Tetrahedron Letters No.33, pp. 2931-2936, 1965. Pergamon Press Ltd.
Printed in Great Britain.

SOLVENT EFFECTS IN CONFORMATIONAL ANALYSIS OF 4-HYDROXYCYCLOHEXANONE[a]

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(Received 11 June 1965; in revised form 2 July 1965)

In a recent communication (1) we have shown that the large differences in the NMR spectra of <u>cis</u>-1,4-cyclohexanediol-3,3,4,5,5-d_5 in D_2O and pyridine can be explained from solvent effects on chemical shifts. We have now observed similar results in the conformational analysis of 4-hydroxycyclohexanone-2,2,6,6-d_4 in D_2O, pyridine and deuterated chloroform (Fig. 1). In contrast to <u>cis</u>-1,4-cyclohexanediol (1), it is the D_2O solvent which gives an apparent first-order spectrum while pyridine and chloroform give deceptively simple spectra. Actually the D_2O spectrum also deviates from first-order. The results are interpreted as being consistent with a rapid equilibrium between the two chair conformations I and II, with differences in spectra resulting from: 1) solvent effects on chemical shifts which in turn lead to strong coupling effects, 2) solvent effects on conformation.

Changes in chemical shifts can cause strong coupling effects (2,3) to come into play giving spectra which can no longer be treated by first-order approximation. In an ABX system of the type $X-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{A}{C}}-B$, where J_{AX} and J_{BX} are not equal, 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}.

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[a] Supported in part by a research grant from the State of Washington Initiative 171 funds for Research in Biology and Medicine. [b] Public Health Service Predoctoral Fellow, Fellowship number 5-F1-GM-18,507-03.

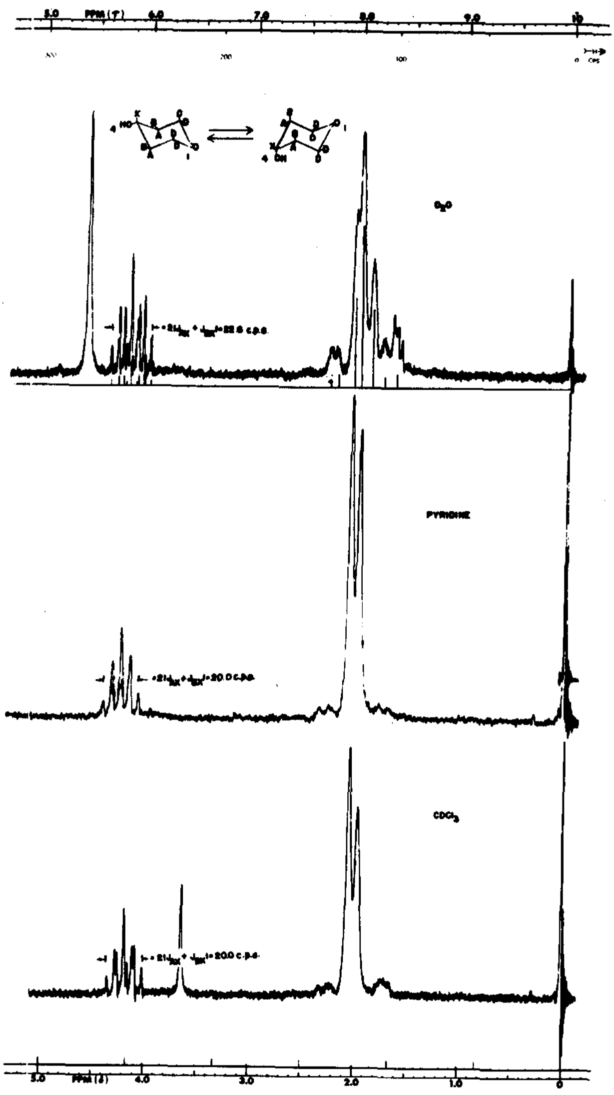
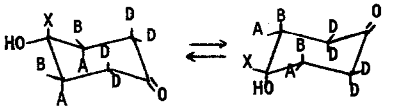


FIG. I

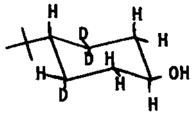
NMR spectra of 4-hydroxycyclohexanone-2,2,6,6-d_4 in D_2O, pyridine and deuterated chloroform at 60 mc. and 37°. T.M.S. and D.S.S. were used as internal references in the organic solvents and D_2O, respectively.

As $(\nu_B - \nu_A)$ approaches J_{AB} proton X is coupled to protons A and B behaving as a set [strong coupling (2) or virtual coupling (3)] and individual values of J_{AX} and J_{BX} 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 $(J_{AX} + J_{BX})/2$ even though J_{AX} and J_{BX} are not actually equal. The same applies to an $(AB)_2X$ system, such as cis-1,4-cyclohexanediol-3,3,4,-5,5-d_5, except that in the limit the signal of the X protons will now give a symmetrical pentuplet with separations equal to $(J_{AX} + J_{BX})/2$.

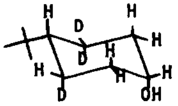
Conformational preference in each solvent was calculated by the signal width method of Garbisch (4) or Feltkamp and Franklin (5), using the partially deuterated trans- and cis-4-tert-butylcyclohexanol-3(axial)5,5-d_3, III and IV respectively, for conformationally homogeneous models. The advantage of this method is that the signal width is equal to $2(J_{AX} + J_{BX})$ and is independent of strong coupling and virtual coupling effects. In each case the signal width of the X proton was measured from a sharp multiplet and is exactly $2(J_{AX} + J_{BX})$.



I II



III



IV

The trans isomer III gave $J_{aa} = 11.0$, $J_{ae} = 4.2$ and $J_{gem} = 12.5$ c.p.s. in deuterated chloroform, and $J_{aa} = 10.7$, $J_{ae} = 4.4$ and $J_{gem} = 12.0$ c.p.s. in pyridine. The signal width of H-1 in III, equal to $2(J_{aa} + J_{ae})$, was found to be 30.6 c.p.s. in chloroform and 30.0 c.p.s. in pyridine.

Accurate values of J_{ea} and J_{ee} could not be obtained from the spectra of the cis isomer but the symmetrical pentuplet of H-1 indicates that $J_{ea} \simeq J_{ee}$ in IV, since $(\nu_B - \nu_A)$ is outside the boundary of strong coupling effects (2,3). The value of $2(J_{ea} + J_{ee})$ was 11.0 in chloroform and pyridine, indicating that $J_{ea} \simeq J_{ee} \simeq 2.7$ c.p.s. at 37°. Chemical shifts measured at

60 mc. for the trans isomer III were as follows: H-1, 210.5 c.p.s.; axial H-2 and H-6 about 83 c.p.s.; equatorial H-2 and H-6, 119 c.p.s. when measured in deuterated chloroform; and H-1, 219.5 c.p.s.; axial H-2 and H-6, about 83 c.p.s.; equatorial H-2 and H-6, 129 c.p.s. in pyridine. The following chemical shifts were obtained for the cis isomer IV: H-1, 241.5 c.p.s.; axial H-2 and H-6, 86 c.p.s.; equatorial H-2 and H-6, 110.5 c.p.s. in deuterated chloroform; and H-1, 250 c.p.s.; axial H-2 and H-6, 86 c.p.s. and equatorial H-2 and H-6, 118.5 c.p.s. in pyridine.

The mole fraction of conformer I (N_I) in the mobile 4-hydroxycyclohexanone system can be calculated from the width of the signal of H-1 in the mobile system, and H-1 in the two conformationally homogeneous models III and IV by the equation

$$N_I = \frac{2[J_{AX} + J_{BX}] - 2[J_{ea} + J_{ee}]}{2[J_{aa} + J_{ae}] - 2[J_{ea} + J_{ee}]} = \frac{w - w_a}{w_e - w_a}$$

where J_{AX} and J_{BX} refer to the mobile system; J_{aa}, J_{ea} and J_{ee} refer to models III and IV; w is the signal band width of H-1 in the mobile system and w_a and w_e are signal widths of H-1 in models IV and III, respectively.

By utilizing $w_a = 11.0$ and $w_e = 30.0$ c.p.s. obtained in pyridine* and the measured value $w = 22.6$ c.p.s. for the mobile system in D_2O, N_I is calculated to be 0.61. This corresponds to 61 ± 4% population of conformer I and a conformational free energy difference of 0.27 kcal/mole for the hydroxyl group in 4-hydroxycyclohexanone in D_2O. The value of w was found to be 20.0 c.p.s. in pyridine and deuterated chloroform. Utilizing the

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*The model compounds III and IV are not sufficiently soluble for measurement in D_2O. The danger of error due to variations of coupling constants with solvent seems minimum 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 (ref. 1) measured in pyridine and 25% acetic acid in D_2O is only 0.5 c.p.s. (unpublished data).

respective w_e and w_a values this gives 47 ± 4% of conformer I in pyridine and 46 ± 4% of conformer I in chloroform. There seems to be little, if any, conformational preference for 4-hydroxycyclohexanone in pyridine or in chloroform. Until better reference models are available it isn't possible to determine if the apparent 3 to 4% predominance of conformer II is real. Models III and IV may not be exactly ideal. Contribution by non-chair flexible forms would narrow the signal but any such contributions are probably small on the basis of calculations of Allinger and co-workers (6) who predict that the ground state energy of the most stable flexible form of cyclohexanone is almost 3 kcal/mole greater than the ground state of the chair conformation. Contribution of a boat conformation stabilized by intramolecular hydrogen bonding would seem unlikely in pyridine and is argued against by the fact that the benzoate ester of 4-hydroxycyclohexanone-2,2,4,4-d_4 gives a 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.w. for protons A and B both in pyridine and chloroform. Furthermore, Stolow (7) was unable to detect any evidence of intramolecular hydrogen bonding in 4-hydroxycyclohexanone by infrared studies in carbon tetrachloride.

The symmetrical pentuplet in pyridine has separations of 5 c.p.s. The increase in multiplicity of the signal of the X proton in chloroform indicates a larger difference in chemical shifts of the A and B protons than in pyridine. The apparent coupling constants of $J_{AX} = 5.7$ and $J_{BX} = 4.2$ do not represent true coupling constants because of strong coupling complications.

The larger population of conformer I in D_2O is substantiated by the following treatment. The spectrum 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 $J_{AX} = 7.0$ and

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*This does not allow accurate calculation of conformational populations because of possible substituent effects on coupling constants.

J_{BX} = 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 III and IV in pyridine the expected coupling constants of a rapid equilibrium between I and II with 61% of conformer I are calculated as

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

$$J_{BX} = N_I J_{ae} + (1 - N_I) J_{ea} = (0.61)(4.4) + (0.39)(2.7) = 3.76 \text{ c.p.s.}$$

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. and calculated $J_{AX} = 7.6$ and $J_{BX} = 3.76$ c.p.s. were placed in the computer program of Wiberg and Nist (8) the resulting theoretical spectrum (reproduced under the experimental spectrum, Fig. 1) gave apparent $J_{AX} = 7.05$ and $J_{BX} = 4.3$ and reproduced the experimental spectrum exactly. When the spectrum was determined in D_2O at 100 mc. $(\nu_B - \nu_A)$ was 20.5 c.p.s. and apparent coupling constants were $J_{AX} = 7.5$, $J_{BX} = 3.8$ c.p.s., values which are in good agreement for the expected coupling constants of a mixture with 61% of conformer I.

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