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(12) See paragraph concerning supplementary material at the end of this paper.
(13) Note that the second term in eq 4 becomes $k_{-1}k_{-2p}/k_{2p}$ and that $k_{-2p}/k_{2p} = k_{-2p}{}^{H}[H^+]/k_{2p}{}^{w} = k_{-2p}{}^{w}/k_{2p}{}^{OH}[OH^-] = k_{-2p}{}^{AH}[RR'NH_2{}^+]/k_{2p}{}^{A}[RR'NH] = k_{-2p}{}^{BH}[BH^+]/k_{2p}{}^{B}[B] = [H^+]/K_a{}^{\pm}$.
(14) Note that the $k_{-2p}{}^{AH}[RR'NH_2{}^+]$ term in eq 12 is equivalent to $k_{-2p}{}^{AH}[H^+][RR'NH]/K_a{}^{AH}$.
(15) Note that the $k_{-2p}{}^{BH}[BH^+]$ term in eq 15 is equivalent to $k_{-2p}{}^{BH}[H^+]\cdot[B]/K_a{}^{BH}$.
(16) The k_4 process probably involves the two steps $T_0 \rightarrow Ph_2C{=}N^+RR' + {}^-CH(NO_2)_2\ (H_2O) \rightarrow Ph_2C{=}O + RR'NH_2{}^+$.
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Rate of Protonation of 2,6-Di-*tert*-butylpyridine by the Hydronium Ion. Steric Hindrance to Proton Transfer

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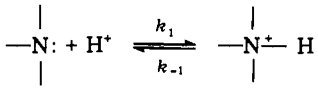
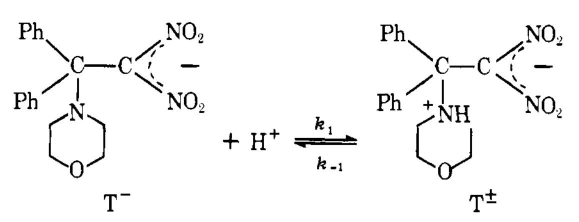
Abstract: The rate of protonation of 2,6-di-*tert*-butylpyridine by the hydronium ion was measured by the temperature-jump method in 20% dioxane–80% water (v/v) at 25 °C. The rate constant is $3.7 \pm 0.8 \times 10^8\ M^{-1}\ s^{-1}$, which is about 50 to 70 times lower than expected for a diffusion-controlled reaction. The rate reduction is attributed to a steric effect and represents one of the first cases where steric hindrance is seen to affect the rate of protonation of a nitrogen base by the *hydronium ion.* The results support the notion that the abnormally low basicity of 2,6-di-*tert*-butylpyridine is due to steric hindrance of solvation rather than due to steric compression of the N-H bond in the protonated base.

Most chemists know by now that thermodynamically favored proton transfers between oxygen or nitrogen acids and bases are usually diffusion controlled or nearly so.[1] In particular, the reaction of an amine with the hydronium ion in aqueous solution (eq 1) has k_1 values in the order of $10^{10}\ M^{-1}\ s^{-1}$ or slightly higher. Table I summarizes some typical rate constants.



$$—\overset{|}{\underset{|}{N}}: + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} —\overset{|}{\underset{|}{N}}{\overset{+}{—}}H \qquad (1)$$

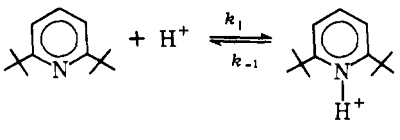
In a recent study of the nucleophilic addition of amines to 1,1-dinitro-2,2-diphenylethylene, we found that protonation of the morpholine adduct T^- on nitrogen by H^+ in 50% aqueous dimethyl sulfoxide (v/v) (eq 2) has a $k_1 = 4.2 \times 10^6\ M^{-1}\ s^{-1}$.[2] This is nearly 10^4 times lower than typical k_1 values for tertiary amines in water (Table I) and was attributed to a steric effect.[3]



(2)

Even though there are numerous precedents of steric hindrance to proton transfer from a *general acid* to a nitrogen base, or from a protonated amine to hydroxide ion or a general base,[1b,2,5] we could not find any report in the literature about steric hindrance to protonation of a nitrogen base by the *hydronium ion.* It therefore appeared desirable to look for examples other than reaction 2 where this phenomenon would be observable.[6]

In view of the rather large steric effect of the two *tert*-butyl groups on the pK_a of di-*tert*-butylpyridine,[7,8] we expected that steric hindrance might significantly lower k_1 in reaction 3. We



(3)

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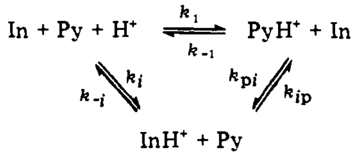
Table I. Rate Constants, k_1, for the Protonation of Amines by the Hydronium Ion in Water

amine	k_1, $M^{-1}\,s^{-1}$	ref
NH_3	4.3×10^{10}	Eigen[a]
piperidine	2.2×10^{10}	Eigen[a]
$(CH_3)_3N$	3.0×10^{10}	Grunwald[b]
$(C_2H_5)_3N$	2.7×10^{10}	Ralph et al.[c]
$(C_6H_5CH_2)_2NCH_3$	1.3×10^{10}	Grunwald et al.[d]
pyridine	$>10^{10}$	Eigen[a]
4-methylpyridine	2.79×10^{10}	Cocivera[e]
2-methylpyridine	2.36×10^{10}	Cocivera[e]
2,4-dimethylpyridine	2.78×10^{10}	Cocivera[e]
2,6-dimethylpyridine	2.88×10^{10}	Cocivera[e]

[a] Reference 1a. [b] E. Grunwald, *J. Phys. Chem.*, **71**, 1846 (1967). [c] Reference 5d. [d] E. Grunwald and E. K. Ralph III, *J. Am. Chem. Soc.*, **89**, 4405 (1967). [e] M. Cocivera, *J. Phys. Chem.*, **72**, 2520 (1968).

Scheme I



report here a temperature-jump study which confirms our hypothesis.

Results and Discussion

Due to the low solubility of di-*tert*-butylpyridine in water, the reaction was studied in 20% dioxane–80% water (v/v); the small amount of organic cosolvent is unlikely to significantly affect our results.[9] The reciprocal relaxation time which for reaction 3 is given by:

$$\frac{1}{\tau} = k_1(\bar{c}_{H^+} + \bar{c}_{Py}) + k_{-1} \tag{4}$$

was determined in unbuffered solutions as a function of di-*tert*-butylpyridine (Py) concentration and pH. We first attempted to follow the reaction by monitoring the change in the absorption of the pyridine or its conjugate acid around 270–280 nm. However, the signal-to-noise ratio was poor, mainly because of a small amplitude due to spectral overlap of the two species and a less than optimal sensitivity of our detection system at these wavelengths. Nevertheless, we obtained some approximate relaxation times in the order of 100 μs for typical runs where $\bar{c}_{Py} \simeq 2 \times 10^{-5}$ M and pH ~5.4. These relatively long relaxation times indicated that proton transfer is considerably slower than diffusion controlled.

More accurate relaxation times were obtained by using bromocresol green as an indicator and monitoring the reaction at 620 nm. In the presence of an indicator, Scheme I applies, where In and InH^+ refer to the basic and acidic forms of the indicator, respectively. Scheme I is characterized by two relaxation times. The first, which is shorter than the heating time of our temperature-jump apparatus, cannot be evaluated numerically, but it is easily detected as a large rapid deflection on the oscilloscope screen. The size of this deflection depends on the indicator concentration but not on the di-*tert*-butylpyridine concentration; in fact it is present even in the absence of di-*tert*-butylpyridine. It must therefore be associated with the $In + H^+ \rightleftharpoons InH^+$ reaction whose rate constants are known to be $k_i = 5.4 \times 10^{10}\ M^{-1}\,s^{-1}$ and $k_{-i} = 8.5 \times 10^5\ s^{-1}$.[10]

The much longer second relaxation time must then be associated with the remaining reactions in Scheme I and is given by:[11]

$$\frac{1}{\tau} = k_{-1} + k_1\left(\bar{c}_{H^+} + \bar{c}_{Py}\frac{1}{1+\alpha}\right) + k_{pi}\left(\bar{c}_{In} + \bar{c}_{PyH^+}\frac{\alpha}{1+\alpha}\right) + k_{ip}\left(\bar{c}_{InH^+} + \bar{c}_{Py}\frac{\alpha}{1+\alpha}\right) \tag{5}$$

with

$$\alpha = \bar{c}_{In}/(K_a^{InH} + \bar{c}_{H^+}) \tag{6}$$

where K_a^{InH} is the indicator acid dissociation constant.

Equation 5 can be simplified to:

$$\frac{1}{\tau} = k_{-1} + k_1\left(\bar{c}_{H^+} + \bar{c}_{Py}\frac{1}{1+\alpha}\right) \tag{7}$$

because the k_{pi} and k_{ip} terms are negligible, for the following reasons. The concentrations associated with the k_1, k_{pi}, and k_{ip} terms are all of the same order of magnitude, so that the relative importance of these terms depends only on the relative magnitude of k_1, k_{pi}, and k_{ip}, respectively. Even in the absence of steric effects, k_1 would be larger than k_{pi} and k_{ip}[12] by up to one order of magnitude.[1] Our preliminary results, in the absence of an indicator, showed that reaction 3 is substantially slower than expected for a sterically *un*hindered system. Thus, if the reaction of the (small) hydronium ion with a bulky base (k_1) is slowed down by a steric effect, steric retardation will be much more pronounced in the reaction of a large acid with the same bulky base (k_{ip}),[12] an expectation which is dramatically confirmed by reaction 2[2] as well as many other reactions.[1] Thus we conclude that k_{ip} and k_{pi} are negligible compared to k_1.[13]

Our results are summarized in Table II. By replacing k_1 with k_{-1}/K_a^{PyH}, where K_a^{PyH} is the acid dissociation constant of the protonated 2,6-di-*tert*-butylpyridine, and rearranging eq 7, one obtains:

$$k_{-1} = \frac{1}{\tau}\left[\frac{\bar{c}_{H^+} + \bar{c}_{Py}/(1+\alpha)}{K_a^{PyH}} + 1\right]^{-1} \tag{8}$$

The last column in Table II shows k_{-1} calculated by solving eq 8. By virtue of the relationship $K_a^{PyH} = k_{-1}/k_1$, one then obtains $k_1 = 3.7 \pm 0.8 \times 10^8\ M^{-1}\,s^{-1}$.

Our k_1 value corresponds to an approximately 50- to 70-fold

Table II. Reciprocal Relaxation Times and k_{-1} for Reaction 3 in 20% Dioxane–80% Water (v/v) at 25 °C[a]

$10^6\bar{c}_{H^+}$,[b] M	$10^5\bar{c}_{Py}$,[c] M	$10^5\bar{c}_{In}$,[d] M	α	$10^5\{\bar{c}_{H^+} + \bar{c}^{Py}/(1+\alpha)\}$, M	$10^{-3}\tau^{-1}$, s^{-1}	$10^{-3}k_{-1}$,[e] s^{-1}
3.24	1.49	1.89	1.11	1.03	8.3 ± 1.6	4.1 ± 0.8
4.78	1.54	1.85	0.99	1.25	9.9 ± 1.9	4.4 ± 0.9
3.63	2.51	1.98	1.14	1.53	8.3 ± 1.6	3.3 ± 0.7
11.2	2.26	1.65	0.66	2.48	12.2 ± 2.4	3.5 ± 0.7
22.9	2.31	1.50	0.41	3.92	15.7 ± 3.1	3.2 ± 0.6
					av	3.7 ± 0.8

[a] μ = 1.0 M (KCl). [b] Calculated as $\bar{c}_{H^+} = 10^{-pH}$ without activity coefficient corrections. [c] $\bar{c}_{Py} = K_a^{PyH}[PyH^+]_0/(K_a^{PyH} + \bar{c}_{H^+})$ with pK_a^{PyH} = 5.00. [d] $\bar{c}_{In} = K_a^{InH}[InH]_0/(K_a^{InH} + \bar{c}_{H^+})$ with pK_a^{InH} = 5.00. [e] From eq 8.

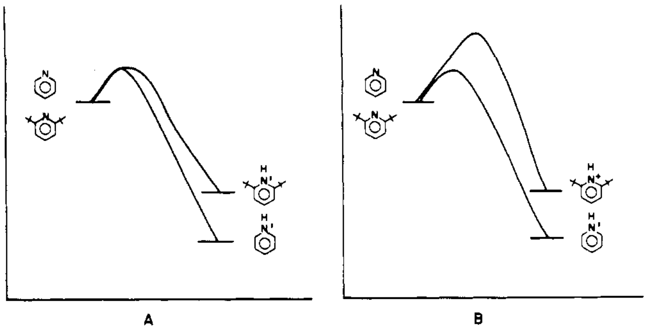
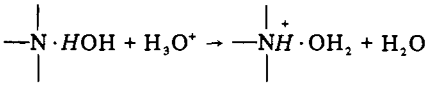


Figure 1. Potential energy vs. reaction coordinate profile for the protonation of pyridine and of 2,6-di-*tert*-butylpyridine, respectively. A shows steric effect affecting k_{-1} step. B shows steric effect affecting k_1 step.

rate reduction compared to the protonation of an unhindered tertiary amine (Table I); this reduction is less dramatic than that for reaction 2 but slightly larger than the one found for the protonation of the sterically hindered anion of dipicrylamine.[6]

Our results are interesting in a different context. Brown et al.,[7] who had observed that 2,6-di-*tert*-butylpyridine is 1.4 pK_a units less basic than expected based on inductive effects, attributed this observation to a steric effect of the two *tert*-butyl groups. This effect was understood to be either a steric compression of the N-H bond in the protonated form or to arise from interference with the solvation of the protonated base. Brown et al. preferred the first interpretation, but subsequent work showed that steric hindrance of solvation is a better explanation, perhaps coupled with some increase in the rotational barrier of the *tert*-butyl group in the protonated form.[8]

Our kinetic results appear to support these latter views. If the main factor were a steric compression of the N-H bond of the protonated base, the decrease in pK_a should come about through an increase in k_{-1} (Figure 1A) rather than a decrease in k_1 (Figure 1B) as observed. The observed decrease in k_1 can in fact account for the entire decrease in pK_a, indicating that k_{-1} is not significantly affected. This interpretation is also consistent with the notion that the protonation of amines by the hydronium ion should be represented by eq 9 as shown by Grunwald et al.[14] Steric hindrance probably affects solvation of both the neutral and the cationic form of the amine, but since solvation is presumably more important for the stabilization of the cationic form the energetic consequences of hindered solvation are mainly felt by the cationic form and by the transition state as shown in Figure 1B.


(9)

$$-\overset{|}{\underset{|}{\mathrm{N}}}\cdot \mathit{H}\mathrm{OH} + \mathrm{H_3O^+} \rightarrow -\overset{|}{\underset{|}{\mathrm{N}}}\overset{+}{\mathit{H}}\cdot\mathrm{OH_2} + \mathrm{H_2O} \qquad (9)$$

Experimental Section

Materials. 2,6-Di-*tert*-butylpyridine (Chemical Samples Co.) was obtained 99% pure. The dihydrochloride[7] was prepared by passing HCl gas through an ether solution of 2,6-di-*tert*-butylpyridine, mp 143 °C. *p*-Dioxane was purified by the method of Fieser,[15] stored over sodium, and distilled as needed. Bromocresol green and KCl were reagent grade and were used without further purification.

pK_a Measurements. The pK_as of 2,6-di-*tert*-butylpyridinium ion and of bromocresol green were determined in 20% dioxane-80% water (v/v) at μ = 1.0 M (KCl) by a standard spectrophotometric procedure, using an acetic acid-acetate buffer.

Kinetics. Our kinetic data were obtained on a Messanlagen temperature-jump apparatus. Jumps of 1.2 °C were used; larger jumps caused cavitation problems even after degassing the solutions. The heating time of the apparatus under our reaction conditions was checked by the indicator method,[16] using bromocresol green and was found to be ~5 μs. In a typical experiment the solution containing the appropriate amounts of 2,6-di-*tert*-butylpyridine, indicator, and KCl was brought to the approximately desired pH by the addition of a few drops of concentrated HCl or KOH. It was then placed into the T-jump cell, thermostated, and degassed. The pH was measured again in the T-jump cell immediately before and after a temperature jump. The pH values before and after the jump were usually not exactly the same, but never varied more than 0.15 unit. In calculating concentrations, the pH value measured after the jump was used. The relaxation times were obtained by averaging at least three oscilloscope pictures.

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(3) The factor of ~10^4 slightly overestimates the rate reduction because reaction 2 was studied in a solvent with a viscosity approximately threefold higher than that of water.[4] This implies that the diffusion-controlled rate constants listed in Table I would be about threefold lower in 50% aqueous dimethyl sulfoxide. Thus the rate reduction due to the steric effect alone is closer to a factor of 1–3 × 10^3.

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(12) Since pK_a^{InH} = pK_a^{PyH}, we have $k_{pi} = k_{ip}$.

(13) We have belabored this point in response to a comment by a referee who suggested that our slow reaction process might be due to the reaction $\mathrm{PyH^+} + \mathrm{In} \rightleftharpoons \mathrm{Py} + \mathrm{InH^+}$ with $k_{pi} = 0.8 \times 10^8\ \mathrm{M^{-1}\ s^{-1}}$. This interpretation would mean that $k_1 \ll k_{pi} = 0.8 \times 10^8$ and imply that protonation of our amine by the hydronium ion is much slower than protonation by a general acid whose pK_a is the same as that of the amine. Even without considering steric effects, this would contradict everything we know about proton transfer reactions.[1,5]

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