(0.244 g, 2 mmol) as done with **18**. The crude product upon flash chromatography yielded 0.45 g of the diacetate **25** (58%), mp 35 °C (mixture melting point, elution with petroleum ether).

Reaction of 26a with Acetic Anhydride and DMAP. To a mixture of acetic anhydride (0.44 g, 4.4 mmol) and DMAP (0.244 g, 2 mmol) was added the carbinol **26a**. The reaction mixture was heated with stirring at 85–90 °C for 4 h. The crude product obtained after the usual workup gave 0.18 g of **27a** (71%, elution with petroleum ether), 0.05 g of **28a** (15%, elution with 1:19 ether–petroleum ether), and 0.04 g of **26a**. The products were compared with the authentic samples.

Reaction of 26b with Acetic Anhydride and DMAP. The reaction was carried out under identical conditions as above with **26b** (0.272 g, 2 mmol), acetic anhydride (0.44 g, 4.4 mmol), and DMAP (0.244 g, 2 mmol). The crude product upon flash chromatography yielded 0.17 g of **27b** (66%, elution with petroleum ether) and 0.08 g of **28b** (18%, elution with 1:19 ether–petroleum ether). The products were compared and confirmed with the authentic samples.

Reaction of 26c with Acetic Anhydride and DMAP. The tertiary alcohol **26c** (0.396 g, 2 mmol) was treated under identical conditions as earlier with acetic anhydride (0.44 g, 4.4 mmol) and DMAP (0.244 g, 2 mmol). The crude product upon purification by flash chromatography yielded 0.13 g of **29** (52%, elution with petroleum ether), 0.158 g of **27c** (46%, elution with petroleum ether), and 0.11 g of unreacted starting alcohol (elution with 1:19 ether–petroleum ether). The products were compared with the authentic samples.

Reaction of Pinacol 1a with Propionic Anhydride and DMAP. To a mixture of propionic anhydride (0.858 g, 6.6 mmol) and DMAP (0.366 g, 3 mmol) was added **1a** (0.354 g, 3 mmol). The reaction mixture was heated with stirring at ca. 80 °C for 4 h. The crude product upon flash chromatography lead to 0.3 g of **30** (71%, elution with 1:19 ether–petroleum ether), 0.085 g of **31** (15%, elution with 1:19 ether–petroleum ether), and 0.07 g of unreacted pinacol (elution with 1:5 ether–petroleum ether). Compound **30**: IR (thin film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (t, 3 H, J = 7.5 Hz), 1.1 (s, 6 H), 1.4 (s, 6 H), 2.23 (q, 2 H, J = 7.5 Hz), 2.9 (s, 1 H, D_2O exchangeable). Compound **31**: IR ($CHCl_3$) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (t, 3 H, J = 7.5 Hz), 1.1 (s, 6 H), 1.27 (d, 3 H, J = 6 Hz), 1.45 (s, 6 H), 2.47 (q, 2 H, J = 7.5 Hz), 3.35 (q, 1 H, J = 6 Hz).

Reaction of 26a with Propionic Anhydride and DMAP. The tertiary alcohol **26a** (0.228 g, 2 mmol) was added with stirring to a mixture of propionic anhydride (0.572 g, 4.4 mmol) and DMAP (0.244 g, 2 mmol). The crude product upon flash chromatography yielded 0.2 g of **32** (75%, elution with petroleum ether), 0.07 g of **33** (21%, elution with petroleum ether), and 0.05 g of unreacted alcohol (elution with 1:19 ether–petroleum ether). Compound **32**: IR (thin film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (t, 3 H, J = 7 Hz), 1.43 (s, br, 13 H), 2.23 (q, 2 H, J = 7 Hz). Compound **33**: IR (CCl_4) 1710, 1730 cm^{-1}; ^1H NMR (CCl_4) δ 1.1 (t, 3 H, J = 6 Hz), 1.3 (d, 3 H, J = 6 Hz), 1.5 (s, br, 13 H), 2.5 (q, 2 H, J = 6 Hz), 3.37 (q, 1 H, J = 6 Hz).

Registry No. **1a**, 76-09-5; **1b**, 2888-11-1; **1c**, 5181-75-9; **1d**, 1124-96-5; **2a**, 19424-29-4; **2b**, 87122-14-3; **2c**, 91328-29-9; **2d**, 91328-31-3; **3**, 91328-26-6; **4**, 91328-40-4; **5**, 91328-32-4; **6**, 5781-64-6; **7**, 91328-28-8; **8**, 91328-30-2; **9**, 20127-81-5; **10**, 91328-27-7; **15**, 76937-02-5; **18**, 69814-59-1; **23**, 520-45-6; **24**, 80649-14-5; **25**, 14019-65-9; **26a**, 590-67-0; **26b**, 617-94-7; **26c**, 599-67-7; **27a**, 16737-30-7; **27b**, 3425-72-7; **28a**, 91328-33-5; **28b**, 91328-34-6; **29**, 612-00-0; **30**, 91328-35-7; **31**, 91328-36-8; **32**, 91328-37-9; **33**, 91328-38-0; DMAP, 1122-58-3; $(CH_3CO)_2O$, 108-24-7; $(C_2H_5CO)_2O$, 123-62-6; 2-(bromomethyl)-4,4,5,5-tetramethyl-1,3-dioxolane, 91328-39-1.

Kinetic Study of the Reaction of *N*-(2,4-Dinitrophenyl)imidazole with Piperidine and *n*-Butylamine

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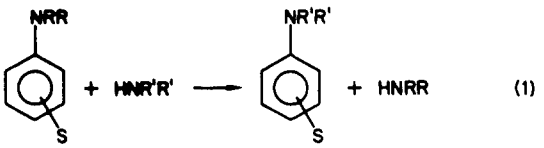
The reaction of *N*-(2,4-dinitrophenyl)imidazole, **1**, with piperidine and *n*-butylamine was studied. The reaction with piperidine is catalyzed by hydroxide ion and by the amine while the reaction with *n*-butylamine is weakly catalyzed by hydroxide ion. The hydrolysis of the substrate competes with the aminolysis reaction. The base catalysis in the reaction of **1** with piperidine is shown to be a consequence of rate-limiting deprotonation of the zwitterionic intermediate complex, followed by spontaneous (noncatalyzed) leaving group expulsion. On the other hand, the small rate aceleration observed in the reaction of butylamine as well as the catalysis of the hydrolysis reaction by *n*-butylamine and piperidine is considered of unclear origin.

Aryl transfer from one amine to another as in eq 1 is considered to be a difficult reaction because the amine nucleophile usually adds to an unsubstituted ring position.[1]



(1)

However, we have found that imidazole is a moderately good leaving group for nucleophilic aromatic substitution[2,3] and (2,4,6-trinitrophenyl)imidazole reacts quite easily with *n*-butylamine,[3] although when piperidine is the nucleophile, the predominant reaction is the hydrolysis of the substrate[4] indicating that piperidine cannot compete with OH^-. This result is quite unexpected since piperidine is usually a better nucleophile than HO^- and *n*-butylamine.[5] We attribute the anomalous behavior of piperidine to steric crowding at the transition state for the formation of the zwitterionic intermediate.

(1) de Rossi, R. H.; Nuñez, A. *J. Org. Chem.* **1982**, *47*, 319 and references cited therein.

(2) de Rossi, R. H.; de Vargas, E. B. *J. Am. Chem. Soc.* **1981**, *103*, 1533.
(3) de Vargas, E. B.; de Rossi, R. H. *Tetrahedron Lett.* **1982**, *23*, 4423.
(4) Unpublished results from this lab.
(5) Bernasconi, C. F.; *MTP Int. Rev. Sci.: Org. Chem. Ser. One* **1973**, *3*, 33.

0022-3263/84/1949-3978$01.50/0

Table I. Reaction of (2,4-Dinitrophenyl)imidazole with Piperidine in Water at 25 °C[a]

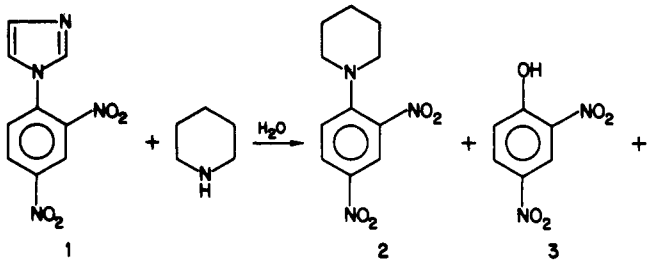
pH	$[Pip]_{eff}$, M	f_A[b]	$10^5 k_{obsd}$, s^{-1}	$10^4 k_A$, M^{-1} s^{-1}	$10^6 k'_H$, s^{-1}
11.18[c]	0.0572	0.682	1.30	1.55	4.1
11.18[c]	0.100	0.770	2.38	1.87	5.5
11.18[c]	0.143	0.796	3.62	2.02	7.4
11.18[d]	0.142	0.822	3.95	2.28	7.0
11.18[d]	0.178	0.864	6.40	3.11	8.7
11.18[d]	0.213	0.876	7.90	3.24	9.8
11.18[d]	0.249	0.895	9.72	3.49	10.2
10.99[e]	0.147	0.848	4.70	2.71	7.1
10.99[e]	0.182	0.934	6.13	3.15	4.0
11.05[e]	0.240	0.996	8.87	3.67	
11.05[e]	0.281	1	13.5	4.80	
10.40[f]	0.0854	1	0.865	1.01	
10.60[f]	0.0982	1	1.18	1.20	
10.83[f]	0.1099	1	1.33	1.21	
11.00[f]	0.0981	0.856	1.42	1.24	2.0
11.40[f]	0.0985	0.859	1.93	1.69	2.7

[a] Solvent contains 2% dioxane; ionic strength 1 M(NaCl); piperidine buffer. [b] Fractional yield of aminolysis product = $[2]_{calcd}/[2]_{calcd} + [3]_{calcd}$. In all cases $[2]_{calcd} + [3]_{calcd} = [1]_0$ within 2%. [c] $[1]_0 = 4.83 \times 10^{-5}$ M. [d] $[1]_0 = 4.66 \times 10^{-5}$ M. [e] $[1]_0 = 4.53 \times 10^{-5}$ M. [f] $[1]_0 = 4.32 \times 10^{-5}$ M.

We have now carried out a study of the reaction of *n*-butylamine and piperidine with (2,4-dinitrophenyl)-imidazole, **1**, which is less reactive than (2,4,6-trinitrophenyl)imidazole but has one unsubstituted ortho position and thus it has less steric requirements.

Results

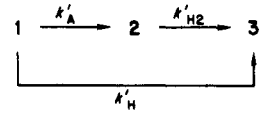
Reactions with Piperidine. The reaction of (2,4-dinitrophenyl)imidazole (**1**) with piperidine leads to the formation of (2,4-dinitrophenyl)piperidine (**2**) and 2,4-dinitrophenol (**3**) (eq 2).



The yield of the aminolysis product is higher than 70% at pH below 11.4 (Table I) but at higher pH the reaction becomes complicated because of the hydrolysis of the product **2** (see below).

The aminolysis reaction is strongly catalyzed by OH^- and the plot of the second-order rate constant k_A (defined in the Experimental Section) vs. $[OH^-]$ is curvilinear (Figure 1). The reaction is also catalyzed by piperidine, with k_A increasing linearly with piperidine concentration (Figure 2) at constant pH.

At OH^- concentrations higher than 0.01 M the hydrolysis of **2** occurs at rates similar to the aminolysis of **1**, thus the system has to be treated as two consecutive and competitive reactions (eq 3).



(3)

In eq 3, k'_A represents the pseudo-first-order rate constant for the piperidinolysis of **1** and k'_{H2} and k'_H are

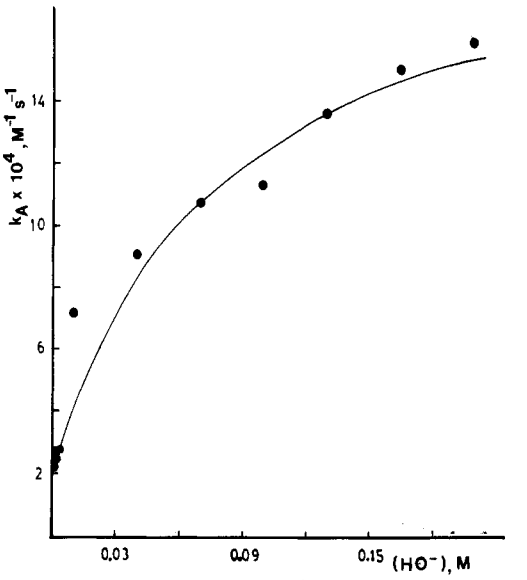


Figure 1. Plot of k_A vs. $[HO^-]$ concentration for the reaction of (2,4-dinitrophenyl)imidazole with piperidine in water at 25 °C. Solvent contains 2% dioxane. Data from Tables I and II. $[Pip]_{eff}$ = 0.188 – 0.192 M. The line was calculated from the values of k_1, k_3^{OH}/k_{-1}, and k_3^{Pip}/k_{-1} given in Table V and $k_2/k_{-1} = 0$.

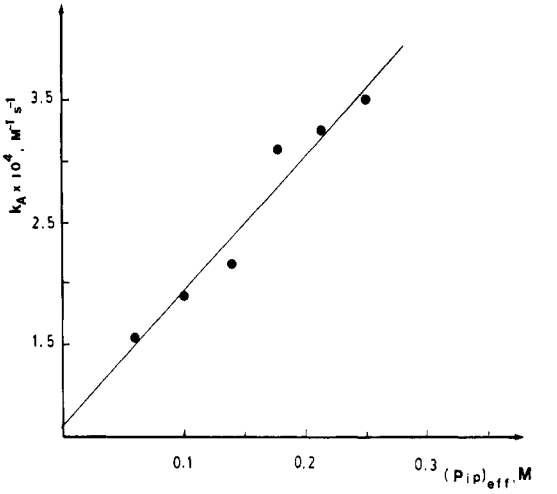


Figure 2. Plot of k_A vs. $[Pip]_{eff}$ for the reaction of (2,4-dinitrophenyl)imidazole with piperidine in water at 25 °C. Solvent contains 2% dioxane. pH = 11.18, ionic strength 1 M (NaCl), slope = 1.07×10^{-3} M^{-2} s^{-1}, intercept = $(8 \pm 1) \times 10^{-5}$ M^{-1} s^{-1}, correlation coefficient = 0.995.

pseudo-first-order rate constants for the hydrolysis of **2** and **1**, respectively. The values of these rate constants were obtained by adjusting the measured absorbance to eq 4.[6,7]

$$A = \frac{[1]_0\,(k'_A)}{k'_{H2} - (k'_A + k'_H)}[e^{-(k'_A+k'_H)t} - e^{-k'_{H2}t}](\epsilon_2 - \epsilon_3) + \epsilon_3[1]_0[1 - e^{-(k'_A+k'_H)t}] \quad (4)$$

(6) Equation 4 is derived from the differential change in **1**, **2**, and **3** with time, which integrated with the boundary conditions $[2]_0 = [3]_0 = 0$ give the following expressions

$$[1] = [1]_0 e^{-(k'_A+k'_H)t}$$

$$[2] = [1]_0 \frac{k'_A}{k'_{H2} - (k'_A + k'_H)}(e^{-(k'_A+k'_H)t} - e^{-(k'_{H2}t)})$$

$$[3] = [1]_0 - [2] - [1]$$

ϵ_2 and ϵ_3 are the extinction coefficients of **2** and **3**, respectively.

Table II. Rate Constants for the Reaction of (2,4-Dinitrophenyl)imidazole with Piperidine at High pH in Water at 25 °C[a]

pH	$[Pip]_{eff}$, M	[NaOH], M	$10^4k'_A$,[b] s^{-1}	$10^4k'_{H2}$,[c] s^{-1}	$10^5k'_H$,[d] s^{-1}
12.26	0.175	0.010	1.26	0.565	0.962
12.44	0.183	0.040	1.67	0.657	3.79
12.59	0.187	0.070	2.02	0.630	6.57
12.70	0.190	0.100	2.14	0.750	9.24
12.79	0.192	0.129	2.64	0.756	11.8
12.87	0.193	0.165	2.92	1.03	13.9
12.93	0.194	0.199	3.09	1.5	16.5

[a] Rate constants calculated by adjusting the absorbance vs. time data to eq 4. Solvent contains 2% dioxane; ionic strength 1 M (NaCl); $[1]_0 = 4.44 \times 10^{-5}$ M. [b] Pseudo-first-order rate constant for the aminolysis of 1. [c] Pseudo-first-order rate constant for the hydrolysis of 2. [d] Pseudo-first-order rate constant for the hydrolysis of 1.

Table III. Reaction of (2,4-Dinitrophenyl)imidazole with *n*-Butylamine in 10% Dioxane–90% Water at 25 °C[a]

$[BuNH_2]_{eff}$, M	f_A[b]	10^5k_{obsd}, s^{-1}	10^4k_A, M^{-1} s^{-1}	$10^6k'_H$, s^{-1}
0.00978[c]	0.929	0.325	3.09	0.23
0.0330[c]	0.955	1.01	2.92	0.45
0.0658[c]	0.973	2.20	3.25	0.60
0.0954[c]	0.955	2.93	2.94	1.30
0.0296[d]	0.947	0.854	2.73	0.45
0.0662[d]	0.952	1.99	2.85	1.00
0.0952[d]	0.925	2.93	2.85	2.20
0.1198[d]	0.942	3.61	2.84	2.10
0.0180[e]	0.996	0.470	2.61	*f*
0.0287[e]	0.944	0.866	2.85	0.48
0.0636[e]	0.936	1.98	2.91	1.27
0.0898[e]	0.945	2.91	3.06	1.60

[a] Ionic strength = 1 M (NaCl), *n*-$BuNH_2$ buffer, $[1]_0 = 4.40 \times 10^{-5}$ M. [b] Fractional yield of aminolysis product = $[4]_{calcd}/[4]_{calcd} + [3]_{calcd}$. [c] pH = 10.80. [d] pH = 10.60. [e] pH = 10.20. [f] Cannot be determined because of the small yield of the hydrolysis product.

The calculated values are summarized in Table II.

Reactions with *n*-Butylamine. The reaction of *n*-butylamine with 1 gives the corresponding products of aminolysis, *N*-(*n*-butyl)-2,4-dinitroaniline 4, and hydrolysis 3.

The rate constant for the aminolysis reaction, k_A, does not change within experimental error when the concentration of *n*-butylamine varies at constant pH with a mean value of $(2.9 \pm 0.1) \times 10^{-4}$ M^{-1} s^{-1} (Table III).

On the other hand, there is not a very significant increase in k_A with the HO^- concentration at constant *n*-butylamine concentration but, the change observed is outside the experimental error. In Figure 3 it can be seen that k_A shows square dependence on HO^- concentration. The same behavior was found using KOH instead of NaOH and KCl as compensating electrolyte (Table IV).

The aminolysis product, *N*-(*n*-butyl)-2,4-dinitroaniline, 4, does not hydrolyze under the reaction conditions, but at hydroxide concentrations higher than 0.1 M unidentified products are formed in about 20%. When the reactions are carried out under N_2 in degassed solutions the unidentified products disappear. Besides, the aminolysis rate is almost unchanged at HO^- concentration below 0.1 M but there is about a 40% decrease in k_A when the concentration of HO^- is 0.2 M which brings the value of k_A to the same value found at lower OH^- concentration. It appears then that the second-order dependence of k_A with the OH^- concentration is related to the presence of O_2 in the system. We have not yet found an explanation for this behavior.

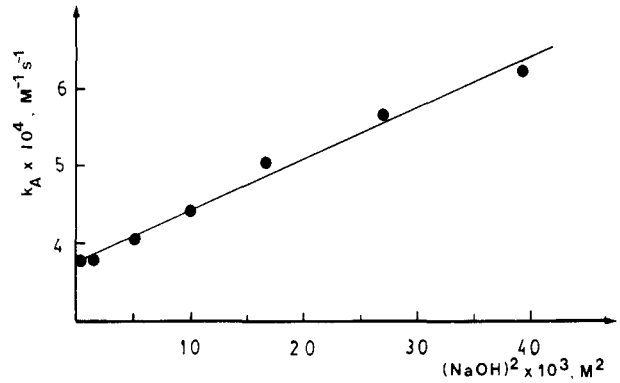


Figure 3. Plot of k_A vs. the square concentration of HO^- for the reaction of (2,4-dinitrophenyl)imidazole with *n*-butylamine in water at 25 °C. Solvent contains 10% dioxane. Data from Table IV. $[n\text{-}BUNH_2]_{eff} = 0.19$ M. Slope = 6.50×10^{-3} M^{-3} s^{-1}. Intercept = 3.80×10^{-4} M^{-1} s^{-1}. Correlation coefficient = 0.997.

Table IV. Reaction of 2,4-Dinitrophenylimidazole with *n*-Butylamine in 10% Dioxane–90% Water at 25 °C. Dependence on Hydroxide Ion Concentration[a]

$[BuNH_2]_{eff}$, M	$[HO^-]$, M	10^4k_{obsd}, s^{-1}	f_A[b]	10^4k_A, M^{-1} s^{-1}	f_H[c]	$10^5k'_H$, s^{-1}
Reactions with NaOH[d]						
0.184	0.010	0.948	0.734	3.78	0.218	2.07
0.184[e]	0.010	0.921	0.694	3.47	0.260	2.39
0.189	0.040	1.29	0.554	3.78	0.394	5.08
0.190	0.070	1.72	0.448	4.05	0.484	8.32
0.191	0.100	2.15	0.392	4.41	0.504	10.8
0.191	0.100	2.15	0.392	4.41	0.507	10.9
0.191[e]	0.099	2.19	0.410	4.70	0.590	12.9
0.191	0.129	2.55	0.369	4.93	0.509	13.0
0.191	0.129	2.61	0.374	5.11	0.514	13.4
0.192	0.165	3.12	0.358	5.82	0.473	14.8
0.192	0.165	3.15	0.333	5.47	0.514	16.2
0.192	0.199	3.42	0.227	4.04	0.642	22.0
0.192	0.199	3.38	0.351	6.20	0.459	15.5
0.192[e]	0.200	3.61	0.209	3.93	0.756	27.3
Reactions with KOH[f]						
0.188	0.010	1.01	0.739	3.97	0.243	2.45
0.191	0.040	1.47	0.543	4.18	0.419	6.16
0.192	0.067	1.90	0.441	4.36	0.502	9.54
0.192	0.101	2.36	0.392	4.82	0.550	13.0
0.192	0.130	2.93	0.365	5.57	0.540	15.8
0.192	0.165	3.30	0.354	6.09	0.520	17.2
0.192	0.201	4.08	0.347	7.40	0.500	20.4

[a] $[1]_0 = 4.40 \times 10^{-5}$ M; ionic strength 1 M. [b] Fractional yield of aminolysis product = $[4]_{calcd}/[1]_0$. [c] Fractional yield of hydrolysis product = $[3]_{calcd}/[1]_0$. [d] NaCl as compensating electrolyte. [e] Reaction made under nitrogen. [f] KCl as compensating electrolyte.

The Hydrolysis Reaction. Our data allow the calculation of the rate of hydrolysis of 1 under several conditions. The pseudo-first-order rate constants k'_H obtained from the reactions of 1 with piperidine (Table II) and *n*-butylamine (Table IV) show linear dependence with the OH^- concentration with slopes 8.2×10^{-4} and 8.6×10^{-4} M^{-1} s^{-1}, respectively. These values agree very well with the second-order rate constant for the hydrolysis of 1 separately determined (in the absence of amine), i.e., 9.6×10^{-4} M^{-1} s^{-1}. In both cases the plots have significant intercepts, which indicates some kind of catalysis of the hydrolysis reaction by the amines. Besides, in the reactions carried out at constant pH, the rate of hydrolysis increases with the concentration of the amine (see for instance the data at pH = 11.18 in Table I and the data reported in Table III). Although these results could be attributed to errors in the determination of k'_H due to the low yield of 3, the increase is too high to be justified only by experi-

(7) The computer program used was modified from the one published: Wiberg, K. B. "Physical Organic Chemistry"; John Wiley and Sons: New York, 1964; p 570. The assistance of Dr. A. B. Pierini is greatly acknowledged.

Table V. Reactions of 1-Substituted-2,4-dinitrobenzenes with Piperidine. Disection of Rate Coefficients of Elementary Steps

1-substituent	pK_a	10^3k_1, M^{-1} s^{-1}	k_2/k_{-1}	k_3^{Pip}/k_{-1}, M^{-1}	k_3^{OH}/k_{-1}, M^{-1}	$10^{-7}k_{-1}$, s^{-1}	$10^{-8}k_3^{Pip}$, M^{-1} s^{-1}
phenoxy[a]	9.99	31.1	0.069	7.86	121	3.3	2.6
imidazole[b]	14.2[c]	2.1	$\ll 1$	0.51	13.8	29[d]	1.48[e]
methoxy[a]	16.7	3.77	10^{-4}	0.15	25.7		2.6

[a] Data in 10% dioxane at 25 °C from ref 7. [b] This work. [c] Walbee, H.; Isensee, R. W. *J. Am. Chem. Soc.* **1955**, *77*, 5488. [d] Calculated from k_3^{OH}/k_{-1} assuming $k_3^{OH} = 4 \times 10^9$ M^{-1} s^{-1} taken from ref 14. [e] Calculated from k_3^{Pip}/k_{-1}.

mental error. Furthermore a similar increase is also observed in related reactions.[8] The rate was measured in degassed solutions in three instances (Table IV) and it was found that the ratio k'_H (N_2)/k'_H (O_2) for the hydrolysis reaction in degassed solutions (under N_2) and the hydrolysis in the normal solutions (under air) increased from 1.15 to 1.46 in 0.01 and 0.19 OH^- concentration, respectively.

The fact that there are changes in the relative yield of products in the reactions of *n*-butylamine with 1 carried out under N_2 and O_2 may indicate the involvement of radical anions and perhaps a mechanism of the type proposed by Abe.[9] However, we do not have enough evidence for this or another mechanism, thus we will not discuss it further. A study of the hydrolysis of **2** is underway and will be reported shortly.

Discussion

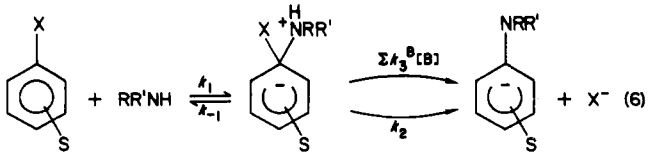
The reaction of (2,4,6-trinitrophenyl)imidazole with *n*-butylamine was found to be specific acid catalyzed,[3] and the suggested mechanism is described in Scheme I.

For this reaction pH independence of the rate was observed at $[H^+] \approx 10^{-9}$ M. The observed second-order rate constant for this mechanism is given by eq 5 and at pH <9 $k_3[H^+]/K_H$ is high and k_1 becomes rate determining.

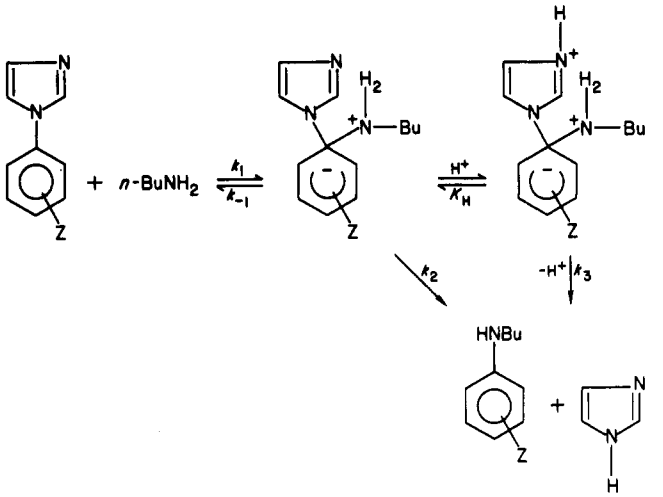
$$k_A = \frac{k_1[k_2 + (k_3/K_H)[H^+]]}{k_{-1} + k_2 + (k_3/K_H)[H^+]} \quad (5)$$

With (2,4-dinitrophenyl)imidazole and *n*-butylamine or piperidine as nucleophiles, the specific acid catalyzed pathway could not be detected because the reactivity of this substrate is lower than that of (2,4,6-trinitrophenyl)imidazole and we could not work at pH lower than 10.2. However, we found that the reaction with piperidine was catalyzed by piperidine and HO^- and the reaction of *n*-butylamine was weakly catalyzed by HO^- although in the last case the mechanism of catalysis is of unclear origin.[10]

The mechanism of base catalysis for the reaction of amines with aromatic substrates is described in eq 6,[5] where k_1 and k_{-1} have the same meaning as in Scheme I, k_3^B and k_2 represent the rate coefficients for the base catalyzed and spontaneous or solvent catalyzed product-forming steps, respectively.



Scheme I



Z = 2,4,6-trinitro

The observed second-order rate constant for the piperidinolysis reaction can be represented by eq 7 (B = OH^- and piperidine).

$$\frac{v}{[1][Pip]} = k_A = \frac{k_1[k_2 + k_3^{OH}[OH^-] + k_3^{Pip}[Pip]]}{k_{-1} + k_2 + k_3^{OH}[OH^-] + k_3^{Pip}[Pip]} \quad (7)$$

The fact that k_A is linearly dependent on the piperidine concentration indicates that $(k_3^{Pip}/k_{-1})[Pip] \ll 1$ which simplifies eq 7 to eq 8 if also $(k_2/k_{-1}) + (k_3^{OH}/k_{-1})[HO^-] \ll 1$.

$$k_A = \frac{k_1k_2}{k_{-1}} + \frac{k_1k_3^{OH}}{k_{-1}}[HO^-] + \frac{k_1k_3^{Pip}}{k_{-1}}[Pip] \quad (8)$$

Then, from the slope of the linear plot (Figure 2) $k_1k_3^{Pip}/k_{-1}$ is reckoned as 1.07×10^{-3} M^{-2} s^{-1}. The value of k_1 is known from the data at high HO^- concentration (see below) thus k_3^{Pip}/k_{-1} can be obtained (Table V).

On the other hand, the curvilinear dependence of k_A on OH^- concentration indicates that under these conditions $k_{-1} \lesssim k_2 + k_3^{OH}[OH] + k_3^{Pip}[Pip]$.

If eq 7 is inverted and the term $k_3^{OH}[OH]$ is considered to predominate over k_2 and $k_3^{Pip}[Pip]$ eq 9 is obtained. A

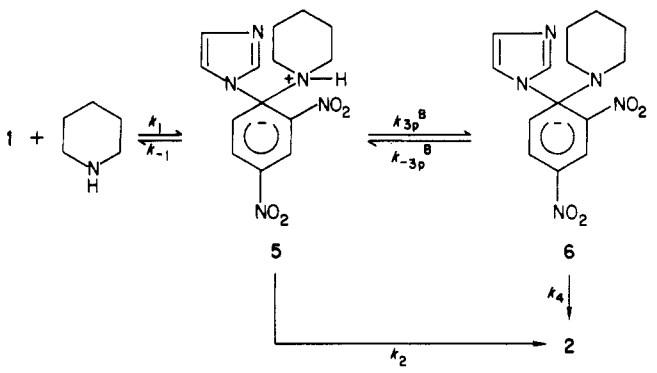
$$\frac{1}{k_A} = \frac{1}{k_1} + \frac{k_{-1}}{k_1k_3^{OH}}\frac{1}{[OH^-]} \quad (9)$$

plot of $1/k_A$ vs. $1/[OH^-]$ should be linear except when the conditions which allow simplification to eq 9 are not fulfilled. From a plot (not shown) based on data in Table II we evaluated k_1 and the ratio k_3^{OH}/k_{-1} (Table V).

The ratio k_2/k_{-1} which in principle could be obtained from the intercept of the linear plot under the conditions of eq 8 and the relationship k_2/k_{-1} = intercept/k_1 − $k_3^{OH}[HO^-]/k_{-1}$ cannot be obtained because it represents a small difference between two large numbers and thus it has too much error, but the data allow the inference $k_2/k_{-1} < 1$ to be made.

(8) Bernasconi, C. F.; de Rossi, R. H.; Schmid, P. *J. Am. Chem. Soc.* **1977**, *99*, 4090.
(9) Abe, T.; Ikegami, J. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3227.
(10) Mild accelerations of unclear origin in nucleophilic aromatic substitution by amines have been discussed by Bunnett and Garst.[11]
(11) Bunnett, J. F.; Garst, R. H. *J. Am. Chem. Soc.* **1965**, *87*, 3875.

Scheme II



From the data on Table V it can be seen that (2,4-dinitrophenyl)imidazole is about 1.8 times less reactive than 2,4-dinitroanisole. On the other hand, the hydrolysis rate ratio is about 1. These data show that in fact there is considerable steric hindrance for the attack of the nucleophile when imidazole is the leaving group, as we have suggested for the low reactivity of piperidine with (2,4,6-trinitrophenyl)imidazole.

Mechanism of Base Catalysis. Several mechanisms have been proposed over the years to explain the experimental observation of general base catalysis in nucleophilic aromatic substitution by amines. The two principal ones

$$k_{3p}^{B} = k_{3p}^{OH}[OH^-] + k_{3p}^{Pip}[Pip] \quad (10)$$

$$k_{-3p}^{B} = k_{-3p}^{OH} + k_{-3}^{Pip}[PipH^+] \quad (11)$$

$$k_4 = k_4^{OH} + k_4^{Pip}[PipH^+] \quad (12)$$

can be discussed with reference to Scheme II in which k_{3p}^{OH} and k_{3p}^{Pip} refer to the deprotonation of the zwitterionic intermediate **5** by OH^- and piperidine, respectively; k_{-3p}^{OH} and k_{-3p}^{Pip} refer to the protonation of the anionic intermediate **6** by the solvent and by piperidinium ion, respectively; k_4^{OH} refers to the noncatalyzed or solvent-assisted leaving group expulsion and k_4^{Pip} refers to the leaving group departure catalyzed by piperidinium ion; k_2 has the same meaning as in the previous scheme.

General base catalysis may experimentally be observed when $k_4 \ll k_{-3p}$ and the term $k_4^{Pip}[PipH^+]$ is significant in eq 12. This mechanism is denominated the SB–GA (Specific base–general acid) mechanism and has been shown to hold in many instances.[5] When $k_4 \gg k_{-3p}^{B}$ and k_{3p}^{B} is partially rate determining ($k_{-1} < k_{3p}^{B}$) the experimentally observed general base catalysis is due to the partially rate-limiting deprotonation of **5**. It was suggested that this is the mechanism of general base catalysis in all nucleophilic aromatic substitutions by amines in protic solvents,[8] but there are some controversies about the generality of this mechanism.[12]

In the present case, elimination of imidazole cannot be a general acid catalyzed reaction because addition of imidazole to the aromatic ring (the microscopic reverse) is not general base catalyzed.[13] Then, general base catalysis must occur by the proton-transfer mechanism ($k_4 > k_{-3p}^{B}$) and k_3^{OH} and k_3^{Pip} in eq 7 have the same meaning as in eq 10 k_{3p}^{OH} and k_{3p}^{Pip}. Assuming that k_{3p}^{OH} is diffusion controlled or nearly so, namely $\sim 4 \times 10^9$ M^{-1} s^{-1},[14] we can calculate k_{-1} and k_{3p}^{Pip}. These values are reported in Table V together with similar data for 2,4-dinitrophenyl phenyl ether and 2,4-dinitroanisole for comparison purposes. It can be seen that k_3^{Pip} is lower and k_{-1} considerably higher than the values for the other substrates as a consequence of steric crowding in the zwitterionic intermediate.

Experimental Section

Materials. (2,4-Dinitrophenyl)imidazole was synthesized from 2,4-dinitrochlorobenzene (1 mmol) and imidazole (2 mmol) in 1 mL of *N*,*N*-dimethylformamide. After 2 h at room temperature in the dark, the solution was poured into ice water, filtered, and washed with water and ethanol. The product, mp 144–144.5 °C (lit[15] mp 141–142.5 °C, lit[16] mp 146–148 °C), was used without further purification. (2,4-Dinitrophenyl)piperidine, mp 92–93 °C (lit[17] mp 92–93 °C), and *N*-(*n*-butyl)-2,4-dinitroaniline, mp 90.5–91 °C (lit[18] mp 90.5–91.5 °C) were prepared and purified by standard methods. 2,4-Dinitrophenol was purified by sublimation, mp 111.5–113 °C (lit[19] mp 112–114 °C). Dioxane was purified as described previously.[2]

Piperidine and *n*-butylamine were refluxed 12 h over Na and distilled with bp 104 and 77 °C, respectively. Twice distilled water in a glass apparatus was used throughout.

All of the inorganic reagents were of reagent grade and were used without further purification.

UV spectra were recorded on a Beckman 24 spectrophotometer and the change in optical density during a kinetic run was measured on the same instrument at the maximum absorption of the aminolysis product (λ 400 nm for (2,4-dinitrophenyl)-piperidine and λ 368 nm for *N*-(*n*-butyl)-2,4-dinitroaniline). pH measurements were carried out on a Seybold digital pH meter at 25 °C. Standard buffers prepared according to procedures in the literature[20] were used to calibrate the electrode.

Kinetic Procedures. Reactions were initiated by adding the substrate dissolved in dioxane to a solution containing all the other constituents. The total dioxane concentration was 2% in the reactions with piperidine and 10% in the reactions with *n*-butylamine. The observed rate constants k_{obsd}, were determined by following the appearance of the aminolysis product at 25 °C and ionic strength 1 M. All kinetic runs were carried out under pseudo-first-order conditions with substrate concentrations of about 4×10^{-5} M. When possible, the reactions were followed to 80–90% conversion, but in the slowest runs the reactions were followed up to 10–50% conversion. In all cases good pseudo-first-order kinetic plots were obtained.

Effective concentrations of amines were calculated from measured pH values and pK_a values of the amines determined by potentiometric titration at ionic strength 1 M.[21]

For the determination of the yield of the aminolysis product an aliquot of the infinity solutions was made acidic with 3.7 M H_2SO_4 in 50% ethanol–water and the absorbance at 400 nm was measured. Under these conditions 2,4-dinitrophenol did not absorb. In some cases the yield was calculated from the absorbance of the infinity solutions measured at two wavelengths and the corresponding extinction coefficients of the species present in the solution.[22] With *n*-butyl amine as nucleophile, the wavelengths used for quantification were 375 and 405 nm while for the reactions with piperidine the wavelengths were 370 and 400 nm. For the reactions followed up to 10–50% conversion A_∞ was calculated from the relative yield of the aminolysis and hy-

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(17) Bunnett, J. F.; Bernasconi, C. F. *J. Am. Chem. Soc.* **1965**, *87*, 5209.

(18) Bunnett, J. F.; Garst, R. H. *J. Am. Chem. Soc.* **1965**, *87*, 3875.

(19) The Merck Index, 8th ed.; Merck & Co.: Rahway, NY, 1968; p 381.

(20) Robinson, R. A.; Stokes, R. H. "Handbook of Chemistry and Physics", 56th ed.; East, R. C., Ed.; CRC Press: Cleveland, 1975–1976; p D-133.

(21) For piperidine $pK_a = 11.42$; for *n*-butylamine $pK_a = 10.84$ (ionic strength = 1 M with NaCl as compensating electrolyte).

(22) Stearns, E. I. In "Analytical Absorption Spectroscopy"; Mellon, M. G., Ed.; John Willey & Sons, Inc.: New York, 1960; Fourth Printing, p 369.

drolysis products determined as previously described in the incompleted reaction and the initial substrate concentration.

Rate coefficients are symbolyzed and were computed as follows: k_{obsd} is the pseudo-first-order coefficient for the disappearance of the substrate as determined from the slope of the plot of ln $(A_\infty - A_t)$ vs. time, k_A is the second-order rate coefficient for the aminolysis reaction and equals k_{obsd}(fractional yield of aminolysis product)/$(RR'NH)_{eff}$, k'_H is the pseudo-first-order coefficient for the hydrolysis reaction and equals k_{obsd}(fractional yield of hydrolysis product), and k_H is the second-order rate coefficient for the hydrolysis reaction and equals $k'_H/[HO^-]$.

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Registry No. 1, 14545-01-8; piperidine, 110-89-4; *n*-butylamine, 109-73-9; 2,4-dinitrochlorobenzene, 97-00-7; imidazole, 288-32-4.

Rates of Acid- and Base-Catalyzed Enolization of *trans*-Hexahydrofluorenone. Concerning Stereoelectronic Control of Enolization

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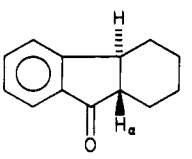
Rates of both acid-catalyzed and base-catalyzed enolization of *trans*-hexahydrofluorenone (*trans*-HHF) have been measured and compared with those for a variety of other ketones. It was found that *trans*-HHF enolizes substantially faster than cyclohexyl phenyl ketone (CPK) in both acid (1800-fold) and base (2650-fold). This rate variation is thought to be due to two factors. (1) In *trans*-HHF the cleaving C–H bond is held rigidly parallel to the π orbital of the ketone. About a factor of 25- to 60-fold is attributed to this stereoelectronic effect. (2) There are steric interactions in the enol of CPK which decrease its rate of enolization by about 40- to 50-fold.

The nature of the transition state for the enolization of aldehydes and ketones has been the object of much attenation in the last 3 decades. In 1956, Corey and Sneen[1] proposed the theory of stereoelectronic control to account for the preferential removal of the 6β proton over the 6α proton in the acid-catalyzed enolization of 3β-acetoxycholestan-7-one to the Δ^6-en-7-ol. This theory requires that the proton be lost in a direction parallel to the π orbital of the carbonyl group. This orientation allows continuous overlap between the C–H bond which is being broken and the π orbital of the carbonyl. Although this idea has been widely accepted[2] and has received theoretical support,[3] the original experimental evidence upon which it is based is inconclusive. In fact the observed selectivity between the axial (6β) and equatorial (6α) hydrogens is only 1.2-fold with HBr as the catalyst in chloroform.[1] For the reverse reaction (ketonization of the enol), the axial hydrogen is gained 1.5 times as often as the equatorial hydrogen; with acetic acid, the relative rates are 9:1. These relatively small rate differences were explained by the authors[1] as being due to an opposing steric effect of the C-10 methyl group.

Subsequent kinetic investigations of enolizations have confirmed a preference for axial reaction but the observed discriminations are generally quite small. For example, Metzger and Casadevall[4] found that the axial hydrogens of *trans*-2-decalone exchange 2- to 3-fold faster than the equatorial hydrogens at both the 1 and 3 positions in acetic acid–sulfuric acid solution. Similarly, Trimitsis and Van Dam[5] showed that the axial protons of 4-*tert*-butylcyclohexanone exchange more rapidly than the equatorial protons in alkaline Me_2SO–water solution (k_{ax}/k_{eq} = 5.5). Lamaty[6] has found similar results for both acid- and base-catalyzed enolizations of *tert*-butylcyclohexanone and 9-methyl-1-decalone (k_{ax}/k_{eq} = 1.6–3.8).

More recently, Fraser and Champagne[7–9] demonstrated that a large stereoselectivity can be observed in suitably designed systems. They found a rate ratio of 73:1 for base-catalyzed exchange of the α protons of a dibenzocycloheptadienone and 290:1 for the protons α to the carbonyl in twistan-4-one. Similarly, Spencer[10] has found that the α protons of *trans*-decalone derivatives are abstracted greater than 100-fold more readily than the equatorial protons.

In view of the apparent requirement for orbital overlap in the enolization of ketones, it might be expected that a ketone with an enolizable proton which is conformationally locked into the correct orientation would enolize exceptionally rapidly compared to a model compound with free rotation. Should this be the case, the implications for the mechanism of a variety of enzymatic reactions is obvious. Of particular interest in this regard is the compound *trans*-hexahydrofluorenone (*trans*-HHF). Molecular



trans-HHF

models show that the cyclopentane ring in *trans*-HHF is

(1) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269–6278.
(2) For a good discussion of "stereoelectronic control" of enolizations, halogenations, and alkylations of carbonyl compounds, see: House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin, Inc.: Menlo Park, CA, 1972; pp 469–473, 587–594 and references therein.
(3) Tee, O. S. *J. Am. Chem. Soc.* **1969**, *91*, 7144–7149.
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