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N.M.R. METHYL SHIFTS AND CONFORMATIONAL EQUILIBRIA OF PROTONATED METHYLCYCLOHEXANONES[1]

T. D. J. D'Silva and Howard J. Ringold
Worcester Foundation for Experimental Biology
Shrewsbury, Massachusetts 01545

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The effect of adjacent carbonium ion centers on the chemical shifts of methyl groups in the n.m.r. spectrum has been the subject of numerous studies (1,2). However, alkyl shifts in systems where partial carbonium ion character has been introduced by protonation of a carbonyl function (e.g. I) have not been previously investigated. The present paper deals with the

I

n.m.r. spectra of various alkyl cyclohexanones in 97.7% sulfuric acid and illustrates that significant methyl shifts may be induced in 2- and 3-methylcyclohexanones. Further, we report a solvent cage effect which permits the formation and trapping of the "less stable" trans-isomer of 2,6-dimethylcyclohexanone in concentrations far greater than are present in a freely equilibrated mixture.

Table I lists the centers of the n.m.r. methyl resonance peaks in deuterochloroform and in sulfuric acid solution[2]. In each instance the methyl group appeared farther downfield in sulfuric acid, Δ representing the shift in c.p.s. The CH_3 substituents of 4-t-butyl- and 4-isopropyl-cyclohexanone, which exhibited Δ values of 6.5 c.p.s., are sufficiently removed from the protonated carbonyl center to reflect the shift due to solvent alone[3]. Therefore shifts greater than 6.5 c.p.s. in C-2 and C-3 substituted cyclohexanones reflect deshielding

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[2]N.m.r. spectra were obtained with a Varian DP/DA-60 spectrometer at a frequency of 60 Mc/S. Tetramethylsilane at 0 c.p.s. was the internal standard in $CDCl_3$ while tetramethylammonium chloride at 192.0 c.p.s. was the standard in sulfuric acid (R.E. Reavili, J. Chem. Soc., 519 (1964).

[3]It may be noted that virtually identical deshielding has been found (T. D. J. D'Silva and H. J. Ringold, unpublished results) for the 19-methyl group of 3-desoxy steroid and the 18-methyl group of 17-deoxy steroids.

Table I. N.M.R. Positions of Methyl Groups of Alkyl Cyclohexanones[2]

Derivative of cyclohexanone		$CDCl_3$ (c.p.s.)	H_2SO_4 (c.p.s.)	$\Delta^{H_2SO_4}_{CDCl_3}$	Δ'
1) 4-t-Butyl-		55.0	61.5	6.5	0
2) 4-Iso-propyl-		56.0 (J = 6.0	62.5 (J = 5.0)	6.5	0
3) 4-Methyl-		62.0 (J = 5.0)	69.7 (J = 4.6)	7.7	1.2
4) 4,4-Dimethyl-		66.5	73.5	7.0	0.5
5) 3-Methyl-		61.3 (J = 5.5)	75.0 (J = 6.0)	13.7	7.2
6) 3,5-Dimethyl-	cis	61.3 (J = 5.5)	75.5 (J = 5.0)	14.2	7.7
	trans	59.2 (J = 6.5)	72.9 (J = 6.2)	13.7	7.2
7) 3,3-Dimethyl-		58.5	72.9	14.4	7.9
8) 3,3,5-Trimethyl-	3(eq)	63.8	80.6	16.8	10.3
	3 (ax)	53.2	65.0	11.8	5.3
	5(eq)	60.9 (J = 5.8)	75.7 (J = 5.1)	14.8	8.3
9) 3,3,5,5-Tetramethyl		63.0	78.5	15.5	9.0
10) 2-Methyl-		61.5 (J = 6.0)	81.0 (J = 6.0)	19.5	13.0
11) 2,2-Dimethyl-		67.0	89.0	22.0	15.5
12) 2,6-Dimethyl-	cis	60.5 (J = 6.0)	82.3 (J = 5.5)	21.8	15.3
	trans	65.8 (J = 6.5)	87.8 (J = 5.5)	22.0	15.5
13) 2,2,6-Trimethyl-	2(eq)	63.0	86.5	23.5	17.0
	2(ax)	71.0	96.5	25.5	19.0
	6(eq)	59.5 (J = 7.0)	83.7 (J = 5.5)	24.2	17.7
14) 2,2,6,6-Tetramethyl-		67.0	93.5	26.5	20.0

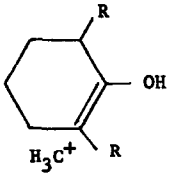
due to the introduction of positive charge at C-1 and are tabulated as $\Delta' = \Delta - 6.5$.

As anticipated, Δ' increased as a function of the distance of the methyl group from the carbonyl function (i.e., from the carbonium ion center at C-1) and was minimal for 4-methylcyclohexanone (1.2 c.p.s.) and 4,4-dimethylcyclohexanone (0.5 c.p.s.). The 3- and 3,5-substituted cyclohexanones exhibited methyl shifts varying from 5.3 to 10.3 c.p.s. The shift (Δ') for a "pure" equatorial substituent at a mono-substituted position may be observed in 3-methylcyclohexanone (7.2 c.p.s.), cis-3,5-dimethylcyclohexanone (7.7 c.p.s.) and in the 5-methyl group of 3,3,5-trimethylcyclohexanone (8.3 c.p.s.). In the trans-isomer of 3,5-dimethylcyclohexanone, which undergoes rapid ring inversion, both methyl groups are equivalent and the Δ' of 7.2 c.p.s. represents the time-average shift for an axial and an equatorial methyl. These values indicate a moderate trend towards greater shifts in the equatorial

isomers. The difference becomes considerably more apparent when the conformation is fixed as in 3,3,5-trimethylcyclohexanone with one methyl substituent at C-3 strictly equatorial and the other strictly axial. The respective Δ' values in this case are 10.3 and 5.3 c.p.s. which indicates also that the shift of an equatorial methyl is greater when it is part of a gem-dimethyl group. The 3,3-dimethyl compound undergoes rapid inversion so that the observed single methyl frequency is the statistical average of an axial and equatorial methyl group. The Δ' value of 7.9 c.p.s. then precisely corresponds to the median value for the fixed gem methyls of 3,3,5-trimethylcyclohexanone.

Due to rapid ring inversion, the methyls of the 3,3,5,5-tetramethyl compound are identical. The observed Δ' of 9.0 c.p.s. is greater than the anticipated value of 7.9 c.p.s. (3,3-dimethylcyclohexanone) which may be due to the severe 1,3-diaxial methyl-methyl interaction and a consequent bond distortion and flattening of the ring.

The 2-methylcyclohexanone derivatives exhibited Δ' values of 13.0-20.0 c.p.s. with the smallest shift appearing in the parent compound (2-methyl cyclohexanone) and the greatest in the 2,2,6,6-tetramethyl derivative[4]. In contrast to the 3-methyl series, Δ' was greater for axial than for equatorial substituents (e.g., 19.0 vs. 17.0 c.p.s. in 2,2,6-trimethylcyclohexanone). Irrespective of conformation, however, the shift in sulfuric acid increased with the degree of substitution about the carbonyl group. This may be due to a conformational effect or to a greater contribution from the carbonium ion resonance of I, which, in turn, can be rationalized via hyperconjugative structures such as II.



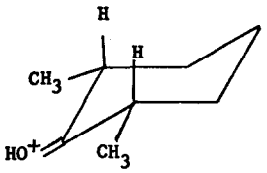
II

The n.m.r. spectrum of 2,-6-dimethylcyclohexanone in sulfuric acid requires additional comment. Immediately after solution, various mixtures of the cis- and trans-isomers gave identical spectra consisting of three methyl peaks located at 79.6, 85.1 and 90.6 c.p.s. The broad center peak, which was the largest, obviously arose as a superimposition of halves of two doublets. Although the peak areas could not be accurately integrated, the

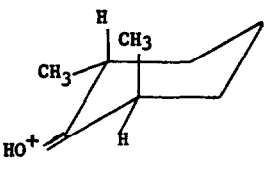
[4] The values in deuterochloroform are in excellent agreement with those reported by S. Bory, M. Fetizon, P. Laszlo and D. H. Williams, Bull. Soc. Chim. France 2541 (1965).

side peaks did not visibly differ in area which indicated the presence of a substantial concentration of the "less stable" trans-isomer in sulfuric acid. Confirmation came from a preparative experiment in which 0.2 ml of 2,6-dimethylcyclohexanone (18% trans-82% cis) was dissolved in 2.0 ml of 97.7% sulfuric acid. After five minutes at 27° the solution was slowly added to a stirred mixture of ice, water and pentane. The washed, dried and concentrated organic extract was analyzed by glc[5] and exhibited 42.4% trans-isomer. Duplicate reactions of 75 minutes duration in 97.7% sulfuric acid gave 43.8 and 44.3% of trans compound[6]. In 70% sulfuric acid and in 72% perchloric acid, reactions followed from 5-360 minutes, exhibited equilibrium concentrations of the trans-isomer of 30.4-31.7% and 33.2-35.2% respectively. In trifluoroacetic acid, an initial mixture of 9% trans-91% cis exhibited 19.3% trans-isomer after six hours.

When the equilibration of 2,6-dimethylcyclohexanone was effected in the presence of dilute acid or base, the mixture contained only 9.4% of the trans compound, a value in fair agreement with the 8.4% reported by Rickborn (3). Therefore as the oxonium (carbonium) salt, whose formation should be complete in concentrated sulfuric acid, either the trans-isomer (B) has become more stable or the cis-isomer (A) has been destabilized. In (A) both methyl groups occupy equatorial positions while in (B) one methyl group is axial at all times. In sulfuric



(A)



(B)

acid solution, the solvent shell about the protonated carbonyl group interacts with an equatorial methyl substituent. Since this non-bonded interaction may be relieved when the methyl group assumes (via enolization) an axial configuration, the energy difference between

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[5]Analysis was carried out on a 12' column (100°) with 10% tricyanoethoxy propane on Chromosorb P.

[6]The total recovery of product was 70-75% in the short term experiments and no side-reaction was detectable. On prolonged standing in sulfuric acid (e.g. 3-days), however, product decomposition was evident.

the two isomers, becomes minimal. Analogy may be drawn to the enolate anions derived from 2-methylcyclohexanone derivatives where the solvent shell about the metal cation destabilizes an adjacent equatorial substituent (4,5). In the case of the anion derived from 2,6-dimethylcyclohexanone, this leads to a relative stabilization of the 6-methyl substituent in an axial position and the consequent isolation of a substantial percentage of the trans-isomer (B) following kinetically controlled protonation (4).

In concentrated sulfuric acid the free energy difference (at 27°) between the cis- and trans-isomers is only 0.17 Kcal/mole while there is a difference of 1.38 Kcal in the freely equilibrated substances[7]. Thus the non-bonded interaction of the two equatorial groups with the sulfuric acid of solvation may be estimated as 1.21 Kcal, or 0.6 Kcal for each equatorial substituent. Similar solvent interactions may affect conformational equilibria in simple oxygen-free carbonium ion systems.

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[7]Assuming trans-isomer concentrations of 43% and 9.4% respectively.

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