Anion Effects on the Aminolysis of Carboxyl-Containing Esters by Triamines in Dimethyl Sulfoxide

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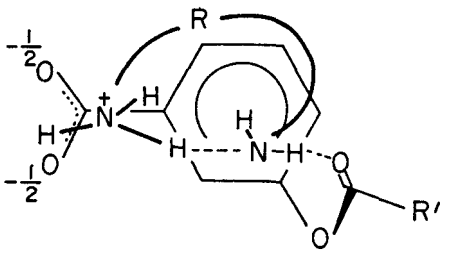
Aminolysis of various carboxyl-containing ester substrates by triamines was kinetically studied in dimethyl sulfoxide (DMSO) in the presence of *p*-toluenesulfonic acid (TSA) or in the presence of sulfuric acid and potassium iodide (KI). In the presence of TSA or KI, the pseudo-first-order rate constants (k_o) were proportional to the total amine concentration (N_o). This stands in marked contrast with the corresponding reactions carried out with sulfuric acid added as the sole additive, in which saturation kinetic behavior of k_o with respect to N_o was manifested. This indicates that complex formation between the ester substrate and the amine is greatly suppressed by the addition of TSA or KI. The second-order rate constants obtained in the presence of TSA or KI were substantially greater than those measured in the absence of any additive. These kinetic features were explained in terms of tight interaction between the protonated amines with I^- or TSA^-. Thus, the results were related to the hydrogen bonding that involves DMSO, bisulfate ion, I^-, TSA^-, and the protonated forms of triamines.

Introduction

Aminolysis of various carboxyl-containing esters by several tetra-, tri-, and diamines has been kinetically investigated in dimethyl sulfoxide (DMSO).[1] The rate data for the aminolysis reactions were measured in the presence or absence of added sulfuric acid. In some reactions, saturation kinetic behavior was manifested, indicating complex formation between the amines and the esters. The complex formation was most efficient when the carboxyl group of the ester substrate was located at the *meta* position to the ester group. In addition, the complex formation was facilitated by hydrophobic amines. In order to explain the positional stereoselectivity and the hydrophobic effects observed in the kinetic study, a structure of the complex (A) was proposed.

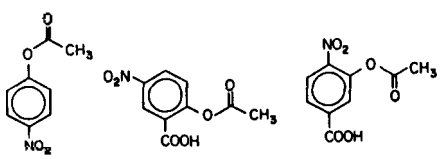


A

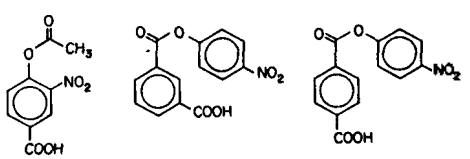
Complex formation between substrates and enzymes is essential for enzymatic reactions. For the formation of an enzyme-substrate complex, polar and hydrophobic interactions between the substrate and the active site of the enzyme play important roles. If both of these interactions are involved, the microenvironment of the active site must be suitable for both of them. Polar interactions would be facilitated by solvents of low polarity, while hydrophobic interactions by those of high polarity. Since both the polar and the hydrophobic interactions that are needed in the formation of complex A are accommodated by DMSO, DMSO may be regarded as a model for microenvironments of enzyme active sites.

Dipolar aprotic solvents such as DMSO lack the ability to stabilize anions through hydrogen bonding, althouh they act as acceptors of hydrogen bonds. The properties of ions in these solvents are, therefore, often intermediate between those in water and the gas phase, providing an important bridge between these two extremes.[2] Thus, the study of complexation in DMSO can provide information for medium effects on nonenzymatic properties and reactions, too.

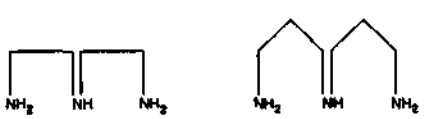
In the present study, aminolysis of various esters (**1**, **2o**, **2m**, **2p**, **3m**, and **3p**) by triamines (III22 and III33) was kinetically investigated in the presence of added potassium iodide (KI) or *p*-toluenesulfonic acid (TSA). The addition of iodide (I^-) or TSA anion (TSA^-) resulted in marked changes in the kinetic behavior. The effects of added anions on the aminolysis rates and complex formation in DMSO are analyzed in terms of intermolecular interactions.



(1) (2o) (2m)



(2p) (3m) (3p)



(III22) (III33)

Experimental Section

Procedures for the preparation and purification of *p*-nitrophenyl acetate (**1**), 2-carboxy-4-nitrophenyl acetate (**2o**), 3-carboxy-6-nitrophenyl acetate (**2m**), 4-carboxy-2-nitrophenyl acetate (**2p**), *p*-nitrophenyl isophthalate (**3m**), *p*-nitrophenyl terephthalate (**3p**), diethylenetriamine (III22), and 3,3'-diaminodipropylamine (III33) have been reported previously.[1] Kinetic measurements and data analysis were also performed as described previously.[1]

Table 1. Values of k_{bi} ($M^{-1}s^{-1}$) for the Ester Aminolysis by III22 and III33 in DMSO[a]

amine additive	III22 none[b]	H_2SO_4[b]	H_2SO_4/KI	TSA	III33 none[b]	H_2SO_4[b]	H_2SO_4/KI	TSA
ester								
1	28	16 (57)	15 (54)	24 (85)	43	37(74)	26(60)	38(79)
2o	38	SK	60 (160)	56 (150)	25	SK	43(170)	38(150)
2m	6.3	SK	19 (300)	13 (210)	13	SK	45(350)	40(310)
2p	7.7	4.3(56)	7.7(100)	7.6(99)	13	SK	22(170)	23(180)
3m	4.2	SK	8.9(210)	7.5(180)	7.2	SK	21(290)	18(250)
3p	3.4	2.4(71)	5.5(160)	5.4(160)	6.0	SK	11(180)	11(180)

[a] *Values in parentheses:* magnitude (%) of each parameter value relative to the k_{bi} measured in the absence of any additive. "SK" indicates that saturation kinetics were manifested. Standard deviations are 5-10% of the parameter values. The amount of added sulfuric acid or TSA was maintained at one third of N_o and the concentration of KI was 0.01M. The rate data were collected at 25 °C under the condition of $N_o \gg S_o$. The N_o concentrations of up to 1.1 mM (III22) or 1.5 mM (III33) were used. [b] ref 1.

Results and Discussion

Aminolysis of the ester substrates were followed under the condition of $N_o \gg S_o$ (N_o; total amine concentration, S_o; initially added oncentration of ester substrate) at 25 °C. Reaction rates were measured in the presence of TSA or KI. The amount of TSA was maintained as one third of N_o. When KI was added, its concentration was fixed at 0.01M, but sulfuric acid was also added in the amount of one third of N_o. The values of pseudo-first-order rate constants (k_o) were measured at several N_o concentrations. The k_o values obtained in the presence of TSA or KI were proportioal to N_o. The second-order rate constants (k_{bi}) calculated therefrom are summarized in Table 1.

The k_o values obtained in the previous study[1] for the aminolysis of the ester substrates by III22 or III33 in the absence of any additive were also proportional to N_o. The corresponding k_{bi} values are included in Table 1.

The aminolysis reactions have been also carried out with sulfuric acid added as the sole additive.[1] Sulfuric acid is fully ionized to form bisulfate ion in DMSO,[3] while the pK_a of bisulfate ion in DMSO is 14.5.[4] The pK_a of conjugate acids of simple amines in DMSO has been reported to be 9-11.5.[5] Although the correct pK_a values of III22 and III33 in DMSO have not been measured, it is clear that the added sulfuric acid converts the amines to the respective ammonium ions quantitatively. Because the amount of the added sulfuric acid was maintained at one third of N_o, the reaction mixture contained both the neutral amine (N; in the concentration of $2N_o/3$) and the protonated amine (NH^+; in the concentration of $N_o/3$). The aminolysis by III22 and III33 under these conditions exhibited complicated kinetic behavior.[1] The k_o values were proportional to N_o for only a limited number of esters, whose k_{bi} values are listed in Table 1. For other esters, the dependence of k_o on N_o manifested saturation behavior, indicating the complex formation between the ester substrate and the amine. Detailed analysis indicated that the direct attack by the protonated forms of III22 or III33 at the ester substrates was negligible within the experimental error limit. The kinetic data measured for the aminolysis by III22 or III33 in the presence of added sulfuric acid, therefore, were analyzed in terms of Scheme 1.[1]

$$N + S \xrightarrow{k_2^o} P$$

Table 2. Parameter Values for the Saturation Kinetics Measured for Aminolysis by III22 or III33 in the Presence of Added Sulfuric Acid[a]

	III22 k_c^+	III22 K_f^+	III33 k_c^+	III33 K_f^+
2o	32	4.5	26	2.0
2m	8.3	7.7	24	4.9
2p	—	—	26	1.0
3m	5.0	6.8	11	5.3
3o	—	—	8.5	1.8

[a] The unit of k_c^+ is 10^{-3} s^{-1} and that of K_f^+ 10^3 M^{-1}. The reactions marked as "SK" in Table 1 are listed in this table. See Table 1 for the details including the reaction conditions.

$$NH^+ + S \underset{}{\overset{K_f^+}{\rightleftharpoons}} NH^+S \xrightarrow{k_c^+} P$$

Scheme 1

The expression of k_o derived from Scheme 1 is eq. 1.

$$k_o = \frac{k_2^o (1-\alpha) N_o + k_c^+ K_f^+ \alpha N_o}{1 + K_f^+ \alpha N_o} \quad (1)$$

Here, α stands for the fraction of the amine protonated by the added acid and k_2^o is the same as k_{bi} obtained when $\alpha = 0$. Saturation kinetic behavior of k_o with respect to N_o is predicted by eq. 1. The values of k_c^+ and K_f^+ obtained in the previous study[1] for the aminolysis of the esters by III22 or III33 in the presence of added sulfuric acid are summarized in Table 2. Under the condition of $K_f^+ \ll 1/\alpha N_o$, eq. 1 becomes eq. 2 with k_o becoming proportional to N_o.

$$k_o = k_2^o (1-\alpha) N_o + k_c^+ K_f^+ \alpha N_o \quad (2)$$

When TSA is substituted for sulfuric acid or KI is added in addition to sulfuric acid, k_o for the aminolysis of **1**, **2o**, **2m**, **2p**, **3m**, or **3p** by III22 or III33 is proportaional to N_o. This stands in marked contrast with the saturation kinetics observed when sulfuric acid was added as the sole additive. The formation constants for complex A are, therefore, greatly reduced by the addition of TSA or KI.

Another distinct kinetic feature discolsed by the addition of TSA or KI is the enhanced values of k_{bi}. The k_{bi} values me-

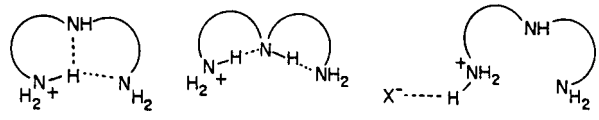
asured for **1** in the presence of TSA or KI agree with the inactivation of the amines upon protonation by the added acid within the experimental limit. On the other hand, the k_{bi} values for the carboxyl-containing esters are significantly greater (Table 1) in the presence of TSA or KI than in the absence of any additive.

In view of the acidity of TSA which is intrinsically much greater than those of benzoic acid derivatives and considering the pK_a values of benzoic acid derivatives in DMSO (pK_a; 6-11)[6], TSA should ionize fully in the presence of excess III22 or III33 in DMSO. In the present study, therefore, one third of the added amine are protonated in the presence of TSA, with *p*-toluenesulfonate ion (TSA^-) present as the major counter-anion. When both sulfuric acid and KI are added, one thrid of the added amine are protonated and iodide ion (I^-) and bisulfate ion are present as the major counter-anions.

Bisulfate, ion, acting as a hydrogen-bond donor, can be hydrogen-bonded to DMSO. On the other hand, hydrogen bonding is not possible between TSA^- or I^- and DMSO as they act only as hydrogen-bond acceptors. Consequently, TSA^- or I^- would interact tightly with the protonated amines, while the protonated amines are relatively free from the counter-anion when bisulfate is the main counter-anion. Association of the protonated amines with TSA^- or I^-, therefore, would inhibit the complex formation between the carboxyl-containing ester substrate and the protonated amine. This explains the disappearance of the saturation kinetic behavior of the protonated forms of III22 and III33 upon the addition of TSA^- of I^-.

The k_{bi} values observed in the presence of TSA or KI are considerably greater than those measured in the absence of any additive. This may be explained in terms of eq. 2, the expression of Scheme 1 under the conditon of $K_f^+ \ll 1/\alpha N_o$. If the second terms of eq. 2 is significantly greater than the first one, k_{bi} should be appreciably larger than $k_2^o(1-\alpha)$. Thus, although the complex formation may not be sufficiently strong to exhibit the saturation kinetic behavior, K_f^+ could be large enough to result in enhanced k_{bi} values. If K_f^+ is still smaller, the second term of eq. 2 should diminish. This is indeed confirmed with **1**, which does not contain any carboxyl group and does not form complexes with the amines.

Alternatively, the enhanced, k_{bi} values observed in the presence of TSA or KI can be explained in terms of the efficient direct attack of the protonated amine at the substrate. When only sulfuric acid is added, the protonated forms of III22 and III33 do not make direct attack at the esters.[1] This was ascribed to the intramolecular hydrogen bonding (B, C) in the protonated forms of the amines that masks all of the nitrogen atoms.[1] As discussed above, the protonated amines would interact tightly with TSA^- or I^-. Association of the ammonium ions with TSA^- or I^- (D) can inhibit the intramolecular hydorgen bonding of structure B or C.



B C D (X = TSA or I)

The amino group of D is available for direct attack at the ester substrates. The attack of D at the carboxyl-containing esters may be electrostatically more favorable than that of neutral amines. This is because the amino group of D is adjacent to a positively charged ammonium group. The electrostatic effect should not operate with **1**, which does not contain a carboxyl group. This agrees with the results obtained with **1**. The enhanced k_{bi} values for the carboxyl containing esters in the presence of TSA^- or I^- are, therefore, also compatible with the intermolecular attack by D.

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References

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