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SOLVENT EFFECTS IN CONFORMATIONAL ANALYSIS OF 1,4-CYCLOHEXANEDIOLS[a]

W. F. Trager[b], B. J. Nist and A. C. Hultric

College of Pharmacy and Department of Chemistry
University of Washington, Seattle, Washington

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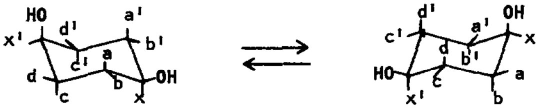
We have observed that the PMR spectrum of cis-1,4-cyclohexanediol obtained in pyridine is very different from that obtained in D_2O. The signal of the methylene protons give a complex multiplet spread over more than 50 c/s in pyridine but give a symmetrical triplet with separation of 2.5 c/s and half-width of about 7 c/s in D_2O. The differences could result from solvent effects on chemical shifts or from solvent effects on conformation. When the same internal reference is used, solvent effects must necessarily result from unequal effects on certain protons in the system. Such effects are well known (1).



1 2

I_a: a, a', b, b', c, c', d, d', x, x' are all H.

I_b: c, c', d, d', x' are D; a, a', b, b', x are H.

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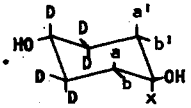
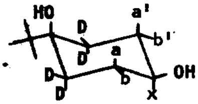
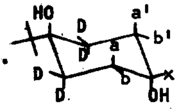
Rapid interconversion between the two energetically identical chair conformations 1 and 2 of the *cis* isomer I_a will give two sets of four protons each: a, a', d, d' form a set of protons with identical chemical shifts, and b, b', c, c' form the other set.

In order to better clarify the problem the following selectively deuterated compounds were prepared: *cis*-1,4-cyclohexanediol-3,3,4,5,5-d_5 (I_b); *trans*-1,4-cyclohexanediol-3,3,4,5,5-d_5 (II); 4-*tert*-butyl-*cis*-4-hydroxycyclohexanol-3,3,5,5-d_4 (III); and 4-*tert*-butyl-*trans*-4-hydroxycyclohexanol-3,3,5,5-d_4(IV).

The spectra of the deuterated *trans*-diol II determined in pyridine and D_2O had identical patterns which are consistent with the chair conformation with a high preponderance of the diequatorial conformer in both solvents. ABX analysis (2) of the spectra from the two solvents gave coupling constants which are almost identical: $J_{ab} = 12.5$, $J_{ax} = 9.6$, $J_{bx} = 3.9$ from the pyridine spectrum, and $J_{ab} = 12.4$, $J_{ax} = 9.6$, $J_{bx} = 4.3$ from the D_2O spectrum. The chemical shifts are given in table I.

TABLE I

Chemical Shifts, ν, c/s from T.M.S. Internal Reference at 60 Mc.

	Pyridine			D_2O or (D_2O-HAc)			Δ(Pyridine vs. D_2O)		
	ν_a	ν_b	ν_x	ν_a	ν_b	ν_x	a	b	x
II. 	91.6	125.4	228.4	74.3	110.3	214.5	17.3	15.1	13.9
III. 	127.0	121.0	226.0	92.2	102.1	210.6	34.8	18.9	15.4
IV. 	131.6	112.4	257.0	107.0	93.6	239.5	24.6	18.8	17.5

The spectrum of the deuterated <u>cis</u>-diol I_b, measured in pyridine, gave essentially a first-order spectrum (Fig. 1) which yielded the following values from the ABX analysis: $\nu_x = 235.1$ c/s; $\nu_a = 124.2$; $\nu_b = 104$; $J_{ab} = 12.4$; $J_{ax} = 6.7$; $J_{bx} = 3.4$. The coupling constant values are consistent with equal populations of the two chair conformations 1 and 2 of structure I_b and provide direct experimental evidence that a rapid interconversion between conformations 1 and 2 does not yield equal values of J_{ax} and J_{bx}. The fallacy of expecting equal J_{ax} and J_{bx} has been explained by Booth (3). By using average values of J_{aa} and J_{ae} (4) the estimated coupling constants obtained by taking the average value between J_{ax} values in conformations 1 and 2, and the average value between J_{bx} values in conformations 1 and 2, turn out to be: J_{ax} about 6-7 c/s and J_{bx} about 3-4 c/s.

When measured in D_2O the PMR spectrum of <u>cis</u>-diol I_b gives a very different pattern (Fig. 1) consisting of a narrow doublet with spacing of 5 c/s centered at 96.5 c/s and a symmetrical quintet centered at 224.5 c/s with spacings of 5 c/s. The spacing agrees well with $\frac{1}{2}(J_{ax} + J_{bx}) = \frac{1}{2}(6.7 + 3.4)$ values from pyridine, and it is the expected spacing (3b) from equilibrium between conformations 1 and 2 should $\nu_a = \nu_b$ because of solvent effects on chemical shifts. The observed spectrum is also consistent with a rapid-equilibrium between all possible flexible conformations (3a).

It should be possible, from the spectra of structures II, III, and IV in a given solvent, to approximate the theoretical chemical shifts of protons a and b in compound I_b undergoing interconversion between conformations 1 and 2 in the same solvent. Compounds III and IV were not sufficiently soluble in D_2O, but it was found that the spectrum of I_b was identical when obtained from D_2O or from a mixture of 25% acetic acid in D_2O as solvent, a solvent mixture in which III and IV were sufficiently soluble. It was therefore assumed that chemical shifts of protons a and b in III and IV obtained in 25% acetic acid in D_2O could be taken as representative of values that would prevail in pure D_2O. Additional supporting evidence for the validity of this assumption was obtained from the fact that the spectrum of the <u>trans</u>-diol II is essentially identical when obtained in pure D_2O or in 25% acetic acid in D_2O.

In order to approximate the average chemical shift of protons a and b in the <u>cis</u>-diol I_b undergoing interconversion between conformations 1 and 2 in a given solvent it is necessary to have good approximations of the chemical shifts of a and of b in each of conformations 1 and 2 in that given solvent (a and a' have identical chemical shifts, as do b and b'). Such approximations are possible from the spectra of II, III and IV if the assumption is made that the equatorial hydroxyl group on C-4 of II and the equatorial <u>tert</u>-butyl group on C-4 of structures III and IV do not affect the chemical shifts of protons a, a' and b, b' in structures II, III and IV. If this assumption is correct then the chemical shift of a, a' and b, b' in conformation 1 of I_b are the same as those of a, a' and b, b' respectively in structure III. In conformation 2 of I_b, a, a' and b, b' are best related to b, b' and a, a' respectively of structure II, except that the hydroxyl group on C-1 of I_b is axial in conformation 2 but equatorial on C-1 of II. A correction can be made for this from the relative chemical shifts of a and a' in structure III vs. IV, and likewise for b and b'. From this information the calculated chemical shift for a and a' in I_b in D_2O-acetic acid mixture is $\frac{92.2}{2} + \frac{(110.3 - 8.5)}{2} = 97$ c/s, and that of b and b' is $\frac{102.1 + (74.3 + 14.8)}{2} =$ 95.6 c/s. The observed doublet resulting from the combined signals of a, a' and b, b' is centered at 96.5 c/s.

In order to determine if the anomalous spectrum of I_b observed in D_2O and D_2O-acetic acid mixture could result from solvent effects on chemical shifts, the theoretical spectrum was obtained by means of the computor NMR

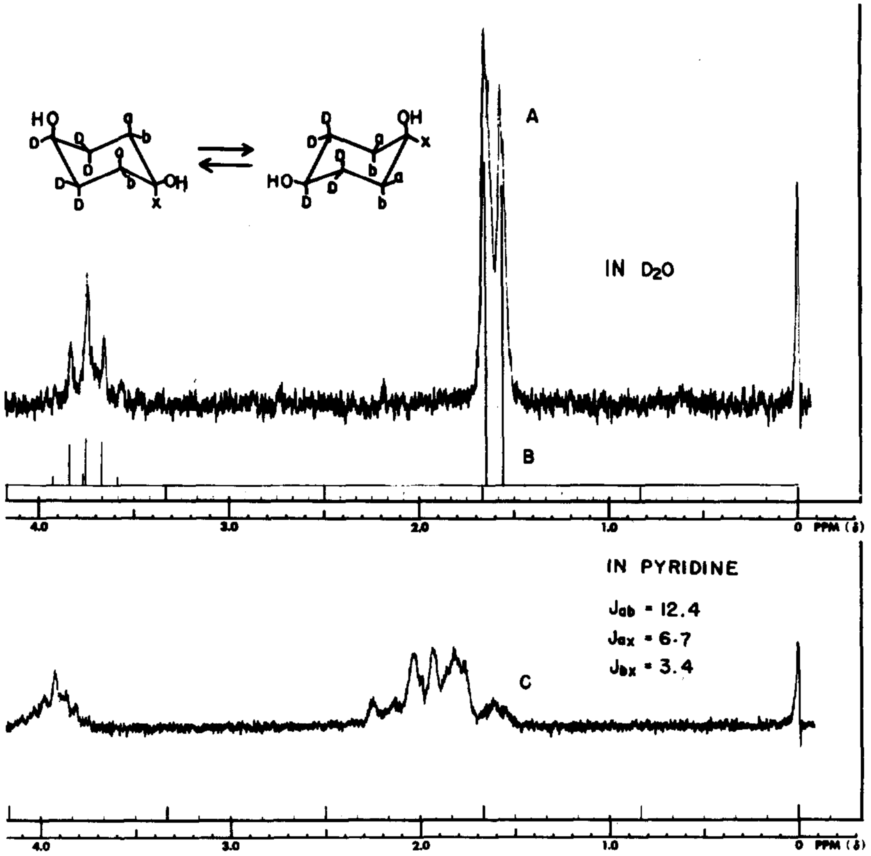


FIG. I

PMR spectra of cis-1,4-cyclohexanediol-3,3,4,5,5-d_5 (I_b): A, in D_2O; C, in pyridine. B is the theoretical spectrum of I_b in D_2O using calculated chemical shifts as explained in the text. The spectra were obtained with a Varian A-60 spectrometer at 37°.

program of Wiberg and Nist (5) using calculated values of $\nu_a = \nu_{a'} = 97$ c/s, $\nu_b = \nu_{b'} = 95.6$ c/s; observed value $\nu_x = 225$ c/s; and coupling constants of $J_{ab} = 12.4$, $J_{ax} = 6.7$, $J_{bx} = 3.4$ obtained from the ABX analysis of the spectra of I_b in pyridine*. The theoretical spectrum so obtained is shown in Fig. 1. The agreement with the observed spectrum is excellent. The use of identical values of 96.5 c/s for the chemical shifts of a and b gave a similar theoretical spectrum with slight differences in the relative intensities of the two components of the doublet. The validity of this treatment is supported by the fact that similar treatment for I_b in pyridine gave a normal first-order calculated spectrum which agreed well with the observed spectrum C, except that the chemical shifts of protons a and b were slightly closer to each other.

Cis- and trans-1,4-cyclohexanediols are known compounds. Compounds I_b and II were obtained by lithium aluminum deuteride reduction of 4-hydroxycyclohexanone-2,2,6,6-d_4 Compounds III and IV were obtained from the reaction tert-butyllithium with 4-hydroxycyclohexanone-2,2,6,6-d_4. Detailed synthesis of these compounds will be reported in a subsequent publication. Acceptable elementary analysis have been obtained.

Temperature variations of 23-105° for I_a in D_2O and 37-137° for I_b in pyridine did not cause any changes in the patterns of the signals of the ring protons in either case.

CONCLUSIONS

The above results, coupled with the fact that the PMR spectra of compound IV definitely establishes the chair conformation for IV in D_2O-acetic acid mixture, lead us to believe that cis-1,4-cyclohexanediol exists in the

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*The validity of the assumption that there is no change in coupling constants in the different solvents is based on the excellent agreement of the coupling constants of the trans-diol II in pyridine and D_2O.

chair conformation undergoing interconversion between energetically equivalent conformations 1 and 2 in D_2O as well as in pyridine. If the bulk of the solvated axial hydroxyl group of I_a or I_b, in D_2O or D_2O-acetic acid, would force the molecule in a flexible or twisted conformation the same results would be expected in structure IV, but this is ruled out by the spectrum of IV. The spectrum of IV also rules out a boat conformation with intramolecular hydrogen bonding between the cis-hydroxyl groups. Such a conformation is therefore highly unlikely for I_a or I_b in D_2O. This contention is supported by the variable temperature study. It also appears unlikely that intramolecular hydrogen bonding would play an important role in aqueous solutions.

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