

A kinetic model for water reactivity (avoiding activities) for hydrolyses in aqueous mixtures – selectivities for solvolyses of 4-substituted benzyl derivatives in alcohol–water mixtures

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For solvolyses of various benzyl substrates in ethanol–water (EW) and methanol–water (MW) mixtures, product selectivities (*S*) are reported for chlorides at 75 °C defined as follows using molar concentrations: $S = ([\text{ether product}]/[\text{alcohol product}]) \times ([\text{water}]/[\text{alcohol solvent}])$. The results support earlier evidence that solvolyses of 4-nitrobenzyl substrates are S_N2 processes, which are not susceptible to mechanistic changes over the whole range of solvents from water to alcohol. *S* values at 25 and/or 45 °C in EW and MW, and additional kinetic data including kinetic solvent isotope effects (KSIE) are reported for solvolyses of 4-nitrobenzyl mesylate and tosylate. A kinetic model, explaining both rates and product, is proposed; a general medium effect due to solvent polarity is combined in one parameter with solvent effects on the nucleophilicity of the water and alcohol molecules acting as nucleophiles in S_N2 reactions. According to this model, as alcohol is added to water the rate of reaction decreases due to a decrease in solvent polarity, but the nucleophilicity of water increases relative to alcohol. The availability of experimental rate and product data over the whole range of solvent compositions from alcohol to water, reveals limitations of alternative approaches using activities. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: kinetics; solvolysis; solvent effects; alcohols; water activity; solvent nucleophilicity; rate-product correlation

INTRODUCTION

The factors influencing the reactivity of water in aqueous solution are vital for an understanding of many chemical and biochemical processes. Environmentally significant reactions occur in dilute aqueous solution, and biochemically important processes occur in the cytoplasm (a relatively concentrated aqueous solution containing protein and other solutes). The thermodynamic activity of water is often quoted as a key factor influencing the reactivity of water in biology and in food chemistry,^[1] and is also included in a thermodynamic analysis of kinetic data for hydrolyses.^[2]

Using transition state theory, rate constants can be related to the activities of initial states (e.g. for hydrolyses of any substrate, the activities of the reagent water and the substrate) and the transition state.^[3] Electrolytes in water often give activity coefficients (γ = activity/concentration) less than unity, and these may be considered as reductions in effective concentrations. Solute activity coefficients much greater than unity are observed for water as solvent (e.g. for alkanes in water, γ exceeds $10^{[8]}$ for decane!);^[4] large γ values can be calculated from solvent effects,^[4] and may be interpreted as an indication of destabilised states,^[3] but there is a conflict with the convenient picture that activity refers to effective concentration.

Alternative approaches include structural studies,^[5] and spectroscopic investigations,^[6] which have the potential to provide an understanding of the reactivity of aqueous solutions. Addition of solutes may 'make' or 'break' water structure,^[7] and/or lead to a change in the number of free lone pairs or free OH groups.^[8] Some of these ideas have been applied to solvolyses,^[8] including hydrolyses in competition with alcoholyses.^[9]

Our approach is based on the well-established, *qualitatively* predictive concepts of Ingold;^[10] when a neutral nucleophile such as water attacks a neutral substrate in an S_N2 reaction, charge develops in the transition state and the rate of reaction increases if the ionising power (polarity) of the solvent (Y , or Y_X where X is the leaving group) increases. The rates of typical solvolytic reactions, can be explained *quantitatively* by predictable changes in substrate sensitivities to Y and solvent nucleophilicity (N). S_N1 reactions, usually have a high sensitivity to Y (or Y_X) and are insensitive to N . As nucleophilic solvent assistance increases (i.e. substrate sensitivities to N increases), the sensitivity to Y (or Y_X) decreases because the positive charge is more delocalised (e.g. by changing from a hindered secondary alkyl gradually to methyl,^[11] or by gradually increasing electron withdrawal in substituted benzyl substrates^[12,13]). Similarly, we have related rates of hydrolysis of sulphonate esters in aqueous sulphuric acid quantitatively to Y_{OTs} and N_{OTs} , in an alternative to the approach based on activities and acidity functions.^[14]

In typical studies of rates of hydrolyses, reactions in aqueous solutions containing added electrolytes and/or aprotic solvents

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lead to a single product. If an alcohol is present in an aqueous solution, two products are usually formed and rate-product correlations can be investigated (e.g. for solvolyses of acid chlorides^[15–18]). We now extend our work to classical S_N2 reactions, and provide new equations linking observed pseudo-first order rate constants and product compositions.

Initially we investigated solvolyses of 4-substituted benzyl chlorides to check for the possibility of mechanistic changes arising from a change in solvent from alcohol to water. Solvolyses of 4-nitrobenzyl substrates were then selected for further study, with a change in leaving group to tosylate (increasing reactivity) and mesylate (increasing reactivity whilst maintaining solubility in highly aqueous systems). Another important feature of this work is that the whole range of alcohol–water mixtures is examined.

RESULTS

If a neutral substrate (e.g. ArCH_2X) reacts with a mixture of alcohol and water solvent (e.g. $\text{ROH}/\text{H}_2\text{O}$ – refer to Eqn (1)), two organic products are formed (ArCH_2OR and ArCH_2OH). Unlike results from many studies involving binary mixtures of water and an aprotic solvent (e.g. acetonitrile), additional information is then available from the selectivity (S , Eqn (2)), in which square brackets refer to molar concentrations (mol dm^{-3}).^[9] Numerical values of S (Eqn (2)) would be unaffected by expressing the ratio of solvent concentrations as mole fractions, but would be altered if solvent activities were incorporated.



$$S = ([\text{ArCH}_2\text{OR}]/[\text{ArCH}_2\text{OH}]) \times ([\text{H}_2\text{O}]/[\text{ROH}]) \quad (2)$$

Selectivities (S) for solvolyses of benzyl chloride and four 4-substituted derivatives (**1**) are given in Table 1. The main aim of the experiments was to determine accurately the yields of product of kinetically controlled reactions in homogeneous solutions. Product compositions are usually examined after reacting the substrate at the specified temperature for about 10 half-lives, but shorter reaction times (1–4 half-lives) were used to obtain S values (Eqn (2)) for solvolyses of derivatives of **1** in ethanol–water (EW) and methanol–water (MW) at 75 °C (Table 1). Addition of 2,6-lutidine to remove the HCl by-product did not significantly affect product compositions, but products were not always formed by kinetic control; oxidation of alcohol products to acids occurred, perhaps because chloride ion may be oxidised to chlorine (Deacon process^[19]), followed by the oxidation of alcohols. Oxidation was minimised by reducing reaction times to less than one half-life and/or by heating the solvents in a stream of nitrogen immediately prior to product studies. Reactions of 4-methoxybenzyl chloride at 75 °C are rapid in comparison with mixing times (ca. 1 s), but almost identical values were obtained at lower temperatures.^[20] New data (Table 1) confirm trends observed previously for solvolyses of benzyl chlorides (**1**, $Z = \text{Cl}$, H, Me and OMe) in 50–95% EW.^[21]

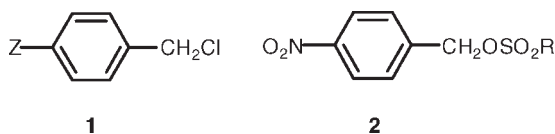


Table 1. Product selectivities (S , Eqn (2)) for solvolyses of 4- Z substituted benzyl chlorides (**1**, $X = \text{Cl}$) in alcohol–water mixtures at 75 °C^a

Alcohol (% v/v)	Substituent Z				
	NO_2	Cl	H	Me	OMe
Ethanol					
90	1.3	1.8 ^b	2.2	1.7	1.7
80	1.7	2.4 ^b	2.6	1.9	1.9
60	2.4	2.9 ^b	2.9	1.9	2.6
40	3.2	3.5 ^b	3.3	1.8	3.4
20 ^c	3.6	4.0 ^b	3.1	1.6	4.1 ^d
10 ^c	3.9 ± 0.2		2.9	1.5	4.4 ^d
5 ^c	4.0 ± 0.4		2.6	1.6	4.5 ^d
Methanol					
90	2.3	2.5	3.2	2.5	3.2
80	2.6	2.9	3.5	2.5	3.5
60	3.5	3.4	3.6	2.4	4.2
40	4.1	3.6	4.0	2.3	5.3
20 ^c	4.4	3.5	4.1	2.2	6.2
10 ^c	4.7	3.0	3.7	2.1	6.3
5 ^c	4.8	3.1	3.7	2.2	6.4

^a Determined by HPLC from the ratio of product areas; typical error in S (± 0.1), although the [ether]/[alcohol] response was assumed to be 1.0 ($\pm 5\%$, based on experimental data); typically 25 μl of a 10% or 20% solution of the chloride in acetonitrile was injected into solvolysis solvent (5 ml), so the solvent also contained 0.5% acetonitrile.

^b The ethyl ether product was not separated sufficiently by HPLC from the chloride starting material, so reactions were carried out for 10 half-lives; our data agree within 0.08–0.11 with published values for 90%, 80% and 60% ethanol–water (Reference [21]).

^c Multiple injections ($5 \times 20 \mu\text{l}$) of a 2% solution of the chloride in acetonitrile were made, so the solvent also contained 2% acetonitrile.

^d Similar values were observed at 50 °C (20%, $S = 4.5$; 10%, 4.5; 5%, 4.6), and for 20% ethanol at 25 °C ($S = 4.4$, Reference [20]).

Experimental difficulties were reduced by studying 4-nitrobenzyl tosylate (**2**, $R = 4\text{-tolyl}$, Table 2). For highly aqueous mixtures, some data were obtained for the more soluble mesylate (**2**, $R = \text{Me}$) to confirm that products were formed from reactions in homogeneous solutions. Much of the required kinetic data has already been published,^[22] and new kinetic data including kinetic solvent isotope effects (KSIE) are in Table 3.

DISCUSSION

Choice of substrate

The nature of intermediates or transition states from solvolyses of benzyl substrates depends on the initial substrate and on the solvent.^[12,13,21–27] For solvolyses of **1**, $Z = \text{OMe}$, the increase in S , as water is added to alcohol can be explained by S_N1 reactions with product formation from a carbocation intermediate.^[28–30] Although S values for **1**, $Z = \text{NO}_2$ are similar to those for **1**, $Z = \text{OMe}$, the mechanism for the former is S_N2 .^[22,31] S values help

Table 2. Product selectivities (*S*, Eqn (2)) for solvolyses of 4-nitrobenzyl tosylate (**2**, R = 4-tolyl) in alcohol–water^a

Alcohol (% v/v)	Ethanol	Methanol	
	45 °C	25 °C	45 °C
97	0.97 (0.89 ^b)	1.74	1.51
95	0.85 (0.95 ^b)	1.93	1.65
93	1.23	2.12	1.88
90	1.12	2.3	2.1
85		2.6	2.3
80	1.40	2.8	2.5
70		3.1	2.8
60	2.1	3.1	3.1
50		3.7	3.3
40	2.7 (2.7 ^b)	3.8	3.5 (3.6 ^c)
30	2.8 (2.7 ^b)	3.8	3.6 (3.6 ^c)
20	2.9 (2.7 ^b)	3.8	3.7 (3.7 ^c)
10	2.8 (2.7 ^b)	3.8	3.7 (3.7 ^c)
5	3.1 (2.8 ^b)	3.7	3.7 (3.7 ^c)

^a Determined by HPLC from the ratio of product areas, and a molar response factor [ether]/[alcohol] of 1.00; typical errors $\pm 5\%$.

^b Selectivity values for 4-nitrobenzyl mesylate (**2**, R = Me) at 45 °C in ethanol–water.

^c Selectivity values for 4-nitrobenzyl mesylate (**2**, R = Me) at 45 °C in methanol–water.

to identify mechanistic changes due to changes in product-determining steps.^[21] Differences from solvolyses of **1**, Z = NO₂ and OMe are apparent for solvolyses of **1**, Z = Me, which shows almost no change in *S* as the solvent composition is varied and is difficult to classify mechanistically.^[26] Variations in *S* are also relatively small for solvolyses of **1**, Z = H. For **1**, Z = Cl, there is

Table 3. Additional kinetic data for solvolyses of 4-nitrobenzyl tosylate (**2**, R = 4-tolyl) and mesylate (**2**, R = Me) in methanol–water at 45 °C^a

Solvent (% v/v)	Rate constant ($k/10^{-4}\text{s}^{-1}$)		
% Methanol	Tosylate	Mesylate	$k_{\text{OTs}}/k_{\text{OMs}}$
100	0.409 $\pm$ 0.006 ^b	0.204 $\pm$ 0.011 ^c	1.99
40	5.18	2.51 $\pm$ 0.01	2.06
30	7.38 $\pm$ 0.14	3.12 $\pm$ 0.02	2.37
20	9.68 $\pm$ 0.24	4.30 $\pm$ 0.02	2.25
10	11.8 $\pm$ 0.6	5.53 $\pm$ 0.09	2.13
5	12.7 $\pm$ 0.2	6.07 $\pm$ 0.02	2.09
Water	13.8 ^d	6.59 $\pm$ 0.04 ^e	

^a Determined conductimetrically in duplicate; errors shown are average deviations.

^b In MeOD, $10^4k = 0.321 \pm 0.007$ so the KSIE is 1.27 ± 0.05 .

^c In MeOD, $10^4k = 0.169 \pm 0.003$ so the KSIE is 1.21 ± 0.08 .

^d Estimated assuming a OTs/OMs ratio of 2.1 (Reference [34]).

^e In D₂O, $10^4k = 5.61 \pm 0.02$, so the KSIE is 1.17 ± 0.02 .

usually an increase in *S* as water is added to alcohol, but the small decrease in *S* in highly aqueous methanol may be due to a change in mechanism. For **1**, Z = NO₂ there is a monotonic increase in *S* as water is added to alcohol, and hence no indication of a mechanistic change as the solvent composition is varied.

S values for 4-nitrobenzyl sulphonates (**2**) in MW depend only slightly on temperature (at 25 and 45 °C, Table 2), and are similar those for 4-nitrobenzyl chlorides (**1**, Z = NO₂) at 75 °C (Table 1). *S* values for mesylates support the reliability of data for tosylates in highly aqueous media, when product ratios could be influenced by formation of non-homogeneous solutions. In previous work, we have found solvolyses of sparingly soluble substrates where rate constants and/or product selectivities may be anomalous, but the solutions appear to be homogeneous.^[32] One explanation is that aggregates of a few molecules may dissociate during the time-scale of the experiment. Data for 4-nitrobenzyl tosylate (**2**, R = 4-tolyl) were selected for further detailed interpretation (see below).

Rate-product correlations^[33]

For second order reactions such as S_N2 processes, the increase in *S* from alcohol to water has been explained by an increase in the nucleophilicity of alcohol relative to water.^[21] New equations are given below to investigate the solvent dependence of the nucleophilicity of both alcohol and water in alcohol–water mixtures.

Equation (2) may be derived on the assumption that *S* is the ratio of two second order rate constants:^[9] $S = k_a/k_w$, where k_a refers to the second order rate constant for formation of ArCH₂OR and k_w refers to the second order rate constant for formation of ArCH₂OH. For any alcohol–water mixture, we assume that the pseudo-first order rate constants can be calculated using Eqn (3) (so there are independent competing second order hydrolysis and alcoholysis reactions). Values of k_a in alcohol, and k_w in water are then derived from Eqns (4) and (5), respectively, using experimentally observed rate constants (k_{obs}).

$$k_{\text{calc}} = k_w[\text{water}] + k_a[\text{alcohol}] \quad (3)$$

$$\text{In pure alcohol: } k_a = \frac{k_{\text{obs}}}{[\text{alcohol}]} \quad (4)$$

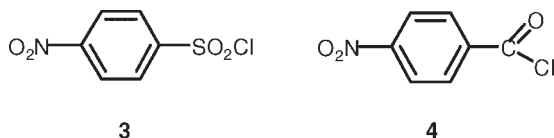
$$\text{In pure water: } k_w = \frac{k_{\text{obs}}}{[\text{water}]} \quad (5)$$

Solvolyses in highly aqueous media reach a plateau (S_{max}) between 30% and 5% alcohol water, and it is assumed that the value of k_a in water containing only a trace of alcohol can be obtained from Eqn (6); in other words, as *S* remains relatively constant from 30% to 5% alcohol, we assume that there will be no sudden changes in this trend between 5% alcohol and water. Similarly a value for k_w in alcohol can be obtained from Eqn (7), where S_{min} is an estimate of the value of *S* in alcohol containing only a trace of water; in this case a short extrapolation from data in 95% and 97% alcohol is required. Equations (4–7) each provide one piece of experimental data (a total of two for water and two for each alcohol), from which the rate constants and product compositions in binary alcohol–water mixtures will be calculated as described below.

$$\text{In water: } k_a = k_w(S_{\text{max}}) \quad (6)$$

$$\text{In alcohol: } k_w = \frac{k_a}{S_{\text{min}}} \quad (7)$$

The calculations based on Eqns (4–7) show that values of k_a and k_w are solvent-dependent (e.g. values of k_a in water are over 60-times greater than the value in ethanol (Table 4)). The following procedure for interpolating values of k_a and k_w in pure solvents to values in mixed solvents was devised. Logarithms of observed first order rate constants for solvolyses of 4-nitrobenzyl tosylate (**2**, R=4-tolyl) correlate well with Y_{OTs} , a measure of solvent ionising power based on solvolyses of 1- and 2-adamantyl tosylates^[34] (Eqn (8), Fig. 1).



Assuming from the results for first order rate constants (Fig. 1) that the second order rate constants for solvolyses of (**2**, R=4-tolyl) also correlate with Y_{OTs} , values of k_a and k_w in any solvent can be calculated by interpolation by adapting Eqn (8). Calculated slopes (m_a and m_w) are shown in Table 4.

$$\log k = mY_{OTs} + c \quad (8)$$

$$(\text{mol \% ether})_{\text{calc}} = \left\{ \frac{k_a[\text{alcohol}]}{k_{\text{calc}}} \right\} \times 100 \quad (9)$$

Values of k_a and k_w calculated from Eqn (8) can be substituted into Eqn (3) to obtain calculated values (k_{calc}) of first order rate constants, and the mol% ether can be calculated from Eqn (9). Small but systematic deviations are seen; calculated rate constants are all slightly too high and the calculated mol% ether are all slightly too low (Table 5). Calculated rate constants for MW mixtures (Table 5) are in good agreement with experimental data, whereas calculated rate constants for EW mixtures are up to 1.5 fold too high. Considering the simplicity of the theory, and the absence of adjustable parameters (only two fixed values of k and of S are required), the results are satisfactory.

According to the above theory, one slope parameter (m) indicates the responses of competing S_N2 solvolyses to changes

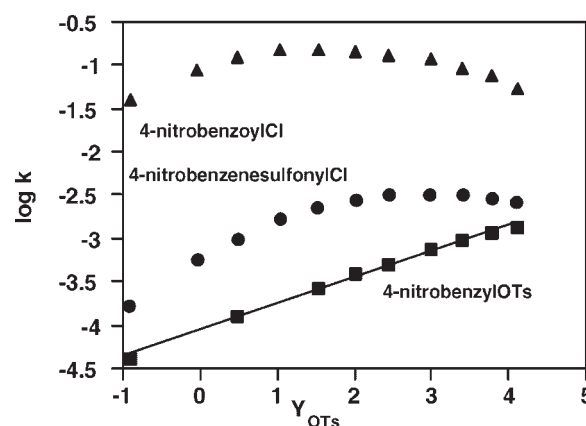


Figure 1. Correlation of logarithms of first order rate constants for solvolyses in methanol–water of 4-nitrobenzyl tosylate (**2**, R=4-tolyl) at 45 °C (slope: 0.304 ± 0.008 , intercept: -4.05 ± 0.02 , $r = 0.998$, $n = 9$), contrasting with those for 4-nitrobenzenesulfonyl chloride (**3**) at 25 °C and 4-nitrobenzoyl chloride (**4**) at 25 °C with Y_{OTs} ; kinetic data from Table 3 and References [16,17,22]; Y_{OTs} values from Reference [34] (for this range of solvents Y_{OTs} and Y_{Cl} behave similarly – refer to Reference [36]).

in Y and N . One parameter may be adequate for these two binary mixtures, because changes in N correlate with changes in Y ^[35]. The variation in m from 0.210 to 0.345 (Table 4) may be explained as follows. When water is added to alcohol: (i) the increase in solvent polarity causes an increase in rates (a well-established effect^[10,11]), (ii) although selectivities (S , Eqn (2)) increase, the nucleophilicities of the incoming nucleophiles (water and alcohol) decrease, (iii) the nucleophilicity of water decreases

Table 4. Calculations of second order rate constants ($M^{-1}s^{-1}$), and slope parameter (m) for rate-product correlations for solvolyses of 4-nitrobenzyl tosylate (**2**, R=4-tolyl) in alcohol–water at 45 °C

Alcohol parameter	Ethanol	Methanol	Equation
k_a (in alcohol) ^a	1.06×10^{-6}	1.70×10^{-6}	4
k_w (in water) ^b	2.49×10^{-5}	2.49×10^{-5}	5
k_w (in alcohol)	1.32×10^{-6}	1.21×10^{-6}	6
k_a (in water)	6.97×10^{-5}	9.20×10^{-5}	7
m_w (slope for k_w) ^c	0.210	0.262	8
m_a (slope for k_a) ^c	0.300	0.345	8

^a Observed first order rate constant from Reference [22].

^b Observed first order rate constant from Table 3.

^c Y_{OTs} data from Reference [34]; refer to Table 5.

Table 5. Calculated and observed rate constants (k) and mol% ether for solvolyses of 4-nitrobenzyl tosylate (**2**, R=4-tolyl) in alcohol–water at 45 °C

% Alcohol (v/v)	Y_{OTs}^a	$k/(10^{-4}s^{-1})$		Mol% ether	
		Calc ^b	Obsd ^c	Calc ^d	Obsd ^e
Methanol–water					
80	0.47	1.32	1.26	77	82
60	1.52	2.92	2.72	60	67
50	2.00	4.10	3.91	52	60
40	2.43	5.43	5.18	44	51
30	2.97	7.72	7.38	36	41
20	3.39	9.82	9.68	26	29
Ethanol–water					
90	−0.77	0.50	0.48	74	76
80	0.00	0.94	0.73	60	63
60	0.92	1.98	1.32	40	50
40	1.97	4.04	2.90	27	36
30	2.84	6.72	4.81	22	27

^a From Reference [34].

^b Equation (3).

^c Kinetic data from Table 3 and Reference [22].

^d Equation (9).

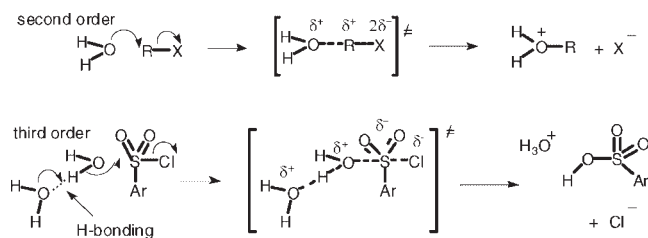
^e From the observed ether/alcohol product ratios.

more sharply than that of alcohol, possibly because additional hydrogen bonds reduce the availability of free lone pairs to act as nucleophiles.^[6] In addition, the positive charge in the attacking solvent nucleophile may be more dispersed by greater hydrogen bonding when water attacks than when alcohol attacks, so values of m_w may be lower than for m_a due to different responses to Y_{OTs} (Table 4).

Figure 1 also shows a clear difference between the linear plot for the S_N2 (second order) solvolyses of **2**, $R = 4$ -tolyl with a low KSIE of 1.2 (Table 3, footnotes b, c and e), and shallow curved plots for solvolyses of **3** and **4**, for which the KSIE is relatively large (>2.0) and rate-product correlations can be achieved assuming that competing solvolyses are third order.^[16,17] It is preferable to choose a Y value corresponding to the leaving group to account for electrophilic solvation effects.^[34] However, differences in shapes between the three plots in Fig. 1 are not due to the selection of Y_{OTs} rather than Y_{Cl} , because these two scales correlate linearly in EW mixtures (solvents of similar electrophilicities).^[36]

The assignment of molecularity to pseudo-first order solvolytic reactions has been controversial for decades, and was initially concerned with the distinction between uni- and bimolecular reactions.^[37–39] As a large dynamic pool of solvent molecules contributes to the observed solvent effect, molecularity is difficult to assign. Nevertheless, third order solvolyses of acid chlorides are well established from the rate equations for alcoholyses in a large excess of relatively inert solvents such as ether and acetonitrile.^[40]

Consequently, we propose a simple picture for second and third order hydrolyses (Scheme 1). Key differences are: (i) the timing of the deprotonation of the solvent nucleophile, and the high KSIE for third order reactions is explained by partial cleavage of an O–H bond in the attacking nucleophile, (ii) the greater extent of charge delocalisation of both positive and negative charges of the transition states in the third order reactions – in several cases,^[15–18] rate-product correlations can be achieved by ignoring the solvent dependence (m , Eqn (8)) of the third order rate constants, (iii) for second order reactions, the charge is more localised and an intermediate (ROH_2^+) may be formed, which is rapidly deprotonated.^[41]



Scheme 1. A simplified picture of some differences between second and third order hydrolyses for RX (second order) and $ArSO_2Cl$ (third order)

Role of activities

The influence of solvent activity on the kinetics of a neutral ester hydrolysis was considered in detail recently.^[2] Using a water activity meter, it was shown that added acetonitrile or THF increases water activity, whereas PEG 400 decreases it. The authors' commented: 'water activity hardly contributes to the observed decrease in rate constant'.^[2] Although activity coefficients were not quoted, these can be calculated from the

Table 6. Activity coefficients (γ) for alcohol–water mixtures

Solvent	γ (water)	γ (alcohol)	$T/^\circ C$
Water (MeOH) ^a	1.000 ^b	1.77	35 ^c
Water (MeOH) ^a	1.000 ^b	1.63	25 ^c
23.4% v/v MeOH	1.007	1.60	35 ^c
23.4% v/v MeOH	1.003	1.53	25 ^c
Water (EtOH) ^a	1.000 ^b	3.9	25 ^d
50.5% v/v EtOH	1.10	2.0	25

^a Effect of alcohol solute in very dilute solution.

^b By definition.

^c Reference [48].

^d Reference [49].

graphical data,^[2] giving values between 0.95 and 1.1. Literature data for water in alcohol–water mixtures also show relatively small activity coefficients (γ , Table 6). Consequently, replacement of water concentration by water activity (e.g. as in Eqn (3)) would have only a small effect, *and the main effects of added organic cosolvents are due to changes in water concentration, solvent polarity^[10] and solvent nucleophilicity.^[11–13,42–44]*

Activity coefficients for alcohols in water show much larger variations (Table 6), and as alcohol is added to water S decreases and γ_{alcohol} decreases ($\gamma = 1.00$ in pure alcohol). However, the order of S values ($S_{\text{MeOH}} > S_{\text{EtOH}} > S_{\text{water}}$) is not the order of γ (or N values^[42–44]).

For S_N1 solvolyses of 1-adamantyl substrates (1AdX) in 50–95% v/v EW at 100 °C, S ($= k_w/k_a$, the inverse of our definition) correlates linearly with the ratio of activity coefficients ($\gamma_{\text{water}}/\gamma_{\text{ethanol}}$) with slopes varying from 0.1 for $X = \text{Br}$ and 0.6 for $X = \text{OTs}$.^[45] Over the full range of compositions, the $\gamma_{\text{water}}/\gamma_{\text{ethanol}}$ ratio varies by over 10-fold at 50 °C,^[46] whereas S values for **2** vary only 3-fold (Table 2); a plot (not shown) of S values (Table 2) versus $\gamma_{\text{ethanol}}/\gamma_{\text{water}}$ is sharply curved, although the region between 50% and 95% EW is approximately linear with a slope of about 0.8. Values of $\gamma_{\text{methanol}}/\gamma_{\text{water}}$ vary only 3.2-fold at 50 °C,^[47] and show a shallow curve when plotted against the 2.5-fold range of S values for **2** at 45 °C. In earlier work,^[21,45] product ratios were obtained by GC for a restricted range of solvent compositions. A wider and more informative solvent range can nowadays be investigated using reverse phase HPLC, and the more extensive data show that ratios of activity coefficients do not adequately explain trends in S values.

CONCLUSIONS

Product selectivities (Table 1) support independent evidence that solvolyses of benzyl chlorides are susceptible to mechanistic changes over the range of reaction conditions from alcohol to water. Solvolyses of 4-nitrobenzyl substrates in alcohol–water mixtures are an exception, and react by classical S_N2 reactions throughout the solvent range.

Rate constants and products of solvolyses of 4-nitrobenzyl tosylate in a full range of alcohol–water mixtures can be explained quantitatively by competing second order reactions based on Eqn (3). The new theory (Eqns (3–9)) leads to rate-product correlations, which explain why S values (defined

by a ratio of second order rate constants, $S = k_a/k_w$)^[9] may be solvent-dependent. Addition of alcohol to water decreases the rate of reaction due to a decrease in solvent ionising power (Ingold rules:^[10] the S_N2 transition state is more polar than the initial state of two neutral species). S decreases because the nucleophilicity of water increases relative to alcohol (possible due to a decrease in hydrogen bonding). Hence, the decrease in S as alcohol is added to water is explained using kinetic rather than thermodynamic concepts (such as activities, which do not account for selectivities when the full range of alcohol–water mixtures is examined).

For second order solvolyses (e.g. of **2**), initial attack by the solvent nucleophile (Scheme 1) is followed by a rapid deprotonation step, and the kinetic isotope effect (KSIE) is low (1.2).^[41] For third order solvolyses (e.g. of **3** and **4**), a second molecule of solvent could act as a general base at the same time as the nucleophilic attack, so the KSIE is larger (2.0).^[15–18] Logarithms of first order rate constants for solvolyses of **2** in MW correlate linearly with Y_{OTs} , but the plots (Fig. 1) for **3** and **4** are shallow curves.

EXPERIMENTAL

Materials

Benzyl chlorides were obtained from Aldrich; and purity was checked by HPLC analysis of methanolysis products; **1**, $X = Cl$, $Z = H$ and Cl were distilled under reduced pressure prior to use. 4-Nitrobenzyl sulphonates were prepared from 4-nitrobenzyl alcohol (Aldrich) by standard methods.^[31] Solvents for solvolyses and chromatography were as described previously.^[15–18]

Solvolyses

Data for chlorides were obtained from solvolyses at 75 °C in 5 ml sealed ampoules. Rate and product data for sulphonates were obtained by injecting a 1% stock solution (10 μ l) into 5 ml of rapidly stirred, thermostated solvent.

Chromatography

Products of solvolyses of chlorides were analysed using a 5 μ m Spherisorb ODS2 chromatography column (15 cm $\times$ 1/4"); typical conditions were: eluent (70% MW), flow rate (1 ml min⁻¹), UV detection ($\lambda = 266$ nm, $A = 0.5$). A more polar eluent (55–60% methanol) was required to separate the products for the tosylate.

Acknowledgements

We are grateful to L. M. Howle (now Pollaud) for preliminary investigations of the benzyl chlorides, N. Asaad, J. R. Conder and D. N. Kevill for helpful discussions, and EPSRC for equipment grants.

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