Temperature Dependence of ^{13}C NMR Spectra of 9-Methylaminoacridinium and 4-Methylaminopyridinium Perchlorate

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The double bond character of the exocyclic carbon-nitrogen bond of 9-methylaminoacridinium ion is less than that of 4-methylaminopyridinium ion since the energy barrier of rotation around this bond is lower by 8 kJ mol^{-1} in the case of the 9-methylaminoacridinium ion.

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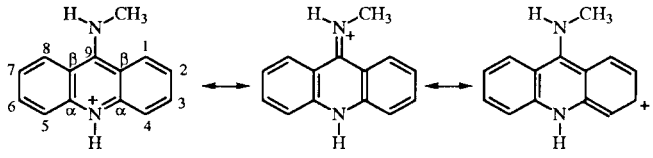
Acid or alkaline hydrolysis of 9-aminoacridine [1] takes place more readily than that of 4-aminopyridine [2]. In the latter case a strong electron-attracting group, such as a nitro-group or a further doubly-bound ring-nitrogen atom (*e.g.* 4-aminopyrimidine) [3], is a prerequisite in order to facilitate the reaction. The introduction of methyls in the amino group has an accelerating effect on the hydrolysis of 9-aminoacridine [3] but in the case for example of 4-aminopyrimidine it has a retarding effect [3]. In view of these results the double bond character of the exocyclic carbon-nitrogen bond of 9-methylaminoacridinium ion was compared with that of 4-methylaminopyridinium ion by examining the temperature dependence of their ^{13}C nmr spectra.

This work was carried out because 9-aminoacridines have antitumor [4a] as well as selective cytotoxic [5] properties which they lose when hydrolyzed [4].

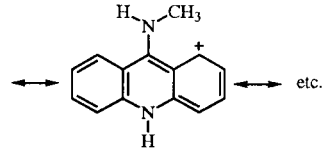
Results and Discussion.

Assignment of the carbon chemical shifts of 9-methylaminoacridinium and 4-methylaminopyridinium perchlorate (Table), which is helpul for the purpose of the present discussion, is based on the ^{13}C nmr spectra of 9-aminoacridine [6] and 4-methylaminopyridine [7] and on a consideration of more resonance structures than **Ia** and **Ib**, such as **Ic** and **Id**, for the 9-methylaminoacridinium ion and of the resonance structures **IIa** and **IIb** for 4-methylaminopyridinium ion.

The spectrum of 9-methylaminoacridinium ion **I** at 7° shows that the two carbon atoms at positions 1 and 8 resonate at δ 122.6 and 127.7 ppm, the two α-carbons at δ 137.9 and 140.9 ppm and the two β-carbons at δ 111.0 and 113.2 ppm, respectively (Table). These chemical shifts are completely separated. Therefore at low temperatures the amine salt exists as structure **IIIa** or **IIIc** and the bond between carbon-9 and the exocyclic amino nitrogen has substantial double bond character. Thus the carbon atoms of each pair mentioned above are non-equivalent and isomerization between structures **IIIa** and **IIIb** is restricted. This spectrum shows also that the two carbons at positions 3 and 6 and the two carbons at positions 4 and



Ia **Ib** **Ic**



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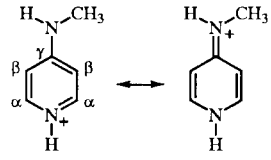
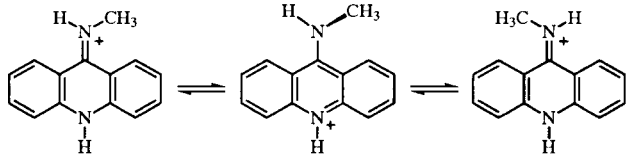


IIa **IIb**

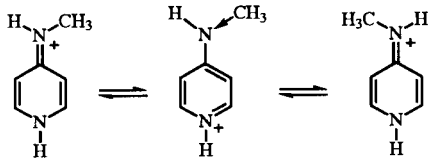
5 are non equivalent and resonate at different δ values (Table) but the separation of these chemical shifts is not complete.



IIIa **IIIb** **IIIc**

The ^{13}C nmr spectrum of the above salt was compared in the same solvent with that of 4-methylaminopyridinium perchlorate (**II**) which showed that at 30° the two α-carbons resonate at δ 138.1 and 140.7 ppm and the two β-carbons at δ 104.7 and 110.5 ppm, respectively (Table), indicating that the bond between the γ-carbon and the exocyclic amino nitrogen has a substantial double-bond character. Therefore at ordinary temperatures the amine

salt exists as structures **IVa** or **IVc**. Thus the two α- and the two β-carbons are non equivalent and isomerization between structures **IVa** and **IVb** is restricted.



IVa **IVb** **IVc**

The temperature dependence of the ^{13}C nmr spectra of 9-methylaminoacridinium and 4-methylaminopyridinium perchlorate was studied within the temperature ranges of 7-52° and 30-77°, respectively, and the coalescence temperatures for the two signals of each pair of carbons mentioned above, were determined and used to calculate the energy barrier of rotation (ΔG*) around the exocyclic carbon-nitrogen bond using standard methods [8] (Table).

Table

^{13}C NMR Chemical Shifts and Energy Barrier of Rotation of C=NHCH$_3$ Bonds in 20% [$^2H_6$]DMSO in 1,2-Dichloroethane

9-MeNH-acridinium ion (7°C)

		δ (ppm)	$T°_c$/ K	ΔG*/ kJ mol^{-1}
α-Carbons	A	137.9	300	58
(A and B)	B	140.9		
β-Carbons	A	111.0	298	58
(A and B)	B	113.2		
1,8-Carbons	A	122.6	305	58
(A and B)	B	127.7		
3,6-Carbons	A	134.6		
(A and B)	B	135.1		
4,5-Carbons	A	123.4		
(A and B)	B	124.0		
2,7-Carbons		118.5		
9-Carbon		157.1		
CH_3 (amino N)		36.4		

4-MeNH-pyridinium ion (30°C)

		δ (ppm)	$T°_c$/ K	ΔG*/ kJ mol^{-1}
α-Carbons	A	138.1	340	66
(A and B)	B	140.7		
β-Carbons	A	104.7	347	66
(A and B)	B	110.5		
γ-Carbon		159.2		
CH_3 (amino N)		29.4		

The ΔG* value for 9-methylaminoacridinium ion is lower than that for 4-methylaminopyridinium ion (Table) by 8 kJ mol^{-1} (≈12% lower) indicating that the double-bond character of the exocyclic carbon-nitrogen bond of the former ion is less than that of the latter ion, mainly because of steric hindrance incurred in the aminoacridinium ion by the presence of the two benzene rings. A similar trend can be expected also in the case of the free forms of 9-methylaminoacridine and 4-methylaminopyridine. Therefore, it can be concluded that the higher reactivity of the free or the protonated form of 9-aminoacridines as compared to that of the free or the protonated form of 4-aminopyridines is not only due to the electron withdrawing properties of the benzene rings in the acridine molecule, but it is also due to steric hindrance to resonance between the amino group and the acridine ring (structures **Ia** and **Ib**) which reduces the double bond character of the exocyclic carbon-nitrogen bond.

The present results are compatible with the observation [3] that the reactivity of 9-aminoacridines towards nucleophilic substitution at carbon-9 increases when methyls are introduced in the exocyclic amino group, in spite of their +/ effect, since the increase in steric hindrance incurred upon methylation causes a further decrease in the double bond character of the exocyclic carbon-nitrogen bond.

EXPERIMENTAL

Materials.

9-Methylaminoacridinium and 4-methylaminopyridinium perchlorate were prepared by mixing an ethanolic solution of 9-methylaminoacridine [9] (0.4 g/50 ml) with an ethereal solution of 4-methylaminopyridine [10] (0.4 g/50 ml), respectively, with an ethereal solution of perchloric acid (upper layer of a 10% mixture of perchloric acid in ether). The precipitates formed were filtered, washed with ether to remove excess perchloric acid and recrystallized twice from absolute ethanol (charcoal). The crystals obtained were dried at 80° and 0.1 Torr to give 9-methylaminoacridinium perchlorate (0.26 g, 65% yield).

Anal. Calcd. for $C_{14}H_{13}N_2ClO_4$: C, 54.47; H, 4.24; N, 9.07. Found: C, 54.23; H, 4.19; N, 9.09.

The second product obtained was 4-methylaminopyridinium perchlorate (0.28 g, 70% yield).

Anal. Calcd. for $C_6H_9N_2ClO_4$: C, 34.55; H, 4.35; N, 13.43. Found: C, 34.63; H, 4.34; N, 13.39.

1,2-Dichloroethane was purified by washing with a 10% potassium hydroxide solution and then with distilled water. After an initial drying with calcium chloride the filtrate was refluxed with charcoal. After filtration it was refluxed with phosphorus pentoxide prior to fractional distillation. The distillate at 83.5° was collected and kept over molecular sieves 4A.

NMR Spectra.

These were recorded on a Bruker AC-300 Spectrometer (300 MHz) attached with a Bruker variable temperature unit (Eurotherm Controller/Programmer Type 818), and are reported in units of δ relative to TMS. The solvent used was a 20% solution of [$^2H_6$]DMSO (kept over molecular sieves 4A) in purified 1,2-dichloroethane. This solvent was kept over molecular sieves (with occasional shaking) for several weeks before use.

REFERENCES AND NOTES

[1] A. Albert and B. Ritchie, *J. Chem. Soc.*, 458 (1943).

[2] A. Albert, Heterocyclic Chemistry, 2nd Ed, Athlone Press, London, 1968, p 123; H. Meislich, Pyridinols and Pyridones, in Pyridine and its Derivatives, Part **3**, E. Klingsberg, ed, Interscience Publishers, 1962, pp 589-590 and references therein.

[3] E. Kalatzis, *J. Chem. Soc. (B)*, 96 (1969).

[4a] A. Ledochowski and S. Skonieczny, *Rocz. Chem.*, **50**, 415 (1976); [b] S. Skonieczny, A. Organiak, A. Snarska, A. Kunikowski, S. Nowak, and A. Ledochowski, *Pol. J. Chem.*, **52**, 2125 (1978).

[5] W. R. Wilson, L. H. Thompson, R. F. Anderson, and W. A. Denny, *J. Med. Chem.*, **32**, 31 (1989).

[6] R. Faure, J.-P. Galzy, J. Barbe, A. L. Boukir, and E.-J. Vincent, *Bull. Soc. Chim. Belg.*, **100**, 639 (1991).

[7] E. Kalatzis and L. Kiriazis, *Chim. Chron., New Ser.*, **21**, 41 (1992).

[8] H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970); E. Breitmaier and W. Voelter, ^{13}C NMR Spectroscopy, Verlag Chemie, New York, 1978, p 85.

[9] A. Albert, The Acridines, 2nd Ed, Edward Arnold, London, 1966, p 307.

[10] J. B. Wibaut and F. W. Broekman, *Recl. Trav. Chim. Pays-Bas*, **80**, 311 (1961).