verse processes are designated $K_{-1} = 1/K_1$, etc. It should be noted that the rate constants k_1, k_{12}, k_2, k_{-2}, k_{-3}, k_{-34}, and k_{-4} are all first-order rate constants i.e., in those reaction steps in which methanol is involved, [MeOH] (~1 M in 90:10 mol % Me_2SO–methanol) does not appear in the rate equations which define the rate constants. This treatment leads to the relationships between rate and equilibrium constants as described above.

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(42) The concerted process in eq 8 and the stepwise process in eq 15 and 16 (Scheme III) are kinetically indistinguishable if the equilibrium in eq 15 is rapidly established relative to that in eq 16, but give rise to different kinetic forms if the proton transfer in eq 15 is a relatively slow process.
(43) The rate equations have been derived on the assumption of a single rate-determining step in each case. Analysis of the equations based on the steady-state assumption (for SH, I, or PH) ultimately leads to the same conclusions as those described in the text. Since the intermediates SH, I, and PH are not present in detectable quantities, the conditions $[S] \gg [SH] + [I] + [PH]$ and $[P] \gg [SH] + [I] + [PH]$ have also been used in deriving the equations.
(44) A simple relationship is evident between the predicted kinetic behavior and the species involved in the activated complex of the rate-determining step. Since non-first-order behavior derives in this system from the dissociation of $TNB{\cdot}OMe^-$ into TNB and MeO^-, then those reaction pathways for which the activation process involves recombination of TNB and MeO^- will be kinetically first order. This recombination occurs in $A^{\ddagger}$, $B^{\ddagger}$, $E^{\ddagger}$, and $F^{\ddagger}$, but not in $C^{\ddagger}$ and $D^{\ddagger}$.
(45) The rate and equilibrium constants in Scheme III have been defined in the same manner as in Scheme II. Thus, $K_{-4'} = 1/K_{4'} = [I][PhNH^-]/[TNB{\cdot}NHPh^-] = k_{-4'}/k_{4'}$. Also, $[PhNH^-]/[MeO^-][PhNH_2] = K_{3'} = k_{3'}/k_{-3'} = 1/K_{-3'}$ and $k_{-3'}$ is by definition a first-order rate constant.
(46) That the expressions for k_{ψ_1} in eq 17 and 18 must be similar to those in cases 3 and 12 (Figure 3), respectively, can be seen by comparing the activated complexes for the processes in eq 14 and 16 with the activated complexes $B^{\ddagger}$ and $F^{\ddagger}$, respectively.
(47) The estimated value is based on $K_{3'} \sim 6.3 \times 10^{-8}$ M^{-1} and $K_{12} \sim 10^{-8}$ M (which gives $[MeO^-] \sim 2 \times 10^{-6}$ M at $[TNB{\cdot}OMe^-K^+]_0 = 4 \times 10^{-4}$ M). The K_3' value is obtained by combining the H_- value[48] of 18.5 in 90:10 mol % Me_2SO–methanol containing 2.5×10^{-2} M CH_3ONa with the pK_a value[49] of 27.3 for aniline. The K_{12} value is obtained by extrapolation of the results in ref 50.
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(52) According to eq 25, an estimate of the equilibrium constant K_{app} for the conversion of $TNB{\cdot}OMe^-K^+$ to $TNB{\cdot}NHPh^-K^+$ can be made using the values obtained for the slope and the intercept of the plot of $k_\delta[S]_e^{1/2}$ vs. $[PhNH_2]$: the ratio slope/intercept $= K_{12}K_3K_4 = K_{app}$. Although a linear plot is in fact obtained, unfortunately the small magnitude of the intercept value obtained in the plot leads to considerable uncertainty in such a procedure. The value obtained for K_{app} was 86 M^{-1} as compared to the measured value 23.2 M^{-1}.
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Intramolecular Nondissociative Proton Transfer in Aqueous Solutions of Tautomeric Heterocycles: a Temperature-Jump Kinetic Study

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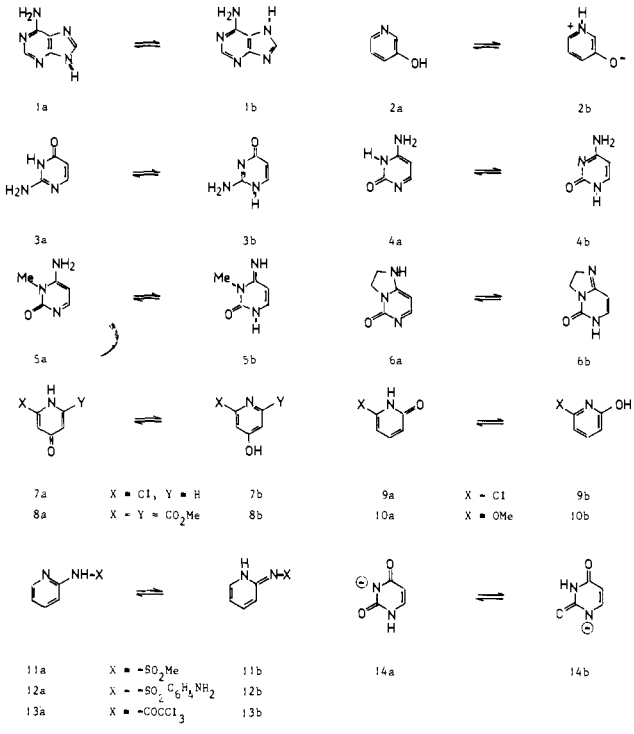
Abstract: The mechanism of tautomeric interconversion in some substituted pyridines, pyrimidines, and imidazoles in aqueous solution is investigated using the T-jump relaxation technique. It is found that when the tautomeric functional groups are remote, tautomeric interconversion occurs through intermediate ionization and dissociation followed by ion recombination. However, when these functional groups get close enough, such as in tautomeric α-substituted pyridines, a direct proton-transfer mechanism not involving intermediate ionic dissociation contributes efficiently to the interconversion rate. The contribution of this process is examined in terms of the nature and geometry of the tautomeric functional groups. Biological implications are discussed.

In aqueous solutions, proton transfers between an acidic –OH or $-^+NH$ group and a basic $-O^-$ or –N group belonging to two independent molecules have been extensively studied[2] and shown[3,4] to be diffusion controlled when thermodynamically favorable. For "carbon" acids and bases such processes are usually much slower, whereas acids and bases involving a sulfur atom behave intermediately in this respect.

By contrast, little is known about the proton-transfer rate when the transfer occurs between two nitrogen atoms or between two oxygen atoms or between a nitrogen and an oxygen atom within the same molecule. In previous papers,[5,6] we used the temperature-jump relaxation method to investigate the mechanism of the tautomeric interconversion of some heterocycles such as the imidazole cycle of adenine,[5] and the pyrimidine cycles of cytosine[6] and 3-methylcytosine.[6] In these cases the tautomeric interconversion proceeds through intermediate ionization to the anionic or cationic form of the substrate, followed by neutralization, with the thermodynamically favorable acid–base reactions being diffusion controlled or nearly so: in any case, no direct or nondissociative proton-transfer mechanism was detected.

On the other hand, fluorescence data on the salicylate anion[7] indicate that the interconversion between the phenolate and the carboxylate forms of the molecule is far too fast to be interpreted by such a model, thereby suggesting that the exchanging proton can jump from one site to another without intermediate dissociation. Furthermore, Grunwald, Meiboom, et al.,[8] from NMR line bandwidth studies of acetic and benzoic

Scheme 1



acid solutions in methanol and water, inferred that the proton of the carboxyl group can be transferred from one oxygen to another through a bridge of solvent molecules by a concerted mechanism.

Thus, in these two examples where the two groups between which the proton is exchanged are quite close to one another, a direct nondissociative proton transfer has apparently been observed. This indicates the possibility that such a mechanism contributes to the tautomeric interconversion when the molecular geometry is favorable. In an effort to assess the structural requirements for such a "direct" proton transfer, we decided to study a class of compounds of various structures whose tautomerism has been extensively studied thermodynamically.[9] Tautomeric pyridines meet the aforementioned requirement. Moreover, these compounds are structurally related to the nucleic acid bases, whose tautomerism has some important genetic implications.[10] Temperature-jump spectroscopy was chosen for this study as it allows a direct observations of the tautomeric equilibrium.

Experimental Section

I. Materials. 3-Hydroxypyridine (**2**) (Merck) (Scheme I) was recrystallized from benzene, then sublimed in a vacuum: mp 127.5 °C. Isocytosine[11] was recrystallized from water: mp 274–277 °C. 2,3 Dihydro-1*H*-5-oxoimidazo[1,2c]pyrimidine (**6**) was synthesized as the chlorhydrate, which was recrystallized from ethanol several times and used as such, its spectral properties being identical with those quoted by Ueda and Fox.[12] 2-Chloro-4-hydroxypyridine (**7**), synthesized[13] by hydrolysis of 2-chloro-4-nitropyridine,[14] was sublimed then recrystallized from water: mp 170 °C. Chelidamic acid dimethyl ester (**8**) was obtained from esterification of chelidamic acid (Aldrich), treated with charcoal, and then recrystallized several times from water and used as the monohydrate: mp 167 °C. 6-Chloro-2-pyridone (**9**) (Aldrich) was recrystallized from aqueous ethanol: mp 128 °C. 6-Methoxy-2-pyridone (**10**), synthesized[15] from 2,6-dimethoxypyridine, was recrystallized from benzene/petroleum ether, then sublimed in a vacuum: mp 104–105 °C. 2-Methanesulfonamidopyridine (**11**), synthesized[16] from 2-aminopyridine, was recrystallized several times from water: mp 203–204 °C. Sulfapyridine (**12**) (Sigma) was recrystallized from ethanol: mp 191.5 °C. 2-Trichloroacetamidopyridine (**13**) was synthesized[17] from 2-aminopyridine and trichloroacetyl chloride in pyridine, and recrystallized from acetone: mp 84 °C.

II. Kinetic Experiments. Temperature-jump experiments were performed with the apparatus and circulating device described previously[5] with the modifications introduced later.[6] Standard experimental conditions were: initial temperature (T_i) = 2 °C and final temperature (T_f) = 10 °C. The use of concentrations from 10^{-5}–10^{-3} M usually brings the interconversion relaxation time into the 10^{-3}–10^{-6}-s time range. A kinetic run consists of at least three series of accumulations of three to nine relaxation spectra. The mean value for the relaxation time and for the corresponding pH were kept for further computations. The pH was continuously measured with a Radiometer type 64 pH meter, equipped with a G202C Radiometer glass electrode and a NaCl reference electrode; the difference between its initial and final value never exceeded 0.05 pH unit. Solutions for the kinetic runs were prepared by dissolving weighed amounts of compounds in 0.2 M solutions of $NaClO_4$, H_2O (Merck reagent grade) in distilled water. The solutions were degassed prior to use. In order to avoid photochemical decomposition, illumination was cut down except when recording the relaxation curve. UV spectra of the solutions diluted in appropriate buffers before and after a kinetic run were identical within experimental error in every case, and the concentrations were determined from the optical densities.

Results

Aqueous solutions of all the compounds, after heating for a few microseconds, show time-dependent optical density variations. Here we are only interested in changes slower than the heating time; other modifications cannot be distinguished from "physical" changes of the extinction coefficients (e.g., due to changes in solvation).

I. Attribution of the Observed Relaxation Spectra. The amplitude (A_λ) of the relaxation process for a two-species equilibrium as monitored by UV spectroscopy is readily derived:[5]

$$A_\lambda = \bar{C}l \frac{K_T}{(1 + K_T)^2} \Delta\epsilon_\lambda \Delta T \frac{\Delta H}{RT_f^2} \qquad (1)$$

Here $\bar{C}$ is the sum of the concentrations of both tautomers at the final temperature T_f, ΔT is the magnitude of the temperature jump, $\Delta\epsilon_\lambda$ is the difference between the molar extinction coefficients of each species at the wavelength λ, ΔH is the reaction enthalpy, and K_T is the tautomeric equilibrium constant.

From eq 1 it can be seen that, for a given compound at a given concentration and temperature: (a) Amplitude is proportional to $\bar{C}$, which is computed as described in the appendix of ref 5. If so, the $A/\bar{C}$ ratio is independent of pH and compound concentration. Like all the other compounds studied here, 2-chloro-4-pyridone (**7**) satisfies this criterion (Figure 1). (b) The wavelength dependence of the amplitude is homothetical to the differential spectrum of the two tautomers. For a given compound, the differential spectrum of the two tautomers is obtained as an approximation, either by taking the difference of the spectra of the two tautomer model compounds in which the tautomeric hydrogen is replaced by a methyl group, or by taking the difference of the spectra of the compound in two solvents of different polarity where it has been shown, from previous studies,[18] to predominate under either tautomeric form.

In Figure 2, it can be seen that for 6-chloro-2-pyridone (**9**) the agreement is excellent between the wavelength dependence of the relaxation amplitude and the differential spectra of **9** in water and in ethanol (solvation effects might explain the slight shift which is observed). This latter condition was satisfied by all compounds studied here except 2-chloro-4-pyridone (**7**), for which the difference of the extinction coefficients of the tautomers[24] is only appreciable for wavelengths below 280 nm, where the poor brightness of the light source imposes working at the fixed wavelength of the 254 nm Hg emission band.

II. Thermodynamic Data. In Table I, the thermodynamic data used in this work, as well as the references of previous

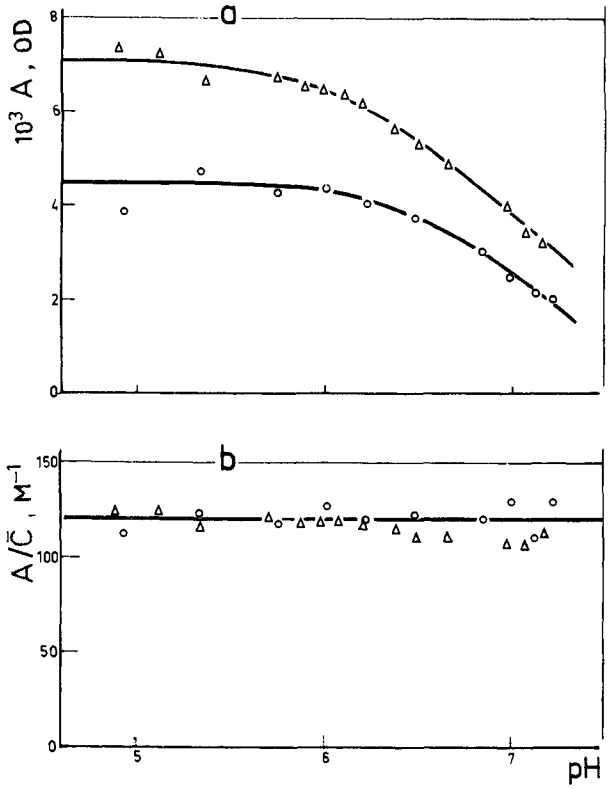


Figure 1. (a) Relaxation amplitude of the tautomeric reequilibration of 2-chloro-4 hydroxypyridine (**7**) as a function of pH. (b) Ratio of the relaxation amplitude to $\bar{C}$ vs. pH. λ 254 nm; concentrations: ○ 3.7×10^{-5} M and △ 5.9×10^{5} M.

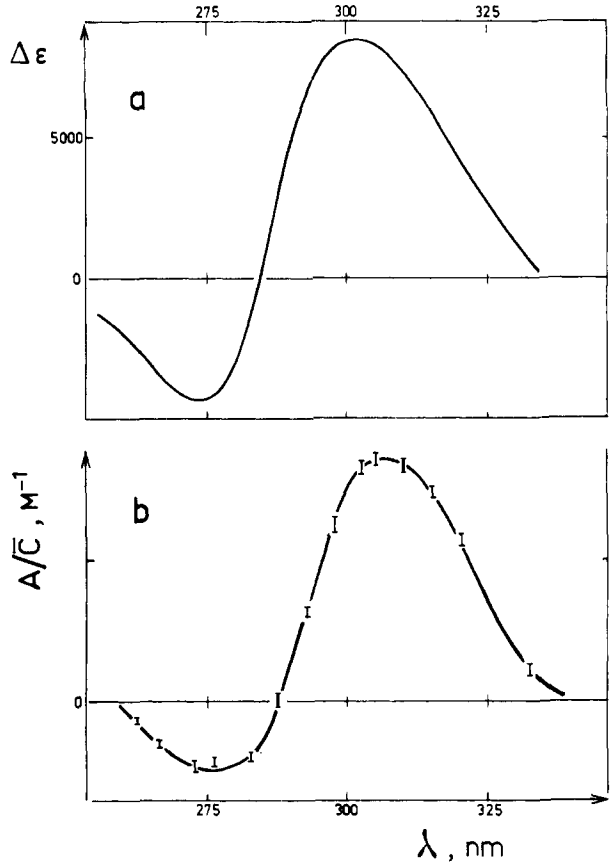


Figure 2. (a) Variations of the molar extinction coefficients difference of 6-chloro-2-pyridone (**9**) in water and in ethanol vs. wavelength. (b) Relaxation amplitude vs. wavelength.

Table I. Thermodynamic Data Used in This Work[h]

Compd	pK_1	pK_2	K_T	Ref of previous studies
1	4.32[23]	10.2[23]	0.28[5]	5
2	4.95[19]	8.99[a]	0.72[b]	19
3	4.00[21]	9.59[21]	0.92[20]	20
4	4.78[23]	12.6[23]	0.00189[6]	6, 22
5	7.75[6,d]	14[6,d]	0.0226[6]	6, 22
6	7.31[a]	12.6[12]	0.24[c]	12
7	2.07[24]	7.26[a]	0.83[25]	24
8	0.5[26,d]	6.33[a,d]	0.33[25]	26
9	−0.18[24]	7.85[a]	0.19[27]	24
10	1.24[a]	9.83[a]	0.02[f]	15
11	1.1[28]	8.63[a]	0.137[g]	17, 28, 29
12	~2.4[a]	8.95[a]	0.033[f]	31
13	<4[a]	~9.3[a]	0.10[g]	17

[a] Determined from UV spectra in NBS buffers. [b] Extrapolated from ref 19a. [c] Determined from UV spectra of the compound and its methylated derivatives. [d] It is assumed that: $pK_{D_2O} - pK_{H_2O} = 0.5$ as suggested by literature data.[2a] [e] The same value was used in H_2O and D_2O. [f] Determined from temperature-jump thermodynamic data. [g] Extrapolated from data in ref 30. [h] Unless specified the data are given at 10 °C and extrapolated to an ionic strength: $\mu = 0$. (When taken from the literature, the data are indicated by the corresponding references).

work on the studied tautomeric equilibria, are given. The tautomeric equilibrium constants determined by the UV spectroscopic method[9] were considered reliable when $K_T > 0.1$ (in this work K_T is taken as the ratio of the minor to the major tautomeric form concentrations). But, when the equilibrium is rather displaced in favor of one tautomer, the temperature-jump spectroscopy affords a more reliable value. Indeed, in this case, it can be seen from eq 1 and van't Hoff's law that a plot of $\ln A_\lambda T^2$ vs. $1/T$ affords a direct measurement of the reaction enthalpy ΔH. Moreover, it is reasonable to assume that $\Delta\epsilon_\lambda$ is almost identical with the difference of the extinction coefficients of the model "fixed" tautomers (in which the transferring hydrogen is replaced by a methyl group). Thus, an estimate of K_T can be computed from eq 1 and the ΔH measurement.

The pK_as for proton gain and for proton loss of the individual tautomers can be computed from the pK_as for proton gain (pK^1) and for proton loss (pK^2) of the substrate and also from K_T by using the following equations:

$$pK_{MH}{}^1 = pK^1 + \log(1 + K_T)$$

$$pK_{HM}{}^1 = pK^1 + \log(1 + (1/K_T))$$

$$pK_{MH}{}^2 = pK^2 - \log(1 + K_T)$$

$$pK_{HM}{}^2 = pK^2 - \log(1 + (1/K_T))$$

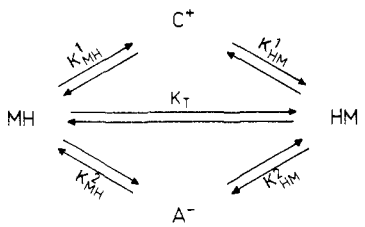
In these equations MH and HM represent the major and minor tautomeric species respectively; p$K_{MH}{}^1$ and p$K_{HM}{}^1$ are the proton gain pK_as and p$K_{MH}{}^2$ and p$K_{HM}{}^2$ are the proton loss pK_as of tautomers MH and HM (Scheme II).

III. Variations of the Relaxation Times with pH and Concentration. For a given compound the relaxation time, τ, varies with pH and concentration. Figure 3 illustrates such variations for 2-chloro-4-pyridone (**7**). In all cases, the dependence of τ^{-1} upon pH and concentration could be fitted by an equation of the following type:

$$\tau^{-1} = k_0 + k_{H^+}\bar{C}_{H^+} + k_{OH^-}\bar{C}_{OH^-} + k_{C^+}\bar{C}_{C^+} + k_{A^-}\bar{C}_{A^-} \quad (2)$$

where $\bar{C}_i$ is the equilibrium concentration of species "i" at the final temperature, and is computed as in the appendix of ref 5 using the thermodynamic data of Table I. C^+ and A^- stand

Scheme II



respectively for the cationic and anionic forms of the substrates. As we shall see the k_{H^+}, k_{OH^-}, k_{A^-}, and k_{C^+} values may be roughly predicted so that, from the knowledge of the $\bar{C}_i$ and the standard error of each kinetic measurements, we may determine which $k_i\bar{C}_i$ terms are negligible under given conditions.

In the least-squares program, which we used in the previous work,[5,6] each relaxation time measurement had the same weight. However, standard errors on the τ measurements are roughly proportional to the τ values and it is therefore preferable to use a weighted multilinear program[31] for data fitting. A diagonal weight matrix $[W]$ is used with $w_{ij} = 0$ if $i \neq j$ and $w_{jj} = \tau_j^2$, τ_j being the jth relaxation time measurement. The correlation coefficient ρ is defined as:

$$\rho^2 - 1 = \frac{\sum_j \left(\frac{\tau_{ej}^{-1} - \tau_{cj}^{-1}}{\tau_{ej}^{-1}}\right)^2}{\sum_j \left(\frac{\tau_{ej}^{-1} - \bar{\tau}^{-1}}{\tau_{ej}^{-1}}\right)^2}$$

$$\equiv \frac{\text{sum of squares due to regression}}{\text{sum of the weighted squares of the } \tau^{-1} \text{ values about their mean}}$$

τ_{ej}^{-1} refers to the jth experimental value; τ_{cj}^{-1} to the jth calculated value; and $\bar{\tau}^{-1}$ to the mean τ^{-1} value.

In Table II several sets of regression parameters are given for each compound. These correspond to different fits: (a) using the constant term, k_0, as a parameter; (b) setting $k_0 = 0$; and sometimes (c) setting the value of a given term k_i, $i \neq 0$. Comparing these fits helps the discussion of the reliability of the parameter values.

Discussion

In all cases, the variations of the relaxation amplitude with the concentration and the pH are consistent with the attribution of the observed relaxation signals to a first-order reequilibration MH $\rightleftharpoons$ HM. Thus, if MH and HM are interconverted through several pathways, the inverse of the relaxation time can be expressed as $\tau^{-1} = \Sigma(k_n^+ + k_n^-)$ where k_n^+ and k_n^- are the first-order rate constants for the reaction along pathway "n".

We shall begin by trying to analyze our results in the light of the model of tautomeric reequilibration through intermediate ionization followed by ion recombination.

I. General Acid-Base Catalysis of the Tautomeric Interconversion. All the compounds studied possess a cationic species and an anionic species common to both tautomers, yet these might not be the major ionized species. The common cation deprotonates to give either tautomer and the common anion protonates to give either tautomer. Thus, the reaction medium contains three acid species (the proton itself, water, the substrate cation) and three basic species (the hydroxyl ion, water, the substrate anion). Therefore, the general acid-base catalysis mechanism implies six different reaction pathways, summarized in Table III.

The contribution of each pathway to the relaxation time can be easily computed by applying the steady-state approximation

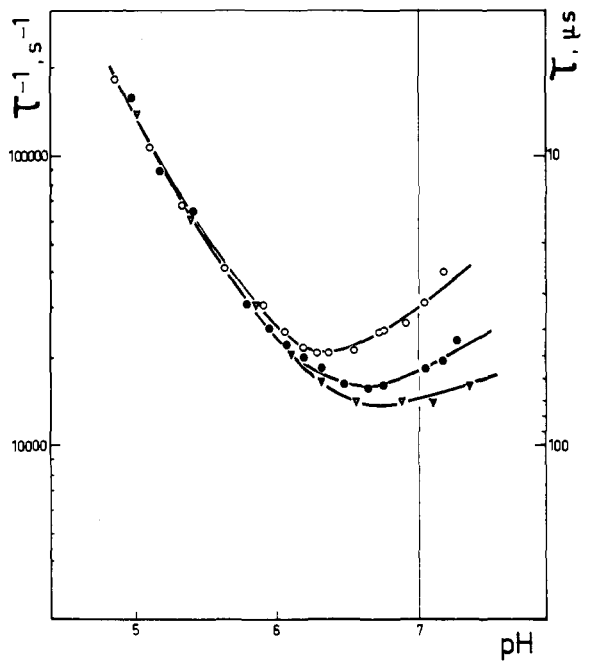


Figure 3. τ^{-1} as a function of pH for 2-chloro-4-hydroxypyridine (7): (—) best fit of the experimental data with eq. 2. Substrate concentrations: ○ 1.3×10^{-4} M, ● 0.59×10^{-4} M, and ▼ 0.37×10^{-4} M; λ 254 nm.

to C^+ in pathway Ia, to C^+ and OH^- in pathway IIIa, to A^- in pathway Ib, and to A^- and H^+ in pathway IIIb. The validity and limits of the steady-state treatment are discussed in the appendix of ref 6. It can then be seen that the reaction pathways from Ia up to and including IIIb account for a kinetic law represented by eq 2, where pathway Ia accounts for the $k_{H^+}\bar{C}_{H^+}$ term, pathway IIa for the $k_{C^+}\bar{C}_{C^+}$ term, pathway Ib for the $k_{OH^-}\bar{C}_{OH^-}$ term, and pathway IIb for the $k_A\bar{C}_A$- term. Pathways IIIa and IIIb account for a constant term in the rate law.

A. Acid Catalysis by the Proton. As shown in Table III, the Ia reaction pathway accounts for the $k_{H^+}\bar{C}_{H^+}$ term with:

$$k_{H^+} = \frac{a_1a_2 + a_{-1}a_{-2}}{a_2 + a_{-1}}$$

which is easily modified to:

$$k_{H^+} = \frac{a_1}{1 + (a_1/a_{-2})(1/K_T)} + \frac{a_{-2}}{1 + (a_{-2}/a_1)(K_T)}$$

where a_a and a_{-2} are the protonation rates of the individual tautomers.

If the protonation reactions of both tautomers are thermodynamically favored, the corresponding rate constants are expected to be diffusion controlled or nearly so. Therefore, the relation $a_1/a_{-2} \sim 1$ must hold, and if $K_T \ll 1$, the expression of k_{H^+} simply reduces to a_{-2}, the protonation rate of the rare tautomers. In any case, it can be shown by simple algebra that k_{H^+} must be between a_1 and a_{-2}, so that the k_{H^+} values can be compared with protonation rates of neutral bases. It has been stated that protonation rates of amines decrease slightly with pK_a.[32] Indeed, it can be seen from Table II that k_{H^+} has a tendency to become smaller when the pK_a of the rare form (proton gain) decreases. Thus, it is only for $pK > 4$ that k_{H^+} appears to be independent of pK, its observed magnitude (from 1.5 to 2×10^{10} M^{-1} s^{-1}) being within the range expected for diffusion-controlled protonation of a neutral base.[3,32-34]

B. Base Catalysis by the Hydroxide Ion. As shown in Table III, pathway Ib accounts for the $k_{OH^-}\bar{C}_{OH^-}$ term with:

$$k_{OH^-} = \frac{b_1b_2 + b_{-1}b_{-2}}{b_2 + b_{-1}}$$

Table II. Rate Constants from Equation 2[a]

	Compd	k_0, s^{-1}	$10^{-10}k_{H^+}$, $M^{-1}s^{-1}$	$10^{-10}k_{OH^-}$, $M^{-1}s^{-1}$	$10^{-8}k_{C^+}$, $M^{-1}s^{-1}$	$10^{-8}k_{A^-}$, $M^{-1}s^{-1}$	ρ	N	10^4 concn range, M
4		1 900 ± 300	1.9 ± 0.3	1.2 ± 0.06	4.2 ± 0.3		0.999 7	35	5.3–36
5	(D_2O, 12 °C)	28 300 ± 1800		0.43 ± 0.03	2.2 ± 0.1		0.994	24	5.3–46
6		9 500 ± 1000		1.26 ± 0.06	2.8 ± 0.14		0.996	21	0.8–3.8
7		6 500 ± 400	0.9 ± 0.02			4.0 ± 0.2	0.999 91	40	0.35–1.2
8	(D_2O, 12 °C)	16 000 ± 1600	0.23 ± 0.01			0.74 ± 0.1	0.998 8	13	2.3–5.1
8[b]	a	55 000 ± 3000 (67 500 ± 2000) (0)	0.25 ± 0.015 (0.21 ± 0.01) (0.5 ± 0.07)			1[b] (−0.2 ± 0.3) (5.2 ± 0.6)	0.991 (0.992) (0.76)	21	2.3–5.1
1		50 ± 90 (0)	1.33 ± 0.03 (1.35 ± 0.002)	0.89 ± 0.06 (0.90 ± 0.06)		3.6 ± 0.4 (3.6 ± 0.4)	0.999 91 (0.999 909)	30	3.13–11.5
2		880 ± 150 (0)	1.17 ± 0.05 (1.33 ± 0.06)	1.42 ± 0.11 (1.64 ± 0.15)	3.8 ± 0.18 (3.6 ± 0.26)	7.0 ± 0.16 (7.25 ± 0.2)	0.999 96 (0.999 91)	34	0.4–4.0
3		370 ± 80 (0)	1.01 ± 0.04 (1.09 ± 0.04)	0.92 ± 0.06 (1.04 ± 0.07)	2.05 ± 0.1 (2.01 ± 0.15)	3.1 ± 0.1 (3.2 ± 0.1)	0.999 96 (0.999 94)	32	3.5–41
9		39 100 ± 900 (0)	0.3 ± 0.01 (0.5 ± 0.1)			3.8 ± 0.25 (10.5 ± 2)	0.999 1 (0.89)	22	1.8–3.8
10		11 400 ± 400 (0)	0.26 ± 0.01 (0.4 ± 0.1)	0.65 ± 0.05 (1.3 ± 0.4)			0.999 7 (0.98)	14	1.3–1.8
11		3 900 ± 400 (0)	0.37 ± 0.03 (0.52 ± 0.07)			1.9 ± 0.2 (3.1 ± 0.4)	0.999 3 (0.995)	20	1.1–2.5
12		6 200 ± 200 (0)	0.3 ± 0.01 (0.43 ± 0.1)			2.3 ± 0.1 (4.2 ± 0.5)	0.999 86 (0.996)	34	0.86–2.0
13		4 000	0.45				*c*		*c*

[a] Unless specified in the first column, these results refer to experiments in ordinary aqueous solution at $T_f = 10$ °C. Standard errors are given. N is the number of kinetic runs. ρ is the correlation coefficient (see text). All the data were fitted with the multilinear relative regression program defined in the text, which explains the small discrepancies with previous work on adenine,[5] cytosine,[6] and 3-methylcytosine, though the same data were used. In order to help the discussion of the significance of the k_0 term, some fitting was performed by forcing this parameter to zero in eq 2. Data thus obtained are given in parentheses. [b] See ref 40. [c] k_{OH^-} and k_{A^-} could not be estimated because of spontaneous decomposition of compound 13; the fitting was performed using the runs corresponding to pH <7, then contributions of pathways 1b and 11b (see text and Table III) are expected to be negligible.

Table III. The General Acid–Base Catalysis Model of Tautomeric Reequilibration

Pathway no.	Pathway	Catalyst	Contributions to the kinetic law
Ia	$H^+ + MH \underset{a_{-1}}{\overset{a_1}{\rightleftharpoons}} C^+ \underset{a_{-2}}{\overset{a_2}{\rightleftharpoons}} H^+ + HM$	H^+	$\frac{a_1a_2 + a_{-1}a_{-2}}{a_2 + a_{-1}}\bar{C}_{H^+}$
IIa/	$C^+ + MH \underset{a_{-3}}{\overset{a_3}{\rightleftharpoons}} HM + C^+$	C^+	$(a_3 + a_{-3})\bar{C}_{C^+}$
IIIa	$H_2O + MH \underset{a_{-4}}{\overset{a_4}{\rightleftharpoons}} C^+ + OH^- \underset{a_{-5}}{\overset{a_5}{\rightleftharpoons}} H_2O + HM$	H_2O	$\frac{a_4a_5 + a_{-4}a_{-5}}{a_5 + a_{-4}}$
Ib	$OH^- + MH \underset{b_{-1}}{\overset{b_1}{\rightleftharpoons}} A^- + H_2O \underset{b_{-2}}{\overset{b_2}{\rightleftharpoons}} OH^- + HM$	OH^-	$\frac{b_1b_2 + b_{-1}b_{-2}}{b_2 + b_{-1}}\bar{C}_{OH^-}$
IIb	$A^- + MH \underset{b_{-3}}{\overset{b_3}{\rightleftharpoons}} HM + A^-$	A^-	$(b_3 + b_{-3})\bar{C}_{A^-}$
IIIb	$H_2O + MH \underset{b_{-4}}{\overset{b_4}{\rightleftharpoons}} A^- + H_3O^+ \underset{b_{-5}}{\overset{b_5}{\rightleftharpoons}} H_2O + MH$	H_2O	$\frac{b_4b_5 + b_{-4}b_{-5}}{b_5 + b_{-4}}$

b_1 and b_2 are the deprotonation rate constants of the individual tautomers by the hydroxide ion. The same reasoning that showed k_{H^+} closely related to the protonation rate of the substrate establishes that k_{OH^-} lies between b_1 and b_{-2}, which are of the same magnitude; thus, the k_{OH^-} term is an approximate measurement of the deprotonation rates of the substrates by the hydroxide ion. These rate constants, being between 1×10^{10} and 1.5×10^{10} $M^{-1}s^{-1}$ at 283 K (Table II), are slightly lower than those observed for protonation and compare favorably to literature rate constants for deprotonation of neutral acids by the hydroxide ion.[3,34,35]

C. Autocatalysis. Since $a_3/a_{-3} = b_3/b_{-3} = K_T$, the kinetic constants a_3, a_{-3} and b_3, b_{-3} are easily computed from the terms k_{C^+} and k_{A^-}, respectively (Table II). It is interesting to compare these autocatalysis rate constants with the rate constants of the following reactions:

$$AH + B^- \rightleftharpoons A^- + BH \quad |\Delta pK| = |pK_{AH} - pK_{BH}|$$

$$A'H^+ + B' \rightleftharpoons A' + B'H^+ \quad |\Delta pK| = |pK_{A'H^+} - pK_{B'H^+}|$$

where AH, BH and $A'H^+$, $B'H^+$ are respectively neutral and cationic acids. Such data are available when the reactants are "normal" oxygen and nitrogen acids and bases. Ahrens and Maass[4,36] found that, in these cases, rate constants are described by a generalized Brønsted equation. In the reaction between two tautomers $|\Delta pK| = |\log K_T|$ and the rate constants appear slightly lower than those reported for dissymmetric reactions (Figure 4).

Several considerations account for these discrepancies: (a) In a reaction between a tautomeric form and the ionized form,

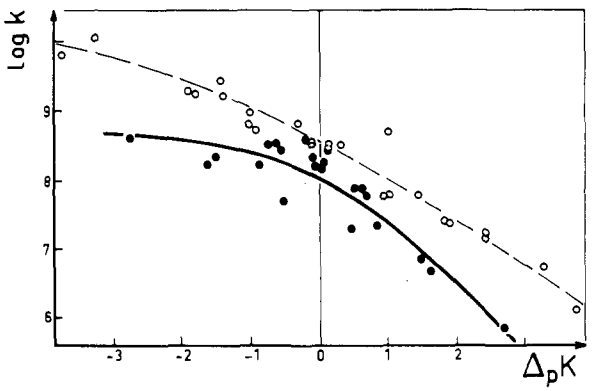


Figure 4. Open circles: logarithmic plot of the rate constants of "normal" acid-base interconversion AH + B (k) → A + BH, vs. ΔpK (data from Ahrens and Maass[4]). Full circles: plot of the autocatalytic rate constants, a_3, a_{-3}, b_3, and b_{-3} vs. ΔpK (for a_3 and b_3 ΔpK = log K'_T and for a_{-3} and b_{-3} ΔpK = log K_T).

only a part of the encounters can lead to tautomeric interconversion, as illustrated by the following scheme. (b) The molecules investigated here are larger than those of Ahrens and Maass,[4] therefore their diffusion coefficients are expected to

$$\mathrm{MH} + \mathrm{C}^+ \begin{cases} \nearrow \mathrm{C}^+ + \mathrm{HM} \text{ efficient encounter} \\ \searrow \mathrm{C}^+ + \mathrm{MH} \text{ inefficient encounter} \end{cases}$$

be lower. Grunwald et al.[37] have studied symmetrical proton transfer (AH ≡ BH, A′ ≡ B′) between molecules of similar dimensions as ours and also found low rate constants. (c) The low proportion of the cation common to both exchanging tautomers explains the undetectable acid autocatalysis in some cases (e.g., adenine[5]).

D. Acid and Base Catalysis by the Water Molecule. From Table III it can be seen that the contributions of pathways IIIa and IIIb to the rate law are independent of pH and substrate concentration. Thus, if these pathways are to account for the pH-independent term, k_0, in the rate law, then the relation $k_0 = k_0^a + k_0^b$ must hold. k_0^a and k_0^b are the contributions of pathways IIIa and IIIb, respectively. Applying the steady-state hypothesis to the ionic intermediates leads to:

$$k_0^a = \frac{a_4a_5 + a_{-4}a_{-5}}{a_{-4} + a_5}$$

and

$$k_0^b = \frac{b_4b_5 + b_{-4}b_{-5}}{b_{-4} + b_5}$$

At equilibrium we have:

$$a_4\overline{C}_{MH} = a_{-4}\overline{C}_{C^+}\overline{C}_{OH^-}$$

and

$$a_{-5}\overline{C}_{HM} = a_5\overline{C}_{C^+}\overline{C}_{OH^-}$$

Thus, the following relation is derived: $k_0^a = [a_{-4}a_5/(a_{-4} + a_5)](\overline{K}_W/\overline{K}_{MH}{}^1 + \overline{K}_W/\overline{K}_{HM}{}^1)$ where $\overline{K}_{MH}{}^1 = \overline{C}_{MH}\overline{C}_{H^+}/\overline{C}_{C^+}$ and $\overline{K}_W = \overline{C}_{H^+}\overline{C}_{OH^-}$.[38] Then it is easily shown that k_0^a lies between $(a_{-4}/2)(\overline{K}_W/\overline{K}_{MH}{}^1 + \overline{K}_W/\overline{K}_{HM}{}^1)$ and $(a_5/2)(\overline{K}_W/\overline{K}_{MH}{}^1 + \overline{K}_W/\overline{K}_{HM}{}^1)$, where a_{-4} and a_5 are the deprotonation rate constants of the two acid sites of the cationic species by the hydroxide ion. Insofar as both sites can be considered independently and bear a positive charge, these rates can be compared to the neutralization rates[3,32-34,39] of alkylammonium and arylammonium ions. These values vary between 2×10^{10} and 4×10^{10} M^{-1} s^{-1}, the mean being somewhat higher than 3×10^{10} M^{-1} s^{-1}.

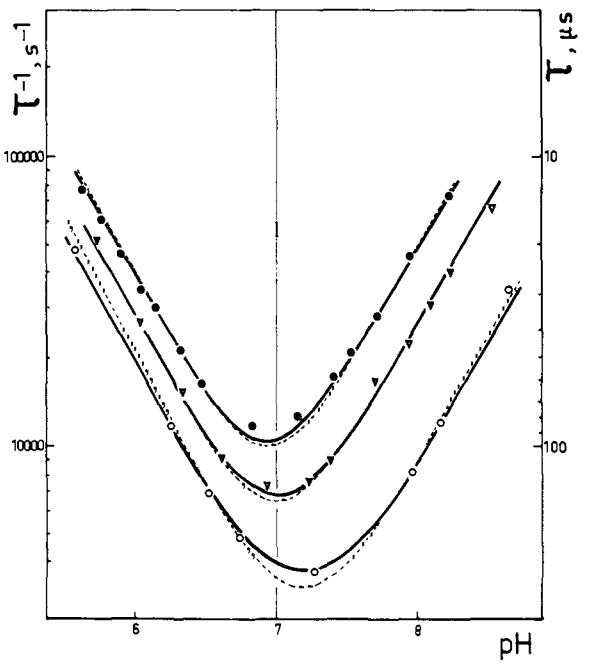


Figure 5. τ^{-1} as a function of pH for 3-hydroxypyridine (**2**) showing the very small difference between the best fit of experimental data with eq 2 (—) and the best fit obtained by setting the constant term in eq 2, k_0 = 0 (- - -). Concentrations: ● 4×10^{-4} M, ▼ 2×10^{-4} M, and ○ 4.2×10^{-4} M; λ 313 nm.

It can be shown analogously that k_0^b lies between $(b_{-4}/2)(\overline{K}_{MH}{}^2 + \overline{K}_{HM}{}^2)$ and $(b_5/2)(\overline{K}_{MH}{}^2 + \overline{K}_{HM}{}^2)$, where $\overline{K}_{MH}{}^2 = \overline{C}_A\overline{C}_{H^+}/\overline{C}_{MH}$, and b_{-4} and b_5 are the protonation rates of the two basic sites of the anionic species and these can be compared to the protonation rates of anionic bases, such as carboxylates and phenolates which lie between 3×10^{10} and 5×10^{10} M^{-1} s^{-1}. Therefore, rate constants a_{-4}, a_5, b_{-4}, and b_5 are expected to be of the same order of magnitude, thereby implying the following: (a) since, in most cases one of the thermodynamic terms $((\overline{K}_W/\overline{K}_{MH}{}^1 + \overline{K}_W/\overline{K}_{HM}{}^1)$ or $(\overline{K}_{MH}{}^2 + \overline{K}_{HM}{}^2))$ is much greater than the other (Table IV), the term k_0 reduces simply to k_0^a or k_0^b; and (b) a "mean" value for the a_{-4} and a_5 (or b_{-4} and b_5) rate constants can be calculated from the value of k_0^a or k_0^b.

It can be seen in Table IV that for compounds **1, 4–8** the "mean" values thus computed compare favorably to the known rate constants for the reactions of a cationic acid with the hydroxide ion or for the protonation of an anionic base. Compounds **2** and **3** yield too high values; but it should be noted in these cases that the k_0 term value is of little significance, since it contributes little to the rate law,[41] as illustrated by the small differences in the fits with and without the constant term as a parameter (Table II and Figure 5). Thus, it is clear that, in all these tautomeric systems, acid and base catalysis by the water suffices to account for the constant term, k_0, in the rate law.

Ahrens,[42] who was the first to apply T-jump relaxation spectroscopy to the tautomerism of heterocycles, reported the existence of an "uncatalyzed" proton transfer to explain the importance of the constant term, k_0, in the rate law of the tautomeric interconversion of 5′-deoxypyridoxal, a 3-hydroxypyridine (**2**) analogue. However, these data may be too imprecise[43] to definitely establish such a conclusion in contradiction with that observed for 3-hydroxypyridine.

II. Contribution of a "Nondissociative" Mechanism for Proton Transfer. For the tautomeric α-pyridines (compounds **9–13**), the constant terms, k_0, are significant, as is shown by the difference between the fits with and without the constant term (Table II), and lead to estimates for the rate constants

Table IV. Analysis of the Water-Catalyzed Tautomeric Interconversion

Compd	$\frac{\overline{K}_W}{\overline{K}_{MH^1}} + \frac{\overline{K}_W}{\overline{K}_{HM^1}}$, M	$\overline{K}_{MH^2} + \overline{K}_{HM^2}$, M	k_0, s^{-1}	$10^{-10} a_{45}$,[a] $M^{-1} s^{-1}$	$10^{-10} b_{45}$,[a] $M^{-1} s^{-1}$
4	1.85×10^{-7}	$<10^{-9}$	1 900	2 ± 0.4	
5	1.5×10^{-5}	$<10^{-10}$	100 000	1.3 ± 0.4	
5 (D_2O)	6.6×10^{-6}	$<10^{-10}$	28 300	0.86 ± 0.1	
6	7.56×10^{-7}	$<10^{-10}$	9 500	$2.5 \pm 0.$	
7	$<10^{-10}$	3.9×10^{-7}	6 500		3.3 ± 0.5
8	$<10^{-11}$	4.4×10^{-6}	55 000		2.5 ± 0.5
8 (D_2O)	$<10^{-11}$	1.8×10^{-6}	16 000		1.8 ± 0.4
1	7.1×10^{-10}	6.6×10^{-10}	50	7 ± 10^b	
2	2.1×10^{-9}	7.4×10^{-9}	880	18 ± 5^b	
3	2.3×10^{-10}	1.8×10^{-9}	370	36 ± 10^b	
9	$<10^{-11}$	1.85×10^{-7}	39 100		42 ± 4
10	$<10^{-10}$	1.4×10^{-8}	11 400		16 ± 2
11	$<10^{-10}$	3.9×10^{-8}	3 900		20 ± 4
12	$<10^{-10}$	6.5×10^{-8}	6 240		19 ± 7
13	$<10^{-10}$	$\sim 5 \times 10^{-9}$	4 000		160 ± 40

[a] a_{45} and b_{45} are the estimates of the "mean" values for a_4, a_{-5}, and for b_4, b_{-5}, respectively (see text). Errors on the $\overline{K}_Y{}^X$ terms are estimated to be ca. 10%. [b] For these compounds the a_{45} and b_{45} estimates cannot be distinguished.

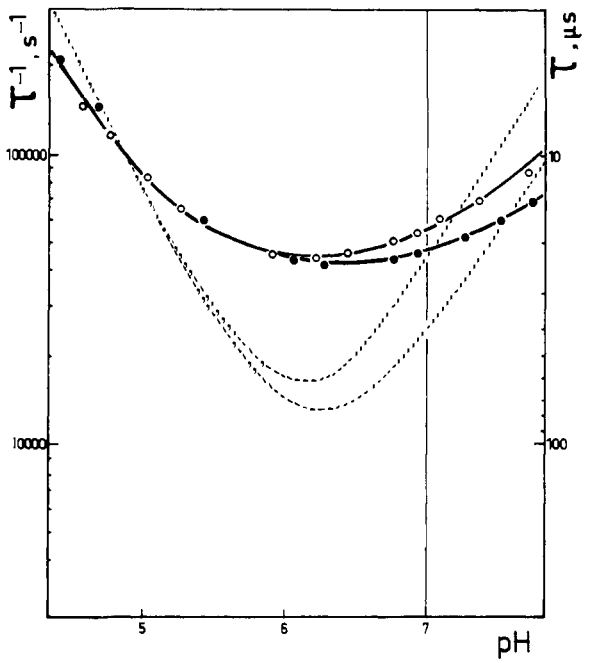
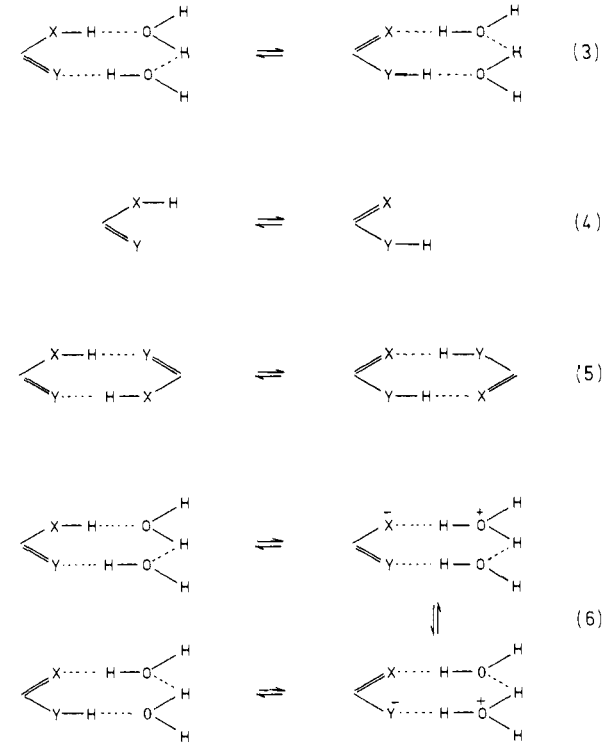


Figure 6. τ^{-1} as a function of pH for 6-chloro-2-pyridone (**9**) showing the contribution of a nondissociative proton transfer: (—) best fit of the experimental data with eq 2; (- - -) best fit obtained when setting the constant term, $k_0 = 2800\ s^{-1}$, the value expected from the base catalysis by water.[44] Concentrations: ○ 3.8×10^{-4} M and ● 1.8×10^{-4} M; λ 313 nm.

Scheme III



which are much higher than 10^{11} $M^{-1} s^{-1}$ (Table IV). Such high values cannot be attributed to protonation rates of anionic bases or deprotonation rates of cationic acids, as only two bimolecular reaction rate constants higher than 10^{11} $M^{-1} s^{-1}$ are known[3] in water: (a) the protonation of the fluoride anion with a 10^{11} $M^{-1} s^{-1}$ rate constant; and (b) the protonation of the hydroxide anion with a 1.6×10^{11} $M^{-1} s^{-1}$ rate constant. Moreover, the fits obtained by imposing a constant term value corresponding to that predicted[44] from acid or base catalysis by water differ significantly from those where the constant term is taken as a parameter, e.g., 6-chloro-2-pyridone (**9**) (Figure 6).

Therefore, we must admit the existence of a mechanism unrelated to the general acid-base catalyzed scheme (Table III). We call this mechanism "nondissociative" as it cannot proceed through the intermediate ionic dissociation of the tautomeric molecule.

Several mechanisms have been proposed for such nondissociative transfers (Scheme III). Using dynamic NMR data, Grunwald et al.[8,45-47] attribute the high constant term values in their rate laws to a concerted bifunctional proton transfer through water molecules (eq 3). However, in the case of cysteine, nondissociative proton-transfer rate constants have been estimated both from NMR data[46] and from ultrasonic relaxation data.[48] The last estimate exceeds the other by several orders of magnitude. To explain this discrepancy, it has been suggested[46] that the proton can also be transferred directly (eq 4). This last transfer would not affect the NMR signals. A concerted bifunctional mechanism has also been reported by Nesmeyanov et al.[49] from NMR data on imidazole and py-

Table V. Influence of Concentration upon the Nondissociative Proton-Transfer Rate Constant[a]

Compd	k_0, s^{-1}	$10^{-8}k_{A^-}$, $M^{-1}\ s^{-1}$	$10^{-10}k_{H^+}$, $M^{-1}\ s^{-1}$	ρ	N	Concn, M
6-Chloro-2-pyridone	38 000 ± 1200	4.4 ± 0.4	0.32 ± 0.015	0.999	10	1.8×10^{-4}
(**9**)	39 900 ± 1000	3.6 ± 0.2	0.28 ± 0.01	0.998	12	3.8×10^{-4}
Sulfapyridine	6 300 ± 400	3.3 ± 0.3	0.26 ± 0.04	0.978	8	0.86×10^{-4}
	6 500 ± 300	2.1 ± 0.17	0.32 ± 0.02	0.9997	13	1.6×10^{-4}
(**12**)	5 800 ± 140	2.3 ± 0.07	0.3 ± 0.01	0.99997	13	2.0×10^{-4}

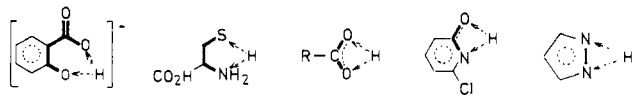
[a] These results were obtained by fitting separately eq 2 with the experimental data corresponding to different substrate concentration.

razole in ether/THF solutions. This time the transfer would occur through two or more substrate molecules (eq 5). However, in the systems described here, it is believed that the low substrate concentrations (under 10^{-3} M) virtually exclude any stacking and furthermore, such a mechanism would imply a substrate concentration dependence of the constant term, k_0; this is not observed when data corresponding to different substrate concentrations are fitted separately (Table V).

Other mechanisms, such as reversible ionization (eq 6), can be imagined, but at present it is not possible to state a preference between them. Further information can be gained from the kinetic study of tautomeric interconversion in varied solvent systems and will be reported later.

III. Structural Requirements for Nondissociative Proton Transfer. The relative positioning of the atoms between which the proton is transferred appears to influence markedly the importance of the nondissociative mechanism in the rate law. The efficiency of such a mechanism appears to decrease with the size of the "cyclic" system involving the tautomeric functional groups and the transferring hydrogen atom.

For six-membered "cycles", such as the salicylate anion system (I), the proton-transfer nondissociative rate constant[7]



I II III III' IV

exceeds $10^8\ s^{-1}$; for five-membered "cycles", such as the cysteine system (II), rate constants are estimated from $10^8\ s^{-1}$ [48] to $10^6\ s^{-1}$ [46] depending on the method of study; for four-membered "cycles", rate constants lie between $10^6\ s^{-1}$ for the carboxylic acid[8] system (III) and $10^3\ s^{-1}$ for pyridines (III'), depending upon the nature of the atoms involved in the transfer. Moreover, preliminary results from this laboratory on the tautomerism of substituted pyrazoles indicate that the contribution to the rate law of the nondissociative proton transfer is weak in the three-membered "cycle" of the pyrazole system (IV). In the here-studied tautomeric molecules having little tendency to form a cyclic system (i.e., the imidazole ring of adenine (**1**), the pyrimidine ring of cytosine (**4**) and isocytosine (**3**), β and γ tautomeric pyridines) the participation of the nondissociative mechanism is likely to be negligible.

Nevertheless, Chang and Grunwald[47] recently reported a dynamic NMR study of prototropic tautomerism giving $k_0 = (1.1 \pm 0.2) \times 10^8\ s^{-1}$ for the N(1)H-N(3)H proton transfer in the uracil monoanion (**14**) and $k_0 = (1.5 \pm 0.5) \times 10^6\ s^{-1}$ in the tautomerism of imidazole. These very high rates would indicate an important contribution from the nondissociative process. Clearly these experiments need some further confirmations.

Apparently the nature of the heteroatoms involved in the proton transfer influences the magnitude of the nondissociatve proton-transfer rate constants, at least for the four-membered "cycles" presented here. Thus, nitrogen to nitrogen transfer as in 2-sulfonylaminopyridines (**11, 12**) and 2-acylaminopyridines (**13**) appears slower than the nitrogen to oxygen transfer in α-pyridones. Furthermore, NMR studies of carboxylic acids[8] show that the transfer is even faster when it occurs between two oxygen atoms: in this case, rate constants of about $10^6\ s^{-1}$ are observed.

IV. Stability of the Abnormal Rare Tautomeric Forms of Uridine and Cytidine. It is interesting to examine the kinetics of the amino-imino tautomerism of cytidine (**15**) and the **16a** ⇌ **16b** tautomerism of uridine (**16**) in the light of our present work.

15a X = ribose 15b

16a X = ribose 16b

At neutral pH, the contribution of the general acid-base catalysis will reduce mainly to the rapid interconversion of the tautomeric form following pathway IIIa for cytidine and pathway IIIb for uridine, as predicted from the pK of the compounds[23] and the tautomeric equilibrium constants.[6,50] The lifetime of the rare forms can then be estimated as follows.

(a) Cytidine (15a ⇌ 15b). The imino form should be present in minute quantities.[6] Thus, the expression for the contribution of the water catalysis to the constant term reduces to $k_0^a = (a_5/2)(\overline{K}_W/\overline{K}_{HM^1})$. a_5 is estimated to be $1.7 \times 10^{10}\ M^{-1}\ s^{-1}$ (Table IV) and the pK of the imino form is taken equal to that of 3-methylcytidine, which leads[6] to $k_0^a = 10^5\ s^{-1}$ for the amino-imino tautomeric interconversion. This system is analogous to α-aminopyridines, and it has been observed that the contribution of the nondissociative nitrogen to nitrogen proton transfers lies between 10^3 and $10^4\ s^{-1}$. An accurate estimate of the lifetime of the rare tautomer can then be obtained by considering the general acid-base catalysis only.

(b) Uridine (16a ⇌ 16b). The equilibrium is greatly displaced in favor of the major form **16a.** Thus, the expression for the contribution of the water catalysis to the rate law reduces to $k_0^b = (b_5/2)(\overline{K}_{HM^2})$. b_5 is taken as equal to $3 \times 10^{10}\ M^{-1}\ s^{-1}$ (Table IV) and the pK of the rare OH form **16b** is estimated from the pK of uridine[23] and the **16a** ⇌ **16b** equilibrium constant.[50]

Then, the water-catalyzed rate constant is computed to be ca. 29 000 s^{-1} at 298 K, which is of the order of magnitude of the nitrogen to oxygen nondissociative proton transfer in α-pyridones. In that case, the nondissociative proton-transfer

mechanism will significantly reduce the lifetime of the rare tautomers as predicted from the general acid and basic catalysis scheme.

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(41) Moreover, a very slight systematic error (e.g., 10^{-6} M of a basic impurity such as HCO_3^- with a catalytic rate constant of $4 \times 10^8\ M^{-1}\ s^{-1}$) could account for a contribution to the k_0 term of $400\ s^{-1}$.
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(44) In the light of the results of Table IV it is reasonable to use $b_4 = b_{-5} = 3 \times 10^{10}\ M^{-1}\ s^{-1}$; then, for 6-chloro-2-pyridone, $k_0{}^b$ is computed to be ca. $2800\ s^{-1}$.
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