Quantitative first principles based kinetic modeling for the synthesis of well-defined macromolecular architectures

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Contents: 2 case studies related to Reversible Addition-Fragmentation chain Transfer (RAFT) polymerization

1. RAFT polymerization of styrene (●) using a trithiocarbonate (●○●)
   ▪ Calculation of addition-fragmentation rate coefficients
   ▪ Application in a microkinetic model

2. The aminolysis of RAFT-macromolecules
   ▪ Determination of the reaction mechanism
   ▪ Calculation of rate coefficients for a variety of RAFT-agents
How do RAFT agents help us to obtain control over the chain length in radical polymerization?

**FRP**

- **Initiator (I)**
- **Monomer (M)**
- **K_d**
- **K_p**

**ACTIVE**

- **K_i**
- **K_r**

**DEAD**

**RAFT exchange**

- **K_add**
- **K_frag**

**RAFT agent**

**DORMANT**

**Used in this work**

- **Azobisisobutyronitrile (AIBN)**
- **Styrene**
- **2-cyano-2-propyl-dodecyl thio-carbonate (CPDT)**
Ab initio calculation of addition-fragmentation reactions using a dimer model: 4 model reactions

Model assumptions
- dimer radical to model macroradical
- ethyl group to model dodecyl group

Ab initio calculation
- scan conformers: B3LYP/6-31G(d)
- geometry optimization and frequencies: B3LYP/6-31G(d)
- ‘single point’ electronic energy: M06-2X/6-311+G(d,p)

Solvation via COSMO-RS

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\[ \text{Lin and Coote, Aust. J. Chem. 2011, 94, 747} \]
Gibbs free energy diagrams of the addition-fragmentation reactions

- Rate coefficients are obtained via classical transition state theory:

\[
K = e^{\frac{-\Delta_r G^°}{RT}} \quad k_+ = \frac{k_BT}{h} e^{\frac{-\Delta^+ G^°}{RT}} \quad k_- = k_+/K
\]

- Stereoisomers are taken into account according to the following formulas:

\[
k_{add} = \frac{1}{n_0} \sum_i k_{add,i} \quad k_{frag} = \frac{\sum_i k_{frag,i}K_i}{\sum_i K_i}
\]
**Deterministic kinetic model based on methods of moments**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Equation</th>
<th>$E_a$ (kJ mol$^{-1}$)</th>
<th>$A$ (L mol$^{-1}$ s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissociation*</td>
<td>$I_2 \rightarrow 2R_0$</td>
<td>129.0</td>
<td>1.6 E +15$^d$</td>
</tr>
<tr>
<td>(Re)Initiation</td>
<td>$R_0 + M \rightarrow R_1$</td>
<td>26.0</td>
<td>4.9 E +07$^e$</td>
</tr>
<tr>
<td>Propagation</td>
<td>$R_i + M \rightarrow R_{i+1}$</td>
<td>32.5</td>
<td>4.2 E +07$^f$</td>
</tr>
<tr>
<td>Combination**</td>
<td>$R_i + R_j \rightarrow R_{i+j}$</td>
<td>0.0</td>
<td>5.0 E +08$^g$</td>
</tr>
<tr>
<td>Addition</td>
<td>$R_0 + TR_0 \rightarrow R_0TR_0$</td>
<td>13.9</td>
<td>7.4 E +06</td>
</tr>
<tr>
<td>Addition</td>
<td>$R_0 + TR_i \rightarrow R_0TR_i$</td>
<td>24.2</td>
<td>1.6 E +07</td>
</tr>
<tr>
<td>Addition</td>
<td>$R_i + TR_0 \rightarrow R_iTR_0$</td>
<td>3.0</td>
<td>9.4 E +06</td>
</tr>
<tr>
<td>Addition</td>
<td>$R_i + TR_i \rightarrow R_iTR_i$</td>
<td>15.4</td>
<td>1.7 E +07</td>
</tr>
<tr>
<td>Fragmentation</td>
<td>$R_0TR_0 \rightarrow R_0 + TR_0$</td>
<td>44.6</td>
<td>9.4 E +12</td>
</tr>
<tr>
<td>Fragmentation</td>
<td>$R_0TR_i \rightarrow R_0 + TR_i$</td>
<td>48.3</td>
<td>1.2 E +13</td>
</tr>
<tr>
<td>Fragmentation</td>
<td>$R_iTR_0 \rightarrow R_i + TR_0$</td>
<td>51.7</td>
<td>2.6 E +12</td>
</tr>
<tr>
<td>Fragmentation</td>
<td>$R_iTR_i \rightarrow R_i + TR_i$</td>
<td>53.2</td>
<td>1.2 E +13</td>
</tr>
</tbody>
</table>

*Initiator efficiency$^b$

$$f_{app} = \frac{D_I}{D_I + D_{term}}$$

**Diffusional limitations**

Via *composite $k_t$ model*$^c$

- for $i < i_{gel}$ and $i < i_{SL}$:
  
  $k_{t,ii}^{app} = k_{t,11}^{app} i^{-\alpha_s}$

- for $i < i_{gel}$ and $i \geq i_{SL}$:
  
  $k_{t,ii}^{app} = k_{t,11}^{app} i_{SL}^{-\alpha_s} i^{-\alpha_l}$

- for $i \geq i_{gel}$ and $i < i_{SL}$:
  
  $k_{t,ii}^{app} = k_{t,11}^{app} i_{gel}^{-\alpha_s} i^{-\alpha_gel}$

- for $i \geq i_{gel}$ and $i \geq i_{SL}$:
  
  $k_{t,ii}^{app} = k_{t,11}^{app} i_{gel}^{-\alpha_s} i_{gel}^{-\alpha_gel}$

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Simulation and experimental validation

\[ T = 80 \, ^\circ C, \quad TCL = 200, \quad CTA:AIBN = 5:1 \]

\[ T = 70 \, ^\circ C, \quad TCL = 400, \quad CTA:AIBN = 5:1 \]
1. RAFT polymerization of styrene using a trithiocarbonate
   - Calculation of **addition-fragmentation** rate coefficients
   - Application in a **microkinetic model**

2. The **aminolysis of RAFT-macromolecules**
   - Determination of the reaction mechanism
   - Calculation of **rate coefficients** for a variety of RAFT-agents
Aminolysis of RAFT agents in aprotic solvents: reaction mechanism

**Reactants**

\[ \text{R}-\text{NH}_2 + \text{RAFT-P}_n \rightarrow \text{R}^{+}\text{NH}_2 \text{Z} \]

**Products**

\[ \text{R}^{+}\text{NH}_2 \text{Z} + \text{P}_n\text{S} \rightarrow \text{RNH} \text{C} = \text{S} \text{P}_n + \text{P}_n\text{S} \text{H} \]

**Steps**

1. **Initial Reaction**
   \[ \text{R}-\text{NH}_2 + \text{RAFT-P}_n \rightarrow \text{ZI} \]

2. **Formation of Intermediate**
   \[ \text{ZI} \rightarrow \text{R}^{+}\text{NH}_2 \text{Z} \]

3. **Nucleophilic Addition**
   \[ \text{R}^{+}\text{NH}_2 \text{Z} + \text{P}_n\text{S} \rightarrow \text{NI} \]

4. **Final Product Formation**
   \[ \text{NI} \rightarrow \text{RNH} \text{C} = \text{S} \text{P}_n + \text{P}_n\text{S} \text{H} \]

**Representations**

- Z = CH₃, phenyl, S, O, N
- RAFT-Pₙ
- R-NH₂
Gibbs Free Energy Diagram for EthylAmine (EA) + Methyl Ethane DiThioate (MEDT)

\[ R = \text{C}_2\text{H}_5 \]
\[ Z, P_n = \text{CH}_3 \]

(Gibbs free energies in kJ mol\(^{-1}\) at 298.15 K)
Amine assisted transition state are asynchronous and early.

\[
\begin{align*}
\text{Evolution of distances along the reaction coordinate}
\end{align*}
\]
Aminolysis of RAFT agents in aprotic solvents: reaction mechanism

- Proton transfer in transition states can be assisted by amines and by thiols

![Chemical Reaction Diagram]

Reactants: $R\text{NH}_2 + \text{RAFT-P}_n$ 

Products: $\text{NH}_2\text{C-S} + \text{P}_n\text{SH}$

Steps:
1. $\text{A} \rightarrow \text{ZI}$
2. $\text{ZI} \rightarrow \text{P1}$
3. $\text{ZI} \rightarrow \text{NI}$
4. $\text{NI} \rightarrow \text{P2}$
5. $\text{ZI} \rightarrow \text{CI}$

Z can be: $\text{CH}_3$, $\text{C}_6\text{H}_5$, $\text{S}$, $\text{O}$, $\text{N}$
Gibbs Free Energy Diagram for EthylAmine (EA) + Methyl Ethane DiThioate (MEDT)

R = C₂H₅
Z,Pₙ = CH₃

Diffusional limitations become important!
The coupled encounter pair model to account for diffusion for TS 6 and 7

\[ \frac{1}{k_{\text{app},+}} = \frac{1}{k_+} + \frac{1}{k_{\text{diff},+}} \]

\[ \frac{1}{k_{\text{app},-}} = \frac{1}{k_-} + \frac{K}{k_{\text{diff},+}} \]

- Diffusion of A+B towards [AB] via the model of Smoluchowski: \( k_{\text{diff}} = 4\pi N_A \sigma D_{AB} \)
  - \( \sigma \) = reaction distance: from ab initio TS geometries
  - \( D_{AB} = \) mutual diffusivity coefficient\(^a\)

\[ D_{AB} = \frac{D_A D_B}{D_{\text{solvent}}} \]

\(^a\) Liu et al. *Ind Eng Chem Res* 2011, 50, 4776.
Diffusivity coefficients based on molecular dynamics

- NVT ensemble in 8 nm³ box for 50 picoseconds

### Table

<table>
<thead>
<tr>
<th></th>
<th>$k_+$</th>
<th>$k_{\text{diff}}$</th>
<th>$k_{\text{app,+}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>R6</td>
<td>$6.2E+12$</td>
<td>$2.1E+09$</td>
<td>$2.1E+09$</td>
</tr>
</tbody>
</table>

### Equation

$$D_{i,\text{THF}} = \frac{1}{6} \lim_{t \rightarrow \infty} \frac{d}{dt} \left( |r(t) - r(0)|^2 \right)$$
Rate and affinity analysis reveal the dominant path and the nature of the elementary steps for the aminolysis of MEDT.
Prediction of conversion profiles for other RAFT-agents

Reaction of $10^{-3}$ mol L$^{-1}$ RAFT-macromolecule with $5 \times 10^{-3}$ mol L$^{-1}$ ethylamine in THF at 25 °C for dithioates, thiobenzoates, xanthates, trithiocarbonates and dithiocarbamates:

- dithiocarbamates are not reactive at room temperature! (in agreement with experiment observations$^a$)
- conversion of xanthates and dithiobenzoates show good agreement with literature$^b$ ($<$factor 2)
- reaction of trithiocarbonates slower than xanthates$^b$

$^a$ Le Neindre et al, Polym Chem 2013, 4, 5577
$^b$ Kabachii et al, Pol Sci Ser A 2006, 48, 717
Conclusion: first principles techniques are a valuable tool to obtain reaction parameters for kinetic models

1. **RAFT polymerization** of styrene with a trithiocarbonate
   - Calculation of **addition-fragmentation** rate coefficients
   - Implementation in microkinetic model
     - conversions
     - chain lengths
     - dispersities

2. **Aminolysis** of RAFT-macromolecules
   - Determining the **dominant mechanism** using ab initio based kinetic model
     - quasi-equilibrated formation of a zwitterion
     - amine-assisted diffusion-limited proton transfer over a complex intermediate towards a neutral intermediate
     - rate limiting amine-assisted breakdown of the neutral intermediate towards the product
   - Simulation of conversion of range of RAFT agents
     - Reactivity: thioates > thiobenzoates > xanthates ≥ trithiocarbonates >> dithiocarbamates
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Questions?