Tetrahedron Letters No.48, pp. 4163-4168, 1970. Pergamon Press. Printed in Great Britain.

RATE-DETERMINING COLLAPSE OF A TETRAHEDRAL INTERMEDIATE IN ESTER AMINOLYSES IN APROTIC SOLVENTS

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(Received in USA 2 September 1970; received in UK for publication 11 September 1970)

We present herein a kinetic investigation of ester aminolyses in aprotic solvents which shows that the reactions proceed by means of a rate-determining collapse of a tetrahedral intermediate, a finding which has not previously been reported. Our work was prompted by conflicting interpretations of a number of recent studies. For example, the overall third-order aminolysis of esters in aprotic media has been described as both a cyclic concerted[2,3] and general base[4] process. Aminolysis mechanisms have usually entailed a tetrahedral intermediate[5], although it has been argued that a direct displacement reaction without an intermediate is preferable[6]. Overall second-order aminolyses have been discussed in terms of both 4-membered cyclic transition states[7] and ionic processes[4]. It has been suggested[7] and denied[6] that primary and secondary amines react via different mechanisms in aprotic solvents. Tertiary amine catalysis has been ascribed to both nucleophilic[8] and general base[9] catalysis. Acceleration by the hydroxyl group in the aminolysis of salicylate systems in nonhydroxylic media has been viewed as a general acid catalysis[9] and as an ion pair effect[10]. Our present observations regarding the rate-determining collapse of a tetrahedral intermediate may have a bearing on these divergent interpretations.

The reactions of a series of substituted phenyl benzoates and phenyl

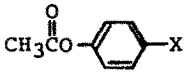
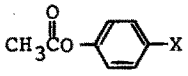
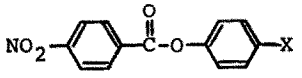
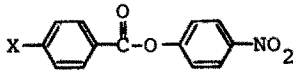
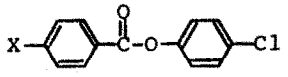
acetates with pyrrolidine have been studied in acetonitrile and chlorobenzene. The reactions follow the rate law given in Eq. 1 when amine is present in large excess.

$$k_{obsd} = k_1 \text{ (amine)} + k_2 \text{ (amine)}^2 + k_3 \text{ (amine)(tertiary amine)} \quad (1)$$

Hammett rho values for these reactions are listed in Table 1. It can be seen that the reaction of pyrrolidine with ester is much more sensitive to substituents in the leaving group than in the acyl portion for both the k_1 and k_2 terms. Thus, k_1 has a rho of 6.24 for p-substituted aryl acetates in acetonitrile, whereas k_1 has a rho of only 1.01 for substituted benzoates in the same solvent. This is opposite the order of sensitivity found for the reaction of esters with hydroxide in aqueous media. The rho values for basic hydrolysis of p-substituted aryl acetates and methyl benzoates are 1.1[11] and 1.93[12], respectively, while the corresponding terms for the aminolysis of substituted benzoate esters have rho values of 1.08 and 1.88[13]. To our knowledge, there is no case of an aqueous aminolysis yielding a rho value that approaches the magnitude of the first three entries in Table 1.

A cyclic transition state (4-membered for k_1, 6-membered for k_2), in which a proton is delivered to the incipient phenoxide in a one-step process[6,7], does not account for the large rho values (Table 1). An electron withdrawing substituent which enhances carbon-oxygen cleavage would also impede oxygen protonation, and the effects would more or less cancel[14]. Likewise, a cyclic process leading to a neutral tetrahedral intermediate via proton transfer to the carbonyl oxygen[2,3,5] is inconsistent with the large rho values, since little bond cleavage between the carbonyl carbon and the ether oxygen would be involved[15]. Nor does simple rate-determining addition of amine (uncatalyzed for k_1, general base catalyzed for k_2) to form a charged tetrahedral intermediate[5] explain the extreme sensitivity of the rate constants to the alcohol portion of the ester[12].

Table I: Hammett rho values for k_1 and k_2 terms of Eq. 1 in the reaction of pyrrolidine with esters at 25°C.

Ester[c]	Solvent	rho k_1	rho k_2
	CH_3CN	6.24 ± 0.17[a]	5.29 ± 0.23
	PhCl	4.02 ± 0.21	6.02 ± 0.01
	CH_3CN	6.07 ± 0.33	4.78 ± 0.15
	CH_3CN	1.02 ± 0.12	b
	CH_3CN	1.01 ± 0.06	2.06 ± 0.02

a. Standard deviation

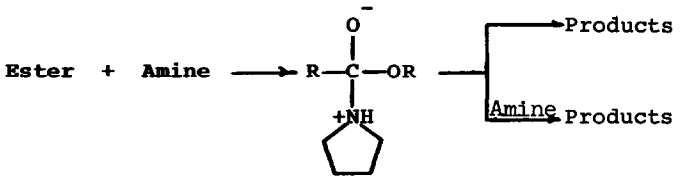
b. No third-order kinetics were observed for p-nitrophenyl leaving groups.

c. Three to five substituents were used to determine the rho values.

The simplest mechanism consistent with our results is a direct displacement reaction with no intermediate. The rho values of 4-6 (Table 1) may be attributed to the developing negative charge on the leaving group. The small rho values for acyl substituents are in agreement with a carbonyl carbon engaged in simultaneous bond breakage and bond formation.

An alternative possibility is a two-step process involving a rate-determining collapse of a tetrahedral intermediate (Eq. 2). The large amount of evidence favoring intermediates in reactions of carboxylic acid deriva-

atives[16] leads us to prefer this mechanism over the direct displacement. Rate-determining collapse of the steady state intermediate means that



(2)

partitioning of the intermediate favors the reverse step in the mechanism[17]. This is reasonable, since the reverse step entails charge neutralization and since pyrrolidine is less basic in acetonitrile than even our best leaving group, p-nitrophenoxide[18].

The observed rho values for the aminolyses are comprised of contributions from both steps of the two-step mechanism. An electron withdrawing substituent in the leaving group would shift the equilibrium step to the right and accelerate the second step, resulting in a large rho value. An electron withdrawing substituent in the acyl portion, while having an accelerative effect on the first step, would inhibit the loss of a negatively charged leaving group. The net result would be a small rho value, as is observed.

A series of runs were performed using an unhindered tertiary amine, triethylenediamine, as an additional component of the system[4,8,9]. The tertiary amine was found to catalyze the aminolysis (k_3 term in Eq. 1). Although the absolute values of k_2 and k_3 changed by more than 10^3 when the substrate and secondary amine were varied, the ratio k_2/k_3 changed by less than a factor of two. The transition states for the k_2 and k_3 reactions are, therefore, similar. This is consistent with Eq. 2 but inconsistent with cyclic mechanisms where both participating amine molecules must bear at least one hydrogen.

Clearly, future work in the area of ester aminolysis in aprotic solvents

must take into consideration the possibility of a rate-determining collapse of a tetrahedral intermediate.

Acknowledgment. Support of this work by the National Science Foundation is gratefully acknowledged. We also wish to express our appreciation to the Petroleum Research Fund for a fourth-year graduate fellowship to J. H. Smith.

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15. Some cleavage is possible even if the amine attack is rate-determining. W. P. Jencks and M. Gilchrist, J. Am. Chem. Soc., 90, 2622 (1968).

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17. The rate-limiting step is determined by the highest point on the energy profile. When $\Delta F^{\ddagger}$ is greater for conversion of a steady state intermediate into products than into reactants, the former is rate-determining.

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