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Correlation analysis in the benzylation of sulfur nucleophiles

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In the nucleophilic substitution reaction of benzyl bromides with three sulfur nucleophiles a linear relationship between the nucleophile discrimination parameter (*s*) and the Hammett substituent constant (σ) is observed.

Keywords: nucleophile discrimination parameter, Hammett substituent constan, benzylation, sulfur nucleophile

Nucleophilic substitution at benzylic carbon atom is of broad synthetic utility. A literature survey on the kinetics of nucleophilic substitution on benzyl halides shows that a wide range of nucleophiles have been used. Some of these nucleophiles are thioureas,[1-3] thiobenzamides,[3,4] anilines,[5] pyridine,[6,7] sulfate,[8] sulfite,[8] urea,[8] thiosulfate,[8,9] and *s*-triazole.[10] In some of these studies the Swain and Scott relationship[11] has been applied and the nucleophile discrimination parameters have been determined. The present study is aimed at the kinetic study of nucleophilic substitution reaction at substituted benzyl bromides using three structurally similar sulfur nucleophiles, 2-mercaptobenzimidazole (2-MBIZ), 2-mercaptobenzothiazole (2-MBTZ) and 2-mercaptobenzoxazole (2-MBOZ) and determining their nucleophilicity constants which are not available in the literature.

Results and discussion

Second-order rate constants of the reaction between benzyl bromides (p-NO$_2$, p-Br, p-CH$_3$ and –H) and the sulfur nucleophiles 2-MBIZ, 2-MBTZ, 2-MBOZ, thiourea and *N*-methylthiourea were determined in methanol medium at 303 K and are presented in Table 1. The nucleophilicity constants of thiourea (4.10)[11] and *N*-methylthiourea (4.00)[12] and the substrate constant '*s*' for benzyl bromide[12] are available in the literature. Using these values, and the Swain–Scott relationship,[11] the nucleophilicity constants of 2-MBIZ, 2-MBTZ and 2-MBOZ were determined. These are 4.58, 3.70 and 3.18 respectively. Correlation of the rate constants of the reactions between *p*-nitro-, *p*-bromo- and *p*-methyl- benzyl bromides and these nucleophiles with their nucleophilicity constants resulted in the following relationships.

$$\begin{array}{llll} \log k = & -7.80 & + \; 1.38\,n & ; \quad r = 0.98 \\ & (0.88) & (0.22) & \qquad (0.23) \end{array}$$

with *p*-nitrobenzyl bromide

$$\begin{array}{llll} \log k = & -6.89 & + \; 1.21\,n & ; \quad r = 0.99 \\ & (0.26) & (0.07) & \qquad (0.07) \end{array}$$

with *p*-bromobenzyl bromide

$$\begin{array}{llll} \log k = & -6.05 & + \; 1.03\,n & ; \quad r = 0.98 \\ & (0.42) & (0.10) & \qquad (0.11) \end{array}$$

with *p*-methylbenzyl bromide.

The values in parentheses are standard errors of the regression coefficients.

The nucleophile discrimination parameters (substrate parameters), s^{11}, which are a measure of the susceptibility towards nucleophilic substitution of the different benzyl bromides are in the order p-NO$_2$ > p-Br > –H > p-CH$_3$. The electron-withdrawing group on the benzene ring increases its susceptibility towards nucleophilic substitution while the electron-releasing group decreases this nature. An attempt to

Table 1 Second-order rate constants, and nucleophile discrimination parameters [Benzyl bromide] = [Nucleophile] = 2.00×10^{-2} mol dm^{-3} Solvent = Methanol Temp = 303 K

Substituent	Nucleophile	$k \times 10^4$/dm^3 mol^{-1} s^{-1}	s	σ^a
–H	Thiourea	113.02	1.10[b]	0.00
	N-methylthiourea	87.54		
	2-MBIZ	401.26		
	2-MBTZ	37.24		
	2-MBOZ	10.62		
p-CH$_3$	Thiourea	166.64	1.03	–0.17
	N-methylthiourea	87.25		
	2-MBIZ	392.32		
	2-MBTZ	70.83		
	2-MBOZ	13.42		
p-Br	Thiourea	145.00	1.21	0.23
	N-methylthiourea	97.65		
	2-MBIZ	416.70		
	2-MBTZ	33.42		
	2-MBOZ	8.92		
p-NO$_2$	Thiourea	125.02	1.38	0.78
	N-methylthiourea	60.04		
	2-MBIZ	250.32		
	2-MBTZ	10.43		
	2-MBOZ	4.26		

[a] From ref. 13.
[b] From ref. 12.

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correlate s and the Hammett substituent constant σ[13] resulted in the following relation

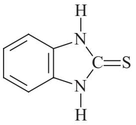
$$\begin{array}{ll} s = \underset{(0.01)}{1.10} + \underset{(0.02)}{0.37\,\sigma} \quad ; & r = \underset{(0.02)}{0.99} \\ n = 4 & \end{array}$$

This excellent correlation indicates that the nucleophile discrimination parameter, s, increases with the increase in the Hammett substituent constant σ.

The second-order rate constants presented in Table 1 suggest that with each substrate the order of reactivity is

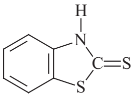
2-MBIZ >> 2-MBTZ > 2-MBOZ

The highest reactivity of 2-MBIZ among the three is probably due to the presence of two nitrogen atoms holding a pair of electrons on either side of >C=S.

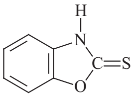


2-MBIZ

which increases the electron-donating capacity of the sulfur atom to form a bond with a benzylic carbon atom. In the other two nucleophiles, only one nitrogen atom and either a sulfur (in 2-MBTZ) or an oxygen atom (in 2-MBOZ) are present.



2-MBTZ



2-MBOZ

Among these two nucleophiles 2-MBTZ reacts faster than 2-MBOZ. This difference in rates is attributed to the difference in the electro-negativities of the oxygen and the sulfur atoms present adjacent to the >C=S group. In 2-MBOZ, the more electronegative oxygen atom pulls electrons towards itself making the electron availability less on S for bond formation with the benzylic carbon atom of the substrate. However, in 2-MBTZ, the less electronegative sulfur atom adjacent to >C=S makes the electron donation easier compared to 2-MBOZ. Therefore 2-MBTZ reacts faster than 2-MBOZ.

Experimental

Materials

Benzyl bromide (Riedel), *p*-nitrobenzyl bromide (Fluka), *p*-methylbenzyl bromide (Fluka), *p*-bromobenzyl bromide (Fluka), 2-mercaptobenzimidazole (Aldrich), 2-mercaptobenzothiazole (Aldrich), 2-mercaptobenzoxazole (Aldrich), thiourea (BDH AnalaR), *N*-methyl thiourea (Fluka) were used without further purification. Methanol (Sd Fine) was distilled using a literature method.

Kinetic measurements

The rates of the reactions between benzyl bromides and the nucleophiles were studied conductometrically at 303 K. The concentration of both the reactants was 2.00×10^{-2} mol dm^{-3}. The second-order rate constants (k) were obtained by plotting $\frac{C_t - C_o}{C_\infty - C_t}$ against time according to the relation[14]

$$k = \frac{C_t - C_o}{C_\infty - C_t}$$

where ‘a’ is the initial concentration of the reactants and C_0, C_t and C_∞ are the conductances of the reaction mixture at the beginning, at time ‘t’ and after completion of the reaction respectively.

With each nucleophile used the corresponding S-benzyl derivative was obtained as the product. This was identified by recording the ir spectrum of the product separated from the reaction mixture. This showed absorption bands around 2700 cm^{-1} and 1400 cm^{-1} indicating the presence of the S-CH$_2$ group.[15]

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