

The Effect of 4-Methyl and 4-Nitro Substituents on the Reactivity of Benzylic Compounds

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The rates of reaction of 4-methylbenzyl halide, benzyl halide and 4-nitrobenzyl halide with various nucleophiles have been determined in acetonitrile.

From the second-order rate constants the rate ratios $k_{(4-Me)}/k_{(4-H)}$ and $k_{(4-NO_2)}/k_{(4-H)}$ have been calculated. These ratios along with some representative values from the literature are presented. The $k_{(4-Me)}/k_{(4-H)}$ ratio varies from 1.2 to 2.3 indicating that the methyl group is rate accelerating for all the reactions. The $k_{(4-NO_2)}/k_{(4-H)}$ ratio varies from 0.28 to 4.7, however, and in addition these ratios are grouped according to the charge of the nucleophile. In general $k_{(4-NO_2)}/k_{(4-H)} > 1$ when the nucleophile is anionic while ≤ 1 when it is uncharged.

These ratios are discussed with respect to recent theories on the prediction of the effect of substituent changes on transition state structures. It is concluded that these rate ratios alone are poor probes for the elucidation of transition state structure.

The Hammett equation is a well-known empirical, linear free energy relationship which correlates structure and reactivity.¹ It has been used extensively to correlate data of benzene derivatives as substrates. There are, however, a number of reactions of 3- or 4-substituted benzylic compounds which show significant deviations from linearity.² In particular non-linear Hammett plots are obtained from simple S_N2 reactions of 3- or 4-substituted benzyl halides. For example, Finckelstein reactions^{3,4} and reactions with thiosulfate ion^{5,6} give U-shaped plots; whereas, L-shaped plots are obtained with Menshutkin reactions⁷ and reactions with triphenylphosphine.⁸

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Upon examining Finckelstein and Menshutkin reaction data it was noticed that reactions of uncharged nucleophiles with 4-substituted benzyl halides had a rate ratio $k_{(4-Me)}/k_{(4-H)} > 1$ and a rate ratio $k_{(4-NO_2)}/k_{(4-H)} < 1$. On the other hand reactions of anionic nucleophiles with the same substrates had $k_{(4-Me)}/k_{(4-H)} > 1$, as with uncharged nucleophiles, but had $k_{(4-NO_2)}/k_{(4-H)} > 1$. It thus appeared that the $k_{(4-NO_2)}/k_{(4-H)}$ rate ratios are apparently grouped according to the charge type of the nucleophile.

A study of the S_N2 reaction of 4-substituted benzyl halides in acetonitrile using charged and uncharged nucleophiles was undertaken to test the generality of these groupings.

EXPERIMENTAL

Acetonitrile was purified as reported⁹ and flushed with nitrogen prior to use. The benzyl halides were prepared and purified as previously.⁸ Pyridine and dimethylaniline were purified by standard procedures. Anhydrous tetraphenylarsonium salts of all the ionic nucleophiles were prepared as previously reported¹⁰ and carefully dried under high vacuum. It was assumed that these salts were completely dissociated in acetonitrile.¹¹ Thiourea, Fluka *puriss.*, was crystallized from water and then several times from acetonitrile. Diethyl sulfide, Fluka *purum*, was treated with metallic sodium and twice distilled under reduced pressure.

The rates of reactions utilizing the uncharged nucleophiles were determined by previously described conductance methods.⁸ Rate constants for the diethyl sulfide nucleophile were calculated from the first 15–30 % of reaction and assuming the mobility of the benzyldiethylsulfonium ions to be comparable with those of the benzyltriethylammonium ions.

Table 1. Second-order rate constants for the reactions of 4-substituted benzyl halides (RX) in acetonitrile.

Nucleophile	RX	<i>t</i> /°C	<i>k</i> ₂ (l mol ⁻¹ s ⁻¹) ^a		
			4-Me	4-H	4-NO ₂
NNN ⁻	RBr	25	4.7 ± 0.2	2.3 ± 0.1	11.0 ± 0.5
NCS _e ⁻	RBr	25	(2.7 ± 0.1) × 10 ⁻¹	(1.4 ± 0.1) × 10 ⁻¹	(3.3 ± 0.2) × 10 ⁻¹
NCS ⁻	RBr	25	(4.4 ± 0.3) × 10 ⁻²	(2.7 ± 0.1) × 10 ⁻²	(5.4 ± 0.3) × 10 ⁻²
OCN ⁻	RBr	25	(12.9 ± 0.5) × 10 ⁻³	(8.3 ± 0.3) × 10 ⁻³	(20.0 ± 1.0) × 10 ⁻³
(H ₂ N) ₂ CS	RI	25	(6.0 ± 0.2) × 10 ⁻²	(3.4 ± 0.1) × 10 ⁻²	(3.8 ± 0.1) × 10 ⁻²
Et ₂ S	RI	50	(10.0 ± 0.3) × 10 ⁻²	(4.9 ± 0.1) × 10 ⁻³	(1.70 ± 0.05) × 10 ⁻³
Py	RI	50	(22.0 ± 0.5) × 10 ⁻³	(18.0 ± 0.5) × 10 ⁻³	(5.0 ± 0.1) × 10 ⁻³
Me ₂ NPh	RI	50	(32 ± 1) × 10 ⁻³	(15.0 ± 0.5) × 10 ⁻³	(3.8 ± 0.1) × 10 ⁻³

^a The errors are average deviations of the mean.

The rates of the ionic nucleophiles were determined by IR employing liquid IR cells. The reaction solutions were kept in a constant temperature bath, 25.0 ± 0.1 °C, and aliquots were withdrawn periodically. The disappearance of the pseudohalide ion was monitored in the 2100 cm⁻¹ region. The difference in wavenumber for maximum absorption of products and reactants was: RNCO, NCO⁻, ~78 cm⁻¹; RSCN, SCN⁻, 98–100 cm⁻¹; RSeCN, SeCN⁻, 86–88 cm⁻¹; RN₃, N₃⁻, 95–100 cm⁻¹.

RESULTS

The second-order rate constants (*k*₂) are presented in Table 1. All kinetic measurements were carried out in dry acetonitrile at either 25.0 or 50.0 °C. For reactions involving the uncharged nucleophiles, the nucleophile concentration was kept in large excess, and first-order rate constants were determined from plots of log (1/*R*_∞ - 1/*R*) vs. *t* where *R* is the resistance. From *k*₁ and the nucleophile concentration *k*₂ could be calculated. The reactions using diethyl sulfide as the nucleophile did not go to completion due to the low carbon basicity of the sulfide; thus, first-order rate constants were obtained from just the first 15–30 % of reaction. When ionic nucleophiles were used, the concentrations of the nucleophile and substrate were equal, and *k*₂ was obtained directly from plots of 1/*C* vs. *t* where *C* is the concentration of the nucleophile.

The *k*_(4-X)/*k*_(4-H) ratios calculated for this study are shown in Table 2 along with some representative values calculated from literature sources. As can be seen, all the *k*_(4-Me)/*k*_(4-H) ratios are > 1 whichever nucleophile

was used. The *k*_(4-NO₂)/*k*_(4-H) ratios are grouped according to nucleophile charge type being > 1 for negatively charged nucleophiles and ≤ 1 for neutral ones. Thiourea, triphenylphosphine and trimorpholinophosphine have *k*_(4-NO₂)/*k*_(4-H) ratios which are close to unity.

DISCUSSION

The detailed mechanism of S_N2 reactions has been, and still is, a matter of controversy.^{12,13} For the sake of discussion here we will adopt the "loose-tight" transition state model of Ko and Parker¹⁴ which may be closest to reality.¹² It has been argued¹⁴ that protic solvents favor "looser" transition states whereas aprotic solvents favor the "tighter" form. Thus, the literature data presented in Table 2 has been limited to dipolar aprotic solvents. The effect of the halogen leaving group on *k*_(4-Me)/*k*_(4-H) and *k*_(4-NO₂)/*k*_(4-H) is shown in Table 3. In general both *k*_(4-Me)/*k*_(4-H) and *k*_(4-NO₂)/*k*_(4-H) decrease as the atomic weight of the halogen decreases, but as can be seen there are notable exceptions. Therefore, some caution must be exercised when attempting to compare reactions with dissimilar leaving groups. The data are discussed with these limitations in mind.

It has been argued^{4-7,15-17} that the sign of the charge on the benzylic carbon atom (*C*_α) in the transition state is substituent dependent in S_N2 reactions of benzylic systems. The charge changes from positive to negative as the substituent is changed from electron-donating to electron-withdrawing. In a "loose" transition state bond breaking is ahead of bond

Table 2. $k_{(4-X)}/k_{(4-H)}$ ratios for nucleophilic substitution of 4-substituted benzyl halides (RX) in dipolar aprotic solvents at 25 °C unless stated otherwise.

No.	Nucleophile	RX	Solvent	$10^4 k_{2,4-H}$ ($l \text{ mol}^{-1} \text{ s}^{-1}$)	$\frac{k_{(4-Me)}}{k_{(4-H)}}$	$\frac{k_{(4-NO_2)}}{k_{(4-H)}}$	Ref.
1	NNN ⁻	RBr	MeCN	23000	2.04	4.71	24
2	NCS ₆ ⁻	RBr	MeCN	1400	1.93	2.40	24
3	NCS ⁻	RBr	MeCN	270	1.78	2.02	24
4	OCN ⁻	RBr	MeCN	83	1.55	2.40	24
5	Br ⁻	RBr ^a	Me ₂ CO	26.8	2.26	4.19	4
6	Br ⁻	RBr	EDA ^b	7.4	6.16 ^b	11.33	3
7	NCS ⁻	RCl	Me ₂ CO	7.8 ^c	1.40	4.44	25
8	(H ₃ N) ₂ CS	RI	MeCN	340	1.76	1.12	24
9	Et ₃ S	RI	MeCN	49 ^d	2.04	0.34	24
10	Ph ₃ P	RBr	MeCN	21	1.62	1.09	8
11	Mor ₃ P	RBr	MeCN	83	1.45	1.03	8
12	(MeO) ₃ P	RBr	MeCN	0.53 ^d	1.40	0.75	26
13	Ph ₃ As	RBr	MeCN	0.98 ^d	1.75	0.56	8
14	Et ₃ N	RBr	MeCN	68	1.91	0.38	8
15	Me ₂ NPh	RI	MeCN	150 ^d	2.13	0.25	24
16	Py	RI	MeCN	180 ^d	1.22	0.28	24
17	Py	RBr	DMF	8.46	1.51	0.68	27
18	Py	RBr	Me ₂ CO	1.22 ^e	1.65	0.92	28

^a The substrate is α -phenylethyl bromide. ^b Ethylenediacetate solvent. 4-Methoxy substituent. ^c At 65 °C. ^d At 50 °C. ^e At 20 °C.

making, and electron-donating substituents stabilize the developing positive charge plus promote its formation. When bond making is ahead of bond breaking, the transition state is considered "tight" with some negative charge on the C_α. Electron-withdrawing substituents can both stabilize this charge and facilitate its development. Recently, theories¹⁸⁻²⁰ for predicting the effect of substituent changes on transition state geometries have been proposed. In general, one must be able to predict the effect of a substituent perturba-

tion on the parallel and perpendicular normal stretching coordinates in the transition state:

parallel motion: N → ← C L →

perpendicular motion: ← N ← C L →

Parallel motion is along the reaction coordinate, and perpendicular motion is orthogonal to the reaction coordinate. Perturbations which effect parallel motion affect the position along the reaction coordinate in accord with the Hammond postulate.²¹ Perturbations affecting per-

Table 3. Trends in $k_{(4-Me)}/k_{(4-H)}$ and $k_{(4-NO_2)}/k_{(4-H)}$ with leaving group.

Nucleophile	RX	Solvent	<i>t</i> °C	$\frac{k_{(4-Me)}}{k_{(4-H)}}$	$\frac{k_{(4-NO_2)}}{k_{(4-H)}}$	Ref.
Ph ₃ As	RI	MeCN	50	1.86	0.59	8
	RBr			1.75	0.56	
Ph ₃ P	RI	MeCN	25	1.67	0.89	8
	RBr			1.62	1.09	
(MeO) ₃ P	RI	MeCN	50	1.47	0.56	26
	RBr			1.40	0.75	
Py	RBr	MeOH	25	2.88	0.51	27
	RCl			2.37	0.35	
	RBr			1.51	0.68	
Py	RCl	DMF	25	2.55	0.66	27

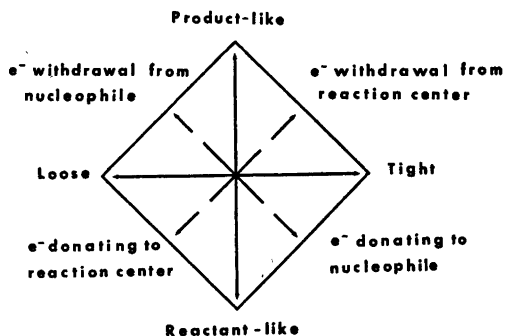


Fig. 1. Pictorial representation of the prediction of substituent effects in S_N2 reactions of benzylic halides.

pendicular motion determine the "tightness" or "looseness" of the transition state. Also, a particular perturbation will affect both the parallel and perpendicular motions. It should be noted that in some cases the effects on these motions oppose each other making even qualitative predictions difficult.²⁰ A summary of the predictions are shown pictorially in Fig. 1. The horizontal and vertical lines refer to the transition state geometries of "loose-tight" (perpendicular motion) and the Hammond postulate (parallel motion), respectively. The dashed diagonal lines refer to perturbation effects on the nucleophile (or leaving group) and on the reaction center (C_α). Thus, an electron-withdrawing substituent attached to the nucleophile can make the transition state both "looser" and more "product-like". However, the prediction of the perturbational effect on C_α , as shown in Fig. 1, applies only when the attacking nucleophile is neutrally charged and the leaving group negatively charged, or when the attacking nucleophile has the same charge but is lighter than the leaving nucleophile. When these conditions are reversed, the reaction center labels must be rotated 90° counter clockwise. The dashed lines should not be taken to imply that a particular perturbation affects both perpendicular and parallel motions equally. The effect on one of the motions may predominate; for example, a transition state may become "tighter" without becoming more or less "product-like".

As can be seen from Table 2 the 4-Me group is rate accelerating, $k_{(4-Me)}/k_{(4-H)} > 1$, which

suggests the development of positive charge on C_α in a "loose" transition state. The small range of the $k_{(4-Me)}/k_{(4-H)}$ ratios compared to four orders of magnitude variation in k_2 also indicates that there is not too much variation in the "looseness" of the transition state. It is interesting to note, however, that the first four entries (1-4) for the charged nucleophiles show a regular decrease in $k_{(4-Me)}/k_{(4-H)}$ with decreasing reactivity. According to the Hammond postulate²¹ the transition state becomes more product like as the reactivity decreases; thus, the decrease in $k_{(4-Me)}/k_{(4-H)}$ could be explained by an increase in bond-making, making the transition state tighter which would reduce the positive charge on the C_α . Evidence from chlorine isotope effects of Grimsrud and Taylor²² support this analysis. It is, therefore, unfortunate that the rest of the data presented in Table 2 is not more amenable to such an analysis.

The most striking feature of the data in Table 2 is the groupings of $k_{(4-NO_2)}/k_{(4-H)}$. All of the anionic nucleophiles have rather large positive $k_{(4-NO_2)}/k_{(4-H)}$ ratios. Two phosphorus nucleophiles and thiourea exhibit only a minimal rate acceleration on going from 4-H to 4- NO_2 substituents: $k_{(4-NO_2)}/k_{(4-H)} \approx 1$. For the rest of the uncharged nucleophiles the reaction rate does decrease upon going from the unsubstituted to the 4-nitro substituted substrate.

The groupings of the $k_{(4-NO_2)}/k_{(4-H)}$ ratios according to nucleophile charge type are in accord with the predictions. Increasing the electron supply at the nucleophile (uncharged to anionic) increases $k_{(4-NO_2)}/k_{(4-H)}$ indicating a shift to "tighter" transition states. In a "tight" transition state the advanced bonding between the nucleophile and the carbon atom would increase the electron density on the carbon. The 4-nitro group in the benzylic system can effectively drain off this excess charge. Anionic nucleophiles, which already have an excess of charge, would be expected to place much more charge on the C_α than uncharged nucleophiles. It is also not unreasonable to expect that while the nitro group stabilizes this charge development, it also encourages it causing the transition state to become "tight" (Fig. 1). The net effect is for the nitro group to really accelerate reactions of the charged nucleophiles. On the other hand un-

charged nucleophiles cannot donate electrons well enough to place bond-making as far ahead of bond-breaking as can charged nucleophiles. As the uncharged nucleophile approaches the C_α , electrons begin to be donated increasing the carbon's electron density. At the same time the nucleophile acquires a partial positive charge; thus, electrons are partially removed from the newly forming bond. This transition state is then not nearly as "tight" as the one involving anionic nucleophiles, in accord with the predictions.

If one looks at the phosphorus and arsenic nucleophiles (Table 2; entries 10–13) an interesting trend in the $k_{(4-NO_2)}/k_{(4-H)}$ ratios will be noticed. The lowest $k_{(4-NO_2)}/k_{(4-H)}$ ratio corresponds to triphenylarsine which is a much weaker base than triphenylphosphine toward both the proton²³ and carbon.⁹ For the phosphorus nucleophiles $k_{(4-NO_2)}/k_{(4-H)}$ increases with phosphorus atom basicity toward carbon as would be predicted⁹ by the decreasing inductive electron-withdrawal of the attached groups. Thus, the increase in $k_{(4-NO_2)}/k_{(4-H)}$ ratios with increasing basicity is in the direction predicted.

Finally, neither $k_{(4-Me)}/k_{(4-H)}$ nor $k_{(4-NO_2)}/k_{(4-H)}$ correlate systematically with the variation in reaction rate between the various reactions or with nucleophile basicity. It appears that these ratios alone are not sensitive enough probes for possible variations in transition state structure. Thus, the data give only general support to theories for predicting changes in transition state geometries caused by substituent effects. The irregularities in the data could possibly be due to specific solvation effects which have not been taken into account.

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