Reexamination of Tris(hydroxymethyl)aminomethane-Catalyzed Hydrolysis of p-Nitrotrifluoroacetanilide

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The tris(hydroxymethyl)aminomethane (Tris)-catalyzed hydrolysis of p-nitrotrifluoroacetanilide was kinetically studied. On the contrary to the previously reported results (R. M. Pollack and T. C.Dumsha, *J. Am. Chem. Soc.*, 1973, **95**, 4463), the dependence of the rate on [Tris] consists of an initial curve portion and a subsequent linear increase. This indicates that erroneous conclusions were made in the reported work due to the insufficient amount of data. The initial portions of the rate[Tris] profiles are attributed to the catalyzed breakdown of the tetrahedral intermediate, and the linear portions to the general base-catalyzed water attack at the substrate.

During our study on catalysis in amide hydrolysis,[1-3] we became interested in the hydrolysis of activated anilides. In this paper, we report that the previously published[4] tris-(hydroxymethyl)aminomethane (Tris)-catalyzed hydrolysis of p-nitrotrifluoroacetanilide (1) was performed inadequately and presented erroneous mechanistic conclusions.

Trifluoroacetanilides are hydrolyzed according to the general scheme of eq 1.[4-9] The formation (k_f) of T^- occurs
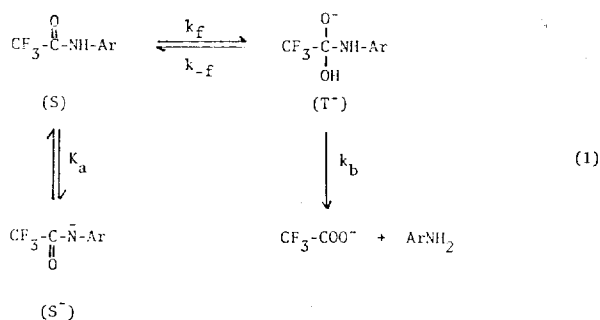
through the attack of hydroxide ion or through the general base-catalyzed water attack at S. Breakdown (k_b) of T^- to products and return (K_{-f}) of T^- to S are subject to catalysis by general acids, general bases, or hydroxide ion.

As general acids or bases can participate in various reaction steps, plots of pseudo-first-order rate constant (k_0) against catalyst concentration are curved and the analysis of such plots is usually complicated.[5-9] The only exception to this is the linear dependence of k_0 on the concentration of Tris reported in the Tris-catalyzed hydrolysis of 1.[4] The Tris-catalyzed rate was proportional to the concentration of the basic form of Tris ([Tris]$_b$) and showed no dependence on hydroxide ion concentration. This result was interpreted in terms of the formation of T^- through hydroxide attack at S and the subsequent general acid catalysis by the conjugtate acid of Tris in the rate-controlling k_b step.[4] If this mechanism is operative, k_0 should be proportional to [Tris·H$^+$][OH$^-$], and, hence, to [Tris]$_b$[H$_2$O].

We have measured the rate data for the Tris-catalyzed

hydrolysis of 1, extending the concentration of Tris (total concentration; 6.25–200 mM) to much lower vaules than those performed in the reported work. In order to check the buffer capacity at the lowest concentration of Tris, kineticd-ata were obtained with 1×10^{-4} M and 1×10^{-5} M 1. Values of k_0 obtained with these concentration of 1 agreed within few per cents (pH 7.23 or 8.06, [Tris]$_{total}$=6.25 mM).

The k_0 values were corrected for the ionization (pK$_a$= 8.2[4]) of S according to eq 2, since S^- is unreactive. Values of [Tris]$_b$ were

$$k_{corr}=k_0(1+K_a/[H^+]) \qquad (2)$$

calculated by using its pK$_a$ of 8.079.[10] The plots of k_{corr} against [Tris]$_b$ measured at pH 7.23 and 8.06 are illustrated in Figure 1. The plots consist of initial curves and subsequent linear lines. As illustrated in this figure, k_{corr} is linearly related to [Tris]$_b$ over the range of [Tris]$_b$
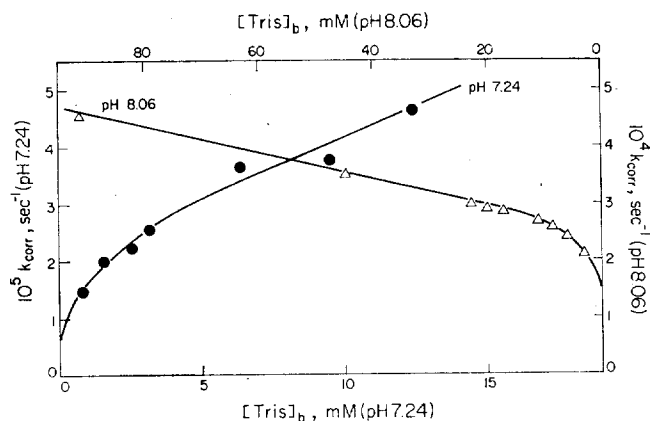
Figure 1. Plots of k_{corr} against [Tris]$_b$ at pH 7.24 (●) or pH 8.06 (△). Linear portions of the curves are drawn with the slopes of 2.13×10^{-3} M^{-1} sec^{-1} (pH 7.24) and 2.31×10^{-3} M^{-1} sec^{-1} (pH 8.06). The corresponding values obtained by Pollack and Dumsha[4] were $2.32 \pm 0.13\times10^{-3}$ M^{-1} sec^{-1} at pH 7.21 and $2.53 \pm 0.29\times10^{-3}$ M^{-1} sec^{-1} at pH 8.06. The ranges of [Tris]$_b$ employed in the study of Pollack and Dumsha were 4–20 mM at pH 7.21 and 28–140 mM at pH 8.06.[4]

employed in the previous study.[4] Slopes of the linear lines drawn in the figure agree well with the second–order rate constants reported previously.[4]

In the reported study, the initial curves in the plot of k_{corr} against $[Tris]_b$ have not been detected, and, consequently, erroneous conclusions were drawn from the insufficient amount of data. Firstly, the spontaneous rate at a given pH was estimated from the intercept of the extrapolated linear portion of the plot. Our results indicate that such extrapolation overestimates the spontaneous rate constants. Several Parameter values have been obtained[4] from these overestimated rate constants, and have been further used in analysis of rate in a later study.[5]

Secondly, general acid catalysis in the k_b path (A) is not likely responsible for the linear portions of Figure 1, on the contrary to the original[4] interpretation. Instead, the initial curve portions are better explained in terms of the catalyzed breakdown (k_b) of T^- as illustrated by A or B, and the linear portions in terms of the catalyzed water attack (k_f) at S as illustrated by C. At weakly acidic pH's, the rate–determining step in the hydrolysis of trifluoroacetanilides is usually the breakdown of T^- (*i.e.* $k_{-f} \gg k_b$).[4-9] At low Tris concentrations, therefore, the overall rate is enhanced by the increases in k_b. With suficiently large amounts of Tris, however, k_b becomes much greater than k_{-f} and the k_f step becomes rate–controlling. Therefore, further increases in Tris concentration can enhance the overall rate only by raising k_f. The present interpretation agrees with the mechanistic information obtained from hydrolysis of trifluoroacetanilides catalyzed by imidazole[5] or various amines.[6,7]

Experimental Section

p–Nitrotrifluoroacetanilide was prepared according to the literature,[11] mp 151.5–152.5 °C (*lit.*[11] 151.5–153.5 °C). Tris was obtained from Sigma and used without further purification. Water was redistilled and deionized before being used in kinetic studies. pH meaurements were performed with a Fisher Accumet Model 525 pH meter. Kinetic measurements

(A)   (B)   (C)
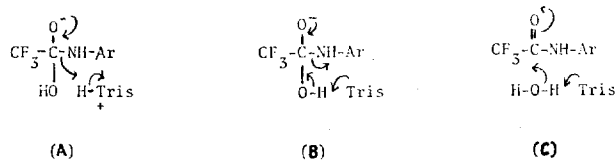
were carried out with a Beckman 5260 UV/vis spectrophotometer equipped with a Haake E52 circulator. Reaction rates were calculated from the absorbance changes at 400 nm. Hydrolysis of **1** was initiated by adding 3 μl of 0.1 M **1** in DMSO to 3 m*l* buffer solution. Pseudo–first–order rate constants were calculated with infinity absorbance readings or by the Guggenheim method. All of the reaction conditions were identical to those descibed in the literature,[4] unless noted otherwise.

References and Notes

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