

Nucleophilic substitution at a benzylic carbon by an ambident nucleophile—A linear free energy relationship

K MADHAVAN, V S SRINIVASAN and
N VENKATASUBRAMANIAN

Department of Chemistry, Vivekananda College, Madras 600 004

MS received 28 December 1978; revised 1 August 1979

Abstract. The kinetics of reaction between benzyl chloride and phenol (or substituted phenols) in the presence of sodium hydroxide have been investigated. A differential application of the effect of substituents on the reaction rate to distinguish between a rate-limiting oxygen or carbon attack has been attempted. Considerable scatter in the Hammett plot for the latter attack points to an essentially O-alkylation. The rate constants correlate well with pK_a values of the different phenols. The influence of salt and solvent on the reaction rate suggests this reaction to be an ion-dipole one.

Keywords. Hammett correlation; O-alkylation evidence; solvent influence; nucleophilic substitution; benzylic carbon; ambident nucleophile.

1. Introduction

Although nucleophilic substitution at a benzylic carbon is a field that has been exhaustively studied, the reaction of an ambident nucleophile at benzylic carbon centre does not seem to have been investigated particularly from the mechanistic point of view. The phenoxide ion, being an ambident nucleophile, can lead to either C-alkylation or to O-alkylation. It is also known that the nature of the product formed depends on solvent conditions. For example, the reaction between benzyl bromide and sodium naphthoxide in dimethyl sulphoxide leads to preferential O-alkylation (Kornblum *et al* 1963a, b; Le Noble and Pureter 1968) while the same reaction leads to a C-alkylation product in $F_3C \cdot CH_2OH$. We report in this paper the result of a kinetic study of the reaction between the phenoxide ion (or substituted phenoxides) and benzyl chloride, a study designed to find out whether the rate-limiting attack is by the phenoxide ion or by a carbon ion.

2. Results and discussion

The kinetics of the reaction between benzyl chloride and phenol have been investigated in binary solvent mixtures of isopropyl alcohol and water in the presence of 0.05 M KOH.

2.1. Dependence on benzyl chloride and phenol

The order with respect to benzyl chloride has been determined by varying the concentration of the substrate under constant concentrations of phenol, potassium hydroxide and solvent composition. The disappearance of benzyl chloride follows a clean first order kinetics for over 75% of the reaction. A similar study also shows that the order with respect to the phenol is also one (table 1).

2.2. Dependence on [KOH]

The rate of the reaction between benzyl chloride and phenol increases with increasing concentration of potassium hydroxide (table 2).

Table 1. Dependence on phenol and benzyl chloride concentration.

[KOH] = 0.25 M Temp. : 50° C.

Solvent : 50% aqueous isopropyl alcohol.

[Benzyl chloride] M	[Phenol] M	$k_2 \times 10^4$ litre mole ⁻¹ sec ⁻¹
0.05	0.25	4.35
0.15	0.25	4.37
0.20	0.25	4.32
0.25	0.25	4.02
0.25	0.05	3.90
0.25	0.10	4.38
0.25	0.20	3.92

Table 2. Dependence of rate on KOH concentration.

[Benzyl chloride] = 0.25 M, [Phenol] = 0.25 M, Temp. : 50° C.

Solvent: 50% aqueous isopropyl alcohol.

[KOH] M	$k_2 \times 10^4$ litre mole ⁻¹ sec ⁻¹
0.50	5.45
0.40	4.81
0.30	4.10
0.10	3.68

2.3. Salt effects

Added salts increase the rate of the reaction (table 3). The small positive salt effect indicates a reaction between an ion and dipolar molecule.

2.4. Substituent effect

The effect of suitably positioned substituents in the phenol on the reaction with benzyl chloride as the substrate was studied with the following substituents-*p*-NO₂, *m*-NO₂, *p*-CH₃, *m*-CH₃, *p*-OCH₃ and *o*-CH₃. The second order rate constants, k_2 , for these reactions are collected in table 4. It is evident from the magnitude of the changes (≈ 3.5 times) in the rate constants that the reaction is very much susceptible to the polar influence, electron-releasing substituents (like *p*-CH₃) accelerate the reaction and electron-withdrawing substituents (like *p*-NO₂) retard the reaction. From these data a quantitative correlation between the influence of the substituents on the reaction rate and their electronegativities (as represented by the Hammett constants) could be established (table 4).

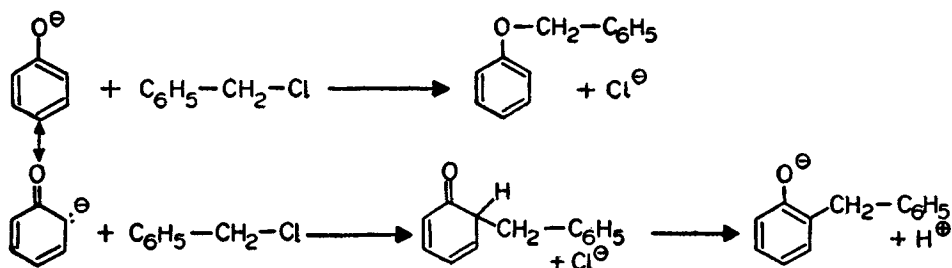
Table 3. Salt effect on the rate of the reaction

[Benzyl chloride]	= 0.25 M	
[Phenol]	= 0.25 M	
[KOH]	= 0.25 M	Salt = NaNO ₃ Temp. = 50° C.
Solvent : 50% aqueous isopropyl alcohol		
[NaNO ₃] M	$k_2 \times 10^4$ litre mol ⁻¹ sec ⁻¹	
0.00	4.03	
0.10	4.61	
0.20	4.97	

Table 4. Substituent effect on the rate of the reaction and correlation of rate with pK_a of phenols.

[Benzyl chloride]	= 0.25 M		
[Phenol]	= 0.05 M		
[KOH]	= 0.05 M		Temp. : 50° C
Solvent: 50% isopropyl alcohol.			
Compounds	$\sigma_o/\sigma_m/\sigma_p$	pK _a	$k_2 \times 10^4$ litre mol ⁻¹ sec ⁻¹
R= H	0	9.98	3.65
<i>o</i> -NO ₂	1.22	7.23	1.99
<i>p</i> -NO ₂	1.27	7.15	1.33
<i>m</i> -NO ₂	0.71	8.40	2.26
<i>o</i> -CH ₃	-0.17	10.28	3.99
<i>p</i> -CH ₃	-0.17	10.26	4.72
<i>m</i> -CH ₃	-0.069	10.09	3.82
<i>p</i> -OCH ₃	-0.268	10.21	4.75

The phenoxide ion, an ambident nucleophile, could conceivably attack either with the oxygen end or the carbon end.



In the former case the phenyl benzyl ether is the product and in the latter, the *o*-benzyl phenol. Although product studies in the present instance, unequivocally establish that the ether is the main product, C-alkylation is always known to be a side reaction. A choice between these two routes can be made by plotting the Hammett relationship in one of the two ways. For attack with the oxygen and the reactivity of a para substituent must correlate with σ_p (or σ_p^-) and meta substituent with σ_m and an ortho substituent with σ_o . For attack by the ortho carbon end, however these substituents would be expected to correlate with σ_m , σ_o , and σ_p (σ_p^-) respectively. Such an analysis had been successfully carried out earlier to choose between two possible mode of attacks in the Boyland-Sims oxidation of aromatic amines (Krishnamurthy 1972; Behrman 1967) with $\text{S}_2\text{O}_8^{--}$ and also in the Elbs oxidation of phenols with $\text{S}_2\text{O}_8^{--}$.

Figures 1 and 2 give the respective Hammett plots of O-alkylation and C-alkylation. Of the two, one for oxygen attack gives a good fit (correlation coefficient = 0.98) with the slope equal to -3.16 (figure 1) and there is no correlation in figure 2. This value is close to the one obtained in the Elbs oxidation of hydroxy pyridines (Krishnamurthy 1972; Elbs 1893) with peroxy-disulphate ($\rho = -3.87$) where the rate limiting oxygen attack has been proposed.

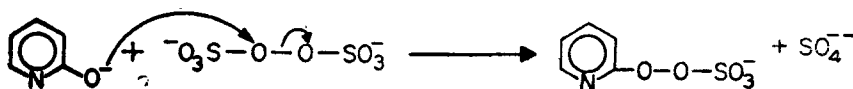


Table 4 also gives the relationship between pK_a value of various substituted phenols and their reactivity with benzyl chloride. The observed rate is in the reverse order of their acid strength, as nucleophilicity is in the reverse order.

2.5. Temperature dependence

The temperature dependence of the variation of phenoxide ion and benzyl chloride was determined between $30^\circ\text{-}50^\circ$. The plot of $\log k_2$ against $1/T$ is linear showing that this reaction exhibits Arrhenius dependence. The activation energy, enthalpy and entropy of activation are collected in table 5. These are of the same order observed for other bimolecular nucleophilic substitution reactions.

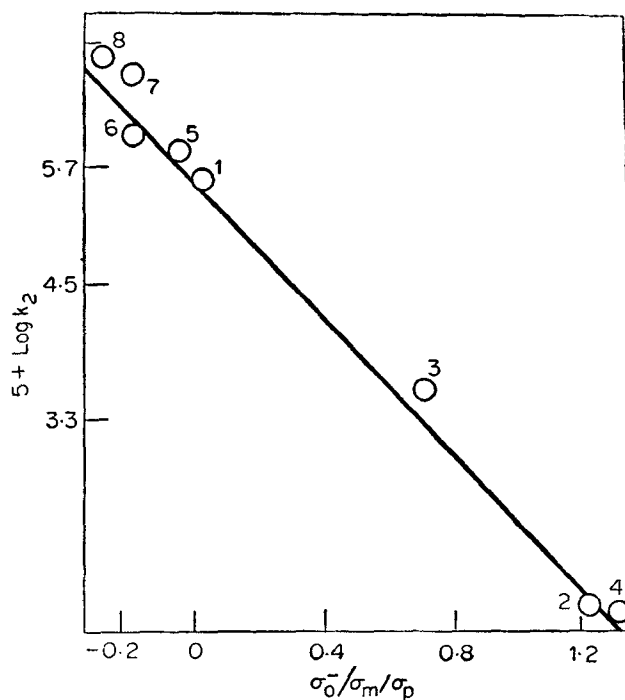


Figure 1. Hammett plot for O-alkylation. $[\text{KOH}] = 0.05 \text{ M}$, Temp. = 50°C . Solvent: 50% isopropyl alcohol - 50% water. $R = 1$. H ; 2. $O\text{-NO}_2$; 3. $m\text{-NO}_2$; 4. $p\text{-NO}_2$; 5. $m\text{-CH}_3$; 6. $o\text{-CH}_3$; 7. $p\text{-CH}_3$; 8. $p\text{-OCH}_3$.

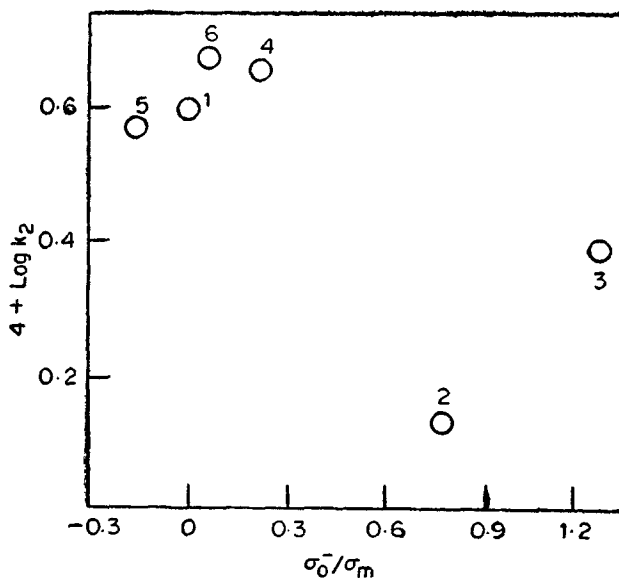


Figure 2. Hammett plot for C-alkylation. $[\text{KOH}] = 0.05 \text{ M}$. Temp. = 50°C . Solvent: 50% isopropyl alcohol - 50% water. 1. H ; 2. $p\text{-NO}_2$; 3. $m\text{-NO}_2$; 4. $p\text{-CH}_3$; 5. $m\text{-CH}_3$; 6. $m\text{-OCH}_3$.

2.6. Solvent influence

The reaction between phenoxide ion and benzyl chloride is well influenced by the solvent system and this is brought out by the rate data of the above reaction in two different solvent systems of varying polarity and dielectric constant (table 6).

Table 5. Temperature dependence and thermodynamic parameters.

[Benzyl chloride]	= 0.25 M
[Phenol]	= 0.05 M
[KOH]	= 0.05 M
Solvent: 50% aqueous isopropyl alcohol.	
Temperature °C	$k_2 \times 10^4$ litre mol ⁻¹ sec ⁻¹
30	0.709
40	1.32
50	3.65
60	5.49
E_a	= 16.36 kcal/mol
ΔH^\ddagger	= 15.76 kcal/mol
ΔS^\ddagger	= 24.85 cal/mol

Table 6. Solvent influence over the rate: variation of isopropyl alcohol and acetone composition.

[Benzyl chloride]	= 0.05 M	
[Phenol]	= 0.25 M	
[KOH]	= 0.25 M	Temp.: 50° C.
Composition of solvent (v/v)	$k_2 \times 10^4$ litre mol ⁻¹ sec ⁻¹	
20% a	4.39	
30% a	3.66	
40% a	3.13	
60% a	1.96	
70% a	1.79	
80% a	1.35	
20% b	6.11	
40% b	4.56	
60% b	3.88	
80% b	2.32	

a = refers to the solvent isopropyl alcohol.

b = refers to the solvent acetone.

The influence of anionic centre in the phenoxide ion is not likely to affect the reaction centre, especially in a solvent of high polarity. Hence the transition state of the reaction is solvated to a greater extent in more polar solvents. As acetone is a dipolar-aprotic solvent, it desolvates more the anion, making it a stronger nucleophile. This explains why the reaction proceeds faster in acetone-water system than in protic isopropanol-water system. A similar trend is observed in the alkaline hydrolysis of esters (Venkoba Rao 1968) and Elbs oxidation of hydroxypyridines in alcohol-water system (Krishnamurthy 1972). As the charge separation in the transition state is not likely to be as large as in the Menschutkin reaction, the effect of increasing or decreasing the solvent polarity on the reaction rate cannot be expected to be as great.

3. Experimental

Phenol and substituted phenols of an extra purity have been used. Wherever necessary they have been purified by conventional methods. Benzyl chloride was purified by distillation under reduced pressure. Equal volumes of phenols (0.25 M) and benzyl chloride (0.25 M) were mixed in the presence of 0.25 M KOH. The course of the reaction was followed by pipetting out 5 ml aliquots of the reaction mixture at various time intervals into a mixture of 10 cc of 1 M HNO₃ and 5 cc of 0.1 M AgNO₃. The excess of AgNO₃ was estimated using standard ammonium sulphocyanide, with ferric ammonium sulphate as indicator. It was established by an independent study that benzyl chloride does not react with silver nitrate under the conditions of the present experiment. Also in the absence of phenol, the alkaline hydrolysis of benzyl chloride is sluggish. The rate constants were evaluated using integrated second order rate expressions and are reproducible within 3%. The product of the reaction between phenol and benzyl chloride under the reaction conditions was identified as phenyl benzyl ether (b.p. 286°–287° C) on a preparatory scale. The O-benzylated product is formed to the extent of 95% whereas C-benzylated product is formed in traces. The ratio of benzyl chloride to phenol concentration reaction has been found to be 1 : 1.

References

- Behrman E J 1967 *J. Am. Chem. Soc.* **89** 2424
Elbs K 1893 *J. Prakt. Chem.* **48** 156, 179
Kornblum N, Berrign P J and Le Noble J 1963a *J. Am. Chem. Soc.* **85** 1141
Kornblum N, Saltzer R and Haberfield P 1963b *J. Am. Chem. Soc.* **85** 1148
Krishnamurthy T K 1972 *Ph.D. Thesis*, University of Madras, Madras
Le Noble J and Pureter 1966 *Tetrahedron Lett.* 1087
Venkoba Rao G 1968 *Ph.D. Thesis*, University of Madras, Madras