Nucleophilic Substitution Reactions of Indan-2-yl Arenesulfonates with Anilines in Methanol

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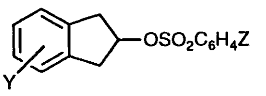
The nucleophilic substitution reactions of (Y)-indan-2-yl (Z)-arenesulfonates with (X)-anilines in methanol at 55.0 °C are reported. Sign reversals in all three second-order cross-interaction constants, ρ_{XY}, ρ_{YZ} and ρ_{XZ}, are observed at non-interaction points $\hat{\sigma}_Z = -0.11$ ($\rho_{XY} = 0$), $\hat{\sigma}_X = -0.02$ ($\rho_{YZ} = 0$) and $\hat{\sigma}_Y = 0.43$ ($\rho_{XZ} = 0$) respectively, which have been ascribed to an unusually large third-order cross-interaction constant, $\rho_{XYZ} = -0.53$, for the reaction series. An S_N2 transition state with a tilted, parallel stacked and displaced structure of the three benzene rings in the nucleophile (X), substrate (Y) and leaving group (Z) is proposed to rationalize the strong three-body coupling manifested by the large ρ_{XYZ} value.

The solvolysis of indan-2-yl arenesulfonates **1**, has been shown



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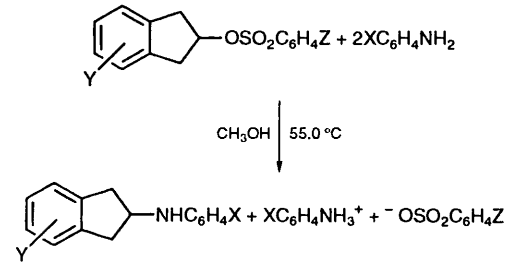
to proceed by the typical S_N2 mechanism.[1] However, it was found that (i) the susceptibility of ρ_{YZ}, eqn. (1)[2] with i,j = X,

$$\log (k_{ij}/k_{HH}) = \rho_i\sigma_i + \rho_j\sigma_j + \rho_{ij}\sigma_i\sigma_j \qquad (1)$$

Y or Z where X, Y and Z are substituents in the nucleophile (X), substrate (Y) and leaving group (Z), respectively, to variation of solvent nucleophilicity, N_{OTs}, was found to be much greater than that to variation of ionizing power, Y_{OTs}, and (ii) the relatively high activation parameters, $\Delta H^‡$ and $\Delta S^‡$, were rather unusual for an S_N2 reaction being similar to those for the limiting S_N1 processes. These features were partly ascribed to hindered approach of the nucleophile (solvent) due to the out-of-plane hydrogens in the adjacent carbons and to the relatively low degree of bond cleavage with delocalized negative charge in the leaving group leading to the low degree of solvent reorganization in the transition state (TS).[1]

In order to obtain further information for the nucleophilic substitution mechanism of the 2-indanyl system **1**, we have



Scheme 1

carried out kinetic studies on the reactions of **1** with anilines in methanol at 55.0 °C (Scheme 1).

Results and Discussion

Table 1 The second-order rate constants k_2 (10^5 dm^3 mol^{-1} s^{-1}) for the reactions of (Y)-indan-2-yl (Z)-benzenesulfonates with (X)-anilines in MeOH at 55.0 °C [eqn. (2)][a]

		Z			
Y	X	*p*-CH$_3$	H	*p*-Cl	*p*-NO$_2$
H	*p*-OCH$_3$	8.28	12.6	27.6	123
	p-CH$_3$	6.22	9.97	23.3	98.2
	H	3.83	5.52	13.3	63.7
	p-Cl	1.63	2.83	6.87	32.0
Br	*p*-OCH$_3$	7.17	9.54	22.4	95.1
	p-CH$_3$	5.08	7.51	16.7	72.2
	H	2.95	4.48	10.3	44.8
	p-Cl	1.39	1.94	4.51	20.2
NO$_2$	*p*-OCH$_3$	4.10	6.86	15.4	67.4
	p-CH$_3$	3.09	4.95	11.5	48.8
	H	1.80	3.20	6.74	29.6
	p-Cl	0.900	1.38	2.95	12.1

[a] Rate coefficients were reproducible to within ± 3%.

The second-order rate constants, k_2, are summarized in Table 1. Rates are faster with a stronger nucleophile and with a better leaving group (LG). A more electron withdrawing substituent (EWS) in the substrate, *e.g.* Y = NO$_2$, leads to a lower rate suggesting that positive charge develops at the reaction centre, C$_2$, in the TS. The simple Hammett coefficients, ρ_X, ρ_Y and ρ_Z, are summarized in Table 2. Good linearities were obtained for these Hammett plots ($r \geqslant 0.990$).

The negative ρ_Y values are consistent with positive charge development at the reaction centre, C$_2$, in the TS. However we note that the magnitude of ρ_X decreases for Y = H and Br in contrast to an increase observed for Y = NO$_2$ with a more EWS in the LG, from Z = *p*-CH$_3$ to Z = *p*-NO$_2$ [Table 2(*a*)]. Again we note such a reversal with the magnitude of ρ_Z; ρ_Z increases for Y = H and Br in contrast to a decrease for Y = NO$_2$ for a more EWS in the nucleophile [Table 2(*c*)].

The reason for this type of reversal in the trends of $|\rho_X|$ and $|\rho_Z|$ with Y becomes clear by considering the sign reversal of ρ_{XZ} in Table 3, where we have listed the cross-interaction constants obtained by subjecting the rate data in Table 1 to multiple linear regression analysis using eqn. (1).[2]

Examination of Table 3 shows that all three second order cross-interaction constants, ρ_{XY}, ρ_{YZ} and ρ_{XZ}, exhibit sign reversal. The sign of ρ_{XZ}, changes from positive for Y = H and Br to negative for Y = NO$_2$.

Table 2 Hammett ρ_i values[a] for Scheme 1

(*a*) ρ_X Values

	Y		
Z	H	Br	NO_2
p-CH_3	−1.42	−1.43	−1.34
H	−1.34	−1.41	−1.39
p-Cl	−1.25	−1.40	−1.45
p-NO_2	−1.18	−1.36	−1.50

(*b*) ρ_Y Values

	X			
Z	*p*-OCH_3	*p*-CH_3	H	*p*-Cl
p-CH_3	−0.42	−0.41	−0.44	−0.35
H	−0.35	−0.41	−0.34	−0.41
p-Cl	−0.34	−0.41	−0.40	−0.40
p-NO_2	−0.35	−0.41	−0.46	−0.56

(*c*) ρ_Z Values

	Y		
X	H	Br	NO_2
p-OCH_3	1.25	1.22	1.28
p-CH_3	1.27	1.23	1.27
H	1.31	1.26	1.27
p-Cl	1.36	1.25	1.23

[a] Correlation coefficients were better than 0.990 in all cases except for the ρ_Y values of X = *p*-OCH_3 with Z = *p*-CH_3 (r = 0.973) and X = *p*-OCH_3 with Z = *p*-NO_2 (r = 0.986) at 99% confidence levels in all cases.

Table 3 Cross-interaction constants, ρ_{ij}, values for Scheme 1

(*a*) ρ_{XY} Values[a]

Z	*p*-CH_3	($\hat{\sigma}_Z = -0.11$)	H	*p*-Cl	*p*-NO_2
ρ_{XY}	0.12	(0.0)	−0.06	−0.26	−0.41
(r)	(0.997)		(0.998)	(0.998)	(0.998)

(*b*) ρ_{YZ} Values[a]

X	*p*-OCH_3	*p*-CH_3	($\hat{\sigma}_X = -0.02$)	H	*p*-Cl
ρ_{YZ}	0.05	0.01	(0.0)	−0.5	−0.22
(r)	(0.998)	(0.998)		(0.998)	(0.998)

(*c*) ρ_{XZ} Values[a]

Y	H	Br	($\hat{\sigma}_Y = 0.43$)	NO_2
ρ_{XZ}	0.23	0.08	(0.0)	−0.16
(r)	(0.998)	(0.998)		(0.998)

(*d*) $\rho_{XYZ} = -0.53$

[a] At 99% confidence level.

It has been shown that[2] if ρ_{XZ}, which can be alternatively defined by eqn. (2), is negative, a more electron donating

$$\rho_{XZ} = \frac{\partial^2 \log k_{XZ}}{\partial\sigma_X \partial\sigma_Z} = \frac{\partial\rho_Z}{\partial\sigma_X} = \frac{\partial\rho_X}{\partial\sigma_Z} \qquad (2)$$

substituent (EDS) in the nucleophile (*i.e.*, a stronger nucleophile), $\delta\sigma_X < 0$, leads to a more positive ρ_Z, $\delta\rho_Z > 0$, (*i.e.*, a greater degree of bond breaking) and a more EWS in the LG, $\delta\sigma_Z > 0$, leads to a more negative ρ_X, $\delta\rho_X < 0$ (*i.e.*, a greater degree of bond formation). In effect, the negative ρ_{XZ} value predicts a 'later' TS for a stronger nucleophile and/or a better LG. Conversely, if ρ_{XZ} is positive, a stronger nucleophile and/or a better LG lead to an 'earlier' TS with a lesser degree of bond-making and -breaking in the TS.

On the other hand, the magnitude of ρ_{XY} and ρ_{YZ} have been shown to be proportional to the degree of bond-making and -breaking in the TS, respectively.[2c]

Thus for Y = H and Br, ρ_{XZ} is positive and hence an earlier TS with decreasing magnitude of ρ_{XY} and ρ_{YZ} will be expected with a stronger nucleophile and a better LG, which is indeed observed for the positive values of ρ_{XY} (Z = *p*-CH_3) and for the negative values of ρ_{YZ} (X = H and *p*-Cl) in Table 3. For Y = NO_2, ρ_{XZ} is negative and a later TS with increasing magnitude of ρ_{XY} and ρ_{YZ} is expected, which is observed for the negative values of ρ_{XY} (Z = H, Cl and *p*-NO_2) and for the positive values of ρ_{YZ} (X = *p*-OCH_3 and *p*-CH_3) in Table 3. The sign reversal of ρ_{XZ} thus results in sign reversals of the other two, ρ_{XY} and ρ_{YZ}, as well as the reversals noted above in the trends of $|\rho_X|$ and $|\rho_Z|$s' variation with σ_Y.

This reaction is the first example in which we obtain both positive and negative ρ_{XZ} within a series of reactions. What are the significance and consequence of the sign reversals observed for second-order cross-interaction constants, ρ_{ij}, in eqn. (1)? In deriving eqn. (1),[2] we ignored pure second-order terms, ρ_{ii} or ρ_{jj}, and higher order terms, ρ_{iij}, ρ_{jjk} *etc.* and ρ_{ijk}. When, however, strong interactions exist in the TS between three substituents, σ_X, σ_Y and σ_Z, through the respective reaction centres, one can extend eqn. (1) to include third-order interactions, [eqn. (3)]

$$\log(k_{ijk}/k_{HHH}) = \rho_i\sigma_i + \rho_j\sigma_j + \rho_k\sigma_k + \rho_{ij}\sigma_i\sigma_j + \rho_{jk}\sigma_j\sigma_k + \rho_{ik}\sigma_i\sigma_k + \rho_{ijk}\sigma_i\sigma_j\sigma_k \qquad (3)$$

which is considered to reflect the intensity of interaction between the three substituents in the TS. Here again the terms involving pure second-order interactions, ρ_{ii} *etc.* and ρ_{iij}, ρ_{jjk}, *etc.*, are neglected since such terms are insignificant in general as the good linearities of the simple (first-order) Hammett plots in Table 2 testify.[2]

The third-order cross-interaction constant, ρ_{ijk}, is normally negligible so that it was not necessary to consider in the reaction series investigated and reported previously by us on the application of cross-interaction constants.[2] Eqn. (3) can be modified to show the (non-interactive) point (*e.g.* $\hat{\sigma}_j$) of sign reversal at which the cross-interaction between σ_i and σ_k disappears.[3]

$$\begin{aligned}\log(k_{ijk}/k_{HHH}) &= \rho^{\circ}{}_i\sigma_i + \rho^{\circ}{}_j\sigma_j + \rho^{\circ}{}_k\sigma_k + \rho^{\circ}{}_{ij}\sigma_i\sigma_j + \rho^{\circ}{}_{jk}\sigma_j\sigma_k + \rho^{\circ}{}_{ik}\sigma_i\sigma_k + \rho_{ijk}\sigma_i\sigma_j\sigma_k = \rho^{\circ}{}_j\sigma_j + (\rho^{\circ}{}_i + \rho^{\circ}{}_{ij}\sigma_j)\sigma_i \\ &\quad + (\rho^{\circ}{}_k + \rho^{\circ}{}_{jk}\sigma_j)\sigma_k + (\rho^{\circ}{}_{ik} + \rho_{ijk}\sigma_j)\sigma_i\sigma_k \qquad (4)\end{aligned}$$

which can be simplified into,

$$\log(k_{ijk}/k_{HHH}) = -\frac{\rho^{\circ}{}_j\rho^{\circ}{}_{ik}}{\rho_{ijk}} + \left(\rho^{\circ}{}_i - \frac{\rho^{\circ}{}_{ij}\rho^{\circ}{}_{ik}}{\rho_{ijk}}\right)\sigma_i + \left(\rho^{\circ}{}_k - \frac{\rho^{\circ}{}_{jk}\rho^{\circ}{}_{ik}}{\rho_{ijk}}\right)\sigma_k \qquad (5)$$

at

$$\hat{\sigma}_j = -\frac{\rho^{\circ}{}_{ik}}{\rho_{ijk}} \qquad (6)$$

where a degree symbol denotes that substituent(s) not included in the subscript is(are) hydrogen(s). The non-interactive point $\hat{\sigma}_j$, is where the cross-interaction between σ_i and σ_k disappears, *i.e.*, the last term on the right hand side becomes zero in eqn. (4).

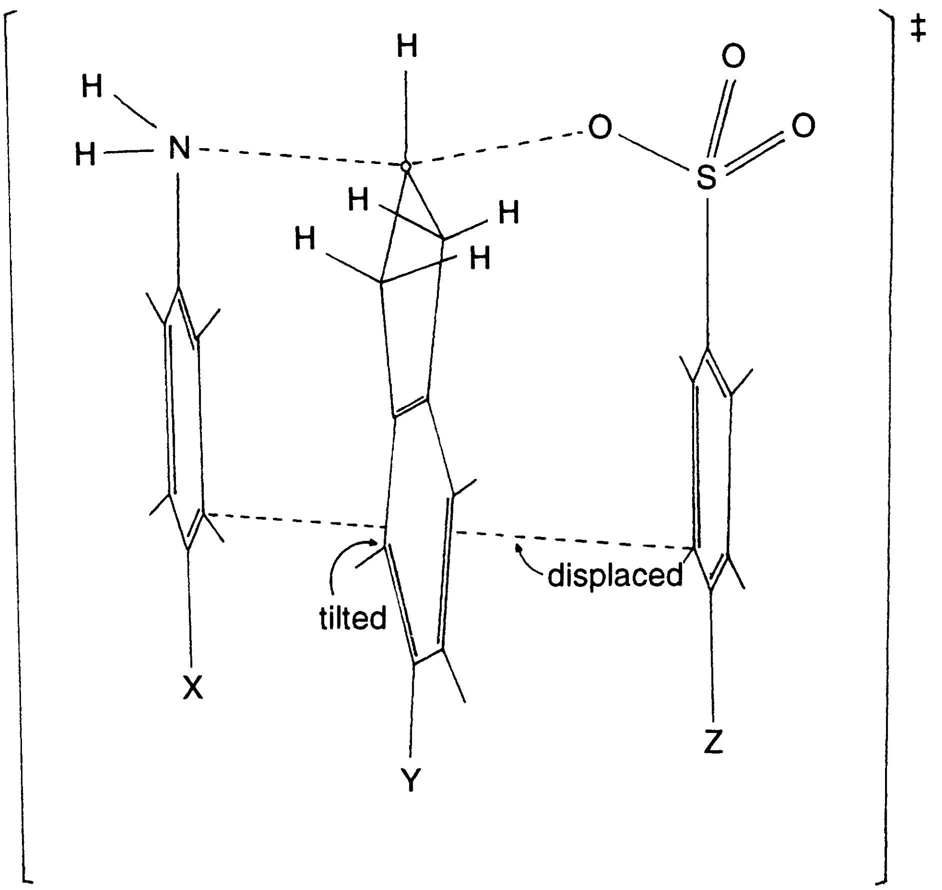


Fig. 1 Proposed transition state structure

Eqn. (5) indicates that at $\hat{\sigma}_j = -\rho^\circ_{ik}/\rho_{ijk}$, the reactivity, log ($k_{ijk}/k_{HHH}$), is the sum of a constant term, $-\rho^\circ_j\rho^\circ_{ik}/\rho_{ijk}$, and the additive effects of σ_i and σ_k. Of course, non-interactive points $\hat{\sigma}_i$ and $\hat{\sigma}_k$, can also be defined similarly.

For the reactions studied in this work, if we let $i = X, j = Y$ and $k = Z$, ρ_{ijk} is found to be $\rho_{XYZ} = -0.53$ with $\hat{\sigma}_Y = 0.43$, which falls somewhere in between Y = Br ($\sigma_Y = 0.31$) and Y = NO_2 ($\sigma_Y = 0.75$).* Since ρ°_{XY} and ρ°_{YZ} are -0.06 and -0.05, respectively, (Table 3), similar calculations lead to $\hat{\sigma}_X = -0.02$ and $\hat{\sigma}_Z = -0.11$, which are quite reasonable (Table 3). Since the ρ°_{XY} and ρ°_{YZ} values are small, ($\rho^\circ_{XY}\rho^\circ_{XZ}/\rho_{XYZ} \cong \rho^\circ_{YZ}$-$\rho^\circ_{XZ}/\rho_{XYZ} \leqslant 0.03$) and $-\rho^\circ_j\rho^\circ_{ik}/\rho_{ijk}$ = constant, the reactivity is reduced to a very simple form, eqn. (7). The reactivity,

$$\log(k_{XYZ}/k_{HHH}) = \rho^\circ_X\sigma_X + \rho^\circ_Z\sigma_Z + \text{constant} \qquad (7)$$

log (k_{XYZ}/k_{HHH}), becomes simply the sum of a constant and the additive effects of the two separate, non-interacting substituents in the two reactant fragments. Using the ρ_X and ρ_Z values (Table 2) and eqn. (7), k_{XYZ} at $\hat{\sigma}_Y = 0.43$ can be calculated. The calculated values are found to agree well with the observed (or interpolated) values in Table 1.

Now we may ask, what is so special about the reaction series studied in this work? First of all, the third order, or three-body, interactions between the three fragments, nucleophile (X), substrate (Y) and LG (Z), are strong in the TS, which was lacking in the initial state, as manifested by a large ρ_{XYZ} value. A large ρ_{XYZ} value can give an observable or realizable non-interactive point $\hat{\sigma}_Y$ ($\hat{\sigma}_X$ or $\hat{\sigma}_Z$), since only in the case of a large ρ_{XYZ} with relatively small ρ°_{XY}, ρ°_{YZ} or ρ°_{XZ}, $\hat{\sigma}_Y$ ($\hat{\sigma}_X$ or $\hat{\sigma}_Z$) falls within the range of substituent (constant) used in the ordinary organic reaction studies,[3] $\hat{\sigma}_Y \cong -1.0 \sim +1.0$ [eqn. (6)]. Thus a strong three-body coupling in the TS with a large ρ_{XYZ} value almost assures the existence of observable non-interactive points at which sign reversal of the second-order cross-interaction constants take place.

It is interesting to note that for second-order interactions, eqn. (1), such a non-interactive point, $\hat{\sigma}_X$ (or $\hat{\sigma}_Y$), leads to an isokinetic phenomenon, *i.e.*, at $\hat{\sigma}_X$ (or $\hat{\sigma}_Y$) $\rho_Y = 0$ (or $\rho_X = 0$) so that the reactivity is constant, log (k_{XY}/k_{HH}) = const.[3] In contrast, in the third-order interactions, eqn. (4), the reactivity becomes additive, eqn. (7), but not isokinetic.

We may speculate as to why the present reaction system has a large three-body coupling in the TS. There is a possibility of three (X, Y and Z) benzene rings stacked together in the TS, Fig. 1, for the reactions of indan-2-yl arenesulfonates with anilines. Our molecular mechanics (MM2) calculations[4] indicated that such a stacked TS structure could be more stable than a TS structure in which X and Z rings are inverted with respect to the Y ring.† Jorgenson *et. al.*,[5] have shown using Monte Carlo simulations of benzene dimer that at the ring centre–ring centre separation of 4–5 Å a tilted 'parallel stacked and displaced' structure is more stable than a face-to-face stacked with the rings in parallel planes or T-structure mainly due to the greater attractive Lennard–Jones interaction energies ($1/r^6$ term). The face-to-face stacked benzene dimer was found to have a repulsive Coulombic interaction between the two π-rings. The structure presented in Fig. 1 resembles such a stacked and displaced structure with slightly tilted X and Z rings

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* The σ_Y values are given by $(\sigma_m + \sigma_p)/2$.[1]

† The stacked reactant structure (two rings are separated by 5.01 Å with $\angle C_2OS$ 114.65°) is slightly more stable (by 0.6 kcal mol^{-1}) than the inverted structure.

relative to the Y ring; the separation of the ring centres is also favourable at *ca.* 4 Å. It is also true that the structure of three rings stacked together as in Fig. 1 is more stabilizing than the two rings stacking as in the benzene dimer.[6] It may also be relevant that the inverted structure of X and Z rings relative to the Y ring should be sterically unfavourable due to the two pairs of the out-of-plane hydrogens attached to the adjacent carbons, as the solvolysis results suggested. If such a 'tilted, stacked and displaced' TS ring structure (Fig. 1) applies to the present system, coupling between the three fragments, X, Y and Z, should certainly be strong and a strong three-body interaction with a large magnitude of ρ_{XYZ} can be expected.

Experimental

The indan-2-yl arenesulfonates and solvent used in this work are as reported previously.[1] The kinetic procedures have also been described.[1,7]

Product Analysis.—Indan-2-yl toluene-*p*-sulfonates was reacted with aniline in methanol at 55.0 °C for 4 days. After removing solvent, the products were separated by a chromatographic column (silica gel, 10% ethyl acetate–hexane). Four product spots were identified in addition to the three solvolysis products:[1] R_f 0.00 ($C_6H_5NH_3{}^+O^-SO_2C_6H_4$-*p*-$CH_3$ salt); 0.17 ($C_6H_4NH_2$); 0.25 (indan-2-yl toluene-*p*-sulfonate) and 0.43 (indan-2-yl anilide). The analytical data are as follows. Indan-2-yl anilide: m.p. 39.5 °C; ν_{max}(KBr)/cm^{-1} 1597, 1458 (C=C arom), 1319, 1176 (SO_2), 3383 (NH) and 1060 and 1024 (C–O); δ_H(60 MHz; $CDCl_3$) 2.6–3.0 (β-H, NH, m, 5 H), 4.3 (α-H, q, H) and 6.3–7.3 (Ph, m, 9 H) (Found: C, 85.9; H, 7.2; N, 6.8. $C_{15}H_{15}N$ requires C, 86.08; H, 7.22; N, 6.70%). $C_6H_5NH_3{}^+O^-SO_2C_6H_4$-*p*-$CH_3$: m.p. 186.0 °C; ν_{max}(KBr)/cm^{-1} 3095, 2644 ($NH_3{}^+$), 1301, 1178 (SO_2), 1539, 1400 (C=C), 1209, 1178, 567 and 480 (SO, $SO_3{}^-$) (Found: C, 58.8; H, 5.9; N, 5.2; S, 11.8. $C_{13}H_{15}NSO_3$ requires C, 58.85; H, 5.70; N, 5.28; S, 12.09%).

Acknowledgements

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