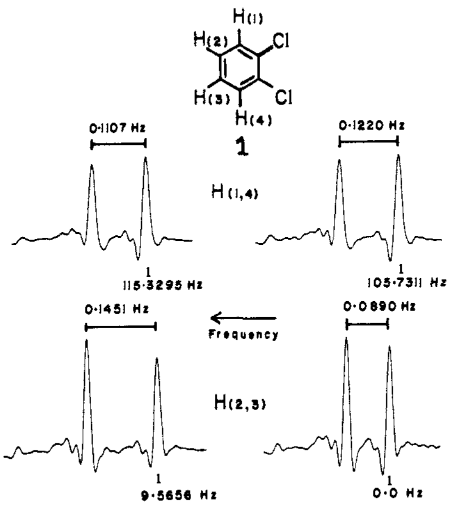

Figure 1. Four doublets arising from second-order *J* splitting, perturbed by D_{14} (top) or D_{23} (bottom), in the AA′BB′ ^{1}H NMR spectrum of **1** at 500 MHz.

Table I. NMR Parameters for **1**

parameter[a]	value, Hz	error,[b] Hz	parameter[a]	value, Hz	error,[b] Hz
$\nu_1 - \nu_2$	105.4249	±0.0004	J_{14}	0.3283	±0.0004
$J_{12} + D_{12}$	8.0667	±0.0005	D_{23}	−0.0175	±0.0005
$J_{13} + D_{13}$	1.5241	±0.0005	D_{14}	−0.0023	±0.0005
J_{23}	7.4879	±0.0005	σ[c]	0.0004	

[a] From MIMER,[3] with $D_{12} = -0.0170$ and $D_{13} = -0.0034$ Hz. [b] 95% confidence limits. [c] Standard deviation of fit of eight variables to 24 corrected line frequencies.[8]

As a practical example, the ^{1}H NMR spectrum of *o*-dichlorobenzene (**1**) in acetone-d_6 at 500 MHz has been measured.[7] This AA′BB′ spectrum should be symmetrical about its center if all *D*'s are zero. In fact, the small second-order *J* splittings (ca. 0.1 Hz) do not occur in a symmetrical fashion, as can readily be seen from Figure 1.

The spectrum of **1**,[8] was fitted by means of the iterative program MIMER.[3] The sums, $J_{12} + D_{12}$ and $J_{13} + D_{13}$, are listed in Table I because the individual parameters cannot be determined to a meaningful accuracy at a single magnetic field. The largest deviation between the experimental and calculated line frequencies with the parameters given in Table I is 0.0006 Hz (0.6 mHz), i.e., 6–8% of the apparent line widths in Figure 1.

In **1**, the vectors formed by the H_{14} pair and the H_{23} pair are parallel, with $r_{14} = 2r_{23}$, so that D_{14} should be equal to $D_{23}/8$, i.e., 2.2 mHz, in agreement with the data in Table I. If the reasonable approximation is made that the chlorine atoms have only a small influence on the alignment of **1**, then a single ordering parameter suffices,[6,9] and calculations show that $S_{zz} = {}^1/_2 \langle 3 \cos^2 \theta - 1 \rangle = -2.3 \times 10^{-6}$, which is similar to the value ($\pm 2.5 \times 10^{-6}$, presumed to be negative) found for benzene-d_1 in acetone-d_6.[10] In order to obtain D_{12} and D_{13}, accurate measurements on **1** at lower fields are being undertaken, and the method described in this paper is being applied to other molecules.[11]

Acknowledgment. The 500-MHz spectrometer was purchased through funds provided in part by the National Science Foundation.

---

(7) Spectra of a 10% solution of **1** in acetone-d_6 were measured on a Bruker AM 500 spectrometer at 23 °C. The spectrum width (SW) was 212 Hz and the acquisition time was 58 s. After applying a Lorentzian–Gaussian resolution enhancement (LB = ca. −0.07 Hz), the FID was zero-filled to 512 K points and Fourier-transformed. The final digital resolution was 0.8 mHz and the apparent line widths were 10–15 mHz (^{1}H T_1's in **1** are greater than 30 s). When no resolution enhancement was applied, the full line width at half-height was 0.07 Hz. The peak frequencies were measured to 0.1 mHz by increasing the SW parameter by a factor of 10 before calling the (interpolating) peak listing routine.

(8) Very small, but systematic, errors were found when fitting the experimental spectrum. The small splittings were made larger by the negative lobes introduced by the resolution enhancement (cf.: Sibisi, S. P. *J. Magn. Reson.* **1982**, *48*, 447–456). The lines of such doublets (separation <150 mHz) in **1** were therefore moved toward the doublet centers by $(0.17 - \Delta\nu)/70$ Hz, where $\Delta\nu$ is the experimental splitting. These corrections ranged from 0.3 to 1.1 mHz, and for the second-order splittings that control the value of D_{14} (see Figure 1), the *difference* in the corrections to the observed splittings was only 0.2 mHz. The final peak positions were the average obtained from three slightly different resolution enhancements of the same FID data. Other data, with smaller acquisition times, gave peak positions in excellent agreement with the above, except for the very closely spaced doublets. Because of the resolution enhancement, the noise in Figure 1 is not random. Other treatments of the data, e.g., maximum entropy (Laue, E. D.; Skilling, J.; Staunton, J. *J. Magn. Reson.* **1985**, *63*, 418–424 and references therein), may have advantages and are being explored.

(9) The symmetry point group of **1** is C_{2v}, and the *z* axis is taken to be perpendicular to the ring plane.

(10) Bothner-By, A. A.; Gayathri, C.; van Zijl, P. C. M.; MacLean, C. *J. Magn. Reson.* **1984**, *56*, 456–462.

(11) Anet, F. A. L.; Kopelevich, M., work in progress. Previously obtained lower field NMR parameters of **1** have insufficient accuracy for the present purpose.

Deuterium Isotope Effects on the Ring Inversion Equilibrium in Cyclohexane: The *A* Value of Deuterium and Its Origin

Frank A. L. Anet* and Max Kopelevich

Department of Chemistry and Biochemistry
University of California
Los Angeles, California 90024

Received November 7, 1985

It has been reported recently that the deuterium in cyclohexane-d_1 prefers the equatorial over the axial position by "about 200 J/mol" (i.e., ca. 50 cal/mol), as shown by three different kinds of NMR measurements.[1] Such an isotope effect is unexpectedly large,[1-5] and this has led us to reinvestigate the problem using Saunder's isotopic perturbation method.[6] We have thereby established that the free energy difference (the *A* value for deuterium[7]) is 6.3 ± 1.5 cal/mol, with deuterium more stable equatorial than axial. Our value is supported by molecular mechanics calculations based in part on experimental vibrational frequencies.

The selectively deuterated cyclohexane-d_{10} *cis*-I and *trans*-I (Figure 1) were chosen for NMR study, since a 1:1 mixture of these isotopomers can be easily prepared and they are very suitable for the application of Saunders' method.[8] The 200-MHz ^{1}H{D} NMR spectrum of this mixture in CS_2 at 25 °C shows two lines

---

(1) Aydin, R.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 985–986; *Angew. Chem.* **1981**, *93*, 1000–1003.

(2) Anet, F. A. L.; Bourn, A. J. R. *J. Am. Chem. Soc.* **1967**, *89*, 760–768.

(3) Bovey, F. A.; Hood, F. P., III; Anderson, E. W.; Kornegay, R. L. *J. Chem. Phys.* **1964**, *41*, 2041–2044.

(4) Chertkov, V. A.; Sergeyev, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 6750–6752.

(5) Data on cyclohexane-d_{11} at about −100 °C show that the intensities of the two ^{1}H NMR peaks are the same within experimental error (ca. 2%).[2-4] An energy difference of 50 cal/mol would give an easily observed intensity difference of about 15%. The results obtained by Ayden and Günther[1] are based on differences between large numbers in the integration of deuteron NMR peaks at low temperatures or on the assumption of extremely good additivity of isotope and temperature effects on chemical shifts. Thus, despite the great experimental care that was taken, the conclusions reached by these authors are not really convincing.

(6) (a) Saunders, M.; Jaffe, M. H.; Vogel, P. *J. Am. Chem. Soc.* **1971**, *93*, 2558–2559 (b) Anet, F. A. L.; Basus, V. J.; Hewitt, A. P. W.; Saunders, M. *J. Am. Chem. Soc.* **1980**, *102*, 3945–3946 and references therein.

(7) The definition of the *A* value as the conformational free energy difference in a *monosubstituted cyclohexane* (Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562–5578) is precise and also very useful, since cyclohexane is the prototype for all other saturated six-membered rings.

(8) Birch reduction of benzene-d_6 was carried out with a mixture of lithium, triethylamine, ethylenediamine, and methanol, and the cyclohexadiene-d_6 was isolated by VPC. The addition of deuterium was done in the presence of Wilkinson's catalyst $[Rh(PPh_3)_3Cl]$ (cf.: Garbisch, E. W., Jr.; Griffith, M. G. *J. Am. Chem. Soc.* **1968**, *90*, 6543–6544). The isotopic purity of I from GC/MS was 95%.

0002-7863/86/1508-1355$01.50/0

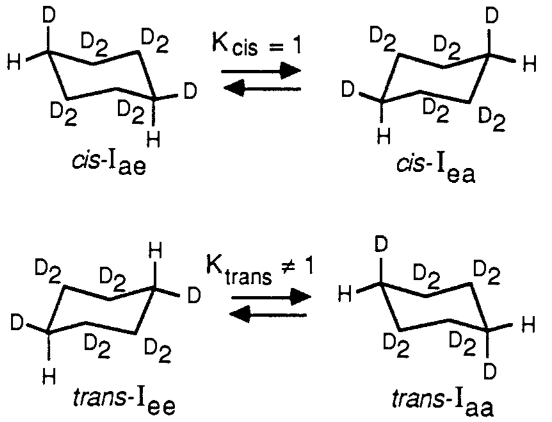

Figure 1. Conformational equilibria in *cis*- and *trans*-I. The e and a labels refer to deuterium in the CHD groups.

of equal areas separated by 0.51 ± 0.02 Hz.[9] In order to assign the peaks of the observed doublet, a separate sample of *trans*-I was prepared[10] and added to the above 1:1 mixture. The more shielded component of the doublet increased in intensity, showing that *trans*-I gave rise to that peak.

An examination of the conformational equilibria in *cis*- and *trans*-I (Figure 1) shows that $K_{cis} = 1$, whereas $K_{trans} \neq 1$. Intrinsic isotope effects[11] on chemical shifts in the two isotopomers of I should be virtually the same.[12] Thus, for example, an axial proton in *cis*-I have the same inherent chemical shift as an axial proton in *trans*-I. A difference in the observed ^1H chemical shifts between the two isotopomers at room temperature then indicates that the equilibrium constant for *trans*-I is not unity.

The chemical shift difference between axial and equatorial protons in cyclohexane-d_{11} is virtually temperature-independent and is equal to 0.478 ppm,[2,3] i.e., 95.6 Hz at 200 MHz, with the axial proton more shielded than the equatorial proton. It follows from the data on I that the ee conformation (i.e., protons axial) in *trans*-I is preferred over the aa conformation. The value of K_{trans} (Figure 1) is calculated to be 0.979 ± 0.004, which gives $\Delta G° = 12.6 \pm 3$ cal/mol. Thus, for a single deuterium, $\Delta G° = 6.3 \pm 1.5$ cal/mol, and this is the *A* value for deuterium (see below).

The stretching frequency in cyclohexane-d_{11} for an equatorial CH group is 31 cm^{-1} higher than that for an axial CH group.[13] Since this value of $\Delta\nu_{ae}$ contributes 12 cal/mol, differences in the bending frequencies must partly cancel the CH stretching contribution. We have therefore carried out molecular mechanics calculations of vibrational frequencies and thermodynamic parameters on these molecules.[14] The stretching force constants for equatorial and axial C–H bonds were adjusted to reproduce $\Delta\nu_{ea}$ exactly; all other force constants were left independent of whether hydrogens were axial or equatorial.[15] With this force field, the calculated $\Delta G°$ (25 °C) for cyclohexane-d_{11} was 6.7 cal/mol, in excellent agreement with our experimental NMR value.[16,17]

Further work on defining precisely the intrinsic isotope effects in I is being undertaken, and the importance of differences in C–H stretching frequencies in controlling equilibrium isotope effects in other molecules is being investigated.

Acknowledgment. We thank Professor H. L. Strauss for providing us with manuscripts of his work before publication and for drawing our attention to the subject of the present paper. The WP-200 NMR spectrometer and the VAX-780 computer were purchased through funds provided in part by the National Science Foundation.

---

[9] Spectra were obtained on a Bruker WP-200 NMR spectrometer at a frequency of 200 MHz. Deuterium decoupling was done through the lock input on the probe. In order to monitor the field homogeneity, a small amount of ordinary cyclohexane was added to the sample, and single FID's were collected in an unlocked mode. The data were transferred to a VAX-780 computer and processed with the NMRI program (Dumoulin, C. L.; Levy, C. G. *J. Mol. Struct.* **1984**, *113*, 299-310. Levy, C. G.; Begemann, J. H. *J. Chem. Inf. Comput. Sci.* **1985**, *25*, 350–357). Lorentzian–Gaussian resolution enhancement was applied, and after zero filling, the FID was Fourier transformed. The final digital resolution was 0.006 Hz per point. All errors quoted in this paper refer to 95% confidence limits, and include our best estimates of systematic errors.

[10] 1,4-Cyclohexanedione-d_8 (Muller, N.; Schultz, P. J. *J. Phys. Chem.* **1964**, *68*, 2026–2028) was reduced with $LiAlH_4$ and the product was converted to the isomeric diacetates from which the high melting trans isomer was isolated. After methanolysis to the diol, tosylation, and treatment with $LiBEt_3D$, the desired cyclohexane-d_{10} was isolated by VPC. Analysis by GC/MS showed an isotopic purity of 64%.

[11] (a) Anet, F. A. L.; Dekmezian, A. H. *J. Am. Chem. Soc.* **1979**, *101*, 5449–5451. (b) Hansen, P. E. H. *Annu. Rep. NMR Spectrosc.* **1983**, *15*, 105–234.

[12] Two *tert*-butylcyclohexane isotopomers (one with a 4-CH_2 and the other with a 4-CD_2 group) have been shown to differ in their 1-CH chemical shifts by only 1 ± 1 ppb as a result of an isotopic change five bonds away (Haddon, V. R.; Jackman, L. M. *Org. Magn. Reson.* **1973**, *5*, 333–338). We estimate that the difference in intrinsic isotope effects between *cis*- and *trans*-I is less than 0.5 ppb (i.e., <0.1 Hz at 200 MHz).

[13] Snyder, R. G.; Aljibury, A. L.; Strauss, H. L.; Casal, H. L.; Gough, K. M.; Murphy, W. F. *J. Chem. Phys.* **1984**, *81*, 5352–5361 and references therein. See also: Wiberg, K. B.; Walters, V. A.; Dailey, W. P. *J. Am. Chem. Soc.* **1985**, *107*, 4860–4867.

[14] Burkert, U.; Allinger, N. L. "Molecular Mechanics"; ACS Monograph Series 177; American Chemical Society: Washington, DC, 1982.

[15] The DELPHI program (van der Graaf, B.; Baas, J. M. A. *J. Comput. Chem.* **1984**, *5*, 314–321) was modified (cf.: Anet, F. A. L.; Anet, R. *Tetrahedron Lett.* **1985**, *26*, 5355–5358) to allow convenient use with isotopes and to allow interaction with a data base on a VAX-780 computer. The adjusted force constants for axial and equatorial C–H stretching were 634 and 647 kcal/(mol Å^2), respectively. Other force constants were from: Boyd, R. H. *J. Chem. Phys.* **1968**, *49*, 2574–2583.

[16] Deuterium atoms in substituted cyclohexanones favor *axial positions* by 3–10 cal/mol, but some of these systems have 1:3 diaxial interactions with methyl groups and this could account for the different sign of the isotope effects from that in cyclohexane itself (Barth, G.; Djerassi, C. *Tetrahedron* **1981**, *37*, 4123–4142 and references therein).

[17] Other properties which are different for axial and equatorial CH groups include ^{13}CH coupling constants[4] and bond lengths.[13]

Tritium Isotope Effects on Carbon-13 NMR Chemical Shifts

Cheryl H. Arrowsmith,† Lars Baltzer,‡ A. Jerry Kresge,*†
Michael F. Powell,§ and Yui S. Tang§

Department of Chemistry, University of Toronto
Toronto, Ontario M5S 1A1, Canada
Department of Organic Chemistry, Chalmers University
of Technology and University of Goteborg
S-412 96 Goteborg, Sweden
Laboratory of Chemical Biodynamics, Lawrence Berkeley
Laboratory, Berkeley, California 94720

Received November 21, 1984

Deuterium isotope effects on carbon-13 NMR chemical shifts can be useful in making spectral assignments, and they are also interesting in their own right.[1] We report here the first determination of tritium isotope effects on carbon-13 NMR spectra.

We measured these isotope effects using acetone labeled with tritium at the 1% level and enriched to 90% with carbon-13 at the carbonyl position. This material was prepared by allowing carbon-13 enriched acetone (ICONS Services, Inc.) to exchange with tritiated water (27 Ci/mL) in the presence of a catalytic amount of sodium hydroxide. The labeled product was separated from water by entrainment in a stream of nitrogen, passage

---

† University of Toronto.

‡ Chalmers University of Technology and University of Goteborg.

§ Lawrence Berkeley Laboratory.

[1] For recent reviews, see: Forsyth, D. A. In "Isotopes in Organic Chemistry"; Buncel, E., Lee, C. C., Eds., Elsevier: New York, 1984; Vol. 6, Chapter 1. Hansen, P. E. *Annu. Rep. NMR Spectrosc.* **1983**, *15*, 105–242.