Molecular optical rotations and structures

Prasad L. Polavarapu *

Department of Chemistry, Vanderbilt University, Nashville, TN 37235 USA

Abstract: Optical rotations of nine different conformers of chiral enflurane [(H)(F)(Cl)C(CF$_2$OCF$_2$H)] have been calculated *ab initio*. The population weighted net specific rotation for the (*R*)-configuration is −1.3 at the 6-31G* level and −1.7 at the DZP level, which is close to the experimental value. As the *ab initio* predicted optical rotations in the majority of the molecules studied to date are found to compare favorably with the experimental values, it appears that optical rotations provide a convenient alternative approach to determine the absolute configuration and predominant conformations of chiral molecules. © 1997 Elsevier Science Ltd

Introduction

Optical activity is an active area of research for molecular structural elucidation. Optical rotation,[1] electronic circular dichroism (ECD),[2] vibrational circular dichroism (VCD),[3] and vibrational Raman optical activity (VROA)[4] are four different properties that are currently being used for this purpose. Although optical rotations in the visible spectral region are measured routinely by chemists to characterize the compounds, the observed optical rotations are related to molecular structures based only on empirical correlations. A practical approach to predict the optical rotations reliably from first principles would be greeted with excitement by many practicing chemists, because a comparison of the predicted and observed optical rotations would enable the determination of the absolute configurations of chiral molecules. In the absence of such predictions, empirical approaches[5] that depend on the bond or atom polarizabilities have found widespread use. The theory of molecular optical rotation[6] has been known for a long time. Numerous developments have taken place in quantum mechanical calculations that make it possible to undertake *ab initio* calculations of optical rotations, but such attempts[7] have not been undertaken in the literature.

The purpose of this communication is to bring the feasibility and success of *ab initio* optical rotations, in elucidating molecular structure, to the attention of practicing chemists. As an illustration, the optical rotations for all possible conformers of enflurane [(H)(F)(Cl)C(CF$_2$OCF$_2$H)] are evaluated and compared with the experimentally measured optical rotation.

The theoretical quantity pertinent here is the electric dipole–magnetic dipole polarizability tensor, given by the expression[8–10]

$$G'_{\alpha\beta} = \frac{-4\pi}{h} \sum_{n \neq s} \frac{\omega}{\omega_{ns}^2 - \omega^2} Im\{\langle \psi_s^0 | \hat{\mu}_\alpha | \psi_n^0 \rangle \langle \psi_n^0 | \hat{m}_\beta | \psi_s^0 \rangle\} \tag{1}$$

where μ_α and m_β are respectively the electric dipole moment and magnetic dipole moment operators; ψ_s^0 and ψ_n^0 represent the ground and excited electronic state wavefunctions respectively; $\omega_{ns} = 2\pi(E_n^0 - E_s^0)/h$, where E_n^0 and E_s^0 are the unperturbed energies of states n and s, respectively; ω is the angular frequency of exciting radiation. It is useful to define the quantity,

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

which is related to the optical rotation ϕ (in radians/cm) as[6]

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* Email: polavaol@ctrvax.vanterbilt.edu

$$\phi = 4\pi N\beta\omega^2(n^2 + 2)/3c^2 \qquad (3)$$

where N represents the number of molecules per unit volume, n represents the refractive index of the medium and $\omega^{-1}G'_{\alpha\alpha}$ are in CGS units. When $\omega^{-1}G'_{\alpha\alpha}$ are expressed in SI units, the right hand side of Eq. 3 is to be multiplied with $\mu_0 c^2/4\pi$. The experimental optical rotations are most commonly reported as specific rotation $[\alpha]$ in units of deg/[dm.(gm/cc)]. The corresponding theoretical quantity is $[\alpha]=3600 \phi V_m/2\pi M$ where M and V_m are respectively the molar mass and molar volume. Using these definitions, a convenient expression for the specific rotation is given[7] as

$$[\alpha] = 0.1343 \times 10^{-3}\beta\bar{v}^2(n^2 + 2)/3M \qquad (4)$$

with β in units of (bohr)[4], M in gm/mol and $\bar{v}$ (wavenumber at which the optical rotation is measured) in cm^{-1}.

An explicit evaluation of the sum over excited states in Eq. 1 can be avoided by noting that, when $\omega_{ns}\gg\omega$, Eq. 1 can be simplified as,[11]

$$\omega^{-1}G'_{\alpha\beta} = -(h/\pi)Im\{\langle(\partial\psi_s/\partial F_\alpha)|(\partial\psi_s/\partial B_\beta)\rangle\} \qquad (5)$$

Amos developed,[11] and implemented,[12] an approach for evaluating Eq. 5 by calculating the derivatives $(\partial\psi_s/\partial F_\alpha)$ and $(\partial\psi_s/\partial B_\beta)$ using the coupled perturbed Hartree–Fock method.[13] Eq. 5 has been evaluated before[14] at the displaced nuclear geometries for calculating the vibrational Raman optical activity intensities. However, the application of Eq. 5 to optical rotations via Eqs 1–4 has been undertaken only recently.[7]

Standard basis sets available in the CADPAC program[12] library were used. The geometries were optimized with the 6-31G* basis set. Two different optical rotation calculations, one with the 6-31G* and another with the DZP basis set, both using the 6-31G* optimized geometries, are reported in Table 1. The specific rotations were calculated for the sodium D-line wavelength (589.3 nm), using a refractive index for enflurane[15] of 1.3025. There are nine possible conformers for enflurane (Figure 1). For an accurate estimate of their populations, free energies which depend on the vibrational frequencies would be required for all conformers. The prediction of accurate vibrational frequencies however would require much higher level calculations than were undertaken here. For this reason, the approximate fractional populations of these conformers were estimated, based on their *ab initio* calculated electronic energies, as $e^{-\varepsilon_i/kT}/\sum_{j=1}^{9}e^{-\varepsilon_j/kT}$ where ε_i is the electronic energy of conformer i, T the temperature and k the Boltzman constant. The net specific rotation was then obtained as the sum of population weighted spectific rotations of all conformers. The reported experimental specific rotation is $[\alpha]_D^{25}=-3.43$ for neat liquid[16] and -4.6 ± 0.7 for 1 M solution of enflurane in hexane solvent.[17] The calculated net optical rotations, -1.3 with 6-31G* basis set and -1.7 with DZP basis set, are approximately within a factor of two to three of the observed values.

The net rotation is a resultant of optical rotations of nine different conformations. Some conformers have larger optical rotations than the others. Although the optical rotation signs predicted for a given conformer are the same in both calculations, the population fractions and magnitudes of optical rotations of individual conformers vary slightly in the two calculations. Yet the net optical rotations have the same negative sign that has been established[16,17] for the (R)-configuration, and the magnitudes are close to the observed value. This observation, along with those on other simple molecules,[7] reflects the reliability of *ab initio* optical rotations in molecular structural elucidation. The *ab initio* optical rotation calculations are much less demanding than the calculations on ECD, VCD or VROA, so a practicing chemist can greatly benefit from these observations when the quantum mechanical programs implementing the optical rotation calculations become widely available.

Acknowledgements

Table 1.

<u>Specific rotations calculated for (R)-enflurane</u>

conformer designation[a]	Population fraction	specific rotation $[\alpha]_D$	population weighted specific rotation
		6-31G* basis set	
EF	0.074	-0.03	-0.00
EF_2	0.091	18.08	1.64
EF_3	0.076	-6.82	-0.52
EF2	0.064	-9.50	-0.61
EF2_2	0.152	-9.17	-1.39
EF2_3	0.157	20.65	3.24
EF3	0.070	-12.06	-0.85
EF3_2	0.154	-24.72	-3.80
EF3_3	0.161	6.25	1.01
Net specific rotation:			-1.3
		DZP basis set[b]	
EF	0.020	-5.10	-0.10
EF_2	0.119	10.19	1.22
EF_3	0.071	-18.10	-1.28
EF2	0.021	-15.13	-0.31
EF2_2	0.173	-14.98	-2.59
EF2_3	0.250	16.97	4.24
EF3	0.019	-11.03	-0.21
EF3_2	0.189	-23.42	-4.42
EF3_3	0.139	12.71	1.77
Net specific rotation:			-1.7

Experimental specific rotation:[c] : $[\alpha]_D$= -3.43 (neat) and -4.6±0.7 (C=1, hexane)

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[a]see Fig.1 for structures

[b]at 6-31G* geometries

[c]from Ref.(16,17)

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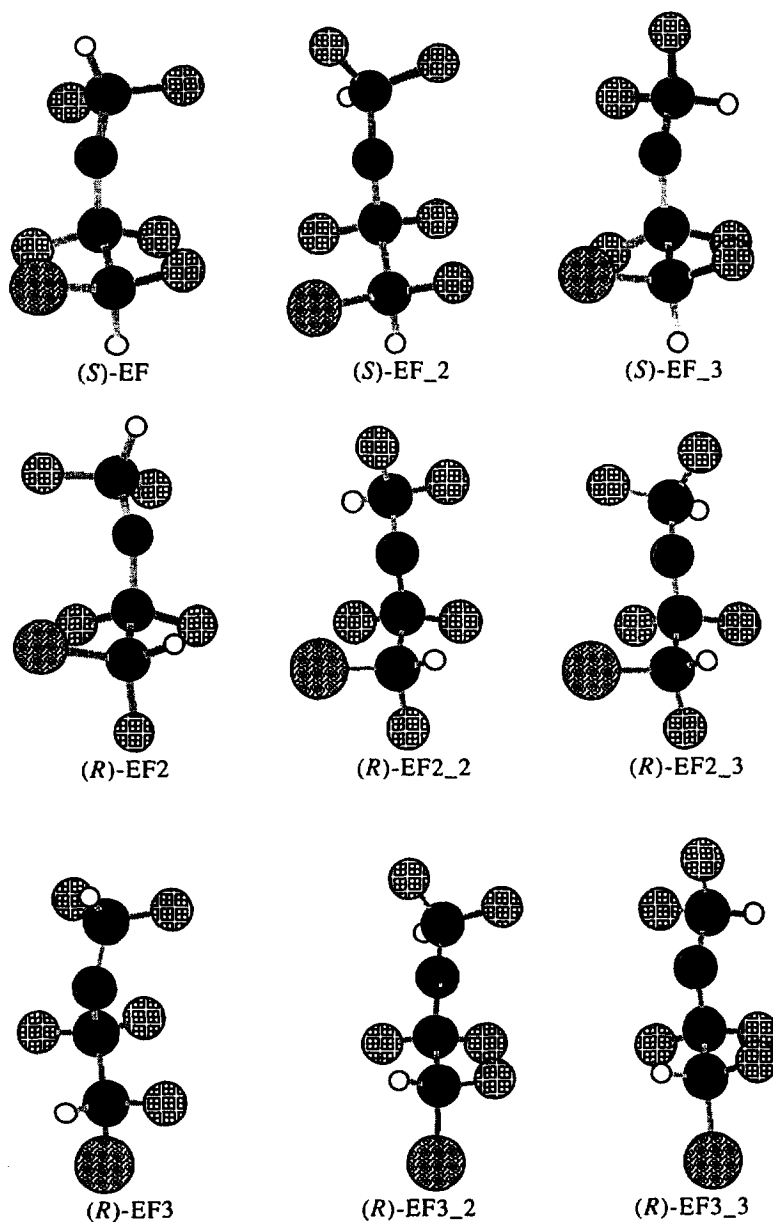
Figure 1. Structures of nine conformers of enflurane.

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