37. Nitrogen-NMR Studies on the Protonation of 2-(Aminomethyl)pyridine and Tris[(2-pyridyl)methyl]amine

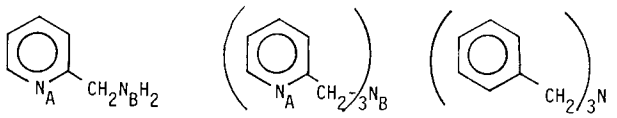
by **Giorgio Anderegg***, **Konstantin Popov**[1]), and **Paul S. Pregosin***

Laboratorium für anorganische Chemie, ETH-Zentrum, Universitätstrasse 6, CH-8092 Zürich

(12.XII.85)

^{14}N- and ^{15}N-NMR spectra have been recorded for 2-(aminomethyl)pyridine (**1**), tris[(2-pyridyl)methyl]amine (**2**), and some of their protonated forms. For **1**, the most basic site is the aliphatic N-atom, whereas for **2** the pyridine N-atoms are more basic, in contrast to what might be expected for a tertiary aliphatic amine.

Introduction. – ^{15}N-NMR (I = ½, natural abundance = 0.36%) is now recognized as a valuable spectroscopic complement in nitrogen chemistry [1]. The constantly increasing ^{15}N-NMR data base [2] combined with theoretical calculations of ^{15}N chemical shifts [3] has helped to develop empirical correlations relating ^{15}N to molecular structure [1] [4].



1 **2** **3**

In the course of earlier measurements [5] on the stability of polyfunctional amine ligands, an apparent inversion in the most basic site of the compounds **1** and **2** was noticed. Compound **1** is thought to be protonated initially at the aliphatic N-atom; whereas for **2**, the pyridine N-atoms are the more basic centers, in contrast to what might be expected for a tertiary aliphatic amine. As there was no immediately obvious explanation for this inversion, we considered it useful to support the stability-constant measurements with nitrogen-NMR data. It is known that protonation of an sp^2 pyridine-type N-atom is accompanied by a relatively large upfield shift in the ^{15}N position of *ca.* 100 ppm [6], whereas protonation of aliphatic amine N-atom gives a much smaller downfield shift of *ca.* 10 ppm [1] [7]. Moreover, the ^{15}N spin-lattice relaxation time, T_1, and nuclear *Overhauser* characteristics of a protonated *vs.* a non-protonated N-atom are sufficiently different as to be of empirical value, with protonated N-atoms often showing large nuclear *Overhauser* enhancements and relatively short T_1's. Consequently, ^{15}N-NMR should be a sufficiently sensitive structural tool from several viewpoints.

Results and Discussion. – The natural abundance ^{15}N{^{1}H}-NMR spectrum of **1** in aqueous solution shows the expected resonances for the sp^2 and sp^3 N-atoms, at δ = 305.3

[1]) Present address: Institute of Physical and Colloidal Chemistry, Moskow Technological University for Food Industry, Moskow, USSR.

and 19.4, respectively. Addition of 1 equiv. of H^+ shifts $\delta(^{15}N)$ for the sp^2 N-atom (henceforth N_A) slightly upfield to $\delta = 294$ and the amine N-atom (henceforth N_B) downfield to $\delta = 28.5$. The magnitude of the latter is consistent with protonation of this center. Addition of a second equiv. of H^+ changes the δ value for protonated N_B only slightly (*ca.* 0.7 ppm), whereas N_A is now found at $\delta = 199.1$, a change of 106.2 ppm from its original position. Clearly, the sequence of protonation is N_B before N_A.

To further substantiate the ^{15}N-NMR experiment, we have measured the ^{14}N-NMR spectrum of the dication (^{14}N has I = 1 with a natural abundance of > 99.6%). Although ^{14}N signals are frequently difficult to detect, due to fast T_1 and T_2 relaxation and the consequent line broadness, quaternarization of an N-site is known [8] to be accompanied by a reduction of the line width. The experimental ^{14}N-NMR spectrum confirms this expectation (see the *Fig.*) and both nitrogen signals are readily observable. The ^{14}N- and ^{15}N-NMR data are in good agreement.

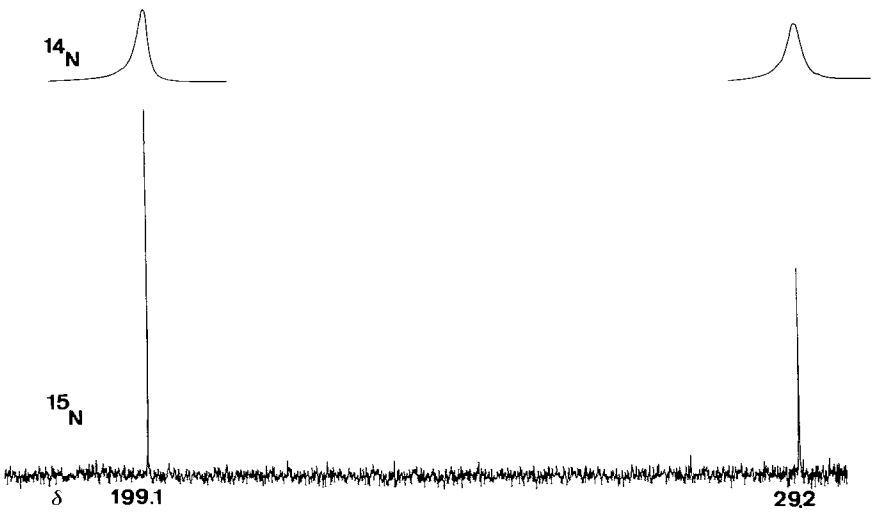


Fig. *^{15}N and ^{14}N* (above) *resonance for* $H_2(\mathbf{1})^{2+}$. The $\Delta\nu_{1/2}$ values for the low- and high-field resonances are 110 and 134 Hz, respectively.

Compound **2** is very sparingly soluble in H_2O; however, it is sufficiently soluble in MeOH for an ^{15}N-NMR measurement. In this solvent, we find N_A at $\delta = 295.3$, but observe no signal for N_B. We assume this is related to the unfavorably long T_1 for the N-atom and, indeed, in none of the subsequent experiments was its resonance observed. In one respect, this inability to locate the N_B absorption represents a loss of information; however, since this failure can only arise when N_B is *not* protonated, there is chemical significance in the negative result. Compound **2** is soluble in an aqueous solution containing 1 equiv. of H^+, and reveals N_A at $\delta = 267.5$. This is a modest highfield shift which we interpret as an average arising from one proton exchanging rapidly over the three N_A sites. Addition of 2 further equiv. of H^+ moves N_A to $\delta = 206.3$, in keeping with complete protonation of all three N-atoms. A saturated solution of **2** in 1M HNO_3 reveals N_A at $\delta = 202.1$, but again no N_B signal. It appears that the trication, arising from protonation

of the N_A sites, is scarcely basic. In the hope of detecting both signals from **2** in 1M HNO_3, an ^{14}N-NMR spectrum of the sample was measured[2]).

Once again, only the signal of the protonated pyridine N-atom is observed. The failure to observe N_B in the ^{14}N-NMR spectrum cannot result from a long T_1, but rather from either a very short $T_2(N_B)$, or chemical phenomena, *e.g.* exchange. To put these observations on N_B in perspective, we have chosen to study the ^{14}N and ^{15}N characteristics of the model compound $(PhCH_2)_3N$ (**3**). The ^{15}N-NMR spectrum of **3** in acetone shows a resonance at $\delta = 57.4$[3]) (Et_3N appears at $\delta = 46.6$ in cyclohexane [2]). The attained S/N ratio suggests a relatively long T_1 for **3**, and indeed, introduction of *ca.* 2×10^{-2} M $Cr(acac)_3$ as relaxation reagent produces a *ca.* six-fold gain in S/N. Interestingly, we were unable to find the ^{14}N resonance of **3** so that it would seem that **3**, like **2**, has a short $T_1(^{14}N)$ but a relatively long $T_1(^{15}N)$.

Table. *^{15}N-NMR Data*[a])

$[H^+]$/[Compound]	**1**		**2**
	N_A	N_B	N_A
0	305.3	19.4	295.3[b])
1	294.0	28.5	267.5
2	199.1	29.2	
3			206.3, 202.1[c])

[a]) Relative to $^{15}NH_3$. [b]) 0.6M MeOH soln. [c]) Sat. soln. in 1M HNO_3.

Despite the experimental difficulties associated with **2** and its protonation, the existing data support the previous observation based on stability constant measurements and protonation constants, *i.e.* that the *tert*-amine N-atom of **2** is considerably less basic than its analog in **1** (see *Experimental*).

The reason for the reduced basicity of N_B in **2** is not completely clear. Possibly, the combined inductive effects of three (2-pyridyl)methyl groups lead to sufficient electron withdrawal such that the basicity of the aliphatic N-atom falls below that of the pyridine N-atoms. ^{1}H-NMR spectroscopy, where inductive effects are relatively important, shows that the CH_2 resonance of **2** at $\delta = 3.85$ is *ca.* 0.3 ppm to *low* field of that for **3** ($\delta = 3.55$). This observation does not prove the inductive-effect hypotheses, but is consistent with this idea. Protonation of the pyridine ring introduces yet another electron-withdrawing influence, with reference to N_B, so that subsequent protonation occurs at the pyridine centers. In any case, compound **2** represents an example of a compound with an aliphatic N-atom whose basicity does not conform to that anticipated for a simple tertiary alkylamine [9].

Experimental. Compound **2** was prepared according to [10]. Compounds **1** and **3** were purchased from *Fluka* and 70% $HClO_4$ was obtained from *Merck*. Protonated **1** was obtained by adding a suitable number of equiv. of 70% $HClO_4$. D_2O was then added such that the protonated species were present at *ca.* 2M concentration.

[2]) T_1 and T_2 for ^{14}N are usually of the order of ms so that a long relaxation time can be excluded; however, this does not exclude the possibility that the signal(s) will be too broad due to very fast relaxation.

[3]) These values were measured relative to CH_3NO_2 and corrected to NH_3 using $\delta(NH_3) = \delta(CH_3NO_2) + 380.2$ [1].

Compound **2** was available as its triply protonated ClO_4 salt (0.6M) and this was treated with 2 or 3 equiv. of KOH (1M) before addition of D_2O. The concentration of these solns. was *ca.* 0.06M.

$^{15}N\{^1H\}$-NMR spectra were measured in natural abundance, with NOE suppression, using a *Bruker WM-250* instrument operating at 25.3 MHz. Chemical shifts are reported relative to external NH_3. The spectra of the derivatives of **1** were measured using a 30 s delay. ^{15}N chemical shifts are considered to be correct to 0.1 ppm.

The pK_a values of the monoprotonated species of **1**, **2**, and **3** are 8.79 [5b], 6.17 [5a] and 5.40, respectively, the latter determined at 25° in glacial AcOH [11].

REFERENCES

[1] G.C. Levy, R.L. Lichter, 'Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy', John Wiley & Sons, New York, 1979.

[2] M. Witanoski, L. Stefaniak, G.A. Webb, in 'Ann. Rep. NMR Spectrosc.', Ed. G.A. Webb, Academic Press, London, 1981, Vol. 11B.

[3] M. Brémond, G.J. Martin, G.A. Webb, D.J. Reynolds, *Org. Magn. Res.* **1984,** *22,* 640; L. Stefaniak, J.D. Roberts, M. Witanoski, G.A. Webb, *ibid.* **1984,** *22,* 201; *ibid.* **1984,** *22,* 209.

[4] T. Axenrod, P.S. Pregosin, G.W.A. Milne, *Tetrahedron Lett.* **1968,** 5293; T. Axenrod, P.S. Pregosin, M.J. Wieder, E.D. Becker, R.B. Bradley, G.W.A. Milne, *J. Am. Chem. Soc.* **1971,** *93,* 6536; P.S. Pregosin, E.W. Randall, A.I. White, *J. Chem. Soc., Chem. Commun.* **1971,** 1602; P.S. Pregosin, E.W. Randall, A.I. White, *J. Chem. Soc., Perkin Trans. 2* **1972,** 1; H. van der Pod, G. van Koten, D.M. Grove, P.S. Pregosin, K.A. Ostoja Starzewski, *Helv. Chim. Acta* **1981,** *64,* 1174; H. Motschi, P.S. Pregosin, L.M. Venanzi, *ibid.* **1979,** *62,* 667.

[5] G. Anderegg, E. Hubmann, N.G. Podder, F. Wenk, *Helv. Chim. Acta* **1977,** *60,* 124; G. Anderegg, *ibid.* **1971,** *54,* 509.

[6] G.C. Levy, C.E. Holloway, R.C. Rosanske, J.M. Hewitt, C.H. Bradley, *Org. Magn. Res.* **1976,** *8,* 643.

[7] V.N. Solkan, V.F. Bystrov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1975,** *23,* 95.

[8] J.P. Kintzinger, J.M. Lehn, *Helv. Chim. Acta* **1975,** *58,* 905.

[9] D.D. Perrin, B. Dempsey, E.P. Serjeant, 'pK_A Prediction for Organic Acids and Bases', Chapman and Hall, London, 1981.

[10] G.G. Anderegg, F. Wenk, *Helv. Chim. Acta* **1967,** *50,* 2330.

[11] S. Bruckenstein, I.M. Kolthoff, *J. Am. Chem. Soc.* **1956,** *78,* 2974.