Linear solvation energy relationship in the reaction between phenacyl bromide and N-methyl aniline

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The reaction between phenacyl bromide and N-methyl aniline has been studied conductometrically in 17 different protic and aprotic solvents. The reaction is overall second order, being first order with respect to each reactant. Correlation of the second order rate constants with different solvent parameters indicates that the solvation of the reactants and the transition state is due to non-specific polarity of the solvent, hydrogen bond donor ability, solvent nucleophilicity, and electrophilicity of the solvent. By statistical analysis, a linear solvation energy relationship is derived and the percentage contribution of each type of solvation is estimated.

Keywords: Solution chemistry, Solvation energy, LSER

The influence of solvent on the rate of any reaction can be described in terms of solvation which is a stabilization process. Two basic viewpoints have been established on the solvation phenomenon. According to the first, a solvent is considered as a homogeneous continuum which surrounds the solute molecules and exerts long range interactions. The strength of these interactions with the solute molecules is described in terms of macroscopic physical properties of the solvent like dielectric constant \( \epsilon \) and refractive index \( n \). According to the second viewpoint, a solvent is considered to be anisotropic and inhomogeneous which exerts short range forces on the solvent molecules. These forces are chemical in nature, and result in the formation of solvation complexes through donor-acceptor bonds which are localized and directed in space. The strength of these interactions is described in terms of solvation parameters, namely, electrophilicity \( E \), nucleophilicity \( B \), hydrogen bond donor acidity \( \alpha \), hydrogen bond acceptor basicity \( \beta \), etc. Thus, the solvent can solvate the solute by exhibiting any of these interactions with the specific sites in the solute.

Hence, the effect of solvent on rate of the reaction can be described in terms of a multiparametric equation which involves different solvation parameters as Eq. (1),

\[
\log k = \log k_o + xX + yY + zZ + \ldots
\] (1)

where \( k \) is the rate constant in any solvent, \( k_o \) is rate constant in an inert solvent which does not solvate the solute at all, \( X, Y \) and \( Z \) are different solvation parameters which are the measures of the solvation abilities of the solvent due to different properties and \( x, y \) and \( z \) are coefficients which describe the susceptibility of \( k \) towards different solvation properties. The above linear solvation energy relationship (LSER) can be derived by studying the rate of reaction in different solvents and subjecting the data to statistical analysis. As part of our work on solvent effects on nucleophilic substitution reaction, we have studied the reaction of phenacyl bromide with N-methyl aniline in 17 different protic and aprotic solvents. Literature survey on role of solvent in rates of reactions indicates that there are extensive studies on the solvent effects in the nucleophilic substitution at \( sp^3 \) and \( sp^2 \) carbon using a variety of nucleophiles. Similar studies using phenacyl halide are limited. However, the substituent effect and nucleophile effect involving phenacyl bromide as substrate and oxidation of phenacyl bromide by \( V^{5+} \), \( Mn^{3+} \) and \( Ce^{4+} \) are reported in the literature. Regarding nucleophilic substitution at \( sp^3 \) carbon atom, phenacyl halides differ from alkyl halides in having carbonyl group adjacent to the methylene carbon bearing the halogen. This results in the high reactivity of phenacyl halide compared to alkyl halide due to stabilization of the carbonium ion by delocalization. Hence, we thought it worthwhile to study the effect of solvent on the nucleophilic substitution on phenacyl bromide with a view to derive linear solvation energy relationship.

Experimental

Phenacyl bromide (Merck) and nucleophile, N-methyl aniline (Aldrich) were used as such without any further purification. The solvents, methanol, ethanol, \( n \)-propanol, \( i \)-propanol, \( n \)-butanol, \( i \)-butanol,
2-butanol, benzyl alcohol, t-butanol acetonitrile, acetone, 2-butanone, cyclohexanone, dimethyl sulphoxide, formamide and dimethyl formamide were all of AR grade and were used after purification wherever necessary. The temperature was maintained constant using a thermostat (INSREF make) with an accuracy of ±0.5 °C. The solutions of appropriate concentrations of the nucleophile and phenacyl bromide were prepared by dissolving a calculated weighed amount of the solute in each solvent. The reactions were initiated by mixing the thermally equilibrated reactants in appropriate solvents. The course of the reaction was followed by measuring the conductance of the reaction mixture at different time intervals using a conductivity bridge (Century) and a glass conductivity cell of cell constant 0.987 cm⁻¹.

Preliminary studies indicated that the reaction is first order with respect to both [phenacyl bromide] and [N-methyl aniline]. The reactions were studied using 0.02 mol dm⁻³ phenacyl bromide and 0.02 mol dm⁻³ N-methyl aniline in 17 different protic and aprotic solvents in the temperature range of 298-318K. The second order rate constants (k_H) were computed¹⁸ using Eq. (2),

\[
k_H = \frac{1}{a} \frac{C_\infty}{C_\infty - C_t}
\]

(2)

where \(C_t\) and \(C_\infty\) are the conductances of the reaction mixture at time \(t\) and after completion of the reaction respectively and \(a\) is the initial concentration of the reactants.

The rate constants thus determined were found to be reproducible with in ±5 % error. The possibility of phenacyl bromide undergoing simultaneous solvolysis was checked by conducting an independent study in methanol and dimethyl formamide without adding the nucleophile under similar experimental conditions. This solvolysis rate constant was found to be nearly 100 times less than the substitution rate constant. Hence, the solvolysis was neglected while determining the substitution rate constants. A PCL personal computer was used to carry out the multiple regression analysis. The regression analysis was carried using Data Analysis which is part of MS Excel. F-test¹⁹ and student t-test¹⁹ were used to know the validity of the tri- and tetra-parametric equations obtained.

The product separated from methanol had a melting point of 97±1 °C. The IR spectral data (KBr) of this compound showed absorption band ∼ 2690 cm⁻¹ and 1400 cm⁻¹ indicating the presence of S-CH₂ group and another band at ∼ 700 cm⁻¹ indicating a thio ether link of C-S-C. These values agreed with the literature values²⁰ of 2700-2600, 1420 and 720 cm⁻¹ respectively, and suggest the formation of S-phenacyl n-methyl aniline.

**Results and discussion**

The second order rate constants were determined in 17 different protic and aprotic solvents in the temperature range 298-318K (Table 1). The data suggest that the rate constants are highly dependent on nature of the solvent. Correlation of the log \(k_H\) values with different solvent parameters, viz., acidity(\(\alpha\)), polarity(\(\beta\)), polarisability(\(\pi^*\)), electrophilicity(\(E\)), nucleophilicity(\(B\)) and hydrogen bond donor acidity(\(\alpha\)), hydrogen bond acceptor basicity(\(\beta\)), and specific polarisability(\(\pi^*\)) did not give satisfactory relationships. A better correlation is observed with solvent nucleophilicity(\(B\)) with following relationship and correlation coefficient:

\[
\log k_H = -3.97 + 1.1 \times 10^{-2} B \quad \text{r = 0.967} \quad \ldots (3)
\]

\[
\text{SE} = (0.11) (0.076 \times 10^{-2}) (0.076)
\]

The values in parentheses are standard errors of the coefficients. The above result indicates that the rate of reaction is merely influenced by a single property of the solvent, that is, nucleophilicity. Addition of a second parameter to this single parametric equation slightly improved the strength of the correlation, and some of these biparametric relationships are as follows:

\[
\log k_H = -3.98 + 1.1 \times 10^{-2} B + 5.6 \times 10^{-2} \pi^* \quad R = 0.968 \quad \ldots (4)
\]

\[
\text{SE} = (0.11) (0.086 \times 10^{-2}) (8.0 \times 10^{-2}) (0.067)
\]

\[
\log k_H = -3.94 + 1.1 \times 10^{-2} B - 5.0 \times 10^{-2} \alpha \quad R = 0.970 \quad \ldots (5)
\]

\[
\text{SE} = (0.11) (0.077 \times 10^{-2}) (5.7 \times 10^{-2}) (0.074)
\]

\[
\log k_H = -3.97 + 1.2 \times 10^{-2} B - 0.21 \beta \quad R = 0.976 \quad \ldots (6)
\]

\[
\text{SE} = (0.096) (0.088 \times 10^{-2}) (0.11) (0.067)
\]

\[
\log k_H = -5.06 + 1.1 \times 10^{-2} B - 2.39 Y \quad R = 0.979 \quad \ldots (7)
\]

\[
\text{SE} = (0.61) (0.072 \times 10^{-2}) (1.33) (0.067)
\]
Due to the internal correlation between B and β, Eq. 6 is not taken into consideration. The introduction of a third parameter yields the following equations:

\[
\log k_B = 5.01 + 1.1 \times 10^{-2} B + 2.28 Y + 2.8 \times 10^{2} \alpha \times 10^{-2}; \quad R = 0.980 \\
\text{SE} = (0.69) (0.14) (7.7 \times 10^{-2}) (0.070) 
\]

(8)

\[
\log k_B = -5.37 + 1.0 \times 10^{-2} B + 2.73 Y + 1.01 P; \quad R = 0.980 \\
\text{SE} = (0.59) (0.069) (1.55) (3.3 \times 10^{-2}) (0.069) 
\]

(9)

\[
\log k_B = -4.76 + 1.2 \times 10^{-2} B + 1.75 Y - 0.16 \beta; \quad R = 0.981 \\
\text{SE} = (0.70) (0.081) (1.38) (1.08) (0.068) 
\]

(10)

\[
\log k_B = -4.76 + 1.2 \times 10^{-2} B + 1.75 Y - 0.16 \beta \\
\text{SE} = (0.62) (0.093) (1.36) (0.12) (0.065) 
\]

(11)

\[
\log k_B = -5.01 + 1.1 \times 10^{-2} B + 2.35 Y - 4.7 \times 10^{-2} \beta; \quad R = 0.982 \\
\text{SE} = (0.61) (0.073) (1.34) (5.2 \times 10^{-2}) (0.068) 
\]

(12)

Due to the internal correlation between B and β, these equations are not taken into consideration. The introduction of a fourth parameter did not increase the correlation co-efficient, however, it increased the explained variance from 0.96 to 0.97. The following four parametric equations are:

\[
\log k_B = -4.65 + 1.2 \times 10^{-2} B + 1.46 Y - 4.2 \times 10^{-2} \alpha - 0.24 \beta; \quad R = 0.984 \\
\text{SE} = (0.69) (0.14) (1.55) (4.6 \times 10^{-2}) (0.22) (0.068) 
\]

(12)

\[
\log k_B = -4.78 + 1.1 \times 10^{-2} B + 1.84 Y - 0.24 \alpha - 1.5 \times 10^{-2} E; \\
\text{R} = 0.986 \\
\text{SE} = (0.59) (0.069) (1.29) (0.13) (0.9 \times 10^{-2}) (0.064) 
\]

(13)

\[
t-\text{stat} = -8.06 15.201.43 -1.84 1.60 
\]

Thus, \( \log k_B \) correlates well with B, Y, α and E, with a correlation coefficient, \( R = 0.98 \). This shows that 97% of the experimental results can be explained by the above relationships. The validity of Eq. (13) is tested by applying statistical tests. The \( F_{\text{cal}} \) is very high (70.28) compared to the table value (\( F_{\text{table}} \), 5.67) at 1% level of significance. This suggests that this LSER is not a chance correlation. The significance of the four independent variables used in this equation was verified by comparing the calculated t values with the statistical table values of t. This comparison indicates that the parameter B is significant at 99.98% confidence level while Y, α and E are significant at 90% confidence level. Correlation of \( \log k_{\text{obs}} \) with \( \log k_{\text{cal}} \) gives the following equation with a good correlation coefficient: \( \log k_{\text{obs}} = 1.03 \log k_{\text{cal}}; \quad (r = 0.940) \)

These tests suggest that the above LSER is not a result of chance correlation between the rate constant and the solvation parameters. The above LSER indicates that the rate of this reaction is influenced by solvent nucleophilicity (B), Polarity parameter (Y) and hydrogen bond donor ability parameter (α) solvent electrophilicity (E). The contributions of these parameters towards total solvation are estimated by normalization of the coefficients. These values are found to be B = 58%, Y = 34%, α = 4%, E = 4%.

Equation (13) shows that the rate of the reaction is strongly influenced by B suggesting that, nucleophilic solvation stabilizes the transition state by interacting with the positive end. Y, which is a function of polarity of the solvent \((Y = (e-1) (2e+1) \text{ where } e \text{ is the dielectric constant}) \) also influences the rate. The positive sign of this coefficient suggests that the transition state is more solvated than reactants due to non specific interaction, i.e., polarity of the solvent. This indicates a charge separation in the transition state. The rate of the reaction is also influenced by α which is a measure of hydrogen bond donor ability of the solvent. The negative sign of the coefficient of α suggests that the interaction between the reactants (especially the oxygen of C=O and Br) and the solvent is more than the transition state-solvent interaction due to hydrogen bond donor ability. E, which is the measure of Lewis acidity or in other words solvent electrophilicity of the solvent, makes a minor contribution to rate. The negative sign of E in the above equation indicates that the reactants are more solvated than the transition state while these solvents decrease the rate of the reaction, while nucleophilic solvents enhance the rate of reaction.

Considering the above, the mode of solvation of the reactants and the transition state can be represented as shown in the Scheme 1.

From the temperature effect on rate, the activation energy \( E_a \), enthalpy of activation, \( \Delta H^* \), entropy of activation, \( \Delta S^* \), and free energy of activation, \( \Delta G^* \), are evaluated and presented in Table 1. The data indicate that the reaction is entropy controlled. These entropy values are all negative suggesting that the transition
Scheme 1

Table 1—Second order rate constants at different temperatures and thermodynamic parameters at 303 K.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$k_2 \times 10^3$ (dm$^3$ mol$^{-1}$ s$^{-1}$) at $T$ (K)</th>
<th>$E_a$ (kJ mol$^{-1}$)</th>
<th>$\Delta H^\circ$ (kJ mol$^{-1}$)</th>
<th>$\Delta S^\circ$ (J K$^{-1}$ mol$^{-1}$)</th>
<th>$\Delta G^\circ$ (kJ mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>8.10 20.90 26.92 67.60</td>
<td>96.71</td>
<td>94.19</td>
<td>26</td>
<td>85.57</td>
</tr>
<tr>
<td>Ethanol</td>
<td>4.57 5.53 8.81 13.82</td>
<td>77.56</td>
<td>75.04</td>
<td>-42</td>
<td>87.83</td>
</tr>
<tr>
<td>n-Propanol</td>
<td>4.50 6.92 10.20 14.91</td>
<td>64.15</td>
<td>61.63</td>
<td>-87</td>
<td>87.86</td>
</tr>
<tr>
<td>i-Propanol</td>
<td>3.30 6.61 10.22 15.83</td>
<td>72.77</td>
<td>70.25</td>
<td>-61</td>
<td>88.65</td>
</tr>
<tr>
<td>n-Butanol</td>
<td>5.01 9.10 16.20 28.74</td>
<td>93.84</td>
<td>91.32</td>
<td>12</td>
<td>87.60</td>
</tr>
<tr>
<td>2-Butanol</td>
<td>10.00 14.52 19.51 27.50</td>
<td>55.54</td>
<td>53.02</td>
<td>-108</td>
<td>85.87</td>
</tr>
<tr>
<td>i-Butanol</td>
<td>7.90 11.73 15.83 22.32</td>
<td>55.54</td>
<td>53.02</td>
<td>-110</td>
<td>86.45</td>
</tr>
<tr>
<td>t-Butanol</td>
<td>1.62 6.51 7.82 9.41</td>
<td>30.64</td>
<td>28.12</td>
<td>-205</td>
<td>90.46</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>25.10 35.50 46.80 60.34</td>
<td>51.71</td>
<td>49.19</td>
<td>-110</td>
<td>83.54</td>
</tr>
<tr>
<td>Acetone</td>
<td>1.45 3.13 4.91 0.95$^b$</td>
<td>76.60</td>
<td>74.08</td>
<td>-55</td>
<td>90.75</td>
</tr>
<tr>
<td>2-Butanone</td>
<td>1.62 1.91 2.33 2.75</td>
<td>50.94</td>
<td>48.42</td>
<td>-139</td>
<td>90.45</td>
</tr>
<tr>
<td>Cyclohexanone</td>
<td>1.95 3.62 4.84 6.82</td>
<td>124.47</td>
<td>121.96</td>
<td>106</td>
<td>89.98</td>
</tr>
<tr>
<td>Dimethyl formamide</td>
<td>10.50 13.50 18.20 21.40</td>
<td>45.96</td>
<td>43.44</td>
<td>-140</td>
<td>85.75</td>
</tr>
<tr>
<td>Dimethyl sulphoxide</td>
<td>19.05 26.32 34.61 48.51</td>
<td>47.87</td>
<td>45.36</td>
<td>-128</td>
<td>84.23</td>
</tr>
<tr>
<td>Formamide</td>
<td>25.72 33.11 51.50 82.62</td>
<td>75.64</td>
<td>73.12</td>
<td>-34</td>
<td>83.92</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>9.77 13.40 16.52 21.60</td>
<td>36.02</td>
<td>33.48</td>
<td>-170</td>
<td>85.92</td>
</tr>
<tr>
<td>Ethoxyethanol$^a$</td>
<td>4.93 5.27 5.55 5.89</td>
<td>95.57</td>
<td>93.05</td>
<td>18</td>
<td>87.64</td>
</tr>
</tbody>
</table>

$^a$ eliminated from statistical analysis as complete set of solvent parameters data is not available.

$^b$ at 298K.
state is more solvated than the reactants. This is naturally expected in all $S_n2$ reactions as there is extensive charge separation. The free energy of activation, $\Delta G^\#$, is nearly constant (87.52±3.16 kJ mol$^{-1}$), indicating that a unified reaction scheme operates in all the solvents. A comparison of the rate of this reaction with the rates of allylation and benzylolation of this nucleophile using the corresponding bromides in our laboratory suggests that the order of reactivity is: phenacyl bromide > benzyl bromide > allylbromide. This is attributed to the carbonium ion present in phenacyl bromide which is adjacent to the carbonyl group.

References
2 Reichardt C, Angew Chem, 18 (1979) 98.