[Chem. Pharm. Bull. 28(9)2653—2657(1980)]

^{13}C NMR Spectral Behavior of N-Substituted-4-piperidones in Methanol. Possibility of Distinguishing between Acetal and Hemiacetal

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(Received March 19, 1980)

The behavior of several N-substituted-4-piperidones in methanol has been studied by ^{13}C nuclear magnetic resonance (NMR) spectroscopy. All the piperidones studied were found to be equilibrium with their hemiacetals in methanolic solutions. The features of N-acyl derivatives were different from those of N-alkyl derivatives and the differences could be accounted for by electronic factors. The chemical shifts of the acetals were also determined and a procedure for distinguishing between hemiacetal and acetal is proposed.

Keywords——acetal; hemiacetal; NMR; methanol; N-alkyl-4-piperidones; N-acetyl-4-piperidone; N-benzoyl-4-piperidone; reversible addition

In the previous paper,[2] it was shown by ^{13}C nuclear magnetic resonance (^{13}C NMR) spectroscopy that N-ethyl-4-piperidone and N-ethyl-3-piperidone, when dissolved in CH_3OH, exist in equilibrium with the corresponding hemiacetals. The reactions are subject to base catalysis. Piperidone derivatives have been known to add alcohol or water under acidic conditions to yield stable hydrochlorides of the acetal or hydrate.[3] However, analogous carbonyl additions in basic solutions have scarcely been studied, probably because of the technical difficulty in detecting the products, which cannot be isolated. The utility of ^{13}C NMR techniques for this purpose was emphasized in our previous report.[2] It was also suggested that ^{13}C NMR can be used to differentiate between hemiacetal and acetal; the chemical shifts at C_3 and C_4 were useful indicators. If this finding is general in piperidone systems, investigations of complicated equilibrium systems involving both hemiacetal and acetal may become possible simply by examining the ^{13}C NMR spectra of the solutions.

In this paper, ^{13}C NMR techniques have been applied to some N-substituted-4-piperidones and related aminoketones other than six-membered rings. The corresponding acetals have also been examined in order to confirm the validity of our proposal.

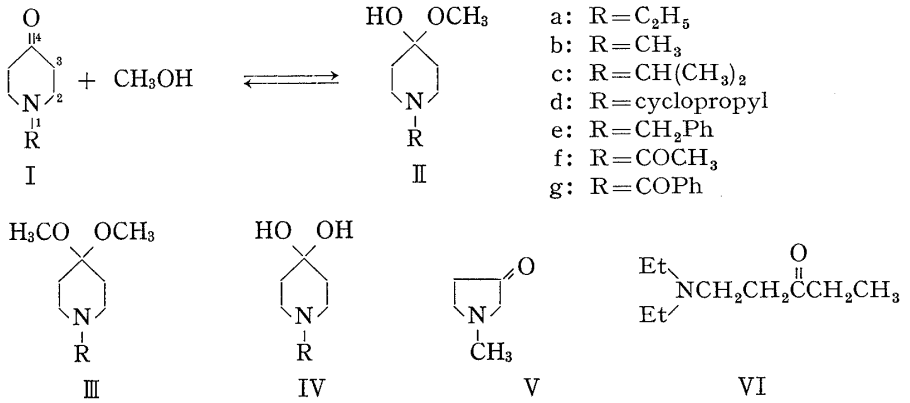


Chart 1

1) Location: *Motoyama-Kitamachi, Higashinada-ku, Kobe, 658 Japan.*
2) C. Yamagami, M. Sugiura, T. Kitazawa, K. Tamura, and N. Takao, *Chem. Pharm. Bull.*, **27**, 2099 (1979).
3) *a*) R.E. Lyle, R.E. Adel, and G.G. Lyle, *J. Org. Chem.*, **24**, 342 (1959); *b*) A.F. Casy, *Experientia*, **20**, 437 (1964); *c*) M.M.A. Hassan and A.F. Casy, *Tetrahedron*, **26**, 4517 (1970) and previous papers.

Results and Discussion

Behavior of N-Substituted-4-Piperidones in Methanol

The compounds studied in this work are illustrated in Chart 1. The ^{13}C NMR spectra were measured and analyzed as described earlier.[2] Since the equilibrium is strongly affected by temperature, the present discussion is not quantitative; the data were simply obtained at the normal operating temperature of the apparatus.

All the 4-piperidones studied, Ia—g, were found to be in equilibrium with their hemiacetal form in methanolic solution.

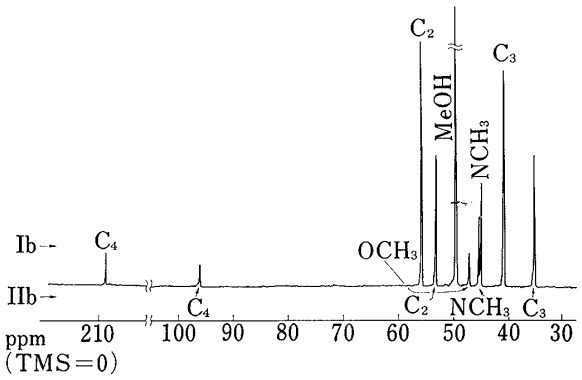
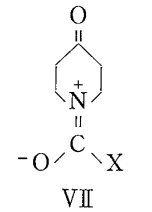


Fig. 1. ^{13}C NMR Spectrum of N-Methyl-4-piperidone (Ib) in MeOH at 30°



VII

X=CH_3, Ph

Chart 2

Table I. Carbon-13 Chemical Shifts of Some N-Substituted-4-piperidones and Their Methyl Hemiacetals in CH_3OH[a]

Compd.	Ketone			Others (N-Substituent)
	C_2	C_3	C_4	
Ia[b]	53.34	41.26	209.87	$-CH_2-$ 51.96, $-CH_3$ 12.43
Ib	55.89	41.20	209.05	$-NCH_3$ 45.32
Ic	49.08	41.87	210.24	-CH- 54.92, $-CH_3$ 18.51
Id	53.91	41.50	210.28	-CH- 38.00, $-CH_2-$ 6.71
Ie	53.55	41.52	210.41	$-CH_2-$ 62.42 -Ph 128.20, 129.18, 129.99, 138.83
If	40.99 45.50	41.38	208.82	$-CH_3$ 21.19, -C=O 171.79
Ig	44 (broad)	41.39	208.62	-C=O 172.80, -Ph 127.85, 129.62, 131.24, 136.49

Compd.	Hemiacetal				Others (N-Substituent)
	C_2	C_3	C_4	$-OCH_3$	
IIa[b]	50.92	35.64	96.15	47.46	$-CH_2-$ 52.63, $-CH_3$ 11.98
IIb	53.40	35.72	95.54	47.38	$-NCH_3$ 45.71
IIc	46.49	35.88	96.21	47.37	-CH- 55.18, $-CH_3$ 18.51
IId	51.57	35.60	96.31	47.42	-CH- 38.93, $-CH_2$-5.95
IIe	51.22	35.70	96.25	47.44	$-CH_2-$ 63.40 -Ph 128.20, 129.18, 130.41, 138.43
IIf	39.99 44.80	35.94 36.74	96.31	47.66	-C=O 171.12, $-CH_3$ 21.19
IIg	40 (broad) 46 (broad)	36.5 (broad)	96.45	47.73	-C=O 172.26 -Ph 127.70, 129.62, 130.89, 136.98

a) Given in ppm downfield relative to TMS.
b) Ref. 2.

^{13}C NMR signals that appeared on dissolving the piperidone Ib—e in CH_3OH could be assigned by analogy with N-ethyl-4-piperidone (Ia)[2] to appropriate carbons of either the ketone I or the hemiacetal II. The observed chemical shifts are given in Table I. The extent of hemiacetal formation is 25—45%, depending on the substituent, at room temperature. One of the spectra is shown in Fig. 1.

At room temperature, N-benzoyl-4-piperidone (Ig) exhibits broad signals due to C_2 carbons as a result of the slow amide rotation, as was reported by Hirsch.[4] On the other hand, the rotational isomers about the C–N bond of N-acetyl-4-piperidone (If) show different chemical shifts for two C_2 carbons (α to nitrogen).[5] These phenomena are also observed in the spectra of hemiacetals, and two C_3 carbons as well as C_2 carbons are seen to be non-equivalent in IIf (see Table I).

Judging from these observations, If appears to have a higher rotational barrier than Ig. The lower rotational barrier in Ig seems to reflect the decrease in double bond character of the C–N bond caused by substitution of the benzoyl group for the acetyl group. In other words, the contribution of structure VII (Chart 2) to benzoyl derivatives is less important than in the case of acetyl derivatives because the carbonyl group in Ig could be conjugated with the benzene ring.

In methanol, these amides (If and Ig) were shown to be different from the other piperidones (Ia—e); that is, both amides react very slowly with CH_3OH but finally produce the hemiacetals (IIf and IIg) as the major component (>60%). Since amides are much weaker bases, the rate of hemiacetal formation is much slower than that of N-alkyl-piperidones and hence the solutions of If and Ig are expected to reach equilibrium only after a long time.

The positions of equilibrium reflect the relative stabilities of the ketone and hemiacetal forms, indicating that the ketone is more stable than its hemiacetal for the substituents a—e, while the reverse is the case for f—g. Aldehydes or ketones bearing one or more electron-attracting groups tend to favor the adduct forms rather than the carbonyl forms.[6] The formal positive charge in VII, therefore, seems to contribute to stabilizing the hemiacetal of the amides IIf and IIg.

In order to discuss the structural factors governing hemiacetal formation of piperidones, we have also examined N-methyl-3-pyrrolidone (V), which is a five-membered ring analog, and 1-diethylamino-3-pentanone (VI), which is an acyclic analog. The ^{13}C NMR spectra of these aminoketones show that they exist in CH_3OH almost completely in the carbonyl form. This finding seems to suggest that the six-membered rings are responsible for the preferential hemiacetal formation in piperidones. The effect of ring size is similar to that observed for the acid-catalyzed acetal formation in ethanolic solutions of cyclic amino ketones;[3b] only 4-piperidones (six-membered ring ketones) yield the corresponding acetals, while ketones of other ring sizes do not. The results were explained in terms of Brown's I-concept as follows: "carbonyl addition in 4-piperidones relieves strain inherent in a six-membered ring containing one trigonal carbon atom and leads to an ideally staggered conformation, not attainable in the five-and seven-ring analogs." The same considerations apply to the facile acid-catalyzed acetal formation from cyclohexanone.[7a,b] In order to see whether or not similar results are obtained in basic media, a methanolic solution of cyclohexanone containing N-methyl-4-piperidone as a catalyst (*ca.* a half equivalent relative

4) J.A. Hirsch, R.L. Augustine, G. Koletar, and H.G. Wolf, *J. Org. Chem.*, **40**, 3547 (1975).
5) *a*) For ^1H NMR studies of amides, see for example, M.T. Rogers, and J.C. Woodbrey, *J. Phys. Chem.*, **66**, 540 (1962), J. Zabicky (ed.) "The Chemistry of Amides," John Wiley and Sons., New York, 1970, p. 1; *b*) When the temperature was raised to *ca.* 60°, these signals of If were observed to be somewhat brodened.
6) *a*) J. Cantacuzène, *Bull. Soc. Chim. France*, **1962**, 762; *b*) J. Zabicky (ed.), "The Chemistry of the Carbonyl Group," Vol. 2, John Wiley and Sons, New York, 1970, p. 14.
7) *a*) O.H. Wheeler, *J. Amer. Chem. Soc.*, **79**, 4191 (1957); *b*) R. Garrett and D.G. Kubler, *J. Org. Chem.*, **31**, 2665 (1966); *c*) J.J. Breen, S.O. Lee, and L.D. Quin, *J. Org. Chem.*, **40**, 2245 (1975).

to cyclohexanone) was analyzed. The hemiacetal formation of cyclohexanone was found negligible. The finding that hemiacetal formation occurs in piperidones but not in cyclohexanone suggests that the relief of strain in a six-membered ketone is not sufficient to account for the reactivity of piperidones in this case.

Considering that the isomeric 3-piperidone also forms a hemiacetal, it appears that the relative positions of the carbonyl group and nitrogen atom have little effect. The following two factors may be involved: (1) piperidone systems are more highly strained than cyclohexanone, (2) the hemiacetals are formed with the intervention of the conjugate acids of piperidones, since the formal positive charge on nitrogen serves to increase the carbonyl reactivities.

An examination of the literature showed that a similar study was carried out on 1-*p*-alkyl-4-phosphorinanone derivatives and their oxides in water; the latter undergo reversible hydration whereas the former, having a structure corresponding to the present case, failed to undergo this reaction to a detectable extent.[7c] If we assume that a similar tendency holds in methanol (though the extent of hemiacetal formation should be larger than the extent of hydration[2]), the factor (2) appears to be more important. For a detailed discussion, information regarding the behavior of cyclohexanones with other hetero atoms would be desirable. A study along this line is now in progress.

Chemical Shifts of Hemiacetals and Acetals

In order to compare the ^{13}C NMR shifts in the above-mentioned hemiacetals with those in the corresponding acetals, the compounds IIIb—g were synthesized and their spectra were measured in the same solvent. Hemiacetals and acetals possessing a common substituent (IIb and IIIb, for example) exhibit similar chemical shifts except at C_3 and C_4. Therefore, only the observed chemical shifts for these two positions are given in Table II. The results show the constancy of chemical shifts at C_4, namely, about 99 ppm for acetals and about 96 ppm for hemiacetals, regardless of the substituent on nitrogen. The chemical shifts at C_4 in some 4,4-*gem*-diols (IV) are also given in Table II (see the footnotes). By comparing the values at C_4 of II, III and IV, the replacement $-OH \rightarrow -OCH_3$ appears to cause a deshielding effect of 3 ppm. The following points should be noted: (1) the upfield shift at C_3 (about 3 ppm) in the acetal compared with the hemiacetal; (2) the downfield shift at C_4 (about 3 ppm) in the acetal compared with the hemiacetal.

Such trends suggest that the signals of C_3 and C_4 can serve as a guide to distinguish between hemiacetal and acetal forms in 4-piperidone derivatives. Since the simultaneous determination of both adducts is impossible or at least difficult by conventional methods such as UV and ^1H NMR spectroscopies, ^{13}C NMR techniques appear to be a powerful tool for investiga-

TABLE II. Comparison of C-13 Chemical Shifts of Hemiacetals and Acetals in CH_3OH[a]

Substituent	Hemiacetal II		Acetal III		$\Delta\delta$[b]	
	C_3	C_4	C_3	C_4	C_3	C_4
a[c,d]	35.64	96.15	32.84	99.37	−2.8	3.2
b[d]	35.72	95.54	32.90	98.83	−2.8	3.3
c	35.88	96.21	33.05	99.50	−2.8	3.3
d[d]	35.33	96.12	32.55	99.27	−2.8	3.2
e	35.44	96.14	32.65	99.18	−2.8	3.0
f	35.94 36.74	96.31	33.05 33.83	99.43	−2.9	3.1
g	36.5 (broad)	96.45	33.4 (broad)	99.37	−3.1	2.9

a) Given in ppm downfield relative to TMS.
b) $\delta_{acetal} - \delta_{hemiacetal}$.
c) Ref. 2.
d) Chemical shifts at C_4 in 4,4-*gem*-diols IV (in H_2O), IVa 93.52, IVb 92.27, IVd 93.03.

tions of carbonyl behavior in hydrolytic solvents. This approach should be particularly effective in acidic media, in which both acetal and hemiacetal might be formed. For example, the method has been successfully applied to the hydrochlorides of the above-mentioned piperidones. The results will be reported elsewhere.

Experimental

^{13}C NMR spectra were recorded with an ANELVA NV-21 spectrometer under the conditions described previously.[2]

Materials——N-Methyl-4-piperidone (Ib), N-benzyl-4-piperidone (Ie), N-acetyl-4-piperidone (If) and N-benzoyl-4-piperidone (Ig) were commercial products.

N-Isopropyl-4-piperidone (Ic): Treatment of isopropyl amine and ethyl acrylate according to the method of Fuson and co-workers[8] gave N-isopropyl bis(2-(ethoxycarbonyl)ethyl)amine (VIII). The amine VIII was then converted to Ic by the Dieckmann ring closure with sodium hydride.[9]

N-Cyclopropyl-4-piperidone (Id): The synthesis of Id was effected essentially in the manner described for Ic except that cyclopropylamine was used as the starting material.

N-Methyl-3-pyrrolidone (V): Pyrrolidone V was prepared according to the reported procedure.[10] ^{13}C NMR (CH_3OH) δ: N–CH_3 42.85, –N$\underline{C}H_2$C=O 63.56, C=O 215.05, –$\underline{C}H_2$CO 38.93, –N$\underline{C}H_2CH_2$– 54.18.

1-Diethylamino-3-pentanone (VI): Aminoketone VI was prepared from ethyl vinyl ketone and diethylamine according to the procedure of Ross and Levine.[11] ^{13}C NMR (CH_3OH) δ: –$COCH_2\underline{C}H_3$ 7.93, –$CO\underline{C}H_2$-CH_3 36.76, –$NCH_2\underline{C}H_2CO$ 39.62, –$N\underline{C}H_2CH_2CO$ 47.86, –$NCH_2C\underline{H}_3$ 11.48, C=O 211.89, –$N\underline{C}H_2CH_3$ 47.58.

Acetals: Acetals IIIa—e were prepared from the corresponding piperidones as described for IIIa.[2] Acetals IIIf, IIIg were easily obtained by mixing the corresponding ketones (If, Ig) and methanol containing a trace amount of HCl.

Acknowledgement The authors are grateful to Misses T. Koimizu and K. Sakai for preparing some materials.

8) R.C. Fuson, Wm. E. Parham, and L.J. Reed, *J. Amer. Chem. Soc.*, **68**, 1239 (1946).
9) N.J. Leonard, M. Ōki, and S. Chiavarelli, *J. Amer. Chem. Soc.*, **77**, 6234 (1955).
10) E.A. Prill and S.M. McElvain, *J. Amer. Chem. Soc.*, **55**, 1233 (1933).
11) N.C. Ross and R. Levine, *J. Org. Chem.*, **29**, 2346 (1964).