Interactive free energy relationships for non-additive multiple substituent effects in base catalysed condensation of benzaldehydes with acetophenones: A kinetic study

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The base-catalysed condensation of benzaldehydes with acetophenones is enhanced by electron-withdrawing substituents in both the starting compounds. The magnitude of p-value obtained for various substituents in the benzaldehyde moiety decreases with the introduction of electron-withdrawing groups in the para position of acetophenone moiety.

The non-additivity of kinetic substituent effects is well known in literature. Owing to lack of general method for treating cumulative effects, the additive model of Jaffe is usually applied and the most outstanding deviations are assigned to some specific interaction. Miller and later Ruasse et al. proposed an empirical free energy relation. These authors added an interaction term to the additivity relation. In the condensation of aromatic aldehydes with ketones yielding chalcones it is possible to evaluate the reaction constant (p) from the Hammett's plot and the effect of substituents on p by varying substituents in either of the two aromatic rings in chalcone, keeping the same substituent in one of the aromatic rings. The purpose of the title investigation is to show that multiple substituent effects (MSEs) can be analysed quantitatively in terms of interactive free energy relationships (IFER) extending classical Hammett-Brown relationship established for one substituent.

Experimental
Benzaldehyde was washed with aq. Na$_2$CO$_3$ and water to remove any trace of benzoic acid and dried over anhydrous CaCl$_2$. Solid benzaldehydes like p-Cl, p-NO$_2$, m-NO$_2$ etc. were recrystallised from ethanol-water mixture. Liquid benzaldehydes like p-CH$_3$, p-OCH$_3$, m-Cl, m-CH$_3$ were distilled before use. Acetophenone and substituted acetophenones (BDH) were used as such. The rate of reaction was followed by withdrawing aliquots (5 ml each) of the reaction mixture at regular time intervals and measuring their absorbances (A$_0$) at 410 nm. Least squares method was used to calculate rate constants and other kinetic parameters. Reactions were conducted in 75% (v/v) ethanol-water mixture in the presence of NaOH.

Results and discussion
The kinetic results are summarised as follows: (i) the orders in [benzaldehyde], [acetophenone] and [OH$^-$] are unity each; (ii) substituents in benzaldehyde and acetophenone moieties affected the rate; (iii) the fastest reaction has the lowest activation energy and vice versa; (iv) the plot of $\log k^*$ versus $1/D$ was linear with a negative slope indicating that probably a negative ion and a dipole is involved in the rate-determining step. These results are similar to those observed by earlier workers and hence the mechanism is suggested on the same lines as in Scheme 1.

$$\text{PhCHO} + \text{PhCOCH$_2$} \xrightleftharpoons{[k]} \text{PhC}^-\text{CH$_2$COPh}$$

$$\text{PhCH} = \text{CHCOPh} \rightarrow \text{PhCHOHCH$_2$COPh} + \text{OH}^-$$

Scheme 1

The rate law corresponding to Scheme 1 is given by Eq. (1)

$$\frac{d\Phi}{dt} = k^* [\text{benzaldehyde}][\text{acetophenone}][\text{OH}^-] \quad \ldots (1)$$

Rate law (1) explains well the experimentally observed results.

The effect of substituents in both the aromatic rings on the rate showed that electron-withdrawing groups increase the rate and vice versa. Although the presence of a particular substituent in both the rings affects the rate, the effect is more pronounced when the substituent is present in the benzaldehyde moiety. The order of reactivities with substituents in benzaldehyde moiety with no substituent in the ketone moiety is $p$-NO$_2 > m$-$\text{NO}_2 > m$-$\text{Cl} > p$-$\text{Cl} > H > m$-$\text{OCH}_3 > p$-$\text{OCH}_3 > m$-$\text{CH}_3 > p$-$\text{CH}_3$ (Table 1). The $p$-value for meta substituents in benzaldehyde was found to be 1.44. Benzaldehydes with substituents at para position fall outside the
Table 1—Rate constants ($k^*$) for the base catalysed condensation of substituted benzaldehydes with acetophenones

<table>
<thead>
<tr>
<th>Substituents in acetophenone moiety (Y)</th>
<th>p-OCH$_3$</th>
<th>m-OCH$_3$</th>
<th>p-CH$_3$</th>
<th>m-CH$_3$</th>
<th>H</th>
<th>p-Cl</th>
<th>m-Cl</th>
<th>m-NO$_2$</th>
<th>p-NO$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>0.935</td>
<td>1.66</td>
<td>0.254</td>
<td>0.813</td>
<td>1.00</td>
<td>2.04</td>
<td>4.07</td>
<td>10.2</td>
<td>11.6</td>
</tr>
<tr>
<td>p-CH$_3$</td>
<td>0.142</td>
<td>0.437</td>
<td>0.102</td>
<td>0.229</td>
<td>0.405</td>
<td>1.01</td>
<td>1.15</td>
<td>3.81</td>
<td>4.94</td>
</tr>
<tr>
<td>m-Cl</td>
<td>3.24</td>
<td>3.98</td>
<td>1.29</td>
<td>2.18</td>
<td>2.63</td>
<td>6.16</td>
<td>8.32</td>
<td>17.8</td>
<td>19.1</td>
</tr>
<tr>
<td>p-Cl</td>
<td>9.63</td>
<td>10.5</td>
<td>6.67</td>
<td>8.13</td>
<td>9.24</td>
<td>13.1</td>
<td>15.8</td>
<td>26.9</td>
<td>28.1</td>
</tr>
</tbody>
</table>

The reaction constants ($\rho$) determined for various substituents in the benzaldehyde moiety keeping a particular substituent in the ketone moiety are presented in Table 2. The value for various substituents in benzaldehyde moiety with no substituent in the ketone moiety is 1.44 at 318 K. This value decreases to 1.25 and 0.72 when the substituents in the ketone moiety are p-Cl and p-NO$_2$ respectively and increases to 1.61 for p-CH$_3$. This clearly shows that electron-withdrawing groups decrease the magnitude of $\rho$-value and vice versa. Introduction of p-NO$_2$ in ketone moiety decreases the negative charge in the transition state and hence the $\rho$-value decreases. When p-CH$_3$, an electron-releasing group is introduced in the ketone moiety, the electron density at the reaction centre is considerably high compared to H or NO$_2$ group, and this appears to increase the sensitivity of reaction to the presence of substituents in X. A linear plot is obtained when $\rho_{XY}$ (obtained from Hammett’s plot for various substituents in benzaldehyde moiety) is plotted against $\sigma_Y$ (for substituents in ketone moiety) with a slope of 0.90 ± 0.02 ($r=0.980$). This type of relationship is different from simple Hammett equation where LFER is operative. Therefore, such relationships are explained in terms of interactive free energy relationships (IFER). To explain such effects we have derived expression (2)

\[
\frac{\rho_{XY} - \rho_{XY,0}}{\sigma_X} = \frac{\rho_{XY} - \rho_{XY,0}}{\sigma_Y} = q \ldots (2)
\]
where $\rho_{X(Y)}$ and $\rho_{Y(X)}$ are reaction constants for substituents benzaldehyde and ketone moieties, respectively with H in the other ring. Similarly $\rho_{Y(X)}$ and $\rho_{X(Y)}$ are reaction constants for various substituents in these aromatic rings respectively with the same substituent in the other ring. $\sigma_X$ and $\sigma_Y$ are substituent constants for substituents in these rings respectively.

Equation (2) must be true whatever be the substituents in the two aromatic moieties. Therefore, the ratios are equal to a constant ($q$) which is known as cross interaction constant. From Eq. (2) it is clear that the reaction constants are not random variables and are directly dependent on substituent constants.

$$\rho_{X(Y)} = \rho_{X(Y)} + q\sigma_Y$$ \ldots (3)

or

$$\rho_{X(Y)} = \rho_{Y(X)} + q\sigma_X$$ \ldots (4)

From Eq. (3) it can be seen that a plot of $\rho_{X(Y)}$ versus $\sigma_Y$ should be linear if $q$ is constant. In the present work a good linear plot is obtained with a slope of $-0.92$ (Fig. 2). Calculation of $q$ values from Eq. (3) shows that it is a constant for the substituents studied indicating the validity of the above equation. This shows that IFER for multiple substituent effects are operative in this reaction. Similar observations have been made for Ce(IV)-chalcone and aromatic anils-BrO$_3^-$ (ref. 8) reactions. The significance of $q$ is that it measures the extent of interaction between the substituent and the reaction centre.

**References**