Correlation analysis in the reactions of benzyl bromide with N-substituted anilines

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The nucleophilic substitution reaction between benzyl bromide and N-substituted anilines in methanol medium suggests that the reactivity of the nucleophiles increases with their pK_a values. A linear relationship exists between the rate and the computed values of the dipole moment and electronegativity of the nucleophiles. The frontier orbital interactions and correlation of rate with HOMO-LUMO gap of the two reactants suggest that the reaction is not orbital controlled but is controlled by the electrostatic interactions between the reactants.

Nucleophilic substitution at benzylic carbon is of broad synthetic utility and has received exceptionally detailed attention by chemists. Fundamental concepts like steric effects, polar effects, nucleophilicity, solvent effects and structure activity correlations have been developed through these studies. As a part of the broad programme on the study of benzylation of secondary amines, we have studied the solvent effect, the effect of nucleophile and the effect of substituent on the rate of the reaction. The present studies deal with the effect of nucleophile, on the rate of reaction of benzyl bromide with N-methyl, N-ethyl and N-phenyl anilines.

Quantum chemistry provides many powerful tools which help us in evaluating electron densities at different atoms of a molecule, in predicting the reaction site, in explaining the order of reactivity of closely related reagents towards a given substrate, in predicting the transition state structure, etc. With this end in view, we have attempted AM1 calculations here to explore the frontier orbital interactions. Correlation analysis of frontier orbital interactions with the order of reactivity of these three nucleophiles with benzyl bromides has also been carried out.

Experimental

Benzyl bromide (RIEDEL) was used without further purification. AnalalR grade diphenyl amine (DPA), N-methyl aniline (NMA) and N-ethyl aniline (NEA) were procured from BDH. Solvent methanol was of Sd-fine make and was distilled before use. Preliminary study of the reaction between benzyl bromide and N-substituted anilines indicated that HBr is one of the products of the reaction. Progress of the reaction was followed by studying the conductance of the reaction mixture at different time intervals. Direct reading digital conductivity bridge (Century make) equipped with a glass conductivity cell was used to measure the conductance of the system. INSREF constant temperature bath was used to maintain the temperature. Accuracy of the bath temperature was maintained at ±0.2°C.

The solutions of nucleophiles of appropriate concentration were prepared by dissolving appropriate volume/weighted quantity in methanol.

The solution of benzyl bromide was prepared 30 min before starting the experiment (to prevent solvolysis) by dissolving the required volume of the compound in methanol. The reactions were initiated by mixing the thermally equilibrated solutions of the nucleophile and the substrate at the appropriate temperatures. The conductance of the reaction mixture was measured at different time intervals (C_t), and after completion of the reaction (C∞). The order of the reaction was established by studying the reaction using 0.02 mol dm⁻³ benzyl bromide and 0.1 mol dm⁻³, 0.2 mol dm⁻³, 0.4 mol dm⁻³ and 0.5 mol dm⁻³ nucleophile. The plot of log ([C∞- C_t] / [C∞]) against time was linear in each case suggesting the first order nature of the reaction. The pseudo first order rate constants k_I (slope×2.303) were found to be proportional to [nucleophile] establishing the order with respect to nucleophile as one. Thus, the reaction is overall second order. The effects of temperature, substituent and nucleophile on rate were studied using 0.02 mol dm⁻³ nucleophile and 0.02 mol dm⁻³ substrate and determining the second order rate constant k_II from the slope of the linear plot of (C_x/C_x-C_t) against time.

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These rate constants determined in duplicate runs were found to be reproducible within ±5% error. The reactions were studied in the temperature range 303-318 K.

Preliminary study of solvolysis of benzyl bromide in the methanol indicated that the solvolysis rate constant is of the order of 10^{-6} s^{-1} at 313 K. The nucleophilic substitution rates are found to be 100 times higher than this. Hence, the solvolysis rates are neglected while studying the substitution reactions.

The product separated from the reaction systems in each case was found to be the corresponding benzyl amine. In the case of diphenyl amine-benzyl bromide system the separated product has a m.pt. of 142 °C. The IR spectrum recorded does not show any sharp absorption band around 3200 cm^{-1} due to N-H. Further, the absorption around 2800 cm^{-1} and 1460 cm^{-1} confirm N-CH_{2} group. This confirms the formation of diphenyl benzyl amine. Similar procedure was followed to identify the products obtained with the other nucleophiles also.

**Results and discussion**

The second order rate constants determined at different temperatures in methanol medium in benzyl bromide - N-substituted anilines system (Table 1) show that the reactivities of the three secondary amines studied in the present system are in the order: DPA > NMA > NEA which is also the order of their \( pK_a \) values. Since there is a conceptual relationship between nucleophilicity and basicity, this trend is expected. Electron donating ability of the nucleophile depends on other factors like electronegativity, polarizability and hardness parameters. These parameters are interrelated and can be calculated from the energies of frontier orbitals (HOMO and LUMO).

To assess the influence of these factors on rate, semiempirical calculations are performed on the reactants used in the present system. These calculations are performed using AM1 method included in the software package MOPAC – 93 (ver. 5.13). Geometry calculations in the ground state were completely optimized (keyword PRECISE, equivalent to GNORM=1.0) until the lowest energy conformation was obtained. Some of the results of these calculations, heats of formation \( \Delta H_f \), dipole moment \( \mu \), energies of frontier orbitals are presented in Table 2. From these values, HOMO-HOMO energy differences of the two reactants \( \Delta E_{H-H} \) and electronegativities of the nuleophiles \( X^0 \) are computed and presented in Table 2 along with the observed rate constants. The data indicate that the decrease in the dipole moment of the amine increases its reactivity with the substrate benzyl bromide according to:

\[
\log k_{II} = - 2.35 \ (0.09) - 0.33 \ \mu \ (0.07) ; \ r = 0.98 \ (0.04)
\]

values in parentheses being standard errors of the estimates. The influence of dipole moment of the nucleophile on its reactivity may be due to the fact that, a dipole perturbs the electronic arrangement at the reaction site.

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>( pK_a )</th>
<th>( k_0 \times 10^4 \ \text{dm}^3 \ \text{mol}^{-1} \ \text{s}^{-1} ) at temp (K)</th>
<th>( E_a ) (kJ mol^{-1})</th>
<th>( \Delta H^\circ ) (kJ mol^{-1})</th>
<th>( \Delta S^\circ ) (JK^{-1} mol^{-1})</th>
<th>( \Delta G^\circ ) (kJ mol^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPA</td>
<td>0.90</td>
<td>22.83, 45.32, 84.72, 31.66, 44.16</td>
<td>91.01</td>
<td>88.50</td>
<td>-3</td>
<td>89.60</td>
</tr>
<tr>
<td>NMA</td>
<td>4.85</td>
<td>16.09, 25.01, 31.66, 44.16</td>
<td>40.97</td>
<td>62.50</td>
<td>-94</td>
<td>91.09</td>
</tr>
<tr>
<td>NEA</td>
<td>5.11</td>
<td>12.50, 20.00, 29.16, 38.88</td>
<td>65.10</td>
<td>38.45</td>
<td>-170</td>
<td>90.06</td>
</tr>
</tbody>
</table>

**Table 1** — Effect of nucleophile on rate constant in the reaction of benzyl bromide with N-substituted anilines in MeOH medium

<table>
<thead>
<tr>
<th>Compound</th>
<th>( \Delta H_f ) (kJ mol^{-1})</th>
<th>( \mu ) (Debye)</th>
<th>( E_{HOMO} ) (ev)</th>
<th>( E_{LUMO} ) (ev)</th>
<th>( \Delta E_{H-H} ) (ev)</th>
<th>( \Delta E_{H-L} ) (ev)</th>
<th>( X^0 ) (ev)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPA</td>
<td>235.59</td>
<td>0.878</td>
<td>-8.823</td>
<td>0.202</td>
<td>1.327</td>
<td>8.233</td>
<td>4.042</td>
</tr>
<tr>
<td>NMA</td>
<td>100.80</td>
<td>1.479</td>
<td>-8.409</td>
<td>0.603</td>
<td>1.201</td>
<td>8.359</td>
<td>3.879</td>
</tr>
<tr>
<td>NEA</td>
<td>74.37</td>
<td>1.626</td>
<td>-8.377</td>
<td>0.676</td>
<td>1.233</td>
<td>8.327</td>
<td>3.853</td>
</tr>
<tr>
<td>BZBr</td>
<td>80.05</td>
<td>1.645</td>
<td>-9.610</td>
<td>-0.050</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>N-benzyl DPA</td>
<td>384.99</td>
<td>1.029</td>
<td>-8.203</td>
<td>0.223</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>N-benzyl NMA</td>
<td>242.96</td>
<td>1.064</td>
<td>-8.521</td>
<td>0.321</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>N-benzyl NEA</td>
<td>222.91</td>
<td>0.935</td>
<td>-8.558</td>
<td>0.406</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HBr</td>
<td>-43.91</td>
<td>1.385</td>
<td>-11.464</td>
<td>1.158</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Table 2** — Results of AM1 calculations in the reactions of benzyl bromide with N-substituted anilines
The data given in Table 2 also indicate that, the energies of HOMOs of the three N-substituted anilines are higher than that of the substrate BZBr suggesting that the electrons are donated by the nucleophiles to the substrate. According to perturbation theory, when nucleophile and electrophile approach each other, their HOMOs interact resulting in the bonding orbitals of the products. These interactions are stronger, when the HOMO orbital energies of the nucleophile and electrophile are closer. These frontier orbital interactions are represented in the Figs 1-3. According to these figures, the formation of bonding orbital is exothermic in the case of HBr and endothermic in the case of second product, i.e., benzyl derivative. Another factor, which governs the reactivity is HOMO-LUMO gap between the nucleophile and the substrate. In the present study, it appears the order of reactivity of the nucleophile does not follow either $\Delta E_{H-H}$ or $\Delta E_{H-L}$. This observation indicates that the reactivity is not orbital controlled but charge controlled\textsuperscript{23}, i.e., the electrostatic interactions between the two reactants play a role in deciding the reactivity of the nucleophile. In the reactions between benzyl bromide and sulphur nucleophiles studied in our laboratory\textsuperscript{24} these...
calculations indicated that the order of reactivity is in consonance with the HOMO-LUMO gap suggesting that, the reactivity is orbital controlled. Since $E_{HOMO}$ is ionization potential and $E_{LUMO}$ is electron affinity, the electronegativity is taken as the sum of these two quantities. $X^0$ values, thus calculated, are given in Table 2. These values indicate that decrease in electronegativity of the nucleophile increases its reactivity towards benzyl bromide. It is attributed to the fact that an atom or group with higher electronegativity binds electrons more tightly and hence does not form bond readily by donating electrons compared to a group with lower electronegativity. The following linear relationship is established between $X^0$ and $\log k_{II}$.

$$\log k_{II} = -0.50 (0.03) - 1.20 X^0 (0.39); \quad r = 0.95 (0.06)$$

The thermodynamic parameters computed and presented in Table 1 indicate that these are also strongly influenced by the nature of the nucleophile. This may be due to solvation of the nucleophiles to different degrees. Solvation of a reagent decreases its energy and stabilizes it.

However, the free energy of activation $\Delta G^*$ is nearly constant ($90.25 \pm 0.84$ kJ mol$^{-1}$) indicating that similar type of reaction scheme operates with the three nucleophiles studied (Scheme 1).

### References