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Conformational Analysis of 4-Hydroxycyclohexanone Oxime by NMR Spectroscopy

By WILLIAM F. TRAGER and ALAIN C. HUITRIC

The conformational free energy of the hydroxyl group of 4-hydroxycyclohexanone oxime has been found to be 0.33 and 0.61 Kcal./mole in pyridine and D_2O, respectively. These values are intermediate to those of the hydroxyl group of cyclohexanol and 4-hydroxycyclohexanone in the corresponding solvents. Comparison of the spectrum of 4-*tert*-butylcyclohexanone-$3_{(\text{axial})}$,5,5-d_3 oxime with that of 4-hydroxycyclohexanone oxime and utilization of the long-range deshielding effect of the oximido group has permitted assignment of the individual resonances in the spectrum of the latter compound to specific hydrogens. Moreover, the comparison of spectra and use of the oximido group long-range deshielding effect has provided an independent check on the validity of the equilibrium positions calculated herein.

The CONFORMATIONAL free energy of the hydroxyl group ($-\Delta G°_{OH}$) in cyclohexane systems has been the subject of extensive investigations over the past 10 years and is now well established. The results are summarized by Eliel and Schroeter (1). Values of 1.25 Kcal./mole in D_2O (2) and 0.83 in pyridine (3) have been obtained for cyclohexanol. It is only recently that comparative studies have been extended to six-membered saturated ring systems containing a hetero atom (4) or a trigonal carbon (5). Since the authors have found a significant difference in the values of $-\Delta G°_{OH}$ for cyclohexanol and 4-hydroxycyclohexanone at similar concentrations in a given solvent (5)[1] it was of interest to extend the investigation to the other six-membered ring compounds containing a trigonal carbon atom. The observation of an unusually large chemical shift difference between the geminal hydrogens adjacent to the oximido group in 4-*tert*-butylcyclohexanone oxime (6) pointed to 4-hydroxycyclohexanone oxime as an attractive system to study both phenomena.

DISCUSSION

Conformational Analysis—Conformational preference of the two chair conformers 1a and 1b, Fig. 1, was determined by the signal width method (5, 7–12) as described for 4-hydroxycyclohexanone (5). The mole fraction of conformer 1a (Na) was obtained from w, the width of the signal of H-4 (hydrogen Z) in the mobile system, and from w_e and w_a, the widths of the signals of H-1 in the two conformationally homogeneous models *trans*- and *cis*-4-*tert*-butylcyclohexanol-$3_{(\text{axial})}$,5,5-d_3, II and III, respectively, by the following relationship (5):

$$Na = \frac{w - w_a}{w_e - w_a}$$

From the spectrum of II in pyridine, w_e was found to be 30.0 c.p.s., Jaa = 10.7, Jae = 4.4, and J_{gem} = 12.0 c.p.s.; and the spectrum of III in pyridine gave w_a = 11.0 c.p.s., $Jea \simeq Jee \simeq 2.7$ c.p.s. (5).

In pyridine the signal of Z has a width w, of 23 c.p.s. which leads to a value of 0.63 for the mole fraction Na of conformer Ia and a free energy difference, $-\Delta G°_{OH}$, of 0.33 Kcal./mole at 37°. In D_2O[2] the width of the signal measured from spectrum E is 24.8 c.p.s., leading to an Na value of 0.73 and $-\Delta G°_{OH}$ of 0.61 Kcal./mole at 37°. The addition of about two equivalents of diethylamine in pyridine did not cause any change in the width of the signal of Z. Addition of slightly over one equivalent of NaOH in D_2O caused an increase of about 0.5 c.p.s. in w. This suggests that there is very little, if any, ionization of the oxime in pyridine under the conditions of the measurements.

Assignment of Signals to Specific Hydrogens—The assignment of the signal of the Z hydrogen is obvious in all spectra. In the 60 Mc. spectra it occurs at τ 6.05 in D_2O and τ 5.91 in pyridine. In the 100 Mc. spectrum in pyridine it occurs at τ 5.88. There is also a slight difference in the chemical shift of the X hydrogen obtained from the 60 and 100 Mc. spectra in pyridine: τ 6.73 at 60 Mc. and

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[1] 0.28 Kcal./mole in D_2O and zero in pyridine for 4-hydroxycyclohexanone.

[2] The model compounds II and III are not sufficiently soluble for measurements in D_2O, and the w_e and w_a values obtained in pyridine were used. The danger of error due to variation of coupling constants with solvent in these rigid systems seems minimal because of the observation that the difference in the width of the signal of H-1 in 4-*tert*-butyl-*cis*-4-hydroxycyclohexanol-3,3,5,5-d_4 (13) measured in pyridine and 25% acetic acid in D_2O is only 0.5 c.p.s.

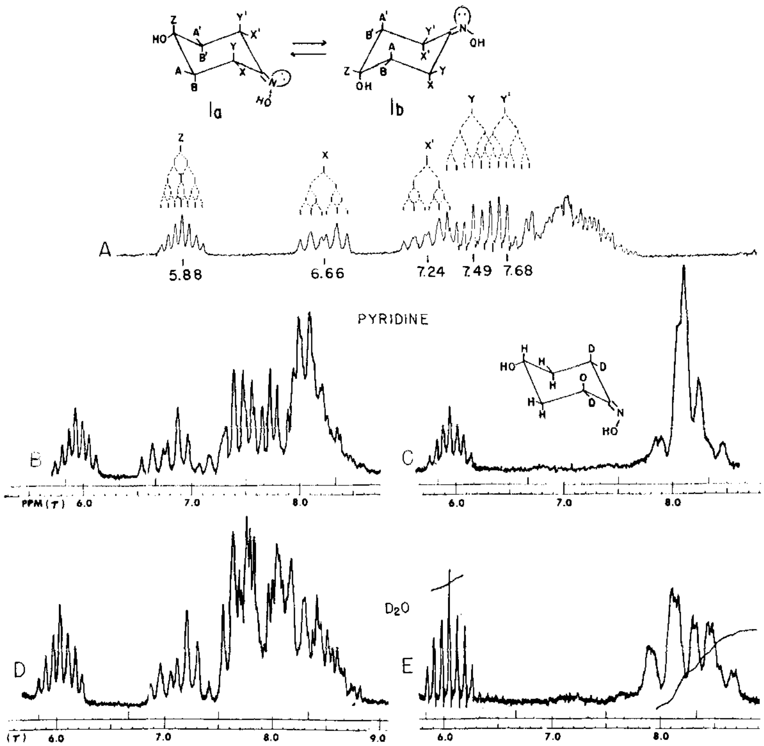
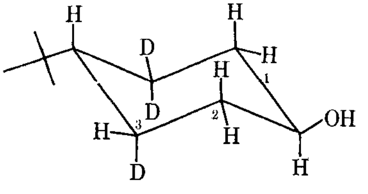
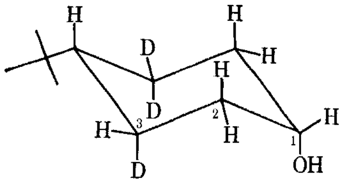


Fig. 1—NMR spectra of 4-hydroxycyclohexanone oxime (A, B, *and* D) *and the 2,2,6,6-*d_4 *analog* (C *and* E) *in pyridine and* D_2O *at 37°;* A *at 100 Mc. in pyridine,* B *and* C *at 60 Mc. in pyridine, and* D *and* E *at 60 Mc. in* D_2O.

τ 6.66 at 100 Mc. Small differences in observed chemical shifts obtained from 60 and 100 Mc. spectra are not uncommon and may arise from nonlinearity in frequency sweep with the 100 Mc. instrument, or also from nonfirst-order spectra. The 60 Mc. spectrum C of the deuterated analog shows that the difference in chemical shifts of A and B, or A′ and B′, is not sufficient to justify the first-order approximation in spectrum B (5). At 100 Mc. the complications from strong coupling and virtual coupling effects will be reduced. Comparison of spectra B and C establishes that the signals of the C-2 and C-6 hydrogens (X, X′, Y, and Y′) fall in the range between τ 6.50 and 7.85 and that the signals of the C-3 and C-5 hydrogens (A, A′, B, and B′) are above τ 7.75.



II



III

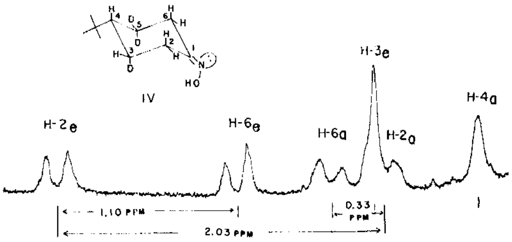


*Fig. 2—NMR spectrum of 4-*tert*-butylcyclohexanone-*$3_{(axial)}$*,5,5-*d_3 *oxime in pyridine at 100 Mc. at 37°.*

In a recent communication (6) dealing with the magnetic anisotropy of the oximido group in 4-*tert*-butylcyclohexanone-$3_{(axial)}$,5,5-d_3 oxime (IV) we have shown a large chemical shift difference between the equatorial hydrogens on C-2 and C-6 and have established the relationship between the signal of a given equatorial hydrogen at C-2 or C-6 and that of its geminal axial hydrogen. More recently experimental proof has been furnished (14) that the greatest deshielding effect of the oximido group results from the proximity of the hydroxyl group rather than from the unshared pair of electrons on the nitrogen as proposed by Saitô *et al.* (15–18). Other investigators have also presented evidence consistent with the largest deshielding effect of the hydroxyl group (19–24). On the basis of this information it is now possible to assign the signals of all hydrogens in IV as shown in the 100 Mc. spectrum measured in pyridine, Fig. 2.

The spectrum of IV, Fig. 2, provides an interesting check on the conformational equilibrium of I as calculated by the signal width method and also permits the assignment of the signals of X, X′, Y, and Y′ in spectrum A, Fig. 1. Both spectra were measured at 100 Mc. in pyridine. In the spectrum of the conformationally homogeneous model IV there is a difference of 1.10 p.p.m. between chemical shifts of equatorial H-2 and H-6, and a difference of 0.33 p.p.m. between axial H-2 and axial H-6. The equatorial H-2 and H-6 in IV correspond to X and X′, respectively, in conformation Ia of 4-hydroxycyclohexanone oxime while in relationship to the oximido group X and X′ of conformer Ib correspond to axial H-2 and H-6, respectively, of IV. It follows, therefore, that the chemical shift difference between X and X′ should be 1.10 p.p.m. in pure conformer Ia and 0.33 p.p.m. in pure conformer Ib. In an equilibrium mixture of conformers Ia and Ib the observed spectrum at any given instant is that due to the weighted time average of the spectra arising from these two conformers. The observed difference between the chemical shifts of X and X′ in the equilibrium mixture will be a function of the populations of the two conformers. This difference for a population of 63% Ia and 37% Ib can be calculated by $[0.63(\nu_X - \nu_{X'})_{Ia} + 0.37(\nu_X - \nu_{X'})_{Ib}] = [0.63(1.10) + 0.37(-0.33)] = 0.57$ p.p.m.[3] The agreement with the observed experimental value of 0.58 p.p.m., spectrum A, is excellent.

A similar treatment for Y and Y′ yields valuable information about their relative chemical shifts and helps to unravel the complex pattern of peaks between about τ 7.35 and 7.85 resulting from the signals of Y and Y′. In conformer Ia hydrogens Y and Y′ are related to axial H-2 and H-6, respectively, of IV and their signals should be 33 c.p.s. apart, at 100 Mc., while in conformer Ib Y and Y′ are related to equatorial H-2 and H-6 of IV and their signals should be 110 c.p.s. apart. The experimental chemical shift difference between Y and Y′ in an equilibrium mixture of 63% Ia and 37% Ib should be $[0.63(\nu_Y - \nu_{Y'})_{Ia} + 0.37(Y - Y')_{Ib}] = [0.63(-0.33) + 0.37(1.10)] = 0.20$ p.p.m., or 20 c.p.s. at 100 Mc., with Y occurring at lower field. The experimental difference of 0.19 p.p.m. with the signal of Y at τ 7.49 and Y′ at τ 7.68 is in very good agreement and is consistent with the complexity of the partially overlapping signals and the relative intensities of the peaks.

Coupling Constants—Direct measurements of coupling constants from spectra A and E, Fig. 1, yield $J_{ZA} = 3.8$ and $J_{ZB} = 7.7$ c.p.s. for 4-hydroxycyclohexanone oxime in pyridine, and $J_{ZA} = 4.1$ and $J_{ZB} = 8.2$ for the deuterated analog in D_2O. The calculated values of J_{ZA} and J_{ZB}, based on the model compounds II and III, for an equilibrium mixture of 63% conformer A are:

$$J_{ZB} = 0.63\ Jaa + 0.37\ Jee = (0.63)(10.7) + (0.37)(27) = 7.7 \text{ c.p.s.}$$

$$J_{ZA} = 0.63\ Jae + 0.37\ Jea = (0.63)(4.4) + (0.37)(2.7) = 3.8 \text{ c.p.s.}$$

By similar calculations the theoretical values for an equilibrium of 73% of conformer Ia are: $J_{ZB} = 4.0$ and $J_{ZA} = 8.5$ c.p.s. The excellent agreement between observed and theoretical values suggests that in pyridine at 100 Mc. and in D_2O at 60 Mc. the difference in chemical shift between A and B is sufficient to be outside of the limits of serious complications from strong coupling effects (5) and that the first-order approximation is applicable to analysis of the Z signal. Strong coupling effects would cause a change in the relative values of observed coupling constants but would not change the sum of the coupling constants and therefore would not affect the width of the signal of Z.

Direct measurements of apparent coupling constants from the signals of X, X′, Y, and Y′ from spectrum A yield $J_{XY} = 14.2$, $J_{YB} = 9.4$, $J_{YA} = 4.0$, and $J_{XA} \simeq J_{XB} = 5.9$ c.p.s. This suggests unusual differences (26) in *J*aa, *J*ee, *J*ae, and *J*ea between C-2 and C-3, or C-6 and C-5, vicinal hydrogens compared to the C-3 and C-4 system. The proximity of the sp² hydridized carbon appears to have some effect on the magnitudes of these vicinal coupling constants. The increase in geminal coupling constants by the proximity of an sp² carbon is reasonably well understood (27) and effects on vicinal coupling constants have been observed in α-halogenated cyclohexanone systems (9, 28–30), but in this system the chemical shift differences between the coupled hydrogens responsible for this part of the spectrum are not sufficient to truly justify the first-order approximation. This difficulty precludes speculation regarding the apparently anomalous vicinal coupling constants between hydrogens on C-2 and C-3 and on C-5 and C-6.

EXPERIMENTAL

The 60 Mc. spectra were determined on a Varian A-60 spectrometer at 37° on solutions of approximately 20% utilizing TMS as the internal standard for spectra determined in pyridine and DSS for the spectra determined in D_2O. Melting points were determined on a Fisher-Johns melting point apparatus.

4-Hydroxycyclohexanone Oxime—To a solution of 20% ammonium hydroxide (16.5 ml., 0.146 mole) was added hydroxylamine hydrochloride (4.6 Gm., 0.081 mole) with stirring. To the resulting solution was added, all at once, a solution of 4-hydroxycyclohexanone (8) (5.5 Gm., 0.048 mole) in 20 ml. of methanol. The reaction mixture was stirred for 20 min. then allowed to stand at room temperature for 22 hr. At the end of this period the reaction mixture was exhaustively extracted with ether. The ethereal extracts were combined, dried over anhydrous sodium sulfate, the mixture filtered, and the ether evaporated. The residue was taken up in ethyl acetate, treated with charcoal, then recrystallized from ethyl acetate yielding 3.4 Gm. (55%) of product, m.p 78–79°. Kahr *and* Berther (31) reported a boiling point of 161–164° at 11 mm. for 4-hydroxycyclohexanone oxime.

4 - Hydroxycyclohexanone - 2,2,6,6 - d_4 - oxime—This compound was obtained in a 30% yield by the slightly modified general method of Shriner, Fuson, and Curtin (32) for preparation of oximes. To a solution containing anhydrous pyridine (5 ml.), 99.8% D_2O (10 ml.), and hydroxylamine hydrochloride (1.0 Gm., 0.015 mole) was added 4-hydroxycyclohexanone-2,2,6,6-d_4 (8) (1.0 Gm., 0.0085 mole). The resulting solution was allowed to stand for 22 hr. then concentrated to approximately 2 ml. on a hot plate. The concentrated solution was extracted with 3 portions of ether, the ethereal

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[3] The minus sign of $(\nu_X - \nu_{X'})_{Ib}$ results from axial H-6 being at lower field (larger ν) than axial H-2 in the model compound IV.

extracts combined, and dried over anhydrous calcium sulfate. The mixture was filtered and the ether evaporated. The residue was dissolved in a minimal amount of warm ethyl acetate, a crystal of 4-hydroxycyclohexanone oxime added, and crystallization allowed to proceed. The product was collected by filtration, m.p. 76–78°.

4 - tert - Butylcyclohexanone - $3_{(\text{axial})}$,5,5 - d_3—This compound was obtained in 85% yield from the chromic acid oxidation of a mixture of *cis* and *trans*-4-*tert*-butylcyclohexanol-$3_{(\text{axial})}$,5,5-d_3 (8) according to the method of Brown and Garg (33). The product was recrystallized from a water–methanol mixture, m.p. 49–50°. Ziegenbein and co-workers (34) reported a b.p. of 84–85° at 7.0 mm. and a m.p. of 49–50° for 4-*tert*-butylcyclohexanone.

4 - tert - Butylcyclohexanone - $3_{(\text{axial})}$,5,5 - d_3-oxime—This compound was obtained in 92% yield by the slightly modified method of Ziegenbein and co-workers (34) for obtaining 4-*tert*-butylcyclohexanone oxime. To a solution of 20% ammonium hydroxide (19 ml., 0.11 mole), hydroxylamine hydrochloride (3.9 Gm., 0.056 mole), and methanol (75 ml.) was added 4-*tert*-butylcyclohexanone-$3_{(\text{axial})}$,5,5-d_3 (5 Gm., 0.033 mole). The resulting solution was stirred for approximately 1 hr. at room temperature and then allowed to stand overnight. As the reaction progressed, the product precipitated, and after standing overnight it was collected by filtration. A second crop of product was obtained by adding water to the filtrate. The crystalline fractions were combined and recrystallized from a water–methanol mixture, m.p. 138–140°. Ziegenbein and co-workers (34) reported a m.p. of 133° for 4-*tert*-butylcyclohexanone oxime.

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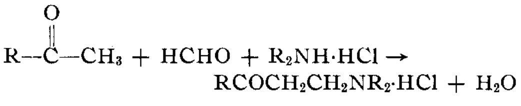
Octamethyleneimine in the Mannich Reaction I

Substituted β-Amino Ketones and Substituted α-Amino Alcohols

By HEINO A. LUTS, J. F. GRATTAN, S. YANKELOWITZ*, and W. L. NOBLES†

A group of Mannich bases, utilizing octamethyleneimine as the amine component, has been prepared. Their preparation and biological activities are given.

Over a period of years, a variety of Mannich bases has been prepared (1–26) for pharmacological testing. A typical Mannich condensation of the type discussed here may be illustrated as follows:



$$\mathrm{R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}CH_3 + HCHO + R_2NH{\cdot}HCl \rightarrow RCOCH_2CH_2NR_2{\cdot}HCl + H_2O}$$

Certain substituted β-aminoketones and derivatives have been reported (2, 3, 5, 7) to show both local anesthetic and antispasmodic activity. The extensive literature dealing with

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