Solvent effect on reactivity trends for base hydrolysis of 2-oxo-, 2-thio- benzopyran-3-thiocarboxamide, and 2-iminobenzopyran-3-carbonitrile

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Kinetics of base-catalysed hydrolyses of 2-oxobenzopyran-3-carboxamide, 2-thiobenzopyran-3-carboxamide, and 2-iminobenzopyran-3-carbonitrile are studied in aqueous methanol mixture and the effect of solvent on change in the activation barrier \( \Delta \Delta G^\ddagger \) is measured. Solvent effects on reactivity trends for base hydrolysis of these compounds have been analysed into initial state and transition state components which are determined from transfer chemical potentials and kinetic data. It is observed that the substituents O, S or N in position two and thiocarboxamide or carbonitrile in position three affect the rate constant and change the activation barrier.

2-oxobenzopyran-3-thiocarboxamide (coumarin-3-thiocarboxamide), 3-halocoumarins, 3-halothiocoumarins and 3-thiocoumarine-2-imine are useful intermediates for the synthesis of biologically active coumarin derivatives \(^1\text{-}^3\), and as building blocks for the synthesis of condensed and spiro coumarins \(^4\).

Some of these compounds have been reported to act as nervous system depressants \(^5\) and antibacterial agents \(^6\). In continuation of the work on 3-bromothiocoumarin and thiocoumarin-3-carboxylate \(^7\), it is reported herein the solvent effects on the kinetics of base hydrolysis of 2-oxobenzopyran-3-thiocarboxamide, 2-thiobenzopyran-3-thiocarboxamide, 2-iminobenzopyran-3-carbonitrile in aqueous methanol mixtures.

Solvent effects on reactivity trends have been investigated for a variety of organic and inorganic reactions \(^8\). Solvent effects on hydrolysis of thiocoumarin \(^9\) have been analysed into initial state and transition state components and the rate of the reaction in binary solvents may be dominated by either initial state or transition state. In this approach the initial state-transition state analysis of solvent effect on reactivity of 2-oxobenzopyran-3-carboxamide, 2-thiobenzopyran-3-carboxamide, and 2-iminobenzopyran-3-carbonitrile has been discussed. It is also shown how these can provide complementary information on the rate of solvation, and how transition state modeling may assist in interpretation.

Materials and Methods

Sodium hydroxide (Analar) solutions were made up from stock solutions, and ionic strength was maintained using sodium chloride (Analar) solutions. Methanol was purified by treatment with magnesium and iodine, with subsequent redistillation. Solvent mixtures were made based on volume percentage.

Kinetics of base hydrolysis were monitored in 10 mm silica cells in the thermostated cell compartment of spectrophotometer JASCO model V530.

Solubility was measured by agitating a generous excess of solid with the appropriate solvent mixture in a thermostated vessel for several hours in the thermostat HAAKE Circulators (F3-K). A portion of supernatant saturated solution was removed and centrifuged rapidly before withdrawing an aliquot, diluting as necessary, and measuring the absorbance at \( \lambda_{\text{max}} \) for the compound in question \(^1\text{6}\).

2-oxobenzopyran-3-thiocarboxamide was prepared by cyclocondensation of cyanothioacetamide with salicylaldehyde, thiation of 2-oxobenzopyran-3-thiocarboxamide by \( \text{P}_2\text{S}_5 \) gave 2-thiobenzopyran-3-thiocarboxamide and also condensation of salicylaldehyde with malononitrile gave 2-iminobenzopyran-3-carbonitrile \(^1\text{1}\).

Results and Discussion

The action of alkali on coumarin and thiocoumarin compounds at room temperature always lead to the opening of the pyrone ring and the formation of the salts of coumarinic acid and thiocoumarinic acid \(^1\text{2}\). So the hydrolysis of 2-oxobenzopyran-3-thiocarboxamide (I), 2-thiobenzopyran-3-thiocarboxamide (II), and 2-iminobenzopyran-3-carbonitrile (III) with sodium hydroxide at 298K was followed spectrophotometrically. It can be inferred from the
spectra that the hydrolysis takes place in one stage and leads to the opening of the pyrone ring, sodium hydroxide being present in large excess over the organic compound.

The rate law for reaction of most coumarin and chromone compounds with hydroxide ion is,

$$-\frac{d[\text{compound}]}{dt} = (k_1 + k_2[OH^-])[\text{compound}] \quad \ldots (2)$$

The hydrolysis of these compounds follows first order kinetics over at least three half-lives.

Observed first order rate constants as a function of sodium hydroxide concentration and volume fraction of methanol (MeOH % vol.) are reported in Tables 1, 2 and 3 at 298K. The kinetic results conform to Eq. (1).

$$-\frac{d[\text{compound}]}{dt} = k_\text{obs}[\text{compound}] \quad \ldots (1)$$
with the $k_1$ term is assigned to rate-determining dissociation of the compounds and the $k_2$ term to rate-
determining attack by $\text{OH}^-$ at the compounds.

The dependence of $k_{\text{obs}}$ on base concentration is
deed linear for the compounds (I), (II), and (III) but
there is no significant intercept of the correlation line.
Hence the hydrolysis follows the rate law with

$$k_{\text{obs}} = k_2 [\text{OH}^-] \quad \ldots \ (3)$$

where $k_2$ is the second order rate constant at
$[\text{OH}^-] \gg [\text{compound}]$. Equation (3) indicated that the
second order process is dominant in the present
solvent mixtures. Values of $k_2$ are computed from a
linear least-squares program of the dependence of
observed rate constants on base concentration at each
aqueous methanol proportion. The change in the
activation barrier $\delta \Delta G^\delta$ for this compound from
water to methanol-water mixtures are derived in
Tables 1, 2, and 3. The change in the activation
barrier $\delta \Delta G^\delta$ is obtained from the ratio of rate
constants,

$$\delta \Delta G^\delta = R \ln \frac{k_{\text{obs}}}{k_2} \quad \ldots \ (4)$$

The comparison of $k_2$ and $\delta \Delta G^\delta$ for coumarin (2-
oxobenzopyran) and thiocoumarin (2-thiobenzopyran)$^9$
and these compounds 2-oxobenzopyran-3-thiocarboxamide (I), 2-thiobenzopyran-3-thiocarboxamide (II), and
2-iminobenzopyran-3-carbonitrile (III) in
aqueous methanol at 298 K:

<table>
<thead>
<tr>
<th>Compounds</th>
<th>MeOH%</th>
<th>10$^3$$k_2$</th>
<th>$\delta \Delta G^\delta$ (compound)</th>
<th>$\delta \Delta G^\delta$ (OH)</th>
<th>$\delta \Delta G^\delta$ (IS)</th>
<th>$\delta \Delta G^\delta$ (compound)</th>
<th>$\delta \Delta G^\delta$ (TS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I)</td>
<td>0</td>
<td>5.03</td>
<td>-1.62</td>
<td>-0.2</td>
<td>-1.82</td>
<td>0.434</td>
<td>-1.386</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>5.03</td>
<td>-1.62</td>
<td>-0.2</td>
<td>-1.82</td>
<td>0.434</td>
<td>-1.386</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>9.66</td>
<td>-3.39</td>
<td>0.1</td>
<td>-3.49</td>
<td>0.855</td>
<td>-2.635</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>19.8</td>
<td>-4.65</td>
<td>1.6</td>
<td>-3.05</td>
<td>1.56</td>
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</tr>
<tr>
<td>(II)</td>
<td>0</td>
<td>2.99</td>
<td>-1.38</td>
<td>-0.2</td>
<td>-1.58</td>
<td>0.508</td>
<td>-1.072</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>5.22</td>
<td>-1.38</td>
<td>-0.2</td>
<td>-1.58</td>
<td>0.508</td>
<td>-1.072</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>9.39</td>
<td>-2.83</td>
<td>0.1</td>
<td>-2.73</td>
<td>0.945</td>
<td>-1.785</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>12.7</td>
<td>-3.38</td>
<td>1.6</td>
<td>-1.98</td>
<td>1.56</td>
<td>-0.42</td>
</tr>
<tr>
<td>(III)</td>
<td>0</td>
<td>5.39</td>
<td>-1.20</td>
<td>-0.2</td>
<td>-1.4</td>
<td>0.5</td>
<td>-0.9</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>8.74</td>
<td>-1.20</td>
<td>-0.2</td>
<td>-1.4</td>
<td>0.5</td>
<td>-0.9</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>49.62</td>
<td>-5.5</td>
<td>0.1</td>
<td>-5.4</td>
<td>1.27</td>
<td>-4.026</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>113.0</td>
<td>-7.54</td>
<td>1.6</td>
<td>-5.94</td>
<td>1.9</td>
<td>-4.04</td>
</tr>
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</table>

In order to assess the various contributions to
reactivity trends of these compounds, we need to
separate solvation effects into initial state and
transition state contributions. At fixed temperature
and pressure, the kinetic data, according to transition
state theory, lead to Gibb’s free energies of activation
$\Delta G^\delta$, i.e., the change in the rate constant on going from
a reference solvent to a medium of mole fraction $x_2$,
\[ \delta_m \Delta G^*= \delta_m \mu^* - [\delta_m \mu^*(A) + \delta_m \mu^*(B)] \quad \ldots (5) \]

where, \( \delta_m \mu^*(A) \) and \( \delta_m \mu^*(B) \) are the transfer chemical potential of the reactants A and B, and \( \delta_m \mu^* \) is the transfer chemical potentials of the transition state.\(^{13,14}\)

The difference in chemical potential on transferring the solute from the reference solvent to the medium will be \( \delta_m \mu^* \); and it can be obtained from the solubility measurements. Thus, from Eqs. (4) and (5), the activation barriers of the initial state and the transition state can be calculated.

The initial state-transition state analysis of the reactivity trends for the base hydrolysis of these compounds are given in Table 5. The transfer chemical potentials for these compounds, \( \delta_m \mu^\text{(comp.)} \), are derived from their solubilities, and transfer chemical potentials for hydroxide ion, \( \delta_m \mu^\text{(OH)} \) are taken from literature.\(^{15}\)

The comparison of the initial state and transition state for thiocoumarin and compound II is shown in Fig. 1. This indicates that as the proportion of methanol increases, these compounds are highly stabilised and hydroxide destabilised a little resulting in an overall markedly stabilised initial state on transferring from water to methanol rich solvent. On the other side the transition state is slightly stabilised from water to 60% MeOH. Thus, the observed decrease in the rate constant as the proportion of methanol increases is ascribed to a greater effect of solvent on the initial state.

The activation energies were calculated from Arrhenius plots by least squares method (Table 6).

### Table 6—Observed first order rate constant (\(k_{obs}\)), Second-order constants (\(k_2\)) for reaction of 2-oxobenzopyran-3-thiocarboxamide (I), 2-thiobenzopyran-3-thiocarboxamide (II), and 2-iminobenzopyran-3-carbonitrile (III) and OH\(^-\) at different temperatures, and derived activation parameters:

<table>
<thead>
<tr>
<th>Temp. °C</th>
<th>[OH(^-)] \times 10^{-2}</th>
<th>0.66</th>
<th>1.33</th>
<th>2.00</th>
<th>2.66</th>
<th>3.33</th>
<th>(k_2\times10^{-2}) dm(^3)mol(^{-1})s(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>0.66</td>
<td>0.91</td>
<td>1.15</td>
<td>1.43</td>
<td>1.95</td>
<td>5.4</td>
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<tr>
<td>20</td>
<td>0.77</td>
<td>1.42</td>
<td>2.04</td>
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<td>10.79</td>
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<tr>
<td>25</td>
<td>1.15</td>
<td>2.41</td>
<td>3.30</td>
<td>4.52</td>
<td>5.65</td>
<td>16.8</td>
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<tr>
<td>30</td>
<td>1.44</td>
<td>2.89</td>
<td>4.35</td>
<td>5.62</td>
<td>7.11</td>
<td>21.2</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>2.25</td>
<td>4.13</td>
<td>5.91</td>
<td>8.01</td>
<td>10.03</td>
<td>29.7</td>
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</tr>
<tr>
<td>40</td>
<td>3.2</td>
<td>5.65</td>
<td>8.32</td>
<td>10.83</td>
<td>13.5</td>
<td>39.9</td>
<td></td>
</tr>
</tbody>
</table>

\(\Delta H^\circ\) (kJ mol\(^{-1}\)) = 51.856

\(\Delta S^\circ\) (J deg\(^{-1}\)mol\(^{-1}\)) = -84.476

---

<table>
<thead>
<tr>
<th>Temp. °C</th>
<th>[OH(^-)] \times 10^{-2}</th>
<th>0.31</th>
<th>0.605</th>
<th>0.815</th>
<th>1.15</th>
<th>1.49</th>
<th>4.35</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>0.24</td>
<td>0.51</td>
<td>0.65</td>
<td>0.89</td>
<td>1.15</td>
<td>3.36</td>
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</tr>
<tr>
<td>20</td>
<td>0.31</td>
<td>0.605</td>
<td>0.815</td>
<td>1.15</td>
<td>1.49</td>
<td>4.35</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>0.38</td>
<td>0.79</td>
<td>1.00</td>
<td>1.41</td>
<td>1.82</td>
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<tr>
<td>30</td>
<td>0.55</td>
<td>1.09</td>
<td>1.53</td>
<td>1.94</td>
<td>2.43</td>
<td>7.19</td>
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<tr>
<td>35</td>
<td>0.74</td>
<td>1.38</td>
<td>1.96</td>
<td>2.62</td>
<td>3.63</td>
<td>10.45</td>
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<tr>
<td>40</td>
<td>1.01</td>
<td>1.94</td>
<td>2.8</td>
<td>3.3</td>
<td>4.54</td>
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</tbody>
</table>

\(\Delta H^\circ\) (kJ mol\(^{-1}\)) = 48.678

\(\Delta S^\circ\) (J deg\(^{-1}\)mol\(^{-1}\)) = -106.431
The kinetics of base hydrolysis of the compounds I, II and III in aqueous solution were carried out at different temperatures. Observed first order rate constants as a function of [NaOH] and temperature are reported in Table 6, from which $k_2$ values have been used to estimate the activation parameters in Table 6 by least squares method of Eyring plots.

**References**