precursor. Cyclization of **2** (95% ee) under standard tin hydride conditions provided **1** in 82% ee. If **2** were enantiopure, then the ee% of **1** would be expected to be 86%. A number of related substrates have been cyclized and most give ees marginally higher than observed for **1** (~90% ee).[45] This new type of chirality transfer relies on the rapid reaction of the intermediate radical **3**. The results demonstrate that **3** cyclizes faster than N–Ar bond rotation (racemization), and thus the product **1** 'remembers' the absolute helicity of the precursor **2**. The work stalled when it proved impossible to assign the absolute configuration of **1** by standard methods;[45] indolinone **1** and several relatives resisted crystallization and derivatization. Rather than continuing this experimental trial and error approach, we switched to the new computational methods for determining the optical rotation of **1**.

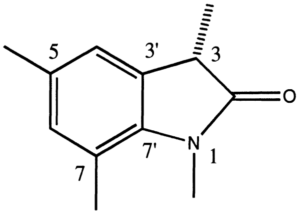


(***P***)**-2** (95% ee)

3

(***S***)**-1**, 82% ee
(86% ee, corrected)
^{1}H NMR yield, 87%
isolated yield, 65%

The measured specific rotation angle in chloroform of a sample resolved by chiral HPLC (100% ee) is −15.6 (*c* 0.79, $CHCl_3$, 23°C).[46] Conformational search in MacroModel[47] with the MM2* force-field and the $CHCl_3$ solvent continuum model provided a single low-energy conformer within a 50 kJ/mol steric energy range. The conformational search using the AMBER force-field also resulted in a closely related single low-energy conformer. These results were consistent with the expectation that indolinone **1** is structurally rigid. For computing the specific rotation angle, the task was therefore simplified to consideration of a single structure obtained from the energy minimization.



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The specific rotation angles were computed using 6-31G and 6-31G* basis sets in the static-field approximation implemented in CADPAC.[39] Input geometries for indolinone **1** were also optimized using ab initio Hartree–Fock methods with 6-31G and 6-31G* basis sets.

Table 1
The C3′–C7′–N1–C2 torsion angle for geometries optimized in Hartree–Fock, force-field, and semi-empirical calculations. This torsion angle is representative of the degree of puckering in the five-membered ring. The C3′–C7′–N1–C2 torsion angles in the crystal structures of structurally related compounds were obtained from the Cambridge crystallographic data bank[48–50]

Method	Torsion angle C3'-C7'-N1-C2 (in degrees)
HF (6-31G)	-0.22
HF (6-31G*)	-0.58
MM2	-0.17
AMBER	0.05
AM1	-1.27
PM3	-5.78
Expt. crystal structures	-0.32[48] 0.80[49] 0.13[50]

Table 2
CADPAC-based specific rotations for (*S*)-**1** using HF (6-31G, 6-31G*), force-field (MM2*, AMBER), and semi-empirical (AM1, PM3) optimized geometries

Geometry →		HF optimization		Force-field opt.		Semi-empirical opt.	
Specific rotation ↓		6-31G	6-31G*	AMBER	MM2*	AM1	PM3
6-31G	$[\alpha]_D$	-25.4	-23.4	-16.7	-19.5	25.1	31.6
6-31G*	$[\alpha]_D$	-29.6	-26.2	-24.2	-22.5	30.9	43.6

Table 1 shows the torsion angle C3′–C7′–N1–C2 for geometries optimized by ab initio Hartree–Fock (HF, 6-31G, 6-31G*), force-field (AMBER, MM2*), and semi-empirical (AM1, PM3) methods.

Optimized geometries of **1** using molecular mechanics, ab initio Hartree–Fock, and semi-empirical AM1 and PM3 methods differed by six degrees in the five-membered ring pucker (Table 1). In order to choose the most accurate geometry, we examined the crystal structures of similar compounds.[48–50] While the actual differences between X-ray structures and various computational models appear minor, computed optical rotation angles for similar ring systems are shown to be sensitive to the ring pucker.[28] The C3′–C7′–N1–C2 torsion angles obtained using ab initio Hartree–Fock optimization with 6-31G and 6-31G* Gaussian basis sets are −0.22° and −0.58°, respectively. The torsion angle C3′–C7′–N1–C2 obtained in the geometries optimized using the MM2* molecular mechanics force field is −0.17° while 0.05° is obtained with the AMBER force field. Torsion angles computed using 6-31G and 6-31G* Gaussian basis sets as well as force field calculations are in good agreement with those found in the crystal structures. The ring pucker in the geometries obtained using AM1 and PM3 semi-empirical methods is considerably larger.[51] For all geometries, specific rotation angles were computed as shown in Table 2.

Table 3
DALTON-based specific rotations for (*S*)-**1** using AMBER, AM1, and PM3 optimized geometries. London (gauge-invariant) as well as non-London atomic orbitals were used

Geometry → Specific rotation ↓	Force-field opt.	Semi-empirical opt.	
	AMBER	AM1	PM3
6-31G; $[\alpha]_D$ London atomic orbitals	-30.0	21.6	55.3
6-31G; $[\alpha]_D$ non-London atomic orbitals	-15.0	32.4	44.8

Table 4
Computed vs experimental specific rotation angles for (*S*)-**1** using AMBER/6-31G at various wavelengths

Wavelength (nm)	Computed [α] (CADPAC)	Computed [α] (DALTON with non-London atomic orbs.)	Observed [α] (*c* 1.13, $CHCl_3$, 23°C)
589	-16.7	-15.0	-15.5
578	-17.4	-15.4	-16.3
546	-19.5	-16.9	-17.8
436	-30.5	-21.6	-23.6

In order to probe basis set effects, the specific rotation angles were computed using both 6-31G and 6-31G* basis sets. As Table 2 shows, the geometries determined with 6-31G and 6-31G* basis sets, and those obtained using molecular mechanics (with MM2* and AMBER force fields) lead to $[\alpha]_D$s that are close to the experimentally determined $[\alpha]_D$ −15.6 (*c* 0.79, $CHCl_3$). Actual values ranged from $[\alpha]_D$ −16.7 (obtained from an AMBER minimized geometry with 6-31G rotation angle calculation) to −29.6 (for a 6-31G optimized geometry with a 6-31G* rotation angle calculation). In contrast, AM1 and PM3 geometries provided positive values ranging from 25.1 to 43.6. Adding polarization functions to the 6-31G basis set increased the value of the optical rotation angles for all geometries but did not change the sign for (*S*)-**1**.

The dynamic method (using DALTON, Table 3) reproduces the trends observed in the static field approximation (CADPAC), in particular the striking contrast between force-field and semi-empirically optimized geometries. This trend is observed both with gauge invariant (London) atomic orbitals as well as with non-London (standard) atomic orbitals.

The average of all specific rotation angles obtained in CADPAC using all the methods (except semi-empirical) shown in Table 2 is −23.4. This clearly allows an assignment of the (*S*)-configuration to the experimentally obtained material, and thus solves the assignment problem for the asymmetric radical cyclization reaction. We also determined the specific rotations at 578, 546 and 436 nm, and compared them to the experimental values (Table 4). The agreement is generally quite good; however, at 436 nm, the limitation of the static field off-resonance approximation (CADPAC) becomes obvious and results in a poorer match between theory and experiment. At lower wavelengths, the dynamic method (DALTON) using non-London atomic orbitals provides higher accuracy.[52]

4. Conclusions

Quite often, synthetic chemists apply novel methodology to prepare new compounds in enantioenriched form, but of unknown relative or absolute configuration. The ensuing configurational assignment problem can be quite tedious, and modern quantum mechanical tools offer a powerful alternative to established (chemical degradation, X-ray) methods. The absolute configuration of indolinone **1** is assigned here using computations of the specific rotation angles. We also compared $[\alpha]_D$ for geometries optimized using both ab initio Hartree–Fock and semi-empirical methods, and molecular mechanics force fields. The effect of the basis set on the specific rotation angles for indolinone was probed, and we found that adding polarization functions to the 6-31G basis set slightly increased the magnitude of the optical rotation angle values but did not change the sign for (*S*)-**1**. Semi-empirical geometry optimization methods were inadequate for reliable $[\alpha]_D$ determination, both with static (CADPAC) and dynamic (DALTON) methods. The wavelength dependence of specific rotations of **1** were probed, and the agreement between theory and experiment was good at wavelengths longer than 500 nm (at lower wavelengths, the static field approximation, which is only valid far from absorption maxima, begins to fail). Excellent agreement at wavelengths as low as 436 nm was observed with the dynamic method (DALTON) using non-London atomic orbitals.

Acknowledgements

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40. The expression for the optical rotational angle, ϕ, in radians, is:[1]

$$\phi = 4\pi N\beta\omega^2(n^2+2)/3c^2 \tag{1}$$

where

$$\beta = -\omega^{-1}(G'_{xx}+G'_{yy}+G'_{zz})/3 \tag{2}$$

G'_{ii} are the diagonal elements of the electric-magnetic polarizability tensor, N is the number of molecules per unit volume, n is the refractive index of the medium, c is the speed of light. The specific rotation angle (measured at the sodium D-line), in units of degrees [dm (g/mL)]$^{-1}$, is:

$$[\alpha]_\mathrm{D} = 1.343\times10^{-4}\ \beta\bar{\nu}^2(n^2+2)/3MW \tag{3}$$

with β in units of (bohr)^4, MW the molar mass in g/mole, and $\bar{\nu}$ the frequency of the sodium D-line in cm^{-1}. From $[\alpha]_\mathrm{D}$, the molar rotation is defined as $[M]_\mathrm{D}=[\alpha]_\mathrm{D}\ MW/100$. We calculate $G'_{\alpha\alpha}$ for the full molecule using:

$$G'_{\alpha\alpha} = -2\sum_{\mathrm{e}\neq\mathrm{g}}\frac{\omega\mathrm{Im}[\langle\Psi_\mathrm{g}^{(0)}|\mu_\alpha|\Psi_\mathrm{e}^{(0)}\rangle\langle\Psi_\mathrm{e}^{(0)}|\mathrm{m}_\alpha|\Psi_\mathrm{g}^{(0)}\rangle]}{\omega_\mathrm{eg}^2-\omega^2} \tag{4}$$

Here, g and e denote the ground and excited states, respectively, $\omega_\mathrm{eg}=\omega_\mathrm{e}-\omega_\mathrm{g}$ is the associated excitation frequency, and μ_α and m_α are the electric-dipole and magnetic-dipole operators oriented along the α-axes. In order to avoid the explicit sum-over-states expression for the electric dipole–magnetic dipole polarizability tensor, Amos applied the static-field approximation. In this regime, Eq. 4 is simplified ($\omega^2 \ll \omega_\mathrm{jn}{}^2$) to:[34]

$$\omega^{-1}G'_{\alpha\alpha} = -2\sum_{\mathrm{e}\neq\mathrm{g}}\frac{\mathrm{Im}[\langle\Psi_\mathrm{g}^{(0)}|\mu_\alpha|\Psi_\mathrm{e}^{(0)}\rangle\langle\Psi_\mathrm{e}^{(0)}|\mathrm{m}_\alpha|\Psi_\mathrm{s}^{(0)}\rangle]}{\omega_\mathrm{eg}^2} \tag{5}$$

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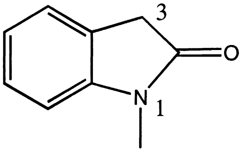

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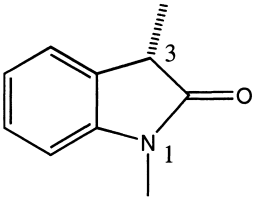

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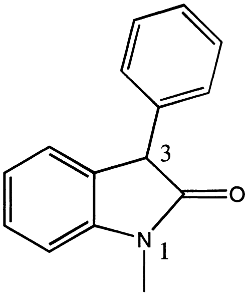

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52. Experimentally, **1** was determined to have an absorption maximum for the first electronic transition at 292 nm with ε=765. Since this transition is far from the sodium-D line, CADPAC and DALTON are in close agreement at probing wavelength >500 nm.