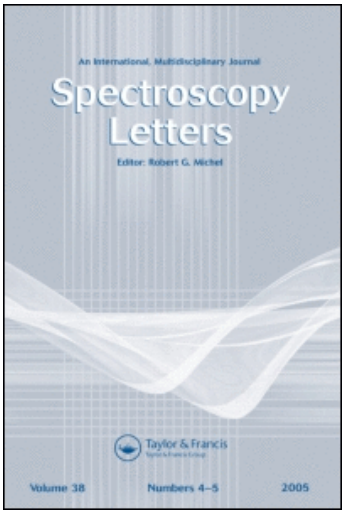

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Natural Abundance Nitrogen-15 NMR: A Study About the Conformation and Protonation Site of Some Quinoline Alkaloids

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NATURAL ABUNDANCE NITROGEN-15 NMR: A STUDY ABOUT THE CONFORMATION AND PROTONATION SITE OF SOME QUINOLINE ALKALOIDS

Key Words: ^{15}N-NMR, quinoline alkaloids.

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ABSTRACT

Natural abundance ^{15}N-NMR spectra were obtained from quinidine, quinine and epi-quinidine. Correlation of the ^{15}N chemical shifts with X-ray studies and minimal energy conformer calculations, reported previously, enabled definite conclusions about the solution conformations of these alkaloids.
Also the protonation of quinidine in $CDCl_3$ was studied. It was determined that the first protonation occurs on the quinuclidine nitrogen and not on the quinoline nitrogen as was reported by Yanuka et al.[1]

INTRODUCTION

^{15}N-NMR, with its very wide range of chemical shifts, and its sensitivity to all sorts of interactions at the nitrogen atom, can be very useful for the study of alkaloids e.g. in Rauwolfia alkaloids it was possible to determine the nature of the quinolizidine ring fusion [2].
Also in the determination of protonation sites ^{15}N-NMR data are of great importance [3].
In this study some quinoline alkaloids were investigated, with the purpose to obtain some information about the solution conformation of these alkaloids. Further the protonation in $CDCl_3$ was investigated, as, on the basis of a ^{1}H-NMR analysis of some alkaloids and their monoprotonated salts in D_2O and $CDCl_3$, Yanuka et al.[1] concluded that through a change of conformation in the nonpolar solvent the protonation site was on the quinoline nitrogen and not on the quinuclidine nitrogen as in the polar solvent. Although their proof was weak and open to all sorts of criticism, their wrong could best be proven by an investigation of the problem using ^{15}N-NMR.

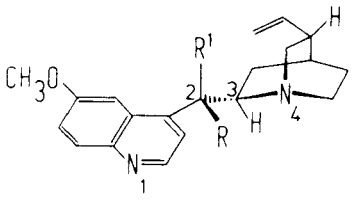
EXPERIMENTAL

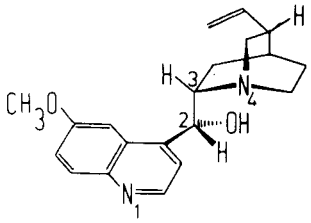
Quinine was obtained as such from a commercial source. Quinidine was prepared from quinidine sulfate. Epi-quinidine was prepared from the hydrochloride. Nitrogen-15 spectra were obtained on a Bruker WM-300 spectrometer equipped with an Aspect-2000 data system and operating at a resonance frequency of 30.3 MHz. Samples were run in 10 mm o.d. tubes in $CDCl_3$, which also served to provide the internal lock. Nitrogen chemical shifts were measured with respect to the

resonance position of a 5 M solution of NH_4NO_3 in 2 M HNO_3 (NH_4^+ 30% enriched) [4,5,6] contained in a 4 mm tube held concentrically within the 10 mm tube. The values are also reported with respect to this standard, which is shielded by -359.0 ppm from nitromethane. Concentrations used were 0.7 M for quinidine and epi-quinidine, and 1.5 M for quinine.
Typical acquisition parameters included a spectral width of 15,000 Hz, an acquisition time of 0.54 s, a flip angle of 30° and a pulse delay of 4 s. In the INEPT experiment an acquisition time of 0.27 s and a pulse delay of 1 s were used.

RESULTS AND DISCUSSION

The ^{15}N chemical shifts of quinidine (1), quinine (2), and epi-quinidine (3) are given in Table 1. The N-1 signal of all three alkaloids appeared as a doublet owing to coupling with the proton on the adjacent carbon. The ^{15}N chemical shifts of quinidine and





1: R = H , R^1 = OH : Quinidine 2: Quinine
3: R = OH, R^1 = H : Epi-quinidine

quinine are almost similar. This can be explained by mirror-image conformations, which is logical, as they would be enantiomers when one neglects the vinyl group located on the outside of the molecule.

TABLE 1

^{15}N Chemical Shifts[a] of the Alkaloids

	N-1	N-4
Quinidine	277.0 d (10)	11.1 s
Quinine	277.0 d (10)	10.6 s
Epi-quinidine	284.7 d (10)	2.5 s

[a] Downfield from external NH_4NO_3 (5M) in HNO_3 (2M) (NH_4^+ 30% enriched).

Also the minimal energy conformer calculations performed by Oleksyn et al.[7] predicted mirror-image conformations for quinidine and quinine. Minima found in these calculations were in accordance with the several X-ray crystallographic studies which have been performed for quinidine[8,9], cinchonine, cinchonidine and epi-quinidine. The crystal structures determined for cinchonine and cinchonidine (structures as quinidine and quinine resp. just lacking the methoxy group) were also mirror-image conformations. No such studies have been reported for quinine. So from the ^{15}N data it can be concluded that quinine has a mirror-image conformation of quinidine as depicted in Fig. 1, in accordance with the above-mentioned literature.

For epi-quinidine a clearly different ^{15}N-NMR spectrum was obtained. An X-ray crystallographic study[10] and the before-mentioned calculations predicted a conformation as for quinidine, placing the hydroxyl in a position relative to N-4 that offers the possibility of hydrogen-bonding. So, the differences in the ^{15}N chemical shifts must be explained by the following

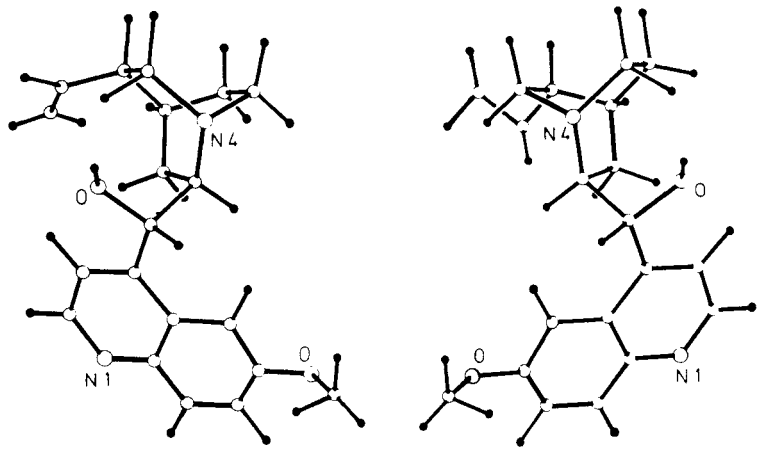


Fig. 1 : Conformation of Quinidine (left) and Quinine (right)

differences: 1) The hydrogen bond and 2) the different position of the hydroxy-group.

For quinidine the protonation in $CDCl_3$ was investigated (Table 2). To observe the first protonation 110 % of an equimolar quantity of trifluoroacetic acid was added. As expected, N-4 was protonated first. The ^{15}N chemical shift could be conveniently determined by means of an INEPT experiment[11], taking advantage of the one-bond ^{15}N-H coupling of 77 Hz. A downfield protonation shift of 10.9 ppm was observed, normal for tertiary amines[12]. After a second addition of trifluoroacetic acid, with the object of protonating N-1, its chemical shift could not be determined using the INEPT experiment. Recording the spectrum in the conventional way revealed a full protonation shift of 94.5 ppm and the absence of any coupling. This must be due to fast proton exchange, indicating the low basicity of this nitrogen. For quinoline, exactly the same protonation shift was determined; this signal did not display any coupling either.

TABLE 2

Protonation Shifts obtained with trifluoroacetic acid[a]

		Chemical shift[b]		Protonation shift
		normal	protonated	
Quinidine	N-1	277.0	182.5	-94.5
	N-4	11.1	22.0	10.9
Quinoline		288.1	193.5	-94.6

[a] For each protonation about 110 % of an equimolar quantity of trifluoroacetic acid was added.

[b] Downfield from external NH_4NO_3 (5M) in HNO_3 (2M). (NH_4^+ 30% enriched).

So, with this experiment it was proved that the quinuclidine nitrogen is, also in $CDCl_3$, first protonated. Also the low basicity of the quinoline nitrogen was demonstrated.

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