Reactivity–Selectivity Relationship and Kinetic Solvent Isotope Effects in Nucleophilic Substitution Reactions

Ikchoon Lee, Han Joong Koh, Young Sook Park and Hai Whang Lee
Department of Chemistry, Inha University, Inchon, 402-751, Korea

Selectivity plots, $\log(k_{X1}/k_{X2})$ *vs.* σ_Y, have been obtained for various nucleophilic substitution reactions: (i) with anilines (N) in methanol (S), k_N/k_S, using literature data for $YC_6H_4CH_2Cl$, YC_6H_4COCl, $YC_6H_4SO_2Cl$, $YC_6H_4COCH_2Br$, $YC_6H_4CH(CH_3)Cl$ and $YC_6H_4CH[C(CH_3)_3]OSO_2C_6H_4NO_2$; and (ii) with kinetic solvent isotope effects (KSIE) in water and methanol, k_{SOH}/k_{SOD}, determined in this work for the same compounds (except for the latter two). The two selectivity plots are shown to be equivalent in applying mechanistic criteria based on four reactivity–selectivity regions identified by the slopes of the selectivity plots, $\Delta\rho_Y$. Straightforward applications were possible in most cases except for the aminolysis of phenacyl bromides and 1-phenylethyl chlorides. For these two, detailed analyses of kinetic results were required, in addition to the reactivity–selectivity considerations, before deciding the reaction mechanism.

Variation of selectivity with substituent has been used in several different forms in the mechanistic interpretation of kinetic data for nucleophilic substitution reactions, eqn. (1), where normally

$$\log(k_{X^1}/k_{X^2}) = \Delta\rho_Y \times \sigma_Y \qquad (1)$$

a stronger nucleophile is assigned to X^1 (k_{X^1}/k_{X^2}) and X^2 is used as a standard nucleophile for comparison. The $\Delta\rho_Y$ value can be considered as a difference in the slopes of the Hammett plots for reactions of substituted (σ_Y) substrates with two different nucleophiles, X^1 and X^2. For example, in the constant selectivity relationship reported by Ritchie,[1] the relative nucleophilicity of a nucleophile, X^1 with water (X^2) is constant (N^+), which is independent of the nature of carbocation (σ_Y), so that $\Delta\rho_Y$ is zero, region I in Fig. 1. Jencks *et al.*,[2] used azide, N_3^-, as X^1 and 50:50 trifluoroethanol-water solvent as X^2 and the selectivity values of k_{X^1}/k_{X^2} were determined by product analysis. They found that for ring-substituted 1-phenylethyl derivatives (σ_Y), $\Delta\rho_Y$ changed sign from negative ($\Delta\rho_Y < 0$, region II) to zero ($\Delta\rho_Y = 0$, region III) and then to positive ($\Delta\rho_Y > 0$, region IV) as the substituent in the substrate is varied from that of electron donating to electron withdrawing, $\sigma_{Y^+} < 0 \rightarrow \sigma_{Y^+} > 0$. A similar reactivity–selectivity relationship for carbocations was reported by Rappoport *et al.*,[3] based on an extensive literature survey, in which they adopted water in 80% acetone, as X^2 and logarithms of the solvolysis rate constant (k_{solv}) of substrates as σ_Y in eqn (1). They found at least four different selectivity regions depending on the reactivity of the carbocations, encompassing all four regions reported by Ritchie[1] and Jencks[2] with negative (region II), zero (regions I and III) and positive (region IV) slopes, $\Delta\rho_Y$, in Fig. 1. The four approximately linear parts have been shown to represent: (i) the region in which the most stable carbocations react with X^1 and X^2 in an activation-limited process, but the barrier is mainly due to solvent reorganization; (ii) the region in which the cations are unstable enough to react at the diffusion-controlled rate with strong nucleophile, *e.g.* $X^1 = N_3^-$, but not with the weaker nucleophile water; (iii) the region of limiting S_N1 process; and (iv) the S_N2 region.

Recently we proposed that the sign of slopes of the logarithm of kinetic solvent isotope effect (KSIE = k_{SOH}/k_{SOD}, where S = H or CH_3) *vs.* σ_Y plots, eqn. (2) can be a useful mechanistic tool.[4] This plot in fact represents the difference of two simple Hammett plots, log k_{SOH} *vs.* σ_Y and log k_{SOD} *vs.* σ_Y, with $\Delta\rho_Y = \rho_{SOH} - \rho_{SOD}$. In this work, we report KSIEs for various nucleophilic substitution reactions and show that the slopes, $\Delta\rho_Y$ in eqn. (2), are in fact equivalent to the $\Delta\rho_Y$ in

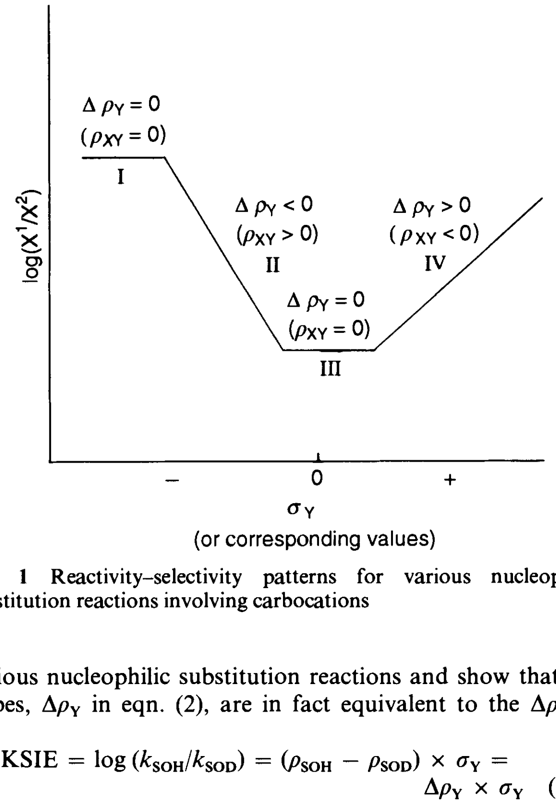


Fig. 1 Reactivity–selectivity patterns for various nucleophilic substitution reactions involving carbocations

$$\log \text{KSIE} = \log(k_{SOH}/k_{SOD}) = (\rho_{SOH} - \rho_{SOD}) \times \sigma_Y = \Delta\rho_Y \times \sigma_Y \qquad (2)$$

eqn. (1) and the sign of the slopes can be similarly interpreted in terms of the four regions in Fig. 1. It has been shown that the sign and magnitude of $\Delta\rho_Y$ in eqn. (2) can be related to that of cross-interaction constants, ρ_{XY}[5] in eqns (3) and (4) where X

$$\log(k_{XY}/k_0) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \qquad (3)$$

$$\rho_{XY} = \frac{\partial^2 \log k_{XY}}{\partial\sigma_X \times \partial\sigma_Y} = \frac{\partial\rho_Y}{\partial\sigma_X} = \frac{\partial\rho_X}{\partial\sigma_Y} \qquad (4)$$

and Y denote the nucleophile and substrate, respectively. It is obvious that eqn (1) [and also eqn. (2)] can be transformed into eqn. (4) by dividing both sides by $\Delta\sigma_X$ ($= \sigma_{X^1} - \sigma_{X^2}$); $\log(k_{X^1}/k_{X^2})$ for a given substituent Y (σ_Y) can be expressed as $\Delta \log k_{XY}$, and hence eqn. (1) becomes

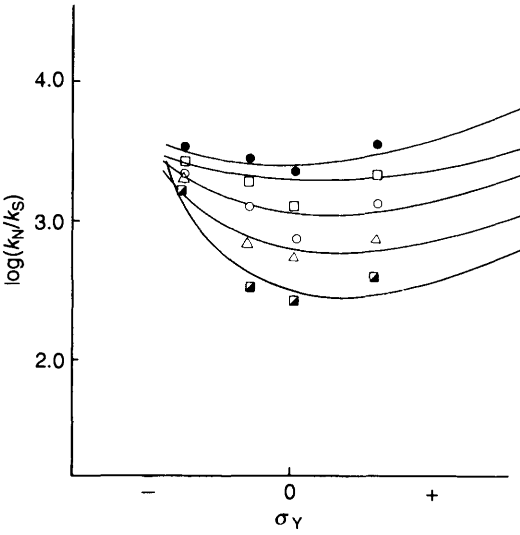


Fig. 2 Plots of log (k_N/k_S) *vs.* σ_Y for the reactions between benzyl chloride and aniline in methanol at 55.1 and 55.0 °C.

$$YC_6H_4CH_2Cl + XC_6H_4NH_2 \xrightarrow[55.1\,^{\circ}C]{CH_3OH} k_N$$

$$YC_6H_4CH_2Cl + CH_3OH \xrightarrow[55.0\,^{\circ}C]{} k_S$$

(●), X = p-CH_3O; (□), X = p-CH_3; (○), X = H; (△), X = p-Cl; (◪), X = m-NO_2.

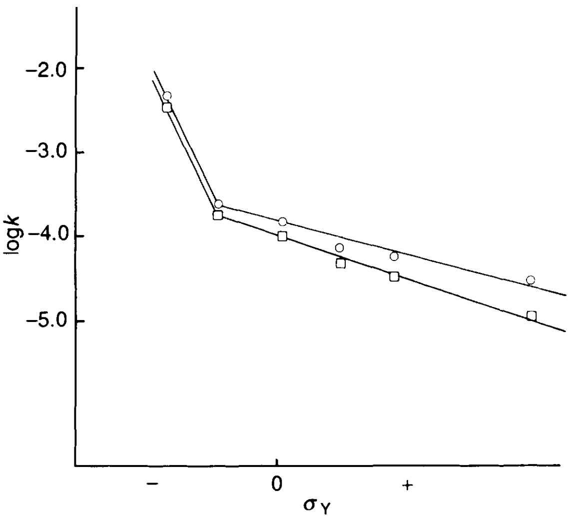


Fig. 3 Hammett ρ_Y plot for the reactions of substituted benzyl chlorides in water at 55.0 °C; (○), H_2O; (□), D_2O

$$\frac{\Delta \log k_{XY}}{\Delta\sigma_Y} = \Delta\rho_Y \quad \rho_{XY} = \frac{\partial\rho_Y}{\partial\sigma_X} \simeq \frac{\Delta\rho_Y}{\Delta\sigma_X}.$$

Since we normally take a stronger nucleophile (more negative or less positive σ_X) for X^1, $\Delta\sigma_X$ is negative so that the sign of ρ_{XY} is opposite to that of $\Delta\rho_Y$, *i.e.*, ρ_{XY} is positive (negative) if $\Delta\rho_Y$ is negative (positive). It has also been shown that the magnitude of ρ_{XY} is proportional to the extent of bond making in the S_N2 transition state (TS).[5] We determined KSIEs for solvolyses of $YC_6H_4CH_2Cl$, YC_6H_4COCl, $YC_6H_4SO_2Cl$ and $YC_6H_4COCH_2Br$ in water and/or in methanol, and the results are discussed together with those of the reactions with aniline. The results for the reactions of 1-phenylethyl chlorides[6] and α-*tert*-butyl benzenesulfonates[7] with anilines and methanol are also included in the discussion, eqn. (5). The selectivities (k_{X^1}/k_{X^2}) are expressed in two different ways using the observed rates: (i) with aniline and methanol; and (ii) with SOH and SOD (S = H or CH_3), for X^1 and X^2 in eqn. (1) respectively.

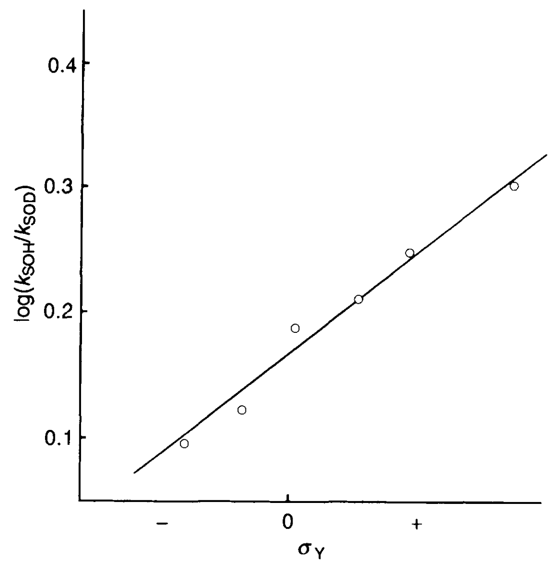


Fig. 4 Plot of log (k_{SOH}/k_{SOD}) *vs.* σ for the solvolyses of substituted benzyl chlorides in water at 55.0 °C

$$\left.\begin{array}{ll} 1 & YC_6H_4CH_2Cl \\ 2 & YC_6H_4COCl \\ 3 & YC_6H_4SO_2Cl \\ 4 & YC_6H_4COCH_2Br \\ 5 & YC_6H_4CH(CH_3)Cl \\ 6 & YC_6H_4CH\,(C(CH_3)_3)OSO_2C_6H_4NO_2\text{-}p \end{array}\right\} + \left\{\begin{array}{l} XC_6H_4NH_2 \\ SOH \longrightarrow (5) \\ SOD \end{array}\right.$$

Results and Discussion

(1) *Reactions of Y-Benzyl Chlorides.*—(*a*) *With X-anilines* (N) *in methanol* (S).[8] The simple Hammett plots of log k_N *vs.* σ_Y are linear with negative slopes, $\rho_Y < 0$ ($\rho_Y = -0.57 \sim -0.59$ for X = p-CH_3O ~ p-Cl), and the rate ratios, k_N/k_S, at 55 °C range from 25 ~ 59. The selectivity plots, log(k_N/k_S) *vs.* σ_Y, are shown in Fig. 2. We note that parallel lines with positive slopes ($\Delta\rho_Y > 0$), corresponding to reactions belonging to region IV in Fig. 1, are obtained with Y = electron-withdrawing substituents indicating that S_N2 mechanism is operative. Since anilines are stronger nucleophiles than methanol (*i.e.*, σ_X is more negative or less positive) $\Delta\sigma_X$ (= $\sigma_{X(N)} - \sigma_{X(S)}$) should be negative and hence ρ_{XY} [eqn. (4)] is negative. However the two electron-donating substituents (Y = p-CH_3O and p-CH_3) are seen to deviate from the straight line plots positively. Especially for Y = p-CH_3O, the differences in selectivity between different nucleophiles (X = p-CH_3O ~ m-NO_2) become very small; this could be due to predominance of S_N1 channel (regions II ~ III in Fig. 1) or alternatively due to increased S_N1 character for this compound. For the two electron-donating substituents, Y = p-CH_3O and p-CH_3, $\Delta\rho_Y$ is near zero or negative so that $\rho_{XY} \cong 0$ or $\rho_{XY} > 0$ [eqn. (4) and Fig. 1]. The regions I ~ IV in Fig. 1 are originally assigned based on product selectivities, not with the observed rate constant ratios. However, discrepancies between the two selectivities or ambiguities arise only in the case of region II since for regions I and IV, the rate determining step coincides with the product forming step and for region III the rate ratios provide clear-cut criteria (*vide infra*). Therefore we must be cautious in interpreting the negative slopes of eqns. (1) and (2) using selectivities based on rate constants.

Table 1 Rate constants and kinetic solvent isotope effects for solvolyses of various substituted benzyl chlorides ($YC_6H_4CH_2Cl$) in water at 55.0 °C

Y	k_{H_2O}/s	k_{D_2O}/s	k_{H_2O}/k_{D_2O}
p-CH_3O	$(33.9 \pm 0.4^a) \times 10^{-4}$	$(29.5 \pm 0.4) \times 10^{-4}$	1.15 ± 0.02^b
p-CH_3	$(2.72 \pm 0.02) \times 10^{-4}$	$(2.29 \pm 0.08) \times 10^{-4}$	1.19 ± 0.04
H	$(1.94 \pm 0.02) \times 10^{-4}$	$(1.36 \pm 0.01) \times 10^{-4}$	1.43 ± 0.02
p-Cl	$(8.45 \pm 0.02) \times 10^{-5}$	$(5.32 \pm 0.01) \times 10^{-5}$	1.59 ± 0.03
m-Cl	$(6.92 \pm 0.05) \times 10^{-5}$	$(4.07 \pm 0.02) \times 10^{-5}$	1.70 ± 0.01
p-NO_2	$(2.84 \pm 0.02) \times 10^{-5}$	$(1.37 \pm 0.01) \times 10^{-5}$	2.07 ± 0.02

[a] Standard deviation from more than triplicate determinations. [b] Standard error; $\{= 1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{\frac{1}{2}}\}$.[9]

Table 2 Rate constants and kinetic solvent isotope effects for solvolyses of various substituted benzyl chlorides ($YC_6H_4CH_2Cl$) in methanol at 55.0 °C

Y	k_{CH_3OH}/s	k_{CH_3OD}/s	k_{CH_3OH}/k_{CH_3OD}
p-CH_3O	$(95.1 \pm 0.3^a) \times 10^{-6}$	$(83.2 \pm 0.6) \times 10^{-6}$	1.14 ± 0.01^b
p-CH_3	$(12.1 \pm 0.02) \times 10^{-6}$	$(9.58 \pm 0.30) \times 10^{-6}$	1.26 ± 0.04
H	$(7.40 \pm 0.20) \times 10^{-6}$	$(5.62 \pm 0.30) \times 10^{-6}$	1.32 ± 0.08
p-Cl	$(3.73 \pm 0.11) \times 10^{-6}$	$(2.51 \pm 0.04) \times 10^{-6}$	1.49 ± 0.05
m-Cl	$(2.96 \pm 0.01) \times 10^{-6}$	$(1.75 \pm 0.05) \times 10^{-6}$	1.69 ± 0.05
p-NO_2	$(10.6 \pm 0.12) \times 10^{-7}$	$(5.60 \pm 0.21) \times 10^{-7}$	1.89 ± 0.07

[a] Standard deviation from more than triplicate determinations. [b] Standard error; $\{= 1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{\frac{1}{2}}\}$.[9]

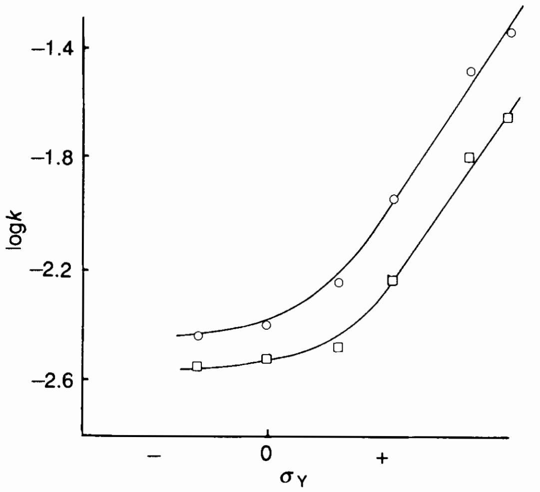


Fig. 5 Hammett ρ_Y plot for the reactions of substituted benzoyl chlorides in methanol at 25.0 °C; (○), CH_3OH; (□), CH_3OD

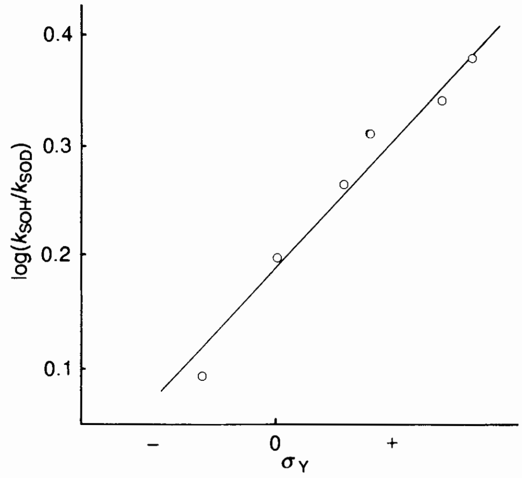


Fig. 6 Plot of $\log(k_{SOH}/k_{SOD})$ *vs.* σ for the solvolyses of substituted benzoyl chlorides in methanol at 25.0 °C

(*b*) *With* SOH *and* SOD (S = H *or* CH_3). The rate data and the kinetic solvent isotope effects, KSIE = k_{SOH}/k_{SOD}, *i.e.*, the selectivities, are summarized in Tables 1 and 2, which are presented graphically in Figs. 3 and 4 for S = H.

We note that the KSIE values are greater than one in all cases. The simple Hammett plots, log k_{SOH} or log k_{SOD} *vs.* σ_Y, in Fig. 3 show two straight lines joined at Y = CH_3 with negative slopes, $\rho_Y < 0$, whereas the selectivity plot, log (k_{SOH}/k_{SOD}) *vs.* σ_Y, in Fig. 4 gives a single straight line with a positive slope, $\Delta\rho_Y > 0$ ($\Delta\rho_Y = +0.25$). The positive slope, corresponding to region IV in Fig. 1, indicates that the hydrolysis proceeds by an S_N2 channel. Methanolysis (S = CH_3), exhibits exactly the same trends as those for the hydrolysis (S = H) in Figs. 3 and 4 with a slightly lower positive slope, $\Delta\rho_Y = +0.21$. Since SOH is a stronger nucleophile than SOD, which is tantamount to a more negative or less positive σ_X for SOH than SOD, the hypothetical $\Delta\sigma_X$ ($= \sigma_{X(SOH)} - \delta_{X(SOD)}$) is negative,[4] thus ρ_{XY} [eqn. (4)] should be negative since $\Delta\rho_Y > 0$ and $\Delta\sigma_X < 0$, as shown for region IV in Fig. 1.

In summary, both aminolyses and solvolyses, of benzyl chlorides are characterized by negative ρ_Y but positive $\Delta\rho_Y$ values ($\rho_{XY} < 0$), and can be classified into the nucleophilic substitution reactions belonging to region IV in Fig. 1, *i.e.*, S_N2 type reactions (with possibility of S_N1 mechanism for aminolysis with X = electron-donating substituents): $k_{SOH}/k_{SOD} > 0$, $\rho_Y < 0$, $\Delta\rho_Y > 0$, $\rho_{XY} < 0$ and belongs to region IV.

(2) *Reactions of* Y-*Benzoyl Chlorides*.—(*a*) *With* X-*anilines* (N) *in methanol* (S).[10] The simple Hammett plots of log k_N *vs.* σ_Y are linear with positive slopes, $\rho_Y > 0$ ($\rho_Y = +2.36 \sim 1.74$ for X = p-CH_3 ~ m-NO_2), and the rate ratios, k_N/k_S, at 35 °C range from 49 ~ 119. The selectivity plots are linear and nearly parallel with positive slopes ($\Delta\rho_Y > 0$) of 2.0 ~ 1.4 for X = p-CH_3 ~ m-NO_2; this means that these reactions have negative ρ_{XY} and belong to region IV, proceeding by the S_N2 mechanism.

(*b*) *With* SOH *and* SOD (S = CH_3). The rates and KSIEs are summarized in Table 3, which are presented in Figs. 5 and 6. The KSIE values are greater than one in all cases. Examination of Fig. 5 reveals that the simple Hammett plots give two straight line parts joined at Y = p-Cl with positive slopes, $\rho_Y > 0$. In contrast, the selectivity plot in Fig. 6 is a single straight line with a positive slope, $\Delta\rho_Y = +0.28$, *i.e.*, $\rho_{XY} < 0$, indicating that the methanolyses of benzoyl chlorides belong also to region

Table 3 Rate constants and kinetic solvent isotope effects for solvolyses of various substituted benzoyl chlorides (YC_6H_4COCl) in methanol at 25.0 °C

Y	k_{CH_3OH}/s	k_{CH_3OD}/s	k_{CH_3OH}/k_{CH_3OD}
p-CH_3	$(3.63 \pm 0.06^a) \times 10^{-3}$	$(3.05 \pm 0.01) \times 10^{-3}$	1.19 ± 0.04^b
H	$(4.33 \pm 0.05) \times 10^{-3}$	$(2.80 \pm 0.05) \times 10^{-3}$	1.55 ± 0.03
p-Cl	$(6.04 \pm 0.02) \times 10^{-3}$	$(3.47 \pm 0.01) \times 10^{-3}$	1.74 ± 0.03
m-Cl	$(11.9 \pm 0.01) \times 10^{-3}$	$(5.81 \pm 0.05) \times 10^{-3}$	2.05 ± 0.02
p-CN	$(30.5 \pm 0.30) \times 10^{-3}$	$(14.6 \pm 0.05) \times 10^{-3}$	2.09 ± 0.02
p-NO_2	$(44.1 \pm 0.40) \times 10^{-3}$	$(19.3 \pm 0.05) \times 10^{-3}$	2.29 ± 0.02

[a] Standard deviation from more than triplicate determinations. [b] Standard error; $\{= 1/k_D[(\triangle k_H)^2 + (k_H/k_D)^2 \times (\triangle k_D{}^2]^{\frac{1}{2}}\}$.[9]

IV *i.e.*, proceed by the S_N2 process. However, there is a possibility of addition–elimination mechanism (S_AN) involving a tetrahedral intermediate with the rate-limiting addition step. If this mechanism applies, the degree of bond formation will be greater than that for S_N2 and we expect the selectivity values to be somewhat greater. The $\Delta\rho_Y = +0.28$, however, does not differ significantly from other values (see Table 7).

In summary, the reactions of benzoyl chlorides are characterized by the KSIE values of greater than one, positive ρ_Y and $\Delta\rho_Y$ (negative ρ_{XY}) values, and can be classified into the S_N reactions in region IV proceeding by S_N2 mechanism: $k_{SOH}/k_{SOD} > 1.0$, $\rho_Y > 0$, $\Delta\rho_Y > 0$, $\rho_{XY} < 0$ and belongs to region IV.

(3) *Reactions of* Y-*Benzenesulfonyl Chlorides.*—(*a*) *With* X-*anilines* (N) *in methanol* (S).[11] The simple Hammett plots of log k_N *vs.* σ_Y are linear with positive slopes, $\rho_Y > 0$ ($\rho_Y = +1.07 \sim 0.57$ for X = p-CH_3 ~ m-NO_2), and the rate ratios, k_N/k_S, at 35 °C range from 27 ~ 91. The selectivity plots are linear with positive slopes ($\Delta\rho_Y > 0$) of $+0.87 \sim +0.25$ for X = p-CH_3 ~ m-NO_2, which indicate again that ρ_{XY} is negative and these reactions belong to region IV proceeding by the S_N2 mechanism.

(*b*) *With* SOH *and* SOD (S = H *or* CH_3). It has been shown that the KSIE values are greater than one in all cases[4] and the simple Hammett plots for Y-benzenesulfonyl chlorides exhibit concave curves for both S = H and S = CH_3.[4] However, the selectivity plots gave good straight lines with positive slopes, $\Delta\rho_Y > 0$ ($\Delta\rho_H = +0.15$ for S = CH_3 and $+0.05$ for S = H at 25 °C) with in turn leads to negative ρ_{XY} values. Thus, the reactions of benzenesulfonyl chlorides, are characterized by $k_{SOH}/k_{SOD} > 1.0$, variation of logk_{SOH} or log k_{SOD} *vs.* σ_Y gives a concave curve, $\Delta\rho_Y > 0$, $\rho_{XY} < 0$ and belongs to region IV proceeding by the S_N2 mechanism.

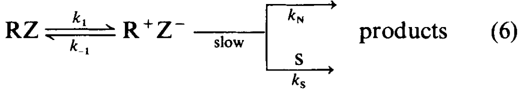
(4) *Reactions of* Y-*phenacyl Bromides.*—(*a*) *With anilines* (N) *in methanol* (S).[12] The simple Hammett plots, logk_N *vs.* σ_Y, are linear with positive slopes, $\rho_Y > 0$ ($\rho_Y = 0.56 \sim 0.63$ for X = p-CH_3O ~ p-Cl), and the rate ratios, k_N(45 °C)/k_S(55 °C), range from 64 ~ 99. The selectivity plots, log(k_N/k_S) *vs.* σ_Y, are linear, and nearly parallel, with negative slopes, $\Delta\rho_Y < 0$ ($\Delta\rho_Y = -0.68 \sim -0.56$ for X = p-CH_3O ~ p-Cl), giving a positive ρ_{XY} ($\rho_{XY} > 0$). This means that the reactions of phenacyl bromides with relatively strong nucleophiles, aniline, belongs to region II in Fig. 1 according to the signs of $\Delta\rho_Y$ [eqn. (1)] and ρ_{XY} [eqn. (4)]. It has often been pointed out that the reactions of $PhCOCH_2Br$ show some unusual features in the application of reactivity–selectivity relationship.[13] One anomaly is that the S_N reactions of $PhCOCH_2Br$ show negative $\Delta\rho_Y$ (positive ρ_{XY}), despite the fact that they exhibit normal S_N2 behaviours in many respects. For many S_N2 type reactions reported, the reaction of phenacyl derivatives with anilines or benzylamines was the only one which had positive ρ_{XY} in contrast to negative ρ_{XY} found for all other S_N2 reactions.[5]

One can speculate that the α-carbonyl group delocalizes electronic charge transferred from a strong nucleophile and stabilizes an addition complex, which proceeds with C_α–Br bond rupture in the rate-limiting step.* This could also be the reason why the interaction between σ_X and σ_Y is so weak *i.e.*, unusually small magnitude of ρ_{XY} ($\rho_{XY} = 0.11$ found for this reaction is much smaller than that, $|\rho_{XY}| \cong 0.7$, for normal S_N2 processes even after allowing for the fall-off of $|\rho_{XY}|$ by half due to an intervening C=O group between the reaction centre, C_α, and the substituent, ρ_Y).

(*b*) *With* SOH *and* SOD (S = H *or* CH_3). The rate constants and KSIEs are summarized in Tables 4 and 5. The KSIE values are all greater than one and the simple Hammett plots gave excellent straight lines with positive slopes, $\rho_Y > 0$. The selectivity plots, log KSIE *vs.* ρ_Y, gave positive values of $\Delta\rho_Y = +0.24$ (for S = H) and $+0.19$ (for S = CH_3) leading to a negative ρ_{XY}. This means that the solvolyses proceed by the normal S_N2 mechanism, *i.e.* belongs to region IV, in contrast to the anomalous behaviour shown by the reactions with strong nucleophiles, aniline, with the opposite signs for $\Delta\rho_Y$ (<0) and ρ_{XY} (>0).

In summary, for the reactions of phenacyl bromides, $\rho_Y > 0$, $\Delta\rho_Y < 0$ and $\rho_{XY} > 0$ for aminolysis, but $\rho_Y > 0$, $\Delta\rho_Y > 0$ and $\rho_{XY} < 0$ with $k_{SOH}/k_{SOD} > 1.0$ for solvolysis. There may be a mechanistic change over from the reaction with a strong nucleophile to that of a weak one.

(5) *Reactions of* 1-(Y-*Phenyl*)*ethyl Chlorides.*—(*a*) *With* X-*aniline* (N) *in methanol* (S).[6] The simple Hammett plots for this reaction log k_N *vs.* σ_{Y^+}, gave two straight line parts joined at $\sigma_{Y^+} \cong 0$ with slopes, ρ_{Y^+}, ranging from $-3.5 \sim -5.5$ for Y = electron-donating substituents, and from $-1.3 \sim -2.5$ for Y = electron-withdrawing substituents, with X = p-CH_3O ~ m-NO_2. The rate ratios, k_N/k_S, had values ranging from 17 ~ 480, and the selectivity plots, log(k_N/k_S) *vs.* σ_{Y^+} gave curves crossing at $\sigma_Y{}^+ \cong -0.2$ as shown in Fig. 7. The slope, $\Delta\rho_{Y^+}$, changes from small negative to very small positive, and hence ρ_{XY} changes sign from positive to negative, for weak nucleophile X = m-NO_2, whereas it is large positive for the relatively strong nucleophiles, X = p-CH_3O ~ p-Cl. It appears that the reaction with m-nitroaniline belongs to region III and others to region IV. However, this reaction had unusually large negative ρ_{XY} (-2.05 for electron-donating and -1.34 for electron-withdrawing Y-substituents) and change of the sign of ρ_X as observed at $\sigma_{Y^+} \cong -0.23$. Other kinetic evidence has led us to conclude that these reactions proceed by an ion-pair mechanism in which the nucleophile attacks the preformed carbocation intermediate (S_N2C^+), eqn. (6) (*vide infra*).



(6)

$$k_{obsd} = Kk_N \quad (7a)$$

$$\text{or} \quad = Kk_S \quad (7b)$$

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* We thank one of the referees for suggesting this possibility.

Table 4 Rate constants and kinetic solvent isotope effects for solvolyses of various substituted phenacyl bromides ($YC_6H_4COCH_2Br$) in water at 55.0 °C

Y	k_{H_2O}/s	k_{D_2O}/s	k_{H_2O}/k_{D_2O}
p-CH_3O	$(8.76 \pm 0.09^a) \times 10^{-6}$	$(7.60 \pm 0.04) \times 10^{-6}$	1.15 ± 0.01^b
p-CH_3	$(1.13 \pm 0.01) \times 10^{-5}$	$(0.890 \pm 0.002) \times 10^{-5}$	1.27 ± 0.01
H	$(2.30 \pm 0.01) \times 10^{-5}$	$(1.58 \pm 0.02) \times 10^{-5}$	1.46 ± 0.02
p-Cl	$(5.28 \pm 0.02) \times 10^{-5}$	$(3.47 \pm 0.03) \times 10^{-5}$	1.52 ± 0.01
p-NO_2	$(33.3 \pm 0.03) \times 10^{-5}$	$(15.8 \pm 0.2) \times 10^{-5}$	2.11 ± 0.03

[a] Standard deviation from more than triplicate determinations. [b] Standard error; $\{= 1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{\frac{1}{2}}\}$.[9]

Table 5 Rate constants and kinetic solvent isotope effects for solvolyses of various substituted phenacyl bromides ($YC_6H_4COCH_2Br$) in methanol at 55.0 °C

Y	k_{CH_3OH}/s	k_{CH_3OD}/s	k_{CH_3OH}/k_{CH_3OD}
p-CH_3O	$(3.37 \pm 0.04^a) \times 10^{-7}$	$(2.67 \pm 0.05) \times 10^{-7}$	1.26 ± 0.03^b
p-CH_3	$(4.15 \pm 0.02) \times 10^{-7}$	$(3.25 \pm 0.03) \times 10^{-7}$	1.28 ± 0.01
H	$(9.12 \pm 0.04) \times 10^{-7}$	$(6.46 \pm 0.06) \times 10^{-7}$	1.41 ± 0.01
p-Cl	$(2.24 \pm 0.02) \times 10^{-6}$	$(1.45 \pm 0.01) \times 10^{-6}$	1.54 ± 0.02
p-NO_2	$(1.67 \pm 0.01) \times 10^{-5}$	$(0.851 \pm 0.01) \times 10^{-5}$	1.96 ± 0.03

[a] Standard deviation from more than triplicate determinations. [b] Standard error; $\{= 1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{\frac{1}{2}}\}$.[9]

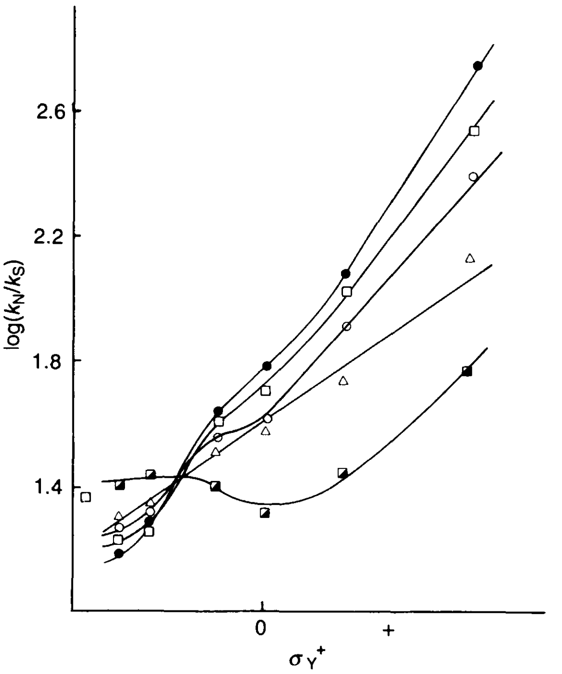


Fig. 7 Plot of $\log(k_N/k_S)$ *vs.* σ_{Y^+} for the reactions between 1-phenylethyl chlorides and anilines in methanol at 65.0 °C.

$$YC_6H_4CH(CH_3)Cl + XC_6H_4NH_2 \xrightarrow{CH_3OH} k_N$$

$$YC_6H_4CH(CH_3)Cl + CH_3OH \longrightarrow k_S$$

(●), X = p-CH_3O; (□), X = p-CH_3; (○), X = H; (△), X = p-Cl; (◩), X = m-NO_2.

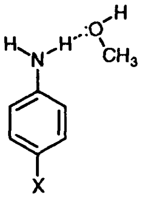
and $$\rho^+_{Y(obsd)} = \rho^+_{eq} + \rho^+_N \qquad (8a)$$

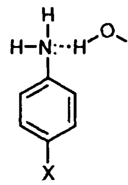
$$\text{or} \quad = \rho^+_{eq} + \rho^+_S \qquad (8b)$$

The ρ^+_{eq} value should be large negative ($\rho^+_{eq} \ll 0$), while ρ^+_N should be small positive ($\rho^+_N > 0$) leading to a moderate negative $\rho^+_{Y(obsd)}$ value. Moreover, the magnitude of $\rho^+_{Y(obsd)}$ should decrease with a stronger nucleophile ($\rho^+_Y = -3.5$ for X = p-CH_3O and -5.5 for X = m-NO_2) and also with an electron-withdrawing Y substituent, (ρ^+_Y values are small negative for Y = electron-withdrawing group), since ρ^+_N becomes large positive with a stronger nucleophile and ρ^+_{eq} becomes small negative with an unstable carbocation of the ion-pair intermediate for Y = electron-withdrawing group, in eqn. (8a).

Furthermore, for this reaction the secondary kinetic isotope effects (SKIE) involving deuteriated aniline nucleophiles, $XC_6H_4ND_2$, were greater than one in all cases. If the reaction were proceeding by a normal S_N2 mechanism, as in the reactions of methyl, ethyl, benzyl derivatives with anilines,[5b] the k_H/k_D values with deuteriated aniline nucleophiles would have been smaller than one, *i.e.*, an inverse secondary kinetic isotope effect would have been observed;[5b] in the normal S_N2 process, the approach of nucleophile, aniline, is expected to hinder N–H(D) stretching and bending vibrations in the TS, leading to frequency increases in the TS with $k_H/k_D < 1.0$.[15,16] The k_H/k_D values of greater than one observed for this reaction, and notably the largest value observed for Y = electron-donating group combined with X = electron-withdrawing group ($k_H/k_D = 1.54$ for Y = p-CH_3 and X = m-NO_2) are consistent with the proposed S_N2C^+ mechanism in which partial N–H bond cleavage *i.e.*, deprotonation, occurs with a general base catalysis by a nearby anion, X^-, or by a methanol molecule. The partial bond cleavage of the N–H(D) bond in the TS will surely cause a normal SKIE of $k_H/k_D > 1.0$. This effect will be greater and hence k_H/k_D (> 1.0) will be larger, the greater is the base catalysis required (with a more delocalized carbocation with Y = electron-donating group), and the weaker is the N–H(D) bond (with the aniline with X = electron-withdrawing group), as evidenced by the observed k_H/k_D values.

One could also argue that the reaction might be a limiting S_N1 (region III), or S_N1 with diffusion limited nucleophilic attack (region II), or desolvation barrier controlled process. However, the following observations lead us to discredit all of these possibilities. (i) The reactions were first order with respect to aniline and overall second order, in contrast to the zero order kinetics required with nucleophile for a limiting S_N1 process. (ii) The ρ_{XY} values are very large negative, instead of $\rho_{XY} = 0$ required for a limiting S_N1 process,[5] and a much smaller negative ρ_{XY} expected for an S_N2 reaction involving desolvation step in which the interaction between N and C_α will be very weak (small $|\rho_{XY}|$) due to long distance.[17a] We note here that from eqn (4), $\rho_{XY} = \partial\rho^+_{Y(obsd)}/\partial\sigma_X = \partial\rho^+_N/\ \partial\sigma_X$ since $\partial\rho^+_{eq}/\partial\sigma_X = 0$ in eqn. (8a). (iii) The selectivities, k_N/k_S, vary over a relatively wide range, 17 ~ 480, so that the nucleophile attack may not be diffusion limited. (iv) For a given aniline nucleophile, the k_N values are dependent on the substrate, and hence the desolvation process cannot be rate limiting. (v) Neither of the two solvation modes, **2** and **3**, leads us to a greater than 1.0 SKIE, $k_H/k_D > 1.0$. In fact these types of


2
H-Type solvation


3
N-Type solvation

hydrogen bonds involving anilines with methanol should be weaker than hydrogen bonds between methanol molecules, since both the solute hydrogen bond acidities and basicities of anilines are in most cases lower than the corresponding values of MeOH[18] precluding the possibility of desolvation barrier control reaction.

Richard *et al.*,[17b] interpreted the negative β_X, *i.e.*, positive ρ_X, obtained for the reaction of amine nucleophiles (XRNH) with 4-$CH_3SArCH(CF_3)^+$ is due to an increase in the strength of the solvent–nucleophile hydrogen bond leading to a decrease in K_d with increasing basicity of the nucleophile in Scheme 1, where $K_d = k_d/k_{-d}$, $k_{obsd} = K_dk_N$ and $\rho^X_{obsd} = \rho^X_d + \rho^X_N$.

$$\begin{array}{l} {}^+CH(CF_3)C_6H_4Y + XRNH{\cdot}HOS \underset{k_{-d}}{\overset{k_d}{\rightleftharpoons}} \\ (Y = 4\text{-}CH_3S) \\ \qquad\qquad XRNH{\cdot}{}^+CH(CF_3)C_6H_4Y + HOS \\ \qquad\qquad\qquad\qquad \downarrow k_N \\ \qquad\qquad XRN\text{–}CH(CF_3)C_6H_4Y + H_2O^+S \end{array}$$

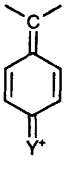
Scheme 1

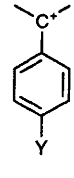
However, the possibility of this type of mechanism can also be ruled out for the 1-phenylethyl chlorides with anilines in methanol, since the strength of the MeOH–aniline hydrogen bond will be weaker than the MeOH–MeOH hydrogen bond.

The positive ρ_X values and $\rho_X = 0$ at $\sigma^+_Y \cong -0.23$ are rationalized as follows. An electron-donating ring substituted (Y) causes the carbocation, R^+, to stabilize by resonance delocalization of positive charge, resulting in an increase in the thermodynamic barrier to carbocation capture by a nucleophile, eqn. (6); this resonance stabilization of the carbocation is, however, accompanied by an increase in the amount of electronic and structural reorganization required for carbocation capture *i.e.*, an increase in the intrinsic kinetic barrier occurs. For the substrates with $\sigma^+_Y < -0.23$ both the thermodynamic and the intrinsic barriers cause carbocation reactivity to decrease. The intrinsic barrier arises because the electronic and structural reorganizations lag behind the N–C_α bond making with proton transfer.[19] This so-called non-perfect synchronization[19] causes negative charge to accumulate on C_α in the TS, *i.e.*, an imbalanced TS[19] is formed, leading to negatively charged N with the positive value of ρ_X. This TS imbalance phenomenon disappears as the ring (Y) substituent is made progressively less electron donating or more electron withdrawing, and a normal S_N2 attack on the carbocation by aniline nucleophile takes place with the normal negative ρ_X values; in the intermediate region of this two extremes with $\rho_X > 0$ and $\rho_X < 0$, the $\rho_X = 0$ value occurs.

Thus, the aminolysis of 1-phenylethyl chlorides in methanol proceeds by an ion-pair mechanism (S_N2C^+), albeit it appears to belong to regions III ~ IV. We can therefore conclude that the regions I ~ IV, shown in Fig. 1 may provide a necessary condition, but not a sufficient condition for the S_N mechanisms.

(*b*) *With* SOH *and* SOD (S=CH_3).[20] The KSIE values for Y = electron-donating group were greater than one ($k_H/k_D > 1.0$) whereas they were inverse type ($k_H/k_D < 0$) for Y = electron-withdrawing group. The slopes of the simple Hammett plots, log k_{SOH} *vs.* σ^+_Y and log k_{SOD} *vs.* σ^+_Y, had large negative values, *i.e.*, $\rho^+_{Y(SOH)} < 0$ (−4.4) and $\rho^+_{Y(SOD)} < 0$ (−3.9). In addition the selectivity plot, log KSIE *vs.* σ^+_Y, also had two linear parts of negative slopes ($\Delta\rho^+_Y =$ −0.11 and −0.71 for Y = electron-donating and -withdrawing substituents, respectively) joined at approximately Y = H. This means that for the methanolysis the selectivity plot belongs to region II in Fig. 1. This is plausible since two extreme forms, **4** and **5**, of the carbocations in the tight ion-pair intermediate, eqn. (6), for Y = electron-donating and -withdrawing groups should require a general base (CH_3OH) catalysis (or deprotonation) and desolvation, respectively, in the TS. This is why we observe $k_H/k_D > 1.0$ for the former and $k_H/k_D < 1.0$ for the latter. Moreover the deprotonation and desolvation processes will be very fast. In this connection, we should note that solvent differs from other nucleophiles in that it is always in the immediate vicinity of the ion-pair intermediate formed, and there is no diffusion step necessary to allow its reaction. This means that for the reaction with solvent the rate determining step coincides with the product forming step, and the negative slope, $\Delta\rho_Y < 0$, is a true indication that the reactions belong to region II with a rate-limiting attack on carbocation. We therefore believe that the mechanisms for aminolysis and methanolysis of 1-phenylethyl chlorides are the same (S_N2C^+) but S_N2 character appears to prevail for the aminolysis whereas the S_N1 character appears to become more favoured for the methanolysis. The reactions of 1-phenylethyl chlorides in methanol is characterized by: $k_{SOH}/k_{SOD} > 1.0$ and $k_{SOH}/k_{SOD} < 1.0$ for Y = electron-donating and -withdrawing substituents, respectivity, $\rho^+_Y < 0$, $\Delta\rho^+_Y < 0$, $\rho_{XY} > 0$ and belongs to region II.


4
Delocalized carbocation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Localized carbocation

(6) *Reactions of* Y-α-tert-*Butyl Arenesulfonates.*—(*a*) *With* X-*anilines* (N) *in methanol* (S).[7] For this reaction, added aniline nucleophiles had no effect on the rates observed. Thus, $k_N = 0$ and $k_N/k_S = 0$ leading to $\Delta\rho^+_Y = 0$ and $\rho_{XY} = 0$ as required by an S_N1 process in region III, in Fig. 1.

(*b*) *With* SOH *and* SOD (S = CH_3).[7] The slopes of the simple Hammett plots, log k_{SOH} *vs.* σ^+_Y and log k_{SOD} *vs.* σ^+_Y, had large negative values of nearly the same magnitude ($\rho^+_Y =$ −3.85) and hence the selectivity plot, log (k_{SOH}/k_{SOD}) *vs.* σ^+_Y, gave negligible slope, $\Delta\rho^+_Y \cong 0$ ($\rho_{XY} = 0$), again as required by an S_N1 reaction belonging to region III in Fig. 1. We therefore conclude that the reactions of α-*tert*-butyl compounds proceed by a prototypical S_N1 mechanism: $\rho^+_Y < 0$, $\Delta\rho^+_Y = 0$, $\rho_{XY} = 0$ and belongs to region III. The results of all six reaction types are summarized in Tables 6 and 7.

Table 6 The slopes of simple Hammett and selectivity plots for nucleophilic substitution reactions with anilines ($XC_6H_4NH_2$) in methanol

Reactant[a]	T/°C	$\rho_Y(\rho_Y^+)$	ρ_{XY}	Ref.
1 $YC_6H_4CH_2Cl$	35.0	−0.63	−0.75	8
2 YC_6H_4COCl	35.0	2.17	−0.68	10
3 $YC_6H_4SO_2Cl$	35.0	0.96	−0.70	11
4 $YC_6H_4COCH_2Br$	45.0	0.61	0.11	12
5 $YC_6H_4CH(CH_3)Cl$	65.0	(−4.19)[b]	−2.05	6
		(−1.62)[c]	−1.34	
6 $YC_6H_4CH[C(CH_3)_3]OSO_2C_6H_4NO_2$-*p*	35.0	−3.85	0	7

[a] Solvent CH_3OH. [b] Y = electron-donating substituents. [c] Y = electron-withdrawing substituents.

Table 7 The slopes of Hammett and selectivity plots for solvolyses with SOH and SOD (S = H or CH_3)

Reactant	Solvent	T/°C	ρ_Y	$\Delta\rho_Y$	r[c]
1 $YC_6H_4CH_2Cl$	H_2O	55.0	−1.06	+0.25	0.990
	D_2O	55.0	−1.29		
	CH_3OH	55.0	−1.10	+0.21	0.985
	CH_3OD	55.0	−1.30		
2 YC_6H_4COCl	CH_3OH	25.0	+1.21	+0.28	0.956
	CH_3OD	25.0	+0.94		
3 $YC_6H_4SO_2Cl$[4]	H_2O	25.0	+0.24[a]	+0.05	0.995
	D_2O	25.0	+0.19[a]		
	CH_3OH	25.0	+0.51[a]	+0.15	0.991
	CH_3OD	25.0	+0.34[a]		
4 $YC_6H_4COCH_2Br$	H_2O	55.0	+1.53	+0.24	0.988
	D_2O	55.0	+1.29		
	CH_3OH	55.0	+1.65	+0.19	0.999
	CH_3OD	55.0	+1.46		
5 $YC_6H_4CH(CH_3)Cl$[6]	CH_3OH	65.0	−5.20[b,d]		
			−3.55[a,d]		
	CH_3OD	65.0	−5.06[b,d]	−0.14[b]	0.997
			−2.80[a,d]	−0.75[a]	0.998
6 $YC_6H_4CH[C(CH_3)_3]OSO_2C_6H_4NO_2$-*p*[7]	CH_3OH	35.0	−3.85[d]	0	
	CH_3OD	35.0	−3.85[d]		

[a] Electron-withdrawing substituents. [b] Electron-donating substituents. [c] Correlation coefficient. [d] ρ_Y^+.

We conclude that the slopes, $\Delta\rho_Y$, of the selectivity plots using the rate ratios can be useful in mechanistic studies for nucleophilic substitution reactions.

(i) A normal S_N2 reaction is characterized by a positive slope, $\Delta\rho_Y > 0$ ($\rho_{XY} < 0$), of the selectivity plot.

(ii) A prototypical limiting S_N1 process is characterized by a zero slope, $\Delta\rho_Y = 0$ ($\rho_{XY} = 0$), of the selectivity plot.

(iii) The log KSIE *vs.* σ_Y plots are equivalent to the selectivity plots and hence the slopes of such plots can be interpreted similarly.

(iv) The selectivity plots give in most cases a single straight line, irrespective of whether the simple Hammett plots are nonliner or linear with negative, or positive slope.

(v) The reactions of phenacyl derivatives with relatively strong nucleophiles show unusual behaviors of negative slope, $\Delta\rho_Y < 0$ ($\rho_{XY} > 0$).

(vi) The reactions of 1-phenylethyl chlorides with anilines proceed by an ion-pair mechanism in which the nucleophile attacks the preformed carbocation, albeit the positive slopes, $\Delta\rho_Y$, appear to indicate that they belong to region IV.

(viii) The methanolysis of 1-phenylethyl chlorides proceed by a general base catalyzed (or deprotonation) or desolvation process depending on whether the substituents are electron-donating or -withdrawing, which are compatible with the negative slope, $\Delta\rho_Y$, and S_N2C^+ mechanism.

Experimental

Materials used are as reported previously.[10] The kinetic solvent isotope effects are determined as described previously.[4,20] In the estimation of k_N/k_S, the k_S values used are obtained by dividing the observed pseudo-first order solvolysis rate constants, k_{obs}, by the methanol concentration at 20.0 °C of 24.7 mol dm^{-3}.[21]

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