THE INFLUENCE OF pH AND TEMPERATURE ON THE DEGRADATION KINETICS OF 4-METHOXY-2-[3-(4-PHENYL-1-PIPERAZINYL)] PROPYL-2,3-DIHYDRO-6-METHYL-1,3-DIOXO-1H-PYRROLO [3,4-c] PYRIDINE IN AQUEOUS SOLUTIONS

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Abstract: The pH-rate profiles for hydrolysis of 4-methoxy-2-[3-(4-phenyl-1-piperazinyl)]propyl-2,3-dihydro-6-methyl-1,3-dioxo-1H-pyrido[3,4-c] pyridine (II) at 333, 343, 353 and 363 K over the pH range 0.4–5.0 was investigated. The decomposition was followed by the HPLC method (LiChrosorb® 100 RP-18 column 250 × 4.0 mm L, dp = 5 µm; mobile phase: acetonitrile – phosphate buffer (pH = 2; 0.01 mole/L) (45: 55, v/v or 30: 70, v/v)). The pH-rate profile indicated specific acid- and base-catalysed reactions as well as spontaneous water-catalysed degradation of two molecules of II (as a dication and monocation). The kinetic strength effect, the pKa value (2.4; 6.2), the pHmin value (2.1) and thermodynamic parameters of the reaction (energy and enthalpy of activation and the frequency coefficient for the specific rate constants) were determined.

Keywords: 4-alkoxy-2,3-dihydro-6-methyl-1,3-dioxo-1H-pyrido[3,4-c]pyridine derivatives; hydrolysis; pH-rate profile

N-[2-hydroxy-3-(4-phenyl-1-piperazinyl)] propyl derivatives of 4-methoxy and 4-ethoxy-6-methyl-1H-pyrido[3,4-c] pyridine-1,3 (2H)-diones (Figure 1) showed potent analgesic activity and were non-toxic (LD50 > 2000 mg/kg) (1). Their ED50 (in 'writhing syndrome' test: 0.4 mg/kg – I, 1.4 mg/kg – III; in 'hot plate' test: 11.9 mg/kg – I, 17.6 mg/kg – III) indicated that compound I was a more active analgesic agent than its ethoxy homologue III. Elimination of the hydroxy group from the side propyl chain in I (compound II) caused also the weakness of the analgesic properties (ED50 for II – 1.03 mg/kg in 'writhing syndrome' test). In the 'hot plate' test compound II displayed a weak analgesic action at a dose of 100 mg/kg (2). Simultaneously, these modifications did not affect the toxicity of the tested compounds (LD50 for II > 2000 mg/kg similarly as in the case of imides I and III). Pharmacological studies pertaining to this group of compounds are in progress. Kinetic studies of the degradation of I have shown that, like in case of another imides e.g., thalidomide (3–5), either in an acidic or basic medium at an increased temperature, instant hydrolysis of the imide bond was observed, leading to the formation of a –COOH in position 3 or 4 of the pyridine ring (product IIa or IIb; M = 412; substrate II, M = 394). In an acidic medium, product IIb was the main product of the degradation of II, whilst in alkaline medium IIa was the main product (8).

The purpose of this study was to investigate the kinetics of II degradation in aqueous solutions as decomposition have shown that during the early stages of these processes, either in an acidic or basic medium at an increased temperature, an instant hydrolysis of the imide bond was observed, leading to the formation of a –COOH in position 3 or 4 of the pyridine ring (product IIa or IIb; M = 412; substrate II, M = 394). In an acidic medium, product IIb was the main product of the degradation of II, whilst in alkaline medium IIa was the main product (8).
EXPERIMENTAL

The compound 4-methoxy-2-[3-(4-phenyl-1-piperazinyl)] propyl-2,3-dihydro-6-methyl-1,3-dioxo-1H-pyrrolo [3,4-c] pyridine (II) was synthesized in the Department of Chemistry of Drugs at the Wrocław University of Medicine, Poland. Oxazepam (an internal standard - i.s.) was a product of Sigma-Aldrich Chemie GmbH (Germany). Other chemicals used were all of analytical reagent grade.

The compounds studied were determined and their decomposition investigated by means of the HPLC method. The analytical system consisted of a Rheodyne 7120 (20 ml fixed–loop injector), an LC 3 – UV detector (Pye Unicam, England), an L-6000 A pump (Merck – Hitachi, Germany) and an A/C transmitter with the software Chromed (Medson, Poland).

The degradation was monitored by the HPLC method (LiChrosorb® 100 RP-18 column 250 × 4.00 mm I.D., dp = 5 mm; mobile phase: acetonitrile – phosphate buffer (pH = 2; 0.01 mole/L) (45:55, v/v – phase A) or (30:70, v/v – phase B). The mobile phase B was only used for the determination of compound II and products IIA, IIB were observed in the acetate buffer (pH = 4.94, µ = 0.50 mole/L, 333 K and pH = 4.97, µ = 0.50 mole/L, 363 K). The flow rate was 1.4 mL/min for mobile phase A and 1.1 mL/min for mobile phase B. UV detection was carried out at 239 nm (8). The HPLC method was selective for determination of active compounds (II) in the presence of its degradation products. The whole validation parameters such as selectivity, linearity, precision, stability of an analite, LOD and LOQ were presented in the previous article (8).

The analysed solution consisted of 1.0 mL sample, 1.0 mL of i.s. (0.15 mg/mL) and 1.0 mL of water. In study conditions, the retention time was approx. 4.0 min for i.s, and 6.5 min for II in mobile phase A or 8.0 min and 17.6 min in mobile phase B, respectively.

The linearity between p/p0, (p, p0, – peak areas of substance II and i.s.) and concentrations of II in 0.01 mole/L HCl ranging from 11.3 µg/mL to 204.8 µg/mL was evaluated. The internal standard was added to the solutions under investigation at a constant concentration of 50 µg/mL. Linearity was also examined for 10 points of 3 replicate injections. The equation for the calibration curve is: y = (0.0147 ± 0.0005) x; (for the equation y = ax + b, the value b was insignificant). The calculated correlation coefficient was > 0.999, thus indicating good linearity.

The precision of the method was determined through the analysis of 6 replicate injections of standard solution containing 23.0 µg/mL and 92.0 µg/mL of substance II dissolved in HCl 0.01 mole/L (i.e., 25% and 100% from the concentration of II at the zero time in kinetic studies) with the internal standard at the constant concentration of 50 µg/mL. The RSDs ≤0.57% were satisfactory.

All the studies in aqueous buffer solutions were performed at 333, 343, 353, 363 K, and a constant ionic strength (µ) of 0.50 mole/L was adjusted for each buffer by adding a calculated amount of the sodium chloride solution (4.0 mole/L). The use of these high temperatures resulted from the hydrolytic stability of this compound at room temperature. In order to shorten the time of analysis and to make the evaluation of thermodynamic parameters, the test of artificial ageing was used at four different temperatures. The mechanism of observed reactions was the same at high temperatures as well as at room temperature (6–8). To obtain the desired pH, the following solutions were used: hydrochloric acid (pH = 0.44–1.49), phosphate buffers (pH = 2.11–3.19), and acetate buffer (pH = 3.40–4.97). The pH values for HCl were calculated from the equation:

\[ \text{pH} = -\log f_{\text{HCl}} \times [\text{HCl}] \]  

(1)

The activity coefficients \( f_{\text{HCl}} \) were taken from the literature (9). Other pH values were measured using a potentiometric pH-meter (CD-401, Elmetron, Zabrze, Poland) at the respective experimental temperatures. The initial concentration of II was about 0.28 mg/mL. When necessary, 2 mL of the obtained solutions were transferred into 5 mL ampoules and sealed. The remaining ampoules were immediately heated to 333, 343, 353 or 363 K, and cooled to room temperature at experimentally determined time intervals. The samples were collected at time intervals depending on the reaction rate at a given pH.

RESULTS AND DISCUSSION

The degradation of II, as a result of hydrolysis is a pseudo-first-order reaction described by the following equation:

\[ \ln(p/p_0) = \ln(p_0/p_s) - k_{\text{obs}} \times t \]  

(2)

where: \( p_0, p \) are the peak area of II at zero and time \( t \) respectively, \( p_s \) is the peak area of i.s. and \( k_{\text{obs}} \) is
the observed rate constant of the pseudo-first-order reaction of II degradation. In the solution of HCl, $k_{ob}$ equals to $k_{pH}$.

The degradation of II was found to be the subject to general acid-base catalysis. The catalytic effect was determined by measuring the rate of degradation at constant pH, ionic strength and temperature; only the buffer concentration at a specific pH was different. The observed rate constant, in the presence of general acid-base catalysis, is represented by the following equation:

$$k_{ob} = k_{pH} + k_B [B]_T$$  \(3\)

where: $[B]_T$ represents the total buffer concentration, $k_{pH}$ is the rate constant at zero buffer concentration, and $k_B$ represents the catalytic effect of the buffers.

An increase of the rate constant for II degradation was observed while a buffer concentration increased at constant pH and temperature. The studies were performed at 3–4 different pH values for each buffer solution. The significant buffer catalysis in the reaction hydrolysis of II was observed in the phosphate buffers and was not observed in the acetate buffers, where the hydrolysis consisted of two stages (Figure 2), according to Scheme 1:

Scheme 1. The mechanism of degradation of II in the acetate buffer.

However, the mechanism of degradation of II in the acetate buffer depended on the temperature and the pH value i.e. in solutions at 333 K, and at pH = 3.50 or 3.58 at 343 K or 353 K, the degradation of compound II was observed until infinity of its concentration ($p_\infty$) was made. Whereas in the solution at pH = 3.40 and 363 K, a complete degradation of II was observed as the pseudo-first-order reaction with a linear dependence $\log (p/p_\infty)$ as a function of time.

Product II A ($t_e \sim 6.1$ min at the mobile phase B) was also observed during the degradation of II in sodium hydroxide solution and product II B ($t_e \sim 5.7$ min at mobile phase B) was also observed in hydrochloric acid (8). In the acetate buffer, however, both these products were observed on the HPLC chromatograms.

The $k_i, k_i, k_j, k_p$ and $K$ (the equilibrium constant of the reaction) were determined using the HPLC method, according to the equations:

$$\ln \left(\frac{P_0}{P_i} \right) = \ln \left(\frac{P_0}{P_i} \right) - k \times t$$  \(4\)

(for $p_i/p_\infty$, observed in the first stage)

$$\ln \left(\frac{P_0}{P_i} \right) = \ln \left(\frac{P_0}{P_i} \right) - k \times t$$  \(5\)

(for $p_i/p_\infty$, observed in the second stage)

$$k = k_i + k_j$$  \(6\)

$$K = \frac{k_{d1}}{k_{d1}} = \frac{c_{II, e}}{c_{IIA, e}}$$  \(7\)

$$k_{pH} = k_1 + k_{-1} + k_2$$  \(8\)

where: $P = p_i/p_\infty$, $P'$ values were calculated from equation (4) for $p_i/p_\infty$, observed in the first stage, $c_{II, e}$ and $c_{IIA, e}$ are the concentration of II and II A in the state of equilibrium, respectively. The dependences of $K$ as a function of hydrogen ion activity ($a_{H+}$) were linear.

The observed rate constants ($k = k_i + k_j$) of the reversible reaction between II and products II A and
IIB (Table 1) did not show any statistically significant differences in the acetate buffer (pH = 4.90, 333 K and pH = 4.97, 363 K).

The effect of ionic strength on the hydrolysis of II was studied at a constant pH (0.46 and 1.39) and temperature (353 K). The results calculated for these pH values and in the ionic strength range $\mu = 0.50 - 1.00$ mole/L and $\mu = 0.05 - 0.50$ mole/L are given in Table 2. The dependences $\log k_{\text{obs}} = f (\sqrt{\mu}/(1 + \sqrt{\mu}))$ are described by the equation:

$$\log k_{\text{obs}} = \log k_0 + 2QZAZB \left(\frac{\sqrt{\mu}}{1 + \sqrt{\mu}}\right)$$

At pH = 0.46 and 1.39, the slopes of plots were positive and equal to $2QZAZB$, where Q is a constant for the solvent at a given temperature. $Z_A$ and $Z_B$ are the charges of reaction species A and B, respectively. This is characteristic of the reaction of two positive-charged species: the dication of II ($\text{IIH}_2^2+$) and the proton.

The semilogarithmic dependence $\log k_{\text{obs}} = f (\sqrt{\mu}/(1 + \sqrt{\mu}))$ is described by the equation:

$$\log k_{\text{obs}} = \log k_0 + 2QZAZB \left(\frac{\sqrt{\mu}}{1 + \sqrt{\mu}}\right)$$

Table 1. Observed rate constants for the degradation of II and formation or degradation of II degradation products

<table>
<thead>
<tr>
<th>Decomposition terms</th>
<th>Compounds</th>
<th>$t_a$ (min)</th>
<th>$k \pm \Delta k$, s$^{-1}$</th>
<th>$-r$</th>
<th>$n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetate buffer, pH = 4.94 333K</td>
<td>II</td>
<td>17.6</td>
<td>$k = (1.57 \pm 0.14) \cdot 10^4$</td>
<td>0.9939</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>IIA</td>
<td>6.1</td>
<td>$k = (1.52 \pm 1.39) \cdot 10^4$</td>
<td>0.9619</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>IIB</td>
<td>5.7</td>
<td>$k = (1.56 \pm 0.45) \cdot 10^4$</td>
<td>0.9937</td>
<td>7</td>
</tr>
<tr>
<td>Acetate buffer, pH = 4.97 363K</td>
<td>II</td>
<td>17.6</td>
<td>$k = (1.72 \pm 0.30) \cdot 10^4$</td>
<td>0.9848</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>IIA</td>
<td>6.1</td>
<td>$k = (4.02 \pm 0.34) \cdot 10^3$</td>
<td>0.9989</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>IIB</td>
<td>5.7</td>
<td>$k = (1.55 \pm 0.32) \cdot 10^3$</td>
<td>0.9800</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 2. The effect of ionic strength ($\mu$) on pseudo-first-order rate constants for the degradation of II at pH = 0.46 and 1.39

<table>
<thead>
<tr>
<th>pH = 0.46 (0.50 mole/L HCl, 353 K)</th>
<th>$\mu$, mole/L</th>
<th>$10^5(k_{\text{obs}} \pm \Delta k_{\text{obs}})$, s$^{-1}$</th>
<th>Parameters of the equation:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\sqrt{\mu}/(1 + \sqrt{\mu})$</td>
<td></td>
<td>$\log k_{\text{obs}} = \log k_0 + 2QZAZB \left(\frac{\sqrt{\mu}}{1 + \sqrt{\mu}}\right)$</td>
</tr>
<tr>
<td>0.50</td>
<td>0.4142</td>
<td>1.01 $\pm$ 0.13</td>
<td>$2QZAZB = 3.82 \pm 0.42$</td>
</tr>
<tr>
<td>0.60</td>
<td>0.4365</td>
<td>1.22 $\pm$ 0.11</td>
<td>$k_0 = 2.60 \cdot 10^4$, s$^{-1}$</td>
</tr>
<tr>
<td>0.70</td>
<td>0.4555</td>
<td>1.42 $\pm$ 0.17</td>
<td>$r = 0.9982$</td>
</tr>
<tr>
<td>0.90</td>
<td>0.4868</td>
<td>1.96 $\pm$ 0.20</td>
<td>$t_a = 28.737 &gt; t_{0.05(4)} = 2.776$</td>
</tr>
<tr>
<td>1.00</td>
<td>0.5000</td>
<td>2.11 $\pm$ 0.22</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>pH = 1.39 (0.05 mole/L HCl, 353 K)</th>
<th>$\mu$, mole/L</th>
<th>$10^5(k_{\text{obs}} \pm \Delta k_{\text{obs}})$, s$^{-1}$</th>
<th>Parameters of the equation:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\sqrt{\mu}/(1 + \sqrt{\mu})$</td>
<td></td>
<td>$\log k_{\text{obs}} = \log k_0 + 2QZAZB \left(\frac{\sqrt{\mu}}{1 + \sqrt{\mu}}\right)$</td>
</tr>
<tr>
<td>0.05</td>
<td>0.183</td>
<td>1.86 $\pm$ 0.12</td>
<td>$2QZAZB = 0.724 \pm 0.157$</td>
</tr>
<tr>
<td>0.10</td>
<td>0.240</td>
<td>2.05 $\pm$ 0.15</td>
<td>$k_0 = 1.36 \cdot 10^4$, s$^{-1}$</td>
</tr>
<tr>
<td>0.20</td>
<td>0.309</td>
<td>2.21 $\pm$ 0.27</td>
<td>$r = 0.9931$</td>
</tr>
<tr>
<td>0.40</td>
<td>0.387</td>
<td>2.64 $\pm$ 0.32</td>
<td>$t_a = 14.719 &gt; t_{0.05(4)} = 2.776$</td>
</tr>
<tr>
<td>0.50</td>
<td>0.414</td>
<td>2.71 $\pm$ 0.30</td>
<td></td>
</tr>
</tbody>
</table>

$t_a$ – t-Student’s test for the value $a = 2QZAZB$.
The influence of pH and temperature on the degradation kinetics of 4-methoxy... 87

(pH) (Figure 3) indicates that specific acid-base hydrolysis of II is composed of hydrogen ion- and hydroxide ion-catalyzed reaction and water-catalyzed decomposition of two dissociated molecules of II. As follows from the semilogarithmic dependence $k$ vs pH, the possible reactions in the water solution in the pH range from 0.44–4.97 are:

- hydrolysis of II as the dication form catalyzed by hydrogen ions:

$$
\text{IIH}_2^{\text{2+}} + \text{H}^+ \rightarrow \text{products, } k_{\text{H}^+}
$$

- spontaneous hydrolysis of II as the dication form under the influence of water:

$$
\text{IIH}_2^{\text{2+}} + \text{H}_2\text{O} \rightarrow \text{products, } k_{\text{H}_2\text{O}}
$$

- hydrolysis of II as the monocation form catalyzed by hydroxyl ions:

$$
\text{IIH}^+ + \text{OH}^- \rightarrow \text{products, } k_{\text{OH}^-}
$$

The overall reaction of hydrolysis can be described by the following equation:

$$
k_{\text{pH}} = k_{\text{H}^+} \times a_{\text{H}^+} \times f_1 + k_{\text{H}_2\text{O}} \times f_1 + k_{\text{OH}^-} \times a_{\text{OH}^-} \times f_2
$$

where:

- $k_{\text{H}^+}$ represents the second-order rate constant for the specific hydrogen ion-catalyzed degradation of the dication form; $k_{\text{H}_2\text{O}}$ and $k_{\text{OH}^-}$ are the first-order constants of the dication and monocation forms of II for the water-catalyzed degradation, respectively; $k_{\text{cor}}$ is the rate constant for the hydroxide ion-catalyzed hydrolysis of the monocation form; $a_{\text{H}^+}$, $a_{\text{OH}^-}$ refer to the hydrogen and hydroxide ion activity; $f_1$, $f_2$ are fractions of the compounds in the dication ($f_1$) and monocation ($f_2$) forms.

The pK$_a$ values of II were determined by a potentiometric titration at room temperature using the graphical method (pK$_{a1} = 2.4$; pK$_{a2} = 6.2$) (Figure 4).

The microscopic rate constant $k_{\text{pH}}$ (Table 3) was calculated by the equation:

$$
k_{\text{pH}} = k_{\text{H}^+} \times a_{\text{H}^+} \times k_{\text{H}_2\text{O}}
$$

using values of $k_{\text{pH}}$ in the pH-region 0.4–1.4. In this pH-region the value $f_1 \rightarrow 1$. The plots $k_{\text{pH}}/f_1 = f (a_{\text{H}^+})$ were linear ($y = ax + b$) and the slopes ($a$) were positive, and equal to $k_{\text{H}^+}$. The value $k_{\text{H}_2\text{O}}$ was calculated as the value $b$ ($k_{\text{H}_2\text{O}} = b$).

The microscopic rate constant $k_{\text{cor}}$ (Table 3) was calculated by the equation:

$$
k_{\text{cor}} = k_{\text{H}^+} \times a_{\text{cor}} + k_{\text{H}_2\text{O}}
$$

using values of $k_{\text{cor}}$ in the pH-region 3.5–5.0. The plots $k_{\text{cor}}/f_2 = f (a_{\text{cor}})$ were linear ($y = ax + b$) and the slopes ($a$) were positive, and equal to $k_{\text{cor}}$. The value $k_{\text{H}_2\text{O}}$ was calculated as the value $b$ ($k_{\text{H}_2\text{O}} = b$).

In spite of the fact that the values $k_{\text{H}_2\text{O}}$ and $k_{\text{H}_2\text{O}}$ were statistically insignificant, these reactions of spontaneous hydrolysis were observed in the semilogarithmic dependence $k$ vs pH. That explains why these values were calculated with significant errors.

The correct choice of equation (10) was verified by...
the correspondence between the calculated theoretical profile of \( \log k = f (pH) \) and the experimental results (Figure 3).

The \( pH_{min} \) values was calculated using the equation:

\[
\text{pH}_{\text{min}} = 0.5 \text{pK}_w + 0.5 \log \left( \frac{k_{H^+}}{k_{OH^-}} \right) \tag{13}
\]

for all temperatures: 333K, \( \text{pH}_{\text{min}} \) = 1.99; 343K, \( \text{pH}_{\text{min}} \) = 2.10; 353K, \( \text{pH}_{\text{min}} \) = 2.21; 353K, \( \text{pH}_{\text{min}} \) = 2.22.

Using the catalytic rate constants derived from the Arrhenius equation \((\ln k = \ln A - a/T)\), the slope \((a)\) of the plots \(\ln k = f (1/T)\) and the value of \(\ln A\) (A–frequency coefficient) for particular reactions were calculated. These values were used for determining energy \( (E_a) \), enthalpy \( (\Delta H^\circ) \) and entropy \( (\Delta S^\circ) \) of activation at 293 K (Table 3).

## CONCLUSIONS

The solutions of \( \text{II} \) exhibits the greatest stability in solutions of \( pH \approx 2.1 \). Although the dependence \( \log k_{cat} = f (pH) \) indicates that in the \( pH \) region 0.4–5.0 hydrogen ion- and hydroxide ion-catalyzed hydrolysis is predominant, water-catalyzed degradation of the dication and monocation forms of \( \text{II} \) occurs in this \( pH \) region, too. The hydrolysis of compound \( \text{II} \) involves general catalysis and specific acid-base catalysis. A significant buffer catalysis in the hydrolysis of \( \text{II} \) is observed in phosphate buffers and is not observed in acetate buffers, where hydrolysis consists of two stages (Figure 2, Scheme 1). This reversible reaction is observed in solutions in the \( pH \) region > 3.5. While compound \( \text{II} \) precipitates in solutions of the \( pH \) region > 5.

## Acknowledgements

The authors thank H. Śladowska and A. Sabiniarz for providing compound \( \text{II} \) for the study.

## REFERENCES


Received: 16.12.2004

### Table 3. Specific rate constants and thermodynamic parameters (293 K) of \( \text{II} \)

<table>
<thead>
<tr>
<th>T, K</th>
<th>( 10^9(k_{H^+} \pm \Delta k_{H^+}) )</th>
<th>( 10^7(k_{OH^-} \pm \Delta k_{OH^-}) )</th>
<th>( 10^6(k_{H_2O} \pm \Delta k_{H_2O}) )</th>
<th>( k_{cat} \pm \Delta k_{cat} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>333</td>
<td>3.50 ± 0.56</td>
<td>1.21 ± 1.24</td>
<td>3.22 ± 7.53</td>
<td>37274 ± 7825</td>
</tr>
<tr>
<td>343</td>
<td>11.0 ± 1.6</td>
<td>3.19 ± 3.39</td>
<td>7.93 ± 1.39</td>
<td>46755 ± 18012</td>
</tr>
<tr>
<td>353</td>
<td>41.2 ± 1.0</td>
<td>4.88 ± 21.97</td>
<td>12.2 ± 36.9</td>
<td>65463 ± 14595</td>
</tr>
<tr>
<td>363</td>
<td>89.3 ± 24.8</td>
<td>3.59 ± 52.60</td>
<td>57.6 ± 28.9</td>
<td>93476 ± 63772</td>
</tr>
<tr>
<td>( E_a, \text{k J mole}^{-1} )</td>
<td>111 ± 28</td>
<td>37.8 ± 84.7</td>
<td>90.9 ± 70.3</td>
<td>31.0 ± 11.6</td>
</tr>
<tr>
<td>( \Delta H^\circ, \text{k J mole}^{-1} )</td>
<td>109 ± 28</td>
<td>35.4 ± 84.7</td>
<td>88.5 ± 70.3</td>
<td>28.6 ± 11.6</td>
</tr>
<tr>
<td>( \Delta S^\circ, \text{J K}^{-1}\text{ mole}^{-1} )</td>
<td>3.74 ± 80.15</td>
<td>-242 ± 244</td>
<td>-77.8 ± 202.4</td>
<td>-64.5 ± 33.4</td>
</tr>
</tbody>
</table>