Novel catalytic effects in ester aminolysis in chlorobenzene†

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The mechanism of glyme catalyzed ester aminolysis in chlorobenzene should be modified by including a new reaction pathway that shows a first-order dependence on the concentration of the phase transfer catalyst and a second-order dependence on butylamine.

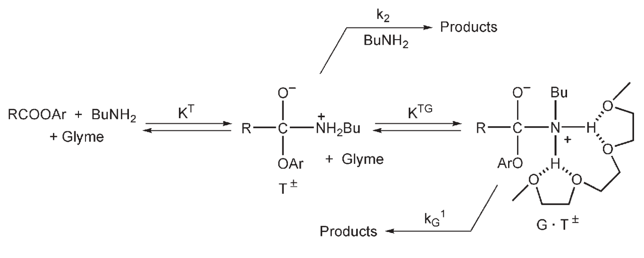
Catalysis by phase transfer agents (crown ethers or glymes) of aminolysis reactions of carboxylic esters is a well studied process.[1–8] The generally accepted catalytic mechanism in aprotic solvents is shown in Scheme 1. Nucleophilic attack of *n*-butylamine on the ester generates a tetrahedral intermediate, $T^{\pm}$.[9–12] This intermediate may either proceed with the catalytic assistance of a second *n*-butylamine molecule or form a complex with the phase transfer agent, $G{\cdot}T^{\pm}$. Subsequently, this complex gives rise to the reaction products in the rate-determining step. From this mechanism, the following rate equation can be obtained:

$$k_{\text{obs}} = k_{\text{B}}[\text{BuNH}_2]^2 + k_{\text{C}}[\text{BuNH}_2][\text{Glyme}] \qquad (1)$$

where the second order term in butylamine corresponds to the base-catalyzed decomposition, $k_{\text{B}} = K^{\text{T}}k_2$. The term of eqn. (1) which shows a first-order dependence on the butylamine and glyme concentrations stands for the reaction pathway catalyzed by the phase transfer agent, $k_{\text{C}} = K^{\text{T}}\,K^{\text{TG}}\,k_{\text{G}}^{1}$.

This reaction mechanism has been widely reported in the literature and the presence or absence of crown ether catalysis has been used as a test to identify the rate-determining step in ester aminolysis in solvents of different polarity[13] and in other mechanistic studies.[14]

In the present communication we report results obtained in our laboratory by studying the butylaminolysis of 4-nitrophenyl acetate and 4-nitrophenyl decanoate in chlorobenzene in the presence of glyme. This glyme was chosen on the basis of Hogan and Gandour's studies,[15–17] that conclude that a glyme with four oxygen atoms in a $–(CH_2OCH_2)_4–$ type subunit provides optimal catalysis for this kind of processes. Catalytic efficiency is due to a specific host–guest interaction between the glyme and the tetrahedral intermediate of the reaction, suggesting the existence of a $G{\cdot}T^{\pm}$ complex where the four oxygens donate electron density in order to stabilize the hydrogens of the ammonium ion of $T^{\pm}$. Given the size of the $–^{+}NH_2–$ fragment, the maximum number of oxygen atoms that will be able to bond is four. The structure of the guest rearranges the host, leading to the recognition of the transition state by the host. The results obtained suggest that the reaction mechanism shown in Scheme 1 needs to be modified through the addition of a new reaction pathway.



Scheme 1

Our kinetic studies were always performed under conditions where the amine concentration was in large excess over that of the carboxylic ester, [ester] = 5.0×10^{-5} M. Pseudo-first-order rate constants, k_{obs}, were obtained from the analysis of absorbance–time profiles, $\lambda = 320$ nm. Fig. 1 shows the influence of butylamine concentration on k_{obs} for the butylaminolysis of 4-nitrophenyl caprate in chlorobenzene at 25 °C at different glyme concentrations. In all cases, a linear and quadratic dependence of k_{obs} on [butylamine] is observed. The existence of this dependence is consistent with an aminolysis mechanism proceeding through the formation of a tetrahedral intermediate in non-aqueous solvents.[18–24] Kinetic data were fitted to an equation of the type:

$$k_{\text{obs}} = a[\text{BuNH}_2] + b[\text{BuNH}_2]^2 \qquad (2)$$

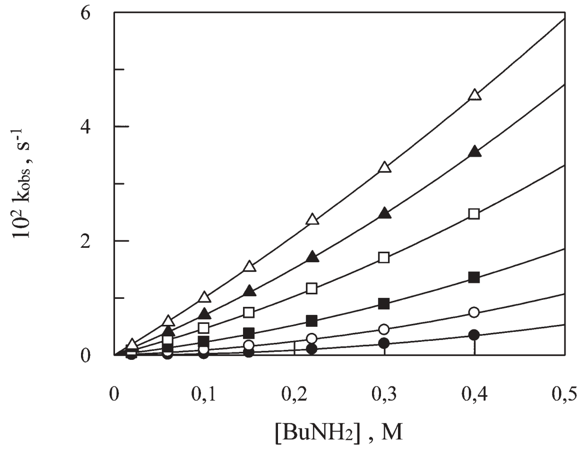


Fig. 1 Influence of *n*-butylamine concentration on k_{obs} for the aminolysis of 4-nitrophenyl caprate. T = 25 °C. [NPC] = 5×10^{-5}M. (●) [Glyme] = 0 M; (○) [Glyme] = 0.1 M; (■) [Glyme] = 0.25 M; (□) [Glyme] = 0.5 M; (▲) [Glyme] = 0.75 M and (△) [Glyme] = 1.0 M.

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Eqn. (2) is formally analogous to eqn. (1), commonly used for the mechanism depicted in Scheme 1. Fig. 2 illustrates the influence of glyme concentration on the *a* and *b* terms of eqn. (2). As can be observed, the *a* term exhibits a linear dependence on [Glyme]. This result is consistent with the mechanism generally accepted for the catalysis by crown ethers and glymes of the aminolysis of carboxylic esters.

The mechanism shown in Scheme 1 predicts that the *b* term should be independent of the glyme concentration. However, the results reported in Fig. 2 for the butylaminolysis of 4-nitrophenyl caprate and 4-nitrophenyl acetate indicate that this term shows a linear dependence on glyme concentration.

The mechanism presented in Scheme 1 needs to be further developed in order to explain the observed kinetic data. The presence of a kinetic term showing a second-order dependence on butylamine concentration and a first-order dependence on glyme concentration may be accounted for by the possibility that the G·T$^{\pm}$ complex may decompose by a base-catalyzed pathway. The proposed mechanism is shown in Scheme 2 along with the new reaction pathway. From this scheme, the following rate equation can be obtained. Previous studies have investigated the influence of glymes or crown ethers on the butylaminolysis rate constant keeping constant the butylamine concentration. In this way only a term that is first order in glyme or crown ether concentration can be detected.

$$k_{\mathrm{obs}} = k_{\mathrm{C}}[\mathrm{Glyme}][\mathrm{BuNH_2}] + (k_{\mathrm{B}} + k_{\mathrm{D}}[\mathrm{Glyme}])[\mathrm{BuNH_2}]^2 \quad (3)$$

Rate constants, k_{C}, for the glyme-catalyzed butylaminolysis of nitrophenyl acetate and nitrophenyl caprate, can be determined from the influence of glyme concentration on the *a* term (Fig. 2).

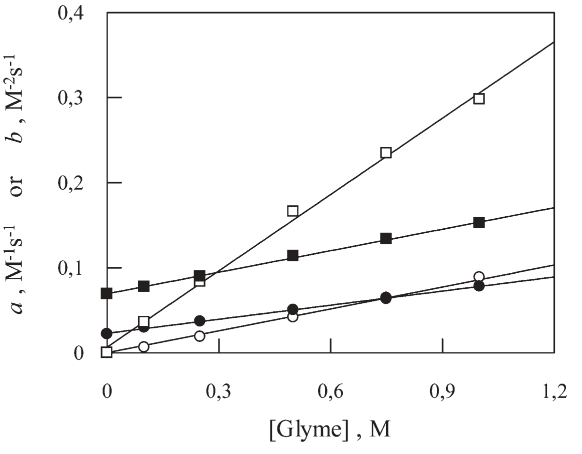
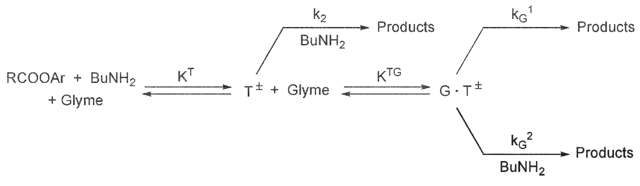


Fig. 2 Influence of glyme concentration on the *a* and *b* terms (eqn. (2)) for the butylaminolysis of 4-nitrophenyl caprate (*a*: ○, *b*: ●) and 4-nitrophenyl acetate (*a*: □, *b*: ■).



Scheme 2

Eqn. (3) accounts for the intercepts in the plots of the influence of [Glyme] on the *b* term (Fig. 2), which correspond to the base-catalyzed decomposition of the intermediate, T$^{\pm}$. Application of eqn. (3) leads to the values of k_{B} for the butylaminolysis of nitrophenyl acetate and caprate respectively. The rate constants can be determined for this new reaction pathway which shows base and glyme catalysis simultaneously. The values of k_{D} for the butylaminolysis of nitrophenyl acetate and caprate respectively can be obtained from eqn. (3) and Fig. 2. Values of k_{C}, k_{B} and k_{D} are shown in Table 1. A tentative explanation on how a butylamine molecule can attach G·T$^{\pm}$ to help the reaction is that one of the two nitrogen–hydrogen bonds breaks in all cases, but frequently it reverses and reforms the G·T$^{\pm}$ complex (since the entities are still bonded together). In turn decomplexation can be assisted (enforced) by transfer of the proton (removed by the glyme from the nitrogen) to a butylamine molecule, then followed by decomplexation as the favoured pathway and regeneration of the carbonyl group and loss of the aryloxide group, in preference to loss of the butyl amino group, giving the aminolysis product.

From the reaction scheme illustrated in Scheme 2, the following microscopic rate equation can be obtained in terms of the equilibrium formation constants of T$^{\pm}$ and the G·T$^{\pm}$ complex.

$$\begin{aligned} k_{\mathrm{obs}} &= k_{\mathrm{G}}^{1}K^{\mathrm{T}}K^{\mathrm{TG}}\,[\mathrm{Glyme}][\mathrm{BuNH_2}] + \\ &(k_2K^{\mathrm{T}} + k_{\mathrm{G}}^{2}K^{\mathrm{T}}K^{\mathrm{TG}}\,[\mathrm{Glyme}])[\mathrm{BuNH_2}]^2 \end{aligned} \qquad (4)$$

This expression is analogous to eqn. (3). Therefore, it is possible to estimate the microscopic meaning of the constants k_{B}, k_{C} and k_{D}: $k_{\mathrm{B}} = k_2K^{\mathrm{T}}$, $k_{\mathrm{C}} = \mathrm{k}_{\mathrm{G}}^{1}K^{\mathrm{T}}K^{\mathrm{TG}}$ and $k_{\mathrm{D}} = K_{\mathrm{G}}^{2}K^{\mathrm{T}}\,K^{\mathrm{TG}}$. From the quotient between the values of k_{C} and k_{D}, the relationship between the spontaneous and base-catalyzed rate constants for the decomposition of G·T$^{\pm}$ can be obtained: $k_{\mathrm{C}}/k_{\mathrm{D}} = k_{\mathrm{G}}^{1}/k_{\mathrm{G}}^{2}$. In all cases, the butylaminolysis rate of 4-nitrophenyl acetate is observed to be faster than that for 4-nitrophenyl caprate. The rate of the butylamine-catalyzed decomposition of the intermediate T$^{\pm}$, k_{B}, is 3 times faster for acetate than it is for caprate. Likewise, the rate of spontaneous decomposition of the G·T$^{\pm}$ complex, k_{C}, is also 3.6 times faster for acetate than for caprate. This difference in reactivity decreases when considering the butylamine-catalyzed decomposition pathway of the G·T$^{\pm}$ complex, k_{D}, showing that the rate constant is 1.5 times larger for acetate than it is for caprate. This result reveals that in both catalytic pathways complexation of the phase transfer agent takes place on the ammonium moiety.

The values obtained for the butylaminolysis of 4-nitrophenyl acetate, $k_{\mathrm{C}}/k_{\mathrm{D}} = k_{\mathrm{G}}^{1}/K_{\mathrm{G}}^{2} = 3.68$ M, and 4-nitrophenyl caprate, $k_{\mathrm{C}}/k_{\mathrm{D}} = k_{\mathrm{G}}^{1}/k_{\mathrm{G}}^{2} = 1.56$ M, suggest that the decomposition pathway of the glyme-intermediate complex to spontaneously give the reaction products is favored against the pathway in which this complex is assisted by an amine molecule to give the corresponding amide.

Table 1 Rate constants for the glyme-catalyzed butylaminolysis of *p*-nitrophenyl acetate and *p*-nitrophenyl caprate

	k_{C}/M^{-2} s^{-1}	k_{B}/M^{-2} s^{-1}	k_{D}/M^{-3} s^{-1}
NPA	3.10×10^{-1}	6.94×10^{-2}	8.43×10^{-2}
NPC	8.59×10^{-2}	2.29×10^{-2}	5.51×10^{-2}

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Notes and references

1 R. D. Gandour, D. A. Walker, A. Nayak and G. R. Newkome, *J. Am. Chem. Soc.*, 1978, **100**, 3608–9.
2 T. Komives, A. F. Marton, F. Dutka, M. Low and L. Kisfaludy, *React. Kinet. Catal. Lett.*, 1980, **13**, 357–9.
3 A. B. Maude and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1995, 691–6.
4 H. Zipse, L. H. Wang and K. N. Houk, *Liebigs Ann. Chem.*, 1996, 1511–1522.
5 H. J. Koh, K. L. Han and I. Lee, *J. Org. Chem.*, 1999, **64**, 4783–4789.
6 L. Baldini, C. Bracchini, R. Cacciapaglia, A. Casnati, L. Mandolini and R. Ungaro, *Chem. Eur. J.*, 2000, **6**, 1322–1330.
7 L. N. Vakhitova, Y. F. Burdina, A. V. Skrypka, A. F. Popov and V. A. Savelova, *Theor. Exp. Chem.*, 2002, **37**, 225–229.
8 L. N. Vakhitova, V. A. Savelova, Y. F. Burdina, I. A. Belousova and A. F. Popov, *Russ. J. Org. Chem.*, 2003, **39**, 968–971.
9 A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, 1974, **96**, 7018–7031.
10 M. J. Gresser and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, **99**, 6970–6980.
11 J. C. Fishbein, H. Baum, M. M. Cox and W. P. Jencks, *J. Am. Chem. Soc.*, 1987, **109**, 5790–5800.
12 J. F. Marlier, *Acc. Chem. Res.*, 2001, **34**, 283–290.
13 A. B. Maude and A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1997, 179–183.
14 L. García-Río, J. R. Leis, J. A. Moreira and D. Serantes, *Eur. J. Org. Chem.*, 2004, 614–622.
15 J. C. Hogan and R. D. Gandour, *J. Am. Chem. Soc.*, 1980, **102**, 2865–2866.
16 J. C. Hogan and R. D. Gandour, *J. Org. Chem.*, 1991, **56**, 2821–2826.
17 J. C. Hogan and R. D. Gandour, *J. Org. Chem.*, 1992, **57**, 55–61.
18 F. Menger, *J. Am. Chem. Soc.*, 1966, **88**, 3081–3084.
19 H. Anderson, C.-W. Su and J. W. Watson, *J. Am. Chem. Soc.*, 1969, **91**, 482–484.
20 F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.*, 1972, **94**, 3824–3829.
21 C.-W. Su and J. W. Watson, *J. Am. Chem. Soc.*, 1974, **96**, 1854–1857.
22 M. J. Pfeiffer and S. B. Hanna, *J. Org. Chem.*, 1993, **58**, 735–740.
23 B. R. Cho, Y. K. Kim and C.-O. M. Yoon, *J. Am. Chem. Soc.*, 1997, **119**, 691–697.
24 C. Melander and D. A. Horne, *J. Org. Chem.*, 1997, **62**, 9295–9297.