

Effect of Substituent and Nucleophile in the Phenacylation of Benzimidazole

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ABSTRACT

The nucleophilic substitution reaction of phenacyl bromide with benzimidazole has been studied conductometrically in methanol medium in the temperature range 303-318K. The reaction is observed to be first order with respect to both [benzimidazole] and [phenacyl bromide]. The reaction is overall second order.

Substituent effect on rate of the reaction suggests that electron withdrawing groups (*p*-NO₂, *p*-Cl, *m*-NO₂) enhance the rate of the reaction compared to the unsubstituted compound, while the electron donating group (*p*-OCH₃) decrease the rate of the reaction compared to unsubstituted compound. The substituted (*p*-OCH₃, *p*-NO₂ and *p*-Cl) and the unsubstituted compound form a linear free energy relationship. From the intersection of lines in the Hammett and Arrhenius plots, the isokinetic temperature is discussed.

Key words: phenacyl bromide, benzimidazole, isokinetic temperature, LFER.

Introduction

Nucleophilic substitution at the phenacylic carbon is of broad synthetic utility and has received considerably significant attention from the organic chemists¹. Fundamental concepts like steric effects, nucleophilicity, solvent effects and structure reactivity correlations have been developed. Literature survey shows that a variety of nucleophiles, thiourea, thiobenzamide, pyridine, quinolines, different aliphatic and aromatic primary and secondary amines, 2-mercapto benzimidazole and 2-mercaptobenzoxazole, have been used in these studies²⁻⁵. As part of our broad programme on the phenacylation of benzimidazole hitherto not reported in the literature, we studied the effect of solvents, on the phenacylation of benzimidazole using, phenacyl bromide. In continuation of this, the present report deals with the effect of the substituent attached to the benzene ring of phenacyl bromide on the rate of phenacylation of benzimidazole.

Experimental

In the phenacylation of benzimidazole, HBr is one of the products. Therefore, the progress of the reaction is followed by measuring the conductance of the reaction mixture at different time intervals. Benzimidazole (Aldrich), phenacyl bromide, *p*-OCH₃, *p*-NO₂, *p*-Cl and *m*-NO₂ phenacyl bromides (

all Merck) were used without further purification. The solvent methanol is of AR grade and is used after purification wherever necessary. The temperature was maintained constant using a thermostat (INSREF make) with an accuracy of $\pm 0.5^{\circ}\text{C}$. The progress of the reaction was followed by measuring the conductance of the reaction mixture at different time intervals. Solutions of benzimidazole of appropriate concentrations were prepared by dissolving weighed quantities in methanol medium. Solutions of phenacyl bromides in methanol were prepared as just 30 minutes before starting the reaction. The possibility of these phenacyl bromides undergoing solvolysis was checked by conducting an independent study. These solvolysis rate constants of *p*-OCH₃, *p*-NO₂, *p*-Cl and *m*-NO₂ and unsubstituted phenacyl bromides in methanol medium were found to be 20.60, 11.26, 9.45 and $13.28 \times 10^{-6} \text{ s}^{-1}$ respectively at 318K. These values are about 100 times less than the substitution rate constants. Therefore these solvolysis rates are not taken into consideration while studying the substitution reactions. During the course of the reaction the conductance of the reaction mixture increases due to the liberation of Br⁻ which has been identified. Therefore the reactions are followed by measuring the conductance of reaction mixture at different time intervals. To establish the order with respect to [benzimidazole] the reactions are studied at 0.02 mol dm⁻³ phenacyl bromide and 0.02 mol dm⁻³ benzimidazole. The plot of $\log[C_{\infty} - C_t]$ is linear with negative slope suggesting that the order with respect to the nucleophile is one according to the equation⁷,

$$k_I = \frac{2.303}{t} \log \frac{(C_t - C_0)}{(C_{\infty} - C_t)}$$

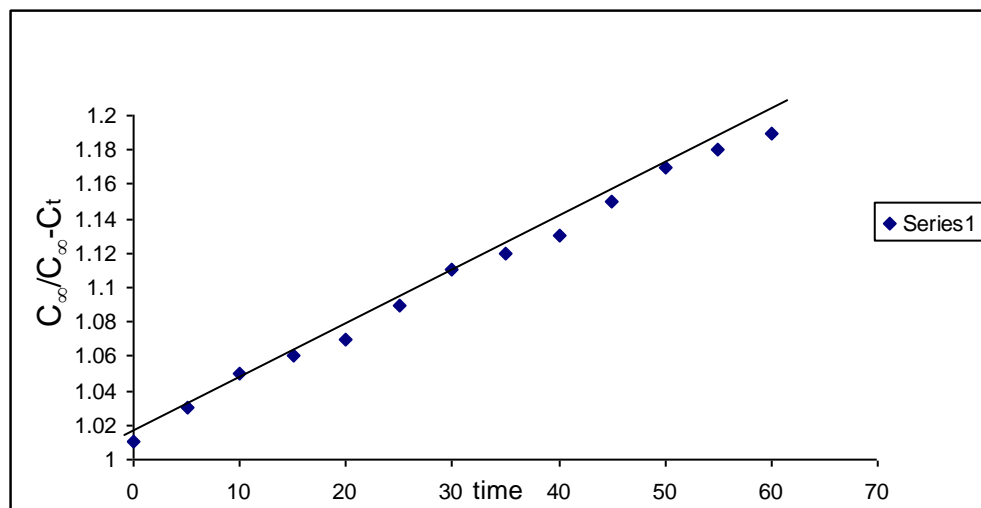
Where C_0 , C_t and C_{∞} are the conductances of the reaction mixture at the beginning, after time t and after completion of the reaction.

The pseudo first-order rate constants are determined from the slope of this plot. These rate constants, determined at 30^oC in methanol medium, are $2.47 \times 10^{-4} \text{ s}^{-1}$, $4.62 \times 10^{-4} \text{ s}^{-1}$ and $9.42 \times 10^{-4} \text{ s}^{-1}$ at 0.1, 0.2, 0.4 mol dm⁻³ phenacyl bromide respectively. The data confirm the first order nature of the reaction with respect to [phenacyl bromide]. Since the reaction is over-all second order, the reactions are studied using [benzimidazole] = [phenacyl bromide] = 0.02 mol dm⁻³.

Second order rate constants k_{II} have been computed from the slopes of the linear plots obtained when $C_{\infty}/(C_{\infty} - C_t)$ is plotted against time according to the equation,

$$k_{II} = \frac{1}{at} \frac{C_t}{C_{\infty} - C_t} \text{-----(1)}$$

Where a is the initial concentration of the reactants. A typical second-order plot is shown in figure 1.



A preliminary study indicated that the solvolysis rates of all the four phenacyl bromides are 100 times less than the substitution rates. Hence, these solvolysis rates were neglected while computing the substitution rates. Further, the solutions of these substrated in appropriate solvent were prepared only 30 min before initiating the reaction to avoid this solvolysis.

The product separated after completion of the reaction(from the ether extract) has a melting point of $125\pm 2^{\circ}\text{C}$. The IR (with KBr) spectrum of this compound indicates the absence of absorption band around 3200 cm^{-1} (due to N-H)⁸ and presence of a band around 2800 cm^{-1} (due to N-CH₂)¹ suggesting the formation of N-phenacyl benzimidazole.

Results and discussion

Effect of substituent (Linear Free Energy Relationship)

A point of great interest in kinetic and mechanistic studies is the influence of substituent present on the substrate on rate of reaction. To assess this effect the present system was studied using *p*-OCH₃, *p*-NO₂, *p*-Cl and *m*-NO₂ substituents on phenacyl bromide in methanol medium and second order rate constants *k* in the temperature range 303-318K have been evaluated. These values (Table-2) indicate that electron withdrawing groups (*p*-NO₂, *p*-Cl, *m*-NO₂) enhance the rate of the reaction compared to the unsubstituted compound, while the electron donating group (*p*-OCH₃) retards the rate of the reaction compared to unsubstituted compound. The substituted (*p*-OCH₃, *p*-NO₂ and *p*-Cl) and the unsubstituted compound form a linear free energy relationship. The order of the ractivity is *p*-NO₂ > *m*-NO₂ > *p*-Cl > -H > *p*-OCH₃. Correlation of log *k* with Hammett's substituent constant σ^{10} gives a linear plot with a positive slope. With exception to *m*-NO₂ the remaining three substituents

fall on a straight line with a positive slope. To verify the applicability of Hammett's linear free energy relationship (LFER)⁹, $\log k_{II}$ is correlated with Hammett's substituent constant σ^{10} in the temperature range 303-318K. The following correlations are obtained,

$$\log k_{II} = -2.09 + 0.66 \sigma, \quad \text{at 303K} \quad ; \quad r = 0.999$$

$$SE = (0.2 \times 10^{-2}) \quad (0.5 \times 10^{-2}) \quad (0.2 \times 10^{-2})$$

$$\log k_{II} = -1.86 + 0.58 \sigma, \quad \text{at 308K} \quad ; \quad r = 0.999$$

$$SE = (0.5 \times 10^{-2}) \quad (1.2 \times 10^{-2}) \quad (0.9 \times 10^{-2})$$

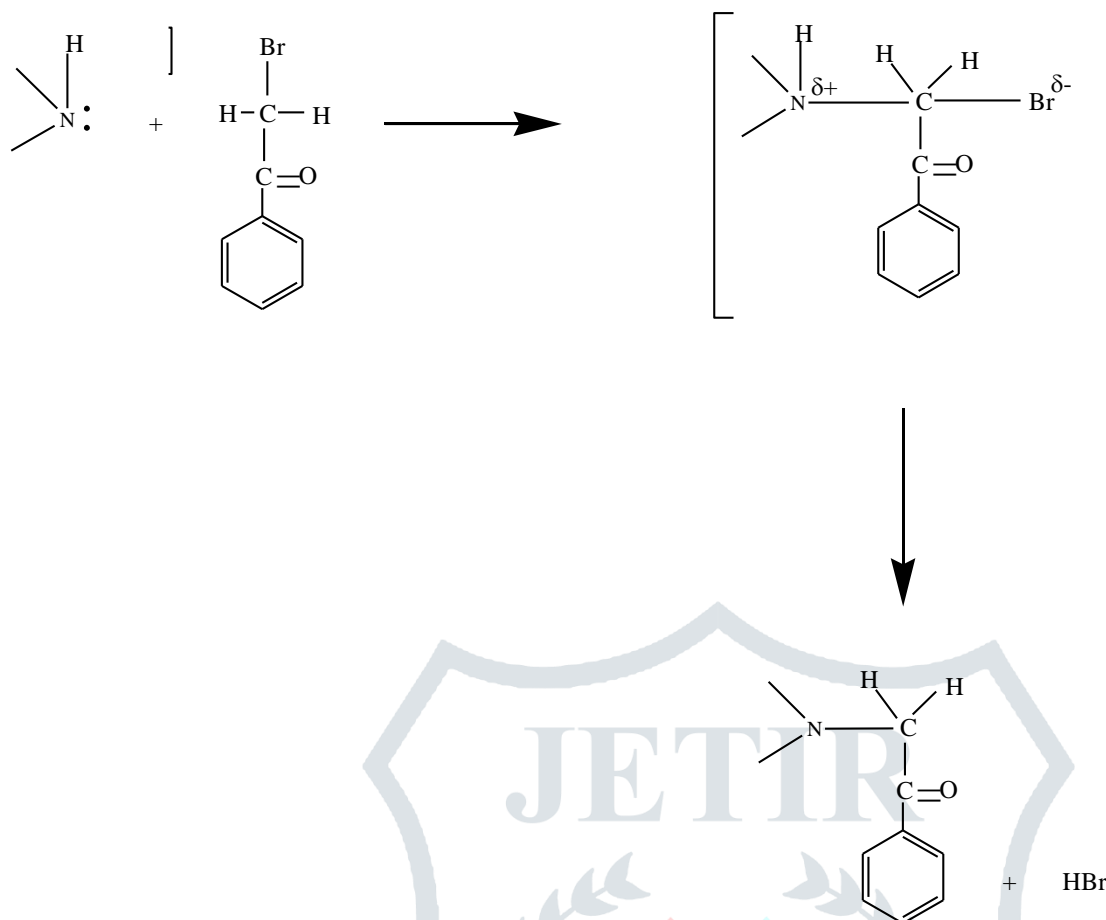
$$\log k_{II} = -1.67 + 0.52 \sigma, \quad \text{at 313K} \quad ; \quad r = 0.999$$

$$SE = (0.15 \times 10^{-2}) \quad (0.35 \times 10^{-2}) \quad (0.27 \times 10^{-2})$$

$$\log k_{II} = -1.51 + 0.49 \sigma, \quad \text{at 318K} \quad ; \quad r = 0.999$$

$$SE = (0.38 \times 10^{-2}) \quad (0.89 \times 10^{-2}) \quad (0.69 \times 10^{-2})$$

The reaction constants, which are the measures of the sensitivity of the reaction towards the electronic effects of the substituents, obtained from these analyses are small ($\rho < 1.0$) and positive, thus indicating the direct displacement of the leaving group by the nucleophile. Increase in temperature decreases the reaction constant and around 55-60°C there is no effect of substituent on rate. Since a positive reaction constant in general indicates a disappearance of positive charge at the reaction centre, i.e., phenacylic carbon atom in the present case, the displacement mechanism shown in scheme-2 may be proposed for the present system^{11,12}.



Isokinetic Temperature

According to Exner¹³, for a given reaction, ρ is influenced by the temperature according to the following relation,

$$\rho = A [1 - \beta/T],$$

Where A is a constant and β is the isokinetic temperature. When $\beta = T$, $\rho = 0$, thus isokinetic temperature is the temperature at which the effect of substituent on rate of reaction vanishes and all the substituted compounds in a given series have the same reactivity. In the present case, correlation of ρ with $1/T$ gives the following equation.

$$\rho = -3.04 + 1106.91/T \quad ; \quad r = 0.975$$

$$SE = (0.56) \quad (174.99) \quad (0.019)$$

Thus the isokinetic temperature is 364.1K.

From the studies of temperature effects on k_{II} the energy of activation E_a and other activation parameters ΔH^\ddagger , ΔS^\ddagger and ΔG^\ddagger are evaluated and recorded in Table-2. These values suggests that there is large variation in E_a and ΔH^\ddagger . Though these values are the least for the most reactive p -OCH₃ phenacyl bromide, there appears to be no correlation with Hammett's substitution constant σ . ΔS^\ddagger values are negative as expected for reaction systems involving polar transition states. According to

Leffler¹⁴, for a reaction series which follows Hammett's LFER, the reaction must be either isoentropic or ΔS^\ddagger should vary linearly with ΔH^\ddagger according to the equation,

$$\Delta H^\ddagger = \Delta H_0^\ddagger + \beta \Delta S^\ddagger,$$

Where β is the isokinetic temperature. This correlation between ΔH^\ddagger and ΔS^\ddagger results in the following equation,

$$\begin{aligned} \Delta H^\ddagger &= 86.93 + 371.60 \Delta S^\ddagger & ; & \quad r = 0.999 \\ \text{SE} &= (0.17) \quad (0.26 \times 10^{-2}) & & \quad (0.1) \end{aligned}$$

Thus the β determined from this correlation is in excellent agreement with value obtained from ρ - T correlation (364.1K). According to Peterson and coworkers¹⁵, in order for an isokinetic relationship between ΔH^\ddagger and ΔS^\ddagger to be significant, the range of observed ΔH^\ddagger ($\Delta\Delta H^\ddagger$) should exceed twice the maximum possible error (δ) in ΔH^\ddagger . In the present system, the calculated values of $\delta = 10.0\text{kJ}$ while $\Delta\Delta H^\ddagger$ is more than 30kJmol^{-1} indicating that the ΔH^\ddagger - ΔS^\ddagger correlation is significant. The isokinetic temperature, β , determined by these two methods is nearer to the temperature at which the reaction is studied. Perhaps this is the reason for a low reaction constant ($\rho < 0.7$) which is a measure of susceptibility of the reaction rate to the electron density changes at the reaction centre. The free energy of activation ΔG^\ddagger is nearly constant suggesting the operation of similar mechanism in each series.

Table – 10 : Second order rate constants at different temperatures and thermodynamic parameters at 303 K.

Solvent = Methanol, [Phenacyl bromide] = [Benzimidazole] = $2.00 \times 10^{-2} \text{ mol dm}^{-3}$

Phac-Br	σ	$k_{II} \times 10^3 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at T/K				E_a (kJ mol ⁻¹)	ΔH^\ddagger (kJ mol ⁻¹)	ΔS^\ddagger (JK ⁻¹ mol ⁻¹)	ΔG^\ddagger (kJ mol ⁻¹)
		303	308	313	318				
-H	0.00	0.91	1.14	1.33	1.50	73.50	70.98	-50.86	86.39
<i>p</i> -OCH ₃	-0.28	0.72	0.97	1.18	1.36	78.76	76.24	-37.12	87.49
<i>p</i> -Cl	0.24	1.06	1.29	1.45	1.62	68.95	66.43	-62.99	85.52
<i>p</i> -NO ₂	0.78	1.42	1.59	1.73	1.88	56.98	54.46	-95.62	83.43
<i>m</i> -NO ₂	0.71	1.31	1.49	1.65	1.79	61.13	58.61	-84.22	84.12

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