Intramolecular nucleophilic assistance in the solvolyses of benzyl derivatives: solvolyses of *o*-nitrobenzyl bromide and tosylate

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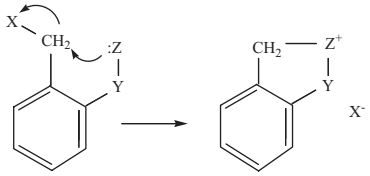
The specific rates of solvolysis of *o*-nitrobenzyl *p*-toluenesulfonate (**1**) have been measured in a wide range of solvents. Comparison with the previously studied *para*-isomer (**2**) indicates very similar behaviour (dominant S_N2 pathway) in solvents without fluoroalcohol content. With an appreciable fluoroalcohol component, the specific rates are considerably higher than those predicted based on the comparison with the solvolysis of **2** and intramolecular participation by the *ortho*-nitro group is implicated. Consistent with this postulate, in 97% 2,2,2-trifluoroethanol, the entropy of activation for the solvolysis is considerably less negative for **1** than for **2**. Measurements in four representative solvents of the specific rates of solvolysis of the bromides led to k_{OTs}/k_{Br} ratios of 10 to 30, consistent with appreciable nucleophilic assistance (by either solvent or nitro group) in the rate-determining step. For the solvents with an appreciable fluoroalcohol content, an analysis using the extended Grunwald–Winstein equation shows a negligible sensitivity towards changes in solvent nucleophilicity and a low (m = 0.27 ± 0.02) sensitivity towards changes in solvent ionising power. The low m value may result from a favourable solvation of the leaving group being partially counterbalanced by an unfavourable solvation of the nucleophilic nitro group.

Keywords: solvolysis, *o*-nitrobenzyl derivatives, intramolecular nucleophilic assistance

About 40 years ago, Andrews, Keefer and coworkers studied the effects of *ortho*-substitution on nucleophilic displacement reactions of benzylic and benzhydrylic derivatives.[1-3] They proposed that *ortho*-substituents which possess a nucleophilic centre are capable of giving intramolecular assistance to reaction, and they showed that, in favourable situations, products consistent with such an interaction are formed. For a benzylic attack, the process can be formulated as in eqn (1). In many instances, the initial product undergoes further reactions with or without opening of the initially-formed ring.



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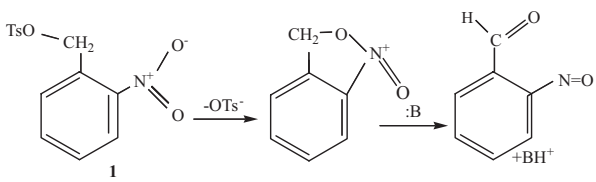
The organic product from the hydrolysis of *o*-nitrobenzhydryl bromide in 90% aqueous acetone was found to be *o*-nitrosobenzophenone,[2] presumably formed by ring closure as in eqn (1) followed by proton removal with ring opening.[3,4] It was further proposed[2] that the *o*-nitro group was much less efficient in competing with alternative pathways in reactions of benzylic systems. A more recent study,[5] at 47.5°C in 50% aqueous acetonitrile, found that, after solvolysis of *o*-nitrobenzyl *p*-toluenesulfonate (tosylate) **1** for 6 h, 35% of *o*-nitrosobenzaldehyde and 65% *o*-nitrobenzyl alcohol were the only observed organic products. The formation of the *o*-nitrosobenzaldehyde was proposed to follow a parallel pathway [eqn (2)] to that previously put forward[2] for the formation of the o-nitrosobenzophenone in the solvolysis of the *o*-nitrobenzhydryl bromide.



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Despite a third of the product apparently being formed as in eqn (2), the overall rate of reaction was only 62% of that for the parallel solvolysis of *p*-nitrobenzyl *p*-toluenesulfonate (**2**), where solvent assistance in an S_N2 process is well established.[6,7] This value is similar to values of 88% reported[2] both for hydrolysis of **1** in 90% aqueous acetone at 32.5°C and for solvolyses of the corresponding chlorides in 50% aqueous acetone at 60°C.[1,8] The values of just a little less than unity for the ratio of the specific rates of hydrolysis suggests the operation of an S_N2 pathway for both **1** and **2**, with a steric retardation of solvent attack upon the *ortho*-isomer **1** being partially counterbalanced by the accompanying operation of an intramolecular attack pathway [eqn (2)], available only for the reactions of **1**.

An alternative pathway for the hydrolyses of **1** would involve an initial direct substitution reaction to give the corresponding alcohol, followed by a slow conversion into *o*-nitrosobenzaldehyde. Such a conversion has been observed in the presence of strong acids,[4,9] but not under the much milder conditions of a low concentration of acid in 50% acetonitrile. Unfortunately, neither the concentration of reactant (which determines the amount of acid produced) nor values for the product ratio as a function of time were reported.

In an attempt to define better the reaction pathways for reactions of *o*-nitrobenzyl derivatives under solvolytic conditions, we have applied the extended Grunwald–Winstein equation[10] [eqn (3)] to the solvolyses of **1**.

$$\log(k/k_o) = l\,N_T + m\,Y_x + c \qquad (3)$$

In eqn (3), k and k_o are the specific rates of solvolysis of a substrate RX in a given solvent and in 80% ethanol, respectively; l is the sensitivity to changes in solvent nucleophilicity (N_T);[11] m is the sensitivity to changes in solvent ionising power (Y_X, for leaving group X);[12] c is a constant (residual) term. This analysis has been coupled with a consideration of activation parameters and with a comparison with corresponding reactions of the *p*-isomer (**2**), thoroughly studied previously in terms of specific rates[7,13] and followed by the application of eqn (3)[14] or related equations.[7,13] Parallel studies of the solvolyses of *o*- and *p*- nitrobenzyl bromides allow the determination of the tosylate/bromide leaving group effect ratios. This ratio is a useful tool in mechanistic investigations of nucleophilic substitution reactions.[15]

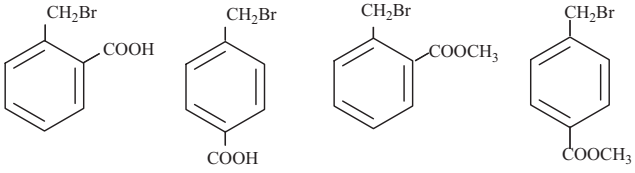
Results

The specific rates of acid production from *o*-nitrobenzyl tosylate (**1**) were obtained in 27 solvents at 45.0°C (Table 1). The solvents consisted of ethanol, methanol, 2,2,2-trifluoroethanol (TFE) and of mixtures of water with these three solvents and with 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), acetone and acetonitrile. Also used in the study was the full range of TFE–ethanol mixtures. The measurements in 80% ethanol (v/v) and 97% TFE (w/w) were also made at three additional temperatures and all four temperatures were used to calculate enthalpies ($\Delta H^{\ddagger}$) and entropies ($\Delta S^{\ddagger}$) of activation (footnotes to Table 1).

The specific rates of solvolyses of *o*-nitrobenzyl bromide were measured at 45.0 or 62.5°C in 80% ethanol, 50% ethanol, 97% TFE, and 70% TFE. Identical determinations with the *para*-isomer were made in 80% ethanol, 50% ethanol, and 70% TFE. These values are given in Table 2. In 97% TFE, the rates for the *para*-isomer were too low for accurate measurement.

Discussion

We have recently reported our studies concerning the utility of eqn (3) in investigations of the reaction mechanisms for the solvolyses of two *ortho*-substituted benzyl bromides, which were known to have the possibility of intramolecular nucleophilic attack at the α–carbon. The substrates used in these investigations were *o*-carboxybenzyl bromide (**3**),[16] *p*-carboxybenzyl bromide (**4**),[16] *o*-carbomethoxybenzyl bromide (**5**),[17] and *p*-carbomethoxybenzyl bromide (**6**).[17]



3 **4** **5** **6**

For the *para*-isomer **4**, an acceptable correlation, using eqn (3) correlation coefficient (R) of 0.973, was obtained[16] over the full range of solvents, with an l value of 1.24 ± 0.09 and an m value of 0.59 ± 0.05. These values are consistent with a bimolecular process with appreciable nucleophilic participation by the solvent. The products were those of direct displacement of bromide by the hydroxylic components of the

Table 1 Specific rates of solvolysis of *o*-nitrobenzyl *p*-toluenesulfonate (k^0) at 45.0°C and a comparison with the corresponding values for the *p*-isomer (k^p), plus N_T and Y_{OTs} values for the solvents, and estimated percentages of overall reaction proceeding by the intramolecular pathway

Solvent[a]	$10^5 k^o/s^{-1}$	$k^o/k^{p\,b}$	N_T[c]	Y_{OTs}[d]	%Intra[e]
100% EtOH	0.980 ± 0.008	0.54	0.37	–1.95	26
90% EtOH	2.40 ± 0.03	0.50	0.16	–0.77	22
80% EtOH	3.74 ± 0.10[f]	0.51	0.00	0.00	23
70% EtOH	5.04 ± 0.02	0.50	–0.20	0.47	23
50% EtOH	10.0 ± 0.1	0.55	–0.58	1.29	19
100% MeOH	2.78 ± 0.05	0.66	0.17	–0.92	17
90% MeOH	4.96 ± 0.03		–0.01	–0.05	17
80% MeOH	7.99 ± 0.08	0.63	–0.06	0.47	14
60% MeOH	16.4 ± 0.1	0.61	–0.54	1.52	14
50% MeOH	23.6 ± 0.2	0.60	–0.75	2.00	13
80% Acetone	0.398 ± 0.003	0.51	–0.37	–0.94	(119)
60% Acetone	1.66 ± 0.03	0.52	–0.52	0.66	78
50% Acetone	3.35 ± 0.08	0.53	–0.70	1.26	56
50% CH_3CN	3.00 ± 0.18[g]	0.65	(–1.06)[h]	1.20	61
100% TFE	3.29 ± 0.06		–3.93	1.77	79
97% TFE	2.87 ± 0.08[i]	33.0[k]	–3.30	1.83	95
90% TFE	2.63 ± 0.04	10.5[k]	–2.55	1.90	108
70% TFE	3.76 ± 0.06	2.8[k]	–1.98	2.00	80
50% TFE	5.07 ± 0.07	1.2[k]	–1.73	2.14	65
97% HFIP	8.32 ± 0.07		–5.26	3.61	100
90% HFIP	4.51 ± 0.07		–3.84	2.90	(118)
70% HFIP	3.82 ± 0.05		–2.94	2.40	102
50% HFIP	4.08 ± 0.08		–2.49	2.26	87
80T–20E[l]	1.93 ± 0.06	3.74	–1.76	0.98	82
60T–40E[l]	1.42 ± 0.09	1.36	–0.94	0.21	69
40T–60E[l]	1.22 ± 0.05	0.81	–0.34	–0.44	53
20T–80E[l]	1.14 ± 0.02	0.57	0.08	–1.18	36

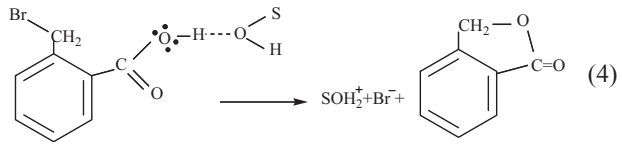
[a]Mixed at 25.0°C on a volume–volume basis, except for TFE–H_2O and HFIP–H_2O mixtures, which are on a weight-weight basis. [b]The k^P values are from ref 7. [c]Values from ref 11. [d]Values from ref 12. [e] Based on estimated $\log k^{intra}$ values, calculated as 0.274 N_T–5.068 (see discussion section). [f]Also values of 1.15 ± 0.01 at 35.1°C, 11.6 ± 0.2 at 58.1°C, and 17.3 ± 0.2 at 62.5°C; activation parameters (based on the four temperatures) of 19.4 ± 0.8 kcal mol^{-1} for $\Delta H^{\ddagger}_{318.2}$ and -17.9 ± 2.6 cal $mol^{-1}K^{-1}$ for $\Delta S^{\ddagger}_{318.2}$. [g]Also a value of 3.87 ± 0.06 at 47.5°C (ref. 5 gives this $10^5 k^0$ value as 3.63 s^{-1}). [h]$N_T\Delta$ value, based on solvolyses of the *S*-methylthiophenium ion (ref 11b). [i]Also values of 0.921 ± 0.031 at 35.1°C, 10.3 ± 0.1 at 58.1°C, and 15.4 ± 0.2 at 62.5°C; activation parameters (based on four temperatures) of 20.4 ± 0.3 kcal mol^{-1} for $\Delta H^{\ddagger}_{318.2}$ and -15.3 ± 1.1 cal $mol^{-1}K^{-1}$ for $\Delta S^{\ddagger}_{318.2}$. [j]Using a value of for $10^5 k^P$ of 0.0869, obtained (ref. 7) from values at other temperatures. [k] Using interpolated $10^5 k^P$ values of 0.251 in 90% TFE, 1.33 in 70% TFE, and 4.17 in 50% TFE (estimated from the values at the volume–volume compositions reported in ref. 7). [l]T–E are TFE–ethanol mixtures.

Table 2 Specific rates of solvolysis of *o*- and *p*-nitrobenzyl bromides (k^o and k^p) and k^o/k^p and k_{OTs}/k_{Br} ratios

Solvent	Temp/°C	$10^5 k^o/s^{-1}$	k_{OTs}/k_{Br}[a]	$10^5 k^P/s^{-1}$	k_{OTs}/k_{Br}[a]	k^o/k^P
80% EtOH	45.0	0.304 ± 0.004	12.3	0.323 ± 0.009	22.7	0.94
80% EtOH	62.5	1.74 ± 0.02	9.9	1.83 ± 0.02		0.95
50% EtOH	45.0	0.813 ± 0.018	12.3	0.891 ± 0.009	20.5	0.91
97% TFE	62.5	0.508 ± 0.005	30.3	[b]		
70% TFE	45.0	0.154 ± 0.003	24.4	0.057 ± 0.002	15.9	2.68

[a]Ratio of the specific rates of solvolyses with tosylate or bromide as the leaving group (tosylate values from Table 1). [b] Very slow reaction.

solvent. For the corresponding *ortho*-isomer **3**, the products in ethanol and aqueous ethanol were primarily (>90%) the phthalide,[16] presumably formed by intramolecular nucleophilic attack by the carboxyl group. Despite the formation of the ring-closed product, application of eqn (3) showed an appreciable dependence on the solvent nucleophilicity value but with a rather inferior correlation (R = 0.933). The l value was 0.90 ± 0.14 and the m value was 0.49 ± 0.10. This combination of observations is best rationalised by invoking general-base catalysis by the solvent to the intramolecular substitution process, with the basicity of the solvent being only approximately related to its nucleophilicity [eqn (4)].



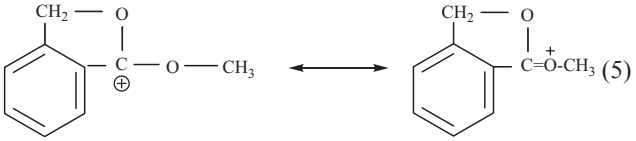
(4)

The *ortho*-isomer **3** reacted considerably faster than the *para*-isomer **4**: by a factor of 59 in 80% ethanol and 157 in 70% TFE (both values at 45°).

If the pathway of eqn (4) is correct, then markedly different behaviour is to be expected for **5,** which has the acidic hydrogen of the carboxylic acid replaced by a methyl group. In contrast, the corresponding *para*-isomer **6** should show solvolytic behaviour not appreciably altered from that observed for **4**. These predictions are borne out in practice.[17] All of the solvolyses of **6** proceed with very similar rates to the corresponding solvolyses of **4**. For the 16 solvents for which values are available under identical conditions, the ratio for the specific rates of solvolyses of **6** relative to **4** varies from 0.8 to 1.7. As one would expect from this observation, the l value of 1.17 and the m value of 0.57 are also very similar to those for **4**.

For solvolyses in solvents without any fluoroalcohol content, a good linear free energy relationship (LFER) was given between the specific rates of solvolyses of **5** and **6** with a slope of 1.00, intercept of 0.05 and correlation coefficient (r) of 0.994. Of especial interest was the observation that placing the specific rates in TFE-containing solvents on the LFER plot, showed appreciable positive deviations for the added data points, consistent with a superimposed intramolecular reaction pathway. In a separate consideration of the solvolyses of **5** in TFE-containing solvents, a good correlation was obtained, after deduction of the predicted intermolecular component, for six solvents using the simple (original[18]) Grunwald–Winstein equation [eqn (3) without the lN_T term]. The slope of a plot of log k against Y_{Br} was 0.24 ± 0.02 (correlation coefficient of 0.999). For reaction of **5** in 100% ethanol about 11% of the ring-closed phthalide was observed, and this percentage rose to 43% in 50% ethanol. The *ortho*/*para* rate ratio was remarkably constant at 1.8 to 2.5 in mixtures of water with ethanol, methanol, and acetone. It rose with increasing TFE content, reaching a value of 69 in 90% TFE.[17]

The intramolecular participation by an *ortho*-nitro group [eqn (2)] will have characteristics similar to those for a carboalkoxy (or carboaroxy[3]) group, where an intermediate as in eqn (5) (formulated for the methyl ester) will be expected.[1] In the recently reported[17] study this then transfers the methyl group so as to give the observed[1,17] phthalide.



(5)

Accordingly, the kinetic behaviour of **1** should be closer to that observed for solvolyses of **5** than that observed for solvolyses of **3**.

While an *ortho*-nitro group was found to function efficiently in the solvolyses of *o*-nitrobenzhydryl bromide, with *ortho*/*para* ratios in the 100–25,000 range, it was found[2] to be much less effective in the solvolyses of **1**, with the *ortho*-isomer reacting in 90% acetone slightly slower than the *para*-isomer, the ratio of 0.88 being identical to that previously observed[17] in 50% acetone for the bromides. It was concluded[2] that the study was "not definitive" as regards nucleophilic participation by the *ortho*-nitro group in the solvolyses of **1** in aqueous acetone. In a subsequent study,[3] it was suggested that participation by an *ortho*-subsituent will be promoted by use of a solvent "less favourably constituted to provide for nucleophilic solvation of carbon at the reaction centre." This statement also provides an early formulation of the concept of stabilisation of developing charge on the α–carbon by nucleophilic solvation. The use of solvents with an appreciable fluoroalcohol content will satisfy the proposed[3] requirement, since the N_T values will be appreciably negative. Indeed the use of these solvents as low nucleophilicity and high ionising power solvents is well established.[11,19,20] The present kinetic studies are carried out with a wide range of solvent type, including solvents rich in TFE and HFIP.

A previous correlation,[14] using eqn (3) of the specific rates of solvolysis of **2** at 45.0°C in 34 solvents, led to a good correlation (R = 0.987) over the full range of solvents with an l value of 1.04 and an m value of 0.65, typical values for an S_N2 process. The present study of the specific rates of solvolysis of **1** shows, as predicted above, behaviour similar to that of **5**. An LFER plot of log(k/k_0) values for **1** (using k values from Table 1) against log(k/k_0) values for **2** (k values from the literature[13]) shows an excellent linear correlation (r = 0.995) in ethanol, methanol, and mixtures of water with ethanol, methanol, acetonitrile, and acetone (Fig. 1); the slope of the plot (m value) is 1.03 ± 0.03 and the intercept is 0.05 ± 0.02 [eqn (6)]. Consistent with this behaviour, for these solvents, the ratio of the specific rates of solvolyses (k^o/k^p) varies only slightly, with a range of 0.50 to 0.66. An earlier value of 0.88 in 90% acetone at 32.5°C has been reported,[2] in the present

$$\log(k/k_o)_{ortho} = 1.03 \log(k/k_o)_{para} + 0.05 \qquad (6)$$

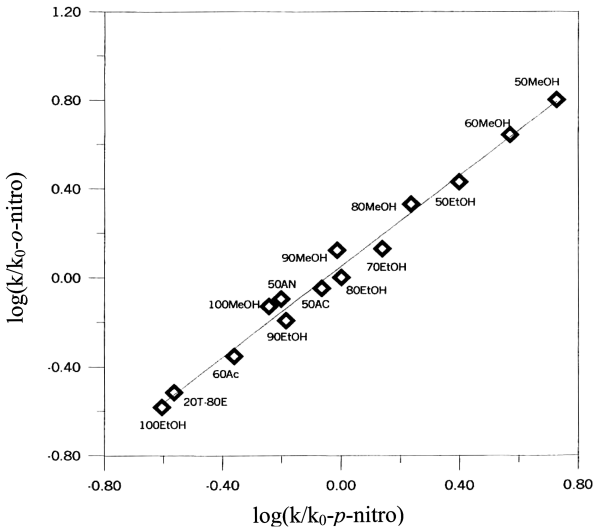


Fig. 1 Plot of log(k/k_o) for solvolyses of *o*-nitrobenzyl tosylate against log(k/k_o) for solvolyses of *p*-nitrobenzyl tosylate at 45.0°C for solvolyses in solvents not containing a fluoroalcohol component.

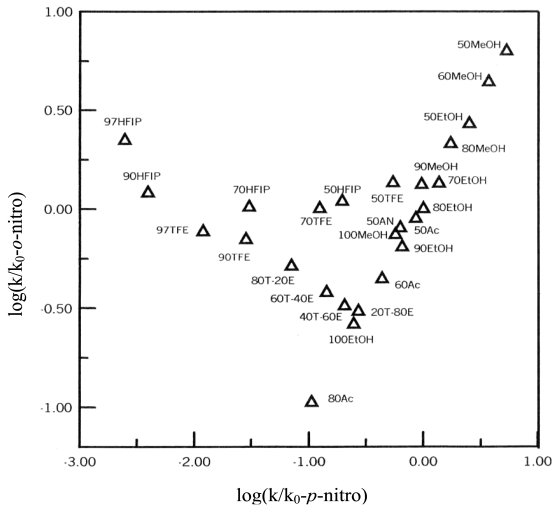


Fig 2 Plot of log(k/k_o) for solvolyses of *o*-nitrobenzyl tosylate against log(k/k_o) for solvolyses of *p*-nitrobenzyl tosylate at 45.0°C for all the studied solvents.

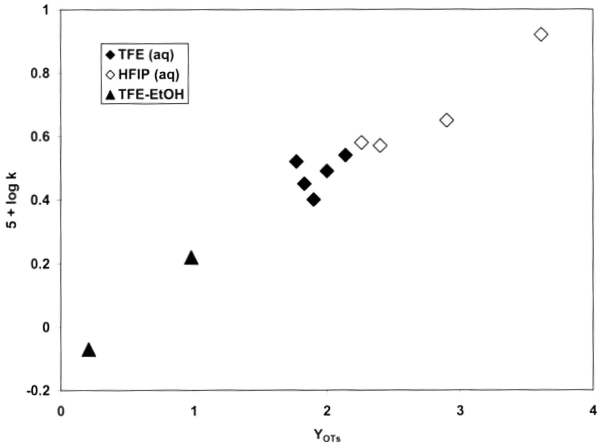


Fig 3 Plot of (5 + log *k*) against Y_{OTs} values for the intramolecular component to the reaction of *o*-nitrobenzyl tosylate.

study only acetone contents of 80% or less were studied. The k^o/k^P ratio is higher for TFE–H_2O solvents, reaching a value of 33 for 97% TFE. Accordingly, the fluoroalcohol-containing solvents lie above the plot shown in Fig. 1, as is demonstrated in Fig. 2. In Fig. 2 the specific rates for *p*-nitrobenzyl tosylate solvolysis in HFIP–H_2O mixtures are estimated values, obtained using values[14] for *l* of 1.04, for *m* of 0.65 and for *c* of 0.00 together with a value for k_o of 7.32×10^{-5} s^{-1} within eqn (3).

The deviations from the plot can be taken as a measure of the extent of an additional mechanism, presumably the intramolecular participation mechanism of eqn (2). With 90% or more fluoroalcohol content, over 95% of the reaction follows the intramolecular pathway. Those solvents with in excess of 60% of the overall reaction proceeding by the intramolecular pathway are listed in Table 3. The listed specific rates are treated by the simple and extended Grunwald–Winstein equations [eqn (3) without or with the lN_T term]. Using uncorrected values, designated as k^o (from Table 1), a plot of the logarithm of the specific rate value against Y_{OTs} leads to a slope (*m* value) of 0.22 ± 0.02, *c* value of –4.90 ± 0.05, *r* value of 0.954, and F-test value of 92 with the one-term equation and 0.03 ± 0.03 for *l*, 0.25 ± 0.04 for *m*, –4.88 ± 0.05 for *c*, 0.960 for *R*, and 47 for the *F*-test value with the two-term equation.

As one would anticipate, the correlations are considerably improved when the estimated values for the intramolecular component (k_{intra}), after subtraction of the S_N2 component, are used in the correlation. With the one-term equation, values are obtained of 0.27 ± 0.02 for *m*, –5.07 ± 0.04 for *c*, 0.980 for *r*, and 213 for the F-test value (Figure 3). There is essentially no improvement to the correlation on application of the two-term equation, with values of –0.02 ± 0.02 for *l*, 0.25 ± 0.03 for *m*, –5.08 ± 0.04 for *c*, 0.981 for *R*, and 104 for the *F*-test value. The data are best described using the one-term equation with k_{intra} values [eqn (7)]. The low *m* value may result from a

$$\log k_{intra} = 0.27 Y_{OTs} - 5.07 \quad (7)$$

combination of internal assistance from the nitro group, which would be expected to lower the value to about 0.5 (the value for methyl *p*-toluenesulfonate solvolyses when eqn (3) is employed[11]), and the influence of the solvent on the nucleophilicity of the nitro group, with increased solvent electrophilicity favouring the expulsion of the leaving group but, also, favouring increased solvation of the nitro group with a reduction in its nucleophilicity. The *c* values can be considered as a measure of the logk_o value (in 80% ethanol) for the intramolecular pathway. It corresponds to a k_o value of 0.85×10^{-5} s^{-1}, 23% of the overall specific rate in this solvent. The k_{intra} values can be calculated for any other compositions of known Y_{OTs} and, for aqueous methanol and ethanol, the percentages of overall reaction proceeding by the intramolecular pathway vary from 13 to 26% (last column of Table 1).

The values calculated for aqueous acetone appear to be unreasonably high. This is especially obvious for the solvolysis

Table 3 Estimated specific rate values, at 45.0°C for the S_N2 component in the solvolyses of *o*-nitrobenzyl tosylate in fluoroalcohol-containing solvents and the accompanying contributions from the intramolecular pathway

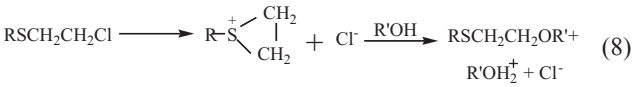
Solvent[a]	$10^5 k^o_{SN2}$[b]/s^{-1}	$\%S_N2$[c]	$10^5 k^o_{intra}$[d]
100% TFE	0.00414	0.13	3.29
97% TFE	0.0221	0.84	2.84
90% TFE	0.131	4.9	2.51
70% TFE	0.689	18.3	3.07
50% TFE	1.57	31.0	3.50
97% HFIP	0.00250	0.03	8.32
90% HFIP	0.0289	0.64	4.48
70% HFIP	0.122	3.2	3.70
50% HFIP	0.294	7.2	3.79
80T–20E	0.270	14.1	1.66
60T–40E	0.568	40.0	0.85

[a]On weight-weight basis, except the TFE–ethanol (T–E) mixtures are on a volume–volume basis. [b]Estimated from the S_N2 values for *p*-nitrobenzyl tosylate using eqn (6). Some of the required *p*-nitrobenzyl tosylate values were by interpolation (TFE–H_2O) or estimated using $\log(k/k_o) = 1.04N_T + 0.65Y_{OTs}$ (ref. 14) [c]Using overall specific rates from Table 1. [d]For each solvent, the k^o_{SN2} values are subtracted from the k^o values of Table 1.

in 80% acetone, where the calculated intramolecular specific rate is 20% higher than the overall experimental value. Also, in Fig. 2, the 80% acetone data point lies considerably below the plot, suggesting that some additional factor may be operating in the aqueous-acetone mixtures. The percentages are also much higher than the aqueous ethanol and aqueous methanol values for 60% and 50% acetone and for 50% CH_3CN. The value of 61% intramolecular rection estimated for 50% CH_3CN is of especial interest because product studies are available[5] at a temperature (47.5°C) which is only slightly higher. The product studies showed a 35% yield of the ring closure/ring opening product, *o*-nitrosobenzaldehyde, and 65% of the direct replacement substitution product, *o*-nitrobenzyl alcohol.

The indicated pathway to the aldehyde is as in eqn (2). However, the ring-closed intermediate could in addition to undergoing proton abstraction from the α–carbon, leading to elimination reaction, also undergo nucleophilic attack at the carbon atom to give a second route to the substitution product. Accordingly, the 35% yield of nitrosoaldehyde must be considered as a *minimum* value for the extent of intramolecular participation, and there is not necessarily any conflict with our estimated value of 61%. The calculations indicate (Table 1) that the intramolecular pathway dominates for solvolyses of **1** in solvents rich in fluoroalcohol and its participation does not fall to below 10% in any of the studied solvents.

The low *m* value observed is reminiscent of the results[21] from correlation analyses of the specific rates of solvolyses of mustard chlorohydrin[22,23] [eqn (8)] and related compounds.[23,24]



(8)

These reactions also involve intramolecular nucleophilic participation and the analyses [eqn (3)] of seven substrates of the general type indicated showed low to negligible *l* values accompanied by *m* values in the range of 0.33 to 0.47.[21] The observation of a low *m* value associated with a low or negligible *l* value is often rationalised in terms of an early transition state. Since the reaction pathway involves intramolecular nucleophilic attack, it should lead to the rather low *m* values that would be predicted, based on S_N2 solvolyses, for a rate-determining nucleophilic attack. These analyses could also be influenced by increased solvent electrophilicity leading to a reduction in the nucleophilicity of the internal nucleophile.

Another measure of the extent of bond-breaking to the leaving group is the k_{OTs}/k_{Br} ratio.[15,25] This is the ratio of the relevant rate coefficients when the only variant is either tosylate or bromide as the leaving group. In Table 2, specific rates are reported for the solvolyses of *o*- and *p*-nitrobenzyl bromides in aqueous ethanol and aqueous-TFE solvents. For two aqueous-ethanol compositions the k^o/k^P specific rate ratio of 0.93 ± 0.02 was almost identical to a value for 0.88 in 50% acetone at 60°C[1,8] and somewhat higher than the corresponding value (Table 1), of 0.53 ± 0.02 for solvolyses of **1**. In 70% TFE, the value rose to 2.7, essentially identical to the value of 2.8 obtained for the solvolyses of **1**.

For solvolyses of *o*-nitrobenzyl derivatives, the k_{OTs}/k_{Br} ratios (Table 2) were in the range of 10 to 12 in aqueous ethanol and somewhat higher, at 24–30, in aqueous TFE. For solvolyses of the corresponding *para*-derivatives, the ratios in aqueous ethanol were larger (20-30) and the ratio in 70% TFE was somewhat lower, at 16. The values in aqueous TFE for solvolyses of the *ortho*-derivatives are, despite the suggestion that they react primarily with intramolecular participation, not appreciably different to the values in aqueous ethanol or to corresponding values for the solvolyses of **2**, instances where solvent attack either dominates or is the exclusive pathway. This is not surprising because k_{OTs}/k_{Br} ratios (in the absence of steric crowding[26]) are usually taken to reflect the charge development on the leaving group, which in turn is closely related to the extent of bond breaking. The attack by solvent or by internal nucleophile will involve similar extents of bond fission to the nucleofuge at the transition state.

The activation parameters have been determined for both **1** and **2** in 80% ethanol and 97% TFE (Table 1). In 80% ethanol, consistent with a bimolecular solvolysis dominating for both substrates, the values are similar. For **1**, the values are 19.4 kcal mol^{-1} for $\Delta H^{\ddagger}$ and –17.9 cal $mol^{-1}K^{-1}$ for $\Delta S^{\ddagger}$ and, for **2**, the respective values are 18.2 kcal mol^{-1} and –20.4 cal $mol^{-1}K^{-1}$. In 97% TFE, the values for **1** are 20.4 kcal mol^{-1} and –15.3 cal $mol^{-1}K^{-1}$, and these values are quite different, especially as regards the $\Delta S^{\ddagger}$ value, to those for **2** of 18.0 kcal mol^{-1} and –29.8 cal $mol^{-1}K^{-1}$. The much higher (less negative) entropy of activation for **1** in 97% TFE is consistent[27] with the proposed change from a bimolecular pathway for **2** to a unimolecular pathway for **1**.

Conclusions

The variation of the specific rates of solvolysis of *o*-nitrobenzyl tosylate (**1**) with solvent composition in mixtures of water with ethanol, methanol, acetonitrile, and acetone closely parallels that for solvolyses of *p*-nitrobenzyl tosylate (**2**). In extending to fluoroalcohol-containing solvents, it has previously been shown[14] that the behaviour of **2** can be correlated over a wide range of solvents using the Grunwald–Winstein equation [eqn (3)], with *l* and *m* values consistent with an S_N2 pathway. However, the specific rates of solvolyses of **1** turn upward, consistent with the incursion of an intramolecular pathway [eqn (2)]. In solvents rich in fluoroalcohol, essentially all of the reaction of **1** follows the intramolecular pathway.

Analysis of the specific rates for intramolecular reaction of **1** in fluoroalcohol-containing solvents by use of the extended Grunwald–Winstein equation shows a negligible dependence on solvent nucleophilicity and the data are best analysed using the simple (original) equation [eqn (3) without the $l\,N_T$ term]. The dependence on solvent ionising power is also low (m = 0.27). Extrapolation to other solvents, using eqn (7), indicates an appreciable contribution (>13%) by the intramolecular pathway across the full range of solvents.

The observation[5] of 35% *o*-nitrosobenzaldehyde [eqn (2)] from solvolysis in 50% acetonitrile at 47.5°C is at a value lower that that estimated in this study (61%) for intramolecular reaction at 45.0°C. This could be due to the approximate nature of the extrapolation or it could be, at least in part, a consequence of substitution (to give the alcohol) accompanying elimination (to give the aldehyde) in the ring-opening reaction of the intermediate formed by the intramolecular attack..

The *m* value of 0.27 is unusually low, especially for a reaction without any appreciable dependence on solvent nucleophilicity. The low value probably results from an inverse relationship between the nucleophilicity of the nitro group in a given solvent and the hydrogen-bonding ability of the solvent, with the latter property also being an important component of the scale of solvent ionising power. The net result of an increase in solvent ionising power would be a balance between improved leaving–group ability and decreased nucleophilicity of the internal nucleophile. Low *m* values were also observed[21] in the correlations of the

specific rates of ring-closure reactions of mustard compounds ($RSCH_2CH_2Cl$) and related substrates.

Studies of the corresponding bromides of **1** and **2** led to k_{OTs}/k_{Br} ratios of 10–30. These are within the range of values for a substitution with rate-determining nucleophilic participation. The values are not informative as to whether this participation is intermolecular or intramolecular. Activation parameters were determined for **1** and **2** in 80% ethanol and 97% TFE. The entropies of activation were similar in 80% ethanol (reactions of both **1** and **2** predominantly bimolecular) but, in 97% TFE, the value for **1** is considerably less negative than for **2**, consistent with the proposed unimolecular and bimolecular pathways.

Experimental

Commercially available *o*-nitrobenzyl bromide (purity 98%) and *p*-nitrobenzyl bromide (purity 99%) were used as received. The *o*-nitrobenzyl *p*-toluenesulfonate (**1**) was prepared as previously described,[2,28] except that, after neutralisation of the reaction mixture with sulfuric acid, the aqueous solution was extracted twice with 50 ml portions of diethyl ether. The combined ether layers were washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure and the product was recrystallised from diethyl ether: m.p. 90–94° (lit.[2] 80–90 dec). Anal. Cald. for $C_{14}H_{13}NO_5S$: C,54·71; H,4·21; N,4·56. Found: C,54·9; H,4·05; N,4·4. Elemental analyses were carried out using a PerkinElmer 2400, Series 2 CHNS/O Analyzer.

The determinations of the specific rates of solvolysis and the purifications of the solvents were as previously described.[11a,29] The regression analyses were carried out using commercially available statistical packages.

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