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Substituent Effect on the Gas Phase Basicity of Pyridine N-Oxide

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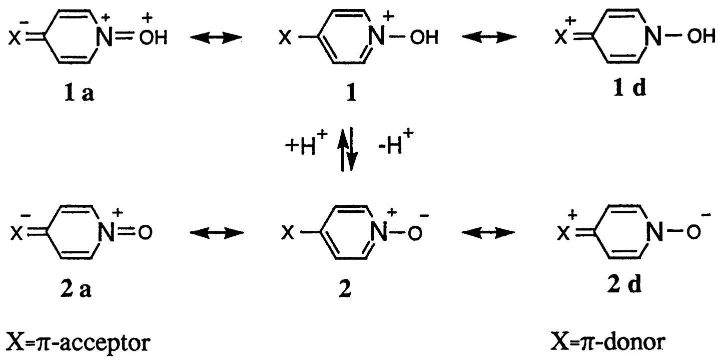
Gas phase basicities of pyridine N-oxides were determined by means of a pulsed ICR spectrometer. It has been shown that the resonance demand for π-acceptors is intrinsically greater in pyridine N-oxide than in pyridine and that the attenuation of substituent effect owing to solvation stabilization is more significant in the former system.

There is continued interest in the interpretation of the substituent effects on reactivity of heterocyclic aromatic compounds.[1-3] We recently analyzed substituent effects on basicities of pyridine[4] and pyridine N-oxide[5] in aqueous solution by means of the LArSR Eq.[6] Results of the LArSR analysis indicate that the contribution of resonance

$$\Delta \mathrm{p}K_a \text{ (pyridine)} = 6.27(\sigma^{\circ} + 0.20\Delta\bar{\sigma}_R^{+} - 0.48\Delta\bar{\sigma}_R^{-}) \qquad (1)$$

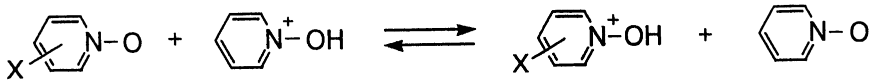
$$\Delta \mathrm{p}K_a \text{ (pyridine N-oxide)} = 2.60(\sigma^{\circ} + 0.59\Delta\bar{\sigma}_R^{+} + 0.22\Delta\bar{\sigma}_R^{-}) \qquad (2)$$

effect relative to that of field/inductive effect is exalted in the pyridine N-oxide system compared with that in the pyridine system while the ρ value is significantly smaller in the former system. The enhanced resonance effect for the basicities of pyridine N-oxides was interpreted in terms of the amphoteric character of the N-O group which interacts efficiently in both directions with π-donors and π-acceptors.[2,5]



Recently it has been found that pyridine N-oxide has essentially the same basicity as pyridine in the gas phase while aqueous solution basicity of pyridine N-oxide is lower than the latter,[7] suggesting that there is a significant difference in solvent effects between pyridine and pyridine N-oxide basicities. This has prompted us to examine the basicities of pyridine N-oxides in the gas phase in order to clarify whether its unique substituent effect behavior inheres in the molecular structure.

The gas phase basicities (GB) of pyridine N-oxides have been determined by measuring equilibrium constants of proton transfer equilibria (3) with a homemade pulsed ion cyclotron resonance (ICR) spectrometer as described previously.[8] Relative gas phase basicities of pyridine N-oxides at 343 K are summarized in Table 1 together with the corresponding pyridines.[3] Unfortunately we could not determine basicities of π-donor substituted pyridine N-oxides because of experimental difficulties.



(3)

Table 1. Relative Gas Phase Basicities of Pyridine N-Oxides and Pyridines

Subst.	$-\Delta$GB/kcal mol^{-1} a) Pyridine N-oxide	 Pyridine$^{b)}$
4-NO_2	13.3	12.6
4-CN	12.0	11.1
3-CN	11.0	12.0
3-F	6.1	7.0
3-Cl	5.6	6.2
3-$COCH_3$	3.0	3.9
3-Me	-2.3	-3.0
H	0.0 (-17.3)$^{c)}$	0.0 (-17.6)$^{c)}$

a) 1 cal = 4.184 J. b) Ref. 3. c) ΔG^o for $NH_4^+ + B \rightleftharpoons BH^+ + NH_3$.

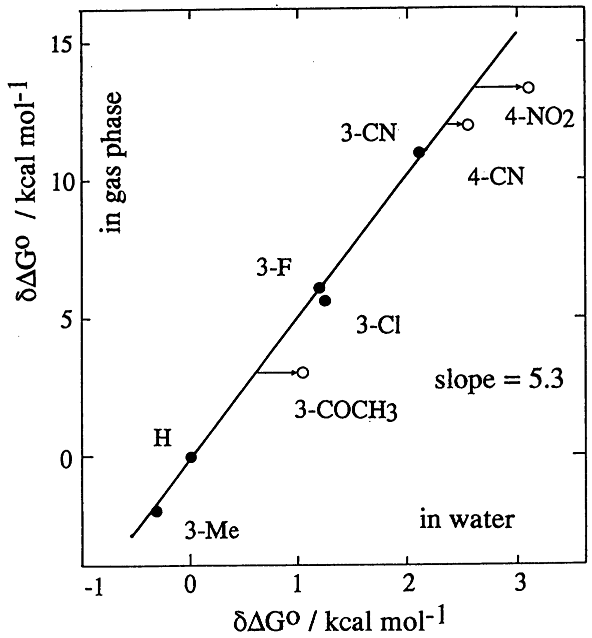


Fig. 1. Gas phase versus aqueous solution basicities for pyridine N-oxides.

In Fig. 1 are plotted the relative gas phase basicities versus aqueous solution basicities for pyridine N-oxides. Although there is not a good linear free energy relationship as a whole, a limited linear correlation is obtained for the 3-substituents except the 3-acetyl group.

$$\delta \Delta G^o_{(g)} = 5.3\delta \Delta G^o_{(aq)} - 0.4 \qquad (R=0.997,\ SD=\pm 0.5\ \text{kcal mol}^{-1}) \qquad (4)$$

The aqueous solvent attenuation factor of 5.3 is larger than that for pyridine basicities.[9] This may be attributed to the large solvation of the neutral pyridine

N-oxide which has the highly polarized N-O group. The deviation of the 3-acetyl group to the right of the regression line reveals the enhanced electron-withdrawing effect in aqueous solution. This may be explained by the strong hydrogen-bonding interaction of the substituent with aqueous solvent because a similar deviation was observed for the pyridine basicity.3) The 4-nitro group also shows a significant deviation to the right but this is not in line with the observation on the pyridine basicity. Taft et al.9,10) found similar deviations of strong para π-acceptors for the phenol acidities, and pointed out that the resonance effect of π-acceptors is enhanced in the electron-rich system owing to solvent effects, the specific substituent solvation assisted resonance effect (SSSAR effect). The present result may be the case because pyridine N-oxide is isoelectronic to phenoxide. A small deviation of the CN group in Fig. 1 also seems to be consistent with a similar result of the phenol acidities.9,10) The exalted resonance contribution to aqueous solution basicities of pyridine N-oxides may be caused in part by the SSSAR effect. Accordingly, it must be quite instructive to compare gas phase substituent effects between pyridine N-oxide and pyridine systems.

Figure 2 illustrates the plot of the gas phase basicities of pyridine N-oxides versus those of pyridines. It is evident that there exists an excellent linear relationship when substituents are limited to 3-substituents including the 3-acetyl group. The 4-nitro and 4-cyano groups show substantially upward deviations from the regression line for 3-substituents, indicating clearly that the resonance contribution of π-acceptors to the pyridine N-oxide basicities is intrinsically greater than that to the pyridine basicities. Furthermore, we infer that the exalted resonance contribution of π-donors in aqueous solution also reflects intrinsic nature of this system because there is no reason to think otherwise. Even though π-donor substituents are modified by solvation, this cannot result in the exaltation of resonance contribution to the pyridine N-oxide basicities. Consequently, the substituent effect on the basicity of pyridine N-oxide is characterized by the exalted resonance demands for π-acceptors and

$$\Delta GB_{(\text{pyridine N-oxide})} = 0.89\Delta GB_{(\text{pyridine})} + 0.1 \quad (R=0.999,\ SD=\pm 0.2\ \text{kcal mol}^{-1}) \qquad (5)$$

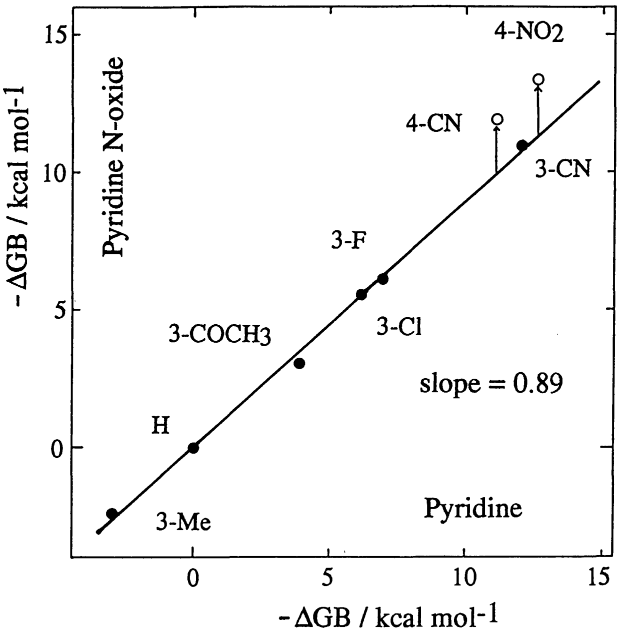


Fig. 2. Relationship of ΔGB of pyridine N-oxides versus corresponding pyridines.

π-donors relative to those of pyridine, being consistent with the LArSR analysis. This may be attributed to the unique functionality of the polarized N-O group. A large charge separation of the N-O group renders the resonance effect of π-acceptors very efficient in the neutral molecule (1a). This is responsible for the enhanced resonance demand for π-acceptors of pyridine N-oxide in reference to that of pyridine which has no resonance contribution like **2a**. This situation is the same as that for the σ^- in reference to σ^o in the benzene system. On the other hand, the resonance effect of π-donors becomes efficient in the conjugate acid (1d), resulting in exalted resonance demand for π-donors. Thus, the LArSR description for the substituent effect on the basicity of pyridine N-oxide illustrates properly its unique substituent effect behavior. Dual resonance parameter for π-donors and π-acceptors is an essential requirement for general description of the substituent effect on the reactivity of N-heteroaromatic compounds in the analogous way to that in benzene system, suggesting that the transmission mechanism of resonance effect of 4-substituent within N-heteroaromatic framework is also interpreted in a similar way to that in the benzene framework.

Finally, it should be noted that the slope of 0.89 shown in Fig. 2 indicates comparable response of the gas phase basicity to the substituent inductive/field effect in both systems while the corresponding ratio for aqueous solution basicities is only 0.41.4) The significantly reduced response of the pyridine N-oxide basicity as well as its low basicity in aqueous solution is due entirely to solvent effects, probably arising from the large substituent effect for solvation on the polarized N-O bond of the neutral molecule.

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