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^{13}C NMR Studies of the Reaction between N-Ethyl-piperidones and Methanol

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^{13}C Nuclear magnetic resonance (NMR) spectra of a series of N-ethyl-piperidones were determined in $CDCl_3$ and in CH_3OH. The spectra of N-ethyl-3-piperidone and N-ethyl-4-piperidone in CH_3OH were complicated compared with those in $CDCl_3$. By examining the ^{13}C chemical shifts, this phenomenon was associated with the equilibrium hemiacetal formation. ^{13}C NMR technique was shown to be a powerful tool for studying such equilibrium systems. Factors controlling the equilibrium are discussed.

Keywords——N-ethyl-piperidones; acetal; hemiacetal; base-catalyzed addition; equilibrium; alcohol; NMR; temperature dependence; hydrogen bond; proton-deuterium exchange

The nuclear magnetic resonance spectra (^1H NMR,[2] ^{13}C NMR[3] and ^{17}O NMR[4]) of a series of 4-piperidones have been extensively studied by several groups of workers and some of their salt forms (hydrochlorides or methiodies) were shown to exist as the corresponding hydrated (or dideuteroxy) form in water (or D_2O). During the course of our investigations of the synthesis of piperidine derivatives starting from N-ethyl-4-piperidone, **1**, in methanolic solution, this aminoketone was found from its ^{13}C NMR spectrum to be in equilibrium with the hemiacetal **4** which could not be isolated (Chart 1). This finding seemed particularly interesting for two reasons. First, little attention has been paid to the addition reaction of a hydrolytic solvent to the carbonyl group in free aminoketones; previous investigations have dealt almost exclusively with the carbonyl addition in aminoketone salts.[2-5] In the second place, the ^{13}C NMR technique has turned out to be useful for distinguishing between hemiacetal and acetal as addition products. Considering that previous workers had difficulty in distinguishing one from the other,[6] application of this new method is valuable, at least for qualitative purposes.

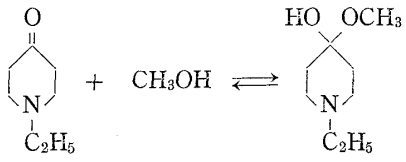

Chart 1

It therefore seemed of interest to investigate the behavior of related piperidone derivatives in methanol by examining their ^{13}C NMR spectra. In this paper, the results of ^{13}C NMR analysis of N-ethyl-4-piperidone under various conditions are described and the case

1) Location: *Motoyama-Kitamachi, Higashinada-ku, Kobe, 658 Japan.*
2) *a*) M.M.A. Hassan and A.F. Casy, *Org. Mag. Res.*, **1**, 389 (1969); *b*) M.M.A. Hassan and A.F. Casy, *ibid.*, **2**, 197 (1970); *c*) M.M.A. Hassan and A.F. Casy, *Tetrahedron*, **26**, 4517 (1970).
3) *a*) A.J. Jones and M.M.A. Hassan, *J. Org. Chem.*, **37**, 2332 (1972); *b*) J.A. Hirsch and E. Havinga, *ibid.*, **41**, 455 (1976).
4) H. Dahn, H.-P. Schlunke, and J. Temler, *Helv. Chim. Acta.*, **55**, 907 (1972).
5) *a*) R.E. Lyle, R.E. Adel, and G.G. Lyle, *J. Org. Chem.*, **24**, 342 (1959) and the references cited therein; *b*) A.F. Casy, *Experientia*, **20**, 437 (1964).
6) *a*) O.H. Wheeler, *J. Amer. Chem. Soc.*, **79**, 4191 (1957); *b*) D.G. Kubler and L.E. Sweeney, *J. Org. Chem.*, **25**, 1437 (1960); *c*) J.M. Bell, D.G. Kubler, P. Sartwell, and R.G. Zepp, *ibid.*, **30**, 4284 (1965); *d*) R. Garrett and D.G. Kubler, *J. Org. Chem.*, **31**, 2665 (1966).

of isomeric piperidone derivatives is also discussed in this connection. The behavior of their hydrochlorides will be the subject of a subsequent paper.

Results

The compounds studied in this work are illustrated in Chart 2, which also gives the observed ^{13}C chemical shifts. Measurements were made on 0.8—1 M solutions in $CDCl_3$ and 1.5—2 M solutions in CH_3OH. No special precautions were taken to keep the concentration constant because our purpose did not require a quantitative study. ^1H NMR data are given in the experimental section.

N-Ethyl-4-piperidone

The ^{13}C NMR spectrum of the base **1** in $CDCl_3$ is shown in Fig. 1. Assignment was easily made with the aid of off-resonance decoupling, relative intensities and the assignment of N-methyl-4-piperidone in the literature.[3a] Compound **1** when dissolved in CH_3OH, displayed additional signals together with those observed in $CDCl_3$, indicative of the presence of a newly formed substance (Fig. 1). A variable temperature study showed that these new signals became predominant as the temperature was lowered (Fig. 1) and, on the other hand, became barely discernible when the temperature was increased to about 60°. Measurement of the same sample in $CDCl_3$ again after removal of CH_3OH gave a spectrum identical with that measured initially in $CDCl_3$. These results are considered to indicate that **1** exists in equilibrium with a second component which is stable only in methanolic solution and that the equilibrium is strongly affected by temperature. Inspection of the spectrum in CH_3OH

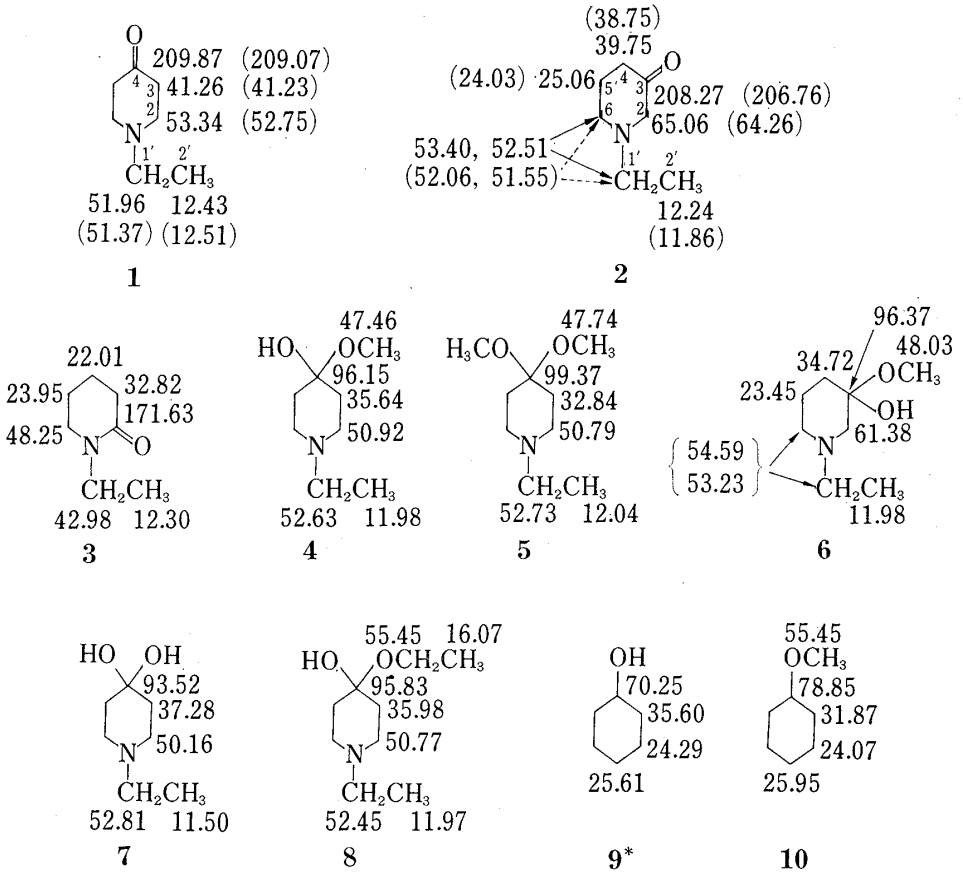

Chart 2. ^{13}C Chemical shifts Determined in the Present Work (ppm Downfield Relative to TMS)

Solvent $CDCl_3$: **1**—**2** (in parentheses) and **9**—**10**, CH_3OH: **1**—**6**, H_2O: **7**, C_2H_5OH: **8**.
* For the reported values, see Ref. 8, pp. 163.

(Fig. 1, B) suggests that the second component no longer possesses a carbonyl group, as shown by the upfield shifts at C_4 (band 11→10, 113.7 ppm) and also at C_3 (band 4→3, 5.6 ppm), compared with the aminoketone **1**. Similar duplication of signals was reported in the PMR spectrum of the salt forms of N-substituted-4-piperidone derivatives in H_2O (or D_2O), and was interpreted in terms of addition of the solvent to the carbonyl function to give the corresponding isolable hydrate.[2] The solution was found to exhibit temperature dependence properties similar to those mentioned above. An analogous reaction may thus occur in the present methanol solution to give the very unstable hemiacetal **4**. The results of assignment of each signal in **4** are presented in Chart 2. For comparison, data on the corresponding stable acetal **5**, cyclohexanol **9** and methoxy cyclohexane **10** are also given.

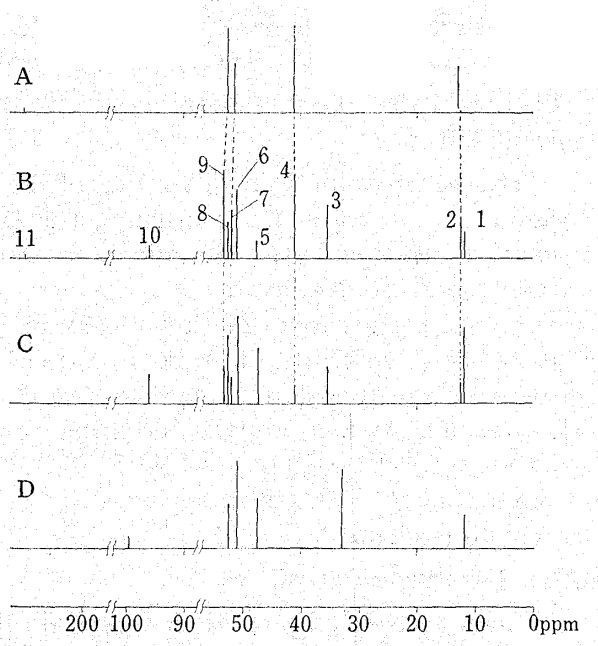

Fig. 1. Stick Diagrams for N-Ethyl-4-piperidone (A; in $CDCl_3$, B; in CH_3OH at room temperature, C; in CH_3OH at −20°) and N-Ethyl-4,4-dimethoxy-piperidine (D; in CH_3OH)

The off-resonance technique applied to the methanol solution of **1** at −20° showed that signals 1 and 5 appear as quartets, signal 10 as a singlet and signals 6 and 8 as triplets. From this observation, peak 1, 5 and 10 were readily assigned to $C_{2'}$, methoxyl carbon and C_4 respectively. The distinction between C_2 and $C_{1'}$ was made on the basis of the two fold greater intensity of the resonance due to C_2. Corroborating evidence for the assignment of the C_3 signals in **1** and **4** was offered by the observation that signals 3 and 4 became multiplets when the sample was measured in CD_3OD. This feature is accounted for by D/H-exchange, known to be characteristic of protons adjacent to a carbonyl function (α-protons).[2,7] The finding of D-atoms even in the hemiacetal **4** is suggestive of rapid equilibrium between **1** and **4**.

Since reported C_4-chemical shifts in the methiodides of 4,4-dihydroxy piperidine derivatives are in the range of 90—102 ppm,[3a] our value of 96.2 ppm seems reasonable in the proposed structure. The ^{13}C NMR spectrum of **5** shows that the C_4-resonance shifts downfield but the C_3-resonance shifts upfield, compared with **4**. This is thought to be associated with the relationship between **9** and **10**, although the parameters are much smaller owing to the cumulative effect of the other methoxyl group.[8]

^1H NMR analysis in CD_3OD solution also supports our interpretation. The spectrum is more complex than that determined in $CDCl_3$, that is, duplication of the methyl triplet in the N-ethyl group and an additional multiplet centered near 1.75 ppm upfield of the ring proton signal in the ketone form **1** were observed, both being diagnostic of the hemiacetal **4**. The above-mentioned multiplet attributable to the α-protons in **4** was seen to decrease with time, as expected from the D/H-exchange concept. The higher field triplet intensity increased with decrease in temperature along with the multiplet due to the α-protons of **4**. This higher field triplet should therefore be associated with **4**, and the lower field one with **1**. The integral ratio of the two triplets corresponds approximately to the intensity ratio of the

7) The D/H-exchange was also confirmed by mass analysis. The recovered sample was shown to contain 1—4 D-atoms.
8) J.B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, 1972, p. 144.

two methyl carbon signals ($C_{2'}$) in the ^{13}C NMR spectrum, although direct comparison of these two values is not very reasonable under the present conditions, which were not strictly controlled as regards concentration and temperature.

Solvent Effect

The behavior of **1** in other hydrolytic solvents was also investigated using ^{13}C NMR techniques. In water or in ethanol, the expected hydrate or hemiacetal was observed to form to a lesser extent. The adduct content (**7**, **8**) as judged by intensities of the methyl carbon signals in N-ethyl groups was only about 20% in both cases, while it amounted to about 45% in the case of methanol solution. This result is consistent with the value of 16% reported for the hydrate content in N-methyl-4-piperidone–water mixture, which is, to our knowledge, an almost unique example of the reaction of the base form of piperidones.[2a] The reaction with *n*-propanol occurred to a much lesser extent (~10%). The order of reactivity, MeOH>EtOH>*n*-PrOH, is the same as that observed in acetal formation of cyclic ketones.[6a] In trifluoroethanol (CF_3CH_2OH), a less nucleophilic solvent, **1** was found to remain unchanged.

Other Piperidone Derivatives

Isomeric N-ethyl-piperidones were also examined. The methanolic solution of N-ethyl-3-piperidone **2** exhibited behavior analogous to that of **1**, including the temperature dependence. The extent of hemiacetal **6** formation estimated from the ^{13}C NMR spectrum determined under conditions similar to those used for the CH_3OH solution of **1**, was about 40%. The ^{13}C NMR spectra of **2** were more complex due to a lack of symmetry. However, by using techniques such as off-resonance, temperature studies and D/H-exchange, spectral assignments were successfully made except the closely placed C_6- and $C_{1'}$-resonances.

The absence of symmetry in **2** leads to increased difficulties in analyzing its ^1H NMR spectra, compared with the symmetrical molecule, **1**. The spectrum of **2** in $CDCl_3$ displayed a Me-triplet in the N-ethyl group and the signal due to α-protons at C_2 appeared isolated from other complicated signals. When **2** was mixed with CD_3OD, the duplication of the former triplet and the reduction of the latter signal intensity may be used as indicators of carbonyl-reacted product. Nevertheless, the information available is much less than that obtained from ^{13}C NMR spectra.

N-Ethyl-2-piperidone **3** showed no tendency to react with methanol, as had been anticipated from its amide character, and hence presented the spectrum of a single species even in CH_3OH. Its ^{13}C NMR analysis was carried out by comparison with the data for N-methyl-2-piperidone.[3b]

Tropinone was examined as a model compound possessing a bridged piperidone ring. Its ^{13}C NMR spectrum in CD_3OD indicated no reaction of the carbonyl function while the D/H-exchange of α-protons takes place. The observed ^{13}C chemical shifts were in agreement with those determined in $CHCl_3$[9] within 1.5 ppm.

Discussion

The reactions of the carbonyl group with alcohols under consideration could be interpreted in terms of general base-catalyzed equilibrium additions to the carbonyl function.[10] Such equilibrium systems in acidic solutions have been extensively studied and much work has been carried out to determine whether the product is hemiacetal or acetal. Conventional methods such as IR, UV and ^1H–NMR spectroscopies have been used in order to detect the conversion of the carbonyl group to adducts. The most widely employed method (UV

9) E. Wenkert, J.S. Bindra, C.-J. Chang, D.W. Cochran, and F.M. Schell, *Acc. Chem. Res.*, **7**, 46 (1974).
10) J. Zabicky (ed.), "The Chemistry of the Carbonyl Group," Vol. 2, John Wiley and Sons., New York, 1970, p. 14.

analysis) consists in following the change in carbonyl absorption ($n\rightarrow\pi^*$) on addition of solvent. This method is accurate, but can provide no direct evidence for the product structure. In addition, it was reported that the presence of a trace of water in the mixture could lead to an erroneous conclusion.[6b-d] The ^1H NMR technique is useful for detecting the compounds present in a system in so far as the spectra contain characteristic signals for each component.[11] It has the disadvantage of being unsuitable for studies in hydrolytic solvents. In fact, measurements in deuterated alcohols mean that the characteristic alkoxy groups in the resulting adducts can not be detected because the entering group itself is deuterated. Moreover partial deuteration of α-protons may complicate the situation due to secondary deuterium isotope effects.[12] In contrast, ^{13}C NMR spectroscopy is free from these shortcomings, and, as shown in the previous section, can supply unambiguous information concerning the species present in a given equilibrium system.

The observed hemiacetal rather than acetal formations are compatible with the general concept that the hemiacetal alone is formed in neutral or basic media, but both may be formed in acidic media.[10] In practice, however, reported examples of such carbonyl additions in the absence of an acid catalyst are by no means numerous.[13] This may be due to the instability of the resulting hemiacetals, in contrast to acetals, many of which can be stably isolated. The observed temperature dependence again agrees with the well-known tendency that a lower temperature favors such addition reactions.

Two important factors may be considered as driving forces for hemiacetal formation: (1) the relief of strain inherent in a six membered ring containing a trigonal carbon atom, (2) the stabilization of the resulting hemiacetal by newly formed hydrogen bonding. The importance of the former factor is confirmed by the well-known fact that carbonyl addition in cyclohexanone is more favored than in cyclic ketones of other ring sizes.[6b] As to the latter factor, it is difficult from our data to conclude how the hydrogen bonding is formed because the effective IR techniques are not applicable to studies in hydrolytic solvents. It is necessary to take into account the possibilities of intramolecular and inter molecular (solute–solute, solute–solvent) hydrogen bonding. In N-ethyl-3-piperidinol, the OH-axial conformer has been found to be more stable owing to intramolecular hydrogen bond formation with the lone pair on the nitrogen atom.[14] Therefore, the analogous contribution could be possible in the case of **6** (Chart 3). However, the corresponding intramolecular hydrogen bonding is hardly to be expected in **4** because the molecule would be forced to take the unfavorable boat conformation. Considering that the solvent is methanol and that methanol solutions of **1** and **2** produce hemiacetals to approximately the same extent, it is more probable that hydrogen bonding occurs mainly with the surrounding solvent molecules. Since water is a stronger nucleophile than methanol, the observed lower reactivity of **1** with water could be accounted for by its self-solvation, as suggested by Wheeler.[6a] This concept also implies that the stabilization of hemiacetal by hydrogen bonded solvation may play an important role in determining the hemiacetal content at equilibrium.

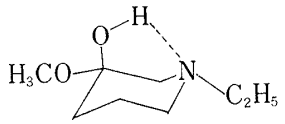

Chart 3

On the other hand, it may safely be said that hydrogen bonding between aminomolecules is not essential on the basis of the ^{13}C NMR spectrum determined with a less concentrated

11) *a*) Y. Fujiwara and S. Fujiwara, *Bull. Chem. Soc. Japan*, **36**, 1106 (1963); *b*) E. Lombardi and P.B. Sogo, *J. Chem. Phys.*, **32**, 635 (1960).
12) *a*) J.M. Jones and M.L. Bender, *J. Amer. Chem. Soc.*, **82**, 6322, (1960); *b*) V.A. Stoute and M.A. Winnik, *Can. J. Chem.*, **53**, 3503 (1975).
13) *a*) B.H. Bakker, H. Steinberg, and Th, J. de Boer, *Rec. Trav. Chim. Pays-Bas.*, **94**, 50 (1975); *b*) E. Adler and G. Andersson, *Ann. Chem.*, **1976**, 1435.
14) *a*) S. Vašíčková, A. Vítek, and M. Tichý, *Coll. Czech. Chem. Commun.*, **38**, 1791 (1973); *b*) R.E. Lyle, D.H. McMahon, W.E. Krueger, and C.K. Spicer, *J. Org. Chem.*, **31**, 4164 (1966).

CD_3OD solution of **1** (*ca.* 0.1 M); this indicated little change in the extent of hemiacetal formation, while no D/H-exchange was observed at this lower concentration.

The unreactivity of tropinone towards methanol can be interpreted in terms of steric inhibition. Lower reactivities of ethanol and *n*-propanol could be attributed partly to steric hindrance and partly to lower nucleophilicities of these solvents.

The role of solvent in promoting the addition reaction is particularly interesting, the other features being essentially the same as those already described in earlier publications on acetal formations in cyclic ketones. (This parallelism between acetal and hemiacetal formations sometimes caused confusion in distinguishing these two processes.) Further work in this direction is in progress by means of conformational analysis. At the same time, our ^{13}C NMR studies will be extended to other equilibrium systems containing unstable species which are difficult to identify by conventional methods.

Experimental

Solvents——Commercially available guaranteed reagents were used without further purification.

Materials——The piperidone, **1**, was prepared according to the method of Fuson and co-workers,[15] and **2** was prepared by the method of Lyle and co-workers.[5a] The products were purified as hydrochlorides by recrystallization from acetone. Dimethyl acetal, **5**, was obtained by treatment of the corresponding ketone **1** with methanolic HCl and crystallization from methanol–ether. Compounds **1**, **2** and **5** were freshly prepared from their hydrochlorides as follows. Aqueous solutions of the hydrochlorides of **1** and **2** were made alkaline with potassium carbonate then extracted with ether. The ether extract was dried and concentrated. The acetal, **5**, was obtained by neutralization of the methanolic solution of its hydrochloride with sodium methoxide. The piperidone, **3**, was prepared by treatment of δ-valerolactum with NaH and then ethyl iodide in benzene. Analytical results were as follows;

N-Ethyl-4-piperidone——PMR ($CDCl_3$) δ: 1.12 (triplet, $J=7$ Hz, N–$CH_2C\underline{H}_3$). δ: 2.6—2.9 (C_2-protons). PMR (CD_3OD) δ: 1.08 (triplet, $J=7$ Hz, N–$CH_2C\underline{H}_3$ (**4**)), δ: 1.13 (triplet, $J=7$ Hz, N–$CH_2C\underline{H}_3$ (**1**)), δ: near 1.75 (multiplet or near triplet, α-ring protons (**4**)), δ: 2.6—2.9 (C_2-protons (**1**)). IR cm^{-1}: $\nu_{C=O}$ 1710 ($CHCl_3$). MS *m/e*: 127 (M^+).

N-Ethyl-3-piperidone——PMR ($CDCl_3$) δ: 1.06 (triplet, $J=7$ Hz, N–$CH_2C\underline{H}_3$), δ: 2.96 (singlet, C_2-protons). PMR (CD_3OD) δ: 1.08 (triplet, $J=7$ Hz, N–$CH_2C\underline{H}_3$ (**2**)), δ: 1.06 (triplet, $J=7$ Hz, N–$CH_2C\underline{H}_3$ (**5**)), δ: 2.97 (singlet, C_2-protons (**2**)). IR cm^{-1}: $\nu_{C=O}$ 1730 ($CHCl_3$). MS *m/e*: 127 (M^+).

N-Ethyl-2-piperidone——PMR ($CDCl_3$) δ: 1.10 (triplet, $J=7$ Hz, N–$CH_2C\underline{H}_3$), δ: 1.6—1.9 (C_4-protons and C_5-protons), δ: 2.2—2.5 (C_3-protons), δ: 3.1—3.4 (C_6-protons), δ: 3.38 (quartet, $J=7$ Hz, N–$C\underline{H}_2CH_3$). IR cm^{-1}: $\nu_{C=O}$ 1625 ($CHCl_3$). MS *m/e*: 127 (M^+).

N-Ethyl-4,4-dimethoxypiperidine——PMR ($CDCl_3$) δ: 1.08 (triplet, $J=7$ Hz, N–$CH_2C\underline{H}_3$), δ: 3.20 (singlet, O–$C\underline{H}_3$), δ: near 1.8 (α-ring protons). MS *m/e*: 173 (M^+).

NMR Spectral Measurements——Spectrometer: ANELVA NV-21. ^1H NMR spectra were obtained at 90 MHz in a CW mode using TMS as a lock and internal reference. ^{13}C FT NMR spectra were recorded at 22.6 MHz in 8 mm tubes also using TMS as an internal reference, except for measurements in water, when *p*-dioxane was used. All chemical shifts were calculated relative to TMS (TMS–dioxane; 67.40 ppm). When the solvent was non-deuterated, a capillary containing D_2O was added to provide the lock signal (D_2O was replaced by $(CD_3)_2CO$ for recording at low temperature). Conditions of FT NMR measurements were: spectral width, 5000 Hz; pulse width, 10—20 μsec; (flipping angle, about 15—25°); acquisition time 0.8 sec; number of data points 8192. In variable temperature experiments, temperatures were measured directly by inserting a thermometer into the probe.

15) R.C. Fuson, Wm. E. Parham, and L.J. Reed, *J. Amer. Chem. Soc.*, **68**, 1239 (1946).