

BIMOLECULAR NUCLEOPHILIC DISPLACEMENT AT TERTIARY CARBON CENTERS: AMINOLYSES OF 2-CYANO-2-PROPYL AND 1-CYANOCYCLOOCTYL ARENESULFONATES†

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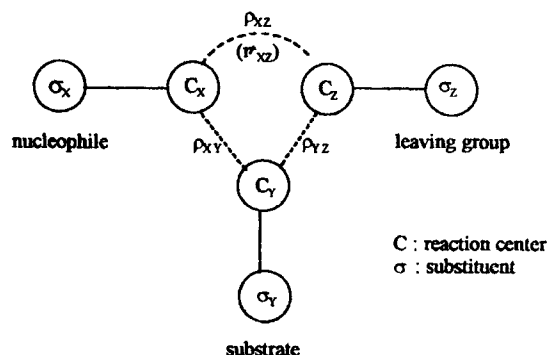
Kinetic studies were carried out on the reactions of anilines with 2-cyano-2-propyl and 1-cyanocyclooctyl arenesulfonates in acetonitrile at 50.0 °C. The second-order rate constants for the former are in general greater than those for the latter but the rates of the two become comparable for a strong nucleofuge. The cross-interaction constants, ρ_{XZ} (and β_{XZ}), are considerably smaller (*ca* -0.04) than those for the primary (*ca* 0.33) and secondary (*ca* 0.12) compounds. The negative sign and small magnitude are consistent with a dissociative S_N2 mechanism with a loose transition state structure. The *ab initio* MO theoretical results for $\text{Cl}^- + \text{RCl} \rightleftharpoons \text{ClR} + \text{Cl}^-$ at the MP2 level (MP2/6-31+G^{*}//MP2/6-31+G^{*}) confirm the looseness of the transition state for the tertiary (R) alkyl compounds. The average $r_{(\text{Cl}^{\cdots}\text{Cl})}^*$ value is 4.88 ± 0.03 Å, which is larger than those for the reactions at primary (4.68 ± 0.02 Å) and secondary (4.80 ± 0.02 Å) carbon centers. Thus a looser transition state with a smaller magnitude of ρ_{XZ} for the tertiary carbon centers has a larger theoretical $r_{(\text{Cl}^{\cdots}\text{Cl})}^*$ value.

INTRODUCTION

In the course of our development work on the cross-interaction constants, ρ_{ij} [equation (1)], where $i, j = \text{X}, \text{Y}$ or Z in Scheme 1, as a mechanistic tool for organic reactions in solution,² we have shown that the magnitude of ρ_{XZ} is inversely related^{2,3} to the overall tightness r_{XZ}^* of the transition state (TS) (Scheme 1), in bimolecular nucleophilic displacement reactions.

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

The greater is $|\rho_{XZ}|$, the tighter the TS is, i.e. the shorter is r_{XZ}^* . In a recent work, we found an interesting and important aspect of this relationship: the magnitude of ρ_{XZ} is a relatively large *constant* value (*ca* 0.29–0.40 in MeCN or MeOH at 45.0–65.0 °C) at a primary carbon, whereas it is a smaller *constant* value



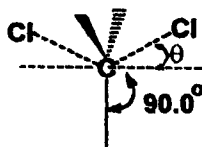
Scheme 1

† Determination of Reactivity by MO Theory, Part 100. For Part 99, see Ref. 1.

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Table 1. ρ_{XZ} values for the reactions of $\text{ROSO}_2\text{C}_6\text{H}_4\text{Z}$ with $\text{XC}_6\text{H}_4\text{NH}_2$

	R	Solvent	T (°C)	ρ_{xz}
Primary compounds	CH ₃	MeCN	65.0	0.32
		MeOH	65.0	0.30
	C ₂ H ₅	MeCN	65.0	0.34
		MeOH	65.0	0.33
	CH ₂ =CHCH ₂	MeCN	45.0	0.37
	CH ₂ =C(CH ₃)CH ₂	MeCN	45.0	0.40
	CH=CCH ₂	MeCN	45.0	0.29
	(CH ₃) ₃ CCH ₂	MeOH	55.0	0.31
	(CH ₃) ₃ SiCH ₂	MeCN	65.0	0.33
		MeOH	65.0	0.31
Secondary compounds	Isopropyl	MeCN	65.0	0.10
	2-Butyl	MeCN	65.0	0.12
	2-Pentyl	MeCN	65.0	0.13
	2-Hexyl	MeCN	65.0	0.13
	3-Pentyl	MeCN	65.0	0.12
	3-Hexyl	MeCN	65.0	0.12
	Cyclobutyl	MeCN	65.0	0.11
	Cyclopentyl	MeCN	65.0	0.11
	Cyclohexyl	MeCN	65.0	0.11
	Cycloheptyl	MeCN	65.0	0.11
				$\Delta\rho_{xz} \approx 0.20$

Table 2. $\text{MP2/6-31} + \text{G}^*$ geometries and activation barriers for the reactions of $\text{Cl}^- + \text{RCl} \rightleftharpoons \text{ClR} + \text{Cl}^-$ 

	R	$r_{(\text{Cl}\cdots\text{Cl})}^*$ (Å)	$\theta(^{\circ})^a$	%CX*	ΔE^* (kcal mol ⁻¹)
Primary compounds	CH_3	4.63	0.0	30.2	7.66
	CH_3CH_2	4.70	7.7	32.3	11.15
	$\text{CH}_2=\text{CHCH}_2$	4.71	6.6	31.8	8.21
	$\text{CH}\equiv\text{CCH}_2$	4.67	6.4	30.9	6.87
	$\text{C}_6\text{H}_5\text{CH}_2$	4.69	5.8	30.8	5.70
	$(\text{CH}_3)_3\text{CCH}_2$	4.65	16.5	35.2	17.96
	$(\text{CH}_3)_3\text{SiCH}_2$	4.66	7.3	30.6	6.94
	Av. 4.67 ± 0.02				
Secondary compounds	Isopropyl	4.79	11.1	35.2	14.00
	2-Butyl	4.79	9.2	35.3	12.19
	2-Pentyl	4.79	9.2	35.2	11.54
	2-Hexyl	4.79	9.2	35.1	11.24
	3-Pentyl	4.81	9.3	35.4	10.32
	3-Hexyl	4.81	9.3	35.3	9.65
	Cyclobutyl	4.81	9.4	35.5	15.21
	Cyclopentyl	4.82	9.4	36.5	13.63
	Cyclohexyl	4.82	16.4	38.9	14.95
	Av. 4.80 ± 0.02				
	$\Delta r^* \approx 0.10 \text{ Å}$				

^a The values reported originally ⁶ were in error; they are 2θ .

(ca 0.10–0.13 in MeCN at 65.0°C) at a secondary carbon center, irrespective of the size of the group attached to the reaction center carbon⁴ (Table 1). These constant ρ_{xz} values suggested that the TS is tight or loose, i.e. r_{xz}^* is short or long, depending on whether the reaction center carbon (C_Y) is primary or secondary, but the TS tightness varies very little with regard to the group attached to C_Y .

These experimental findings have been confirmed by *ab initio* MO calculations with the 6–31 + G^* basis sets including electron correlation effects at the second-order Möller–Plesset level⁵ (MP2) on the identity exchanges $X^- + RX \rightleftharpoons XR + X^-$ with $X = F$ and Cl . The MP2 (MP2/6–31 + G^* /MP2/6–31 + G^*) results indicated that the TS tightness, $r_{(X...X)}^*$, is relatively constant for R with primary [for seven primary R groups, $r_{(Cl...Cl)}^* = 4.67 \pm 0.02 \text{ \AA}$]⁶ and secondary [for ten secondary R groups, $r_{(Cl...Cl)}^* = 4.81 \pm 0.03 \text{ \AA}$]^{6,7} carbon centers, respectively, with a difference in $r_{(Cl...Cl)}^*$ between primary and secondary carbon centers of ca 0.10 Å (Table 2).

Thus a tighter TS with a greater experimental ρ_{xz} value (for the primary carbon centers) has a smaller theoretical $r_{(X...X)}^*$ value. Moreover, the TS tightness is relatively constant, i.e. $|\rho_{xz}| \approx \text{constant}$ and $r_{(X...X)}^* \approx \text{constant}$, for the reactions at a particular type of carbon center, i.e. primary or secondary, irrespective of the size and kind of the group or groups attached to the reaction center carbon.

In this work, we extended our studies to tertiary carbon centers. We determined the ρ_{xz} values experimentally for the reactions of 2-cyano-2-propyl (CPA) and 1-cyanocyclooctyl arenesulfonates (COA) with anilines in acetonitrile at 50.0°C, and the $r_{(Cl...Cl)}^*$ values theoretically for the identity exchanges of $X^- + RX \rightleftharpoons XR + X^-$ with $X = Cl$ and two tertiary carbon centers, R, at the same level of theory as we used previously for the primary and secondary carbon series (MP2/6–31 + G^* 1//MP2/6–31 + G^*).⁵

RESULTS AND DISCUSSION

Kinetics in solution

One might have expected the reactions of tertiary substrates to proceed by the limiting S_N1 mechanism as we have found for *α-tert*-butylbenzyl and adamantyl arenesulfonates for which the nucleophile had no effect on the rate and the nucleophile selectivity, ρ_X or β_X , was zero.⁸

The reactions of CPA and COA with anilines in acetonitrile at 50.0°C, however, followed clean second-order kinetics [equation (2)] with $k_0 = 0$. This change of mechanism to S_N2 from the normally S_N1 type mechanism for the tertiary carbon centers seems to result from a strong electron acceptor (CN) attached directly to the tertiary carbon. The second-order rate constants, k_2 , obtained are summarized in Table 3.

Table 3. Second-order rate constants, k_2 ($\times 10^4 \text{ l mol}^{-1} \text{ s}^{-1}$), for the reactions of Z-substituted 2-cyano-2-propyl and 1-cyanocyclooctyl arenesulfonates with X-substituted anilines in acetonitrile at 50.0°C

	X	Z			
		p-CH ₃	H	pCl	p-NO ₂
2-Cyano-2-propyl	p-OCH ₃	3.07	4.92	10.1	40.8
	p-CH ₃	1.96	3.11	6.26	25.7
	H	1.08	1.76	3.39	14.3
	p-Cl	0.435	0.674	1.39	5.54
1-Cyanocyclooctyl	p-OCH ₃	0.891	1.85	4.93	45.6
	p-CH ₃	0.575	1.17	3.18	28.4
	H	0.296	0.636	1.68	14.5
	p-Cl	0.135	0.274	0.714	6.39

$$k_{\text{obs}} = k_0 + k_2[\text{aniline}] \quad (2)$$

Table 3 reveals that rates are faster in general for CPA but become comparable for the two compounds when the leaving ability of the nucleofuge becomes strong, i.e. with $Z = p\text{-NO}_2$. This could be an indication that there is a greater degree of leaving group departure for COA than for CPA with a comparable degree of bond making in the TS; a greater degree of bond cleavage required in the TS will lead to a higher energy barrier for COA but a facile bond cleavage with a strong acceptor in the leaving group will lower the activation barrier sufficiently for COA so that the rates will become comparable to those for CPA. The effect of a strong acceptor in the leaving group on the rate can be greater for COA since the bond cleavage is more important in the TS. This interpretation is supported by the magnitude of the Hammett and Brønsted coefficients, ρ_X (ρ_{nuc}), β_X (β_{nuc}), ρ_Z (ρ_{lg}) and β_Z (β_{lg}) in Table 4.

We note that the magnitude of ρ_X (and β_X) is similar but that of ρ_Z (and β_Z) is greater for COA than for CPA, suggesting that the degree of bond formation is similar but that of bond cleavage is greater for COA in the TS.

The rate data in Table 3 were subjected to multiple regression analysis using equation (1) with $i, j = X, Z$, and the cross-interaction constants derived² are collected in Table 5. The sign of ρ_{xz} (and β_{xz}) is negative; according to our experience, this is in line with a dissociative type of S_N2 mechanism for which a stronger nucleophile ($\delta\sigma_X < 0$) and a stronger nucleofuge ($\delta\sigma_Z > 0$) lead to a later TS ($\delta\rho_X < 0$ and $\delta\rho_Z > 0$) in accordance with the alternative definition of ρ_{xz} .^{2,9}

$$\rho_{xz} = \frac{\partial^2 \log k_{xz}}{\partial \sigma_X \partial \sigma_Z} = \frac{\partial \rho_Z}{\partial \sigma_X} = \frac{\partial \rho_X}{\partial \sigma_Z} (< 0) \quad (3)$$

The magnitude of ρ_{xz} (and β_{xz}) is unusually small, and interestingly the average value of 0.04 ± 0.01 is approximately one-third of the ρ_{xz} value for the secondary series

convincing. However, very large reactant systems involving tertiary reaction centers were difficult to handle in the kinetic experimental work owing to unstable reactants and products and also required excessive computation times (over six non-hydrogen atoms) in the MP2 calculations. These difficulties are, no doubt, caused by the CN group present, which ensures that the reaction proceeds by an S_N2 rather than an S_N1 pathway.

EXPERIMENTAL

Materials. Acetone, cyclooctane, trimethylsilyl cyanide and benzenesulfonyl chlorides used in the preparation of substrates, 2-cyano-2-propyl and 1-cyanocyclooctyl arenesulfonates, were Aldrich GR grade. The solvent acetonitrile was Merck GR grade, which was further distilled over phosphorus pentoxide. Anilines were Aldrich GR grade and were recrystallized or redistilled before use.

Preparation of substrates. Acetone cyanohydrin¹⁰ was prepared by dissolving sodium hydrogensulfite in cold water and adding acetone dropwise followed by sodium cyanide. The product was extracted with methylene chloride prior to proceeding to the next step in the synthesis.

1-Cyanocyclooctanol¹¹ was prepared by adding 80 ml of anhydrous methylene chloride to cyclooctanone (1.0 equiv.) followed by a small amount of zinc iodide and trimethylsilyl cyanide (1.1 equiv.), and reacting the mixture for 12 h at 40°C. To the crude cyclooctyl trimethylsilyl cyanohydrin, 50 ml of 3 M hydrochloric acid were added and reacted at 40°C. After 2 h, this mixture was extracted with diethyl ether and the extract was washed with 1 M sodium thiosulfate and then dried over $MgSO_4$. After filtration and removal of the solvent under reduced pressure, the product, 1-cyanocyclooctanol, was obtained by column chromatography.

Benzenesulfonic anhydride¹² was obtained by adding phosphorus pentoxide to benzenesulfonic acid and heating at 100–150°C. The product was then extracted for the synthesis in the next step. Sulfonate derivatives of acetone cyanohydrin and 1-cyanocyclooctanol were prepared by mixing 40 ml of ethanol (4 mmol), pyridine (4.1 mmol) and benzenesulfonic anhydride (excess) and reacting at room temperature. After adding cold water and extraction with methylene chloride, the extract was washed with 10 ml of 1 M HCl and with brine twice. The extract was then dried over $MgSO_4$. After removing the solvent under reduced pressure, the final product was obtained by column chromatography. The analytical data obtained by NMR spectrometry (JEOL, 400 Mh) are as follows.

2-Cyano-2-propyl benzenesulfonate: liquid, δ_H ($CDCl_3$) 1.88 (6H, s, $2CH_3$), 7.58 (2H, t, $J=8.06$ Hz, *meta*), 7.67 (1H, t, $J=7.33$ Hz, *para*), 7.98 (2H, d, $J=7.33$ Hz, *ortho*); δ_C 28.46, 75.13, 118.06, 127.85, 129.20, 129.26, 134.27; MS, m/z 75.13, 118.06, 127.85, 129.20, 129.26, 134.27; MS, m/z 225 (M^+).

2-Cyano-2-propyl tosylate: liquid, δ_H ($CDCl_3$) 1.87 (6H, s, $2CH_3$), 2.46 (3H, s, CH_3), 7.37 (2H, t, $J=8.06$ Hz, *meta*), 7.86 (2H, d, $J=8.06$ Hz, *ortho*); δ_C 21.69, 28.45, 74.24, 118.14, 127.50, 129.53, 134.11, 145.45; MS, m/z 239 (M^+).

2-Cyano-2-propyl *p*-chlorobenzenesulfonate: liquid, δ_H ($CDCl_3$) 1.89 (6H, s, $2CH_3$), 7.56 (2H, t, $J=8.06$ Hz, *meta*), 7.92 (2H, d, $J=8.06$ Hz, *ortho*); δ_C 28.51, 75.47, 117.92, 129.37, 135.07, 140.84; MS, m/z 259 (M^+).

2-Cyano-2-propyl *p*-nitrobenzenesulfonate: m.p. 85–86°C; δ_H ($CDCl_3$) 1.92 (6H, s, $2CH_3$), 8.18 (2H, d, $J=8.79$ Hz, *meta*), 8.43 (2H, d, $J=8.79$ Hz, *ortho*); δ_C 28.51, 76.47, 117.57, 124.50, 129.34, 150.98; MS, m/z 270 (M^+).

1-Cyanocyclooctyl benzenesulfonate: liquid, δ_H ($CDCl_3$) 1.49–2.42 (14H, m, cyclooctyl), 7.57 (2H, t, $J=8.06$ Hz, *meta*), 7.66 (1H, t, $J=8.06$ Hz, *para*), 7.92 (2H, d, $J=7.33$ Hz, *ortho*); δ_C 21.02, 24.12, 27.20, 34.82, 83.15, 117.68, 127.79, 129.21, 134.05, 137.42; MS, m/z 293 (M^+).

1-Cyanocyclooctyl tosylate: liquid, δ_H ($CDCl_3$) 1.51–2.43 (14H, m, cyclooctyl), 2.46 (3H, s, CH_3), 7.35 (2H, t, $J=8.06$ Hz, *meta*), 7.85 (2H, d, $J=8.06$ Hz, *ortho*); δ_C 21.02, 21.69, 24.12, 27.20, 34.82, 82.83, 117.95, 127.85, 129.80, 134.48, 145.46; MS, m/z 307 (M^+).

1-Cyanocyclooctyl *p*-chlorobenzenesulfonate: liquid, δ_H 1.51–2.42 (14H, m, cyclooctyl), 7.54 (2H, t, $J=8.06$ Hz, *meta*), 7.91 (2H, d, $J=8.06$ Hz, *ortho*); δ_C 21.05, 24.12, 27.20, 34.93, 83.58, 111.76, 129.32, 135.84, 140.87; MS, m/z 327 (M^+).

1-Cyanocyclooctyl *p*-nitrobenzenesulfonate: liquid, δ_H ($CDCl_3$) 1.51–2.34 (14H, m, cyclooctyl), 8.13 (2H, t, $J=8.79$ Hz, *meta*), 8.43 (2H, d, $J=8.79$ Hz, *ortho*); δ_C 21.08, 24.12, 12.27, 27.20, 34.97, 83.64, 117.41, 124.35, 129.29, 140.98, 150.93; MS, m/z 338 (M^+).

Kinetic procedure. Kinetic procedures were as reported previously.^{4,7,9}

Product analysis. The substrates were reacted with aniline at 50.0°C in acetonitrile under the same reaction conditions as used in the kinetic runs. However, we failed to isolate the product, anilide, owing to its extreme instability. However, we followed the reaction in CD_3CN by NMR (Jeol, 400 MHz). For the reaction of 2-cyano-2-propyl *p*-chlorobenzenesulfonate with *p*-methoxyaniline, the original peak at 1.89 ppm (methyl peak for benzenesulfonate moiety) decreased while a new peak at 1.84 ppm (CH_3 peak for anilide moiety) grew as the reaction proceeded. The shift of the peak was found to occur since CH_3 changes from a CO moiety to a CN moiety; the peak was weak since CH_3 groups are present beyond one C (tertiary) atom. For the reactions of 1-cyanocyclooctyl *p*-chlorobenzenesulfonate with

p-methoxyaniline, similar trends were found, although the multiple appearance of a CH₂ peak at 2.10–1.75 ppm made the identification difficult. We analyzed the reaction mixture by GC and NMR but found no peak corresponding to any olefins formed. We believe that there is no or an undetectable amount of elimination product formed so that the conductivity changes measured represented pure displacement reaction products.

Computational method. The basis sets and computational levels and procedures used were the same as those applied to the primary and secondary carbon centers.^{6,7} We report two types of results: HF (HF/6-31 + G*//HF/6-31 + G*) and MP2 (MP2/6-31 + G*//MP2/6-31 + G*).⁵ All calculations were carried out using the Gaussian 92 programs.¹³ Geometries of the reactants and TSs were optimized and all positive eigenvalues and only one negative eigenvalue, respectively, in the Hessian matrix were identified to confirm the equilibrium and TSs in all the HF level calculations.¹⁴

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