Pergamon

Tetrahedron Letters 40 (1999) 8901–8904

TETRAHEDRON
LETTERS

Definitive evidence for a stepwise mechanism: a downward curvature in the plot of k_{obs} versus amine concentrations in aminolysis reactions of dibenzo[1,2]oxathiin-6-oxide

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Received 31 August 1999; revised 27 September 1999; accepted 1 October 1999

Abstract

Pseudo-first-order rate constants (k_{obs}) have been measured spectrophotometrically for aminolyses of dibenzo[1,2]oxathiin-6-oxide. The plot of k_{obs} vs amine concentrations exhibits a downward curvature which levels off as the amine concentration increases. Such a downward curvature is proposed as definitive evidence for a stepwise mechanism, which is supported by the microscopic rate constants determined. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: amines; kinetics; mechanisms; sulfinic acids; sulfinic acid derivatives.

Nucleophilic substitution reactions of carbon-, phosphorous- and sulfur-centered substrates have been intensively studied due to the interest in biology as well as in chemistry.[1] Reactions of carboxylic esters with amines have been generally understood to proceed in a stepwise mechanism in which the rate-determining step changes from breakdown to formation of the addition intermediate as the nucleophilic amine becomes more basic than the leaving group by 4–5 pK_a units.[2–4] However, the corresponding reactions with oxygen nucleophiles are still controversial, i.e., an S_N2-like concerted mechanism[5] vs a two-step addition–elimination mechanism.[6]

Similarly, nucleophilic substitution reactions of sulfur-centered substrates have been suggested to proceed either one-step concertedly or stepwisely.[7–10] Various structure–reactivity correlations have been discussed in favor of a two-step mechanism.[7,8] Oxygen isotope exchange experiments have supported the presence of an addition intermediate in the acid catalyzed hydrolysis of sulfinate esters,[9] although efforts to detect such an oxygen isotope exchange were not successful in the alkaline hydrolysis of sulfinate esters.[10]

However, aminolysis reactions of sulfur-centered esters have not been investigated greatly, and therefore, the reaction mechanism is not completely understood. We performed reactions of

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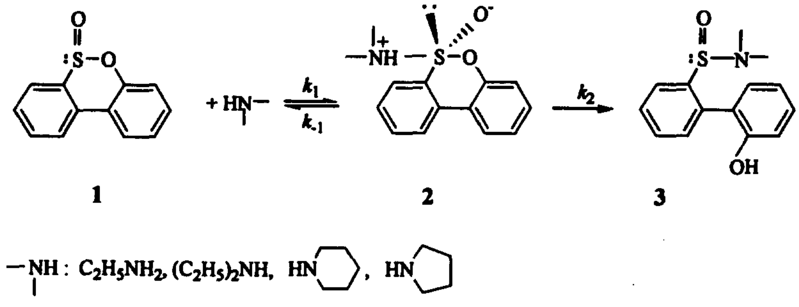
PII: S0040-4039(99)01908-5

dibenzo[1,2]oxathiin-6-oxide (**1**) with primary and secondary amines in H_2O as shown in Scheme 1, and found downward curvatures in the plots of k_{obs} vs amine concentrations. We wish to report for the first time the downward curvature observed in the present aminolysis as definitive evidence for a stepwise mechanism.



Scheme 1.

Reactions were followed by monitoring the disappearance of **1** at 270 nm spectrophotometrically. All the reactions obeyed pseudo-first-order kinetics over 90% of the total reaction. The pH of each amine stock solution was kept constant by making self buffered solution in order to suppress formation of hydroxide ion by solvolysis, i.e., the amine stock solution was made with equiv. mole of amine and amine hydrochloride. The kinetic results are demonstrated graphically in Fig. 1. Interestingly, the plots of k_{obs} vs [amine] show downward curvatures which level off as the concentration of amine increases. The plots of k_{obs} vs [amine] have been reported to be linear or curved upwardly when the second amine molecule behaves as a general base catalyst.[11,12] Such a downward curvature as in Fig. 1 has never been reported for the aminolysis of esters.

Downward curvatures in the plots of k_{obs} vs [nucleophile] have often been reported for nucleophilic substitution reactions of alkali metal ethoxides with C, P and S centered esters in anhydrous ethanol,

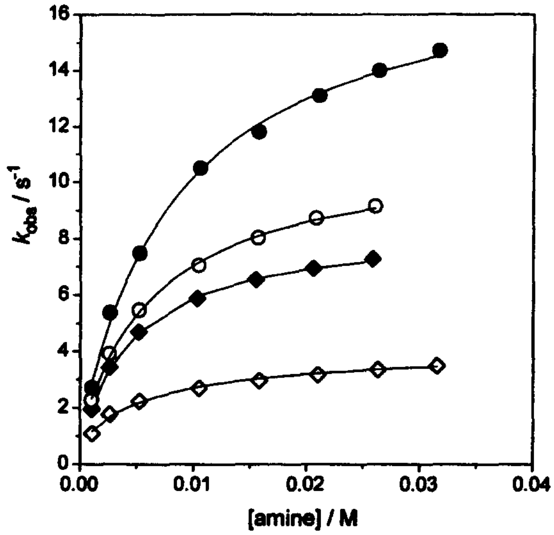


Figure 1. Plots of k_{obs} vs amine concentrations for the reaction of **1** with pyrrolidine (●), piperidine (○), diethylamine (◆) and ethylamine (◇) in H_2O at 25.0±0.1°C. The points are experimental data and the lines are drawn according to Eq. 1. [1]=8.0×10^{-5} M

and attributed to inhibition by ion-paired alkali metal ethoxides.[13,14] Since the present reactions were performed in H_2O, ion paired species would not be responsible for the curvilinear trace in Fig. 1. This argument can be strongly supported from the corresponding reaction with *p*-nitrophenyl acetate in the same reaction condition, i.e., the plot of k_{obs} vs [amine] was found to be linear.[15]

The downward curvature in Fig. 1 is similar to the one observed in Michaelis–Menten type kinetics[16] which account for enzyme catalyzed kinetics, i.e., fast formation of an appreciable amount of substrate–enzyme complex and followed by slow decomposition to the products. Therefore, one might attribute the downward curvature in Fig. 1 to the nature of reaction mechanism.

Eq. 1 has been derived[17] using the improved steady-state approximation to account for a two-step reaction which proceeds through an appreciable amount of intermediate **2**. [N] and c represent the concentration of nucleophile and the rate constant for the reaction of **1** with OH^- and H_2O, respectively.

$$k_{obs}=k_1k_2[N]/\{k_1[N]+k_{-1}+k_2\}+c \qquad (1)$$

In this case, the plot of k_{obs} vs [N] should reach a maximum and then flatten out as the concentration of nucleophile increases. If a reaction proceeds without building up an appreciable amount of intermediate, the well-known steady-state approximation can be applied. In this case, $k_1[N]$, the first term in the denominator in Eq. 1 does not appear, and therefore, the plot of k_{obs} vs [N] should be linear. This is not the case for our experimental results as shown in Fig. 1.

Eq. 1 can be rearranged to give Eq. 2. If a reaction proceeds through a metastable intermediate, the plot of $1/(k_{obs}-c)$ vs 1/[N] should be linear. In fact, linear plots have been obtained. Therefore, the present aminolysis is proposed to proceed in two steps with formation of a metastable addition intermediate (**2**) which decomposes slowly to the product (**3**), as shown in Scheme 1.

$$1/(k_{obs}-c)=1/k_2+(k_{-1}+k_2)/k_1k_2\cdot 1/[N] \qquad (2)$$

Further support for a stepwise mechanism can be provided by determination of the microscopic rate constants, k_1, k_{-1} and k_2 in Scheme 1. The $1/k_2$ values have been calculated from the intercepts of the linear plots of $1/(k_{obs}-c)$ vs 1/[N]. The k_1 and k_{-1} values have also been calculated from a nonlinear regression method for all the amines studied.

As shown in Table 1, there is no distinct difference in the magnitude of each microscopic rate constant between primary and secondary amines, and between acyclic and cyclic amines. However, importantly, the magnitude of k_2 values is much smaller than that of k_{-1} values for all the amines studied. Therefore, the microscopic rate constants clearly suggest that the aminolysis of **1** proceeds in two steps, i.e., fast formation of a metastable intermediate **2** followed by slow decomposition to the product **3**. This argument is consistent with the preceding proposal based on the downward curvature shown in Fig. 1. Therefore,

Table 1

Summary of microscopic rate constants for the aminolysis of **1** in H_2O at 25.0±0.1°C[a]

Amine	pK_a[b]	$k_1/\ M^{-1}s^{-1}$	$k_{-1}/\ s^{-1}$	$k_2/\ s^{-1}$	$c/\ s^{-1}$
ethylamine	10.63	26,700	163	3.30	0.705
diethylamine	10.98	32,000	140	7.82	0.622
piperidine	11.22	30,600	193	10.2	0.984
pyrrolidine	11.27	36,700	301	17.2	1.10

[a] The uncertainty of the microscopic rate constants is estimated to be less than 10% based on the repeated experiments.

[b] pK_a data taken from reference 18.

we propose that the present aminolysis of **1** proceeds in two steps and the downward curvature shown in Fig. 1 is definitive evidence for a stepwise mechanism for the aminolysis of a sulfinate ester **1**.

Acknowledgements

The authors are grateful for the financial support from the Ministry of Science and Technology of Korea (KISTEP-98-N6-01-01-A-08 and KOSEF-981-0303-017-2).

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