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Protolytic Kinetics of Some Pyridine Derivatives in Non-buffered Aqueous Solution

Isao Ando, Kikujiro Ujimoto, and Hirondo Kurihara*
Department of Chemistry, Faculty of Science, Fukuoka University,
Nanakuma 11, Nishi-ku, Fukuoka 814-01

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The deprotonation rates of the conjugate acids of 2,2′-bipyridine and pyridine, and the protonation rates of 2-aminopyridine and 4-aminopyridine were measured in non-buffered aqueous solution by means of a stopped-flow pH jump method. These pyridine derivatives showed quite slow protolytic behavior, similar to that of 1,10-phenanthroline and cyclopentadienes: the deprotonation rate constants of conjugate acids of 2,2′-bipyridine and pyridine are $(4.8\pm0.7)\times10^{-1}$ and $(6.0\pm2.2)\times10^{-2}\ \mathrm{s}^{-1}$, respectively. The deprotonation rates of barbituric acid and acetylcyclopentadiene as authentic samples were also measured. Their deprotonation rate constants are in good agreement with the literature values, this demonstrates the validity and the applicability of the stopped-flow pH jump method. This method is superior to the NMR method for the determination of the protontransfer rates of azaaromatic compounds.

It is well known that a proton transfer plays an important role in the reactions in aqueous solution such as complex formation, acid and base catalyses, and enzymatic reaction. In order to clarify the reaction mechanism in aqueous solution, it is necessary to evaluate accurately the contribution of the proton transfer process involved in the reaction. So far the proton transfer reactions of a wide variety of compounds have been kinetically studied by many investigators.[1–13)] It was reported that the proton transfer reactions of nitrogen acids and oxygen acids are very fast and their protonation reactions are diffusion-controlled, whereas carbon acids and β-diketones undergo quite slow protolytic reactions.

Previously, we examined the proton transfer reactions of 1,10-phenanthroline, 2-aminopyridine, and 3-aminopyridine by means of a stopped-flow pH jump method, and found that the conjugate acids of these azaaromatic compounds undergo slow deprotonation reactions.[14)] So far as we know, these are the first nitrogen acids displaying a slow deprotonation reaction. In order to further investigate the proton transfer reaction of nitrogen acids, in this study the proton transfer rates of 2,2′-bipyridine, pyridine, 2-aminopyridine, and 4-aminopyridine were measured in non-buffered aqueous solution, by means of a stopped-flow pH jump method. The reliability of this method for determining proton transfer rates was also tested by the use of authentic samples with known rate constants.

Experimental

Materials. 2,2′-Bipyridine (bpy), pyridine (py), and 2-aminopyridine (2-ampy) were purchased from Wako Pure Chemical Industries, Ltd., and 4-aminopyridine (4-ampy) and barbituric acid from Nakarai Chemicals, Ltd. Sodium acetylcyclopentadienide (Na-accp) was synthesized from cyclopentadiene according to the method described in the literature[15)] and stored under an atmosphere of nitrogen. All other chemicals were of guaranteed grade and used without further purification.

The stock solution of each compound was prepared by dissolving a weighed amount of it in deionized, distilled water. The solution of Na-accp was freshly prepared before each measurement.

pK_a Measurements. pK_a values of the conjugate acids of py, 4-ampy, and accp were determined spectrophotometrically by the use of a JASCO Uvidec-2 digital spectrophotometer equipped with a water-jacketed cell holder, as described in the previous paper.[14)] The measurements were carried out at 25 °C in the cases of py and 4-ampy and at 30 °C in the case of accp. The ionic strengths of py and 4-ampy solutions were adjusted to $0.20\ \mathrm{mol\ dm^{-3}}$ and that of accp to $0.50\ \mathrm{mol\ dm^{-3}}$ with sodium chloride. The wavelengths employed to determine the concentration ratios of the deprotonated to the protonated species in the sample solutions at various pH values were 256 nm for py, 263 nm for 4-ampy, and 314 nm for accp. The absorbance of accp solution at the time immediately after preparation was used in order to rule out any effects due to decomposition.

Kinetic Measurements. The rates of deprotonation and protonation reactions were measured by the use of a Union RA-1300 stopped-flow spectrophotometer by the following pH jump method. For measuring the deprotonation rate, the pH of a sample solution was adjusted with hydrochloric acid or perchloric acid to values lower than pK_a value of the conjugate acid of the sample. For determining the protonation rate, the pH of the solution was adjusted with sodium hydroxide solution to values higher than the pK_a value. As a perturbing solution, which causes a perturbation of the acid dissociation equilibrium of the sample solution owing to a pH jump up or down by mixing, we used a sodium hydroxide solution or hydrochloric acid at the concentration appropriate for pH jumps smaller than about one pH unit. The ionic strengths of the solutions were adjusted to $0.20\ \mathrm{mol\ dm^{-3}}$ with sodium chloride or sodium perchlorate.

Equal volumes of the sample solution and the perturbing solution were mixed rapidly by a pressure drive device. The changes in absorbances of the mixture were followed at the wavelengths of 300, 256, 302, 263, 257, and 314 nm for bpy, py, 2-ampy, 4-ampy, barbituric acid, and accp, respectively, and were stored in a high speed memory unit and displayed on an X-Y recorder as a function of time. The kinetic measurements using basic solutions were carried out under an atmosphere of purified nitrogen.

Each rate constant for deprotonation and protonation reactions was obtained from fifteen or twenty kinetic runs. The calculation of rate constants was performed by the use of a Hewlett-Packard HP9825A/S desktop computer according to the method reported previously.[14)]

The deprotonation rates of barbituric acid and accp were also measured in non-buffered systems under the same experimental conditions as in the literature.[7,21]

Results and Discussion

Buffers used to keep the pH of a system constant after pH jumping occasionally accelerate the rate of proton transfer in a striking manner. Therefore, the application of the stopped-flow pH jump technique to rate determinations in buffered solutions is rather limited. Recently, we have shown that in non-buffered systems the stopped-flow pH jump method is applicable for the determination of the rate constants for the proton transfer reactions of weak acids.[14] Thus, we utilized the same method for measuring the proton transfer rates of py, bpy, 2-ampy, and 4-ampy in this investigation.

The spectra of the protonated and the deprotonated species of the present azaaromatic compounds were essentially the same as those in the literature.[16–20] Figure 1 shows a typical example of the spectral change of bpy caused by pH jumping, measured by a rapid scanning technique. The comparison between the spectra of the protonated and the deprotonated species revealed that the proton transfer process can be followed spectrophotometrically by the pH jump method.

As in the case of the previous study,[14] the apparent first-order rate constants observed for deprotonation reactions of the present samples, k_{dpo}, were dependent on hydroxide ion concentration, and the apparent second-order rate constants observed for protonation reactions, k_{po}, were dependent on hydrogen ion concentration. This indicates that the proton transfers of the present compounds also proceed in the following reaction scheme:[14]

$$\mathrm{HL^+} \underset{k_{\mathrm{p}}}{\overset{k_{\mathrm{dp}}}{\rightleftharpoons}} \mathrm{L} + \mathrm{H^+}, \tag{1}$$

$$\mathrm{HL^+} + \mathrm{OH^-} \underset{k_{\mathrm{H_2O}}}{\overset{k_{\mathrm{OH}}}{\rightleftharpoons}} \mathrm{L} + \mathrm{H_2O}, \tag{2}$$

where $\mathrm{HL^+}$ and L are the protonated and the deprotonated species of the sample. The k_{dp} and k_{p} denote the rate constants for the deprotonation of $\mathrm{HL^+}$ and for the protonation of L, respectively, and k_{OH} and $k_{\mathrm{H_2O}}$ those for the protolysis of $\mathrm{HL^+}$ with $\mathrm{OH^-}$ and for the hydrolysis of L, respectively.

Since k_{dpo} and k_{po} are defined as

$$-\mathrm{d}[\mathrm{HL^+}]/\mathrm{d}t = k_{\mathrm{dpo}}[\mathrm{HL^+}] - k_{\mathrm{po}}[\mathrm{L}][\mathrm{H^+}], \tag{3}$$

their values at reaction time zero, $(k_{\mathrm{dpo}})_0$ and $(k_{\mathrm{po}})_0$, can be expressed as functions of $[\mathrm{H^+}]_0$ and $[\mathrm{OH^-}]_0$ in the following equation:

$$(k_{\mathrm{dpo}})_0 = k_{\mathrm{dp}} + k_{\mathrm{OH}}[\mathrm{OH^-}]_0, \tag{4}$$

$$(k_{\mathrm{po}})_0 = k_{\mathrm{p}} + k_{\mathrm{H_2O}}([\mathrm{H_2O}]/[\mathrm{H^+}]_0), \tag{5}$$

where $[\mathrm{H^+}]_0$ and $[\mathrm{OH^-}]_0$ denote the concentrations of hydrogen and hydroxide ions at reaction time zero in the mixture of the sample and the perturbing solutions. For obtaining k_{dpo}, k_{po}, $[\mathrm{H^+}]$ and $[\mathrm{OH^-}]$ at any reaction time, the change in pH of the mixed solution caused by the proton transfer of sample was evaluated from the absorbance change of $\mathrm{HL^+}$, presuming that the ionic product of water holds constant at any time of the reaction.

The plot of $(k_{\mathrm{dpo}})_0$ against $[\mathrm{OH^-}]_0$ and the plot of $(k_{\mathrm{po}})_0$ against $[\mathrm{H_2O}]/[\mathrm{H^+}]_0$ yielded straight lines, as shown in Figs. 2 and 3 for py and 2-ampy, respectively. The values of k_{dp} and k_{OH} (or k_{p} and $k_{\mathrm{H_2O}}$) were obtained from the intercept and the slope of the linear regression line given in Fig. 2 (or Fig. 3).

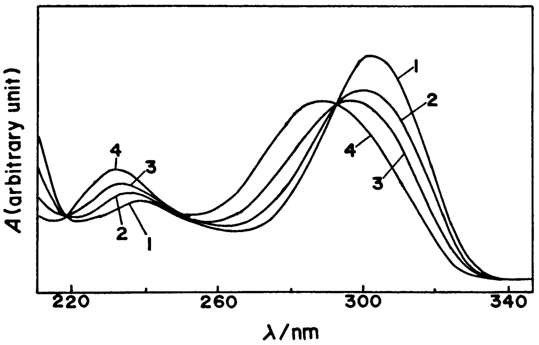

Fig. 1. Rapid scanning spectra of 2,2′-bipridine during the protolytic reaction.
[bpy] = 5.00×10^{-5} mol dm^{-3}; initial pH: 2.00, final pH: 4.49. Curve 1: 0—10 ms, 2: 190—200 ms, 3: 390—400 ms, 4: 790—800 ms.

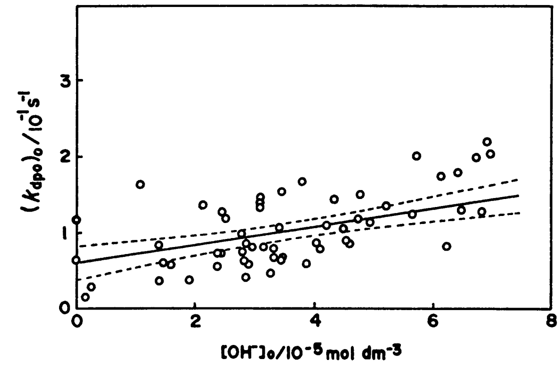

Fig. 2. Plot of $(k_{\mathrm{dpo}})_0$ against $[\mathrm{OH^-}]_0$ for pyridine. Solid line: the linear regression line for the plot, broken line: the intervals of the 0.95 confidence for the linear regression.

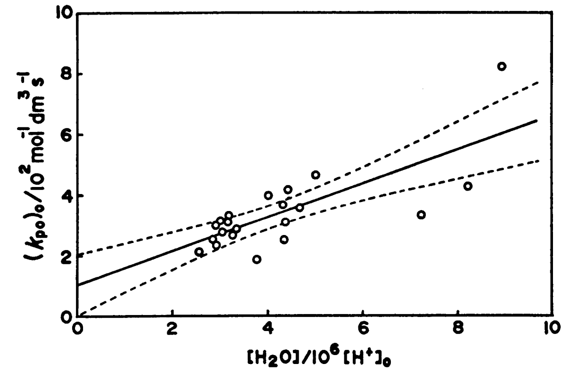

Fig. 3. Plot of $(k_{\mathrm{po}})_0$ against $[\mathrm{H_2O}]/[\mathrm{H^+}]_0$ for 2-aminopyridine.
Solid line: the linear regression line for the plot, broken line: the intervals of the 0.95 confidence for the linear regression.

TABLE 1. RATE CONSTANTS AND pK_a VALUES[a]

Sample	pK_a	k_{dp}/s^{-1}	k_{OH}/mol^{-1} dm^3 s^{-1}
Barbituric acid	4.00[b]	5.3±0.9	(2.9±3.3)×10^4
accp	8.96±1.05	(2.9±6.7)×10^{-3}	(4.7±0.7)×10^2
bpy	4.40[c]	(4.8±0.7)×10^{-1}	(9.3±5.7)×10^4
phen	5.00[d]	(2.5±0.8)×10^{-1} [d]	(1.2±0.7)×10^4 [d]
py	5.31±0.34	(6.0±2.2)×10^{-2}	(1.2±0.5)×10^3
3-ampy	6.17±0.13[d]	(1.8±0.6)×10^{-2} [d]	(7.4±1.6)×10^2 [d]
2-ampy	6.86±0.20[d]	(4.2±3.6)×10^{-3} [d]	(8.7±2.8)×10^2 [d]

Sample	pK_a	k_p/mol^{-1} dm^3 s^{-1}	k_{H_2O}/mol^{-1} dm^3 s^{-1}
2-ampy	6.86±0.20[d]	(1.0±1.1)×10^2	(5.5±2.3)×10^{-5}
4-ampy	9.26±0.37	(0.3±17)×10^5	(4.0±0.9)×10^{-4}

a) Values are shown together with the 0.95 confidence intervals. b) The value was taken from Ref. 21. c) The value was taken from L. G. Sillen and A. E. Martell, The Chem. Soc., Spec. Publ., No. 17 (1964). d) The values were taken from Ref. 14.

Table 1 summarizes pK_a and the rate constants for the azaaromatic compounds obtained in this study and in the previous paper,[14] together with those for barbituric acid and accp employed as authentic samples. The k_{dp} values of the authentic samples in non-buffered systems were in good agreement with the reported values, 10 s^{-1} for barbituric acid[1,21] and 2.5×10^{-3} s^{-1} for accp.[7] The k_{OH} value of accp also agreed well with that observed by Okuyama *et al.*[7] in buffered systems (2.0×10^2 mol^{-1} dm^3 s^{-1}). This fact adds a strong support to the validity of the present method for the determination of the rate constants of the proton transfer in non-buffered systems. Thus, the present study has again demonstrated that the rates of the deprotonation reactions of the conjugate acids of the azaaromatic compounds are slow and comparable to those of carbon acids.

The rate constants of the deprotonation, k_{dp} and k_{OH}, for the present azaaromatic compounds decrease with increasing basicity, while those of protonation, k_p and k_{H_2O}, increase with the increasing basicity. The correlations of the logarithms of k_{dp} and k_{OH} with pK_a for the azaaromatic compounds are shown in Fig. 4. Figure 4 also includes the correlations for cyclopentadienes (kinetic data obtained by a stopped-flow method),[7] alkylamines[22-24] and methyl-substituted pyridines[25,26] (by NMR method) for comparison. The log k_{dp} *vs.* pK_a plot for the azaaromatic compounds gives a straight line with a slope of −0.93, while the plot for the cyclopentadienes forms a straight line with a slope of −0.33. The log k_{OH} *vs.* pK_a plots of these two groups also give straight lines, but their slopes are different from each other. These facts imply that the azaaromatic compounds and the cyclopentadienes differ in proton transfer mechanism, though the rate constants for both groups are similar. The slow protolytic reaction of carbon acids including cyclopentadienes has been attributable to the following factors:[4] (i) the electronic and the structural reorganizations on going from the acid to its conjugate base, (ii) the small hydrogen-bonding ability with solvent and (iii) the accompanying reorientation of solvation. Okuyama *et al.*[7] proposed that the nuclear reorganization of carbon is the main factor retarding the proton transfer of cyclopentadienes. On the other hand, we can not explain at present the reason for the slow deprotonation reaction of the azaaromatic compounds.

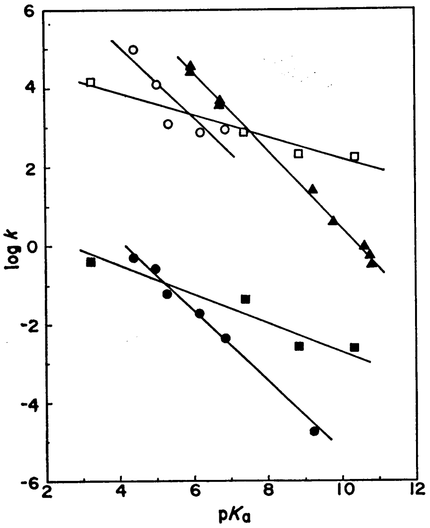

Fig. 4. The correlations between logarithms of the rate constants and pK_a for the azaaromatic compounds in this study (●, ○), the cyclopentadienes (■, □), and the alkylamines and the methyl-substituted pyridines (▲). Solid symbols are the k_{dp} plots and open symbols are the k_{OH} plots.

It is noteworthy that the k_{dp} values determined by the NMR method for the alkylamines and the methyl-substituted pyridines are higher by several orders of magnitude than those for the azaaromatic compounds and the cyclopentadienes. Although the k_{dp} values for the aminopyridines are lower by a factor of 10^7 than those for the methylpyridines, as shown in Fig. 4, it is unlikely that there is such a significant difference in the mechanism of their protolytic reactions. In fact, our preliminary experiment for the deprotonation reaction of 2-methylpyridinium ion showed that the k_{dp} is about 10^{-2} s^{-1}, comparable to the k_{dp} values of the aminopyridines.[27] Accordingly, the fact that the k_{dp} values for the azaaromatic compounds greatly differ from those for the alkylamines and the methylpyridines may be attributed to the difference in the experimental conditions used for rate-determination. In the present study, the rates were determined in dilute azaaromatic solutions (10^{-5}—10^{-4} mol dm^{-3}) at moderate pH. On the other hand, the rates for the alkylamines and the methylpyridines were determined by means of the NMR method in highly concentrated solutions (more than 0.02 mol dm^{-3}) at higher acidity. It has been reported that in concentrated solution two or more molecules of 1,10-phenanthroline form a stacking compound which can take one proton in acidic solution.[28,29] Though there is no evidence for stacking in the cases of pyridine derivatives, the difference in the concentration of solutes may alter the observed protolytic phenomena. Furthermore, the deprotonation rates determined by NMR method may include the contribution from the proton exchange between R_3N and R_3NH^+ in the crowded state.

Thus, we may conclude that the deprotonation reaction of the conjugate acids of azaaromatic compounds may depend upon the concentration. We believe that the stopped-flow pH jump method is superior to the NMR method for the rate determination, since NMR measurements are usually carried out in highly concentrated solutions in which some intermolecular interactions might affect the rate of the reaction.

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