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IMIDAZOLE AS LEAVING GROUP IN AROMATIC NUCLEOPHILIC SUBSTITUTION REACTIONS

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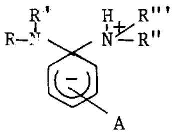
Abstract: The reaction of N-(2,4,6-trinitrophenyl) imidazole with n-butylamine is pH dependent. A mechanism involving acid catalyzed leaving group departure is suggested.

The reactions of amines with activated aromatic substrates have been widely used to establish the multistep nature of the mechanism of aromatic nucleophilic substitutions.[1] The most often studied substrates have alkoxides or halide ions as leaving group but reactions where the nucleophile as well as the leaving group are amines have seldom been reported.[2] These reactions have the special feature that in the zwitterionic intermediate 1 the C_1 is bonded to two nitrogen atoms.



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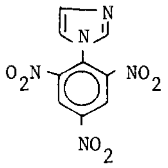

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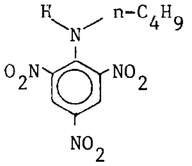

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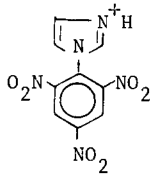

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We report here on our studies of the reaction of N-(2,4,6-trinitrophenyl) imidazole 2 with n-butylamine in water solution. Although 2 is a picramide, it is very reactive toward nucleophilic attack at the carbon bearing the amine and leads to the formation of N-n-butyl-2,4,6-trinitroaniline 3 in yields higher than 60%. The hydrolysis product, picric acid, is formed competitively.

The unusual feature of this reaction is that the second order experimental rate constant, k_A defined as in eq. 1, increases as the pH decreases and tends to level off at low pH (Figure). The highest pH used was 10.99 and we could not work at higher pH because the rates become too fast for our experimental techniques.

$$k_A = \frac{v}{(2)\ (\text{n-ButNH}_2)} \tag{1}$$

Although the total increase is relatively small, it is well outside the experimental error. Since the decrease in pH involves an increase in the concentration of n-butylammonium ion which might exert some specific salt effect, we carried out a series of reactions at constant ionic strength and variable concentration of $(CH_3)_4N^+Cl^-$ as model for $n\text{-}ButN^+H_3$ ion (Table). It can be seen that the increase in concentration of this salt causes a decrease in rate. Besides there is no change in the rate constant when the total concentration of the buffer of $n\text{-}ButNH_2/n\text{-}ButN^+H_3$ is changed at constant pH. We conclude that the reaction is specific acid catalyzed.

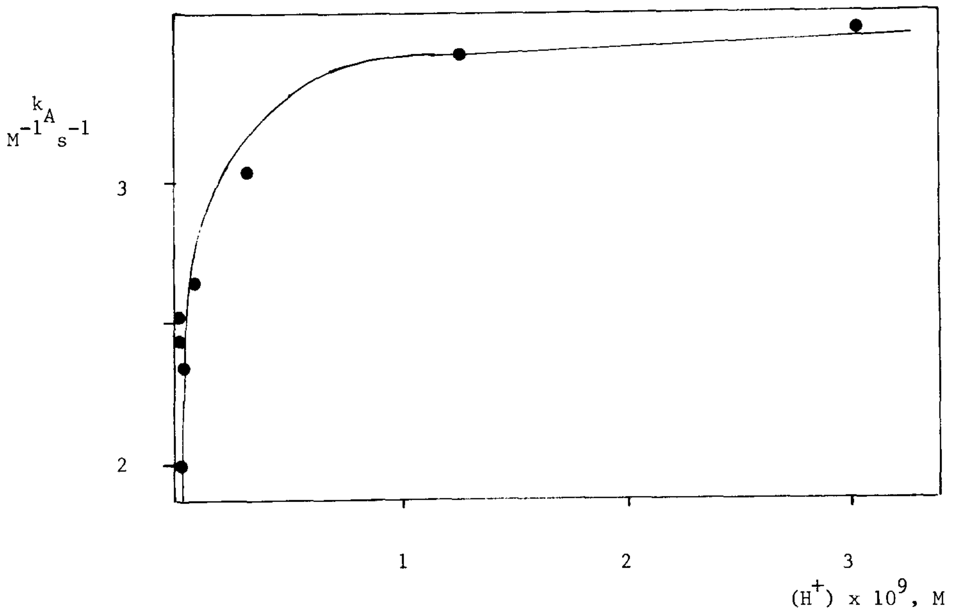


Figure: Effect of hydrogen ion concentration on k_A. $8.52 < pH < 10.99$. At $pH < 9.90$ a Borax buffer was used while at higher pH the buffer was $n\text{-}ButNH_2/n\text{-}ButN^+H_3$. T: 25°C. Solvent: 2% Dioxane/water. Ionic strength 1 M (NaCl). The solid line was calculated from eq. 5 with $k_2/k_{-1} = 0.3$ and values of k_1 and $k_3/K_H\ k_{-1}$ given in the Text.

Table: Reaction of $n\text{-}ButNH_2$ with 2 in water at 25°C as a function of $(CH_3)_4N^+Cl^-$ concentration.[a]

$(CH_3)_4N^+Cl^-$ (M)	k_A $(M^{-1}\ s^{-1})$[b]
0.981	1.57 (79)
0.363	1.91 (84)
0.091	2.04 (83)
	2.04 (85)

[a] pH = 10.71, buffer $n\text{-}ButNH_2/n\text{-}ButN^+H_3$, $(2)_o = 3.82 \times 10^{-5}$ M, $\mu = 1$ M (NaCl). [b] Values in parenthesis are yield of 3, the remainder is picric acid.

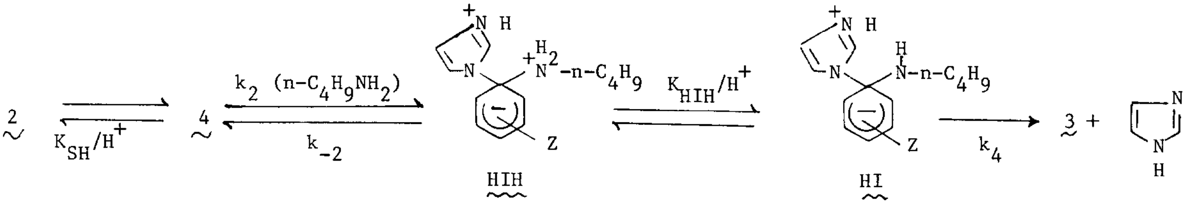
The possibility of partition of the substrate between protonated (4) and unprotonated (2) forms, with both forms reacting with rate constants k_1 and k_2, respectively, to give product, can be discarded because the pK_{SH} of 4 is 3.44;[3] thus under all our reaction conditions $K_{SH} >> (H^+)$.

Therefore, k_A is given by eq. 2, which predicts a linear dependence of k_A with (H^+) and is contrary to our experimental results.

$$k_A = k_1 + \frac{k_2}{K_{SH}} (H^+) \qquad (2)$$

A mechanism that should give the same pH dependence is depicted in Scheme I for which the observed rate constant under the conditions of our study ($K_{SH} >> (H^+)$) is given by eq. 3 which simplifies to eq. 4 when $k_{-2}\ (H^+)/K_{HIH} >> k_4$. Since pH independence is observed when $(H^+) \approx 10^{-9}$, and the pK_{HIH} is likely to be 2-3 units lower than the pK of n-ButNH$_2$,[4] k_{-2}/k_4 must be >10-100 for eq. 4 to hold. This ratio of rate constants means that n-ButNH$_2$ which is about 3 units more basic than imidazole is a better leaving group, contrary to what we would expected.

Scheme I

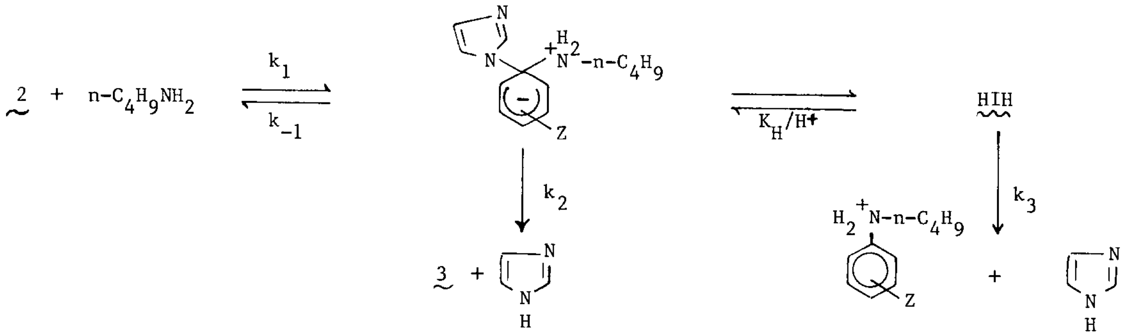


Z = 2,4,6-trinitro

$$k_A = \frac{k_4\ k_2\ (H^+)/K_{SH}}{k_{-2}\ (H^+)/K_{HIH} + k_4} \qquad (3) \qquad\qquad k_A = \frac{k_2}{k_{-2}} \cdot \frac{K_{SH}}{K_{HIH}} \cdot k_4 \qquad (4)$$

We have considered other mechanisms that predict a pH dependence like the observed. For instance, nucleophilic addition at the carbon 3 of the substrate forming a 1:3 σ complex,[5] or others that involve several steps but the analysis of the kinetic data obtained lead us to suggest the mechanism of Scheme II as the most likely to be responsible for the observed specific acid catalysis.

Scheme II



The observed rate constant for this mechanism is given by eq. 5 which can be rearranged to eq. 6.

$$k_A = \frac{k_1\ (k_2 + \left[k_3/K_H\right]\ (H^+))}{k_{-1} + k_2 + \left[k_3/K_H\right]\ (H^+)} \qquad (5) \qquad\qquad \frac{k_A}{k_1 - k_A} = \frac{k_2}{k_{-1}} + \frac{k_3}{K_H\ k_{-1}}\ (H^+) \qquad (6)$$

The value of $k_1 = 3.54\ M^{-1}\ s^{-1}$ can be obtained from the pH-independent rate observed at low pH; then a plot of the left hand side of eq. 6 vs. (H^+) yields $k_3/K_H\ k_{-1} = 2.67 \times 10^{10}\ M^{-1}$ as the slope. The intercept of this plot is very uncertain so that the value of k_2/k_{-1} cannot be determined. The fact that the catalyzed pathway is detected allows the inference that $k_2/k_{-1} < 1$.[1] Since the maximun value expected for K_H is that corresponding to the ionization of imidazole,[6] it can be infered that $k_3/k_{-1} > 1.6 \times 10^3$. Thus the less basic imidazole is a better leaving group than the more basic n-ButNH$_2$, as expected.

It is remarkable that the general base catalyzed pathway usually observed in nucleophilic aromatic substitution reactions when the ratio k_2/k_{-1} is smaller than one does not compete in this system with the specific acid catalyzed pathway. This behavior may be tentatively attributed to a low rate of abstraction of the proton from $\underset{\sim}{5}$ due to steric crowding.[7]

The low k_2/k_{-1} indicates that the intramolecular catalysis for expulsion of the leaving group from the intermediate $\underset{\sim}{5}$ (k_2 step)[8] is very inefficient and cannot compete with external protonation of the tertiary nitrogen by the solvent (k_3/K_H step). This is the first time where a specific acid catalyzed pathway for leaving group expulsion is observed for a nucleophilic aromatic substitution reaction.

Work is in progress to determine the generality of this behavior in reactions with other amines.

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