# Limitations of the Transition-state Variation Model. Part 3. Solvolyses of Electron-rich Benzenesulphonyl Chlorides

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Rate constants for solvolyses of 4-methoxy-2,6-dimethylbenzenesulphonyl chloride **3** (Z = OMe) and of 4-methyl- and 4-methoxybenzenesulphonyl chlorides **4** (Z = Me and OMe) are reported for aqueous binary mixtures with acetone, ethanol and methanol. Some additional rate constants are reported for aqueous acetonitrile and dioxane mixtures, as well as product selectivities (*S*) in alcohol–water mixtures. For each binary mixture, rates of solvolyses of **3** (Z = OMe) *vs.* $Y_{Cl}$ or *Y* are approximately bilinear. As water is added to alcohol, *S* values for solvolyses of **3** (Z = OMe) pass through a maximum and for solvolyses of 4-methoxybenzenesulphonyl chloride **4** (Z = OMe) the position of the maximum shifts to more aqueous media. For solvolyses of 4-methylbenzenesulphonyl chloride **4** (Z = Me), *S* values are shifted such that they reach a plateau rather than a maximum, and the rate–rate profiles with $Y_{Cl}$ are approximately linear rather than bilinear. All of the rate–rate profiles show 'dispersion' into separate correlations for the various binary mixtures. These substituent effects follow the same trends as corresponding solvolyses of benzoyl chloride and strengthen recent proposals that solvolyses of **3** (Z = Me) proceed *via* competing (dual) reaction channels.

Product selectivities in aqueous alcohols and rate–rate profiles in aqueous binary mixtures probe product and rate-determining steps of solvolytic reactions. These two types of mechanistic criteria provide information not available by other methods, and the results for solvolyses of carboxylic acid chlorides have been analysed in terms of competing (dual) reaction channels rather than the transition state variation model.[1,2] We are currently extending this work to solvolyses of sulphonyl chlorides.[3]

In mixed alcohol–water mixtures, the products of reactions of acid chlorides are an acid and an ester, and product selectivities (*S*) are defined by eqn. (1). *S* is constant for the solvolyses

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

of 2,4,6-trimethylbenzoyl chloride **1** and of *p*-methoxybenzoyl chloride **2** (Z = OMe) in ethanol– and methanol–water mixtures,[1] but for solvolyses of **2** (Z = Cl and H) *S* increases and

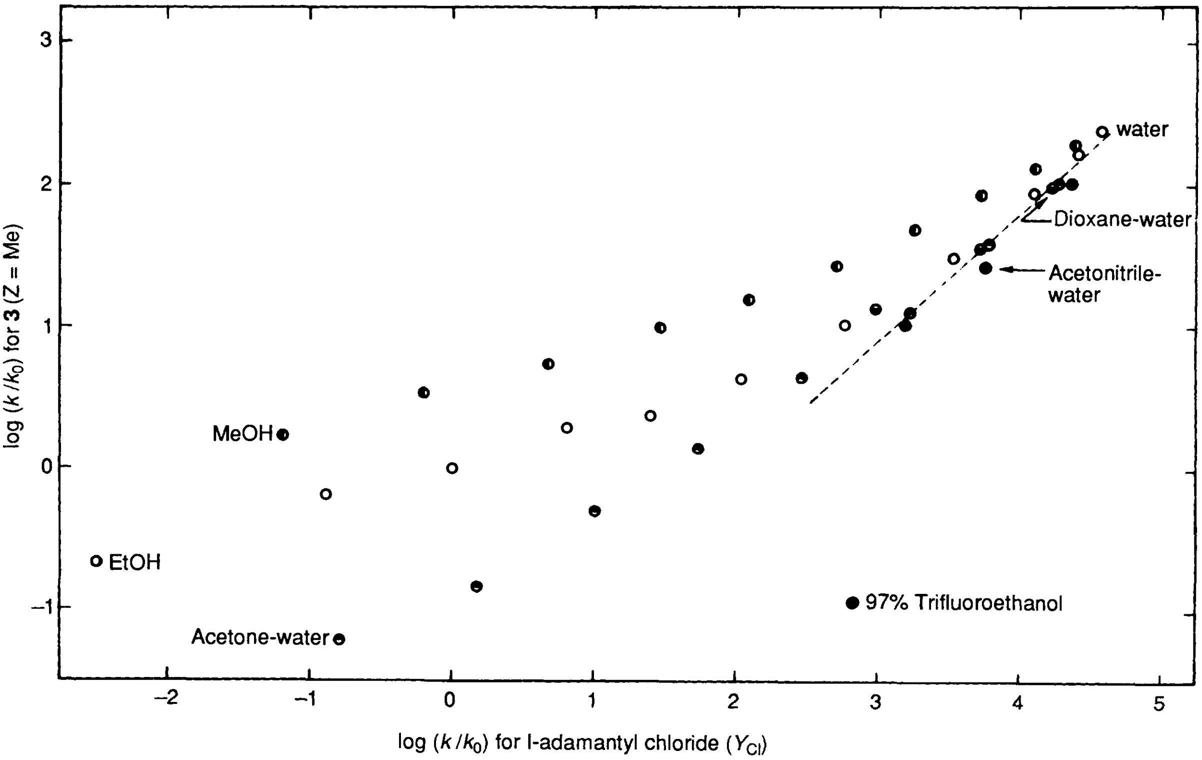


Fig. 1 Plot of logarithms of rate constants for solvolyses of 4-methoxy-2,6-dimethylbenzenesulphonyl chloride **3** (Z = OMe) with $Y_{Cl}$; kinetic data from Table 1 and $Y_{Cl}$ values from refs. 3 and 10; solvent codes: ◐, methanol–water; ○, ethanol–water; ◓, acetone–water; ◒, dioxane–water; ●, acetonitrile–water and trifluoroethanol–water. The slopes of the correlations are: (*a*) for the dashed line through the nine data points for water, 10–20% dioxane–water, 10–30% acetone–water and acetonitrile–water: slope = 0.90 ± 0.05 (*r* = 0.989); (*b*) for the four data points MeOH to 70% methanol–water: slope = 0.29 ± 0.01 (*r* = 0.998); for the five data points EtOH to 60% ethanol–water; slope = 0.28 ± 0.01 (*r* = 0.997).

**Table 1** Rate constants ($k$) for solvolyses of 4-methoxy-2,6-dimethylbenzenesulphonyl chloride **3** (Z = OMe) in aqueous binary mixtures at 25 °C[a]

| Solvent % v/v | $k/10^{-3}$ s$^{-1}$ Ethanol | Methanol | Acetone | Acetontrile | Dioxane |
|---|---|---|---|---|---|
| 100 | 0.248 | 1.96[b] | | | |
| 90 | 0.76 | 4.13 | | | |
| 80 | 1.18 | 6.56 | 0.0715 | 0.115 | 0.0578 |
| 70 | 2.28 | 11.7 | 0.177 | | |
| 60 | 2.80 | 19.1 | 0.604 | 0.605 | 0.614 |
| 50 | 5.24 | 33.2 | 1.68 | | |
| 40 | 12.5 | 58.8 | 5.41 | 3.39 | 5.58 |
| 30 | 37.5 | 103 | 15.4 | 13.0 | 16.0 |
| 20 | 105 | 158 | 46.9 | 32.6 | 44.8 |
| 10 | 195 | 237 | 122 | 120 | 118 |
| Water[c] | 287 | 287 | 287 | 287 | 287 |

97% w/w trifluoroethanol–water, $k = (1.41 \pm 0.01) \times 10^{-4}$

[a] Determined conductimetrically in duplicate; average deviation typically ±3%. [b] In MeOD, $k = (1.24 \pm 0.04) \times 10^{-3}$, hence $k_H/k_D = 1.58 \pm 0.05$. [c] Solvent contained 0.2–0.4% acetonitrile.

**Table 2** Rate constants ($k$) for solvolyses of 4-methoxybenzenesulphonyl chloride **4** (Z = OMe) in aqueous binary mixtures at 25° C[a]

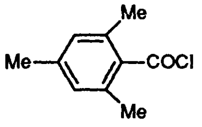
| Solvent % v/v | $k/10^{-3}$ s$^{-1}$ Ethanol | Methanol | Acetone | Acetonitrile | Dioxane |
|---|---|---|---|---|---|
| 100 | 0.022 | 0.128 | | | |
| 90 | 0.0599 | 0.302 | 0.0093 | 0.0090[b] | |
| 80 | 0.126 | 0.514 | 0.0212 | 0.023[b] | |
| 70 | 0.228 | 0.984 | 0.0437 | 0.051[b] | |
| 60 | 0.350 | 1.60 | 0.0856 | 0.102[b] | |
| 50 | 0.616 | 2.23 | 0.191 | | |
| 40 | 0.987 | 3.67 | 0.414 | 0.280 | |
| 30 | 2.27 | 4.48 | 0.975 | 0.671 | 1.21[c] |
| 20 | 4.23 | 5.53 | 1.96 | 1.81 | 2.16[c] |
| 10 | 5.00 | 6.00 | 3.17 | 3.97 | 3.59[c] |
| Water[d] | 6.50 | 6.50 | 6.50 | 6.50 | 6.50 |

[a] Determined conductimetrically in duplicate; average deviation typically ±3%. [b] Interpolated from data given in ref. 5. [c] Interpolated from data given in ref. 6(*a*). [d] Solvent contained 0.2–0.4% acetonitrile; literature value: 6.57 (ref. 7).

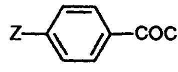
**Table 3** Rate constants ($k$) for solvolyses of 4-methylbenzenesulphonyl chloride **4** (Z = Me) in aqueous binary mixtures at 25 °C[a]

| Solvent % v/v | $k/10^{-3}$ s$^{-1}$ | | | Dioxane[b] | |
|---|---|---|---|---|---|
| | Ethanol | Methanol | Acetone | Ref. 6 | Ref. 8 |
| 100 | 0.0198[c] | 0.11 | | | |
| 90 | 0.0646 | 0.244 | 0.0046 | | 0.0022 |
| 80 | 0.112 | 0.445 | 0.0147 | | 0.0134 |
| 70 | 0.171 | 0.709 | 0.0424 | 0.0403 | 0.042 |
| 60 | 0.244 | 1.12 | 0.0904 | | 0.0108 |
| 50 | 0.400 | 1.57 | 0.174 | 0.229 | 0.248 |
| 40 | 0.584 | 2.21 | 0.343 | | 0.52 |
| 30 | 1.71 | 2.92 | 0.801 | 1.04 | 0.94 |
| 20 | 2.48 | 3.35 | 2.14 | 1.80 | |
| 10 | 3.08 | | 2.50 | 2.85 | |
| Water[d] | 3.64 | 3.64 | 3.64 | 3.64 | 3.64 |

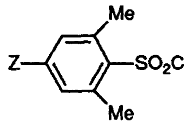
[a] Determined conductimetrically in duplicate; average deviation typically ±3%. [b] Two sets of literature values shown; data from ref. 6 required interpolation or extrapolation from data at 30 °C, and data in ref. 8 were calculated from %w/w compositions (average value plotted in Fig. 3). [c] Data from ref. 9. [d] Solvent contained 0.2–0.4% acetonitrile; average of literature values: 3.8 (ref. 7).



**1**



**2**



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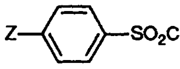


**4**

then decreases as water is added to the alcohol;[2] also, $S_{max}$ occurs at less aqueous solvent compositions as electron donation by the substituent Z increases.[2] Interpretation of these

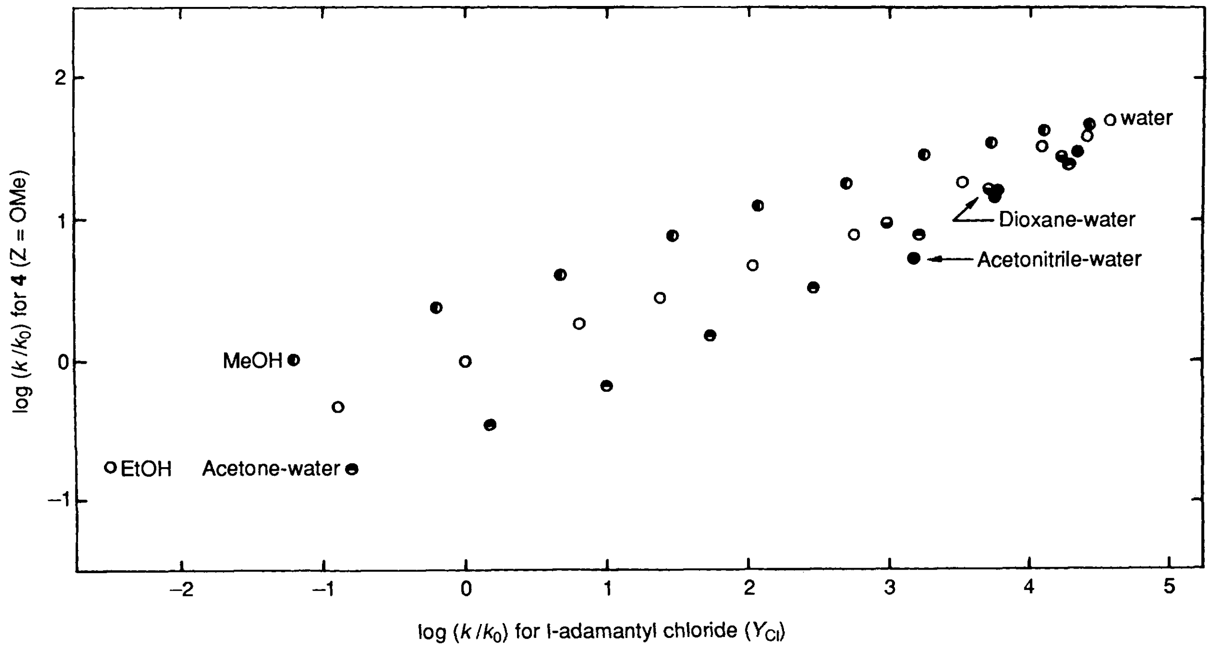


**Fig. 2** Plot of logarithms of rate constants for solvolyses of 4-methoxybenzenesulphonyl chloride **4** (Z = OMe) with $Y_{Cl}$; kinetic data from Table 2 and $Y_{Cl}$ values from refs. 3 and 10; solvent codes as for Fig. 1

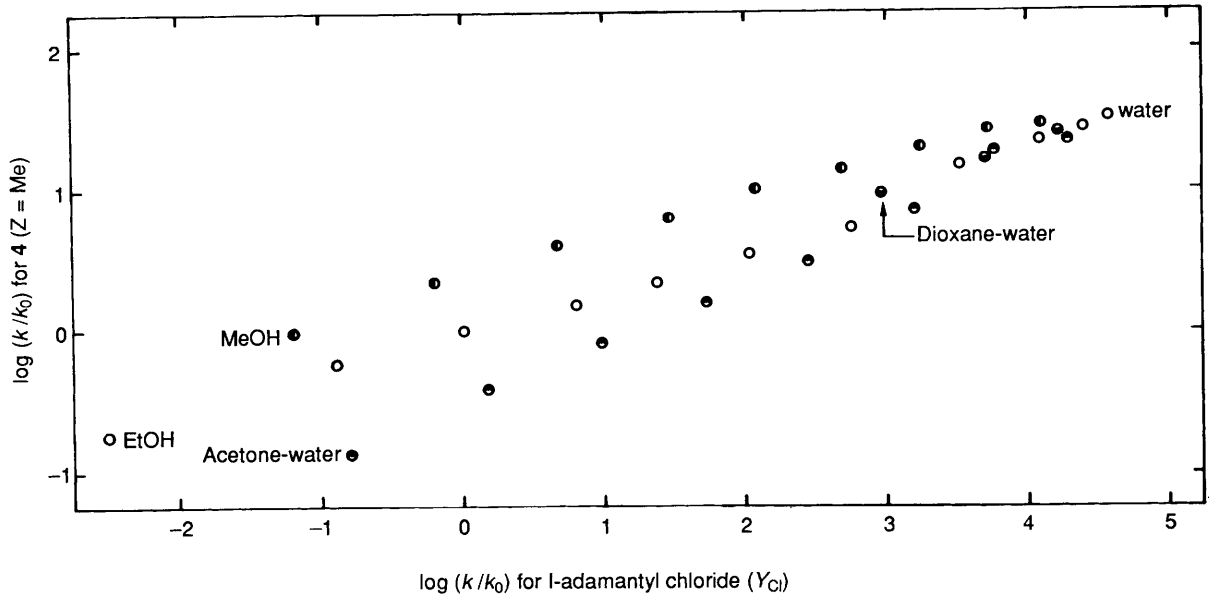


**Fig. 3** Plot of logarithms of rate constants for solvolyses of 4-methoxybenzenesulphonyl chloride **4** (Z = Me) with $Y_{Cl}$; kinetic data from Table 3 and $Y_{Cl}$ values from refs. 3 and 10; solvent codes as for Fig. 1

**Table 4** Product selectivities [$S$, eqn (1)] for solvolyses of 4-methoxy-2,6-dimethylbenzene sulphonyl chloride **3** (Z = OMe), 2,4,6-trimethylbenzenesulphonyl chloride **3** (Z = Me), 4-methoxybenzenesulphonyl chloride **4** (Z = OMe) and 4-methylbenzenesulphonyl chloride **4** (Z = Me) in alcohol–water at 25 °C[a]

| | Substrate | | | |
|---|---|---|---|---|
| | **3** (Z = OMe) | **3** (Z = Me)[b] | **4** (Z = OMe) | **4** (Z = Me) |
| Ethanol–water mixtures[c] | | | | |
| 90E | 1.7 | 1.5 | 1.6 | 1.0 |
| 80E | 2.4 | 2.5 | 2.3 | 1.5 |
| 60E | 3.7 | 3.8 | 3.8 | 2.6 |
| 50E | 3.9 | 4.1 | 3.9 | |
| 40E | 3.7 | 4.6 | 4.2 | 3.0 |
| 30E | 3.2 | 3.4 | 3.9 | |
| 20E | 2.6 | 3.1 | 3.6 | 2.9 |
| 10E | 2.4 | 2.9 | 3.4 | 3.0 |
| 5E | 2.4 | 2.4 | 3.2 | 2.7 |
| Methanol–water mixtures[c] | | | | |
| 90M | 2.7 | 1.9 | 2.5 | |
| 80M | 3.4 | 2.4 | 4.2 | 2.2 |
| 60M | 4.3 | 3.6 | 4.4 | 3.5 |
| 40M | 4.3 | 4.4 | 6.0 | 4.5 |
| 20M | 3.4 | 3.9 | 5.9 | 4.2 |
| 10M | 3.1 | 3.5 | 5.2 | 4.5 |
| 5M | | 3.3 | 5.1 | 4.4 |

[a] Determined by at least duplicate HPLC analyses of two independent solutions. [b] Data from ref. 3. [c] Solvents are %v/v.

results in terms of two competing reaction channels, differing in selectivity, is supported by 'breaks' in rate–rate profiles of solvent effects.[2,4] The mechanism operating on the less aqueous side of the 'break' shows a low response to changes in solvent polarity, and the other mechanism shows a high response.

Products of solvolyses of 2,4,6-trimethylbenzenesulphonyl chloride **3** (Z = Me) in aqueous binary mixtures show maxima in $S$ values for ethanol- and methanol–water mixtures, and rate constants show a 'break' in the rate–rate profile *vs.* $Y_{Cl}$ for acetone–water mixtures.[3] However, the reaction channel operating in more polar solvents for solvolyses of **3** (Z = Me) was not as clearly visible as the corresponding channel for solvolyses of benzoyl chloride **2** (Z = H).[2] Because the mechanistic change occurs in more aqueous media, there are few solvent compositions available before pure water is reached to define the shape of the rate–rate profile in more aqueous media. Hence, an initial aim of this work was to investigate a more electron-rich substrate, so that the position of mechanistic change would again shift to less aqueous solvent compositions and there would then be more solvent compositions available to define the more aqueous side of the 'break'.

A second aim was to probe the potential-energy surface by evaluating substituent and solvent effects for solvolyses of compounds closely related to **3** (Z = Me). We now report rate and product data for solvolyses of three electron rich benzenesulphonyl chlorides **3** (Z = OMe), **4** (Z = OMe) and **4** (Z = Me). These results strengthen the previous interpretation,[3] and also show significant differences between solvolyses of benzoyl **2** and benzenesulphonyl chlorides **4**.

## Results

Kinetic data for solvolyses of **3** (Z = OMe) are given in Table 1, for 4-methoxybenzenesulphonyl chloride **4** (Z = OMe) are in Table 2, and for 4-methylbenzenesulphonyl chloride **4** (Z = Me) are in Table 3. These results are plotted *vs.* $Y_{Cl}$ in Figs. 1–3 ($Y_{Cl}$ is a measure of solvent ionising power, based on solvolyses of 1-adamantyl chloride[10]). Product selectivities ($S$), defined by eqn. (1) using molar concentrations,[11] are given in Table 4.

## Discussion

Rate–rate profiles (Fig. 1), kinetic solvent isotope effects (KSIE) and $S$ values (Table 4) are similar for solvolyses of **3** (Z = OMe and Me), and any small differences are qualitatively as expected: the KSIE in methanol of 1.58 ± 0.05 for **3** (Z = OMe) is less than the value of 1.68 ± 0.02 for **3** (Z = Me), and values of $S$ (Table 4) reach a maximum in less aqueous solvent compositions for **3** (Z = OMe) than for **3** (Z = Me). There is a 'break' in the rate–rate profile for solvolyses of **3** (Z = OMe) in aqueous acetone and the dashed line (Fig. 1) is an estimate of the solvent effect for the reaction channel favoured by more polar media. These results establish a second example of competing reaction channels for solvolyses of sulphonyl chlorides.[3]

Rate ratios for solvolyses of **3** (Z = OMe/Z = Me) vary from

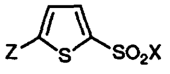
< 1 in less aqueous acetone–water mixtures to 1.6 in methanol, 3.4 in water and 5.3 in 97% trifluoroethanol–water. Larger effects are observed for solvolyses of benzoyl chlorides **2**—rate ratios for **2** (Z = OMe/Z = Me) vary from 3.0 in methanol to 10 in 20% acetone–water and 16 in 97% trifluoroethanol–water.[2,12] Solvolyses of corresponding sulphonyl chlorides **4** (Z = OMe/Z = Me) show even smaller rate ratios than **3**, varying from 1.1 in methanol to 1.8 in water and 2.0 in 90% acetone–water. The low reactivity of **3** (Z = OMe) in aqueous acetone leads to a high degree of dispersion (the tendency of different binary mixtures to give separate correlation lines[13]) between these results and those for aqueous alcohols (compare the dispersion in Fig. 1 with Figs. 2 and 3).

The rate–rate profile (Fig. 2) does not show a well-defined 'break' for solvolyses of **4** (Z = OMe) in acetone–water. Although there are indications of a weak 'break' at $Y_{\mathrm{Cl}} = 1$, this does not fit into the general pattern of results, and a line through all of the data points for acetone–water mixtures (Fig. 2) is of acceptable precision (slope 0.46 ± 0.02, $r = 0.993$). As expected, the value of $S$ (Table 4) for solvolyses of this less electron-rich substrate **4** (Z = OMe) reaches a maximum in more aqueous solvent compositions (about 30% methanol–water and 40% ethanol–water) than for solvolyses of **3** (Z = OMe).

Following the trends outlined above, solvolyses of **4** (Z = Me) in acetone–water show no 'break' in the rate–rate profile (Fig. 3), and least-squares analysis shows a line of slope 0.451 ± 0.013 ($r = 0.997$). Significantly, $S$ values in alcohol–water mixtures reach a plateau rather than a maximum (Table 4), indirectly supporting the link between 'breaks' in rate–rate profiles and maxima in $S$ values.[3]

The mechanistic change to the reaction channel with a low response to variations in solvent polarity occurs in much more electron-rich substrates for solvolyses of sulphonyl chlorides **3** and **4** than for solvolyses of corresponding benzoyl chlorides **1** and **2**. These results are consistent with known tendencies that sulphonyl chlorides are more susceptible to nucleophilic attack; also sulphonyl cations are much less stable than acylium cations.[14,15]

In solvents of low polarity (*e.g.* 95% acetone–water and ethanol), substituent effects on solvolyses of thiophene-2-sulphonyl chlorides **5** (X = Cl) are similar to those of benzoyl chlorides **2**.[16] Dissected rate constants for solvolyses of benzoyl chlorides **2** show that substituent effects on this 'less polar' channel are small, with rate constants for Z = H being only 20% greater than for Z = Me.[2] Nevertheless, the qualitative trend is as expected, a reaction favoured by electron withdrawal, and therefore it is slightly surprising that solvolyses of **3** (Z = OMe) are nearly double those for (Z = Me) in ethanol and methanol when the 'less polar' reaction channel appears to be dominant. These unusual results may be associated with a high positive charge on the sulphonyl chloride in the initial state.[17]



**5**

The reactivity of the sulphonyl chlorides **3** and **4** is of interest because of their use as protecting groups.[15] Peptide sulphonamide derivatives of **3** (Z = OMe) are recommended over compounds derived from **3** (Z = Me) or **4** (Z = OMe or Me), particularly for the protection of the guanidino function of arginine, because of their higher reactivity during a trifluoroacetolysis deprotection step[18]—we estimate about a rate factor of 10 because trifluoroacetic acid is even less nucleophilic than trifluoroethanol.[19]

Solvolyses of **4** (Z = Me) in acetone–water mixtures are about three times faster than corresponding solvolyses of the thiophene derivative **5** (X = Cl, Z = Me), for which data on bromides and fluorides **5** (X = Br, F) are also available.[16] To the earlier suggestion[16] that solvolyses of these substrates are $S_N2$ reactions, we would add the possibility of general-base catalysis,[3,11] because in water the KSIE for solvolyses of benzenesulphonyl chlorides **4** is higher than expected and increases as electron withdrawal by the substituent Z increases.[20]

## Conclusions

Substituent effects on solvolyses of benzenesulphonyl chlorides **3** and **4** are less than for solvolyses of the corresponding benzoyl chlorides **1** and **2**. For solvolyses of benzenesulphonyl chlorides **3** and **4**, electron donation by the substituent (Z) in the aromatic ring contributes little to the stabilisation of positive charge developed during heterolysis of the bond to chlorine. This supports the choice[3] of $Y_{\mathrm{Cl}}$ or $Y$ as the solvent parameter for rate–rate profiles (Figs. 1–3), rather than the $Y_{\mathrm{BnCl}}$ scale suggested recently for solvolyses in which substantial positive charge is delocalised onto an aromatic ring.[21,22]

Breaks in rate–rate profiles (*e.g.* Fig. 1) and reversals in trends of selectivity values (Table 4) show that solvolyses of **3** (Z = OMe and Z = Me) occur by competing reaction channels. Because of the small substituent effect, there are only small differences between the results for these two compounds **3** (Z = OMe and Z = Me), and it was not possible to observe much more clearly the reaction channel favoured in more polar media.

Solvolyses of the less electron rich substrate **4** (Z = Me) showed no break in the rate–rate profile and no reversal in trend of product selectivity, as observed for solvolyses of *p*-nitrobenzoyl chloride **2** (Z = $NO_2$).[11] A change in substituents from **4** (Z = OMe) to **4** (Z = Me) appears to be just sufficient to 'cut off' the reaction channel favoured in more polar media, thus strengthening the link between breaks in rate–rate profiles and reversals in trends of product selectivities for solvolyses of more electron-rich sulphonyl chlorides **3** (Z = OMe and Z = Me).

These results further document the concept of dual reaction channels as an important supplement to the transition-state variation model.[23–28]

## Experimental

4-Methoxy-2,6-dimethylbenzenesulphonyl chloride **3** (Z = OMe) was prepared by chlorosulphonation of 3,5-dimethylanisole (Aldrich);[18] 4-methylbenzenesulphonyl chlorides **4** (Z = Me) (BDH, recrystallised) and 4-methoxybenzenesulphonyl chlorides **4** (Z = OMe) (Lancaster Synthesis) were checked for purity by HPLC analysis of their methanolysis products. Rates and products were obtained as described previously.[1]

## Acknowledgements

This work was supported by the Korean Science and Engineering Foundation. We are also grateful to the SERC (UK) for an equipment grant, and to J. S. Davies for helpful comments.

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*Paper* 0/05756H
*Received* 28*th December* 1990
*Accepted* 20*th March* 1991