Conformational Analysis Using ab Initio Vibrational Spectroscopy: 3-Methylcyclohexanone

F. J. Devlin and P. J. Stephens*

*Department of Chemistry, University of Southern California
Los Angeles, California 90089-0482*

Vibrational spectra are exquisitely sensitive to molecular structure. In particular, different conformers of a molecule exhibit very different spectra. Consequently, vibrational spectroscopy is a powerful tool in determining the numbers, relative energies, and structures of the populated conformers of a flexible molecule: i.e., conformational analysis (CA).[1] In the case of achiral molecules, CA can be based on either unpolarized absorption ("IR") or linearly polarized Raman spectra. In the case of chiral molecules, the phenomena of vibrational circular dichroism (VCD)[2,3] and Raman optical activity (ROA)[3] are also available.

A fundamental requirement for the practical application of vibrational spectroscopy to CA is a theoretical methodology capable of reliably predicting vibrational spectra. Recent developments in ab initio density functional theory (DFT) have greatly enhanced the accuracy and efficiency of this methodology in calculating vibrational frequencies, unpolarized absorption intensities, and VCD intensities.[4,5] As a result, the analysis of the vibrational unpolarized absorption and circular dichroism spectra of mixtures of conformers is now practicable using DFT for a large range of molecular size. In this paper we illustrate the capabilities of ab initio DFT via the CA of the chiral molecule 3-methylcyclohexanone (**1**).

There have been many studies of conformational equilibria in substituted cyclohexanones.[1,6] In the specific case of **1**, literature values for the free energy difference between the equatorial-methyl and axial-methyl conformers (**1e** and **1a**) are given in Table 1. All studies have concluded that **1e** is preponderant, in agreement with theoretical expectations.[1]

The IR absorption spectrum of **1** has been measured in CCl$_4$ and CS$_2$ solutions; the spectra are very similar. The spectrum in the mid-IR spectral region is shown in Figure 1. Spectra predicted for **1e** and **1a** are also shown. Ab initio calculations have been carried out using DFT, the hybrid functional B3PW91,[10] the [5s4p2d/3s2p]/TZ2P basis set,[11] and analytical derivative methods[4,5] via the Gaussian program, as described previously.[12] Cursory examination shows that the spectrum of **1e** is much closer to the experimental spectrum than is the spectrum of **1a**. It follows immediately that **1e** is the dominant conformer present. Com-

Table 1. Experimental Conformational Energy Difference of **1**[a]

ΔG	method	solvent	ref
0.50	electronic CD	ether/isopentane/ethanol	7
0.75	electronic CD	methylcyclohexane	7
1.1	NMR	CDCl$_3$[b]	8
1.62	REMPI	gas phase	9
0.76/1.23	vibrational spectroscopy	CCl$_4$(CS$_2$)	this work

[a] Energy difference of **1a** and **1e**; in kcal/mol. [b] **1** is complexed with Yb(fod)$_3$shift reagent.
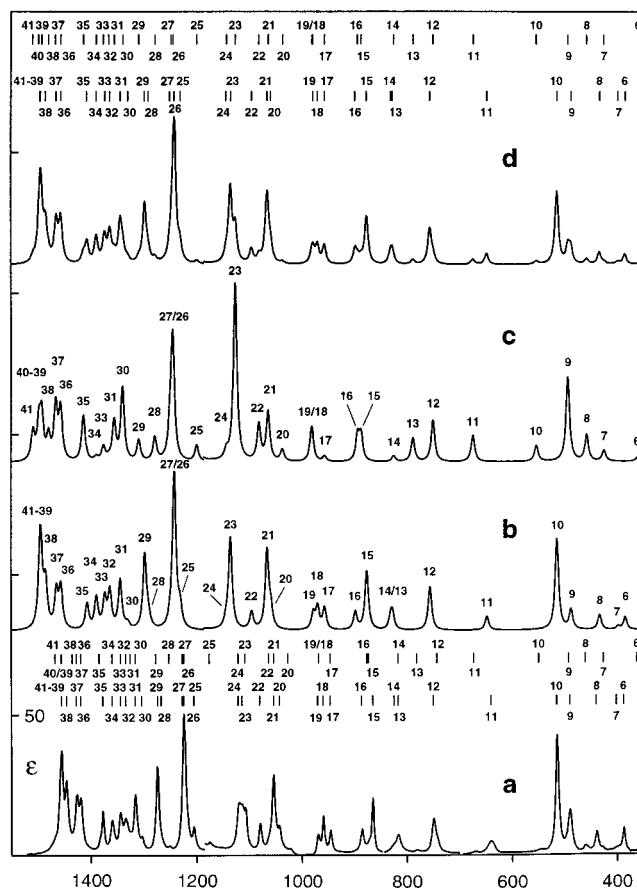

Figure 1. Unpolarized absorption spectra of **1**. a: experimental spectrum in CCl$_4$ (1.18 M, 1520−845 cm^{-1}, and 700−350 cm^{-1}) and CS$_2$ (1.20 M, 845−700 cm^{-1}). Resolution was 1 cm^{-1}. b: DFT/B3PW91/TZ2P spectrum of **1e**. c: DFT/B3PW91/TZ2P spectrum of **1a**. d: DFT/B3PW91/TZ2P spectrum of mixture of **1e** (79%) and **1a** (21%). In a−d, the spectra above 1185 cm^{-1} have been multiplied by 0.5. In b−d, Lorentzian band shapes are assumed; $\gamma = 4.0$ cm^{-1}. Fundamentals are numbered. In a and d, the lower and upper rows of vertical bars indicate the experimental and calculated frequencies of the fundamentals of **1e** and **1a** respectively.

parison of the predicted spectrum of **1e** to experiment, allowing for the expected overall shift to higher frequencies,[13] leads to the unambiguous assignment of almost all of the fundamentals 6−41 of **1e**. However, many observed bands cannot be so assigned. Comparison to the predicted spectrum of **1a** leads to the conclusion that almost all of these bands can be assigned as fundamentals of **1a**. Fundamentals 6, 7, 8, 10, 11−13, 15/16, 20, 22, 23, 25, 28, 31, 35, and 41 are clearly visible and unambigu-

(1) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Wiley-Interscience: New York, 1965.

(2) Stephens, P. J.; and Lowe, M. A. *Annu. Rev. Phys. Chem.* **1985**, *36*, 213.

(3) Nafie, L. A. *Annu. Rev. Phys. Chem.* **1997**, *48*, 357.

(4) (a) Johnson, B. G.; Frisch, M. J. *Chem. Phys. Lett.* **1993**, *216*, 133. (b) Johnson, B. G.; Frisch, M. J. *J. Chem. Phys.* **1994**, *100*, 7429.

(5) Cheeseman, J. R.; Frisch, M. J.; Devlin, F. J.; Stephens, P. J. *Chem. Phys. Lett.* **1996**, *252*, 211.
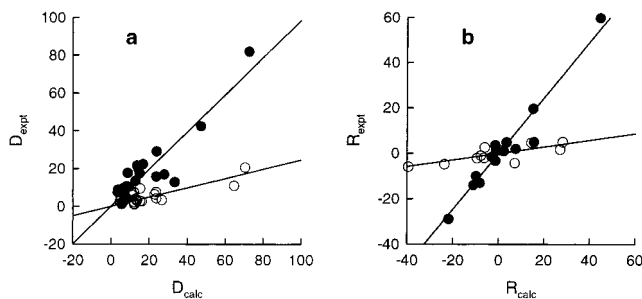
(6) See, for example: Allinger, N. L.; Freiberg, L. A. *J. Am. Chem. Soc.* **1962**, *84*, 2201; Cotterill, W. D.; and Robinson, M. J. T. *Tetrahedron* **1964**, *20*, 765, 777; Allinger, N. L.; Blatter, H. M.; Freiberg, L. A.; Karkowski, F. M. *J. Am. Chem. Soc.* **1966**, *88*, 2999.

(7) Lightner, D. A.; Crist, B. V. *Appl. Spectrosc.* **1979**, *33*, 307.

(8) Abraham, R. J.; Chadwick, D. J.; Griffiths, L.; Sancassan, F. *J. Am. Chem. Soc.* **1980**, *102*, 5128.

(9) Cornish, T. J.; Baer, T. *J. Phys. Chem.* **1990**, *94*, 2852.

(10) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372, 5648. (b) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.

(11) Stephens, P. J.; Jalkanen, K. J.; Amos, R. D.; Lazzeretti, P.; Zanasi, R. *J. Phys. Chem.* **1990**, *94*, 1811.

(12) Devlin, F. J.; Stephens, P. J.; Cheeseman, J. R.; Frisch, M. J. *J. Phys. Chem.* **1997**, *101*, 6322, 9912.

(13) Devlin, F. J.; Stephens, P. J. *J. Phys. Chem.* **1999**, *103*, 527.

Figure 2. Comparison of calculated and experimental dipole strengths, a, and rotational strengths, b. ● and ○ denote fundamentals of **1e** and **1a**, respectively. In a, fundamentals 6–12, 14–16, 18–20, 22, 23, 25, 28–30, 35, and 38 of 1**e** and 6–13, 15, 16, 20, 22, 23, 25, 28, 29, 31, 35, 38, and 41, of **1a** are included. In b, fundamentals 15, 16, 18–20, 22, 23, 25, 28–31, 35, and 38 of **1e** and 15, 16, 20, 22, 23, 25, 28, 29, 31, 35, 38, and 41 of **1a** are included. *D* and *R* are in 10^{-40} esu^2 cm^2 and 10^{-44} esu^2 cm^2, respectively.

ously assignable. Thus, with very few exceptions the experimental spectrum of **1** can be completely assigned to fundamentals of **1e** and **1a**. These assignments are detailed in Figure 1.

Quantitative deconvolution of the observed absorption spectrum is achieved via Lorentzian fitting.[12] The agreement of calculated and experimental frequencies is typical of DFT/TZ2P calculations using hybrid functionals,[12,13] supporting our assignments. Comparison of the dipole strengths obtained for bands identifiable with a single mode of one conformer to corresponding calculated values is shown in Figure 2. Linear fits for bands assigned to **1e** and to **1a** yield slopes of 0.98 and 0.25, respectively. Assuming equal accuracy of the calculated dipole strengths of the two conformers, the ratio of these slopes, 0.26, equals the ratio of their populations, i.e., the conformational equilibrium constant. The equilibrium constant corresponds to a free energy difference ΔG_c of 0.76 kcal/mol ($T = 293$ K). The percentage populations of **1e** and **1a** are 79 and 21%, respectively. The spectrum of **1** predicted using these populations of **1e** and **1a** is shown in Figure 1d.

VCD spectroscopy[2] provides strong support for the analysis of the absorption spectrum of **1**. The mid-IR VCD spectrum of R-**1** in CCl$_4$ is shown in Figure 3, together with predicted spectra for R-**1e** and R-**1a**. Ab initio calculations have been carried out using DFT, B3PW91, TZ2P, and analytical derivative methods[5] via the Gaussian program, as described previously.[12] Atomic axial tensors (AATs) were calculated using gauge-invariant atomic orbitals (GIAOs).[5c] The differences in predicted VCD spectra for **1e** and **1a** are enormous. That for **1e** is in good overall qualitative agreement with the experimental spectrum, while for **1a** there is no obvious resemblance. The VCD spectrum thus unambiguously confirms the predominance of **1e** in CCl$_4$ solution. At the same time, close examination reveals features in the VCD spectrum which cannot be assigned to **1e** and are attributable to **1a**. The most prominent is the negative VCD at 1176 cm^{-1} due to mode 25 of **1a**. Modes 20, 22, 23, and 28 are also clearly observed. Quantitative deconvolution of the VCD spectrum is achieved via Lorentzian fitting.[12] Comparison of the rotational strengths obtained from bands identifiable with a single mode of one conformer to corresponding calculated values is shown in Figure 2b. Linear fits to the rotational strengths of bands assigned to **1e** and **1a** yield slopes of 1.23 and 0.15, respectively. The ratio of these slopes is 0.12, corresponding to $\Delta G_c = 1.23$ kcal/mol ($T = 293$ K) and percentage populations for **1e** and **1a** of 89 and 11% respectively. The VCD spectrum of **1** predicted using these populations of **1e** and **1a** is shown in Figure 3d.

The absorption and VCD spectra yield values of the free energy difference between **1e** and **1a**, ΔG_c, of 0.76 and 1.23 kcal/mol, respectively. Prior experimental studies have yielded a range of values (Table 1): 1.62 kcal/mol in the gas phase[9] and 0.5–1.1 kcal/mol in condensed phases.[7,8] The average of our results is close to the value obtained in CDCl$_3$ solution.[8] Taken together,
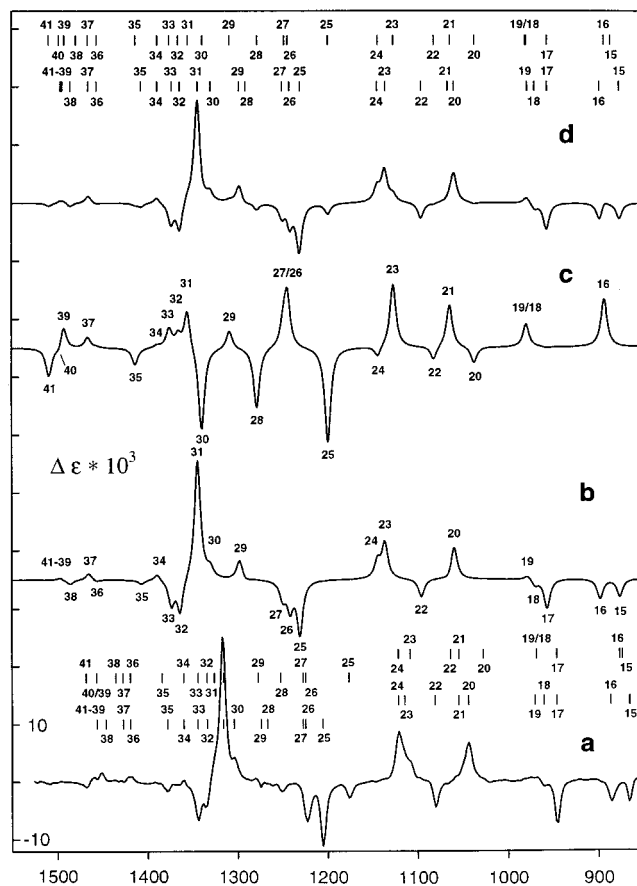
Figure 3. VCD spectrum of R(+)-**1**. a: experimental spectrum in CCl$_4$ (1.18 M). Resolution was 4 cm^{-1}. b: DFT/B3PW91/TZ2P spectrum of **1e**. c: DFT/B3PW91/TZ2P spectrum of **1a**. d: DFT/B3PW91/TZ2P spectrum of mixture of **1e** (89%) and **1a** (11%). In b–d, Lorentzian band shapes are assumed; $\gamma = 4.0$ cm^{-1}. Fundamentals are numbered. In a and d, the lower and upper rows of vertical bars indicate the experimental and calculated frequencies of the fundamentals of **1e** and **1a** respectively.

it appears that (1) solvent effects substantially lower ΔG_c and (2) ΔG_c decreases with increasing solvent polarity.

The DFT/B3PW91/TZ2P energy difference of **1e** and **1a** is 1.47 kcal/mol. Inclusion of a solvent of dielectric constant 2.23 (equal to that of CCl$_4$) using the Onsager model[14] and the polarized continuum model (PCM)[15] gives 1.52 and 1.51 kcal/mol, respectively. The isolated molecule value is in reasonable agreement with the experimental gas phase ΔG_c. However, the predicted solvent effect is in disagreement with experiment both in sign and order of magnitude.

We have demonstrated that vibrational transitions associated exclusively with **1e** and **1a** can be identified. Further studies of both the intensities and the temperature-dependence of these transitions are planned in order to provide more accurate values of ΔG_c for a wide range of solvents. These in turn will permit the accuracies of currently available solvent models to be tested more stringently.

The results obtained in this work provide a foundation for reliable analysis of the Raman and ROA spectra of **1**. Prior study of these spectra using ab initio theory used the Hartree–Fock (HF) method and small basis sets and ignored the **1a** conformation.[16] As a result, the Raman spectrum was both incorrectly and incompletely assigned.

(14) Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 4776.
(15) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117.
(16) Polavarapu, P. L.; Black, T. M.; Barron, L. D.; Hecht, L. *J. Am. Chem. Soc.* **1993**, *115*, 7736.