

## Nucleophilic Substitution Reaction of 1-Phenylethyl Chlorides in Methanol

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Nucleophilic substitution reactions of 1-(Y-phenyl)ethyl chlorides with X-anilines have been investigated in methanol at 65.0 °C. An isokinetic point is obtained at  $\sigma_Y^+ = ca. -0.23$  with  $\rho_X = 0$ ; the sign of  $\rho_X$  changes at this point from positive for the relatively strong electron donating Y substituents to negative for the more electron withdrawing Y substituents.

The magnitude of the cross-interaction constant,  $\rho_{XY}$ , between the substituents X and Y is unusually large with the relatively small magnitude of  $\rho_X^\circ$  resulting in an observable isokinetic point at

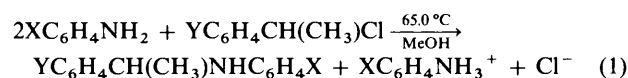
$$\sigma_Y^+ = -\frac{\rho_X^\circ}{\rho_{XY}} = -0.23.$$

These results are interpreted in terms of a transition state (TS) structure in which nearly complete bond formation between the nucleophile and cation formed in an ion-pair preequilibrium is coupled with a TS imbalance phenomenon. The results of kinetic isotope effect studies involving deuteriated anilines and methanol are also in line with this mechanism.

Solvolyses of various 1-phenylethyl derivatives have attracted considerable attention, mainly because of the possible involvement of an ion-pair process as an alternative to the concerted  $S_N2$  mechanism.

Shiner *et al.*,<sup>1</sup> concluded, based on their  $\alpha$ - and  $\beta$ -deuterium isotope effect studies, that the solvolysis of a series of substituted 1-phenylethyl halides [1-(Y-phenyl)ethyl halides] proceeds by either the admixture of some  $S_N2$  displacement or nucleophilic attack on a tight ion-pair intermediate. Tidwell and co-workers<sup>2</sup> have shown that the solvolysis of 1-(Y-phenyl)ethyl tosylates with Y = electron-withdrawing substituent (EWS) proceeds by the ion-pair mechanism, while Richard and Jencks<sup>3</sup> reached similar conclusions in their studies with Y = *p*-NO<sub>2</sub> and *p*-CH<sub>3</sub>. In the presence of the azide ion, which is much more nucleophilic than solvent molecules, a concurrent  $S_N2$  reaction was proposed to occur.

In this work, we report on the kinetic studies of the nucleophilic substitution reactions of 1-(Y-phenyl)ethyl chlorides with X-substituted anilines in methanol at 65.0 °C, eqn. (1). In contrast to the direct displacement ( $S_N2$ ) mechanism found for the reactions of 1-(Y-phenyl)ethyl arenesulfonates with anilines<sup>4</sup> and azide ion,<sup>3b</sup> the change of the leaving group (LG)



X = *p*-CH<sub>3</sub>O, *p*-CH<sub>3</sub>, H, *p*-Cl or *m*-NO<sub>2</sub>

Y = *p*-CH<sub>3</sub>, *p*-C(CH<sub>3</sub>)<sub>3</sub>, *m*-CH<sub>3</sub>, H, *p*-Cl, *m*-Cl or *p*-NO<sub>2</sub>

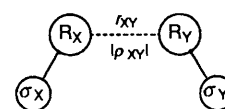
to a much smaller chloride ion has led us to surprisingly different results which are in favour of the ion-pair mechanism. We have also determined the cross-interaction constants  $\rho_{XY}$ , eqn. (2),<sup>5</sup> the magnitudes of which vary inversely with distance,  $r_{XY}$ , between the two reaction centres in the nucleophile (R<sub>X</sub>)

$$\log(k_{XY}/k_{HH}) = \rho_X\sigma_X + \rho_Y\sigma_Y + \rho_{XY}\sigma_X\sigma_Y \quad (2)$$

and the substrate (R<sub>Y</sub>), Scheme 1; a large magnitude of  $\rho_{XY}$

**Table 1** Second-order rate constants ( $k_2 \times 10^5 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ) for the reactions of 1-phenylethyl chlorides with anilines in methanol at 65.0 °C

Y	X				
	<i>p</i> -CH <sub>3</sub> O	<i>p</i> -CH <sub>3</sub>	H	<i>p</i> -Cl	<i>m</i> -NO <sub>2</sub>
<i>p</i> -CH <sub>3</sub>	628	666	704	795	936
<i>p</i> -C(CH <sub>3</sub> ) <sub>3</sub>	567	551	573	586	675
<i>m</i> -CH <sub>3</sub>	107	95.5	82.3	71.4	54.2
H	58.5	47.3	37.9	33.5	19.1
<i>p</i> -Cl	44.0	36.7	25.7	20.1	9.10
<i>m</i> -Cl	16.8	11.9	8.68	4.95	1.81
<i>p</i> -NO <sub>2</sub>	5.65	3.49	2.01	0.878	—



**Scheme 1**

obtained in this work for reaction (1) is taken as indicative of nearly complete bond formation in the transition state (TS).

### Results and Discussion

The second-order rate constants ( $k_2$ ) for reaction (1) are summarized in Table 1. The rate is seen to increase with a more electron-donating substituent in the substrate (Y = EDS) indicating that the positive charge developed on C<sub>2</sub> is stabilized by an EDS in the TS. The rate increases with a stronger EWS in the nucleophile (X = EWS) for the relatively strong EDS in the substrate [Y = *p*-CH<sub>3</sub> and *p*-C(CH<sub>3</sub>)<sub>3</sub>], but decreases (with a more EWS in the nucleophile) for Y substituents which are only mildly electron donating or electron withdrawing. This reversal of the trends in the nucleophilic reactivity with the electron withdrawing Y substituent is graphically presented in Fig. 1. We note that there are two distinct straight lines joined at Y = H ( $\sigma_Y^+ = 0$ ) for  $\log k_2$  vs.  $\sigma^+$  plots, the Y = EDS providing a straight line part with a steeper slope. The reversal of the

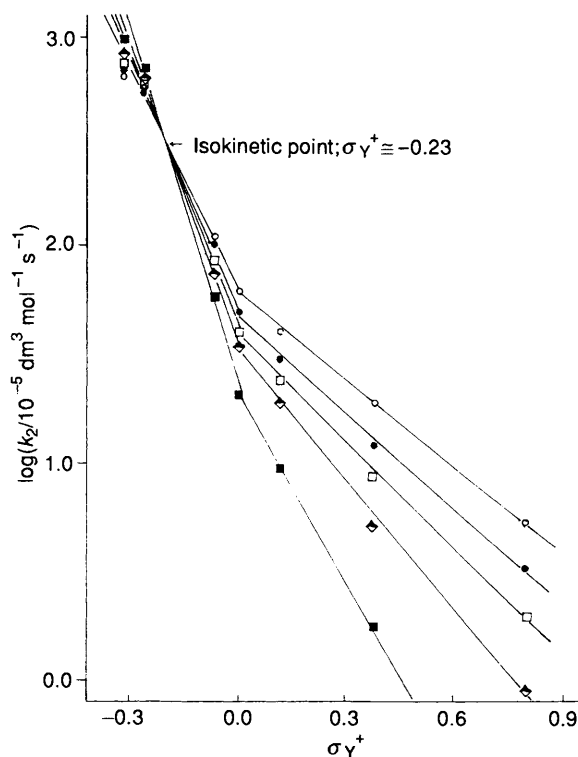


Fig. 1 Hammett  $\rho_Y^+$  plots for the reactions between 1-phenylethyl chlorides and in anilines in methanol at 65.0 °C. X: *p*-CH<sub>3</sub>O, ○; *p*-CH<sub>3</sub>, ●; H, □; *p*-Cl, ◇; *m*-NO<sub>2</sub>, ■.

Table 2 (a) Hammett  $\rho_X$  and Brønsted  $\beta_X$  values and (b)  $\rho_Y^+$  values for the reactions of 1-phenylethyl chlorides with anilines in methanol at 65.0 °C

(a)		
Substituent (Y)	$\rho_X$	$\beta_X$
<i>p</i> -CH <sub>3</sub>	0.18	-0.06
<i>p</i> -C(CH <sub>3</sub> ) <sub>3</sub>	0.08	-0.03
<i>m</i> -CH <sub>3</sub>	-0.29	0.10
H	-0.47	0.16
<i>p</i> -Cl	-0.69	0.23
<i>m</i> -Cl	-0.95	0.33
<i>p</i> -NO <sub>2</sub>	-1.60	0.57

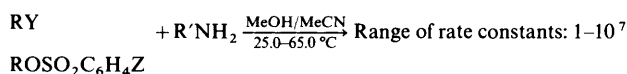
(b)		
Substituent (X)	$\rho_Y^+$ (EDS)	$\rho_Y^+$ (EWS)
<i>p</i> -CH <sub>3</sub> O	-3.46	-1.30
<i>p</i> -CH <sub>3</sub>	-3.79	-1.48
H	-4.19	-1.62
<i>p</i> -Cl	-4.54	-1.62
<i>m</i> -NO <sub>2</sub>	-5.54	-2.54

reactivity trends occurs at  $\sigma_Y^+ = ca. -0.23$ , which may be considered as an isokinetic point,<sup>6</sup> *i.e.* for the substrate with a substituent with  $\sigma_Y^+ = -0.23$  the nucleophilicities of the substituted anilines are equal so that an identical rate constant,  $k_2$  (isokinetic), is obtained irrespective of the substituent in the nucleophile, X. The Hammett  $\rho_Y^+$  and  $\rho_X$  ( $\rho_{nuc}$ ) values for variations of substituents in the substrate ( $\sigma_Y^+$ ) and nucleophile ( $\sigma_X$ ), respectively, are summarized in Table 2. The reversal of the nucleophilicity trends of substituted anilines is more clearly demonstrated by the reversal of the sign of  $\rho_X$  ( $\rho_{nuc}$ ) from positive for the strongly EDS [Y = *p*-CH<sub>3</sub> and *p*-C(CH<sub>3</sub>)<sub>3</sub>] to negative for the lesser EDS and the EWS for Y in Table 2, the plots of which are displayed in Fig. 2.

This means that the charge developed in the TS on the reaction centre, N, of the aniline changes from negative for Y = EDS to positive for Y = EWS. It is quite unusual, in fact there is no precedent that we are aware of, to find a negative charge development on the reaction centre of a nucleophile in the TS, since in the nucleophilic substitution reaction electronic charge is normally transferred from the nucleophile to the substrate in the TS so that the reaction centre, N, in the nucleophile is expected to become more positive (or less negative) as the bond is formed between C<sub>α</sub> and N in the TS.<sup>7</sup>

One might suspect that the reactivity is controlled by the desolvation barrier. Dewar *et al.*, have shown theoretically that for the nucleophilic substitution of carboxylic derivatives by anionic nucleophiles the barriers to reactions in solution are due entirely to the energy needed to desolvate the anions in order that the other reactant can approach.<sup>8</sup> Jencks *et al.* have presented experimental evidence for such desolvation-barrier controlled reactions using the reactions of quinuclidines with 2,4-dinitrophenyl phosphate and phosphorylated pyridine. A decrease in the rate constants was observed with increasing basicity of the nucleophile with a negative  $\beta_X$  ( $= \beta_{nuc} = ca. -0.2$ ) which corresponds to the positive  $\rho_X$  values found in this work.<sup>9</sup>

It is, however, highly unlikely that such a mechanism applies to the reactions of 1-phenylethyl chlorides with anilines in methanol at 65.0 °C, eqn. (1), since we have not found a case with  $\rho_X > 0$  in our studies of various nucleophilic substitution reactions of alkyl and aryl derivatives with anilines and benzylamines under similar reaction conditions,<sup>5</sup> Scheme 2.



R = alkyl or aryl group; Y = halide; R' = XC<sub>6</sub>H<sub>4</sub> or XC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub> and X,Z = substituents

#### Scheme 2

The reversal of the sign of  $\rho_X$ , and the possible existence of the isokinetic substrate ( $\sigma_Y^+ = ca. -0.23$ ) for which  $\rho_X = 0$ , provide interesting and conclusive evidence that the simple Hammett  $\rho$  value cannot be a measure of the degree of bond formation,<sup>10</sup> because a change from a negative to positive degree of bond formation is certainly an absurd interpretation of such a reversal of the sign of  $\rho_X$ .

However, this type of phenomenon is expected from eqn. (2a)

$$\log(k_{XY}/k_{HH}) = \rho_X^\circ \sigma_X + \rho_Y^\circ \sigma_Y + \rho_{XY} \sigma_X \sigma_Y \quad (2a)$$

where  $\rho_X^\circ = \rho_{XH} = \rho_X$  (Y = H) and  $\rho_Y^\circ = \rho_Y$  (X = H). At an isokinetic point,  $\hat{\sigma}_X$  or  $\hat{\sigma}_Y$ , the rate ratio,  $k_{XY}/k_{HH}$ , becomes constant, as shown in eqn. (3).

$$\begin{aligned} \log(k_{XY}/k_{HH}) &= \rho_X^\circ \hat{\sigma}_X + (\rho_Y^\circ + \rho_{XY} \hat{\sigma}_X) \sigma_Y \\ &= -\frac{\rho_X^\circ \rho_Y^\circ}{\rho_{XY}} = \text{constant} \end{aligned}$$

$$\text{where } \hat{\sigma}_X = -\frac{\rho_Y^\circ}{\rho_{XY}} \text{ and } \hat{\sigma}_Y = -\frac{\rho_X^\circ}{\rho_{XY}} \quad (3)$$

For the nucleophilic substitution reactions of benzoyl and benzyl halides with anilines, Shpan'ko<sup>11</sup> has demonstrated the existence of  $\hat{\sigma}_X$ , and in two cases  $\rho_Y$  values observed actually passed through the isokinetic point with change of sign at  $\hat{\sigma}_X$  (for which  $\rho_Y = 0$ ). The calculated value of  $\hat{\sigma}_Y = -0.23$  using eqn. (3) in the present work agrees well with that obtained by interpolation above.

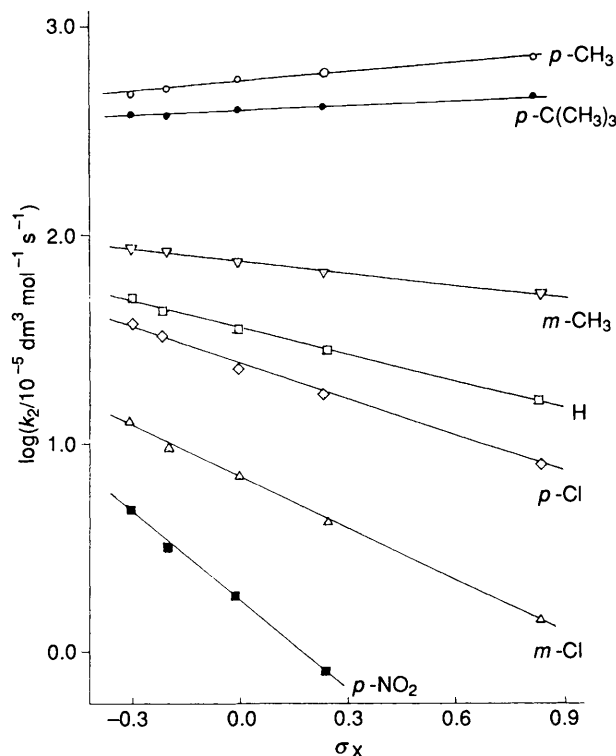


Fig. 2 Hammett  $\rho_X$  plots for the reactions between 1-phenylethyl chlorides and in anilines in methanol at 65.0 °C

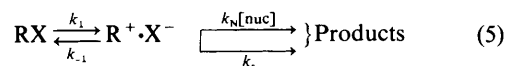
The  $\rho_Y^+$  values are relatively large with Y = EDS and with a more EWS in the nucleophile, reflecting a greater positive charge delocalization into the ring with Y = EDS and with X = EWS. The  $\rho_Y^+$  values for solvolyses in MeOH are well within the range of  $\rho^+$  values reported for various other solvents.<sup>16,3</sup> A somewhat smaller magnitude of  $\rho_Y^+$  is obtained for MeOD ( $\rho_Y^+ = -5.06$ ) compared with the corresponding value for MeOH ( $\rho_Y^+ = -5.25$ ). It is interesting to note that the  $\rho_Y^+$  value for MeOH is similar to that of *m*-NO<sub>2</sub>-aniline, implying that the nucleophilicities of the two species are similar.

Product analysis has shown that the elimination pathway can be excluded. Moreover, Jencks and co-workers<sup>3a</sup> reported that the salt effect on 1-phenylethyl carbocation stability is relatively small and unlikely to cause a major change in reaction mechanism. We investigated the salt effect on the reactivity using low concentrations of KCl in the reaction system. The results in Table 3 show that for the *p*-*tert*-butyl derivative there is a common ion effect of rate depression at very low salt concentrations, but as the KCl concentration is increased the ionic strength effect becomes dominant as is the case with the unsubstituted compound. The ionic strength ( $\mu$ ) effect on  $k_s$  for the unsubstituted compound is normal [eqn. (4)]<sup>12</sup> with

$$k_s' = k_s(1 + b\mu) \quad (4)$$

$b = 14.5$ . Correctly reflecting that the reactants are both neutral and substrate concentrations used are low (*ca.* 10<sup>-3</sup> mol dm<sup>-3</sup>), the salt effect is small as expected and in agreement with the conclusions of Jencks *et al.*<sup>3a</sup>

The results in Tables 1–3 are consistent with an ion-pair (S<sub>N</sub>2 C<sup>+</sup>) mechanism in which direct S<sub>N</sub>2 displacement takes place on the cation (R<sup>+</sup>) of the tight ion pair (R<sup>+</sup>·X<sup>-</sup>) formed in a pre-equilibrium, [eqn. (5)].<sup>1,2</sup> The observed  $k_2$  from eqn. (6) is therefore given by eqn. (7), which in turn leads to eqn. (8), where  $\rho_c$  represents the susceptibility of charge development on C<sub>α</sub> to the change in the substituent Y as the C<sub>α</sub>-N bond is formed and  $\rho_{eq}$  is for the ion-pair equilibrium. The  $\rho_{eq}$  is known to



$$k_{obs} = k_s + k_2[nuc] \quad (6)$$

$$k_2 = k_N \cdot K \text{ where } K = \frac{k_1}{k_{-1}} \quad (7)$$

$$\rho_Y^+ (\text{observed}) = \rho_c + \rho_{eq}, \rho_c > 0 \text{ and } \rho_{eq} < 0 \quad (8)$$

be very large and negative ranging from  $-10$  to  $-12$  and  $\rho_c$  is expected to be positive since transfer of negative charge from N to C<sub>α</sub> will reduce the positive charge on C<sub>α</sub>. Thus the  $\rho_Y^+$  values given in Table 2 are the results of the sum of these two values; for X = EDS  $\rho_c$  will be a relatively greater positive value whereas for X = EWS  $\rho_c$  will be a relatively smaller positive value so that  $\rho_Y^+$  is less negative for X = EDS compared to X = EWS. The electron-withdrawing Y substituents exhibit smaller  $\rho_Y^+$  values, probably due to the smaller negative  $\rho_{eq}$  value in eqn. (8) since such substituents destabilize the cation intermediate. Two extreme forms of the cation intermediate are conceivable depending on Y: practically no positive charge delocalization, **I**, and effectively completely delocalized, which is stabilized by specific solvation of the positively charged Y group, **II**. The positive  $\rho_X$  values in

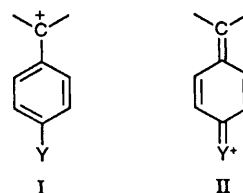
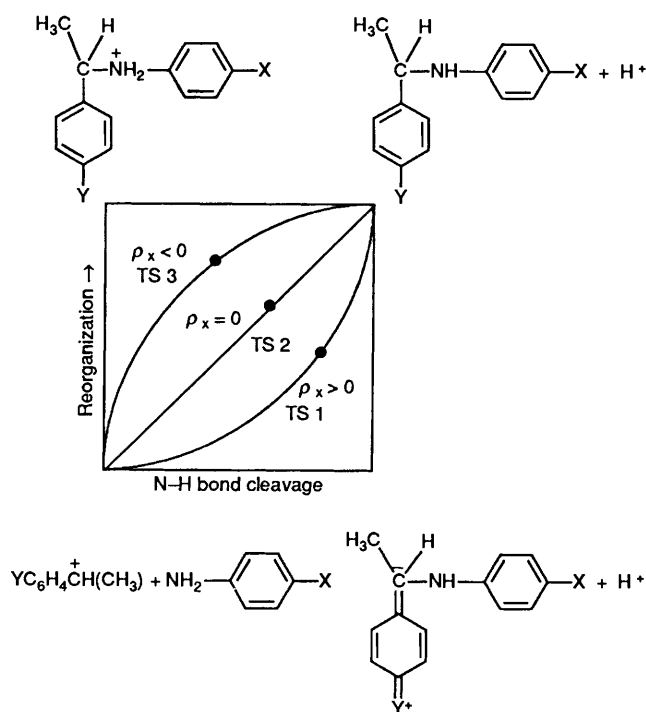


Table 2 for the relatively strong electron donating Y substituents [Y = *p*-CH<sub>3</sub> and *p*-C(CH<sub>3</sub>)<sub>3</sub>] can be rationalized by the TS imbalance concept advocated by Jencks<sup>3,13</sup> and Bernasconi.<sup>14</sup> When the nucleophile attacks and forms the N-C<sub>α</sub> bond with the delocalized cation form, **II**, instantaneous charge delocalization and solvent reorganization cannot take place, since delocalization of developing negative charge transferred from the deprotonated N on aniline into the solvated positive charge at Y lags behind proton transfer, partly because C<sub>α</sub> in this form has very low positive charge. As a result, negative charge accumulates on C<sub>α</sub> in the TS (leading to  $\rho_X > 0$ ) prior to delocalization into Y<sup>+</sup> through the ring, and reorganizes the solvent around Y<sup>+</sup> eventually. The accumulation of negative charge on C<sub>α</sub> will be greater with a stronger electron donating substituent X in the nucleophile (X = *p*-OCH<sub>3</sub>) and thus  $\rho_c$  [eqn. (8)] will have a relatively large positive value leading to a smaller negative  $\rho_Y^+$  value as observed (in Table 2). For Y = EWS the delocalized cation form **II** is relatively unstable and the localized form **I** will prevail. In this form, the substituent Y has only a polar effect on C<sub>α</sub>, which develops synchronously with charge transfer<sup>14</sup> leading to no TS imbalance. An isokinetic point can be realized or actually observed in the experiment when  $|\rho_{XY}|$  is large but  $\rho_X^o$  or  $\rho_Y^o$  is relatively small, [ $\delta_X$  or  $\delta_Y$  is given by eqn. (3)] so that the  $\delta_X$  ( $\delta_Y$ ) value falls within the range of substituent constants normally used (*ca.*  $-1.0$ – $1.0$ ) in the experiment. This should mean that the interaction is large (large  $|\rho_{XY}|$ ), most often due to a large degree of bond formation, but charge transfer or charge delocalization/solvent reorganization is small in the TS. This is precisely the condition for the appearance of the transition state imbalance phenomenon. We therefore conclude that a large TS imbalance (Im) should be

**Table 3** Solvolysis rate constants,  $k_s$ ,<sup>a</sup> (s<sup>-1</sup>), with KCl (mol dm<sup>-3</sup>) added

	[KCl]			
	0.0 <sup>c</sup>	0.01	0.03	0.04
C <sub>6</sub> H <sub>5</sub> CH(CH <sub>3</sub> )Cl	2.54 ± 0.02	2.71 ± 0.08	2.94 ± 0.31	3.12 ± 0.24
<i>p</i> -(CH <sub>3</sub> )CC <sub>6</sub> H <sub>4</sub> CH(CH <sub>3</sub> )Cl	6.84 ± 0.01	6.47 ± 0.09	6.67 <sup>b</sup>	6.84 ± 0.13

<sup>a</sup> Average of 4–9 determinations. Errors shown are the mean deviations. <sup>b</sup> From single determination. <sup>c</sup> These values are uniformly greater by *ca.* 10% than those in ref. 17 due to the different grade of purchased (Merck HPLC) MeOH solvent used without purification in these measurements.



**Fig. 3** More O'Ferrall-Jencks diagram for the nucleophilic substitution of 1-phenylethyl cation by aniline. TS 2 corresponds approximately to  $\sigma_Y^+ = -0.23$  for which the nucleophiles become isokinetic, *i.e.*  $\rho_X = 0$ .

accompanied by a large  $|\rho_{XY}|$ ,<sup>15</sup> *i.e.* eqn. (9), and the TS

$$\text{Im} \propto |\rho_{XY}| \quad (9)$$

imbalance is most likely to occur when the isokinetic point is realized, as in the present work, or the point  $\delta_X$  (or  $\delta_Y$ ) is not far away from the range of substituent constants normally used in organic rate measurements (*ca.*  $-1.0 \sim 1.0$ ).

A More O'Ferrall-Jencks type structure-reactivity diagram can be constructed as in Fig. 3. The lower left corner represents the reactants, the cationic intermediates **I** and **II** and aniline, the upper right corner the products, while the lower right corner is a hypothetical intermediate with deprotonated zwitterionic structure and the upper left corner is an intermediate whose positive charge is localized on the nitrogen atom. The progress variables are the degree of proton transfer with concurrent N–C<sub>α</sub> bond formation (horizontal axis) and the degree of positive charge localization on the nitrogen atom with concurrent N–C<sub>α</sub> bond formation synchronously with reorganization (vertical axis). A synchronous development of the two progress variables would correspond to the diagonal reaction coordinate for which  $\rho_X$  ( $\rho_{\text{nuc}}$ ) = 0. The observed reaction coordinate for a relatively strong electron-donating Y substituent is shown by the lower curved line for which  $\rho_X$  is positive, while that for Y = EWS is the upper curved line with  $\rho_X < 0$ . When there

is no TS imbalance, the observed curves are expected to be in the upper region with  $\rho_X < 0$  where the degree of reorganization of the delocalized structure **II** required is either very small or synchronous with the deprotonation process, *i.e.* N–H bond cleavage. At TS 1, the deprotonation with concurrent C<sub>α</sub>–N bond formation has progressed much ahead of reorganization of the delocalized cation structure **II**, whereas at TS 3 the N–H bond has cleaved very little, with extensive C<sub>α</sub>–N bond formation and reorganization of the delocalized structure. At TS 2, the situation is intermediate, *i.e.* N–H bond cleavage and reorganization are synchronous. In all cases, C<sub>α</sub>–N bond formation is extensive in the TS. The extensive C<sub>α</sub>–N formation in the TS is supported by the large magnitude of the cross-interaction constant  $\rho_{XY}$  in Table 4. Reference to this Table reveals that the magnitude of  $\rho_{XY}$  of  $-2.05$  (Y = EDS) and  $-1.34$  (Y = EWS) are very large compared with those for the normal S<sub>N</sub>2 reactions ( $|\rho_{XY}| = \text{ca. } 0.70$ )<sup>5</sup> and are similar to that for the reaction of benzoyl fluorides with anilines, which is known to have very extensive bond formation in the TS.<sup>5</sup> In fact, the magnitude of  $\rho_{XY}$  observed in the present work for Y = EDS is the largest value ever reported, suggesting that the bond-making process between N and C<sub>α</sub> is nearly complete.

Nearly complete formation of the C<sub>α</sub>–N bond in the TS is also supported by the normal ( $k_H/k_D > 1.0$ ) deuterium kinetic isotope effect involving deuterated aniline nucleophiles (XC<sub>6</sub>H<sub>4</sub>ND<sub>2</sub>)<sup>16</sup> in Table 5. The  $k_H/k_D$  value will be greater than unity only when the primary KIE is operative, *i.e.* the N–H(D) bond is being broken in the TS, since otherwise a closer approach of the nucleophile toward C<sub>α</sub> will result in an inverse secondary KIE due to the two hindered N–H(D) vibrations in the TS.<sup>16</sup> We note in Table 5 that  $k_H/k_D$  is greater than unity in all cases, reflecting partial bond cleavage of the N–H(D) bond; the primary KIE ( $k_H/k_D > 1.0$ ) due to a cleaving N–H(D) bond is countered and partially cancelled by the concurrent inverse secondary KIE ( $k_H/k_D < 1.0$ ) of the second N–H(D) bond whose vibrational modes are hindered in the TS. However, the greater than unity  $k_H/k_D$  value in all cases reflects a dominant effect of the primary KIE of the cleaving N–H(D) bond over the inverse secondary KIE of the other non-cleaving N–H(D) bond. In agreement with a greater degree of bond formation and hence a greater degree of N–H bond cleavage with Y = EDS, the  $k_H/k_D$  values are greater with Y = EDS. The N–H(D) bond breaking should be facilitated by an electron-withdrawing group in the nucleophile (X = EWS), so that  $k_H/k_D$  also becomes greater with X = EWS.

The kinetic solvent isotope effect (KSIE),  $k_{\text{SOH}}/k_{\text{SOD}}$ , can provide a useful mechanistic criterion on the S<sub>N</sub> reactions.<sup>16</sup> The Hammett type plot, logKSIE *vs.*  $\sigma$ , gave positive slopes,  $\Delta\rho_Y = \rho_{\text{SOH}} - \rho_{\text{SOD}} > 0$  for the S<sub>N</sub>2 and general base-catalysed and/or addition-elimination (S<sub>A</sub>N) type of mechanisms, whereas the methanolysis of 1-phenylethyl chlorides at 65.0 °C gave a negative slope  $\Delta\rho_Y < 0$ .<sup>17</sup> The fact that SOH is a stronger nucleophile<sup>19</sup> is tantamount to the relation  $\sigma_X^H < \sigma_X^D$ , since a stronger EDS with a more negative  $\sigma_X$  leads to a stronger nucleophile. This means that the  $\rho_{XY}$  values [eqn. (2)] for S<sub>N</sub>2 and S<sub>A</sub>N reactions are negative, since

**Table 4** Comparison of cross-interaction constants ( $\rho_{XY}$ ) for the reactions of benzyl, benzoyl and 1-phenylethyl derivatives with anilines in methanol<sup>5</sup>

Substrate	YC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> -		YC <sub>6</sub> H <sub>4</sub> CO-		YC <sub>6</sub> H <sub>4</sub> CH(CH <sub>3</sub> )-		
	-OSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Z	-Cl	-Cl <sup>a</sup>	-F <sup>b</sup>	-OSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Z <sup>c</sup>	-Cl <sup>d</sup> (EDS)	-Cl <sup>d</sup> (EWS)
$\rho_{XY}$	-0.62	-0.75	-0.68	-1.67	-0.21	-2.05	-1.34

<sup>a</sup> 35.0 °C. <sup>b</sup> 55.0 °C. <sup>c</sup> 25.0 °C. <sup>d</sup> 65.0 °C, this work.

**Table 5** The kinetic isotope effects for the reactions of 1-phenylethyl chlorides with deuterated anilines in deuterated methanol at 65.0 °C

X	Y	$k_H/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	$k_D/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	$k_H/k_D$
<i>p</i> -CH <sub>3</sub> O	<i>p</i> -CH <sub>3</sub>	$(6.28_4 \pm 0.14_4) \times 10^{-3a}$	$(5.13_3 \pm 0.12_4) \times 10^{-3}$	$1.22_4 \pm 0.04_1^b$
<i>p</i> -CH <sub>3</sub> O	<i>m</i> -Cl	$(1.68_0 \pm 0.02_7) \times 10^{-4}$	$(1.64_5 \pm 0.04_6) \times 10^{-4}$	$1.02_1 \pm 0.03_3$
<i>m</i> -NO <sub>2</sub>	<i>p</i> -CH <sub>3</sub>	$(9.36_1 \pm 0.11_3) \times 10^{-5}$	$(6.08_3 \pm 0.10_4) \times 10^{-5}$	$1.53_9 \pm 0.03_3$
<i>m</i> -NO <sub>2</sub>	<i>m</i> -Cl	$(1.81_3 \pm 0.03_7) \times 10^{-5}$	$(1.24_5 \pm 0.01_9) \times 10^{-5}$	$1.45_4 \pm 0.03_7$

<sup>a</sup> Standard deviation. <sup>b</sup> Standard error ( $= 1/k_D[(\Delta k_H)^2 + (k_H/k_D)^2 \times (\Delta k_D)^2]^{1/2}$ ).<sup>18</sup>

$\Delta\rho_Y$  is positive and  $\Delta\sigma_X (= \sigma_X^H - \sigma_X^D)$  is negative; for most of S<sub>N</sub> reactions, the observed  $\rho_{XY}$  values were

$$\rho_{XY} = \frac{\Delta\rho_Y}{\Delta\sigma_X} = \frac{(+)}{(-)} < 0$$

actually negative.<sup>5</sup> If the sign of  $\Delta\rho_Y$  is negative, as in the present work,  $\rho_{XY}$  reverses to positive. In relatively rare

$$\rho_{XY} = \frac{\Delta\rho_Y}{\Delta\sigma_X} = \frac{(-)}{(-)} > 0$$

examples of positive  $\rho_{XY}$ , the TS was quite tight with relatively large negative charge development at the reaction centre,<sup>5</sup> which is quite similar to the TS structure proposed in this work.

On account of both the stronger nucleophilicity of SOH<sup>19</sup> and the stronger acidity of SOD,<sup>19</sup>  $k_H$  should be greater than  $k_D$  and hence  $k_H/k_D > 1.0$  as was observed for Y = EDS.<sup>17</sup> This is true with Y = EDS since the more facile deuteron transfer (compared to proton) in an attack of the delocalized cation, II, should lead to a greater TS imbalance, similar to the species at the lower right corner in Fig. 3, with greater rate retardation for SOD (*vide supra*). However, for the localized cation, I, with Y = EWS, the nucleophile, SOH or SOD, must come quite close to the C<sub>α</sub> atom in the near complete bond formation in the TS, which has a similar structure to the species at the upper left corner in Fig. 3. The near tetrahedral geometry of the water oxygen changes to trigonal on bond formation with an increase in the O-H stretching force constants. This will result in an inverse secondary kinetic isotope effect,  $k_H/k_D < 1.0$ ,<sup>20</sup> as indeed was observed.<sup>17</sup>

Thus the KSIE results are also compatible with the mechanism proposed in this work for the reactions with anilines.

## Experimental

**Materials.**—Merck analytical grade methanol was used without further purification. Anilines were purified as described previously.<sup>21</sup> Preparation of deuterated anilines were as described previously.<sup>22</sup> The analysis (NMR spectroscopy) of the deuterated aniline showed more than 99% deuterium content, so no corrections to KIEs for incomplete deuteration were made. In the preparation of substituted 1-phenylethyl chloride,<sup>23</sup> the corresponding acetophenone was treated with reducing agent (LiAlH<sub>4</sub>) to produce 1-phenylethyl alcohol, which was then converted to 1-phenylethyl chloride by reaction with thionyl chloride in dry chloroform at room temperature.

The products were vacuum distilled and separated by column chromatography.

**Kinetic Procedures.**—Rates were measured conductimetrically at  $65.0 \pm 0.05$  °C in methanol and deuterated methanol. The conductivity bridge used in this work was a self-made computer interface automatic A/D converter conductivity bridge and the conductivity cell was placed in a Pyrex pressure bottle with a tightly sealed cap to prevent leakage of methanol vapour. Substrates were injected with a syringe. The vapour pressure inside the bottle is expected to rise, with a corresponding rise in the boiling point. The rise of external pressure (max. ca. 2 atm), however, is not significant enough to affect the observed rates. Pseudo-first-order rate constants,  $k_1^{\text{obs}}$ , were determined by the Guggenheim method<sup>24</sup> with a large excess of aniline; [1-PEC] =  $10^{-3}$  mol dm<sup>-3</sup> and [aniline] = 0.15–0.60 mol dm<sup>-3</sup>. Second-order rate constants,  $k_2$ , were obtained from the slope of a plot of  $k_{\text{obs}}$  vs. [aniline] with more than four concentrations of aniline, shown in eqn. (10).

$$k_{\text{obs}} = k_s + k_2[\text{aniline}] \quad (10)$$

The methanolysis rate constants,  $k_s$ , given as an intercept of the plot, agreed with the methanolysis rate constants determined independently. The linearity of the plot [eqn. (10)] was good with correlation coefficients of better than 0.998 with 99% confidence limit.<sup>25</sup> The  $k_2$  values listed in Table 1 are the averages obtained by more than triplicate runs and were reproducible to within  $\pm 3\%$ .

**Product Analysis.**—1-(*p*-Cl-Phenyl)ethyl chloride was reacted with excess aniline with stirring for more than 13 half-lives at 65.0 °C in methanol, and the products were isolated by evaporating the solvent under reduced pressure. The TLC analysis of the product mixture gave four spots (silica gel, glass plate, 10% ethyl acetate/hexane).  $R_f$  values: 0.63 [*p*-Cl-C<sub>6</sub>H<sub>4</sub>CH(CH<sub>3</sub>)OCH<sub>3</sub>], 0.52 [*p*-Cl-C<sub>6</sub>H<sub>4</sub>CH(CH<sub>3</sub>)NHC<sub>6</sub>H<sub>4</sub>-*p*-CH<sub>3</sub>], 0.22 (*p*-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>), 0.05 (*p*-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>NH<sub>3</sub><sup>+</sup>Cl<sup>-</sup>).

The product mixture was treated with column chromatography (silica gel, 10% ethyl acetate/hexane). Analysis of the products, *p*-Cl-C<sub>6</sub>H<sub>4</sub>CH(CH<sub>3</sub>)OCH<sub>3</sub>, *p*-Cl-C<sub>6</sub>H<sub>4</sub>CH(CH<sub>3</sub>)NHC<sub>6</sub>H<sub>4</sub>-*p*-CH<sub>3</sub>, *p*-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>NH<sub>3</sub><sup>+</sup>Cl<sup>-</sup>, gave the following results.

*p*-Cl-C<sub>6</sub>H<sub>4</sub>CH(CH<sub>3</sub>)OCH<sub>3</sub>.  $\delta$ (60 MHz, CDCl<sub>3</sub>), 1.4 (CH<sub>3</sub>, 3 H, d), 3.2 (OCH<sub>3</sub>, 3 H, s), 4.3 (CH, 1 H, q), 7.2 (phenyl, 4 H, s) (Found: C, 63.3; H, 6.5. Calc. for C<sub>9</sub>H<sub>11</sub>OCl: C, 63.35; H, 6.50%.)

*p*-Cl-C<sub>6</sub>H<sub>4</sub>CH(CH<sub>3</sub>)NHC<sub>6</sub>H<sub>4</sub>-*p*-CH<sub>3</sub>.  $\delta$ (60 MHz, CDCl<sub>3</sub>), 1.4 (CH<sub>3</sub>, 3 H, d), 2.2 (*p*-CH<sub>3</sub>, 3 H, s), 3.8 (NH, 1 H, s), 4.3 (CH<sub>3</sub>, 1 H, q), 6.3–7.2 (phenyl, 8 H, m) (Found: C, 73.3; H, 6.61; N, 5.6. Calc. for C<sub>15</sub>H<sub>16</sub>NCl: C, 73.3; H, 6.6; N, 5.7%.)

*p*-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>NH<sub>3</sub><sup>+</sup>Cl<sup>-</sup>.  $\delta$ (60 MHz, [<sup>2</sup>H<sub>6</sub>]DMSO), 2.3 (*p*-CH<sub>3</sub>, 3 H, s), 7.2 (phenyl, 4 H, s), 9.4–10.6 (NH<sub>3</sub>, 3 H, br) (Found: C, 58.5; H, 7.1; N, 9.7. Calc. for C<sub>7</sub>H<sub>10</sub>NCl: C, 58.5; H, 7.0; N, 9.75%.)

No UV peak ( $\lambda_{\text{max}} = \text{ca. } 282, 244 \text{ nm}$ ) corresponding to alkene, formed by an elimination reaction, was detected.

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