Novel change in rate-determining step within an E1cB mechanism during aminolysis of a sulfamate ester in acetonitrile

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The observation of biphasic Brønsted plots (β_1 *ca.* 0.7 and β_2 *ca.* 0) in the aminolysis (alicyclic amines, pyridines) of 4-nitrophenyl *N*-benzylsulfamate 1a in MeCN is interpreted as being due to a mechanistic change from $(ElcB)_{irrev}$ to $(ElcB)_{rev}$; the change in rate-determining step occurs at approximately the pK_a of 1a and other more basic substrates give straight line plots; an entropy study supports the change from a bimolecular to a unimolecular mechanism.

Recently in our laboratory we have been studying the elimination-addition reactions of sulfamoyl chlorides with anilines[1] and of sulfamate esters with a series of amines[2] (pyridines, alicyclic amines and quinuclidines) in $CHCl_3$ and MeCN. The mechanism was seen as being E2 with ElcB-like character. UV kinetics fitted the rate law $k_{RR'NH}$[RR′NH][ester], and good straight line Brønsted type plots were obtained in this work. In particular, the aminolysis of the 4-nitrophenyl *N*-benzyl ester **1a** in $CHCl_3$ at 37 °C gave straight line Brønsted plots.[2] However, we have now found that this ester in MeCN at 37 °C gives curved plots with similar series of amines (Fig. 1). These plots are essentially biphasic with slopes β_1 *ca.* 0.7 at lower pK_as and β_2 *ca.* 0 at higher pK_as and are best interpreted in terms of a mechanistic change within the ElcB mechanism from $(ElcB)_{irrev}$ (amines of lower pK_a) to $(ElcB)_{rev}$ (amines of higher pK_a). The change from general to specific base catalysis expected for such a mechanistic change[3] is clearly evident in Fig. 1. The situation may be represented by Scheme 1. At lower amine pK_as the rate-determining step is the bimolecular formation of the conjugate base of the substrate **2** and the second step is relatively rapid departure of the leaving groups and formation of products *p*-nitrophenol and sulfamide ($k_2 >> k_{-1}$[RR′NH_2^+]). The reaction path from **2** to products may involve an *N*-sulfonylamine ($BnN{=}SO_2$)[1,2,4]

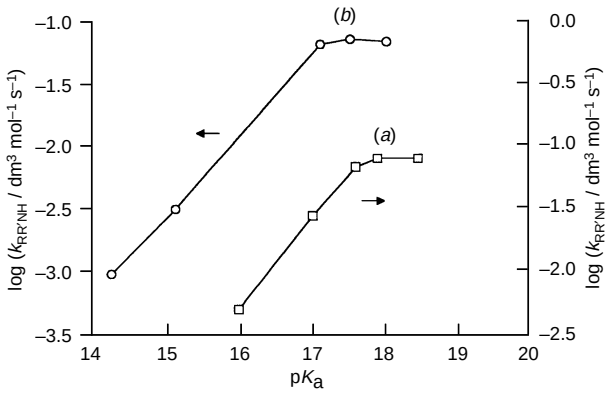
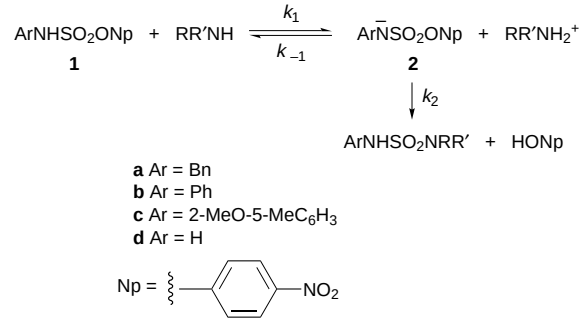


Fig. 1 Biphasic Brønsted plots for the aminolysis of **1a** in MeCN 37 °C: (*a*) alicyclic amines from left to right: morpholine, 1-formylpiperazine, 1-(2-hydroxyethyl)piperazine, 1-(2-aminoethyl)piperazine and piperazine; (*b*) pyridines from left to right: 2-aminopyridine, 2-amino-4-methylpyridine, 4-aminopyridine, DMAP and 4-pyrrolylpyridine

Further support for this mechanistic change comes from an activation study using morpholine, 1-(2-aminoethyl)piperazine and piperazine [Fig. 1(*a*)] and DMAP and 4-pyrrolylpyridine [Fig. 1(*b*)] with the ester **1a** in MeCN. The observed entropy changes ($\Delta S^{\pm}$, J K^{-1} mol^{-1}) are (temperature range in parenthesis): morpholine −262 (17–47 °C), 1-(2-aminoethyl)piperazine −59 (17–47 °C), piperazine −11 (17–47 °C), DMAP −124 (15–43 °C) and 4-pyrrolylpyridine −32 (15–46 °C). These entropy changes support the onset of a unimolecular $(ElcB)_{rev}$ mechanism as the basicity of the catalytic amine is increased, and with piperazine and 4-pyrrolylpyridine the reaction should proceed substantially *via* this mechanism. Typical values of $\Delta S^{\pm}$ for the $(ElcB)_{rev}$ mechanism lie[5] in the range of *ca.* +150 to − 40 J K^{-1} mol^{-1} and these authors also report much more negative entropies (−55 to −170 J K^{-1} mol^{-1}) for studies on related substrates undergoing $B_{AC}2$, S_N2 and E2 mechanisms. $\Delta S^{\pm}$ values of −163 to −130 J K^{-1} mol^{-1} have been reported for the $(ElcB)_{irrev}$ mechanism.[6]

When the substrate was **1b** using the same set of alicyclic amines in MeCN, surprisingly a straight line Brønsted plot was obtained (β = 0.19) [Fig. 2(*b*)]. Again with a slightly less basic ester **1c** no curvature was seen in the Brønsted plot (β = 0.35) using a set of pyridine bases [Fig. 2(*a*)]. The reason for this behaviour became apparent when we measured[7] and calculated[8] pK_as in MeCN for the esters **1**. The values obtained (calculated in parenthesis) were: **1a** 17.68 ± 0.5 (~ 16.5 ± 0.5),[9] **1b** 19.1 ± 0.1 (19.5 ± 0.5) and **1c** 18.56 ± 0.3 (~ 18.87 ± 0.5).[9] The ester **1a** showed curvature because the catalytic bases used are sufficiently strong to remove the substrate proton, the k_1 step becomes unimportant kinetically and k_2 dominates giving the observed $(ElcB)_{rev}$ mechanism. A referee has pointed out that the plots in Fig.1 are analogous to classical Eigen plots, and in keeping with this the changeover in rate-determining step occurs at about the pK_a of **1a**, i.e. ΔpK = 0; in the case of the other two esters studied the available amines are all less basic than the substrate, and the NH proton is not extensively removed and a change in rate determining step is therefore not observed with these esters.



Scheme 1

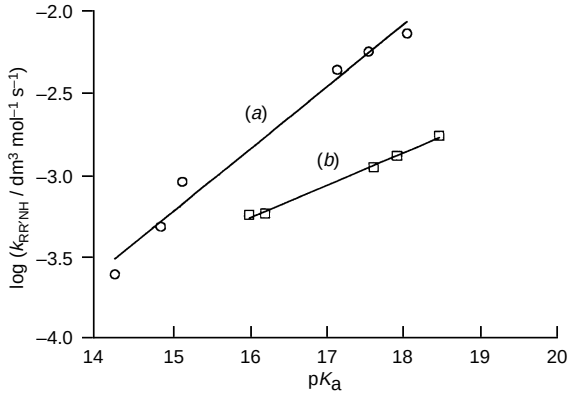


Fig. 2 Brønsted plots for the aminolysis of sulfamate esters in MeCN at 37 °C: (*a*) pyridines from left to right: 2-aminopyridine, 2,4,6-trimethylpyridine, 2-amino-4-methylpyridine, 4-aminopyridine, DMAP and 4-pyrrolylpyridine using **1c**; (*b*) alicyclic amines from left to right: morpholine, thiomorpholine, 1-(2-hydroxyethyl)piperazine, 1-(2-aminoethyl)piperazine and piperazine using **1b**

In $CHCl_3$ we have never observed curvature in Brønsted plots with **1a**, **1b** or with 4-nitrophenylsulfamate **1d** and various series of amines. This may be due to a more substantial difference in basicity between the substrates and the catalytic amines in this medium compared to MeCN. This view can be at least qualitatively supported by considering the Gibbs energy differences ($\Delta\Delta G$) for the ionization of the substrates and the conjugate bases $RR'NH_2^+$ in solvents of differing relative permittivity.[10]

Change in rate-determining step within an ElcB reaction path involving carbanions has been demonstrated by a number of groups.[11–15] However such a change involving nitrogen acids has not been clearly demonstrated previously; Caplow[16] has obtained a very similar plot (β_1 *ca.* 0.77 and β_2 *ca.* 0) to those in Fig.1 for the decomposition of carbamates in water in the presence of various amines, but has interpreted it differently. Hence the present work is the first clear-cut example of this ElcB mechanistic change not involving a carbon acid.

Notes and References

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8 Using the Advanced Chemistry Development (ACD) Inc., Canada, pK_a program, which calculates pK_a in water, 8.0 was added to the values obtained since this was the approximate difference between calculated (for H_2O) and experimental values (in MeCN) for the various series of amines studied.
9 These are approximate values since the calculations had to be performed without the *p*-nitro group. The program cannot calculate pK_a for compounds with > 20 atoms other than hydrogen.
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Received in Cambridge, UK, 23 February 1998; 8/01505H