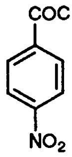
Stoichiometric Solvation Effects. Part 1. New Equations Relating Product Selectivities to Alcohol–Water Solvent Compositions for Hydrolyses of *p*-Nitrobenzoyl Chloride

T. William Bentley* and Robert O. Jones
Department of Chemistry, University College of Swansea, Singleton Park, Swansea, UK SA2 8PP

Rate constants at 25 °C are reported for solvolyses of *p*-nitrobenzoyl chloride (**1**) in water, D_2O, and in acetonitrile–water, ethanol–water and methanol–water mixtures, and activation parameters are reported for solvolyses in water and in 5% ethanol– and methanol–water. Product selectivities are reported at 25 °C for a wide range of ethanol–water and methanol–water solvent compositions. A general theory is developed for third order solvolytic reactions in alcohol–water mixtures, for which there are four competing reactions with the following rate constants: k_{aa} where alcohol is nucleophile and general base; k_{aw} where alcohol is nucleophile and water is general base; k_{wa} where water is nucleophile and alcohol is general base; and k_{ww} where water is nucleophile and general base. Values of k_{aa} and k_{ww} can be obtained from the observed first order solvolysis rate constants in the pure solvents. Two independent equations including product composition and solvent stoichiometry are devised to evaluate the two 'hidden' rate constants, k_{wa} and k_{aw}, and first order rate constants for solvolyses of **1** in methanol– and ethanol–water mixtures are then calculated from the four third order rate constants and the solvent stoichiometry. The results indicate that medium effects, other than those determined by solvent stoichiometry, make only a minor contribution to the solvent dependence of the first order solvolysis rate constants. Stoichiometric solvation effects also account for solvolyses in acetone– and acetonitrile–water mixtures, if it is assumed that water is nucleophile and either water or the cosolvent acts as general base.

Many acyl transfer reactions in protic solvents involving esters,[1] amide derivatives[2] and acid chlorides[3] are third order overall, and it is thought that one molecule of solvent acts as nucleophile and a second molecule acts as a general base.[4] For reactions of carboxylic acid chlorides, kinetic order in protic solvent has been evaluated directly from rate constants in acetonitrile containing small amounts of methanol (up to ~ 1 mol dm^{-3}, *i.e.* < 5% v/v), and observed first order rate constants for methanolyses of carboxylic acid bromides and chlorides have been analysed in terms of simultaneous second and third order processes.[3] In the third order process, methanol probably acts as both nucleophile and general base, because large rate enhancements are observed when chloride ion (a base in acetonitrile) is added but only minor rate enhancements are observed when phenol (an electrophilic catalyst) is added.[3] The other process (first order in substrate, first order in methanol) may be pseudo second order, and may involve methanol as nucleophile with acetonitrile, present in large excess, acting as general base.[3b] Similar results have been obtained for aminolyses involving primary and secondary amines.[5]

Ethanolyses of *p*-nitrobenzoyl chloride (**1**) are second order in ethanol up to 5 mol dm^{-3} (*i.e.* extending to the solvolytic range) in solvents such as ether, dioxane, acetone, nitromethane, as well as acetonitrile, all of which are capable of forming hydrogen bonds to the ethanol. Although, ethanolyses in non-hydrogen bonding solvents such as cyclohexane are first order in ethanol, associated alcohol may be the attacking species in all these solvents.[6]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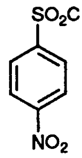
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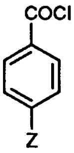
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For corresponding solvolyses in alcohol–water mixtures, interpretations based on a third order mechanism are more complex, but significant new information is available because two products are formed; instead of one nucleophile (methanol) there are two, so there are four possible third order rate constants: (i) k_{aa} for a mechanism in which one molecule of alcohol is nucleophile and a second molecule is a general base; (ii) k_{aw} in which alcohol acts as nucleophile and water is general base; (iii) k_{wa} in which water is nucleophile and alcohol is general base; (iv) k_{ww} in which water is both nucleophile and general base.

The k_{aa} terms can be evaluated from the experimentally observed first order rate constants in pure alcohols ($k_{aa} = k_{obs}/[ROH]^2$); similarly k_{ww} can be obtained from the observed first order rate constant in water ($k_{ww} = k_{obs}/[H_2O]^2$).[7] However in solvolyses, such large amounts of solvent are present that: (i) kinetic order in solvent cannot be determined directly (an analogous problem arises with acetonitrile in the examples[3] discussed above); (ii) medium effects due to variations in third order rate constants with changes in solvent compositions need to be considered. Also, the kinetic forms of the k_{aw} and k_{wa} terms are the same, first order in alcohol and first order in water. Hence, from kinetic data alone, it is difficult to determine a reliable three-term rate law [*e.g.* see eqn. (4), below] and it is impossible to determine the four-term rate law.

An interpretation of third order solvolytic reactions in alcohol–water mixtures in terms of third order rate constants and their associated medium effects was first attempted for solvolyses of *p*-nitrobenzoyl chloride (**1**) in ethanol– and methanol–water mixtures.[7] A model including adjustable parameters for medium effects was devised to fit the kinetic data,[7] and this was shown to predict satisfactorily the product data assuming that the contribution from k_{wa} was negligible. We now report a more general and less arbitrary procedure.

Beginning with the product data, two independent values of each of the two 'hidden' rate constants k_{wa} and k_{aw} are obtained from two new equations involving the product ratios and the solvent stoichiometry (as before[7] k_{aa} and k_{ww} are calculated directly from observed first order rate constants in pure solvents). The new equations are evaluated for solvolyses of **1** in ethanol- and methanol-water mixtures.

Theory.—Product selectives (*S*) for solvolyses of acid chlorides in alcohol-water mixtures (giving an acid and an ester), can be related to the molar solvent ratio using eqn. (1).

$$S = [\text{ester}]_{\text{prod}}[\text{water}]_{\text{solv}}/[\text{acid}]_{\text{prod}}[\text{alcohol}]_{\text{solv}} \quad (1)$$

If these reactions simply involved competitive attack upon the substrate by either water or ethanol, and medium effects were absent, *S* values [eqn. (1)] would be independent of solvent composition (this ideal situation is approached in nucleophilic substitutions *via* solvent separated ion pairs).[8] For solvolyses of **1**, *S* increases at least four-fold from solvolyses in a high percentage of alcohol (ethanol or methanol) to 60% alcohol-water, and reactivity also increases.[7] When more water is present, the first order rate constants decrease, so there is an unusual maximum in plots of rate constants *vs.* solvent composition.[7] Although there is not a simple explanation of these results, the following theory avoids complex aspects of reactivity in aqueous solution such as solvent activity, initial-state solvation effects, solvent sorting and solvent structure.[9] An example where changes in activity coefficients do not account for the solvent dependence of ethanolyses of a primary perchlorate in a variety of ethanol-aprotic cosolvent mixtures has been reported recently.[10]

According to a third order kinetic model, the rate of production of ester is given by eqn. (2), the rate of production of acid is given by eqn. (3), and the observed first order rate constant is given by eqn. (4). A typical experiment would involve $[\text{ArCOCl}] < 10^{-3}$ mol dm^{-3} with essentially no changes during solvolysis in values of [alcohol] and [water]. The observed product ratio is given by the ratios of eqns. (2) and (3).

If k_{aw}[alcohol][water] is about ten-fold greater than $k_{aa}[\text{alcohol}]^2$ (*e.g.* in highly aqueous media), the k_{aa} term can be ignored; *S* is then given by eqn. (5), and its reciprocal simplifies to eqn. (6).[11] Alternatively, if k_{wa}[alcohol][water] is about ten-fold greater than $k_{ww}[\text{water}]^2$ (*e.g.* in highly alcoholic media), the k_{ww} term can be ignored; *S* is then given by eqn. (7), which simplifies to eqn. (8).

$$\mathrm{d}[\text{ester}]/\mathrm{d}t = \{k_{aa}[\text{alcohol}]^2 + k_{aw}[\text{alcohol}][\text{water}]\}[\text{ArCOCl}] \quad (2)$$

$$\mathrm{d}[\text{acid}]/\mathrm{d}t = \{k_{wa}[\text{alcohol}][\text{water}] + k_{ww}[\text{water}]^2\}[\text{ArCOCl}] \quad (3)$$

$$k_{obs} = k_{aa}[\text{alcohol}]^2 + (k_{aw} + k_{wa})[\text{alcohol}][\text{water}] + k_{ww}[\text{water}]^2 \quad (4)$$

$$S = \{(k_{aw}[\text{alcohol}][\text{water}])/(k_{wa}[\text{alcohol}][\text{water}] + k_{ww}[\text{water}]^2)\} \times [\text{water}]/[\text{alcohol}] \quad (5)$$

$$1/S = (k_{wa}/k_{aw})([\text{alcohol}]/[\text{water}]) + k_{ww}/k_{aw} \quad (6)$$

$$S = \{(k_{aa}[\text{alcohol}]^2 + k_{aw}[\text{alcohol}][\text{water}])/k_{wa}[\text{alcohol}][\text{water}]\} \times [\text{water}]/[\text{alcohol}] \quad (7)$$

$$S = (k_{aw}/k_{wa})([\text{water}]/[\text{alcohol}]) + k_{aa}/k_{wa} \quad (8)$$

These equations provide two independent measures of the ratio of k_{aw}/k_{wa}, knowing only the *S* values and the solvent compositions. From eqn. (6), a plot of 1/*S vs.* [alcohol]/[water] is predicted to be linear with a slope given by k_{wa}/k_{aw}; then knowing k_{ww} from the first order rate constant in pure water, absolute values of k_{aw} can be obtained from the intercept and then a value of k_{wa} can be obtained from the slope. From eqn. (8), a plot of *S vs.* [water]/[alcohol] is predicted to be linear with a slope given by k_{aw}/k_{wa}; knowing k_{aa} from the first order rate constant in pure alcohol, a second value of k_{wa} can be obtained from the intercept and then a second value of k_{aw} can be obtained from the slope. It should be emphasised that product selectivity data over different ranges of solvent compositions, and different rate constants in pure solvents (either k_{aa} or k_{ww}) are needed to obtain k_{wa} and k_{aw} from eqns. (6) or (8).

A choice needs to be made of a suitable model reaction, relatively unsusceptible to mechanistic change over wide variations in solvent compositions—a solvent change from water to ethanol reduces S_N1 reactivity by *ca.* 10^7, so there is a strong possibility of mechanistic change over such a wide solvent range.[12]

Results

Because of our earlier work,[7] the substrate chosen to test this new theory was *p*-nitrobenzoyl chloride (**1**), and to avoid complex solvation effects such as those observed in *tert*-butanol-water[13] or butoxyethanol-water mixtures,[1c] solvolyses in ethanol-water and methanol-water were investigated further. First order rate constants are given in Table 1, in which previous kinetic work[7] is extended. Reliable data for hydrolyses of sparingly-soluble substrates in highly aqueous media are difficult to obtain, and it was not possible to obtain satisfactory results for hydrolysis of **1** in water at 5 °C, as rate constants were not reproducible and all values were lower than expected from an Arrhenius plot of data at 15–35 °C (Table 2). The reliability of the other data is supported by the activation parameters (Table 2), which are very similar for water and 5% alcohol-water.

Product selectivities [eqn. (1)] are given in Table 3. Our previous study[7] of product selectivities was repeated, and then extended to obtain the extra data needed to test eqn. (8). Agreement between the two studies is good, with variations between the two independent *S* values typically < 5%. However, there is a significant discrepancy for the values of *S* in 30% and 20% ethanol-water where the present results are lower than those obtained previously.[7] Agreement is satisfactory for 40% ethanol-water (3.93 this work; 4.18, ref. 7) but we now observe a decrease in *S* in 30% ethanol-water (*S* = 3.73; *cf.* 4.89, ref. 7) and in 20% ethanol-water (*S* = 3.79; *cf.* 5.18, ref. 7). A similar but less marked decrease in *S* occurs in methanol-water mixtures, although this was not apparent from previous work[7] because only solvent compositions ⩾ 20% alcohol-water were investigated.

Discussion

A Possible Mechanistic Change for Solvolyses of p-*Nitrobenzoyl Chloride* (**1**).—The decrease in *S* in < 40% alcohol-water mixtures was an unexpected result, although reliable selectivity data are difficult to obtain for rapid reactions of sparingly soluble solutes in alcohol-water. We have found previously that *S* values can depend on the method of mixing, and it appears that higher *S* values are obtained when mixing and disaggregation of solute do not occur sufficiently rapidly.[19] Hence, it appears that aggregation of solute may have led to the

Table 1 Rate constants (k/s^{-1}) for solvolyses of *p*-nitrobenzoyl chloride (**1**) in aqueous ethanol, methanol and acetonitrile at 25 °C[a]

Solvent (%, v/v)	Ethanol[b]	Methanol[b]	Acetonitrile[c]
100	1.16×10^{-2}[d]	$(4.08 \pm 0.01) \times 10^{-2}$[e]	
98	$(1.73 \pm 0.01) \times 10^{-2}$	$(5.20 \pm 0.05) \times 10^{-2}$	
95	$(2.65 \pm 0.01) \times 10^{-2}$	$(6.65 \pm 0.12) \times 10^{-2}$[f]	$(5.78 \pm 0.18) \times 10^{-4}$
90	3.58×10^{-2}[g]	$(8.97 \pm 0.02) \times 10^{-2}$	$(1.89 \pm 0.04) \times 10^{-3}$
80	4.80×10^{-2}[h]	$(1.25 \pm 0.01) \times 10^{-1}$[e]	$(5.10 \pm 0.03) \times 10^{-3}$
70	5.80×10^{-2}[g]	$(1.53 \pm 0.04) \times 10^{-1}$[j]	
60	$(6.90 \pm 0.02) \times 10^{-2}$	$(1.51 \pm 0.01) \times 10^{-1}$[e]	$(1.15 \pm 0.03) \times 10^{-2}$
50	$(7.51 \pm 0.03) \times 10^{-2}$	$(1.46 \pm 0.01) \times 10^{-1}$[j]	
40	$(8.07 \pm 0.04) \times 10^{-2}$	$(1.35 \pm 0.01) \times 10^{-1}$	$(2.38 \pm 0.03) \times 10^{-2}$
30	$(7.77 \pm 0.04) \times 10^{-2}$[i]	$(1.18 \pm 0.01) \times 10^{-1}$[j]	
20	$(6.87 \pm 0.08) \times 10^{-2}$	$(9.47 \pm 0.12) \times 10^{-2}$	$(4.75 \pm 0.02) \times 10^{-2}$
10	$(6.02 \pm 0.02) \times 10^{-2}$[j]	$(7.61 \pm 0.05) \times 10^{-2}$[j]	
5	$(5.57 \pm 0.03) \times 10^{-2}$[k]	$(6.39 \pm 0.06) \times 10^{-2}$[k]	
Water	$(5.55 \pm 0.05) \times 10^{-2}$[k,l]		
D_2O	$(3.18 \pm 0.04) \times 10^{-2}$[j,m]		

[a] Determined conductimetrically at least in duplicate; errors shown are average deviations. [b] From ref. 7, except where stated otherwise. [c] Determined by S. J. Norman (Swansea). [d] Average of values given in refs. 14–16. [e] Ref. 17. [f] Triplicate measurement of rate constant. [g] Ref. 15. [h] Average of values given in refs. 15 and 16. [i] Quadruplicate measurement of rate constant. [j] This work. [k] This work; see also Table 2. [l] Eight measurements; also ref. 18: $k = 0.062$ s^{-1}. [m] Also ref. 18: $k = 0.031$ s^{-1}.

Table 2 Activation parameters for solvolyses of *p*-nitrobenzoyl chloride (**1**) in highly aqueous media[a]

Solvent	T/°C	k/s^{-1}	$\Delta H^‡$/kcal mol^{-1}	$\Delta S^‡$/cal mol^{-1} K^{-1}
Water	35.0	$(1.29 \pm 0.01) \times 10^{-1}$	15.0	−14.0
	25.0[b]	$(5.55 \pm 0.05) \times 10^{-2}$		
	15.0	$(2.20 \pm 0.03) \times 10^{-2}$		
5% Ethanol	35.1	$(1.41 \pm 0.03) \times 10^{-1}$	15.0	−14.0
	25.0	$(5.58 \pm 0.03) \times 10^{-2}$		
	15.0	$(2.34 \pm 0.01) \times 10^{-2}$		
	4.8	$(8.68 \pm 0.02) \times 10^{-3}$		
5% Methanol	35.1	$(1.51 \pm 0.05) \times 10^{-1}$	14.8	−14.5
	25.0	$(6.39 \pm 0.05) \times 10^{-2}$		
	15.0	$(2.64 \pm 0.01) \times 10^{-2}$		
	4.8	$(9.79 \pm 0.02) \times 10^{-3}$		

[a] Determined conductimetrically at least in duplicate by injecting 10 mm^3 of a 0.1% solution of **1** into 6 cm^3 of solvent for each solvolysis. [b] Eight measurements of the rate constant.

high S values for solvolyses of **1**, previously reported in 30% and 20% ethanol–water.[7]

Unlike in kinetic studies, where it is possible to ignore the early or later stages of a reaction in the calculation of rate constants, it is clearly not possible to ignore the early stages of a reaction in studies of product selectivities. In solutions sonicated to remove CO_2, we obtained satisfactory first order kinetics for solvolyses of **1** in 5 and 10% alcohol mixtures immediately (< 0.5 s) after injecting a very dilute solution of the substrate (0.1 or 0.2% in acetonitrile) into the thermostatted solvent. Having established suitable mixing conditions from kinetic studies, these conditions were then used to investigate the product ratios in the highly aqueous solvents. S values for 5–30% alcohol–water, determined 6–8 times for each solvent composition with different sizes of injection, depended on the mixing conditions and S values tended to be higher when larger amounts of substrate were injected. Results shown in Table 3 are for the most dilute reaction conditions. The tendency for S to decrease in < 40% alcohol–water mixtures (Table 3) is almost certainly significant experimentally.

The maximum in S values (Table 3) in 30–40% alcohol–water solvent compositions is consistent with a tendency for a mechanistic change from a general base catalysed reaction channel to an S_N2–S_N1 channel.[20] The maximum in S tends towards more aqueous solvent compositions as the substituent becomes more electron withdrawing (Table 4). Also the mechanistic change occurs in more aqueous compositions than the maximum in S.[20] Hence, the decrease in S in highly aqueous mixtures (Table 3) could be explained by the beginning of a mechanistic change for solvolyses of **1**.

Other mechanistic indicators are insufficiently sensitive to confirm or disprove the suggested mechanistic change. Although our value for the solvent isotope effect (H_2O/D_2O) of 1.75 ± 0.05 (Table 1) is lower than the previously published values of 2.0[18] and 2.3,[21] it is almost the same as the values of 1.76[21] and 1.82[22] for *p*-nitrobenzenesulfonyl chloride (**2**). The mechanistic change for sulfonyl chlorides requires more electron-donating substituents (by comparison with carboxylic acid chlorides),[23] so **2** is less likely to change mechanisms than **1**. The mechanistic change for solvolyses of *p*-chlorobenzoyl chloride (**3**, Z=Cl) is accompanied by a > 10-fold increase in rate from 40% alcohol–water to pure water,[20] whereas **1** gives a rate decrease (Table 1); as the rate constants for solvolyses of **1** in water (0.055) and 20% acetonitrile–water (0.047) are very similar (Table 1), it seems likely that a second mechanism is contributing only a small part to the observed rate constant in pure water.

To avoid uncertainties associated with the interpretation of the rate and product data, solvent mixtures containing < 40% alcohol have been excluded from the following experimental tests of eqn. (6). However, the main conclusions of this work would not be affected adversely if it were concluded that S

Table 3 Product selectivities [S, eqn. (1)] for solvolyses of *p*-nitrobenzoyl chloride (**1**) in alcohol–water mixtures at 25.0 °C[a]

Solvent (%, v/v)	Ethanol		Methanol	
	[Ester]/[Acid][b]	S	[Ester]/[Acid][c]	S
99[d,e]	16.8	0.52	85.8	1.84
98[e,f]	9.83	0.62	45.4	2.11
95[g]	5.34	0.91	22.6	2.66
92[g]	4.11	1.17	17.1	3.34
90[g]	3.62	1.30	14.8	3.70
85[g]	2.85	1.64	11.3	4.47
80[g]	2.34	1.89	9.41	5.27
70[g]	1.82	2.53	7.26	6.97
60[g]	1.45	3.13	5.51	8.21
50[g]	1.13	3.66	4.07	9.16
40[h]	0.809	3.93	3.09	10.4
30[h]	0.494	3.73	1.94	10.2
20[h]	0.293	3.79	1.06	9.5
10[i]	0.117	3.44	0.465	9.4
5[j]	0.0510	2.9	0.218	9.2
2[j]	0.0177	2.8	0.076	8.4
1[j]	0.0083	2.7	0.036	8.1

[a] Determined by HPLC for duplicated solvolyses. [b] Corrected for 0.3% acid impurity in the sample of **1**. [c] Corrected for 0.2% acid impurity in the sample of **1**. [d] Actual compositions by Karl–Fischer analysis: 99% MeOH = 99.06%, 99% EtOH = 99.05% EtOH; S is corrected for these compositions. [e] Injected 10 mm^3 of a 5% w/w solution of **1** in acetonitrile into 5 cm^3 of solvent. [f] Actual compositions by Karl–Fischer analysis: 98% MeOH = 97.98%; 98% EtOH = 98.09% EtOH; S is corrected for these compositions. [g] Injected 15 mm^3 of a 5% w/w solution of **1** in acetonitrile into 5 cm^3 of solvent. [h] Injected 30 mm^3 of a 0.5% w/w solution of **1** in acetonitrile into 5 cm^3 of solvent. [i] Injected 50 mm^3 of a 0.25% w/w solution of **1** in acetonitrile into 5 cm^3 of solvent. [j] Injected 10 mm^3 of a 0.2% w/w solution of **1** in acetonitrile into 5 cm^3 of solvent.

Table 4 Range of solvent compositions spanning the maximum S value for solvolyses of *para*-Z-substituted benzoyl chlorides (**3**) in alcohol–water mixtures at 25 °C

Substituent Z	Solvent range (%, v/v alcohol)		Ref.
	Ethanol–water	Methanol–water	
OMe	no max. obsd.	no max. obsd.	20
Me	98–90	98–90	20
H	90–70	98–80	20
Cl	60–50	70–50	20
NO_2	50–20	50–5	[a]

[a] This work; see Table 3.

values reached limiting values of 3.3 ± 0.6 in highly aqueous ethanol–water mixtures and 9 ± 1 in highly aqueous methanol–water mixtures.

Experimental Tests of Eqns. (4), (6) *and* (8).—The theory outlined above can be tested experimentally in six stages: (i) the linearity of plots based on eqn. (6) needs to be established in more aqueous mixtures (*e.g.* 0–80% alcohol–water), and the linearity of plots based on eqn. (8) needs to be established in more alcoholic mixtures (*e.g.* 90–99% alcohol–water); (ii) the ratios k_{aw}/k_{wa} can be compared from both the slopes of eqn. (6) and eqn. (8)—even if there are medium effects on k_{aw} and k_{wa}, as we proposed previously,[7] it is still possible that the ratio k_{aw}/k_{wa} could be approximately constant; (iii) absolute values of k_{aw} and k_{wa} based on slopes and intercepts of eqn. (6) or (8) can be compared; (iv) individual contributions from the four competing reactions can be calculated, and the validity of the assumptions used to derive eqns. (6) and (8) can be checked; (v) first order rate constants calculated from eqn. (4) over the whole range of alcohol–water solvent compositions can be compared with the experimentally observed values—the theory requires input of only two rate constants, one in pure water and one in pure alcohol, but in the simplest form of the theory outlined above, it is assumed that there are no solvent effects other than solvent stoichiometry—in general, it would be expected that the third order rate constants would be dependent on solvent composition; (vi) the product composition over the whole range of alcohol–water mixtures can also be predicted from eqns. (2)–(4), and can be compared with the experimental values—for values of k_{aw} and k_{wa} derived from eqn. (8), the only experimental product compositions used as initial data input are those in 90–99% alcohol–water.

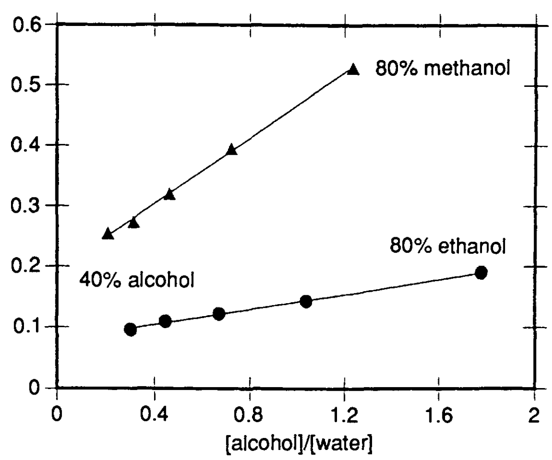

Fig. 1 Plot of $1/S$ *vs.* alcohol/water molar ratio [eqn. (6)] for solvolyses of *p*-nitrobenzoyl chloride (**1**); data from Table 3; for ethanol–water (▲): slope = 0.272 ± 0.006, intercept = 0.194 ± 0.004, r = 0.999; for methanol–water (●): slope = 0.062 ± 0.002, intercept = 0.079 ± 0.002, r = 0.999

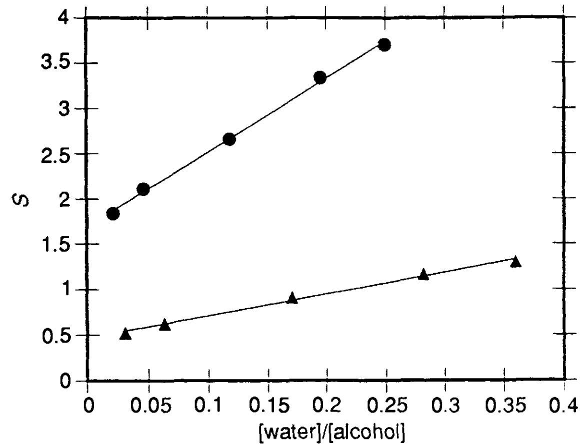

Fig. 2 Plot of S *vs.* water/alcohol molar ratio [eqn. (8)] for solvolyses of *p*-nitrobenzoyl chloride (**1**); data from Table 3; for ethanol-water (▲): slope = 2.40 ± 0.12, intercept = 0.47 ± 0.03, r = 0.996; for methanol-water (●): slope = 8.15 ± 0.22, intercept = 1.70 ± 0.04, r = 0.999

Although this relatively simple theory is unlikely to give accurate results, the above stages provide a unique opportunity to analyse and to investigate systematically the cause(s) of discrepancies in order to gain further insights into the factors influencing reactivity in aqueous solution.[9]

Plots (Fig. 1) of $1/S$ *versus* the alcohol/water molar ratio [eqn. (6)] from 40% to as high as 80% v/v alcohol–water are linear (r = 0.999), and the curved plots (not shown) of S *versus* the water/alcohol molar ratio [eqn. (8)] have precise linear regions between 99 and 90% alcohol–water (Fig. 2, r = 0.999 for MeOH and r = 0.996 for EtOH). Also the linear regions of Figs. 1 and 2 are at least four-fold broader than the extrapolations required to obtain the intercepts. Hence, the

Table 5 Ratios of third order rate constants k_{aw}/k_{wa} derived from $1/S$ and S plots for solvolyses of *p*-nitrobenzoyl chloride (**1**) in alcohol–water mixtures at 25 °C

Plot	Solvent range (%)	Slope	k_{aw}/k_{wa}	Eqn.
$1/S$[a]	80–40 EtOH	0.272 ± 0.006	3.67 ± 0.07	(6)
S[b]	90–99 EtOH	2.40 ± 0.12	2.40 ± 0.12	(8)
$1/S$[a]	80–40 MeOH	0.0620 ± 0.002	16.1 ± 0.6	(6)
S[b]	90–99 MeOH	8.15 ± 0.22	8.15 ± 0.22	(8)

[a] Fig. 1. [b] Fig. 2.

Table 6 Third order rate constants ($10^5\,k$/dm^6 mol^{-2} s^{-1}) for solvolyses of *p*-nitrobenzoyl chloride (**1**) in alcohol–water mixtures at 25 °C calculated from slopes and intercepts of Figs. 1 and 2[a]

Alcohol	Plot	k_{ww}	k_{aa}	k_{aw}	k_{wa}
EtOH	$1/S$	1.80[b]	3.95[c]	9.27	2.52
	S	1.80[b]	3.95[c]	20.2	8.40
MeOH	$1/S$	1.80[b]	6.69[d]	22.8	1.41
	S	1.80[b]	6.69[d]	32.1	3.94

[a] Details of slopes and intercepts are given in the legends to the Figs. [b] Calculated from the observed first order rate constant in pure water (Table 1). [c] Calculated from the observed first order rate constant in pure ethanol (ref. 7). [d] Calculated from the observed first order rate constant in pure methanol (ref. 7).

Table 7 Comparisons of observed results with calculated first order rate constants and calculated % ester for solvolyses of *p*-nitrobenzoyl chloride (**1**) in alcohol–water mixtures at 25 °C

	First order rate constant/s^{-1}		Yield ester (%)	
Solvent (%)	Obsd.[a]	Calcd.[b]	Obsd.[c]	Calcd.[b]
90 EtOH	0.0358	0.0344	78.4	77.5
80 EtOH	0.0480	0.0532	70.1	71.8
60 EtOH	0.0690	0.0783	59.2	64.2
40 EtOH	0.0807	0.0871	44.7	55.1
20 EtOH	0.0687	0.0795	22.7	39.3
90 MeOH	0.0897	0.0781	93.7	93.1
80 MeOH	0.125	0.107	90.4	89.9
60 MeOH	0.151	0.142	84.6	84.6
40 MeOH	0.135	0.145	75.5	77.3
20 MeOH	0.095	0.116	51.5	62.0

[a] Table 1. [b] Rate constants from the S plot [eqn. (8), Table 6] substituted into eqn. (4). [c] Table 3.

following calculations based on the slopes and intercepts of Figs. 1 and 2 are expected to be reliable. Very similar results were obtained by rearranging eqns. (6) and (8), so that k_{aw} and k_{wa} could be obtained from either slopes or intercepts, as in Eadie–Hofstee (EH) plots;[24] the only significant difference between the two types of plot is the value of k_{aw} from Fig. 2, eqn. (8), for which EH gives a 5% higher value for ethanol–water—significantly, this is the only one of our four correlations (Figs. 1 and 2) with $r < 0.999$.

Ratios of k_{aw}/k_{wa} for ethanol–water (Table 5), calculated from the slopes of $1/S$ plots (Fig. 1) and S plots (Fig. 2), agree within a factor of 1.5 and ratios for methanol–water agree within a factor of two. Values of k_{aw} (Table 6) appear to be reliable within a factor of about two, but values of k_{wa} are smaller and more uncertain—the two values of k_{wa} differ by over three-fold in ethanol–water and slightly less than three-fold in methanol–water (Table 6). These results support our previous rate-product correlation[7] in showing that the k_{aw} term is dominant, but contrary to our previous work[7] the k_{wa} term appears to be significant, particularly in ethanol–water.

A major cause of the different values of k_{aw}/k_{wa} (Table 5), from the $1/S$ [eqn. (6)] and the S [eqn. (8)] plots, appears to be a failure of the assumption required for eqn. (6) that the k_{aw} term is much greater than the k_{aa} term; in 40% alcohol–water the k_{aw} term is calculated to be over 10 times larger than the k_{aa} term but in 80% alcohol it is predicted to be only about twice as large. Hence, the k_{aa} term contributes significantly to the calculated value of k_{aw}, and so the ratios k_{aw}/k_{wa} (Table 5) derived from the $1/S$ plots are too high. The results show that very good linear relationships (Fig. 1) do not alone verify the assumptions on which the derivation of eqn. (6) is based.

In contrast, even in 90% alcohol–water, the k_{wa} term is calculated to be over ten times larger than the k_{ww} term, supporting the assumption used to derive the S plot [eqn. (8)], and the following tests of eqn. (4) will be based solely on predictions from S plots (Fig. 2, Table 6).

Predicted first order rate constants (Table 7) agree typically within 10% of the observed values, providing very strong support for the validity of eqns. (2)–(4). The solvent composition giving the rate maximum is reproduced correctly in 40% ethanol–water, and almost exactly in methanol–water (calcd. 60%; obsd. 70%). Analysis of the contributing terms shows that the maxima are due mainly to the large k_{aw} terms. The calculated % ester (Table 7) is in excellent agreement with the observed values from highly alcoholic media to 40% methanol–water, and agreement is satisfactory down to 60% ethanol–water mixtures; deviations in more highly aqueous media are consistent with a competing reaction channel, having a lower S value, becoming increasingly important in more aqueous media (as implied by the results in Table 4).

Minor refinements to the theory could be made. A lower value of the third order rate constant k_{ww} could be adopted if there is a significant contribution to the observed first order rate constant in pure water from a second channel. A lower k_{ww} would improve the agreement between calculated and observed first order rate constants in 20% alcohol, but also would further increase the discrepancies between calculated and observed % ester (Table 7). A correction for a discrepancy in % ester requires that the magnitudes of the other third order rate constants (particularly the dominant rate constant k_{aw}) decrease very slightly as water is added to ethanol *e.g.* a 25% reduction from pure ethanol [the reference solvent for k_{aa}, k_{aw}, and k_{wa} for predictions based on eqn. (8)] to 40% ethanol–water is all that would be required, and this corresponds to a Grunwald–Winstein m value of only -0.02—even smaller than the very small value of -0.08 for the k_{aw} term, incorporated into our previous kinetic model for these solvolyses.[7]

A slightly larger medium effect would be required if the possibility of mechanistic change for solvolyses of **1** in water were ignored. According to the third order kinetic model, the limiting value of S in highly aqueous media is given by k_{aw}/k_{ww}.[7] Taking limiting values of 3.3 ± 0.6 for ethanol–water and 9 ± 1 for methanol–water mixtures (Table 3), the value of k_{aw}/k_{ww} predicted from S values in 90–99% alcohol–water mixtures [eqn. (8), Table 6] is two to three-fold too high. This discrepancy could be explained by an m value of about -0.1.[7]

Implications for Reactions in Other Aqueous Mixtures.—A plot of $\log k_{obs}/[\text{water}]^2$ against Y values for solvolyses of **1** in acetone–water gives an m value of -0.18, which we previously assumed to be the solvent dependence of the k_{ww} term.[7] It now appears that this value may be too negative, and we have investigated another possible explanation of the solvent dependence of these third order hydrolysis rate constants. Eqn. (9) shows the expected dependence of stoichiometric solvation for hydrolyses in acetone- or acetonitrile–water, where the third order rate constant k_{wc} involves water as nucleophile with the cosolvent as general base.[3] Although $k_{obs}/[\text{water}]^2$ varies only

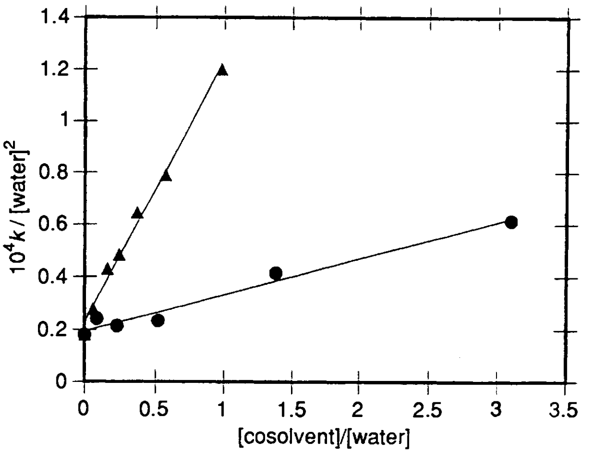

Fig. 3 Plot of calculated third order rate constant (10^4k) *vs.* cosolvent/water molar ratio for solvolyses of *p*-nitrobenzoyl chloride (**1**) in acetone–water (▲): slope (from water to 80% acetone–water) = (1.01 ± 0.04) × 10^{-4}, intercept = (2.28 ± 0.20) × 10^{-5}, r = 0.996, kinetic data summarised in ref. 7; acetonitrile–water (●): slope = (1.38 ± 0.11) × 10^{-5}, intercept = (1.94 ± 0.16) × 10^{-5}, r = 0.987; kinetic data from Table 1 (95% acetonitrile excluded)

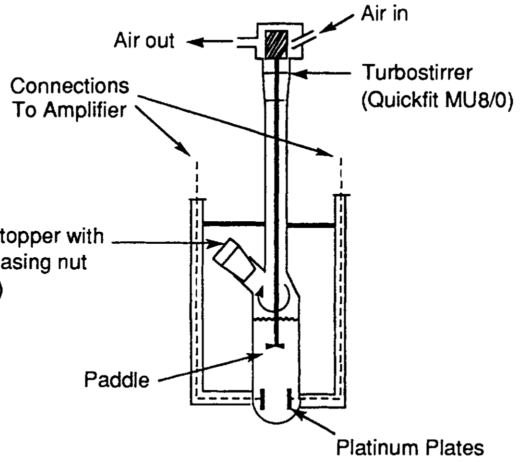

Fig. 4 Stirred conductivity cell for relatively fast solvolytic reactions (see also experimental sections of this paper and of ref. 19).

between 1.8 and 2.4 × 10^{-5} dm^6 mol^{-2} s^{-1} between water and 60% acetonitrile–water, eqn. (9) gives good plots up to 90% acetonitrile–water and also up to 80% acetone-water (Fig. 3). Slopes (acetone > acetonitrile) are consistent with known hydrogen bond acceptor abilities; *i.e.* acetone (β = 0.48)[25] is probably a more effective general base than acetonitrile (β = 0.31).[25] However, the value of 1.0 × 10^{-4} dm^6 mol^{-2} s^{-1} for k_{wc} in acetone–water (Fig. 3) is over five-fold larger than k_{ww}, so the proximity of acetone may increase the nucleophilicity of the water.[26] The possibility that 'inert' cosolvents such as acetone, acetonitrile and dioxane could act as general bases in reactions of binary aqueous mixtures has been considered previously,[27] but it is not yet accepted. Further investigations are in progress.

$$k_{obs}/[\text{water}]^2 = k_{ww} + k_{wc}[\text{cosolvent}]/[\text{water}] \quad (9)$$

$$k_{obs}/[\text{water}]^2 = k_{ww} + k_{wc}[\text{cosolvent}]/[\text{water}]^2 \quad (10)$$

Alternatively, solvents such as acetonitrile[28,29] and acetone[30] are known to be nucleophiles in solvolytic reactions, and eqn. (10) would apply to a solvolysis involving water as both nucleophile and general base, competing with attack by the cosolvent as nucleophile (general base catalysis would not be possible). However, this eqn. fits the data less satisfactorily than eqn. (9), as might have been expected when relatively large concentrations of water are present. The cosolvents might act as nucleophiles when very small amounts of water are present; possibly, this additional pathway could account for the deviations of points for 90% acetone and 95% acetonitrile from the main trends shown in Fig. 3.

Conclusions

Eqns. (6) and (8) provide useful empirical linear relationships between product selectivities (S) and solvent stoichiometry for solvolyses in alcohol–water mixtures. The slopes and intercepts of these correlations can be related to the four third order rate constants contributing to the solvolyses of *p*-nitrobenzoyl chloride (**1**). The satisfactory rate–product correlation (Table 7) strongly supports the theory and the third order rate constants on which the derivations of eqns. (6) and (8) are based. Medium effects, identified by comparing first order rate constants predicted by eqn. (4) with the observed values (Table 7) appear to be very small. Eqns. (6) and (8) could be applied to solvolyses of many other substrates, and deviations from the equations may be helpful in identifying mechanistic changes, *e.g.* deviations from eqn. (6) in < 40% alcohol–water for solvolyses of **1**. The solvent dependence of the first order rate constants for solvolyses of **1** in acetone–water and in acetonitrile–water can be explained by a solvent independent k_{ww} term (second order in water), if another term (first order in the aprotic solvent and first order in water) is added to the rate law.

Experimental

p-Nitrobenzoyl chloride (**1**) was recrystallised several times from dry dichloromethane and light petroleum (b.p. 60–80 °C): m.p. 75 °C (lit.,[31] 75 °C). The amount of acid impurity was 0.3 ± 0.1% (by HPLC analysis of the methanolysis product—traces of acid were identified by making 'oversized' injections, followed by a correction of peak areas for the large injection sizes; the analyses were confirmed by adding known, small extra amounts of acid impurity and reanalysing). Methyl *p*-nitrobenzoate m.p. 95 °C (lit.,[31] 95 °C) and ethyl *p*-nitrobenzoate m.p. 57.5 °C (lit.,[31] 57 °C) were both recrystallised from chloroform and light petroleum (b.p. 60–80 °C). Ethanol and methanol were dried by heating under reflux with magnesium alkoxide and distilled. Karl Fischer analysis showed 0.04% w/w water in dried methanol and 0.03% w/w water in dried ethanol. Acetonitrile was dried over phosphorous pentoxide and distilled. Water was double-distilled conductivity grade, and aqueous solutions were prepared by mixing appropriate volumes at room temperature.

Standard solutions of methyl *p*-nitrobenzoate and ethyl *p*-nitrobenzoate were made up in dry acetonitrile. Standard solutions of the *p*-nitrobenzoic acid product were made by dissolving an appropriate amount of **1** in 50/50 acetonitrile–water and allowing it to hydrolyse to the acid.

Kinetic data were collected conductimetrically using a high precision digital voltmeter (Solartron 7066 Datastore), which was set up under computer control (BBC Master Microcomputer) to collect up to 50 readings from a stirred conductivity cell (Fig. 4). The dimensions of the cell and the method of mixing were as described previously.[17] The buffering effect of absorbed carbon dioxide[32] was avoided either by sonicating the solvolysis medium or by performing a preliminary solvolysis in the cell. The cell, based on a design by Watt,[33] was stirred by an air-driven turbostirrer (using a cylinder of compressed gas or more recently by a small compressor), and ideally the paddle was located well above the electrodes to avoid the appearance of significant numbers of air bubbles between the electrodes. With the relatively large volume of solvent located above the electrodes, each kinetic run required 7–8 cm^3 of solvent, rather than the 2–3 cm^3 used previously[17] to minimise the usage of more expensive solvents. Rate constants were obtained using the LSKIN first order kinetics program,[34] run on an Amstrad PC. All rate constants were determined at least in duplicate.

Product ratios were determined by reverse phase HPLC using 60/40 methanol–water containing 1% acetic acid as eluent at a flow rate of 1 $cm^3 min^{-1}$. A 15 cm Spherisorb S5 ODS2 column, having about 8500 theoretical plates, was used with an HPLC system consisting of an LDC Milton Roy 'Promis' autosampler; LDC Milton Roy 'Constametric 3000' solvent pump; LDC Milton Roy 'Spectromonitor 3100' variable wavelength UV detector set at 261 nm, and an LDC Milton Roy 'CI-4100' computing integrator. Concentrations $< 10^{-4}$ mol dm^{-3} were necessary for the more aqueous solutions and concentrations used for the product studies were within a factor of two of those giving good first order kinetics from immediately after injection to $> 95\%$ reaction. The mixing apparatus used was a turbostirred vessel, with almost exactly the same dimensions as the conductivity cell (Fig. 4).

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