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Effect of the Substituent in the Benzylation of Piperazine

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The reaction between piperazine and substituted benzyl bromides was studied in methanol medium and the second order rate constants were determined. Correlation of log k with Hammett's substituent constant resulted in a non linear plot. This non linearity was attributed to the operation of substituent effect on two steps of the reaction scheme to different extents.

Key Words: Piperazine, Substituent effect, Hammett's equation, Reaction constant, Nucleophile, Kinetics.

INTRODUCTION

Nucleophilic substitution at benzylic carbon has received a significant attention. Literature survey shows that a variety of nucleophiles[1-4] have been used in these studies. The kinetic studies on these reactions help us in drawing important conclusions regarding mechanism, steric effects, solvation of the reagents, nucleophilicity substituent effects, *etc*. As a part of our broad programme on the study of the kinetics of the reactions of benzyl bromides with nitrogen nucleophiles, we report in the present communication the results of the substituent effects observed when piperazine (PPZ) which is a cycloaliphatic amine, is used as the nucleophile.

EXPERIMENTAL

Benzyl bromide (Riedel), *p*-NO_2, *p*-CH_3, *p*-Br benzyl bromides (Fluka) and piperazine (Sd-fine) were used without further purification. Solvent methanol (Sd-fine) was used after distilling following the literature method. Temperature was maintained constant using a thermostat (INSREF make). Solutions of piperazine of appropriate concentrations were prepared by dissolving required weighed quantities in methanol. The solutions of benzyl bromides were prepared by dissolving either weighed quantity or required volume of the substance in methanol. The reactions were initiated by mixing the required volumes of the solutions of both the reagents. Preliminary studies indicated that Br^- was one of the products formed. Therefore, the progress of the reaction was followed by measuring the conductance of the reaction mixture at different time intervals. The conductance of the solution was measured using a digital conductivity bridge (CENTURY make) and a glass conductivity cell with cell constant 0.5

cm^{-1}. The possibility of the substrates benzyl bromides, undergoing solvolysis was checked by conducting an independent study in the absence of piperazine. The solvolysis rate constants of *p*-CH_3, *p*-NO_2, *p*-Br and unsubstituted benzyl bromides were found to be 19.19, 9.21, 8.44 and 12.82 × 10^{-6} s^{-1}, respectively at 313 K. These values are about 100 times less than the substitution rate constants. Hence these solvolysis rates are not taken into consideration while studying the substitution reactions. As a precautionary measure the solutions of benzyl bromides were prepared just 0.5 h before starting the reaction. To establish the order of the reaction, the reactions are studied using 0.02 mol dm^{-3} piperazine and 0.10, 0.20 and 0.40 mol dm^{-3} benzyl bromide and the rate constants are calculated. In each case the plot of log $[(C_\infty - C_t/C_\infty)]$ against time is linear[5]. C_t and C_∞ are conductances of the reaction mixture at time t and after completion of the reaction. This observation indicates that the reaction is first order with respect to [piperazine]. The first order rate constants calculated from the slopes of these straight lines are proportional to the initial concentrations of benzyl bromide suggesting that the reaction is first order with respect to [benzyl bromide] also. Since the reaction is overall second order experiments are conducted using [piperazine] = [benzyl bromide] = 0.02 mol dm^{-3}. In each case the plot of $\frac{C_\infty}{C_\infty - C_t}$ against time is linear according to the equation[5]

$$k = \frac{1}{at}\left[\frac{C_\infty}{C_\infty - C_t}\right]$$

where 'k' is second order rate constant and 'a' is the initial concentration of the reactants and 't' is time. From the slope of this linear plot the second order rate constant is computed. A typical second order plot is shown in Fig. 1. The same procedure is followed for all the benzyl bromides studied.

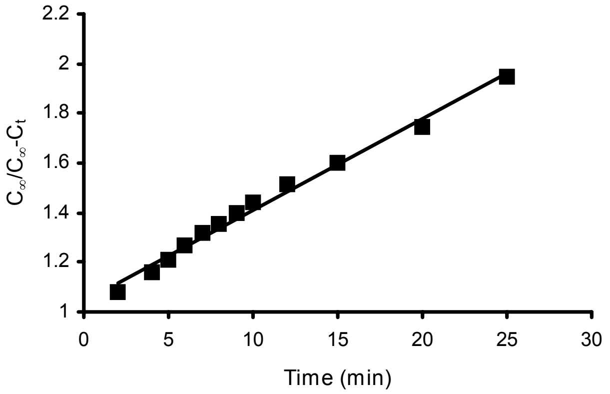


Fig. 1. Plot of C_∞/C_∞-C_t *vs.* time

The product separated, after completion of the reaction was analyzed by recording its IR spectrum and mass spectrum. The IR spectrum has an absorption band around 2800 cm^{-1} indicating N-CH_2 bond. The absence of sharp peak around 3300 cm^{-1} which is present in the nucleophile indicates that N-H hydrogen is substituted. The mass spectrum shows a molecular ion peak 267 m/z indicating that the product is $C_4H_8N_2$ $(CH_2C_6H_5)_2$ suggesting that both the N-H hydrogens are replaced by the benzyl groups. Thus the stoichiometric equation can be written as

$$C_4H_{10}N_2 + 2\ C_6H_5CH_2Br \rightarrow C_4H_8N_2(CH_2C_6H_5)_2 + 2\ HBr$$

RESULTS AND DISCUSSION

The second order rate constants determined in the reactions of substituted and unsubstituted benzyl bromides with piperazine are presented in Table-1. In each case the reactions are studied in the temperature range 298-318 K using methanol as the solvent. These values suggest that there is no marked effect of the substituent on the rate. At each temperature, the reactivity of unsubstituted benzyl bromide reacts faster than the substituted benzyl bromides. An attempt to apply Hammett's equation by correlating log k with the substituent constant σ resulted in non-linear plots as shown in Fig. 2. In the studies of substitutent effect on rate using 2-mercapto benzoxazole[6], diphenyl amine[7], piperidine[8] as nucleophiles linear Hammett's relationships are observed.

TABLE-1
EFFECT OF SUBSTITUENT ON RATE CONSTANT
[BENZYL BROMIDE-PIPERAZINE SYSTEM]
Solvent:Methanol; [BZBr] = [PPZ] = 0.02 mol dm^{-3}; T* = 303 K

BZBr	σ	k × 10^4 dm^3 mol^{-1} s^{-1} T/K					E_a (kJ mol^{-1})	*ΔH$^\#$ (kJ mol^{-1})	*ΔS$^\#$ (JK^{-1} mol^{-1})	*ΔG$^\#$ (kJ mol^{-1})
		298	303	308	313	318				
-H	0.00	233.32	366.66	835.00	1598.00	3100.00	76.55	74.03	-28	82.58
p-CH_3	-0.17	205.00	277.7	416.6	666.00	1208.32	52.65	50.13	-110	83.54
p-Br	0.23	224.36	316.66	433.32	500.00	700.98	40.20	37.68	-149	82.93
p-NO_2	0.78	175.00	237.52	333.33	448.00	603.24	47.86	45.36	-126	83.68

According to Hammett a linear relationship between log k and σ with a slope ρ exists only when σ is independent of the nature of the reaction and when ρ is not influenced by the nature of the substituent[9]. In contrast to large number of reactions which show linear log k-σ relationship there are also examples of reactions which show deviation from linearity[10,11]. This is attributed to a gradual change in the reaction mechanism or rate determining step when one passes from electron donating to electron with-

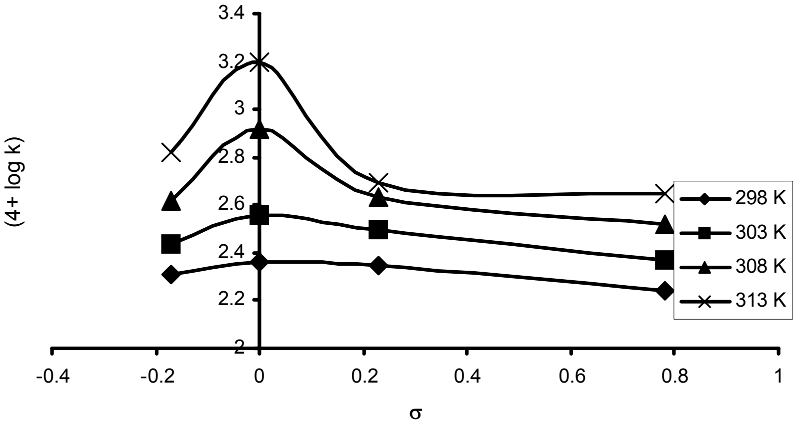
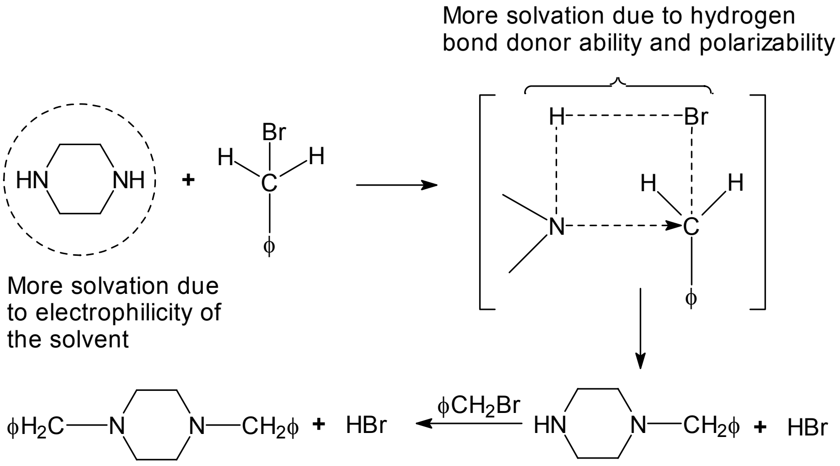


Fig. 2. Hammett's plot of log k *vs.* σ (Benzyl bromide - piperazine system)

drawing sustituents. In the present system, though the reaction follows second order kinetics, being first order each in benzyl bromide and piperazine the mass spectrum of the product (Fig. 3) shows the presence of two benzyl systems in the piperazine ring. This indicates a stepwise displacement of two hydrogen atoms of the piperazine by two substrate molecules.



These two steps are susceptible to substituent effect. When the extent and order of the substituent effect on rates of such steps are different, in general, there is a breakdown in the Hammett's relationship. When one step is accelerated by electron withdrawing/donating groups while the second step is retarded to the same extent, we may not observe the substituent effect at all[9]. May be in the present case the two steps shown above are not influenced by the substituent to the same extent leading to a breakdown in the Hammett's relationship.

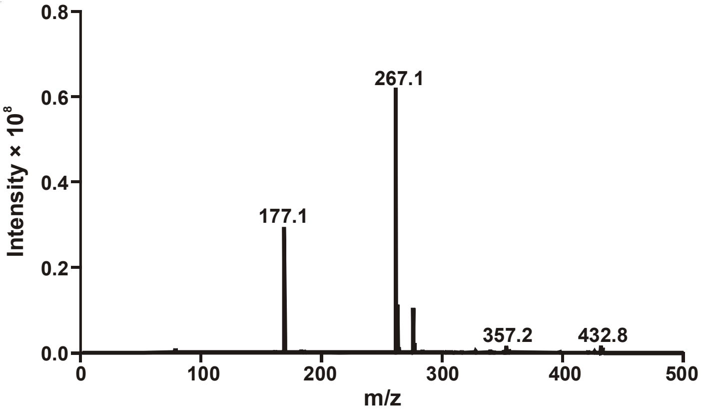


Fig. 3. Mass spectrum of the product recovered from BZBr-PPZ system

From the slopes of the Arrhenius plots, the energy of activation E_a and hence the enthalpy of activation $\Delta H^{\#}$, the entropy of activation $\Delta S^{\#}$ and the free energy of activation $\Delta G^{\#}$ are evaluated and recorded in Table-1. $\Delta S^{\#}$ values are negative as expected for the reactions involving polar transition states. $\Delta H^{\#}$ and $\Delta S^{\#}$ are related by the following equation,

$$\Delta H^{\#} = 92.0 - 385.0\ \Delta S^{\#}$$

The isokinetic temperature, β obtained from this relation is 385 K which is below the room temperature. The rate constants recorded in Table-1 also indicate that as the temperature is lowered the effect of the substituent on rate becomes less.

The free energy of activation $\Delta G^{\#}$ is nearly constant ($\Delta\ \Delta G^{\#} \pm 0.60$ kJ mol^{-1}) suggesting the operation of similar mechanism with all the benzyl bromides.

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