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THE CONFORMATIONAL PREFERENCE (A VALUE) OF DEUTERIUM IN MONODEUTERIOCYCLOHEXANE FROM DEUTERON INTEGRATION AT LOW TEMPERATURES

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Summary: The A value of deuterium in cyclohexane-d_1 is shown to be 8.3 ± 1.5 cal/mol by peak integration of the deuteron NMR spectrum at -95 °C; this is in disagreement with a previous measurement (22 ± 5 cal/mol) by this method reported by Aydin and Günther, but is close to the A value (6.3 ± 1.5 cal/mol) deduced previously from data on cyclohexane-d_{10} isotopomers.

The equatorial-axial conformational preference of deuterium in cyclohexane-d_1 (I), i.e., Winstein's A value for deuterium, is difficult to measure because it is very small. In cyclohexane-d_{11}, which should have almost the same conformational equilibrium as I, three groups have found that the deuterium, within a percent or two, exhibits no conformational preference, as shown by low-field (60 and 100 MHz) ^{1}H NMR intensities at low temperature.[1,2,3] Aydin and Günther[4] (AG) have reported that integration of the high-field (400 MHz ^{1}H frequency) deuteron signals in I at -85 °C gives an equilibrium constant of 1.060 ± 0.014 favoring the equatorial position, corresponding to an A value of 22 ± 5 cal/mol. However, integration of peaks that are even slightly overlapped is very susceptible to systematic errors caused by phasing errors and unsymmetrical line shapes; AG do not mention taking any special precautions in their integration measurements. These workers obtained data from two other NMR methods, which gave (rounded) A values of 60 and 80 cal/mol (the errors in these numbers, as calculated by us from the data given by AG, are ± 30 and ± 25 cal/mol, respectively), but it has been pointed[5] out that these methods depend on additivities of isotope shifts holding to an unrealistic degree and to minute frequency differences. The large scatter in the three numbers [mean (rounded) = 50 cal/mol] obtained by AG is consistent with substantial systematic errors.[6]

Anet and Kopelevich[5] (AK) have found an A value of 6.3 ± 1.5 cal/mol by an analysis of the perturbation of the conformational equilibria in two diastereomeric cyclohexane-d_{10} isotopomers and have shown that this value is compatible with cyclohexane vibrational frequencies. Siehl,[7] in a recent review on isotope effects, discounts AK's results on what we believe to be incorrect grounds,[8] and he ignores AK's criticism of AG's methods. We have now reinvestigated the A value of deuterium using AG's low-temperature deuteron integration method, which is certainly theoretically sound, if experimentally difficult. A Bruker AM500 spectrometer (deuteron frequency of 76.77 MHz) was employed. The precautions taken to avoid systematic errors are described below.[9]

1. The temperature of the probe was constant to 0.1 °C. Deuteron spectra could be accumulated for more than five minutes in an unlocked mode without any observable field or homogeneity drifts. A 5mm broad-band probe was tuned to deuterium and broad-band proton decoupling was applied so that the two peaks in I at -95 °C had virtually the

same widths and line shapes. The criterion for shimming the magnetic field was the absolute symmetry of the peaks at half height combined with the best possible symmetry nearer the base of the peaks at the level of the ^{13}C satellites (Figure 1).

2. As the two deuteron signals in I are separated by only 36.2 Hz and have significant widths (1.3 Hz at -95 °C in CS_2), they overlap to a small extent (Figure 1) and this makes it difficult to obtain unbiased integrals. A very flat base line was achieved by a special phasing procedure appropriate for quadrature detection with alternating sampling of the real and imaginary FID data, as used on Bruker spectrometers.[10] A rather wide spectral width (1400 Hz) was chosen with an acquisition time of 3 s and zero filling of the FID to 64 K points was employed prior to the Fourier transform. An exponential broadening function of 0.1 to 0.2 Hz was applied to the FID. The above procedure also gave almost perfectly phased peaks; a small zero-order phase correction (<2°) was sometimes applied to correct a slight asymmetry in the peaks. Calculations were done to show that the finite pulse width (6 μs, 70° tilt angle) and the filter band width (1800 Hz) used did not result in a differential gain for the two cyclohexane signals. To avoid saturation, the pulse repetition time (3 s) was made much longer than the measured deuterons T_1's (0.275 ± 0.10 s). The absence of spurious peaks in the region of the cyclohexane resonances was checked at about 0 °C.

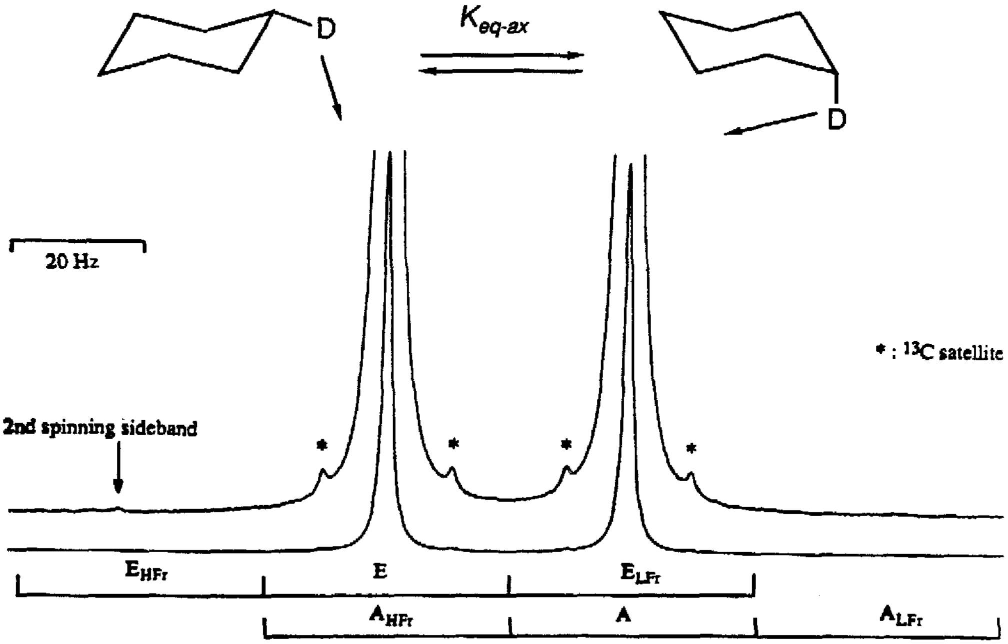

Figure 1 76.77 MHz ^2H {^1H} NMR spectrum of 10% cyclohexane-d_1 in CS_2- CD_2Cl_2 (10:1) at -95 °C, showing the regions used for peak integration. The equatorial and axial peaks are separated by 0.4715 ppm (36.2 Hz).

3. Exactly eight data sets, each consisting of a sum of 64 FID's, were obtained under the above conditions in one operating run. All eight sets were used in the integral calculations, which were carried out after all the FID data had been obtained; no data was rejected for any reason. The following protocol was used to measure the integrals. Four equal and adjacent regions were defined, as shown in Figure 1. The axial peak is assumed to have finite intensity only in the regions A, A_{HFr}, and A_{LFr}. Similarly, the equatorial peak has intensity only in E, E_{HFr}, and E_{LFr}. Thus, the experimental integral in the A region consists of the true axial peak integral plus E_{LFr}. But, to a good approxim-

ation, $E_{LFr} = A_{LFr}$ (note that E_{LFr} need not be the same as E_{HFr}, because of possible peak asymmetry near the base line). Thus, the corrected integral of the axial and equatorial peaks are A - A_{LFr} and E - E_{HFr}, respectively.

4. With the standard protocol given above, corrected integrals for the axial and equatorial peaks were obtained separately by the two authors and are shown in Table I. Additionally, in order to reduce the possibility of conscious or unconscious bias on the part of the present authors, Dr. Mike Geckle, using the above protocol, obtained an independent set of integrals from the same data (Table I), but without knowing the origin of the data, or having any preconceived idea of the relative integral values.

Table I Deuterium A Value and Integrals for the Axial and Equatorial Deuteron Peaks in Cyclohexane-d_1,

Data Set Number	Integral Values (as $K_{eq\text{-}ax}$)				Deuterium A Value (cal/mol)
	FALA[a]	DJOL[b]	MG[c]	Mean	
1	0.9779[e]	0.9768	0.9877	0.9808	6.9
2	0.9798	0.9765	0.9777	0.9780	7.9
3	0.9705	0.9716	0.9871	0.9764	8.5
4	0.9763	0.9718	0.9777	0.9753	8.9
5	0.9771	0.9767	0.9833	0.9790	7.5
6	0.9788	0.9759	0.9822	0.9790	7.5
7	0.9736	0.9729	0.9749	0.9738	9.4
8	0.9752	0.9701	0.9776	0.9743	9.2
			Grand mean[d]:	0.977 ± 0.002	8.2 ± 0.9

[a] Integration done by F. A. L. Anet. [b] Integration done by D. J. O'Leary. [c] Integration done by M. Geckle.
[d] Errors are standard deviations. [e] 0.9787 and 0.9782 with Lorentzian-Gaussian resolution enhancements (*LB* = *-1.0* Hz, GB = 0.3 and 0.15 respectively).

Table I shows that the A value of deuterium from the present work is 8.2 ± 0.9 cal/mol; some personal biases are evident in the integral values in Table I, e.g., MG's integrals are systematically low compared to the other integrals. The error estimate based on random errors therefore needs to be increased, perhaps to about ± 1.5 cal/mol. It seems clear, however, that our results on cyclohexane-d_1 do not bear out the high A value (22 ± 5 cal/mol) reported by AG, but they are in fairly satisfactory agreement with AK's A value of 6.5 ± 1.5 cal/mol based on cyclohexane-d_{10}. To test the accuracy of the present results, it is planned to measure accurate integrals at -95 °C in the deuteron spectra of *cis*- and *trans*-cyclohexane-1,4-d_2 and in the proton spectrum of cyclohexane-d_{11}.

Acknowledgments. The National Science Foundation and NIH provided partial funding of the 500 MHz NMR spectrometer. We are indebted to Dr. Mike Geckle for kindly determining the (blind) integrals.

References and Notes

1. Anet, F. A. L.; Bourn, A. J. R. *J. Am. Chem. Soc.* **1967**, *89*, 760-768.
2. Bovey, F. A.; Hood, F. P., III; Anderson, E. W.; Kornegay, R. L. *J. Chem. Phys.* **1964**, *41*, 2041-2044.
3. Chertkov, V. A.; Sergeyev, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 6750-6752.
4. Aydin, R.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 985-986.
5. Anet, F. A. L.; Kopelevich, M. *J. Am. Chem. Soc.* ***1986***, *108*, 1355-1356.

6. The 82 cal/mol figure comes from the deuterium one-bond (${}^{1}\Delta$) isotope shifts on ${}^{13}C$ in $C_6H_{11}D$ (41.32 Hz) and $C_6H_{10}D_2$ (1,1-d_2 isomer) (82.98 Hz) with respect to C_6H_{12}. Because the 82.98 Hz figure in the inversion-symmetrical 1,1-d_2 isomer consists only of an intrinsic isotope shift, AG claim that the intrinsic isotope shift in $C_6H_{11}D$ must be 82.98 /2 or 41.49 Hz, and therefore that the difference (0.17 Hz) between this number and 41.32 Hz can be ascribed to an equilibrium isotope shift in $C_6H_{11}D$. Although isotope shifts are "strictly " additive when measured with moderate accuracy (errors of a few percent), deviations of the order of 1 to 3 % are calculated and observed in more accurate studies (Jameson, C. L.; Osten, H.-J. *J. Chem. Phys.* **1984**, *81*, 4293-4299; Wasylishen, R. E.; Friedrich, J. O. *J. Chem. Phys.* **1984**, *80*, 585-587). Thus, the calculated intrinsic isotope shift for $C_6H_{11}D$ may have an error of ± 41.49/100 or ± 0.4 Hz, and this makes the above 0.17 Hz difference also have at least an error of this magnitude. Clearly, no useful data on the equilibrium isotope shift in $C_6H_{11}D$ can be obtained from these data.

The 58 cal/mol figure is the result of an isotopic perturbation of equilibrium analysis, but with such a small low-temperature chemical shift difference (4.85 Hz) that the method has low accuracy (cf. the 94 Hz shift used in this kind of procedure in reference 5). The room temperature ${}^{1}\Delta$ isotope shift in $C_6H_{11}D$, which is 42.02 Hz, differs from the mean (42.07 Hz) of the low temperature axial and equatorial ${}^{1}\Delta$ isotope shifts (39.64 Hz and 44. 49 Hz) by 0.05 ± 0.05 Hz. In order to account for the different temperature of the two measurements, AG add -0.07 ± 0.03 Hz to the room temperature ${}^{1}\Delta$ value of 42.02 Hz before comparing it to the calculated mean value. This correction is obtained from the temperature dependence of ${}^{1}\Delta$ in $C_6H_{10}D_2$ (1,1-d_2 isomer). However, precise additivity in the temperature coefficients of the isotope shifts in $C_6H_{11}D$ and $C_6H_{10}D_2$ may not hold; a non-additivity of 0.05 Hz in a shift of ca 40 Hz would allow an A value of 8 cal/mol for deuterium.

7. Siehl, H.-V. *Adv. Phys. Org. Chem.* **1987**, *23*, 63-163.

8. Siehl claims that heavily deuterated molecules may not be suitable for isotopic perturbation analysis; our theoretical calculations (molecular mechanics and *ab initio*, Anet, F. A. L.; Kopelevich, M., unpublished work and reference 5) show that there is almost no difference between equilibrium isotope effects in $C_6H_{11}D$ and C_6HD_{11}. Siehl argues that AG's A value should be preferred over AK's because the latter have data only at room temperature, but the basic problem is that AG's results are invalid because of large systematic errors.[5, 6] The uncertainty in the A value given in reference 5 arises from possible small uncorrected intrinsic isotope effects. Work, which is currently in progress, indicates that the error (±1.5 cal/mol for 95% confidence limits) given previously[6] may be slightly optimistic and should be considered to correspond to one rather than two standard deviation; The A value for deuterium obtained from 1,1-dimethylcyclohexane-4-d_1 (cf. Anet, F. A. L.; Kopelevich, M. *J. Am. Chem. Soc.* **1986**, *108*, 2109) is 3.8 cal/mol (Anet, F. A. L.; Kopelevich, M. unpublished work).

9. Ultra-accurate integration seems to be a poorly investigated subject, cf. Biali, S. E.; Rappoport, Z.; Hull, W. E. *J. Am. Chem. Soc.* **1985**, *107*, 5450-5459. Peak subtraction in, e.g., NOE measurement, can be done to 0.1% because the identity of the peak shapes (and overlaps with adjacent peaks) leads to excellent cancellation of errors (Sanders, J. K. M.; Mersh, J. D. *Prog. NMR Spectrosc.* **1982**, *15*, 353-400).

10. The frequency-independent and frequency-dependent phase corrections (PC0 and PC1) were set to 270 and 180° respectively. With the transmitter frequency set on resonance for a peak, a microprogram [1 ZE; 2 D1; 3 P1 PH1;4 D5; 5 D5 PH0; 6 D6 ADC; 7 RCYC = 2 PH2; with PH1 = 0, 2, 1, 3 and PH2 = R0, R2, R1, R3] was used to phase that peak by adjusting the value of PH0 (360). The other peaks were then phased by adjustments of the delay (D5) between the end of the pulse and the start of data acquisition and/or by slight variations in the filter band-width parameter (FW). This procedure, which has been used by other workers in the past, does not appear to have been published. We thank Dr. Mike Geckle for suggesting this method and for help in its implementation.

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