

NMR Conformational Analysis of 4-Hydroxycyclohexanone and 1,4-Cyclohexanediols

Coupling Constants Averaging Induced by Conformational Equilibria and by Strong Coupling Effects—Role of Solvent

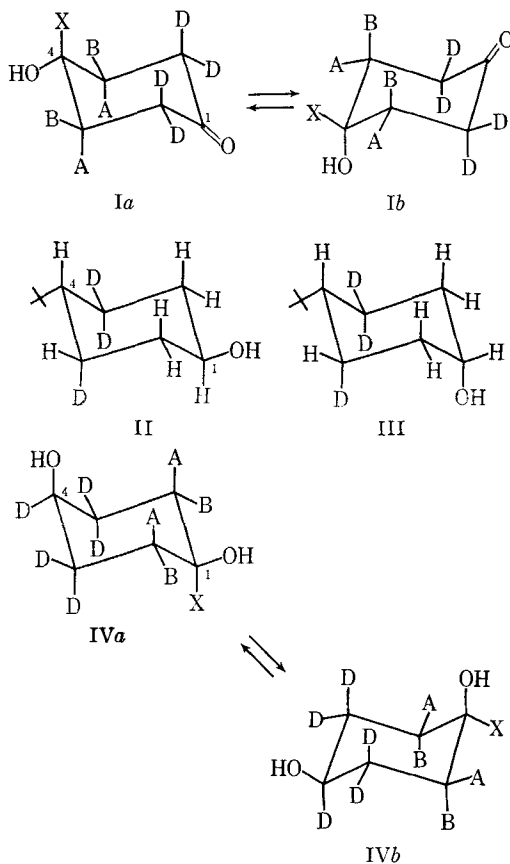
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Significant differences are observed in the NMR spectra of *cis*-1,4-cyclohexanediol and 4-hydroxycyclohexanone measured in different solvents. For the diol the differences are shown to arise from averaging of coupling constants through strong coupling effects. The differences for the ketone result from a combination of the same factors plus differences in conformational equilibria. A discussion of the averaging of coupling constants due to conformational equilibria and due to strong coupling effects is given. The signal band width method for determination of conformational equilibria is shown to be independent of strong coupling effects.

FAILURE to recognize complications resulting from averaging of coupling constants due to strong coupling effects can lead to serious errors in the interpretation of NMR spectra. Early warnings concerning these complications were given by several authors (1-3). In two previous communications concerned with the conformational analysis of *cis*-1,4-cyclohexanediol (4) and 4-hydroxycyclohexanone (5) by NMR, the observation of solvent effects on chemical shifts leading to deceptively simple spectra, as well as solvent effects on conformational equilibria, has been reported. In both cases of solvent effects, the changes produced in the observed spectra are associated with averaging of coupling constants, but of different kinds. The studies were made possible by the use of selectively deuterated compounds. In the present paper the synthesis of the deuterated compounds is reported, and a discussion of averaging of coupling constants due to conformational equilibria and due to strong coupling effects is presented.

DISCUSSION

In a mobile cyclohexane system such as *Ia* and *Ib* the observed coupling constants J_{XA} and J_{XB} represent the weighted time average values of what they would be in either pure *Ia* or pure *Ib*. That is, $J_{XA} = NaJ_{aa} + (1 - Na)J_{ee}$ and $J_{XB} = NaJ_{ee} + (1 - Na)J_{ea}$, where Na represents the mole fraction of the compound in conformation *Ia*, J_{aa} and J_{ee} are axial-axial and equatorial-equatorial coupling constants, respectively. If the individual values of J_{XA} (J_{aa} in *Ia*, and J_{ee} in *Ib*) and J_{XB} (J_{ee} in *Ia*, and J_{ea} in *Ib*) in pure *Ia* and *Ib* are known, then the conformational position can be calculated from observed coupling constants (6) measured directly



from the spectrum, providing that the first-order approximation is valid. This is not always the case because the situation is often complicated by strong coupling effects (1-3).

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In an ABX system of the type $X-C-A-B$,

where $J_{XA} \neq J_{XB}$, a first-order spectrum is possible providing the difference between the chemical shifts of A and B ($\nu_B - \nu_A$) is large compared to J_{AB} .

As $(\nu_B - \nu_A)$ approaches J_{AB} proton X is coupled to protons A and B behaving as a set, and individual values of J_{XA} and J_{XB} can no longer be obtained directly from the spectrum. In the limit where $\nu_B = \nu_A$, the signal of X yields a symmetrical triplet with separations equal to $(J_{XA} + J_{XB})/2$ even though J_{XA} and J_{XB} are not actually equal. The same applies to an $(AB)_2X$ system, such as 4-hydroxycyclohexanone-2,2,6,6- d_4 (I), or *cis*-1,4-cyclohexanediol-3,3,4,5,5- d_5 (IV) except that in the limit the signal of the X proton will now give a symmetrical pentuplet with line separations equal to $(J_{XA} + J_{XB})/2$. Thus both conformational equilibria and strong coupling effects tend to average coupling constants, but fortunately in an intrinsically different manner that permits separation of the two effects.

As stated above, the observed coupling constants, J_{XA} and J_{XB} , in a mobile cyclohexane in equilibrium between two chair conformations represent the weighted time average values of what they would be in each of the two alternate chair conformations. Hence, not only the individual magnitudes of J_{XA} and J_{XB} but also the sum of the coupling constants, and, therefore, the width of the signal of the X proton equal to $2(J_{XA} + J_{XB})$ is dependent upon the position of the equilibrium between chair conformations Ia and Ib or IVa and IVb (7-10). Changes in the width of the signal of the X proton reflect a change in the position of the equilibrium. On the other hand strong coupling effects will tend to average the individual values of J_{XA} and J_{XB} and thus cause changes in the pattern of the signal, but in this case the sum of the coupling constants remains constant. The important thing to recognize is that complications from strong coupling effects in systems such as $(Ia \rightleftharpoons Ib)$ or $(IVa \rightleftharpoons IVb)$ prevent the calculation of individual values of J_{XA} and J_{XB} by first-order approximation, but since the sum $2(J_{XA} + J_{XB})$ is not affected, the width of the signal of the X proton truly reflects the position of the equilibrium.

In the case of *cis*-1,4-cyclohexanediol-3,3,4,5,5- d_5 (IV) equal population of the two chair conformations is expected, and the individual values of observed J_{XA} and J_{XB} should be about 7 c.p.s. and 3.5 c.p.s., respectively (11, 12), providing that $(\nu_B - \nu_A)$ is large with respect to J_{AB} . As the ratio $(\nu_B - \nu_A)/J_{AB} \rightarrow 0$, strong coupling effects become operative and J_{XA} and J_{XB} tend to average out. In the limit where $\nu_B = \nu_A$, the signal of the X proton will appear as a symmetrical pentuplet with line separations equal to $(J_{XA} + J_{XB})/2$, about 5 c.p.s., and the combined signals of the A and B protons will give a doublet with the same separation of about 5 c.p.s.

4-Hydroxycyclohexanone—The NMR study was done with 4-hydroxycyclohexanone-2,2,6,6- d_4 (I) in order to simplify the spectra. Spectra of I were obtained in three different solvents: pyridine, D_2O , and $CDCl_3$ (Fig. 1). Pyridine and $CDCl_3$ both yielded deceptively simple spectra while in D_2O the observed spectrum is more closely first order. The results are interpreted as being consistent with a rapid equilibrium between the two chair conformations (Ia and Ib) with the differences in the spectra resulting from solvent effects on conformation and/or solvent effects on chemical shifts.

Conformational preference in each solvent was calculated by the signal width method of Garbisch

(7) or Feltkemp and Franklin (8-10) using the partially deuterated *trans* and *cis*-4-*tert*-butylcyclohexanol-3(axial),5,5- d_3 , II and III, respectively, for conformationally homogeneous models. The advantage¹ of this method over the method employing individual coupling constants (6) is that the observed signal width of the X proton is dependent only upon the conformational equilibrium and not upon strong coupling effects (1-3). Moreover, since vicinal coupling constants in cyclohexane systems are generally much less sensitive than chemical shifts to remote structural changes, the chosen models are suitable for reasonable approximation of the conformational equilibrium by the signal width method but are entirely inadequate for calculation by the chemical shift method (13). That this is so becomes apparent from the fact that the chemical shift of the X proton in 4-hydroxycyclohexanone-2,2,6,6- d_4 (I) both in pyridine and $CDCl_3$ is downfield from the signal of H-1 in III in the corresponding solvent.

The *trans* reference model (II) gave $J_{aa} = 11.0$, $J_{ae} = 4.2$, and $J_{gem} = 12.5$ c.p.s.² in $CDCl_3$ and $J_{aa} = 10.7$, $J_{ae} = 4.4$, and $J_{gem} = 12.0$ c.p.s. in pyridine. Accurate values of J_{ea} and J_{ee} could not be obtained from the spectrum of the *cis* isomer (III), but the symmetrical pentuplet of H-1 indicates that $J_{ea} \approx J_{ee}$ in III, since $(\nu_B - \nu_A)$ is outside the boundary of serious strong coupling effects. The value of $2(J_{ea} + J_{ee})$ was 11.0 in $CDCl_3$ and pyridine, indicating that $J_{ea} \approx J_{ee} \approx 2.7$ c.p.s. at 37°. The signal width of H-1 in II, equal to $2(J_{aa} + J_{ae})$ was found to be 30.6 c.p.s. in $CDCl_3$ and 30.0 c.p.s. in pyridine.

The mole fraction N_a of conformer Ia in the mobile 4-hydroxycyclohexanone system can be calculated from the width of the signal of H-4 in the mobile system, and H-1 in the two conformationally homogeneous models II and III by the equation:

$$N_a = \frac{2[J_{XA} + J_{XB}] - 2[J_{aa} + J_{ae}]}{2[J_{aa} + J_{ae}] - 2[J_{aa} + J_{ee}]} = \frac{W - W_a}{W_e - W_a}$$

where J_{XA} and J_{XB} refer to the mobile system; J_{aa} , J_{ae} , J_{ea} , and J_{ee} refer to the models II and III; W is the signal band width of H-4 in the mobile system, W_a and W_e ³ are signal width of H-1 in models III and II, respectively. The accuracy of the results will depend on the reliability of the chosen conformationally homogeneous models. In the present case, the models may not be ideal and the calculated mole fractions of conformer Ia should be considered good approximations rather than absolute values; but the relative values in the different solvents are very reliable.

By utilizing $W_a = 11.0$ and $W_e = 30.0$ c.p.s. obtained in pyridine⁴ and the measured value $W =$

¹ In nonfirst-order spectra it is possible to use the individual coupling constant method if the actual coupling constants can be calculated by complete analysis. Very often this is not possible because of overlapping of signals in the upper field region.

² Signs are not assigned, although it is generally understood that geminal coupling constants are of opposite signs to vicinal coupling constants.

³ The symbols used are those of Feltkemp and Franklin (9). It should be noted that W_a refers to the width of the X proton when the substituent is axial and the X proton equatorial.

⁴ The model compounds II and III are not sufficiently soluble for measurement in D_2O . The danger of error due to variations of coupling constants with solvent seems minimal because of the observation that the difference in width of the signal of H-1 in 4-*tert*-butyl-*cis*-4-hydroxycyclohexanol-3,3,5,5- d_4 measured in pyridine and 25% acetic acid in D_2O is only 0.5 c.p.s.

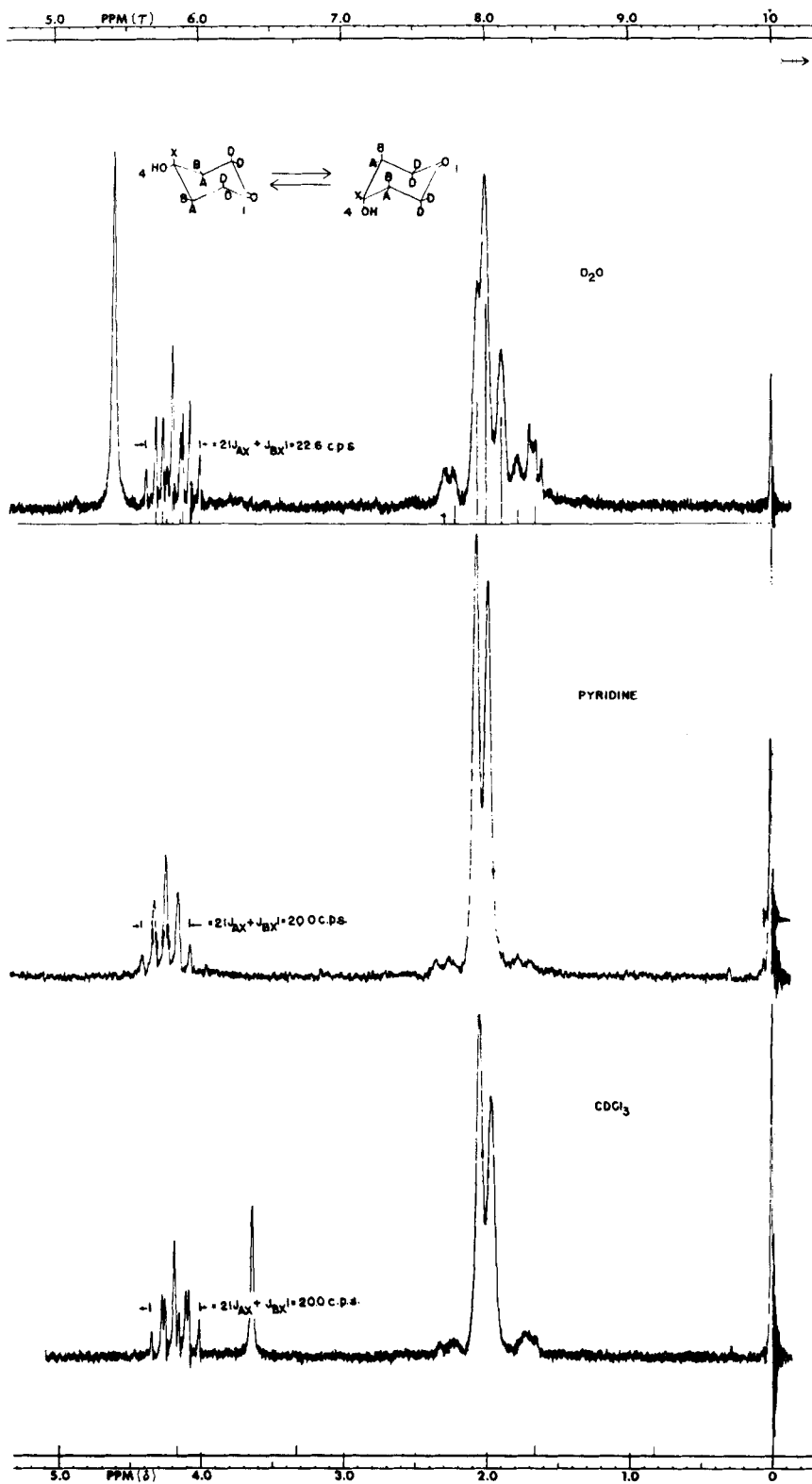


Fig. 1—NMR spectra of 4-hydroxycyclohexanone-2,2,6,6-d₄ in D₂O, pyridine, and deuterated chloroform at 60 Mc. and 37°. TMS and DSS were used as internal references in the organic solvents and D₂O, respectively. The calculated spectrum is shown beneath the observed spectrum in D₂O.

22.6 c.p.s. for the mobile system in D₂O, N_a is calculated to be 0.61. This corresponds to a $61 \pm$

4% population of conformer Ia and a conformational free energy difference of 0.27 Kcal./mole for the

hydroxyl group in 4-hydroxycyclohexanone in D₂O. The value W was found to be 20.0 c.p.s. in both pyridine and CDCl₃. Utilizing the respective W_e and W_a values this gives $47 \pm 4\%$ of conformer Ia in pyridine and $46 \pm 4\%$ of conformer Ia in CDCl₃. The apparent 3 to 4% predominance of conformer Ib is probably not real and probably reflects the fact that models II and III are not exactly ideal. Moreover, a small contribution ($\approx 1\%$) by nonchair flexible forms which would tend to narrow W is possible based on calculations of Allinger and co-workers (14), who predict that the ground state energy of the most stable flexible form of cyclohexanone and 4-methylcyclohexanone is about 3 Kcal./mole greater than the ground state of the chair conformation. Contribution of a boat form stabilized by intramolecular hydrogen bonding is argued against by the fact that the benzoate ester of 4-hydroxycyclohexanone-2,2,6,6-*d*₄ gives the typical pentuplet with signal width of 19.2 c.p.s. for the X proton and a doublet with separation of about 4.8 c.p.s. for the combined signals of the A and B protons in pyridine and in chloroform. There is no possibility of hydrogen bonding in the esters. Furthermore, Stolow (16) was unable to detect any evidence of intramolecular hydrogen bonding in 4-hydroxycyclohexanone by infrared studies in carbon tetrachloride.

The larger population of conformer Ia in D₂O is substantiated by the following treatment. The spectrum in D₂O gives $\nu_X = 251$; $\nu_B = 124.8$; $\nu_A = 112.2$, and $J_{AB} = 13.5$ c.p.s. The apparent coupling constants of $J_{XA} = 7.0$ and $J_{XB} = 4.3$ are erroneous because $(\nu_B - \nu_A) = 12.6$ is within the range of strong coupling complications. By utilizing the coupling constants obtained from II and III in pyridine the expected coupling constants of a rapid equilibrium between Ia and Ib with 61% of conformer Ia are calculated as:

$$J_{XA} = NaJ_{aa} + (1 - Na)J_{ee} = (0.61)(10.7) + (0.39)(2.7) = 7.6 \text{ c.p.s.}$$

$$J_{XB} = NaJ_{ab} + (1 - Na)J_{eb} = (0.61)(4.4) + (0.39)(2.7) = 3.76 \text{ c.p.s.}$$

When the observed chemical shift of $\nu_X = 251$, $\nu_B = 124.8$, $\nu_A = 112.2$ c.p.s., observed $J_{AB} = 13.5$ c.p.s.⁵ and calculated $J_{XA} = 7.6$ and $J_{XB} = 3.76$ c.p.s. were placed in the computer program of Wiberg and Nist (15), the resulting theoretical spectrum [reproduced under the experimental spectrum (Fig. 1)] gave apparent $J_{XA} = 7.05$ and $J_{XB} = 4.3$ and reproduced the experimental spectrum exactly.

The results thus indicate that the $-\Delta G_{OH}^\circ$ value of the hydroxyl group in 4-hydroxycyclohexanone is essentially zero in pyridine and CDCl₃, whereas it is 0.27 Kcal./mole in D₂O. The observed solvent effects on conformation are in agreement with the findings of Eliel (17), who postulated that the conformational equilibrium of the hydroxyl group in a cyclohexane system is a function of solvent where the $-\Delta G_{OH}^\circ$ value is greater for proton donating solvents such as water or alcohols. A solvent effect on chemical shifts of the signals of the A and B protons of 4-hydroxycyclohexanone whereby $(\nu_B - \nu_A)$ is smaller in pyridine than in CDCl₃ is indicated by the difference in the multiplicity but

identical width of the signal of the X proton in the two solvents.

cis-1,4-Cyclohexanediol—The NMR spectrum of this compound obtained in pyridine was found to be very different from that obtained in D₂O (4). In order to simplify the spectra the deuterated *cis*-1,4-cyclohexanediol-3,3,4,5,5-*d*₆ (IV) was prepared and used for this study. In contrast to 4-hydroxycyclohexanone-2,2,6,6-*d*₄, it is pyridine which gives the approximately first-order spectrum, while D₂O gives the deceptively simple spectrum for IV (Fig. 2). The results are interpreted as being consistent with a rapid equilibrium between the two energetically equivalent chair conformations IVa and IVb, with differences in spectra arising from solvent effects on chemical shifts. The width of the signal of the X proton of IV in both pyridine and D₂O is 20.2 c.p.s., even though it appears as a seven-peak multiplet in the former solvent and symmetrical pentuplet in the latter. Calculation of the mole fraction of conformer IVa in the mobile *cis*-1,4-cyclohexanediol system utilizing the partially deuterated *trans* and *cis*-4-*tert*-butylcyclohexanol-3 (axial), 5,5-*d*₈, II and III, respectively, for conformationally homogeneous models and the signal width method of Garbisch (7) or Feltkamp and Franklin (8–10), leads to a $48 \pm 4\%$ population of conformer IVa. This result is in excellent agreement with expected 50% population of conformer IVa and attests to the reliability of the method.

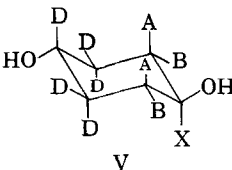
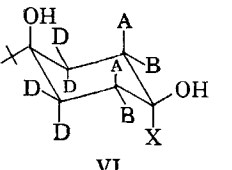
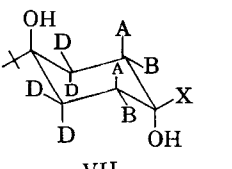
The measured values of J_{XA} and J_{XB} for IV in pyridine are 6.7 and 3.4 c.p.s., respectively. Utilizing the model compounds II and III, once again: $J_{XA} = (J_{aa} + J_{ee})/2 = (10.7 + 2.7)/2 = 6.7$ and $J_{XB} = (J_{eb} + J_{ee})/2 = (2.7 + 4.4)/2 = 3.6$ c.p.s., a result in good agreement with the observed couplings and one that should prevail in a system approaching first order. The line separation of the pentuplet in D₂O is 5.0 c.p.s., and this is in excellent agreement with the expected apparent coupling constant $(J_{XA} + J_{BX})/2 = (6.7 + 3.6)/2 = 5.1$ c.p.s. for a system under the influence of strong coupling in the limit where $\nu_A = \nu_B$. Thus, *cis*-1,4-cyclohexanediol-3,3,4,5,5-*d*₆ provides excellent experimental examples of the phenomenon of averaging of coupling constants due to conformational equilibria and averaging of coupling constants due to strong coupling effects. It also provides an excellent example of complications from strong coupling effects due to solvent effects on chemical shifts.

In an attempt to clarify the solvent effects on chemical shift and provide another method for checking the above results, the following selectively deuterated compounds were prepared: *trans*-1,4-cyclohexanediol-3,3,4,5,5-*d*₆ (V); 4-*tert*-butyl-*cis*-1,4-cyclohexanediol-3,3,5,5-*d*₄ (VI); and 4-*tert*-butyl-*trans*-1,4-cyclohexanediol-3,3,5,5-*d*₄ (VII) (Table I).

It should be possible, from the spectra of structures V, VI, and VII in a given solvent, to approximate the theoretical chemical shifts of the protons A and B in *cis*-1,4-cyclohexanediol-3,3,4,5,5-*d*₆ (IV) undergoing interconversion between conformations IVa and IVb in the same solvent. Compounds VI and VII were not sufficiently soluble in deuterium oxide, but it was found that the spectra of IV were identical when obtained from D₂O or from a mixture of 25% acetic acid in D₂O as solvent, a solvent mixture in which VI and VII were sufficiently soluble.

⁵ The calculated spectrum is unaltered when J_{AB} is replaced by $-J_{AB}$.

TABLE I—CHEMICAL SHIFTS OF DEUTERATED COMPOUNDS PREPARED^a

	Pyridine			D ₂ O or (D ₂ O-HAc)			Δ(Pyridine vs. D ₂ O)		
	ν_A	ν_B	ν_X	ν_A	ν_B	ν_X	a	o	x
 V	91.6	125.4	228.4	74.3	110.3	214.5	17.3	15.1	13.9
 VI	127.0	121.0	226.0	92.2	102.1	210.6	34.8	18.9	15.4
 VII	131.6	112.4	257.0	107.0	93.6	239.5	24.6	18.8	17.5

^a Chemical shifts (from ABX analysis), ν c.p.s. from TMS internal reference at 60 Mc.

It was therefore assumed that the chemical shifts of protons A and B in VI and VII obtained in 25% acetic acid in deuterium oxide could be taken as representative of values that would prevail in pure D₂O. Additional supporting evidence for the validity of this assumption was obtained from the fact that the spectra of *trans*-diol V when obtained in pure D₂O or in 25% acetic acid in D₂O are essentially identical.

In order to approximate the average chemical shift of protons A and B in IV undergoing interconversion between conformations IVa and IVb in a given solvent it is necessary to have good approximations of the chemical shifts of A and B in each of the conformations IVa and IVb in that given solvent. Such approximations are possible from the spectra of V, VI, and VII if the assumption is made that the equatorial hydroxyl group on C-4 of V and the equatorial *tert*-butyl group on C-4 of structures VI and VII do not appreciably affect the chemical shifts of protons A and B in structures V, VI, and VII. If this assumption is correct, then the chemical shifts of A and B in conformation IVa are the same as those of A and B, respectively, in structure VI. In conformation IVb, A and B are best related to A and B, respectively, of structure V except that the hydroxyl group at C-1 of IV is axial in conformer IVb but equatorial on C-1 of V. A correction can be made for this from the relative chemical shifts of A in structure VI versus VII and likewise for B. From this information the calculated chemical shift for A in IV in D₂O-acetic acid mixture is $92.2/2 + (110.3 - 8.5)/2 = 97$ c.p.s. and that of B is $102.1/2 + (74.3 + 14.8)/2 = 95.6$ c.p.s. The observed doublet resulting from the combined signals of A and B is centered at 96.5 c.p.s.

The theoretical spectrum was obtained by means

of the NMR computer program of Wiberg and Nist (15), using the calculated values of $\nu_B = 97$ c.p.s., $\nu_A = 95.6$ c.p.s., observed value $\nu_X = 225$ c.p.s., and coupling constants of $J_{AB} = 12.4$,⁶ $J_{XA} = 6.7$, and $J_{XB} = 3.4$ c.p.s. The theoretical spectrum so obtained is shown in Fig. 2. The agreement with the observed spectrum is excellent.

Similar treatment gave excellent agreement between the calculated and observed spectrum of IV in pyridine. In this case compound V was replaced by compound II as reference model.⁷ The chemical shifts of the A and B protons of II in pyridine are 84 and 129 c.p.s., respectively. The calculated chemical shifts of the A and B protons in the mobile system IV of $\nu_A = 124$, $\nu_B = 105$ c.p.s. are in excellent agreement with the experimental values of $\nu_A = 124.2$ and $\nu_B = 104$ c.p.s. The larger difference in the chemical shifts of the A and B protons of IV in pyridine compared to D₂O is in agreement with the observation (18) that the 1,3-diaxial deshielding effect of the hydroxyl group is larger in pyridine than in other solvents investigated, including the protic solvents methanol-*d*₄ and acetic acid.

EXPERIMENTAL

The NMR spectra were determined on a Varian A-60 spectrometer at 37° utilizing TMS as the internal standard for spectra determined in pyridine and CDCl₃ and DSS for spectra determined in

⁶ The calculated spectrum is unaltered if J_{AB} is replaced by $-J_{AB}$.

⁷ Compound V in pyridine exists as a mixture of the two chair conformers with about 15% of the diaxial form (unpublished results). By using Anet's (19) $-\Delta G_{OH}^\circ$ value of 1.25 for the hydroxyl group in cyclohexanol in D₂O compound V is calculated to exist to the extent of 98% in the diequatorial conformation in D₂O.

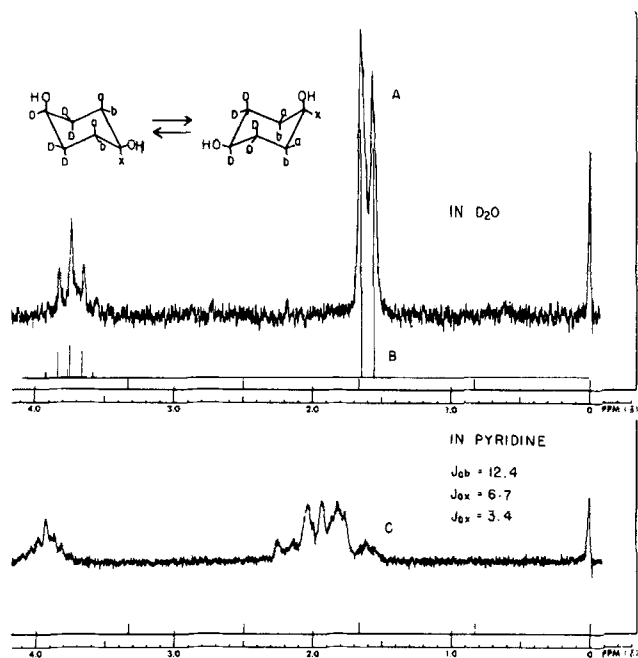


Fig. 2—NMR spectra of cis-1,4-cyclohexanediol-3,3,4,5,5-d₅ in D₂O and pyridine at 60 Mc. and 37°. TMS and DSS were used as internal references in pyridine and D₂O, respectively. B is the calculated spectrum using calculated chemical shifts as explained in the text.

D₂O. The concentration of the sample solutions varied between 20 and 25% w/v. Melting points were determined on a Kofler hot-stage.

4-Hydroxycyclohexanone—This compound was prepared in a 27% over-all yield as follows. Commercially available 1,4-cyclohexanediol was converted to 4-hydroxycyclohexyl benzoate (42%) by the method of Jones and Sondheimer (20). The 4-hydroxycyclohexyl benzoate thus obtained was oxidized to 4-ketocyclohexyl benzoate (90%) by the general method of Brown and Garg (21), and finally 4-ketocyclohexyl benzoate was converted to 4-hydroxycyclohexanone (72%) by the method of Jones and Sondheimer (20).

4-Hydroxycyclohexanone-2,2,6,6-d₄ (I)—A solution of 4-hydroxycyclohexanone (25 Gm., 0.22 mole) in 99.8% D₂O (35 Gm., 1.8 moles) containing anhydrous potassium carbonate (0.30 Gm., 0.0022 mole) was allowed to stand at room temperature for 24 hr. The D₂O-water solution was removed from the partially deuterated 4-hydroxycyclohexanone by vacuum distillation. The receiver flask was cooled in a mixture of dry ice-isopropyl alcohol while the distilling flask was warmed in an oil bath (never above 50°). When all of the D₂O-water solution had been removed, the process was repeated twice and the product distilled under reduced pressure, b.p. 70° at 0.2 mm.

cis and trans-1,4-Cyclohexanediol-3,3,4,5,5-d₅ (IV and V)—A mixture of IV and V was obtained by lithium aluminum deuteride reduction of I in ether. The mixture thus obtained was separated by the method described by Brown and Zweifel (22) for a mixture of nondeuterated IV and V.

4-tert-Butyl-cis- and trans-1,4-cyclohexanediol—Anhydrous ether (500 ml.) was added to a 1-L. three-neck flask fitted with a mechanical stirrer, a 500-ml. additional funnel having a nitrogen inlet, a rubber stopper holding a low temperature thermometer, and a nitrogen outlet. A source of dry nitrogen

was then fixed to the nitrogen inlet while the nitrogen outlet was fixed to a gas wash bottle containing mineral oil. The system was thoroughly flushed with dry nitrogen, and a slow stream of nitrogen passed through the system for the entire experiment. A solution (100 ml., 1.86 M) of *tert*-butyllithium (0.186 mole) in pentane was pipetted into the addition funnel. The pipet had been dried and helium gas blown through it just prior to use. The reaction flask was slowly immersed in a large Dewar flask containing a mixture of dry ice-isopropyl alcohol and the ether cooled to -72°. Vigorous stirring was initiated and the *tert*-butyllithium was added to the ether at such a rate as to maintain the temperature near -70°. The addition took approximately 30 min. A solution of 4-hydroxycyclohexanone (6.0 Gm., 0.0537 mole) in anhydrous ether (300 ml.) was transferred to the addition funnel and then added dropwise to the *tert*-butyllithium-ether-pentane solution, with vigorous stirring, over a period of 2 hr. The temperature was maintained at -72° throughout. Upon completion of the addition the reaction mixture was allowed to stir vigorously at -72° for another 24 hr., and then allowed to slowly warm to room temperature over a period of 4-5 hr. The reaction mixture was treated with 25 ml. of methanol followed by 75 ml. of water. The ethereal layer was separated and the aqueous layer extracted 3 times with ether. The ethereal extracts were combined, dried over anhydrous calcium sulfate, and the ether evaporated, yielding a mixture of 4-*tert*-butyl-*cis*- and *trans*-1,4-cyclohexanediol (5.4 Gm., 60%) and some unreacted 4-hydroxycyclohexanone. Analysis of the crude product by gas chromatography at 200° on a 5 ft. column of 20% basic Carbowax on Chromosorb indicated a 7.3 to 1.3 to 1.4 ratio of 4-*tert*-butyl-*cis*-1,4-cyclohexanediol to 4-*tert*-butyl-*trans*-1,4-cyclohexanediol to unreacted 4-hydroxycyclohexanone. Recrystallization from acetone yielded pure 4-*tert*-butyl-

cis-1,4-cyclohexanediol as large cubical crystals, m.p. 165.5–166°. After recovering most of the *cis* isomer from acetone the pure 4-*tert*-butyl-*trans*-1,4-cyclohexanediol was obtained by crystallization from *n*-heptane–isopropyl alcohol mixture, and finally from pure *n*-heptane as fine needles, m.p. 141.5–142°.

Anal.—Calcd. for C₁₀H₂₀O₂: C, 69.70; H, 11.70. Found: (*cis*) C, 70.21; H, 11.76; (*trans*) C, 70.08; H, 11.57.

4-*tert*-Butyl-*cis*- and *trans*-1,4-cyclohexanediol-3,3,5,5-d₄ (VI and VII)—Pure *cis* VI and *trans* VII were obtained by the addition of *tert*-butyllithium to I as described in the preceding section for the corresponding nondeuterated compounds.

1-*tert*-Butylcyclohexen-4-ol-2,6,6-d₃—A crystal of iodine and a boiling chip were added to a mixture of *cis* VI and *trans* VII (10.0 Gm., 0.0568 mole) contained in a 50-ml. flask fitted with a Dean-Stark water collector. The mixture was heated in an oil bath to 160° and the temperature maintained between 155 and 160° for approximately 15 min. At the end of this period the residual product was transferred into a large sublimator prior to solidification. The material was sublimated and the resulting crystalline product recrystallized from a mixture of methanol and water yielding 7.4 Gm. (80%) of product, m.p. 80–82°. Stolow and co-workers (23) report a m.p. of 86–86.5° for the corresponding nondeuterated compound.

***trans* and *cis*-4-*tert*-Butylcyclohexanol-3(axial)-5,5-d₃ (II and III)**—The compounds were obtained by low pressure catalytic hydrogenation of 1-*tert*-butyl cyclohexen-4-ol-2,6,6-d₃ in purified acetic acid (24) with platinum oxide as catalyst according to the procedure described by Sauvage *et al.* (25) for a series of cyclohexenes. The calculated amount of hydrogen was picked up in 1.5 hr., when 8.0 Gm. of alkene was hydrogenated in 15 ml. of acetic acid with 0.8 Gm. of catalyst. After removal of the catalyst, water was added to the acetic acid solution to induce crystallization. Cooling and filtration yielded 7.2 Gm. (80%) of a mixture of II and III in ratio of 3 to 7 as determined by gas chromatography using a basic Carbowax column.

The *cis* and *trans* isomers were separated by column chromatography on neutral alumina using petro-

leum ether, mixtures of petroleum ether and benzene, and mixtures of benzene and diethyl ether. In a typical experiment 1.5 Gm. of the mixture was chromatographed on 30 Gm. of alumina to yield 1.1 Gm. of pure III, m.p. 80–82°, and 0.3 Gm. of pure II, m.p. 78–79°. This *cis* isomer (III) was eluted with the petroleum ether–benzene mixtures up to 100% benzene, and the *trans* isomer (II) was obtained with benzene and mixtures of benzene and diethyl ether up to 30% of ether. Winstein and Holness (26) have reported a m.p. of 78–79° for nondeuterated II and 81–82° for nondeuterated III.

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