JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. **12**, 747–750 (1999)

Kinetics and mechanism of aminolysis of aliphatic esters in aprotic solvents

Agu-Tõnis Talvik, Ants Tuulmets* and Evi Vaino

Institute of Organic Chemistry, University of Tartu, 2 Jakobi St., Tartu 51014, Estonia

Received 4 March 1999; accepted 5 June 1999

ABSTRACT: Kinetic studies were carried out on the aminolysis reactions of substituted aliphatic esters in a variety of aprotic solvents. The reaction rate is strongly affected by inductive and steric effects of substituents in the acyl group, rising more than 10^4-fold from cyanoacetate to trifluoroacetate. The quantitative treatment of solvent effects revealed a rate decrease by the polarity and π-basicity of the solvents, and also an accelerating effect of the polarizability of solvents. Cyclic transition states were assumed for both the first and second-order (in amine) reactions. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: ester aminolysis; mechanism; structure effects; solvent effects

INTRODUCTION

The mechanism of ester aminolysis in aprotic media was subjected to a detailed analysis in the classical work of Menger and Smith.[1] They proposed the general Scheme 1 for ester aminolyses.

Scheme 1

It was concluded that the collapse of the tetrahedral intermediate was rate determining, and that the intermediate expels the leaving group in an unprotonated state (i.e. as a phenoxide ion rather than phenol). Negative activation energies were found for the aminolysis of electrophilic esters with good leaving groups such as 4-nitrophenyl trifluoroacetate.[2] Although $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ > 0$, for these compounds $\Delta H^{\neq}_{obsd} = \Delta H^\circ + \Delta H^{\neq} < 0$, where $\Delta H^{\neq}_{obsd}$ is the observed enthalpy of activation, $\Delta H^{\neq}$ is the enthalpy of activation for the passage of the intermediate to the transition state and ΔH° is the enthalpy of formation of the complex from the free reactants.

However, it is hard to believe that $|\Delta H^\circ| > |\Delta H^{\neq}|$ holds in non-polar media for a zwitterionic transition state. However, an activation energy of -23 kJ mol^{-1} has been found[3] for an aminolysis of isobutyl trichloroacetate in heptane, a reaction which involves a leaving group incomparably inferior to 4-nitrophenolate. On the other hand, it is not clear what kind of requirements should be satisfied by the acyl and alkoxy (aryloxy) groups of an ester in order to obtain the relationship $|\Delta H^\circ| > |\Delta H^{\neq}|$ necessary for the appearance of a negative activation energy.

This investigation was undertaken with a view to the further elucidation of the questions above. In order to cover aliphatic esters hitherto never subjected to the kinetic investigations of aminolysis, we made use of gas–liquid chromatography (GLC), which unfortunately imposed some restrictions on the accuracy of kinetic measurements in comparison with that attainable by means of spectral methods.

RESULTS AND DISCUSSION

In the first series of experiments the structure of the esters was varied. Decane was used as the solvent. Reaction kinetics was determined from the changes in the concentrations of both the ester and the alcohol. In all cases the rate of disappearence of the ester was equal to the rate of formation of the alcohol, within experimental error. The initial rate of the reaction was determined and calculated as a mean value of the rates for both changes. For each ester and for each reaction temperature two doubly differing initial concentrations of amine were used. The experimental order of the reaction in amine, n, was determined from the equation $\log v_0 = \text{constant} + n \log [\text{amine}]_0$, where v_0 is the initial rate of the reaction. The mean value for n was 1.8 ± 0.3 which indicates a second-order process dominating in the aminolyses of all the esters investigated. Therefore, in the limits of the

**Correspondence to:* A. Tuulmets, Institute of Organic Chemistry, University of Tartu, 2 Jakobi St., Tartu 51014, Estonia.
Contract/grant sponsor: Estonian Science Foundation.

CCC 0894–3230/99/100747–04 $17.50

Table 1. Kinetic data for the butylaminolysis of butyl esters RCOOBu in decane solution

R	T(°C)	log k_2[a]	$\Delta H^{\neq}$[b]	$\Delta S^{\neq}$[c]
H	20	-3.43 ± 0.04	-11.8	-351
	60	-3.63 ± 0.05		
$NCCH_2$	20	-4.93 ± 0.02	-15.5	-392
	60	-5.21 ± 0.02		
Cl_3C	20	-1.83 ± 0.03	-14.1	-328
	60	-2.08 ± 0.02		
F_2HC	20	-1.55 ± 0.04	-10.4	-309
	60	-1.72 ± 0.03		
F_3C	20	-0.51 ± 0.05	-13.2	-290
	60	-0.74 ± 0.06		

[a] k_2 in $dm^6\,mol^{-2}\,s^{-1}$.
[b] $kJ\,mol^{-1}$.
[c] $J\,mol^{-1}\,K^{-1}$.

amine concentrations used, the reaction can be considered to a first approximation as a second-order reaction in amine, and thus log v_0 − log $[ester]_0$ − 2 log $[amine]_0$ = log k_2. Results are presented in Table 1. The typical relative standard deviation of the rate constants was 10%. The error of the estimated activation enthalpies was about 3 $kJmol^{-1}$.

In a second series of experiments, the reaction medium was varied for butylaminolyses of butyl formate and butyl trichloroacetate. The kinetics of the reaction were determined with a large excess of the amine over the ester. Values for the first-order rate constant, k_I, obtained from kinetic curves were analyzed according to the linear equation

$$\frac{k_I}{[amine]_0} = k_1 + k_2[amine]_0 \qquad (1)$$

The usual number of runs for a linear treatment varied from 10 to 13. The typical relative standard deviation of the obtained parameters was 5%. The final results are presented in Table 2. The influence of the acyl group structure on the rate of the reaction can be analyzed[4] with the correlation equation

$$\log k = \log k^{\circ} + \rho^*\sigma^* + \delta E_s \qquad (2)$$

where k° is the rate constant for the standard compound, σ^* and E_s are inductive and steric substituent constants and ρ^* and δ are sensitivity constants.

The necessary inductive and steric constants were taken from Ref. 5. In order to keep hydrogen as the standard substituent, the scales of the parameters were shifted by 0.49 and 1.24 units, respectively. Kinetic data for 20 °C from Table 1 can thus be expressed in the form

$$\log k_2 = -(3.47 \pm 0.11) + (3.39 \pm 0.12)\sigma^* + (1.75 \pm 0.09)E_s$$

and those for 60 °C in the form

$$\log k_2 = -(3.66 \pm 0.12) + (3.44 \pm 0.13)\sigma^* + (1.80 \pm 0.10)E_s$$

The correlation coefficient and the standard error for both relationships are 0.999 and 0.05, respectively. The successful description of aminolysis kinetics by the Taft equation is consistent with a considerable contribution of a tetrahedral structure to the transition state of the reaction, as suggested previously[1,2]. At the same time, excellent correlations indicate the same mechanism for all the esters under consideration at both temperatures.

Another aspect of structure effects deserves special consideration. It appeared that activation enthalpies for all the esters are slightly negative and nearly independent of the substituents in the acyl group while the relative rate of the reaction is determined foremost by the entropy factor. Comparison of this conclusion with those made by Neuvonen[6] for ester hydrolysis in acetonitrile, where similar changes in structure caused a decrease in the $\Delta H^{\neq}_{obsd}$ value from 32.7 to $-18.9\,kJ\,mol^{-1}$, demonstrates a completely different behaviour of esters in the reactions.

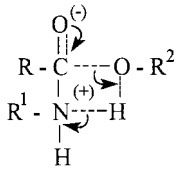
If a low or negative value for the observed activation

Table 2. Kinetic data for the butylaminolysis of esters in various solvents at 20 °C

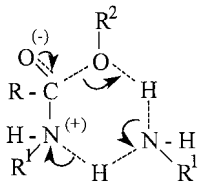
	Butyl formate		Butyl trichloroacetate
Solvent	$k_1 \times 10^{5a}$	$k_2 \times 10^{5b}$	$k_2 \times 10^{2b,c}$
Heptane	2.30 ± 0.95	21.9 ± 1.1	2.98 ± 0.07
Decane	—[c]	27.5 ± 1.5	3.25 ± 0.19
Cyclohexene	—	—	2.17 ± 0.09
Toluene	3.69 ± 0.45	3.21 ± 0.48	8.51 ± 0.20
1,2-Dichlorobenzene	2.39 ± 0.18	3.41 ± 0.27	1.62 ± 0.05
Bromobenzene	7.49 ± 0.52	5.64 ± 0.63	—
Iodobenzene	45.1 ± 2.6	15.0 ± 3.3	—

[a] $dm^3\,mol^{-1}\,s^{-1}$.
[b] $dm^6\,mol^{-1}\,s^{-1}$.
[c] No reliable k_1 term.

enthalpy is related to the strongly negative enthalpy of the first equilibrium step in Scheme 1, a comparable positive enthalpy change should be assumed for the rate-limiting step. Independence of this enthalpy change from the structure of acyl groups can hardly be expected for the first step of the reaction. Consequently, structure dependence must be compensated by a reverse relationship in the next step. In the limiting step, something disfavoured by the electronegative acyl components should occur. At the same time, the intrinsic entropy of activation can be only slightly influenced by the acyl group structure and the observed relative entropy changes should be mainly determined by the entropy change in the first step. The occurrence of cyclic transition state structures **1** and **2** in first- and second-order reactions in amine, respectively, preceded by the formation of cyclic intermediates (see below) can be appropriate to the considerations above.



1



2

The observed activation entropy varying between -290 and -392 J mol^{-1} K^{-1} for the whole set of esters in decane solution does not preclude cyclic transition states. Our data for structure relationships allow a strict consideration of the cyclic transition state only for the second-order reaction in amine. As for the first-order reaction, the extension of the idea was strongly inspired by relationships found for the aminolysis of benzoyl fluoride.[7] These appeared to be highly consistent with our results for the first-order aminolysis of esters. As a consequence, a similarity of the mechanisms can be expected. Variation of the medium conditions affects both the reactions fairly similarly also.

Our list of solvents was made up with provision for different polarity and polarizability. In addition, some of the solvents are weak bases (π-donors[8]). According to Ref. 9, we consider the polarity, Y, and the polarizability, P, as

$$Y \equiv \frac{\varepsilon - 1}{2\varepsilon + 1} \quad \text{and} \quad P \equiv \frac{n^2 - 1}{n^2 + 1}.$$

There are a number of ways to specify the general basicity of a solvent, but the most reliable seems to be the B-scale,[10] derived from IR shifts of phenolic hydroxyl in tetrachloromethane. Medium effects can then be expressed by the Koppel–Palm equation:[9]

$$\log k = \log k_0 + yY + pP + bB \tag{3}$$

From the data in Table 2, we obtained for formate

$$\log k_1 = -(10.77 \pm 0.89) - (7.20 \pm 1.43)Y + (23.69 \pm 3.42)P - (0.017 \pm 0.005)B$$

$$r = 0.991; \qquad s = 0.14$$

$$\log k_2 = -(6.53 \pm 0.51) - (5.35 \pm 0.78)Y + (12.23 \pm 1.94)P - (0.020 \pm 0.003)B$$

$$r = 0.992; \qquad s = 0.08$$

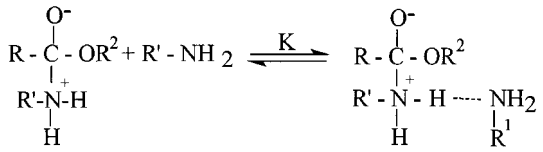
and for trichloroacetate

$$\log k_2 = -(5.22 \pm 0.85) - (6.59 \pm 1.21)Y + (15.44 \pm 3.39)P - (0.0040 \pm 0.0051)B$$

$$r = 0.994; \qquad s = 0.05$$

Thus, the polarity of the solvent decreases ($Y < 0$) and the polarizability of the medium increases ($P > 0$) the rate of the aminolysis reaction irrespective of the structure of the ester and of the order in amine. The transition states of all reactions considered should be clearly *less* polar than the initial states. The result corroborates earlier doubts[7,11] on the occurrence of a localized zwitterionic transition state. Convincingly more preferable are structures **1** and **2** with diffuse charge distribution, supported also by an accelerating effect of polarizability. However, this is not necessarily true for the aminolysis of phenolic esters in polar media.[12] Our experimental data do not provide much information on the relationship between first- and second-order pathways of the reaction. We can only refer to the fact that for a less reactive ester (formate) the routes are closely competitive (Table 2). In the case of an ester of higher reactivity (trichloroacetate), only a second-order reaction could be detected. A similar feature was found[7] for the aminolyses of benzoyl and 4-nitrobenzoyl fluorides, where the ratio k_2/k_1 increased by a factor of about 20 when a 4-nitro group was introduced. It is not clear why this should be so, but the tendency of amines to form complexes may be significant. An amine can appear as an electron donor and as an electron acceptor simultaneously. Nagy *et al.*[13] have demonstrated the occurrence of a complex between the amine and the carbonyl compound. Accordingly (by analogy with Ref. 14) an equilibrium mixture of two tetrahedral intermediates **3** and **4** should occur (Scheme 2).

Probably the value of K becomes greater for more electrophilic esters, the ratio k_2/k_1 increasing similarly. Intermediates **3** and **4** participating in the equilibrium (Scheme 2) can rearrange via an intramolecular attack to



3 **4**

Scheme 2

metastable cyclic intermediates,[1,7] which are structurally very close to transition states **1** and **2**. This step is accompanied by a considerable loss of entropy in the system but allows a well concerted rearrangement of electron density due to which the further crossing of the transition state requires only a moderate increase in enthalpy. Thus we have arrived at a possible explanation of negative activation enthalpies in ester aminolysis, principally consistent with that offered in the literature.[13] However, our experimental data, particularly for the ester series, can be considered as only preliminary. Therefore, more and better experimental data are necessary to reach firm conclusions. The investigation of ester aminolyses is being continued in our laboratory and further evidence of the statements above will be added in a later paper.

EXPERIMENTAL

The reaction was carried out in a stainless-steel cell with two pits at its bottom. In one of the hollows a solution of the ester was placed, and in the other a solution containing amine and the internal standard (heptane, tridecane, tetradecane or pentadecane) in an appropriate solvent, usually 1 cm^3 of both solutions. The reaction cell was thermostated and the reaction was started with vigorous shaking of the reactor. Depending on the rate of the process, the initial concentration of the amine in the reaction mixture was from 0.01 to 1.0 mol dm^{-3}. Samples were taken with a microsyringe through the silicone-rubber cap of the cell and immediately analysed by GLC with a Tsvet chromatograph (column 2.5 m × 3 mm i.d.) equipped with a Hewlett-Packard integrator. The concentrations of the ester or the product alcohol were calculated and plotted against time. The initial rate of the reaction, V_0, was determined as the slope of the tangent of the kinetic curve at $t = 0$. The rate constant k_1 was calculated by a differential method. Control experiments showed virtual irreversibility of the reaction under the used conditions.

Acknowledgements

We are grateful to the Estonian Science Foundation for the support of this work.

REFERENCES

1. F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.* **94**, 3824–3829 (1972).
2. T. D. Singh and R. W. Taft, *J. Am. Chem. Soc.* **97**, 3867–3869 (1975).
3. T. Laasik, A. Uri and A. Tuulmets, *Org. React. (USSR)* **15**, 571–575 (1978).
4. R. W. Taft, *J. Am. Chem. Soc.* **74**, 3120–3129 (1952).
5. R. W. Taft, in *Steric Effects in Organic Chemistry*, edited by M. S. Newman, and N. B. Chapman, Chapt. 13. Wiley, New York (1956).
6. H. Neuvonen, *J. Chem. Soc., Perkin Trans. 2* 951–954 (1995).
7. M. Jedrzejczak, R. E. Motie, D. P. N. Satchell and R. S. Satchell, *J. Chem. Soc., Perkin Trans. 2* 1471–1479 (1994).
8. O. B. Nagy, M. Muanda and J. B. Nagy, *J. Phys. Chem.* **83**, 1961–1969 (1979).
9. I. A. Koppel and V. A. Palm, in *Advances in Linear Free Energy Relationships*, edited by N. B. Chapman and J. Shorter, Chapt. 5. Plenum Press, New York (1972).
10. I. A. Koppel and A. I. Paju, *Org. React. (USSR)*, **11**, 121–138 (1974).
11. A. Tuulmets and A. Talvik, *Proc. Estonian Acad. Sci. Chem.*, **44**, 101–104 (1995).
12. H. J. Koh, S. I. Kim, B. C. Lee and I. Lee, *J. Chem. Soc., Perkin Trans. 2* 1353–1357 (1996).
13. O. B. Nagy, V. Reuliaux, N. Bertrand, A. van der Mensbrugghe, J. Leseul and J. B. Nagy, *Bull. Soc. Chim. Belg.* **94**, 1055–1074 (1985).
14. N. S. Nudelman and D. Palleros, *J. Org. Chem.* **48**, 1607–1612 (1983).

