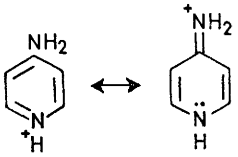
INDO Theoretical Studies of 4-Aminopyridine and Protonated 4-Aminopyridine

By **Charles U. Pittman**, jun.,* **Onallah M. Attallah**, and **Lowell D. Kispert**,* College of Arts and Sciences, University of Alabama, University, Alabama 35486

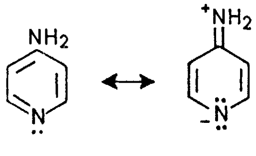
Geometry optimized INDO calculations have been performed on 4-aminopyridine (2) and protonated 4-aminopyridine (1) in order to compare their optimized geometries, π-bond orders, C(4)–NH_2 rotational barriers, charge densities, and π-electron distributions. It had previously been shown that 4-aminopyridine falls far off a linear correlation of ΔG° and ΔS° for the protonation equilibria of a series of 4-substituted pyridines. The calculations support the concept that a very high rotational barrier in (1) could cause this deviation. The contribution of a quinonoid resonance hybrid (1b) to (1) was greater than (2b) to (2). The π-cloud in (1) is polarized toward the ring nitrogen, relative to (2), and the C(4)–NH_2 rotational barrier in (1) (27.3 kcal mol^{-1}) is larger than in (2) (14.7 kcal mol^{-1}).

THE basicity of substituted pyridines has been extensively investigated.[1-15] 4-Aminopyridine appears to be especially interesting in this work. Early studies, summarized by Jaffé and Jones,[16] indicated that the solution basicities were well correlated by σ-values rather than by σ^+-values. This was surprising because it was anticipated that the positive charge in protonated 4-aminopyridine would be extensively delocalized into the less electronegative amino-nitrogen thus requiring the intervention of σ^+ constants. Jaffé[16] speculated that no great change in the contribution of the quinonoid structures (1b) and (2b) took place going from conjugate acid to the free base.



a b

(1)

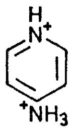


a b

(2)

Taft *et. al.*[17] reported that the gas-phase basicity of pyridine was greater than that of ammonia and similar to that of $(CH_3)_2NH$. This observation suggests that the stability afforded the pyridinium ion (1) by differential polarization of the π molecular orbital, between gas and aqueous phases, and other solvation effects were as large or larger than the hybridization effect. CNDO/2 Calculations of the relative proton affinities of 4-substituted pyridines were made using conventional geometries and bond distances.[17] They showed a linear free energy relationship, with a slope of *ca.* 3.6, existed between the calculated gas-phase proton affinities and the experimental free energies of aqueous ionization. However, in those studies, *calculations* on (1) or (2) *were not* performed. Unlike Taft, Ramsey and Walker[18] concluded that a separate order of gas and solution phase substituent effects in the pyridine series was not necessary. This was based on a linear correlation of aqueous pK_a values with ionization potentials of the π_s orbital determined by photoelectron spectroscopy and assigned from CNDO/2 calculations.

A careful calorimetric study by Liotta *et al.*[19] determined the ΔH°_i and ΔS°_i for the ionization of substituted pyridinium ions. Of the 12 compounds studied, only 4-aminopyridine deviated from the $\Delta\bar{G}^\circ_i$ *versus* $\Delta\bar{S}$ correlation clearly exhibited by the other substituents. Since prior studies unequivocally showed that monoprotonation of 4-aminopyridine occurs only on the ring nitrogen[20,21] and that the diprotonated species, (3) can be formed only in strongly acidic solutions,[22] tautomeric equilibrium in (1) cannot be invoked to account for this



(3)

---

[1] A. Fischer, W. J. Galloway, and J. Vaughn, *J. Chem. Soc.*, 1964, 3591.

[2] A. Albert, *Phys. Methods Heterocylic Chem.*, 1963, **1**, 1; 1971, **4**, 1.

[3] J. M. Essery and K. Schofield, *J. Chem. Soc.*, 1961, 3939.

[4] N. Ikebawa, Y. Sata, and T. Maeda, *Chem. Pharm. Bull. Japan*, 1954, **2**, 205.

[5] J. M. Essery and K. Schofield, *J. Chem. Soc.*, 1961, 3939.

[6] M. R. Chakrabarty, C. S. Handloser, and M. W. Mosher, *J.C.S. Perkin II*, 1973, 939.

[7] C. L. Liotta, E. M. Perdue, and H. P. Hopkins, jun., *J. Amer. Chem. Soc.*, 1973, **95**, 2439.

[8] J. J. Christensen, D. E. Smith, M. D. Slade, and R. M. Izatt, *Thermochim. Acta*, 1972, **5**, 35.

[9] R. G. Bates and H. B. Hetzeer, *J. Res. Nat. Bur. Stand., Sect. A*, 1960, **64**, 427.

[10] L. Sacconi, P. Paoletti, and M. Ciampolini, *J. Amer. Chem. Soc.*, 1960, **82**, 3831.

[11] R. A. Jones and A. R. Katritzky, *J. Chem. Soc.*, 1959, 7317.

[12] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1959, 2384.

[13] H. H. Jaffé and G. O. Doak, *J. Amer. Chem. Soc.*, 1955, **77**, 4441.

[14] H. C. Brown and S. R. Mihm, *J. Amer. Chem. Soc.*, 1955, **77**, 1723; H. C. Brown and D. H. McDaniel, *ibid.*, p. 3752.

[15] R. T. Evans and H. C. Brown, *J. Org. Chem.*, 1962, **27**, 3127.

[16] H. H. Jaffé and H. L. Jones, *Adv. Heterocyclic Chem.*, 1964, **3**, 224.

[17] M. Taagepera, W. G. Henderson, T. C. Brownlee, J. L. Beauchamp, D. Holtz, and R. W. Taft, *J. Amer. Chem. Soc.*, 1972, **94**, 1369.

[18] B. G. Ramsey and F. A. Walker, *J. Amer. Chem. Soc.*, 1974, **96**, 3314.

[19] C. L. Liotta, E. M. Perdue, and H. P. Hopkins, *J. Amer. Chem. Soc.*, 1974, **96**, 7308.

[20] A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 1948, 2240.

[21] S. J. Angyal and C. L. Angyal, *J. Chem. Soc.*, 1952, 1461.

[22] M. L. Bender and Y. L. Chow, *J. Amer. Chem. Soc.*, 1959, **81**, 3929.

phenomenon. It was suggested that the unusual stability of (1) was due to substantial stabilization by (1b).[19] The entropy of ionization of (1) was 6 cal K^{-1} mol^{-1} more positive than predicted by the $\Delta\bar{G}^\circ_i$ *versus* $\Delta\bar{S}^\circ_i$ plot which agrees with a greater amino-group rotational barrier in (1) than in (2) and thus a substantial contribution by (1b). However, solvation effects clouded this interpretation.

In view of the interest in the contributions of hybrids (1b) and (2b) [to (1) and (2), respectively] and the lack of agreement in the interpretation of gas-phase basicity data,[17,18] we performed a series of SCF–MO calculations, in the INDO approximation,[23,24] on both (1) and (2). Their geometries were completely optimized with respect to energy in contrast to previous CNDO/2 calculations.[17,18] It has frequently been noted that (1b) would be expected to make a larger contribution to (1) than (2b) does in (2) based on simple resonance considerations.

RESULTS AND DISCUSSION

MO Calculations, at the INDO level, were performed using the QCPE No. 141 CINDO program,[25] modified for use on a Univac 1110 computer. Each bond length and angle was successively optimized against energy (brute force method) for two complete iterations, at which point the structure was within 0.020 kcal mol^{-1} of the hypersurface minimum. We have successfully used this method previously to study charged systems.[26–31]

The importance of optimizing geometry (against using assumed geometries) has recently been pointed out with increasing frequency.[25–31] For example, e.s.r. hyperfine couplings of the benzyl radical, incorrectly predicted using assumed geometries,[32] were correctly predicted using a geometry closer to the optimum (INDO).[33] Compared to an assumed geometry of (2), it was found that the optimized geometry was 4.53 kcal mol^{-1} more stable and exhibited a distinct quinonoid deformation (Figure 1). Similarly, using (1), already partially optimized, complete optimization resulted in a 10.2 kcal mol^{-1} stabilization.

In order to evaluate the relative contribution of hybrid (1b) to (1) compared with hybrid (2b) to (2), the following calculated quantities of (1) and (2) were compared: (1) optimized geometries, (2) π-bond orders, (3) C(4)–NH_2 rotational barriers, (4) charge distributions, and (5) π-orbital electron distributions. These results are summarized in Figures 1—4.

A greater quinonoid deformation exists in the calculated optimized geometry of (1). Thus the C(2)–C(3) and C(4)–NH_2 bond lengths are shorter in (1) while the C(3)–C(4) length is greater. These differences are quite pronounced (see Figure 1). Furthermore, the C(6)–N(1)–C(2) and C(3)–C(4)–C(5) angles in (1) are smaller, while the N(1)–C(2)–C(3) and C(2)–C(3)–C(4) angles are greater. This is in agreement with a greater contribution of (1b) to (1) than of (2b) to (2). The π-bond orders provide further evidence for this conclusion (see Figure 2). The C(4)–NH_2 and C(2)–C(3) π-bond orders in (1) are larger than those of (2), while the N(1)–C(2), and C(3)–C(4) π-bond orders are smaller. Again, the magnitude of these differences is substantial.

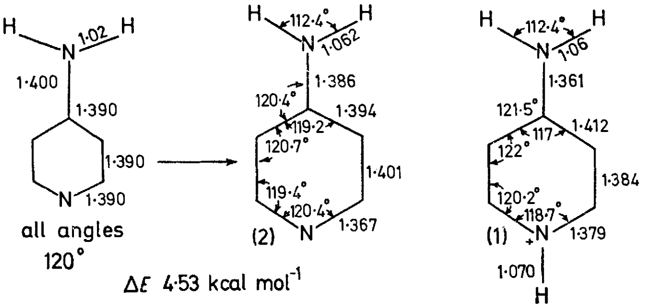


FIGURE 1 Optimized calculated (INDO) geometries of protonated 4-aminopyridine (1) and 4-aminopyridine (2)

Of particular interest is the C(4)–NH_2 bond's rotational barrier. It is predicted to be 27.3 for (1) against only 14.7 kcal mol^{-1} in (2). The difference (12.6 kcal mol^{-1}) is large. Even if the calculated barriers are in error, there is little doubt that a large difference between (1) and (2) should be expected.

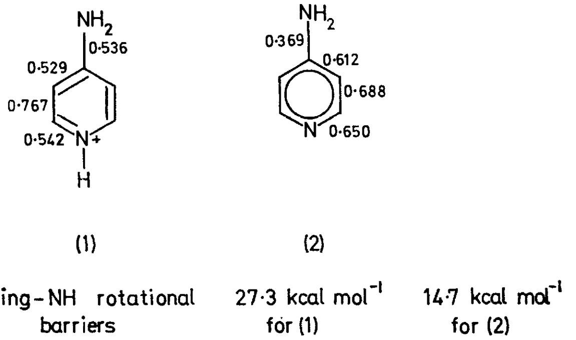


FIGURE 2 Calculated (INDO) π-bond orders and amino-group rotational barriers in (1) and (2)

If the barriers were actually as large as those

---

[23] J. A. Pople, D. L. Beveridge, and P. A. Dobosh, *J. Chem. Phys.*, 1967, **47**, 2026.

[24] J. A. Pople and D. L. Beveridge, 'Approximate Molecular Orbital Theory,' McGraw-Hill, New York, 1970.

[25] J. A. Pople, D. L. Beveridge, and P. A. Dobosh, *J. Chem. Phys.*, 1967, **47**, 2026.

[26] L. D. Kispert, C. Engelman, C. Dyas, and C. U. Pittman, jun., *J. Amer. Chem. Soc.*, 1971, **93**, 6948.

[27] L. D. Kispert, C. U. Pittman, jun., D. L. Allison, T. B. Patterson, jun., C. W. Gilbert, jun., C. F. Hains, and J. Prather, *J. Amer. Chem. Soc.*, 1972, **94**, 5979.

[28] C. U. Pittman, jun., T. B. Patterson, jun., and L. D. Kispert, *J. Org. Chem.*, 1973, **39**, 471.

[29] C. U. Pittman, jun., L. D. Kispert, and T. B. Patterson, jun., *J. Phys. Chem.*, 1973, **77**, 494.

[30] C. U. Pittman, jun., A. Kress, and L. D. Kispert, *J. Org. Chem.*, 1974, **39**, 378.

[31] C. U. Pittman, jun., A. Kress, T. B. Patterson, P. Walton, and L. D. Kispert, *J. Org. Chem.*, 1974, **39**, 373.

[32] J. A. Pople and D. L. Beveridge, *J. Chem. Phys.*, 1968, **49**, 4725.

[33] D. L. Beveridge and E. Guth, *J. Chem. Phys.*, 1971, **55**, 458.

calculated, there would not be significant internal rotation in either (1) or (2). However, if the large difference in the barriers is accepted and significant rotation in (2) was occurring, then the behaviour of the equilibrium (1) $\rightleftharpoons$ (2) in the $\Delta G^\circ{}_i$ *versus* $\Delta S^\circ{}_i$ correlation could be partially accounted for.

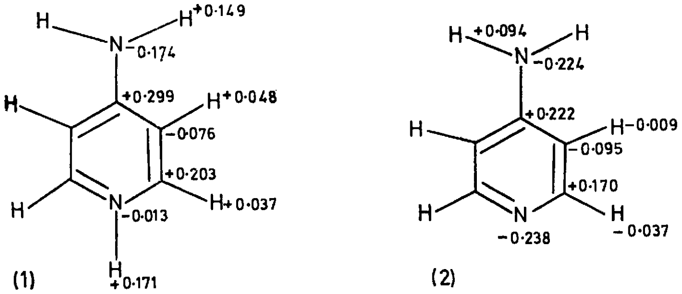


FIGURE 3 Calculated (INDO) charge distributions in (1) and (2)

The total charge distribution in (1) and (2) (Figure 3) again supports a greater contribution of (1b) relative to (2b). In particular, the electron density on the amino nitrogen is greater in 2. Since the total charge distribution is the net effect of both π- and σ-electrons, the relative contributions of (1b) and (2b) are more clearly examined by studying the π-electron distribution (Figure 4). Two features stand out. First, the π-electron density at the amino nitrogen is less in (1) (1.75) than in (2) (1.87). Thus, more π-electron density has been removed from the amino-nitrogen in (1) [*i.e.* (1b) is proportionately more important than (2b)]. This donation of π-electron density should increase the density on the ring nitrogen in (1) more than in (2). This was found [$q_{pz} = 1.50$ for N(1) in (1) *versus* 1.15 in (2)]. Thus, protonation at the ring nitrogen results in a distinct polarization of the π-electrons towards N(1).

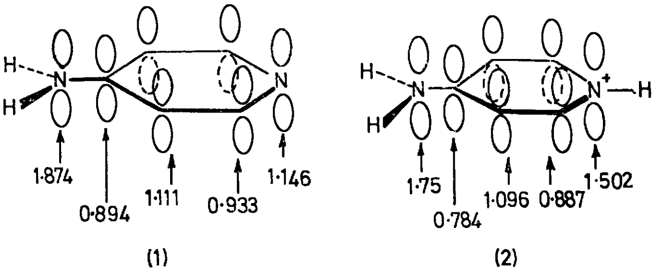


FIGURE 4 Calculated (INDO) electron distribution in the π-orbitals of (1) and (2)

All features of the calculations support a substantially greater contribution of (1b) to (1) than of (2b) to (2). Thus, Jaffé's speculation,[16] that no marked change existed in the contribution of (1b) to the conjugate acid *versus* (2b) in the free base, appears invalid. The large (27.3 kcal mol^{-1}) C(4)–NH_2 rotational barrier in (1), and its value relative to that in (2) (14.7 kcal mol^{-1}), provide strong support for Liotta's [19] suggestion that 4-aminopyridine's large deviation from the $\Delta \bar{G}^\circ{}_i$ *versus* $\Delta \bar{S}^\circ{}_i$ correlation is due to substantial stabilization of (1) by (1b). This causes the C(4)–NH_2 rotational barrier in (1) to be significantly larger than in (2). Although our calculations do not take solvation into account, it is difficult to envisage solvation causing a large relative change in the C(4)–NH_2 rotational barriers of (1) and (2). However, solvation effects may be operating in other ways to influence the $\Delta \bar{G}^\circ{}_i$ *versus* $\Delta \bar{S}^\circ{}_i$ correlation, and these INDO studies are not a justification for neglecting solvation effects.

[5/696 *Received*, 14*th April*, 1975]