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Behavior of Hydrochlorides and Methiodides of N-Substituted 4-Piperidones in Methanol

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The behavior of hydrochlorides and methiodides of several N-substituted 4-piperidones in CH_3OH has been studied by ^{13}C nuclear magnetic resonance (NMR) spectroscopy. All the piperidone salts studied were observed to exist as their hemiacetal form at room temperature, in contrast to the case of free piperidones, where an equilibrium mixture of ketone and hemiacetal was obtained. This difference could be accounted for by the effect of the positive charge on nitrogen, which increases the instability of the salt of the keto-form. Acetal formation was observed only in more acidic solutions. The corresponding O- and S-analogs were also examined in CH_3OH, and it was found that they are converted readily to the acetals in the presence of trace amounts of acid. The reaction mechanisms of these compounds and piperidone salts are compared and discussed. ^{13}C NMR techniques were found to be useful for studying the equilibrium system containing both hemiacetal and acetal.

Keywords——NMR; methanol; hemiacetal-acetal equilibrium; addition to carbonyl bond; N-substituted 4-piperidone hydrochlorides; N-substituted 4-piperidone methiodides; tetrahydropyran 4-one; tetrahydrothiopyran 4-one

The reversible addition of alcohol to a carbonyl double bond forms a hemiacetal, which reacts with another molecule of alcohol to give an acetal. It is considered that hemiacetal formation is subject to genaral acid and/or base catalysis, while acetal formation is catalyzed only by acids.[2] This difference has been used to distinguish between the hemiacetal and the acetal.[3] In our previous studies,[4] N-substituted 4-piperidones were found by ^{13}C NMR spectroscopy to be in equilibrium with their hemiacetals in CH_3OH at room temperature (Chart 1). It was also shown that ^{13}C NMR techniques provide unambiguous evidence of whether the adduct is the hemiacetal or the acetal. Though piperidone bases could not form acetals in CH_3OH due to the basic character of the solutions, it would be of interest to examine the behavior of hydrochlorides of these piperidones in alcohol because in these cases the acidic conditions may induce acetal formation. In fact, several investigators have isolated acetals of piperidones from acidic alcoholic solutions.[5] In this report, our ^{13}C NMR study has been extended to the hydrochlorides and the methiodides of N-substituted 4-piperidones in methanolic solutions. In order to acquire information on the effects of hetero atoms, the corresponding O- and S- analogs were also examined.

Results

The compounds studied in this work are illustrated in Chart 1. A well dried hydrochloride was mixed with methanol to prepare 1—1.5 M solution (in the case of methiodide, a saturated

1) Location: *Motoyama-Kitamachi, Higashinadaku, Kobe, 658 Japan.*
2) J. Zabicky(ed.), "The Chemistry of the Carbonyl Group," Vol. 2, John Wiley and Sons, New York, 1970, p. 14.
3) R. Garrett and D.G. Kubler, *J. Org. Chem.*, **31**, 2665 (1966).
4) *a*) C. Yamagami, M. Sugiura, T. Kitazawa, K. Tamura, and N. Takao, *Chem. Pharm. Bull.*, **27**, 2099 (1979); *b*) C. Yamagami, M. Sugiura, K. Tamura, and N. Takao, *Chem. Pharm. Bull.*, **28**, 2653 (1980).
5) *a*) S.M. McElvain and R.E. McMahon, *J. Amer. Chem. Soc.*, **71**, 901 (1949); *b*) P. Brookes and J. Walker, *J. Chem. Soc.*, **1957**, 3173; *c*) A.F. Casy, *Experientia*, **20**, 437 (1964).

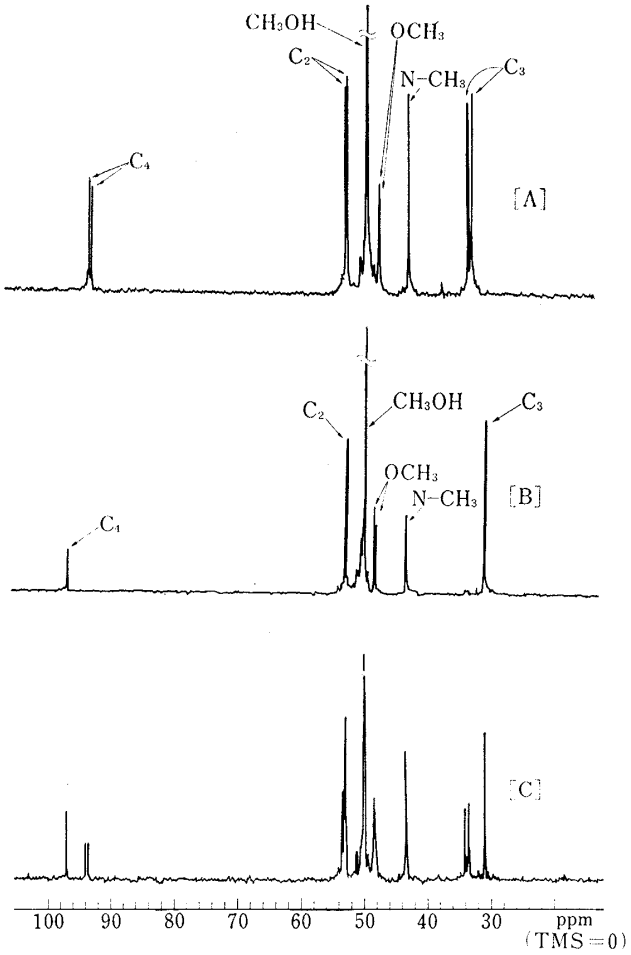
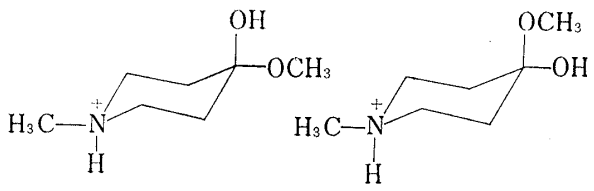


Fig. 1. ^{13}C NMR Spectra of N-Methyl 4-Piperidone Derivatives in CH_3OH

[A]: Hydrochloride of N-methyl 4-piperidone in CH_3OH at room temperature (hemiacetal).
[B]: Hydrochloride of the dimethylacetal of N-methyl 4-piperidone.
[C]: [A]+H^+, at room temperature (hemiacetal+acetal).



1a **1b**

Chart 2

Table I. Comparison of the C-13 Chemical Shifts of Hemiacetals and Acetals in CH_3OH[a)]

Compds.	Salt Form	Hemiacetal		Acetal	
		C_3	C_4	C_3	C_4
1	HCl	33.24	94.20	30.52	97.36
2	HCl	33.45	93.46	30.92	96.86
		34.01	93.90		
2	CH_3I	31.45	93.48	28.72	96.84
3	HCl	33.28	93.87	30.87	97.32
		33.83	94.30		
3	CH_3I	31.12	93.61	28.28	96.81
		31.20	93.70		
4	HCl	33.40	93.91	30.98	97.32
		34.01	94.40		
5	HCl	33.10	93.98	30.59	97.35
		33.61	94.36		
6	HCl	33.10	93.78	30.10	96.78
		33.67	94.18		
6	CH_3I	31.06	93.60	28.38	96.87
		31.38	93.75		
7		37.19	95.54	34.34	98.70
8		38.04	96.54	35.32	99.55

a) Given in ppm. downfield from TMS.

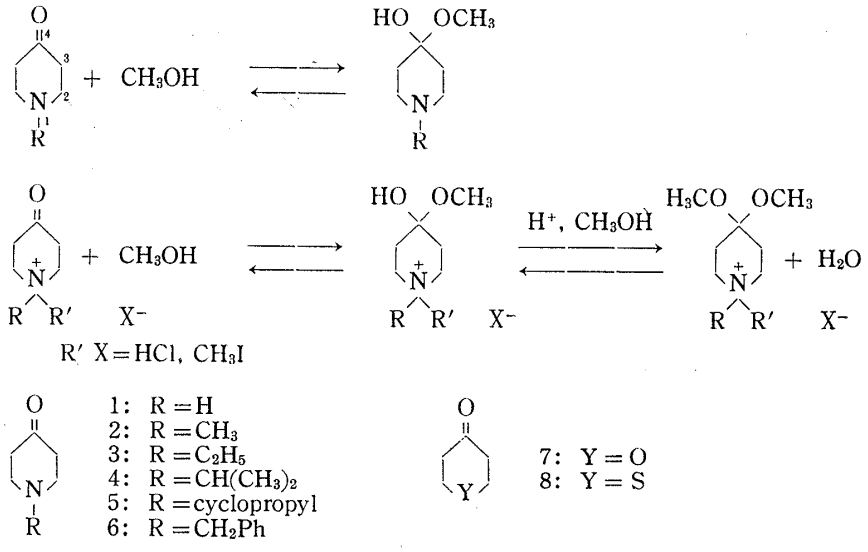
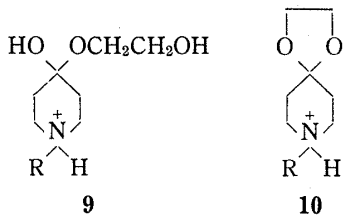


Chart 1

solution was used), and this was examined by ^{13}C NMR spectroscopy at room temperature as described earlier.[4] Signal assignments for piperidone derivatives were made by comparison with the data for the corresponding free bases reported in the previous papers.[4] Others were assigned by analogy with the piperidones. For comparison, the dimethyl acetals were independently prepared, and their spectra were also measured. Our procedure for distinguishing between the hemiacetal and the acetal in 4-piperidones was as follows; in going from the hemiacetal to the acetal, (that is, C–OH→C–OCH_3) we expect: 1) a downfield shift of about 3 ppm at the carbinyl carbon (C_4), and, 2) an upfield shift of about 3 ppm at the adjacent carbons (C_3).[4] Applying this method to the present study, all the piperidone salts (HCl and CH_3I salts) were proved to exist almost completely as the hemiacetal form in CH_3OH at room temperature. For example, the spectrum of the hydrochloride of N-methyl 4-piperidone(2-HCl) is shown in Fig. 1 together with that of its dimethyl acetal. The methanolic solution of 2-HCl exhibits no carbonyl carbon (which should appear in the range of 200—210 ppm) and instead, as can be seen from Fig. 1[A], the C_4-carbon signal appears at 93—94 ppm and the $-OCH_3$ carbon signal at about 48 ppm, indicating the existence of the hemiacetal of 2-HCl. This assignment appears to be valid for the following reasons. In spectrum [A], signals of ring carbons appear as two close but separated lines, which may be related to the configurational isomers with a predominant *eq.* N–CH_3 group, as shown in Chart 2. (In contrast, the spectrum of the free amine consists of single lines as a result of the rapid N-inversion.)[4b]

Similar results were obtained for other piperidone salts examined in the present study except for 1-HCl and 2-CH_3I which exhibit all signals as single lines because they are symmetrically substituted at the nitrogen. The spectrum of the acetal of 2-HCl (Fig. 1 [B]) shows the non-equivalence of the two methoxyl groups, confirming the fixed orientation of the N-methyl group. Since conformational analysis is not the subject of this study, this will be discussed in detail elsewhere. As for the chemical shifts, C_3 and C_4 in all hemiacetal and acetal salts are somewhat shielded relative to those of the corresponding free base[4b] due to the protonation shift or the methiodation shift,[6] but our criterion for distinguishing between hemiacetal and acetal still holds valid: the structural change, hemiacetal→acetal, for 2-HCl results in an upfield shift of 2.8 ppm at C_3 and a downfield shift of 3.2 ppm at C_4, if we take for convenience the average of the double lines as the chemical shift for the hemiacetal of 2-HCl (33.73 ppm for C_3 and 93.68 ppm for C_4 respectively). The values show excellent agreement with those for free piperidones.[4b] The observed chemical shifts for other piperidone salts are summarized in Table I.



9 **10**

Chart 3

When we made a solution of hemiacetal salts more acidic by adding a small amount of acid, acetal formation became obvious and a spectrum composed of signals due to the hemiacetal and the acetal was obtained. However, complete conversion into the acetal was not observed at room temperature even after a long time (Fig. 1 [C]).

For comparison, 2-HCl and 3-HCl were examined in ethyleneglycol which is known to produce ethylene acetals easily. In this alcohol, the acetal may be easily derived by intramolecular condensation from the hemiacetal (Chart 3). The ^{13}C NMR spectra of 2-HCl and 3-HCl in this alcohol each exhibit, nonetheless, only a set of double-line type signals assignable to the hemiacetal at room temperature.[7]

In order to examine the effect of temperature, the spectra of 2-HCl and 3-HCl were meas-

6) *a*) A.J. Jones and M.M.A. Hassan, *J. Org. Chem.*, **37**, 2332 (1972); *b*) J.J. Van Luppen, J.A. Lepoivre, R.A. Dommisse and F.C. Alderweireldt, *Org. Mag. Res.*, **12**, 399 (1979).

7) Chemical shifts at C_4 for **9** (R=Et) are 93.8 ppm and 94.2 ppm in comparison with the value of 104.9 ppm for **10** (R=Et).

ured at about 60° in CH_3OH and at about 90° in ethylene glycol, and we observed that a considerable amount of acetal was present together with the hemiacetal, and sometimes also with ketone. (It is known that the equilibrium shifts to the side of the keto form at elevated temperature.[2,4a,8] A methanolic solution of 3-HCl was also examined at a lower temperature (−60°); but the result was essentially the same as that obtained at room temperature except that the spectral pattern of the hemiacetal showed a small change.

On the other hand, N-acetyl 4-piperidone **11** and N-benzoyl 4-piperidone **12** (which cannot form hydrochlorides) and other 1-hetero 4-cyclohexanones, **7**[9] and **8**,[9] were found to undergo facile acetal formation in the presence of a trace of acid. It has already been mentioned that **11** and **12** are in equilibrium with their hemiacetal in neutral methanol.[4b] Similar behavior was observed in the cases of **7** and **8**. The addition of a trace of acid to these neutral solutions at room temperature resulted in complete acetal formation. The ^{13}C NMR data for **7** and **8** are included in Table 1.

Discussion

In view of the fact that the free base of piperidones is in equilibrium with the hemiacetal in CH_3OH, it seems of interest that their salt form tends to shift the equilibrium almost completely to the hemiacetal. This is probably because the positive charge on nitrogen results in an increase in the polarization of the carbonyl group, and consequently results in pronounced instability of the salt of the keto form. This view is consistent with the earlier finding that recrystallization of the salts of 1-HCl from wet solutions gives stable hydrates of the carbonyl, reflecting the high reactivity (instability) of the carbonyl group.[10]

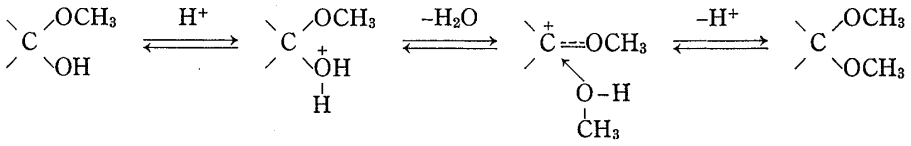


Chart 4

As to the acetal formation of hydrochlorides, our results suggest that an additional amount of acid is required to effect the reaction. It is generally considered that acetal formation is initiated by protonation at the hydroxyl group of the hemiacetal to produce a carbonium ion intermediate which reacts with another molecule of alcohol (Chart 4). Most acetals thus produced are more stable than the hemiacetals, and it is sometimes difficult to stop the reaction at the stage of the hemiacetal. In the case of a hydrochloride, protonation occurs preferentially at nitrogen, the more basic atom, and never at a hydroxyl group, as long as free amine remaines. Only after all the amino group are protonated would the acid begin to exert its catalytic effect. This might be the reason why Casy stated in his report regarding the preparation of piperdone acetals that he treated the basic ketone with a slight excess of acid at room temperature.[5c] It is considered that neither the hydrochlorides nor the methiodides are favorable for conversion into the acetals, since protonation at the hydroxyl group must be accomplished on a already positively charged (N^+) molecule, which is certainly more difficult than protonation of a neutral molecule. Thus, a part of the hemiacetal hydrochlorides and methiodides remained unchanged in a medium containing only a slight excess of acid. This consideration again explain the facile and complete acetal formation observed in the neutral compounds **7**,**8**, **11** and **12**, where a proton can be readily attached to a hydroxyl group.

8) J.M. Bell, D.G. Kubler, P. Sartwell, and R.G. Zeep, *J. Org. Chem.*, **30**, 4284 (1965).
9) For the ^{13}C NMR data for the keto forms, see J.A. Hirsch and E. Havinga, *J. Org. Chem.*, **41**, 455 (1976).
10) R.E. Lyle, R.E. Adel, and G.G. Lyle, *J. Org. Chem.*, **24**, 342 (1959).

At elevated temperature, deprotonation from the amino group becomes rapid, and therefore a liberated proton would have a chance to exert its catalytic effect on acetal formation.

It should be noted that even the O- and S-analogs, **7** and **8**, form hemiacetals under neutral conditions. In previous papers, we have considered the equilibrium between piperidones and their hemiacetal as a base-catalyzed one and suggested the following two factors as the driving force[4b]: 1) a relief of strain in piperidone rings, 2) the intervention of the conjugated acid of piperidone. However, in view of the observation that neutral compounds such as **7** and **8** yield hemiacetals, the second factor is not necessarily important. The effect of hetero atoms on carbonyl additions is not clear at the present stage.

In conclusion, this work has shown that ^{13}C NMR techniques provide an excellent tool for detecting simultaneously all the species contained in the equilibrium system, ketone$\rightleftarrows$hemiacetal$\rightleftarrows$acetal, provided that the reaction rates are appropriate for ^{13}C NMR measurements.[4b] This method is valuable because the direct detection of hemiacetals, in most cases, is impossible or at least difficult by conventional methods such as UV and ^{1}H NMR.[4a] The present success suggests that detailed information could be obtained on the behavior of such carbonyl compounds in hydrolytic solvents.

Experimental

^{13}C NMR Measurements——^{13}C NMR spectra were measured with an ANELVA NV-21 spectrometer under the conditions described previously.[4a]

Materials——The compounds 1, 2, 6, 7 and 8 are commercial products. The other piperidones and all the acetals were prepared in the manner described previously.[4]