Kinetics and mechanism of reaction of barbituric acids with
p-dimethylaminobenzaldehyde and N,N-dimethyl-p-nitrosoaniline

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The condensation reactions of barbituric acid (I) and thiobarbituric acid (II) with p-dimethylaminobenzaldehyde (III) and N,N-dimethyl-p-nitrosoaniline (IV) in methanolic medium have been investigated spectrophotometrically at 10-55°C. These reactions follow overall second order kinetics, first order each in reactants. The rate-determining step involves dehydration of the aldol intermediate (XI). From the dependence of the rate constants on temperature activation parameters have been calculated. The solvent effect on the reaction rate has been investigated and the rate decreases with decrease in dielectric constant.

5-Barbituric and thiobarbituric acid derivatives show considerable pharmacological and biochemical significance and a good number of synthetic approaches towards these are available in literature. In view of the absence of any kinetic investigation on the reactions of these compounds with aldehydes and nitroso compounds, we undertook the title investigation.

Materials and Methods

Barbituric acid (I), thiobarbituric acid (II) (Aldrich), p-dimethylaminobenzaldehyde (III) and N,N-dimethyl-p-nitrosoaniline (IV) (BDH) were used as received. The derivatives of 5-barbituric (V, VI) and thiobarbituric (VII, VIII) acids were prepared by refluxing equimolar amounts of I/II with aldehyde (III) or the nitroso compound (IV) in methanol. The products were recrystallized several times from ethanol.

Spectral grade solvents (BDH or E. Merck) were used. The absorbance measurements were carried out on a Shimadzu UV-200 S double beam spectrophotometer, using 1 cm matched silica cells. The rate of reaction in all the cases was followed up to ≥ 70% completion.

Kinetic measurements

Equal volumes of freshly prepared solutions (0.01 mol dm⁻³) of I/II and III/IV were mixed in such away that the initial concentrations of I/II and those of III/IV were usually 2.0 × 10⁻³ mol dm⁻³.

Aliquots of the reaction mixture were withdrawn at different time intervals and diluted rapidly to a definite volume by adding the same solvent, then the absorption was recorded at λ_max of the product (acid derivative) against a blank containing the acid. Some experiments for the reaction of acid (I) with aldehyde (III) were, however, carried out at 25°C to test the reaction order and the optimum initial concentrations of the reactants. The amounts of the derivatives formed at different time intervals were calculated applying Beer’s law. The ε_max was determined as the slope of the plot of absorbance versus [acid derivative].

Results and Discussion

The reaction was found to be of first order
each in [I/II] and in [III/IV]. Plots of \(1/(\alpha - \rho) - 1/\alpha\) versus time for reactions (I) + (III) and (II) + (III) were linear passing through the origin up to 80% completion of the reaction, whereas the reactions (I) + (IV) and (II) + (IV) showed a deviation from the first order plots after about 40% completion. These linear rate plots indicate that the reactions follow second order kinetics. The values of the apparent second order rate constants \(k_{\text{obs}}\) were obtained from the slope of these plots. Such plots at different temperatures are shown in Fig. 1, for the reaction (II) + (III). In certain cases, slight curvature is noted in the initial stages of the reactions, which may be attributed to inefficient mixing of the reactants. The experiments were performed in duplicate at each temperature and the average rate constants were calculated. The rate constants \(k_{\text{obs}}\) at 40°C, the activation energies \(E_a\) and the frequency factors \(A\) are listed in Table 1.

Barbituric acid (I) and thiobarbituric acid (II) exist in tautomeric forms, each of which has an active methylene group. This is supported by charge density data which reveal higher charge density at C-2 and C-7 carbons.

The magnitude of rate of the reaction of acid I/II with the aldehyde (III) is greater than that of nitroso compound (IV) (Table 1). This can be attributed to the negative charge density on the carbonyl or nitroso O-atom. Furthermore, the reaction rate of aldehyde or nitroso compound with acid (I) is lower than that with acid (II). This can be attributed to the differences in the positive charge densities on C-2 and C-7 carbons.

**Mechanism**

It is generally agreed\(^{2b,4b,5}\) that the present reactions proceed through an anion intermediate as shown in Scheme 1. The first step involves the formation of an anion (IX). This ionization step is induced by the aldehyde or the nitroso compound. The first and second steps are normally fast\(^6\). The third step involves the addition of the cation (X) to the acid anion (IX), forming the aldol intermediate (XI). Since the third step involves charge neu-

![Second order plots of \(1/(\alpha - \rho) - 1/\alpha\) versus time for the reaction of thiobarbituric acid (II) with \(p\)-dimethylaminobenzaldehyde (III) in MeOH](image1)

**Table 1** – Rate constants \(k_{\text{obs}}\), activation energies \(E_a\), frequency factors \(A\) and thermodynamic parameters of activation for the reaction of barbituric (I) and thiobarbituric (II) acids with aldehyde (III) and nitroso compound (IV) in methanol.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>(k_{\text{obs}} \times 10^2) (dm(^3)mol(^{-1})s(^{-1}))</th>
<th>(E_a) (kJ mol(^{-1}))</th>
<th>(\log_{10} A)</th>
<th>(\Delta G^{*##}) (kJ mol(^{-1}))</th>
<th>(\Delta H^{*##}) (kJ mol(^{-1}))</th>
<th>(\Delta S^{*##}) (J mol(^{-1}) K(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid (I)-aldehyde</td>
<td>6.03</td>
<td>17.42</td>
<td>25.76</td>
<td>84.11 ± 2.75</td>
<td>14.81 ± 0.93</td>
<td>-221.39 ± 3.24</td>
</tr>
<tr>
<td>Acid (I)-nitroso compound</td>
<td>1.35 b/4.75</td>
<td>12.17</td>
<td>19.95</td>
<td>88.00 ± 3.26</td>
<td>9.57 ± 0.65</td>
<td>-250.59 ± 5.41</td>
</tr>
<tr>
<td>Acid (II)-aldehyde</td>
<td>211.84</td>
<td>28.11</td>
<td>42.89</td>
<td>74.85 ± 2.91</td>
<td>25.51 ± 1.33</td>
<td>-157.62 ± 2.80</td>
</tr>
<tr>
<td></td>
<td>15.76 a</td>
<td>18.93</td>
<td>27.91</td>
<td>81.61 ± 4.05</td>
<td>16.33 ± 0.28</td>
<td>-208.57 ± 2.73</td>
</tr>
<tr>
<td></td>
<td>1.47 b</td>
<td>15.30</td>
<td>22.75</td>
<td>87.78 ± 4.13</td>
<td>12.69 ± 0.98</td>
<td>-239.90 ± 4.91</td>
</tr>
<tr>
<td>Acid (II)-nitroso compound</td>
<td>36.76; 62.89</td>
<td>20.25</td>
<td>31.01</td>
<td>79.40 ± 3.82</td>
<td>17.65 ± 0.30</td>
<td>-197.29 ± 3.06</td>
</tr>
</tbody>
</table>

* At 40°C; ** Calculated using Arrhenius equation; *** Calculated using Eyring equation; a in EtOH; b in isopropanol.
neutralization reaction, it is also expected to be very fast. The fourth step involves the dehydration of the aldol intermediate (XI) to produce the condensation product (XIII). Since the last dehydration step is the only one involving cleavage of bonds, it is likely to be considered as the slowest rate-determining step and consequently leads to Eq. (1).

\[
\text{Rate} = \frac{d[\text{XI}]}{dt} = K_\text{d}[\text{XI}] \quad \ldots (1)
\]

Substituting the equilibrium constants \(K_1\), \(K_2\), and \(K_3\) defined by steps (i), (ii), and (iii) in Scheme 1 into Eq. (1) yields

\[
\text{Rate} = k_d K_1 K_2 K_3 [\text{I/II}][\text{III/IV}] \quad \ldots (2)
\]

From Eq. (2), one can conclude that

\[
k_{\text{obs}} = k_d K_1 K_2 K_3 \quad \ldots (3)
\]

Equation (2) shows that the reaction follows second order kinetics, first order each in [I/II] and [III/IV]. The apparent second order rate constant \((k_{\text{obs}})\) is therefore a product of the three equilibrium constants of the first three steps \((K_1\), \(K_2\), and \(K_3\)) and the rate constant \((k_d)\) of the fourth step. The second order rate constant \((k_d)\) could not be evaluated since no data are available for the equilibrium constants \(K_1\), \(K_2\), and \(K_3\).

The rate of the reactions was studied over a temperature range from 10 to 55°C in methanolic medium. The results are summarized in Table 1. The experimentally observed rate constants \((k_{\text{obs}})\) were applied to the rate-determining step because there was no way of calculating \(k_d\) in Eq. (3). As shown in Fig. 2, the plots of \(-\ln(h/KT)\) \(k_{\text{obs}}\) versus \(1/T\) of Eyring equation, were linear from which the activation parameters were calculated by the least squares method (Table 1). The solvation energies of the aldehyde (III) and the nitroso compound (IV) cations have been calculated to be \(-5.269\) eV and \(-5.125\) eV in methanol, respectively. Therefore, the activation energy which is required for the reaction with the aldehyde (III) cation is higher than that required for the reaction with the nitroso compound (IV) cation. Thus, the \(E_a\) value for the reaction of acid (I)/(II) with the nitroso compound (IV) is less than that with the aldehyde (III), Table 1. The values of frequency factors \((A)\) calculated in the present study are in good agreement with those reported for bimolecular reactions. The free energy change of acti-
vation ($\Delta G^*$) shows a weak dependence on the acid I/II, the aldehyde (III) or the nitroso compound (IV), indicating that there is no change in mechanism for such related series of reactions. On the other hand, the entropy of activation ($\Delta S^*$) depends on the acid used (Table 1). The high negative $\Delta S^*$ values for reactions (I)+(III) and (I)+(IV) as compared to reactions (II)+(III) and (II)+(IV), respectively, may indicate that the extent of solvation of the corresponding acid anion is more in the former than in the latter ones. The solvation energies of the anions of acids (I) and (II) have been calculated to be $-4.227$ eV and $-3.785$ eV in methanol, respectively.

It is evident from the data in Table 1 that the rate of the reaction decreases with decrease in solvent dielectric constant in the order: MeOH > EtOH > isopropanol. The increase in solvent dielectric constant will increase the solvation of the reactants through H-bond formation. It is also clear that the activation energy ($E_a$) increases with increase in the solvent dielectric constant. The solvation energies of the acid (II) anion and the aldehyde (III) cation have been calculated in methyl, ethyl and isopropyl alcohols and the values are $-3.785$, $-3.744$, $-3.691$ eV for the aldehyde (III) cation, respectively. Therefore, the activation energy which is required for the reaction (II)+(III) increases in the order methanol > ethanol > isopropanol, Table 1.

The thermodynamic parameters of activation $\Delta G^*$, $\Delta H^*$, and $\Delta S^*$ corresponding to the reaction of acid (II) with aldehyde (III) in the various organic solvents used, are also given in Table 1. It is evident that, $\Delta G^*$ is independent of the solvent used, indicating that the reaction mechanism is also the same.

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