Mechanistic Implications of Zero-Order Kinetics in Kinetic Resolutions

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SUPPORTING INFORMATION

A. Kinetic expressions
B. Kinetic modelling
   Scheme 2a
   Two catalyst case
   Scheme 2b
C. Experimental protocols for (salen)Mn-catalyzed epoxidation
The cycle below is that of Scheme 2a for kinetic resolution. For the case of reversible binding of the substrates followed by rate-limiting product formation, the rate law (assuming pre-equilibrium binding) is given by the equation below:

\[ r_{\text{total}} = r_R + r_S \]

\[
\begin{align*}
    r_{\text{total}} &= \frac{k_{R,\text{lim}} K_{R,\text{eq}} [R] [\text{cat}]_{\text{total}}}{1 + K_{R,\text{eq}} [R] + K_{S,\text{eq}} [S]} + \frac{k_{S,\text{lim}} K_{S,\text{eq}} [S] [\text{cat}]_{\text{total}}}{1 + K_{R,\text{eq}} [R] + K_{S,\text{eq}} [S]}
\end{align*}
\]

The simplified rate laws for Cases i-iv, with \( k_{R,\text{lim}} > k_{S,\text{lim}} \):

Case i: \( K_{R,\text{eq}} \approx K_{S,\text{eq}} = \) both low

\[
    r_{\text{total}} = \left( k_{R,\text{lim}} [R] + k_{S,\text{lim}} [S] \right) \cdot K_{\text{eq}} \cdot [A] \cdot [\text{cat}]_{\text{total}}
\]

Case ii: \( K_{R,\text{eq}} \approx K_{S,\text{eq}} = \) both high

\[
    r_{\text{total}} = \left( \frac{k_{R,\text{lim}} [R] + k_{S,\text{lim}} [S]}{[R] + [S]} \right) \cdot [A] \cdot [\text{cat}]_{\text{total}}
\]

Case iii: \( K_{R,\text{eq}} \neq K_{S,\text{eq}} = \) both high

\[
    r_{\text{total}} = \left( \frac{k_{R,\text{lim}} K_{R,\text{eq}} [R] + k_{S,\text{lim}} K_{S,\text{eq}} [S]}{K_{R,\text{eq}} [R] + K_{S,\text{eq}} [S]} \right) \cdot [A] \cdot [\text{cat}]_{\text{total}}
\]

Case iv: \( K_{R,\text{eq}} = \) high; \( K_{S,\text{eq}} = \) low

\[
    r_{\text{total}} = \frac{k_{R,\text{lim}} + k_{S,\text{lim}}}{K_{R,\text{eq}} [R]} \cdot [S] \cdot [\text{cat}]_{\text{total}} = k_{R,\text{lim}} \cdot [A] \cdot [\text{cat}]_{\text{total}}
\]

Only Cases iv and simplifies to zero order kinetics in the enantiomeric substrates, even though the catalyst is “saturated” with bound substrate in Cases ii, iii, iv, and v. The same result is obtained when the treatment is extended to consider steady-state rather than pre-equilibrium conditions.
B. Kinetic Modelling

Scheme 2a

<table>
<thead>
<tr>
<th>Rate constant</th>
<th>Case i</th>
<th>Case ii</th>
<th>Case iii</th>
<th>Case iv</th>
<th>Case v</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{R,f}$ (l.mol$^{-1}$.min$^{-1}$)</td>
<td>10000</td>
<td>10000</td>
<td>10000</td>
<td>10000</td>
<td>100000</td>
</tr>
<tr>
<td>$k_{R,b}$ (min$^{-1}$)</td>
<td>10000</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>$k_{R,lim}$ (l.mol$^{-1}$.min$^{-1}$)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>$k_{S,f}$ (l.mol$^{-1}$.min$^{-1}$)</td>
<td>10000</td>
<td>10000</td>
<td>10000</td>
<td>10000</td>
<td>10000</td>
</tr>
<tr>
<td>$k_{S,b}$ (min$^{-1}$)</td>
<td>10000</td>
<td>100</td>
<td>200</td>
<td>10000</td>
<td>10000</td>
</tr>
<tr>
<td>$k_{S,lim}$ (l.mol$^{-1}$min$^{-1}$)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

$[A]_0 = 1.0$ M; $[R]_0 = [S]_0 = 0.5$ M; $[\text{cat}] = 0.01$ M

Modelling was carried out using Copasi simulator (official test release 1). (Copyright © 2005 by Pedro Mendes, Virginia Tech Intellectual Properties, Inc. and EML Research, gGmbH. All rights reserved.)

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The plots below show the relative concentrations of catalytic species within the cycle as a function of conversion for the four cases treated in Figure 1. The plots confirm that the catalyst is “saturated” ([cat] = low) until > 50% conversion for all cases except Case i, in which [cat] is the major species. Saturation occurs in Cases ii, iii, and iv, but only in Cases iv and v is the non-eroding product ee observed.
Two-catalyst network:

\[
\begin{align*}
R + \text{catA} & \underset{k_{-AR}}{\rightleftharpoons} \text{catAR} & R + \text{catB} & \underset{k_{-BR}}{\rightleftharpoons} \text{catBR} \\
S + \text{catA} & \underset{k_{-AS}}{\rightleftharpoons} \text{catAS} & S + \text{catB} & \underset{k_{-BS}}{\rightleftharpoons} \text{catBS} \\
\text{catAR} + \text{sub} & \underset{k_{\text{lim,AR}}}{\rightarrow} \text{prodR} + \text{catA} & \text{catBR} + \text{sub} & \underset{k_{\text{lim,BR}}}{\rightarrow} \text{prodR} + \text{catB} \\
\text{catAS} + \text{sub} & \underset{k_{\text{lim,AS}}}{\rightarrow} \text{prodS} + \text{catA} & \text{catBS} + \text{sub} & \underset{k_{\text{lim,BS}}}{\rightarrow} \text{prodS} + \text{catB}
\end{align*}
\]

\[
\begin{align*}
k_{AR} &= 10000 \\
k_{AR} &= 100 \\
k_{AS} &= 10000 \\
k_{AS} &= 10000 \\
k_{\text{lim,AR}} &= 10 \\
k_{\text{lim,AS}} &= 1 \\
k_{BR} &= 10000 \\
k_{BR} &= 100 \\
k_{BS} &= 10000 \\
k_{BS} &= 10000 \\
k_{\text{lim,BR}} &= 2 \text{ (blue, Case b) or 1 (pink, Case a)} \\
k_{\text{lim,BS}} &= 1
\end{align*}
\]

\([R]_0 = [S]_0 = 0.5 \text{ M}; \ [\text{sub}]_0 = 1 \text{ M}. \ [\text{catA}] = 0.005 \text{ M}; \ [\text{catB}] = 0.005 \text{ M}.\]

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Kinetic Modeling Scheme 2b

Parameters for modelling:

- $k_{lim} = 1 \text{ mol}^{-1}\text{min}^{-1}$
- $k_S = 10, 20, 50, 100 \text{ mol}^{-1}\text{min}^{-1}$
- $k_R = 1000 \text{ mol}^{-1}\text{min}^{-1}$

Modelling was carried out using Copasi simulator (official test release 1). (Copyright © 2005 by Pedro Mendes, Virginia Tech Intellectual Properties, Inc. and EML Research, gGmbH. All rights reserved.)

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Even at very high $k_{rel}$ values, the product ee vs conversion curve shows the expected for first order kinetics.

Plots for $k_{rel}$ according to first order (left) and zero order (right) kinetics. Curvature in zero order plots increases as $k_{rel}$ increases.
Kinetic resolution of (Z)-4-phenyl-3-buten-2-ol (1) under pseudo zero-order conditions

Preparation of (±)-(Z)-4-Phenyl-3-buten-2-ol (1)[15] A 1.0 M solution of sodium borohydride in ethanol (0.7 cm³) was added to a stirred solution of nickel(II) acetate tetrahydrate (170 mg, 0.68 mmol) in ethanol (40 cm³) under nitrogen. The addition of the reducing agent was accompanied by an immediate change in colour from a clear green solution to a finely divided black suspension. To this suspension was added ethylenediamine (80 mg, 1.33 mmol) and 4-phenylbut-3-yn-2-ol (775 mg, 5.30 mmol). The vessel was purged with hydrogen and the reaction mixture stirred vigorously under a hydrogen atmosphere for 3 h. The consumption of substrate was followed by gas chromatography. Once all the substrate had been consumed, activated charcoal was added and the reaction was filtered through a plug of Celite and washed through with diethyl ether. The filtrate was washed with water (50 cm³), dried over anhydrous magnesium sulfate and evaporated under reduced pressure to leave a yellow oil which was analysed by ¹H NMR spectroscopy to determine product distribution (100% conversion, (Z)-(1) / (E)-(1) / 4-phenyl-3-butan-2-ol = 85:2:13). This material was purified by column chromatography on silica gel using hexane → hexane–ethyl acetate (5:1) as eluent to yield pure Z-alkene 1 (382 mg, 49%) as a colourless oil (> 99 % Z by GC and NMR analysis). An analogous procedure using (R)-4-phenylbut-3-yn-2-ol (81 % ee; prepared by (R)-Alpine-borane mediated asymmetric reduction of 4-phenyl-3-butyn-2-one)[25] gave (R)-1 (which was diluted with racemic 1 to give a sample of 65 % ee).
Preparation of Iodosobenzene (PhIO) oxidant (**2**)[3] A 15% aqueous solution of sodium hydroxide (18.6 cm$^3$, 69.9 mmol) was added dropwise to solid *iodosobenzene diacetate* (5.0 g, 15.5 mmol) over a 5 min period. The resulting suspension was stirred for a further 2 h at room temperature. Water (30 cm$^3$) was then added and the reaction stirred vigorously for 5 min. The crude product was collected under suction, returned to the reaction flask and washed with a further 30 cm$^3$ of water. The solid was then collected on a sinter funnel, washed with water (30 cm$^3$) and dried. The pale yellow solid was tritutrated with chloroform (30 cm$^3$), filtered and dried to afford *iodosobenzene* **2** (3.13 g, 92%) as an off-white solid. The oxidant (**2**) was stored in a freezer.

Preparation of [((*S*,*S*)-N,N'-*Bis*(3-tert-butylsalicylidene)-trans-1,2-cyclohexanediamine manganese(III)] chloride (**3**)[4] Manganese acetate tetrahydrate (320 mg, 1.31 mmol) and (*S*,*S*)-N,N'-*bis*(3-tert-butylsalicylidene)-trans-1,2-cyclohexanediamine (270 mg, 0.62 mmol) were reacted under aerobic conditions in EtOH to yield a brown solid. This was purified by column chromatography on silica eluting with dichloromethane–ethanol (10:1) to afford the manganese complex **3** (200 mg, 62%) as a dark brown solid, mp 305–306 °C (lit.,[4] 309.5–310.5 °C) (Found C, 62.3; H, 7.0; N, 5.15. C$_{28}$H$_{36}$ClMnN$_2$O$_2$·H$_2$O requires C, 62.2; H, 7.1; N, 5.2%); $\nu_{\text{max}}$ (solid)/cm$^{-1}$ 2937m, 2866w, 1610s, 1592s, 1545s, 1417m, 1390m, 1329m, 1291m, 1194m, 1144m, 870m and 755s; $m/z$ (FAB) 488 (M$^+$ – Cl, 100%).

Kinetic resolution of (Z)-4-phenyl-3-buten-2-ol (1). The following procedure is an adaptation of the method of Adam *et al.*[5] Naphthalene (internal standard for GC analysis, 11 mg) was added to a stirred solution of rac-(Z)-4-phenyl-3-buten-2-ol **1** (45 mg, 0.30 mmol, 0% ee) in dichloromethane (3.0 cm$^3$). The mixture was stirred for 5 min at ambient temperature and a “$t_0$ sample” removed for analysis by gas chromatography (see conditions below). Commercial 4-phenyl pyridine-$N$-oxide (**4**, 12 mg, 0.06 mmol) was added and stirring continued for 5 min before adding catalyst (*S*,*S*)-**3** (19 mg, 0.03 mmol). After a further 10 min, iodosobenzene (**2**) (67 mg, 0.30 mmol) was rapidly introduced in small portions. Samples were then periodically removed from the reaction and immediately quenched by addition to a vial containing dimethyl sulfide (0.1 cm$^3$) and diethyl ether (0.5 cm$^3$). The samples (consisting of a dark-coloured suspension in CH$_2$Cl$_2$ / diethyl ether) were filtered through a small plug of silica gel, washing through with diethyl ether. The fractional conversion and alkene (1) ee were
determined by gas chromatography \([\text{CHIRALDEX} \, \gamma-\text{TA}; \, 30 \, \text{m}; \, \text{i.d.} \, 0.25 \, \text{mm}; \, 95 \, ^\circ\text{C}; \, 3.0 \, \text{ml min}^{-1}: \]
retention times: naphthalene 16.5, \((S)-1 \, 42.5\) and \((R)-1 \, 44.1\) min). An identical run was conducted using \((R)-(Z)-4\)-phenyl-3-buten-2-ol \((1) \, (45 \, \text{mg}, \, 0.30 \, \text{mmol}, \, 65\% \, \text{ee})\) and \((\pm)-3 \, (19 \, \text{mg}, \, 0.03 \, \text{mmol}).\)

<table>
<thead>
<tr>
<th>time (min)</th>
<th>With ((\pm)-1, ,(S,S)-3) conversion (%) (ee,(R, %))</th>
<th>With ((R)-1, ,(\pm)-3) conversion (%) (ee,(R, %))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
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<tr>
<td>4</td>
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</tr>
<tr>
<td>5</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>7.5</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td>10</td>
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<td>51</td>
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<tr>
<td>60</td>
<td>71</td>
<td>56</td>
</tr>
</tbody>
</table>

The increasing \(ee\) with \((R)-1\) (65 \% ee at time 0) and \((\pm)-3\) confirms that there is a non-first order dependency of global rate on alkene \((1)\) concentration.\(^{[6S]}\) The PhIO is sparingly soluble and mass-transfer may well be rate-limiting. The products of oxidation of \((1)\) under these conditions is a 50:50 mixture of \textit{cis}- and \textit{trans- threo}-epoxy alcohols \((5)\).\(^{[5S]}\)

References