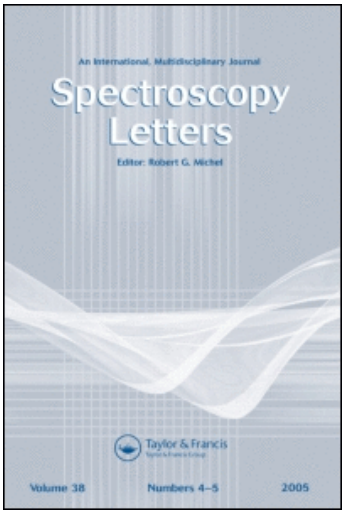


Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

A ^{13}C-NMR Study of Some 9-Ahinoacridines and Their Cations in Relation with Tautomaric Problems

Jean-Pierre Galy[a]; Robert Faure[a]; Jacques Barbe[b]; José Elguero[c]
[a] Laboratoire de Chimie Organique Physique, University d'Aix-Marseille III, Marseille Cédex 13, France [b] G.E.R.C.T.O.P., Faculté de Pharmacie, Marseille Cédex 5, France [c] Instituto de Química Médica, Madrid, Spain

To cite this Article Galy, Jean-Pierre , Faure, Robert , Barbe, Jacques and Elguero, José(1988) 'A ^{13}C-NMR Study of Some 9-Ahinoacridines and Their Cations in Relation with Tautomaric Problems', Spectroscopy Letters, 21: 8, 809 — 818
To link to this Article: DOI: 10.1080/00387018808082343
URL: http://dx.doi.org/10.1080/00387018808082343

SPECTROSCOPY LETTERS, 21(8), 809-818 (1988)

A ^{13}C-NMR STUDY OF SOME 9-AMINOACRIDINES AND THEIR CATIONS IN RELATION WITH TAUTOMERIC PROBLEMS

KEY WORDS: ^{13}C-NMR, Tautomerism, Protonation, Rotation about a C(sp^2)-N(amino) bond

Jean-Pierre Galy and **Robert Faure**
Laboratoire de Chimie Organique Physique, Université d'Aix-Marseille III, Av. Escadrille Normandie Niemen, 13397 Marseille Cédex 13, France

Jacques Barbe
G.E.R.C.T.O.P., Faculté de Pharmacie, 27 Bd Jean Moulin, 13385 Marseille Cédex 5, France

José Elguero
Instituto de Química Médica, C.S.I.C., Juan de la Cierva, 3. 28006 Madrid, Spain

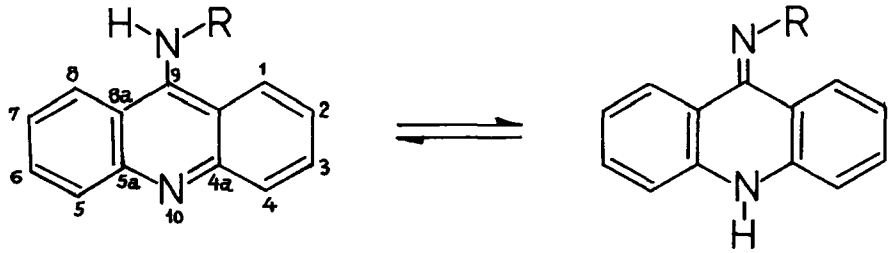
ABSTRACT

^{13}C-NMR chemical shifts have been measured for some 9-aminoacridine derivatives, substituted on positions 9 and 10, in DMSO and for some related salts in D_2O. The results are discussed with regard to amino/imino tautomerism, structure of the cations, and slow rotation about a formal C-N double bond.

INTRODUCTION

In a previous work dealing with ^{13}C-NMR spectroscopy of acridines[1] two 9-aminoacridines (9-aminoacridine itself **1** and 9-methylaminoacridine **2**)

Table 1.-Chemical shifts of the ring carbon atoms (solvent, DMSO-d_6)



Compound	C-1(8)	C-2(7)	C-3(6)	C-4(5)	C-4a(5a)	C-8a(9a)	C_9
1[1], R=H	121.7	123.5	130.1	128.7	149.0	113.2	150.5
2[1], R=CH_3	121.2	124.5	129.7	126.8	147.5	115.4	152.1
3, R=n-C_4H_9	121.5	124.5	129.7	128.7	148.6	114.9	152.6
4, R=n-C_6H_{13}	121.2	124.8	130.0[a]	125.8[b]	147.1[b]	116.8[a]	152.6
5, R=$CH_2C_6H_5$	119.2	124.6	132.8	122.3	140.0	111.5	
	120.4	125.4	134.7	123.3	141.7	114.1	155.4
Average	119.8	125.0	133.8	122.8	140.8	112.8	
6, (see text)	118.3	125.5	129.8	113.7	140.0	118.3	
	120.9	128.7	130.5	115.0	142.4	120.9	152.3
Average	119.6	127.1	130.2	114.4	141.2	119.6	

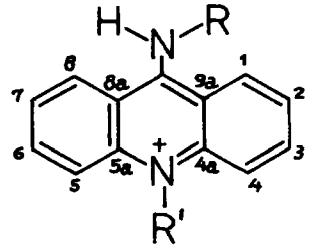
[a] Broad; [b] Very broad.

Table 2.-Chemical shifts of the N-substituents (solvent DMSO-d_6)

Compunds	
3, R=n-C_4H_9	50.0(CH_2-α), 33.2(CH_2-β), 19.7(CH_2-γ), 13.7(CH_3)
4, R=n-C_6H_{13}	50.4(CH_2-α), 31.0(CH_2-β, CH_2-γ), 26.2(CH_2-δ), 22.0(CH_2-ε), 13.7(CH_3)
5, R=$CH_2C_6H_5$	51.9(CH_2), 138.2(C-1'), 126.7(C-2'), 128.4(C-3'), 127.0(C-4')
6, (see text) n-C_3H_7	54.5(CH_2-α), 25.7(CH_2-β), 11.8(CH_3)
$CH_2C_6H_5$	49.8(CH_2), 136.5(C-1'), 125.8(C-2'), 128.6(C-3'), 126.8(C-4')

were recorded in dimethylsulfoxide (DMSO) and in trifluoroacetic acid (TFAA). Nothing unusual was observed and the signals were assigned without difficulty (Tables 1 and 3). However, when the methyl group was changed by a longer alkyl group (n-propyl, n-butyl, or n-hexyl) appearance of broad signals became common. In this paper we report some examples of this behaviour and we propose an explanation that can account for it.

Table 3.–Chemical shifts of ring carbon atoms (solvent D_2O)



Compound	C-1(8)	C-2(7)	C-3(6)	C-4(5)	C-4a(5a)	C-8a(9a)	C_9
8[1], R=R'=H[a]	124.1	126.8	138.1	120.2	140.7	112.7	159.1
9[1], R=CH_3, R'=H[a]	126.0	126.0	137.3	120.1	141.2	114.0	160.4
10, R=C_2H_5, R'=H	123.3[b]	124.5	135.6	118.1	138.3[b]	110.8[b]	155.1
11, R=H, R'=C_2H_5	124.3	125.1	137.5	117.0	139.0	111.5	156.4
12, R=n-C_3H_7, R'=H	123.4[b]	124.7	136.0	118.4	138.0[b]	111.0[b]	156.3
13, R=H, R'=n-C_3H_7	124.7	125.3	137.7	117.5	139.8	111.7	156.6

[a] Solvent = TFAA; [b] Broad.

EXPERIMENTAL

Compounds **3**, **4**, **5**, and **6** have already been described.[2,3] Salts **9** - **12** have been prepared similarly.[4] ^{13}C-NMR spectra were recorded at 50.32 MHz on a Bruker AM 200 (Centre Interuniversitaire de RMN de Marseille). Samples were dissolved in [$^{2}H_6$]DMSO or in D_2O, the deuterium signal providing field-frequency lock; the concentration was 20-30% (w/v). Chemical shifts are expressed in ppm from tetramethylsilane. Typical conditions were as follows: pulse width, 8 μs (ca. 60°); repetition time, 2 s; spectral width, 12 kHz; data points, 16 384.

RESULTS AND DISCUSSION

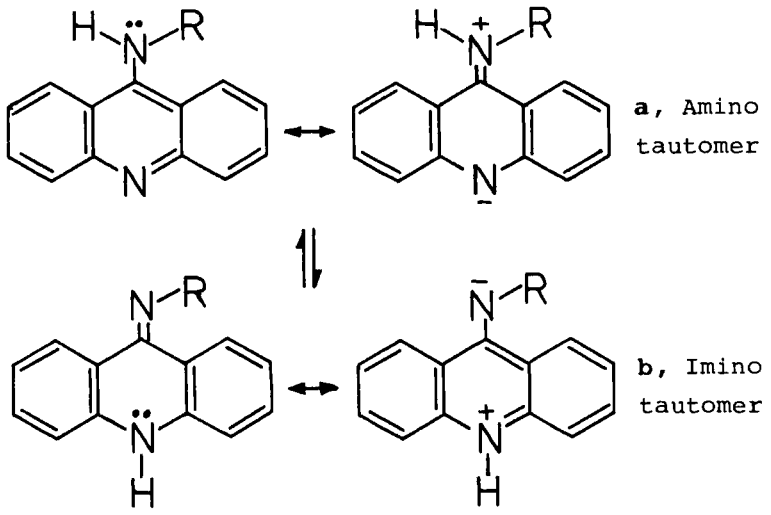
Neutral Species

The spectra of 9-n-butylaminoacridine **3** (Tables 1 and 2) are similar to that of 9-methylaminoacridine **2**.[1] However, when the spectra of 9-n-hexylaminoacridine **4** were recorded, the signals corresponding to carbons C-3(6) and C-8a(9a) were broad and those corresponding to C-4(5) and C-4a(5a), very broad (Table 1). Three explanations are possible.

i) Slow rotation about the C-9/N bond in the amino tautomer.

ii) Slow rotation about the C-9/N bond in the imino tautomer.

iii) Slow prototropic exchange between amino and imino tautomers.

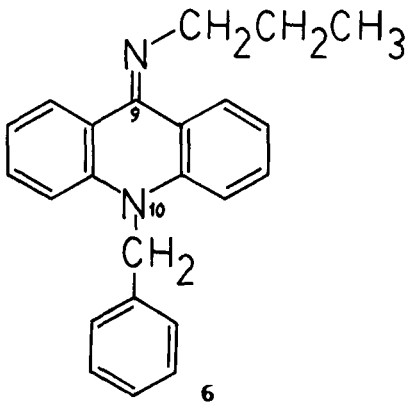


It is difficult to estimate the rotational barriers in such tautomers, but it is safe to assume that it will be lower in the case of the amino tautomer **a** that in the case of the imino one **b**. Addition of a drop of TFAA suppresses the broadening.

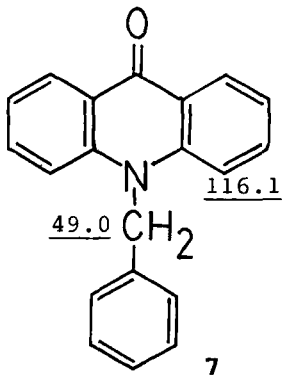
The spectrum of 9-benzylaminoacridine **5** (Table 1) is characterized by the splitting of all signals except C-9. These are narrow and their averaged values (Table 1) are very different compared to the preceding aminoacridines.

The study of compound **6** (9-n-propylimino-10-benylacridane) provides an explanation for the behaviour of compound **5**.

The spectra of **5** and **6** are quite similar (See Table 1, averaged values), the main difference being the shielding of C-4(5) (122.8 114.4) in compound **6**. This difference is due to the presence of the 10-benzyl group (compare with compound **7**).[5] Three consequences



6



7

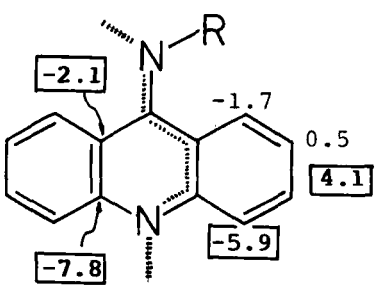
may be drawn from these results:

i) Compound **5** exists in the imino form, **5b**.

ii) In the conditions of our experiment (50 MHz, room temperature), rotation about the C-9/N bond in imino structures **5** and **6**, is blocked (narrow signals).

iii) The broadening observed for compound **4** is not due to slow rotation about the C-9/N bond in tautomer **4b**.

If we calculate now the chemical shift differences between a typical amino tautomer, e.g. **3a**, and an imino tautomer, **5b** (averaged values), the following $\Delta\delta$ values in ppm are found:



As it can be seen, the larger the differences, the broader the corresponding signals in the spectrum of

Table 4.-Chemical shifts of the N-substituents (solvent, D_2O)

Compound	
10, R=C_2H_5	44.2(CH_2), 15.0(CH_3)
11, R'=C_2H_5	43.6(CH_2), 13.0(CH_3)
12, R=n-C_3H_7	50.6(CH_2-α), 23.4(CH_2-β), 11.0(CH_3)
13, R'=n-C_3H_7	49.6(CH_2-α), 21.1(CH_2-β), 10.3(CH_3)

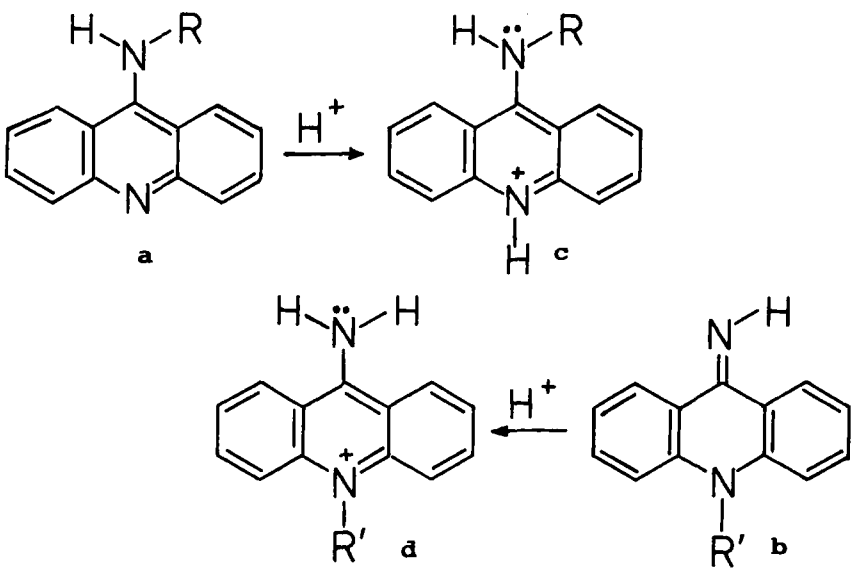
4. We conclude that the origin of the broadening of the signals corresponding to carbons C-3(6), C-4(5), C-4a(5a), and C-8a(9a) in compound **4** is due to a slow prototropic exchange between tautomers **4a** and **4b**. However, the observed chemical shifts being closer to **3a** than to **5b**, the equilibrium must be shifted towards the amino tautomer. The fact that addition of a drop of TFAA to the DMSO solution of **4** produces a narrowing of the broad signals without modification of the chemical shifts (less than 0.2 ppm) is simply a consequence of the increase of the tautomeric rate due to acid catalysis.[6]

Concerning tautomerism, it is worth noticing that this is the first example known[6] of the effect of alkyl substituents on the amino $\rightleftharpoons$ imino tautomerism. In general alkyl substituents have little effect on the equilibrium constant.[6] Acridine, due to its somewhat less aromatic character (compared with pyridine) shows a remarkable sensitivity to the nature of R. When

R = H, CH_3, or n-C_4H_9, the amino tautomer, **1a, 2a, 3a,**, is the only one present in DMSO solution. When R = $CH_2C_6H_5$ the equilibrium is completely shifted towards the imino tautomer, **5b**. When R = n-C_6H_{13}, both tautomers are present, but the amino one, **4a**, clearly predominates.

Cations

When the spectra of 9-aminoacridine **1** and 9-methylaminoacridine **2** were recorded in TFAA nothing abnormal was observed[1] and the structures **8** and **9** were assigned to the corresponding cations (Table 3). The hydrochlorides **10-13** have the substituent on the exocyclic amino group (**10, 12**) or on the endocyclic N-10 (**11, 13**). The chemical shifts gathered in Table 3 prove that both cations have the same structure **c** or **d**.



This is an expected result since the protonation on the other nitrogen would not result in a cyanine-like stabilization. What is surprising is that some signals C-1(8), C-4a(5a), and C-8a(9a) are slightly broad in compounds **10c** and **12c** but not in isomeric structures **11d** and **13d**. The most reasonable explanation is a slow rotation about the C-9/N bond, which is only apparent in **c** structures owing to the fact that both substituents on the amino group are different (H and R). The fact that slow rotation is not observed in neutral molecules, tautomer **a**, is a consequence of the difference in double bond character of the C-9/N bond between structures **a** and **c**. The considerable increase in activation energy produced by protonation in dimethylaminoazines is well documented.[7]

REFERENCES

[1] R. Faure, J.P. Galy, E.J. Vincent, J. Elguero, A.M. Galy, and J. Barbe, Chem. Scripta, 15, 62 (1980).

[2] J.P. Galy, J. Elguero, E.J. Vincent, A.M. Galy, and J. Barbe, Heterocycles, 14, 311 (1980).

[3] J.P. Galy, E.J. Vincent, A.M. Galy, J. Barbe, and J. Elguero, Bull. Soc. Chim. Belg., 90, 947 (1981).

[4] J.P. Galy, unpublished results.

[5] R. Faure, A. Mahamoud, J.P. Galy, E.J. Vincent, A.M. Galy, and J. Barbe, Spectrosc., 14, 223 (1981).

[6] J. Elguero, C. Marzin, A.R. Katritzky, and P. Linda, The Tautomerism of Heterocycles, Academic Press, New York, 1976.

[7] M. Oki, Application of Dynamic NMR Spectroscopy to Organic Chemistry, VCH Publishers, Florida, 1985, p. 90.

Date Received: 06/01/88
Date Accepted: 07/11/88