Aminolysis of sulfamate esters in non-aqueous solvents. Use of Brønsted coefficients (β_{nuc}) to assign E2 and E1cB mechanisms

William J. Spillane * and Chris Brack

Chemistry Department, National University of Ireland, Galway, Ireland

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A series of Hammett ρ_{acyl} values for the aminolysis in chloroform and acetonitrile at 37 °C of the sulfamate esters $RNHSO_2OC_6H_4NO_2$-4 (R = XC_6H_4-, X = 4-MeO, 4-Me, 3-Me, H, 4-Br and 3-Cl) have been measured using piperidine and a set of five pyridines. Hammett ρ_{pyr} values have also been measured for various esters using a set of pyridines with varying substituents in the pyridine ring. A series of Brønsted β_{nuc} values have been measured for the sulfamate esters. All the available β_{nuc} values for sulfamate ester aminolysis have been compared and from this it has been possible to make mechanistic assignments to E1cB (β_{nuc} *ca.* 0.7 and *ca.* 0) and E2 (β_{nuc} 0.17 to 0.54) pathways. In the case of the E2 mechanism those reactions with lower β_{nuc} values are thought to have little N_β–H bond-breaking but this process is well advanced giving carbanionic E1cB-like characteristics to the E2 mechanism for reactions with larger β_{nuc} values. Thermodynamic data ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) support these interpretations.

Recently we have been looking at elimination mechanisms in the reactions of sulfamate esters **1**, particularly aminolysis with various sets of catalytic bases in non-aqueous solvents.[1–3] In this work both E2 and E1cB and variants of these mechanisms have been recognized by employing a number of techniques including linear free energy relationships, activation studies and comparisons with model substrates. *N*-Sulfonylamines, [RN=SO_2], though clearly involved in studies in aqueous media[4,5] and in the aminolysis of sulfamoyl chlorides, RNH-SO_2Cl,[6] do not appear to be involved in the aminolysis of esters **1** in non-aqueous media.[1]

In this paper we report a series of ρ_{acyl} values for variation of substituents X in the acyl (R) portion of the substrate **1** and for variation of the catalytic base for a fixed substrate **1**. Second, a number of Brønsted β_{nuc} values have been obtained and compared with previously measured values. This comparison appears to offer an answer at least for sulfamate ester eliminations to one of the classic dilemmas in eliminations, namely, is the mechanism E1cB or E2?[7,8] Third, enthalpies and entropies of activation have been determined for some reactions.

$$\underset{\mathbf{1}}{RNHSO_2OC_6H_4NO_2\text{-}4} + R'NH_2 \xrightarrow[\text{organic solvent}]{k_2} RNHSO_2NHR' + HOC_6H_4NO_2\text{-}4$$

Scheme 1

Results and discussion

Using a set of 4-nitrophenyl *N*-X-phenylsulfamates, a series of ρ_{acyl} values have been measured by employing the bases shown in Table 1. The Hammett plots are shown in Fig. 1 for the five pyridines in chloroform. The trend in the data is obvious and starting from the strongest base, piperidine, there is a decrease in the ρ_{acyl} values down to 3-chloropyridine. This indicates a diminishing interaction between the 'acyl' substituents and the reaction centre, less N_β–H cleavage and a progression from a partial carbanion-like transition state to a more central E2 type mechanism as the pK_a of the base decreases. A change in solvent from chloroform to acetonitrile for 4-DMAP almost doubles the ρ_{acyl} value to −1.53. This supports a shift towards the opposite end of the 'E2 spectrum' to give a more E1cB-like mechanism and a recurring value of *ca.* −1.8 for ρ_{acyl} in these systems has been interpreted in favour of E1cB type mechanisms involving transient sulfonylamine intermediates.

Table 1 Hammett ρ_{acyl} values for reaction of 4-nitrophenyl *N*-X-phenylsulfamates[a] with various bases in chloroform and acetonitrile at 37 °C

Base[b]	pK_a	Solvent	ρ_{acyl}	*r*	Ref.
Piperidine	11.24	$CHCl_3$	−1.19[c]	0.99	1
4-Me_2NPyr	9.61	$CHCl_3$	−0.91[d]	0.99	1
2-NH_2, 4-MePyr	7.53	$CHCl_3$	−0.84[d]	0.98	This work
2-EtPyr	5.89	$CHCl_3$	−0.74[d]	0.98	This work
Pyr	5.25	$CHCl_3$	−0.70[d]	0.98	This work
3-ClPyr	2.84	$CHCl_3$	−0.58[d]	0.98	This work
4-Me_2NPyr	9.61	CH_3CN	−1.53[c]	0.99	This work

[a] 1×10^{-4} mol dm^{-3}. [b] The range of base concentrations used to determine k_{obs} were normally 0.05 to 0.25 mol dm^{-3}; k_2 values, in dm^3 mol^{-1} s^{-1}, were determined from plots of k_{obs} *vs.* [base]. The pK_as given in column 2 refer to measurements in water (see ref. 1). [c] Using compounds **1** with R = XC_6H_4 (X = 4-MeO, 4-Me, 3-Me, H and 3-Cl). [d] Using the same five compounds (footnote *c*) and also the 4-Br ester.

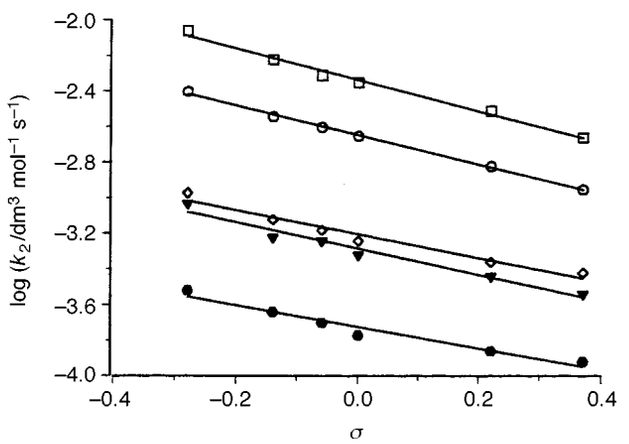

Fig. 1 Hammett plots for reaction of 4-nitrophenyl *N*-X- (= 4-MeO, 4-Me, 3-Me, H and 3-Cl) -phenylsulfamates in chloroform at 37 °C with 4-DMAP (□), 2-NH_2, 4-Mepyr (○), 2-Etpyr (▼), Pyr (◇) and 3-Clpyr (●). The slopes (ρ_{acyl}) and correlation coefficients for the lines are in Table 1.

In Table 2 ρ_{pyr} values have been determined using eight

Table 2 Hammett ρ_{pyr} values for reaction of sets of pyridines[a,b] with various sulfamate esters[c] in chloroform at 37 °C

Substrate R = in **1**	σ^{*}[d]	ρ_{pyr}	r	n	Ref.
H	—	−1.71	0.99	8[e]	1
Bn	0.22	−1.40	0.96	7[e]	1
4-$MeOC_6H_4$-	0.36	−1.26	0.98	5	This work
4-MeC_6H_4-	0.46	−1.22	0.96	5	This work
3-MeC_6H_4-	0.48	−1.20	0.98	5	This work
Ph	0.60	−1.22	0.97	5	This work
4-BrC_6H_4-	0.74	−1.15	0.98	5	This work
3-ClC_6H_4-	0.85	−1.08	0.97	5	This work

[a] The pyridines used ($\sigma/\Sigma\sigma$ in parentheses) were as follows: 4-Me_2N (−0.83), 2-NH_2, 4-Me (−0.41), 2-Et (−0.13), H (0.0) and 3-Cl (0.37). [b] See footnote *b*, Table 1. [c] 1×10^{-4} mol dm^{-3}. [d] See *Exploring QSAR, hydrophobic, electronic and steric constants* by C. Hansch, A. Leo and D. Hoeckman, ACS, Washington DC, 1995 and Y. Nagar, H. Matsumoto, T. Nakano and H. Watanabe, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 2560. [e] See ref. 1 for details of pyridines used.

Table 3 Brønsted β_{nuc} values for aminolysis of 4-nitrophenyl *N*-X-phenylsulfamates[a] in chloroform and acetonitrile at 37 °C

Substrate R = in **1**	β_{nuc}	r	n[b]
4-$MeOC_6H_4$-	0.21	0.99	6
4-MeC_6H_4-	0.20	0.97	6
3-MeC_6H_4-	0.20	0.98	6
Ph	0.20	0.98	6
4-BrC_6H_4-	0.18	0.98	6
3-ClC_6H_4-	0.17	0.97	6
Ph	0.29	0.99	7[c]

[a] See footnotes *a* and *b*, Table 1. [b] In the first six runs the first six bases in Table 1 were used in $CHCl_3$. [c] In this run the following seven pyridines (pK_as in acetonitrile were calculated—see ref. 3): 4-pyrrolo- (18.06), 4-DMAP (17.56), 4-amino- (17.15), 2-amino-4,6-dimethyl- (15.63), 2-amino-4-methyl- (15.13), 2,4,6-trimethyl- (14.85) and 2-amino- (14.25) were employed.

different sulfamates separately. The trend seen in the ρ_{pyr} values corresponds almost to increasing electron-demand of the R portion of the substrate as gauged by the available σ^{*} values. The ρ_{pyr} values indicate that there is just a small amount of positive change on the pyridine nitrogen in the transition state of the elimination since the ρ value for the ionization of pyridinium ions is 5.7.[9] The β_{nuc} values of Table 3 corroborate this and show that the extent of proton transfer to pyridine must be small in chloroform but somewhat greater in acetonitrile (last row in Table 3). In the latter solvent, which has a much larger relative permittivity than chloroform (36 and 4.8 respectively), a shift to a more carbanionic E1cB-like mechanism seems possible. Certainly in terms of a More O'Ferrall–Jencks diagram the reaction in acetonitrile will have a significant horizontal component corresponding to proton transfer in the transition state. Much more can be made of these β_{nuc} values by looking at a 'family' of values such as those shown in Table 4. Here the two important values from Table 3 are grouped with other β_{nuc}s that have been measured recently.

In very general terms the E2 mechanism tends to give rise to β_{nuc} values from *ca*. 0.2 to *ca*. 0.6 and an $(E1cB)_{irrev}$ mechanism often has a β_{nuc} of 0.7 or higher.[10–13] However care is needed in interpreting particular β_{nuc} values to support E2 or E1cB mechanisms since the larger rather than the smaller β_{nuc} value may be associated with an E2 mechanism.[14] In the case of the reactions under study here recently[3] it was shown that β_{nuc} values of *ca*. 0.7 and then *ca*. 0 from biphasic Brønsted plots could be clearly associated with an $(E1cB)_{irrev}$ mechanism and an emerging $(E1cB)_{rev}$ mechanism in acetonitrile. Other reactions of sulfamate esters in acetonitrile give β_{nuc} values which were much lower than 0.7 (see Table 4) and these reactions must be E2 in nature but with varying degrees of N_β–H and perhaps S_α–ONp cleavage. The more substantial proton transfer

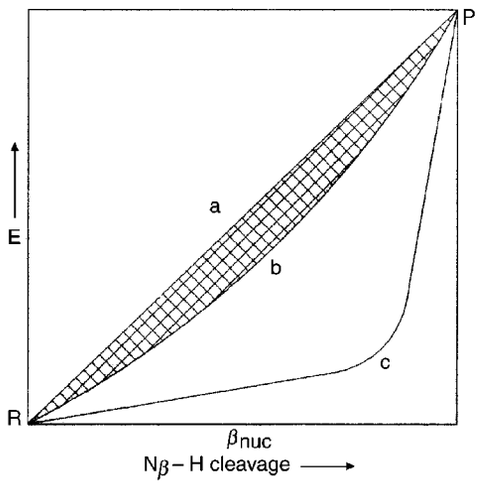

Fig. 2 More O'Ferrall–Jencks diagram for sulfamate aminolysis *via* E2 and E2–E1cB-like mechanisms. R = reactants *i.e.* B + RNH-SO_2ONp, P = products *i.e.* $BH^+ + RNHSO_2NHR' + {}^-ONp$ and the bottom right hand corner is the $(E1cB)_{irrev}$ segment *i.e.* $BH^+ + RN{}^-SO_2ONp$. Line 'a' running diagonally from R to P represents a central E2 mechanism. Line 'b' represents an E2 mechanism with substantial N_β–H cleavage *i.e.* an E2–E1cB-like mechanism. Line 'c' illustrates an $(E1cB)_{irrev}$ mechanism.

($\beta_{nuc} = 0.38$) for **1**, R = 2-MeO, 5-MeC_6H_3 compared to **1**, R = Ph (β_{nuc}=0.29) may be due to the slightly higher acidity of the former. The values of 0.52 and 0.54 in chloroform have been attributed to a greater amount of proton transfer when strong quinuclidine and alicyclic amine bases were employed. The last entry in Table 4 is for the reaction of *N*-phenylsulfamoyl chloride with a series of anilines in CH_3CN. This reaction is believed to involve *N*-sulfonylamines.[6] In the last column in Table 4 mechanistic assignments have been made based on the above analysis.

These mechanistic nuances can be represented quite well on a More O'Ferrall–Jencks diagram (Fig. 2). The diagonal line a represents a central E2 mechanism and may reflect the situation where low β_{nuc} values of *ca*. 0.2 have been measured in this work. The higher values of 0.29, 0.38 and particularly 0.52 and 0.54 (Table 4) are represented by line b and imaginary lines in the shaded area of Fig. 2. The line c should represent a full blown $(E1cB)_{irrev}$ mechanism (corresponding to β_{nuc} *ca*. 0.7).

In Table 5 some thermodynamic data is given for reactions in both $CHCl_3$ and CH_3CN. The change from pyridine in $CHCl_3$ to a more basic pyridine, 4-DMAP, in $CHCl_3$ lowers the enthalpy (faster reaction) but increases the change in entropy on moving from the ground to the transition state. One may interpret this as being due to a greater separation of charge in the '4-DMAP transition state' compared to the 'pyridine transition state'. A change of mechanism is unlikely since elsewhere a good isokinetic relationship for a wide range of bases was established for the aminolysis of **1**, R = H in $CHCl_3$.[1] In CH_3CN the changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are considerable and seem to support a change to an E2–E1cB-like mechanism—a proposal supported above by a ρ_{acyl} of −1.53 (Table 1) and a β_{nuc} of 0.29 (Table 3).

In conclusion the aminolysis of sulfamate esters in $CHCl_3$ and CH_3CN generally takes place by an E2 type mechanism. The type of E2 mechanism may vary from a 'central' one to one with considerable E1cB-like character. In certain cases in CH_3CN $(E1cB)_{irrev}$ and $(E1cB)_{rev}$ mechanisms occur and these are characterized by biphasic Brønsted plots having slopes of *ca*. 0.7 and *ca.* 0 respectively.

Experimental

Details of the materials used and the synthesis of the sulfamate

Table 4 Brønsted β_{nuc} values for aminolysis of sulfamate esters in chloroform and acetonitrile at 37 °C

Substrate R = in **1**	Solvent	Bases	β_{nuc}	Ref.	Mechanistic characterisitcs
Ph	$CHCl_3$	Piperidine + pyrs	0.20	This work	E2, little N_β–H cleavage
H	$CHCl_3$	Pyrs	0.31	1	E2, reasonable N_β–H cleavage
Bn	$CHCl_3$	Pyrs	0.21	1	E2, little N_β–H cleavage
Bn	$CHCl_3$	Quinuclidines	0.52	1	E2, extensive N_β–H cleavage, E1cB-like
Bn	$CHCl_3$	Alicyclics	0.54	1	Ditto
Ph	CH_3CN	Pyrs	0.29	This work	E2, reasonable N_β–H cleavage
Ar[a]	CH_3CN	Pyrs	0.38	3	E2, moderate N_β–H cleavage
Ph	CH_3CN	Alicyclics	0.19	3	E2, little N_β–H cleavage
Bn	CH_3CN	Pyrs	*ca.* 0.7 and *ca.* 0	3	$(E1cB)_{irrev}$ and with stronger bases $(E1cB)_{rev}$
Bn	CH_3CN	Alicyclics	*ca.* 0.7 and *ca.* 0	3	Ditto
$PhNHSO_2Cl$[b]	CH_3CN	Anilines	0.59	6	E2–E1cB like

[a] Ar = 2-MeO, 5-MeC_6H_3-. [b] The Brønsted plot was previously made using pK_as measured in DMSO giving β_{nuc} of 0.62. The plot reported here was made with pK_as measured in CH_3CN—see K. Izutsu, *Acid Base Dissociation Constants in Dipolar Aprotic Solvents*, IUPAC chem. data series no. 35, Blackwell Scientific Publications, Oxford, 1990.

Table 5 Activation data[a] for reactions of 4-nitrophenyl *N*-X-phenylsulfamates with pyridine and 4-(dimethylamino)pyridine

Substrate R = in **1**	Pyr in $CHCl_3$[b]		4-Me_2NPyr in $CHCl_3$[c]		4-Me_2NPyr in CH_3CN[d]	
	$\Delta H^‡$/kJ mol^{-1}	$\Delta S^‡$/J mol^{-1} K^{-1}	$\Delta H^‡$/kJ mol^{-1}	$\Delta S^‡$/J mol^{-1} K^{-1}	$\Delta H^‡$/kJ mol^{-1}	$\Delta S^‡$/J mol^{-1} K^{-1}
4-$MeOC_6H_4$-	75	−59	63	−83	48	−137
4-MeC_6H_4-	73	−69	66	−77	50	−134
3-MeC_6H_4-	76	−62	61	−92	48	−144
Ph	81	−46	62	−88	51	−136
4-BrC_6H_4-			68	−73		
3-ClC_6H_4-	78	−58	70	−70	53	−139

[a] Four temperatures were used in all Arrhenius plots ($r \geq 0.95$). The $\Delta H^‡$ and $\Delta S^‡$ values are accurate to within ±2.0 and ±5.0 respectively. [b] *T*/K 294–320. [c] *T*/K 292–316. [d] *T*/K 296–320.

esters have been reported previously.[1] The conduct of the kinetic runs has also been described and product studies carried out in these reactions have been given previously. The k_{obs} s^{-1} and k_2 dm^3 mol^{-1} s^{-1} rate constants used to calculate the data in Tables 1–3 and 5 are available.[15]

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