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Reference Data

^{1}H, ^{13}C and ^{15}N NMR and GIAO CPHF calculations on two quinoacridinium salts

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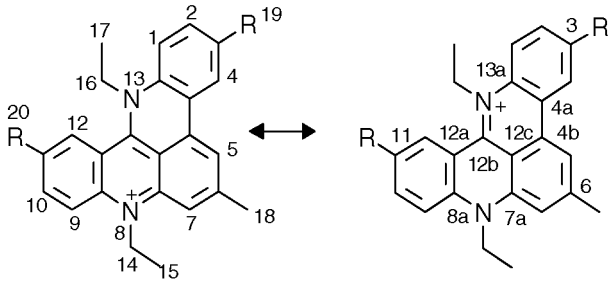
ABSTRACT: The complete ^{1}H, ^{13}C and ^{15}N NMR assignments of two closely related quinoacridinium salts, 8,13-diethyl-6-methyl-8*H*-quino[4,3,2-*kl*]acridinium iodide and, 8,13-diethyl-3,6,11-trimethyl-8*H*-quino[4,3,2-*kl*]acridinium iodide, are described. The multinuclear 1D NMR and 2D shift-correlated NMR techniques HMQC, HSQC and HMBC were applied, accompanied by *ab initio* GIAO CPHF calculations of shielding constants. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; ^{15}N NMR; 2D NMR (HMBC, HSQC, HMQC); GIAO CPHF calculations; quinoacridine salts; synthesis

INTRODUCTION

The synthesis of the 'pyridoacridines' and related compounds have been published[1,2] and their biological activity (cytotoxic, mutagenic or antibacterial properties) depends both on the number of phenyl rings and on the type of substituents.[3,4] NMR spectra of pyridoacridines, isolated from a new group of marine alkaloids, have recently been reported.[1,2,5–7]

In the course of our studies on the synthesis of hemicyanine and cyanine dyes, it was observed that a new heterocyclic salt 8,13-diethyl-6-methyl-8*H*-quino[4,3,2-*kl*]acridinium iodide (**1**) is formed;[8,9] condensation of the quinaldinium salt bearing methyl groups at the phenyl ring affords the corresponding substituted quinoacridinium salt 8,13-diethyl-3,6,11-trimethyl-8*H*-quino[4,3,2-*kl*]acridinium iodide (**2**) (see Scheme 1).



1 (R = H), **2** (R = CH_3)

Scheme 1. The quinoacridinium cations with atom numbering.

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RESULTS AND DISCUSSION

For the reliable assignment of the ^{1}H, ^{13}C and ^{15}N spectra, 2D NMR methods and theoretical calculations had to be applied. The NMR data for **1** and **2** are collected in Tables 1 and 2, respectively.

The discrimination between the chemical shifts of two *N*-ethyl groups at the N-8 and N-13 atoms in **2** was decisive and was deduced by the analysis of the calculated nitrogen shielding constants and the ^{1}H–^{15}N and ^{1}H–^{13}C HMQC spectra. According to the resonance forms (two of the 18 possible are illustrated in Scheme 1), the positive charge can be located at N-8 and/or N-13, which means that it is delocalized over the molecule. Nitrogen N-13 shows a slightly pyramidal configuration of bonds in the crystal;[8] however, it results from overcrowding (presence of ethyl groups). The calculated shielding constants of **1** (Table 1) showed that N-8 is significantly more shielded than N-13, and therefore the signal of ^{15}N at −243.9 ppm in the spectrum of **1** (−244.6 ppm for **2**) was assigned to N-8 and the signal at −235.8 ppm (−236.8 ppm for **2**) to N-13. The ^{1}H–^{15}N correlation showed that the peak of N-8 was bonded to ^{1}H signals of H-7, H-9 and H-15, whereas the N-13 peak was bonded to H-1 and H-17.

Unambiguous assignments of the ^{1}H and ^{13}C chemical shifts for both ethyl groups made possible the identification of other proton and carbon signals, by analysing the HSQC, HMQC and HMBC spectra.[10] The remainder of the skeleton of **1** was deduced from the HMBC experiment optimized for $J = 5$ Hz. Two-, three- and four-bond ^{1}H–^{13}C cross peaks were observed (Fig. 1). The assignments for **2** were made mainly on the basis of the HMQC and HSQC spectra.

The calculated carbon shielding constants for **1** were used to confirm the assignments of ^{13}C NMR spectra. A linear correlation between theoretical and experimental results was obtained (Fig. 2) for aromatic carbons. Usually, successful correlations are obtained between shielding constants (calculated using x-ray crystal geometry) and chemical shifts for solid compounds.[11] The good correlation, with $R = 0.99$, shows that the heterocyclic skeleton is rigid in solution. The discrimination between C-12a and C-12b is easy because these signals are at two extremes of the plot; however, assuming that the tendency for shielding is reproduced properly, the less differentiated carbons can also be assigned.

EXPERIMENTAL

Synthesis

All compounds were synthesized (Scheme 2) and purified in the laboratory of Physical Organic Chemistry, Warsaw University. The purity of the quinolines was checked by TLC.[6] 2,6-Dimethylquinoline was synthesised according to the Doebner and von Miller method. Ethylation was done by heating 2,6-dimethylquinoline with ethyl iodide, as described in a previous paper.[6] A new derivative of quinoacridine, 8,13-diethyl-3,6,11-trimethyl-8*H*-quino[4,3,2-*kl*]acridinium iodide (**2**) was obtained by analogy with our procedure[8] by heating 1-ethyl-6-methyl-quinaldinium iodide with piperidrine (2 : 1 mol/mol) in ethanol. The red product was recrystalized from methylene chloride (yield 78.5%) (m.p. 199–200 °C). Elemental analysis: C62.56, H5.39, N6.21; $C_{26}H_{27}N_2I$ requires C63.16, H5.50, N5.67%.

NMR spectra

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX500 spectrometer operating at 500.13 MHz for ^{1}H and 125.75 MHz for ^{13}C. Saturated solutions of quinoacridinium salts (ca 30 mg) in DMSO-d_6 were prepared; the temperature was stabilized at 300K. All 1D and 2D experiments (HMQC, HSQC and HMBC)[10] were run using the programs from the Bruker software library. The values of $J(^{13}C, ^{1}H)$ were measured in the gated decoupled spectra, obtained with a relaxation delay $\Delta_1 = 1.5$ ms and a gated-off decoupler delay $\Delta_2 = 1$ ms. For ^{1}H–^{13}C 2D experiments the ^{1}H spectral width was 4640 Hz and the ^{13}C width was 22 936 Hz. Typically 2048 data points were acquired. The spectrum was collected as 1024 × 512 blocks of data and was processed by sinusoidal multiplication in each dimension followed by symmetrization of the final data matrix after zero filling in the F_1 dimension.

Reference Data

Table 1. ^{15}N, ^{13}C and ^{1}H chemical shifts and 2D heteronuclear correlations for **1** [DMSO-d_6, δ(ppm); reference TMS) and shielding constants, σ(ppm)

No.	Type C, H, N	$^{13}C/^{15}N$, σ(ppm)	$^{13}C/^{15}N$, δ(ppm)	^{13}C, (J) (Hz)	n-Bond connectivities* (C → H) ^{3}J	^{2}J	^{4}J	^{1}H, δ(ppm) (J,Hz)
1	CH	84.05	120.47	dd 164.2; 6.9	H-3			8.14, d (8.3)
2	CH	65.68	130.65	dd 165.0; 8.5	H-4			7.86, dd (8.3; 1.2)
3	CH	73.69	126.77	dd 165.0; 7.7	H-1			7.68, t (7.5)
4	CH	72.88	124.43	dd 162.7; 7.7	H-2			8.62, d (7.5)
4a	C	80.51	123.20	s	H-1, H-3, H-5			
4b	C	60.57	130.96	s		H-5		
5	CH	89.34	115.64	dd 168.0; 6.5	H-7			8.32 s
6	C	42.71	148.16	q 5.4		H-18		
7	CH	93.51	112.75	dt 163.4; 5.4	H-5, H-18			7.94 s
7a	C	49.34	138.77	s	H-14			
8	N	145.70	−243.9					
8a	C	49.25	141.80	t 6.2	H-10, H-12, H-14			
9	CH	85.49	116.69	dd 165.7; 7.0	H-11			8.18, d (9.0)
10	CH	57.40	135.76	dd 165.0; 8.5	H-12	H-9		8.07, dd (7.8; 1.2)
11	CH	80.75	122.63	dd 166.5; 7.7	H-9			7.61, t (7.8)
12	CH	67.60	129.08	dd 165.0; 7.7	H-10			8.38, d (8.4)
12a	C	91.35	114.95	s	H-9, H-11			
12b	C	28.87	152.69	s	H-12, H-16			
12c	C	90.10	115.18	t 5.2	H-5, H-7		H-12	
13	N	129.51	−235.8					
13a	C	61.40	136.28	t 3.1	H-2, H-4, H-16			
14	CH_2	156.39	43.04	td 142.0; 4.1		H-15		4.78, q (7.0)
15	CH_3	185.69	11.86	q 128.0		H-14		1.54, t (7.0)
16	CH_2	153.96	51.97	td 145.0; 3.1		H-17		5.07, q (6.8)
17	CH_3	185.63	15.37	qd 128.7; 3.1		H-16		1.14, t (6.8)
18	CH_3	179.20	22.60	qd 128.0; 4.6	H-5, H-7			2.76, s

Table 2. ^{15}N, ^{13}C and ^{1}H chemical shifts and 2D heteronuclear correlations for **2** [DMSO-d_6, δ(ppm); reference TMS]

No.	Type C, H, N	$^{13}C/^{15}N$, δ(ppm)	n-Bond connectivities (C → H or N → H) ^{3}J	^{2}J	^{4}J	^{1}H, δ(ppm) (J,Hz)
1	CH	120.47				8.00, d (8.5)
2	CH	132.09		H-4	H-1	7.67, dd (8.5; 1.5)
3	CH	132.55	H-1			
4	CH	124.40	H-2		H-1	8.42, s
4a	C	123.34	H-1, H-5			
4b	C	131.12	H-4	H-5	H-1	
5	CH	115.59	H-18			8.26, s
6	C	148.04		H-7, H-18		
7	CH	112.68	H-5, H-18			7.86, s
7a	C	138.88	H-14		H-5	
8	N	−244.6	H-7, H-9, H-15			
8a	C	140.31	H-10, H-12, H-14			
9	CH	117.13				8.07, d (9.0)
10	CH	137.60	H-12			7.89, dd (9.0; 1.5)
11	CH	136.85	H-9	H-12		
12	CH	128.02	H-10		H-9	8.13, s
12a	C	115.19	H-9	H-12		
12b	C	152.05	H-12, H-16		H-5, H-7, H-9	
12c	C	115.44	H-5, H-7		H-12	
13	N	−236.8	H-1, H-17			
13a	C	134.60	H-2, H-4, H-16	H-1		
14	CH_2	43.21		H-15		4.73, q (7.0)
15	CH_3	12.12		H-14		1.53, t (7.0)
16	CH_2	51.97		H-17		5.05, q (6.8)
17	CH_3	15.37		H-16		1.12 t (6.8)
18	CH_3	22.86	H-5, H-7			2.76, s
19	CH_3	20.86	H-2, H-4			2.54, s
20	CH_3	20.56	H-10, H-12			2.54, s

Reference Data

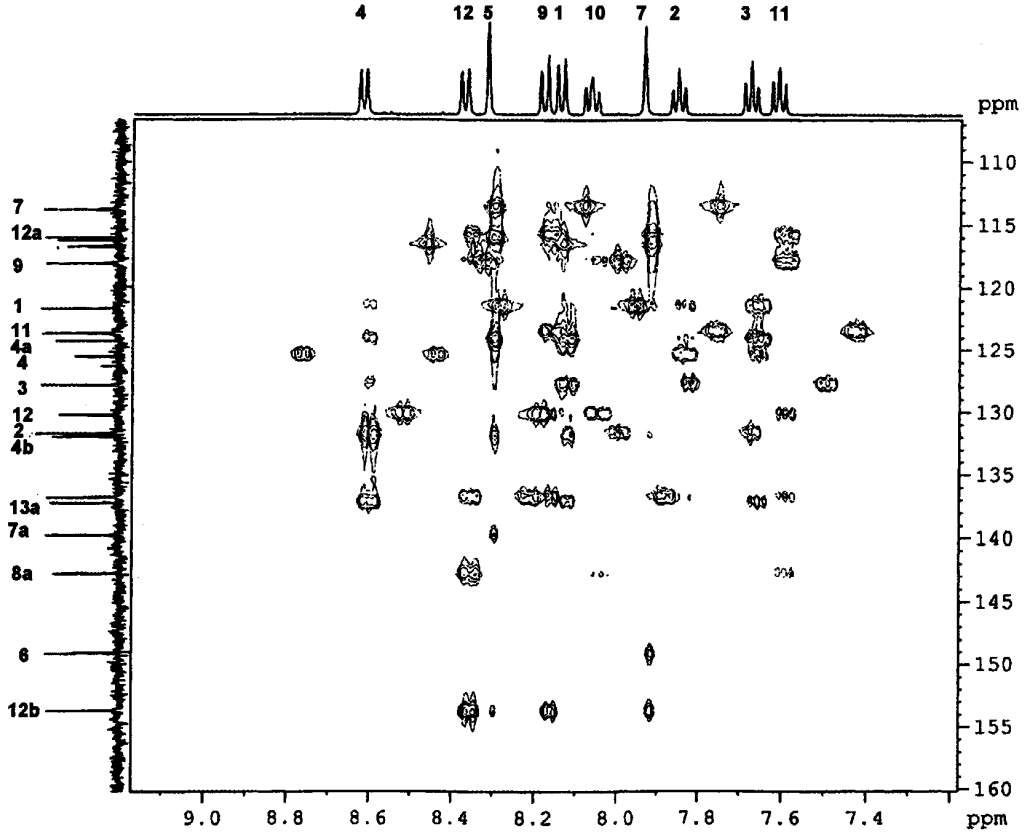


Figure 1. $^{1}H-^{13}C$ HMBC spectrum of quinoacridinium salt **1**.

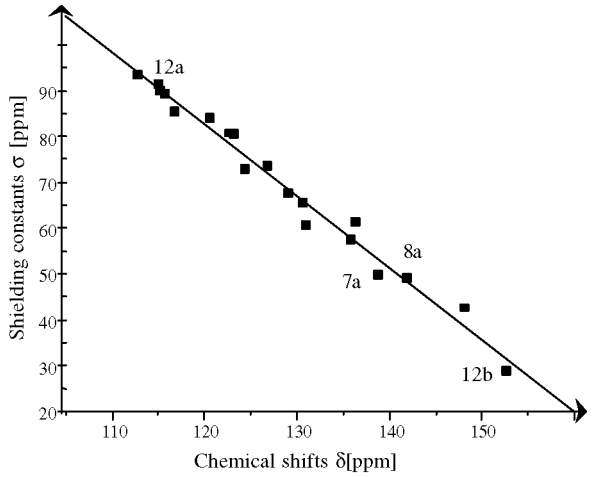
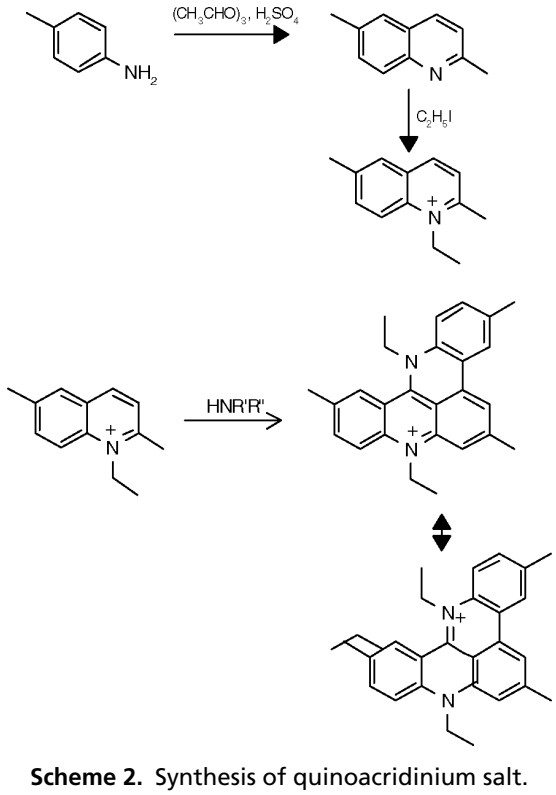


Figure 2. Plot of calculated shielding constants σ(ppm) versus ^{13}C chemical shifts δ(ppm) in DMSO for aromatic carbons of **1**. $\sigma = 270.4-1.565\delta$; $r = -0.991$.

Two-dimensional $^{1}H-^{15}N$ NMR measurements were carried out on a Varian UNITY plus 500 spectrometer using the phase-sensitive gradient-selected inverse technique. The experiments were optimized for $^{2}J/^{3}J$ coupling constants of ca 6 Hz (D6 = 0.08 s) and performed with four scans of 128 echo and four scans of 128 anti-echo accumulations; 2D experimental data were zero-filled to 512 points along the nitrogen direction. The chemical shifts were referenced against internal TMS (^{1}H, ^{13}C) and external neat CH_3NO_2 (^{15}N).



Scheme 2. Synthesis of quinoacridinium salt.

Reference Data

Calculations

The shielding constants were calculated using the GIAO CPHF approach implemented in the Gaussian 98 package[12] with the standard 6–31G** basis set on molecular geometry taken from the semi-empirical calculation by the PM3 method using the HyperChem 5.02 package.[13] The conformations of ethyl groups and the shieldings for ethyl groups carbons were not analysed.

Acknowledgements

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