New Rate–Product Correlations for General-base Catalysed Reactions in Alcohol–Water Mixtures†

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Selectivities (*S*) for solvolyses of *p*-nitrobenzoyl chloride (**1**), *p*-nitrobenzenesulfonyl chloride (**2**), *p*-nitrobenzyl chloride (**3**; Z = NO_2) and *p*-methoxybenzyl chloride (**3**; Z = OMe) in alcohol–water mixtures are consistent with third-order terms in the rate law, including terms for nucleophilic attack and general-base catalysis by water and/or alcohol. The results document new rate–product correlations and new reactivity–selectivity relationships, which help to define 'normal' behaviour from which deviations can be identified for further investigations.

Rate-product correlations have played a central role in mechanistic evidence for nucleophilic substitution reactions, *e.g.* in distinguishing between S_N2 and S_N1 mechanisms,[1] and in resolving the phenonium-ion problem.[2] The currently used 'azide clock' is based on a rate–product correlation between carbocation attack by solvent (k_s) in competition with attack by azide (k_{Nuc}).[3] For a substrate RX in the solvent (SOH) with low concentrations of the added nucleophile (Nuc), and if the products are RNuc and ROS, the selectivity (*S*) is given by eqn. (1) based on molar concentrations; the validity of the equation can be shown by varying [Nuc] in an essentially constant reaction medium.

$$S = k_{Nuc}/k_s = [RNuc][SOH]/[ROS][Nuc] \qquad (1)$$

There is a corresponding definition of *S* for solvolyses in alcohol–water mixtures or in mixtures of two different alcohols. To maintain an approximately 'constant' solvent, *ternary* solvent systems have been employed.[3b] We now report a new rate–product correlation, which provides useful kinetic and mechanistic information for nucleophilic substitutions in a wide range of *binary* alcohol–water mixtures.

Solvolyses of *p*-nitrobenzoyl chloride (**1**) in binary mixtures are second order in protic solvent(s), and it has been proposed that one of the solvent molecules acted as a nucleophile while the other acted as a general base.[4] Hence, four terms are required for a third-order kinetic analysis. Reaction in water is denoted by a third-order rate constant k_{ww} (calculated from $k_{obs}/[water]^2$), and the other terms are: k_{wa}, water acts as nucleophile and alcohol acts as general base; k_{aw}, alcohol acts as nucleophile and water acts as general base; k_{aa}, alcohol acts as nucleophile and a second molecule of alcohol acts as general base.[4] The k_{aa} term ($k_{aa}[alcohol]^2$) has been shown[4] to be unimportant in solvent compositions more aqueous than 80% alcohol. If the k_{aa} term is ignored, *S* [based on eqn. (1)] is given by eqn. (2) and its reciprocal simplifies to eqn. (3).

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

$$1/S = (k_{wa}/k_{aw})([alcohol]/[water]) + k_{ww}/k_{aw} \qquad (3)$$

Although medium effects on the rate constants are expected,[4] if the two *ratios* of rate constants in eqn. (3) are independent of solvent, it is predicted from eqn. (3) that a plot of 1/*S* vs. [alcohol]/[water] should be linear. Appropriate plots (Fig. 1) for solvolyses of **1**, (Z = NO_2) in ethanol- and methanol–water are close to linear from water up to 80% alcohol, although the ethanol–water plot appears to be slightly curved. The very low slope of the methanol–water plot confirms that k_{aw} is much

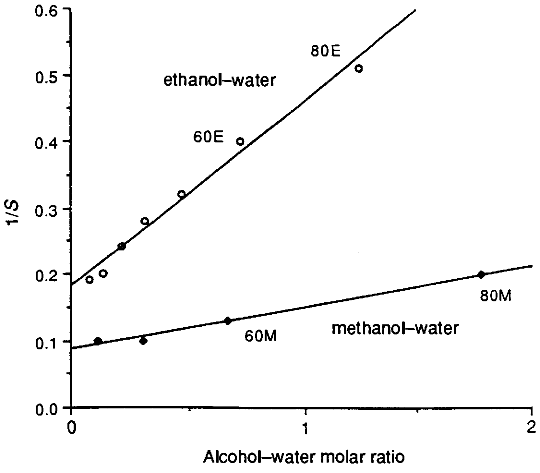

Fig. 1 Correlation of 1/*S* (*S* values from ref. 4) with solvent composition [eqn. (3)] for solvolyses of *p*-nitrobenzoyl chloride (**1**; Z = NO_2) in alcohol–water mixtures: slopes 0.28 ± 0.02 (c = 0.18 ± 0.01, r = 0.992) for ethanol–water and 0.063 ± 0.005 (c = 0.087 ± 0.004, r = 0.995) for methanol–water

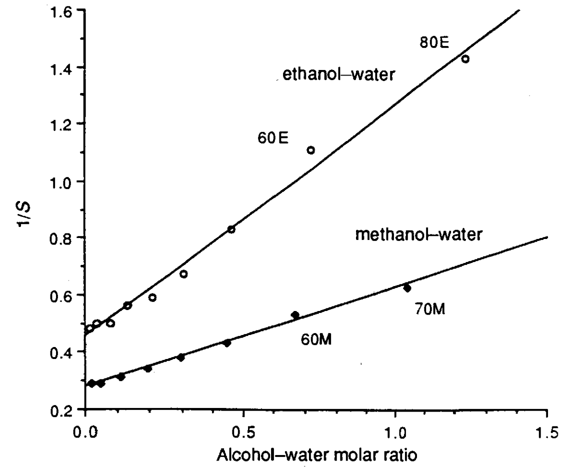

Fig. 2 Correlation of 1/*S* with solvent composition [eqn. (3)] for solvolyses of *p*-nitrobenzenesulfonyl chloride (**2**; Z = NO_2) in alcohol–water mixtures: slopes 0.81 ± 0.03 (c = 0.45 ± 0.02, r = 0.995) for ethanol–water and 0.35 ± 0.01 (c = 0.28 ± 0.01, r = 0.997) for methanol–water

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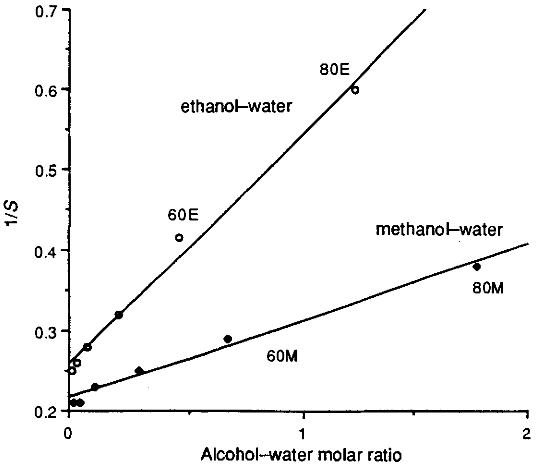


Fig. 3 Correlation of $1/S$ with solvent composition [eqn. (3)] for solvolyses of *p*-nitrobenzyl chloride (**3**; $Z = NO_2$) in alcohol–water mixtures: slopes 0.285 ± 0.015 ($c = 0.26 \pm 0.01$, $r = 0.995$) for ethanol–water and 0.096 ± 0.006 ($c = 0.215 \pm 0.005$, $r = 0.992$) for methanol–water

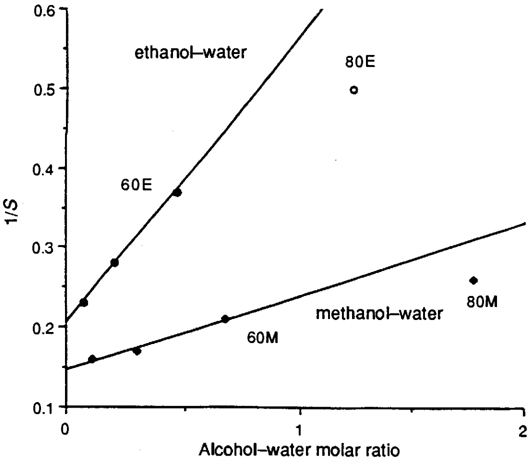


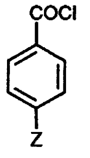
Fig. 4 Correlation of $1/S$ (S values from ref. 5) with solvent composition [eqn. (3)] for solvolyses of *p*-methoxybenzyl chloride (**3**; $Z = OMe$) in alcohol–water mixtures: slopes 0.36 ± 0.01 ($c = 0.204 \pm 0.003$, $r = 0.9997$) up to 60% ethanol–water and 0.092 ± 0.013 ($c = 0.147 \pm 0.006$, $r = 0.990$) up to 60% methanol–water

more important than k_{wa} (but k_{wa} is not negligible for ethanol–water mixtures as assumed previously[4]). Eqn. (3) is in agreement with our previous derivation of a maximum value of S in highly aqueous media where [alcohol] is very small and S_{max} is then given by k_{aw}/k_{ww}.[4]

The scope of eqn. (3) is indicated by new results for solvolyses of **2** ($Z = NO_2$) and **3** ($Z = NO_2$)—see Figs. 2 and 3. The slopes of the plots for methanol–water are larger than for solvolyses of **1** ($Z = NO_2$), implying increasing contributions from k_{wa}. Again the ethanol–water plots may be slightly curved, and a more precise linear plot would be obtained by limiting the solvent range to water to 60% alcohol–water . Our previous work[4] was based on curve fitting of observed rate constants, followed by a *prediction* of the product composition. Eqn. (3) provides an alternative means of investigating rate–product correlations relating observed products to observed first-order rate constants, but allowances for the medium effects on the third-order rate constants will usually be needed.[4]

A possible further extension of eqn. (3) is to 'stable' carbocations. Nucleophilic attack by water on all carbocations with an appreciable lifetime may be general-base catalysed.[6] Solvolyses of **3** ($Z = OMe$) show common-ion rate depression in 50% (v/v) trifluoroethanol–water,[7] consistent with formation of a cationic intermediate, and selectivity data (Fig. 4) fit eqn. (3) very well from water up to 60% alcohol–water mixtures. In such S_N1 reactions, the observed first-order rate constants will not be related to the products,[1] and the selectivity data provide mechanistic information only about the product-determining step(s).[8]

Two 'normal' patterns or trends of selectivity values (S) in alcohol–water mixtures are now established. Constant S, with $S < 1$ in ethanol–water mixtures, appears to be characteristic of product formation from a solvent-separated ion pair,[9] probably with general-base catalysis by the counteranion.[10] Alternatively, when S values fit eqn. (3), there is general-base catalysis by a second molecule of solvent. The scope of eqn. (3) is currently being extended to reactions of more stable carbocations. Deviations from expected trends warrant further investigation and have provided evidence for mechanistic changes for solvolyses of **1** (Z = Cl, H and Me),[11] and for electron-rich derivatives of **2**.[12] Solvolyses of other benzyl substrates **3** (Z = Cl, H, Me) do not fit either of the 'normal' patterns[13] and we are now in a strong position to interpret solvolyses of these classic substrates, which are still not fully understood.[5,7,14–16]



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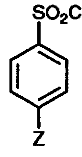

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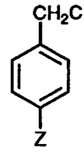

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