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Application of Proton NMR Shift Reagents to the Stereochemical Analysis of Nicotine

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Recently the proton NMR contact shift has received considerable attention.[1-4] In previous papers[5,6] we have discussed the proton paramagnetic shifts of piperidines using nickel and cobalt diacetylacetonate (Ni(AA)$_2$ and Co(AA)$_2$), as well as their application to the stereochemical analysis of some tropane alkaloids. This communication will deal with the application of these paramagnetic shifts to the 220 MHz-NMR-spectrum analysis of nicotine and to the determination of its conformation.

In contrast to the case of the 60 MHz NMR spectrum,[7] this high-frequency NMR technique demonstrated the presence of two triplet signals at δ 3.27 (J=8Hz) and 3.11 (J=8Hz) ppm and a quartet peak at δ 2.34 (J=8Hz) ppm (Fig. 1). These signals can unquestionably be assigned to the methine and methylene protons positioned alpha to the nitrogen in the pyrrolidine ring. In order to assign these signals to particular hydrogens, the contact and pseudocontact shifts of these signals with Co(AA)$_2$, Ni(AA)$_2$, and tris(benzoylacetonato)europium Eu(BA)$_3$ were used effectively. Since the proton magnetic resonance of a particular proton was found to shift from its normal value in proportion to the concentration of the added

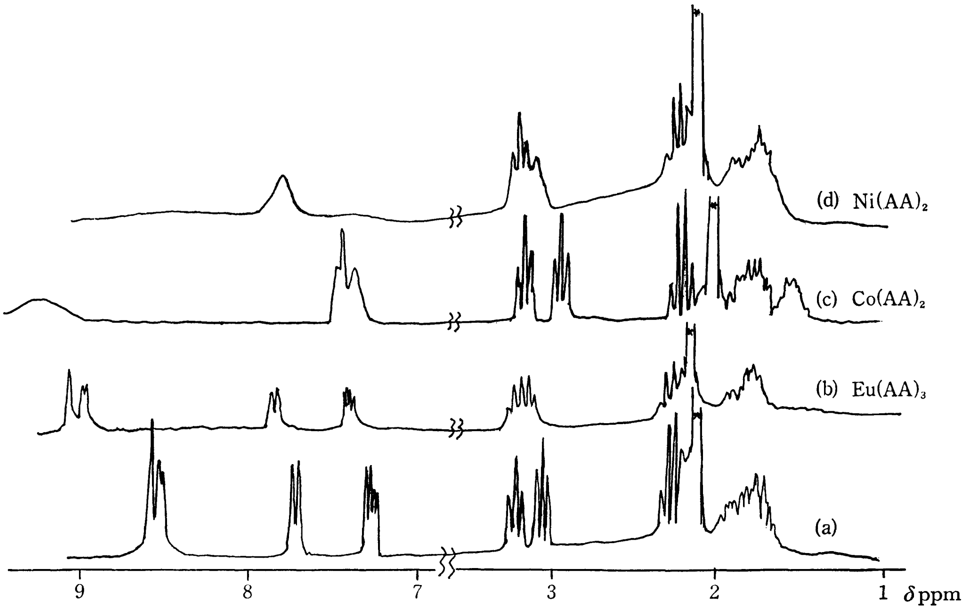

Fig. 1. Proton spectra of nicotine at 220 MHz.
(a) normal diamagentic spectrum in CDCl$_3$ with TMS reference. Same system but with (b) Eu(BA)$_3$, 0.1 mol, (c) Co(AA)$_2$, 0.03 mol, (d) Ni(AA)$_2$, 0.02 mol added.
* N-methyl signal.

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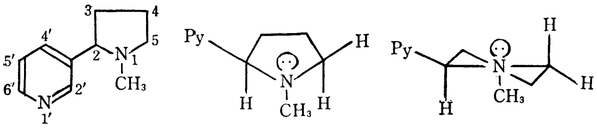
Table 1. Chemical shifts and relative contact shifts[a)] for nicotine coordinated with the metal chelates

(+ and − mean up- and downfield shifts respectively, in CDCl, internal standard TMS at 220 MHz)

	2′	4′	5′	6′	2	5ax	5eq	3	NCH_3
δ ppm	8.53	7.70	8.47	3.11	3.11	2.34	3.27	−1.8[b)]	2.16
$Ni(AA)_2$	−[c)]	−10.0	−[c)]	−[c)]	−5.4	0	0	0	0
$Co(AA)_2$	−10.0	+ 3.5	−1.5	−10.0	+1.8	+0.8	+0.7	+2.6	+1.5
$Eu(BA)_3$	−10.0	− 3.1	−3.1	− 9.1	−1.9	−0.5	−0.5	−1.6	−1.3

a) The observed shifts are normalized to give a value of 10.0 for the largest proton shift.
b) Signals are overlapped one another and the exact chemical shift can not be determined.
c) Line broadening is so great that the exact position is not obvious.



(1)　(2)　(3)

Scheme. 1

metal chelates,[5,8)] we are interested only in the relative shifts for various protons. The results are summarized in Table 1.

From these data the following conclusions were drawn: i) Since the 2, 5′ and 6′-hydrogens were shifted dramatically, the nitrogen lone-pair of pyridine, not that of pyrrolidine, is the binding site of the metal chelates. ii) On the addition of $Ni(AA)_2$ or $Co(AA)_2$, the triplet signal at δ 3.11 ppm shifted downfield or upfield respectively. This behavior is similar to that of the methyl in the β-picoline spectrum;[8)] the signal was, consequently, assigned to 2-hydrogen. iii) On the basis of the coupling features, a triplet signal at δ 3.27 ppm and a quartet at δ 2.34 ppm were analyzed to be quasi-equatorial and -axial protons respectively at C_5 position. iv) As far as energy is concerned, two conformers, an envelope form (**2**) and a half-chair form (**3**), are conceivable for the pyrrolidine ring.[9)] In **2**, the quasi-equatorial and -axial protons are in *cis* and *trans* relationships to the pyridyl group respectively, while in **3** the relationships are the reverse. It is well known that the observed paramagnetic shift using $Co(AA)_2$ is the sum of the isotropic contact shift and the anisotropic pseudocontact shift, which is proportional to the geometric factor, $f=(3\cos^2\theta-1)/r^3$, where r is the distance between the resonating proton and the Co atom and where θ is the angle between the Co–N axis and the $\boldsymbol{r}$ vector.[10)] Since the contact shift with $Ni(AA)_2$ was not observed on the protons attached to the pyrrolidine ring, and since the ratios of the spin densities at the various protons would be the same for the Co(II) and Ni(II) systems,[5)] the upfield shifts of *N*-methyl, C_3, and C_5-protons must be due only to the anisotropic pseudocontact shift caused by the cobalt t_{2g} orbital.[8)] It is also known that, in the case of the rare earth chelates of Eu(III), the observed downfield shifts are probably caused by the predominant pseudocontact term and that, therefore, they depend upon the geometric factor.[10,11)] Assuming the nitrogen-metal length to be 2 Å,[5)] the molecular model of nicotine indicates that the amount of the geometric factor is qualitatively in the order of: the C_3-quasi-axial proton>*N*-methyl protons> C_5-quasi-axial ≈ -equatorial protons in the case of **2**, while it is: the C_3-quasi-axial proton> *N*-methyl ≈ C_5-quasi-axial protons > the C_5-quasi-equatorial proton in the case of **3**. The fact that the observed relative amount of the paramagnetic shift of each proton is in accord with the case of **2** and not of **3** indicates that the conformation of the pyrrolidine ring is in an envelope form.

It is well established that the chemical shift of a proton positioned at the *cis* configuration to the nitrogen lone-pair is in a lower field than that of *trans*.[12)] The fact that the chemical shift of the quasi-equatorial proton (δ 3.27 ppm) is in a lower field than that of the quasi-axial proton (δ 2.34 ppm) is consistent with the case of **2** and supports the aforementioned conclusion.

The above discussion is an example of the usefulness of contact and pseudocontact shifts with $Ni(AA)_2$, $Co(AA)_2$ and $Eu(BA)_3$ in analyzing complex spectra and in solving stereochemical problems. Further applications of these phenomena to alkaloids as well as to natural-product chemistry are now in progress.

Experimental

All the materials used in this study except $Eu(BA)_3$ were commercially available ones. The $Ni(AA)_2$ and $Co(AA)_2$ were dried at 60°C *in vacuo* overnight before use. The $Eu(BA)_3$ was supplied by Dr. T. Suzuki of this department.[13)]

The spectra were observed with a Varian HR-220 spectrometer for $CDCl_3$ solutions containing varying amounts of nicotine and $Co(AA)_2$, Ni(AA), or $Eu(BA)_2$. The proton-resonance shifts were measured relative to the internal TMS. The spectra were recorded after each of the successive additions of a few milligrams of the metal chelates.

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[11)] D. R. Eaton, *ibid.*, **87**, 3097 (1965).

[12)] M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *ibid.*, **86**, 3364 (1964) and references therein.

[13)] We wish to thank Dr. T. Suzuki for his generous supply of samples of $Eu(BA)_3$. For the synthesis of this compound, see S. Y. Tyree, Jr. (ed.), "Inorganic Synthesis," Vol. 9, McGraw-Hill Book Co., New York (1967), p. 37.