Reactivity within Confined Nano-spaces

Larry Wolf

Group Meeting
11-17-09
Encapsulating Cyclobutadiene

The Taming of Cyclobutadiene**

By Donald J. Cram,* Martin E. Tanner, and Robert Thomas

Cyclobutadiene, (CH)$_4$, is the Mona Lisa of organic chemistry in its ability to elicit wonder, stimulate the imagination, and challenge interpretive instincts.

hemicarcerand

Anslyn, E. V; Dougherty, D. A. Modern Physical Organic Chemistry
Self-Assembled nanocapsules binding outline

via Coordination

via Hydrogen Bonding

via Template-mediated Hydrophobic Effects
Rebek’s “softball”

Softball Welcomes Guests

1.2 equiv B at 343

1.2 equiv B at 298

Host alone in p-xylene at 298

0.7 equiv A at 323 K

0.7 equiv A at 273 K

Host alone in chloroform-\textit{d}
Template Mediated Self-assembly of a Cavitand

Gibb, B. C. J. Am. Chem. Soc. 2003, 125, 650
Encapsulation

Figure 1. (a) Aromatic region of the $^1$H NMR spectra (500 MHz, D$_2$O, sodium borate, pH = 8.9) of host 1. (b) 2:1 mixture of 1 and 2. Host concentration 1 mM. Color-coding as per structure 1.

C-18 Me shifts to -1.0 ppm

Tetrahedral Anionic Coordination Capsules (Raymond)

Up to 450 Å³ cavity

Crystal Structure Representations

$K_5[Et_4N]_7[Fe_4L_6]$
Encapsulation of Quaternary Ammonium Hosts
Cationic Coordination Capsules

FIG. 3 Monitoring of the titration of 3a with 4 by $^1$H NMR (400 MHz, D$_2$O, external TMS). The ratios 3a:4 are: a, 1:1; b, 1:2; c, 1:4; d, 1:8. Components (signals) are as follows: uncomplexed 3a (peaks A$_1$ and A$_2$); complexed 3a (peaks B$_1$ and B$_2$); uncomplexed 4 (peaks a$_1$, a$_2$, a$_3$, and a$_4$); complexed 4 (peaks b$_1$, b$_2$, b$_3$, and b$_4$).
Energy Considerations

\[ A + B \xrightarrow{k_a} C \]

\[ v = \frac{d[C]}{dt} = k_a[A][B] \]

\[ NR + A + B \rightleftharpoons (NR \rightleftharpoons A \cdot B) \xrightarrow{k_b} (NR \rightleftharpoons C) \rightleftharpoons NR + C \]

\[ v = \frac{d[C]}{dt} = k_b[(NR \rightleftharpoons A \cdot B)] \]

Extremes and Selectivity Consequences

Extreme 1: Increase in effective concentration

\[
\Delta G^\#_{NR} = \Delta G^\#_{bulk} \\
[(NR \gg A\cdot B)] > [A][B]
\]

Extreme 2: change in activation parameters (\( \Delta G^\#_{NR} \neq \Delta G^\#_{bulk} \))

\[
\Delta G^\#_{NR} < \Delta G^\#_{bulk}
\]

Cationic Guests: Making Amines Strong Bases

$S + H^+ + 1 \overset{K_1}{\rightarrow} SH^+ + 1$

$K_4$

$H^+ + [S \subset 1] \overset{K_3}{\rightarrow} [SH^+ \subset 1]$

$K_2$

$K_{eff} = \frac{[SH^+ \subset 1]10^{-pK_a}}{[S][1]10^{-pH}}$

Amine Scope and Encapsulation Data

Table 2. Binding Constants, Energies, and Shifts in the Effective Basicity for Encapsulated Amines

<table>
<thead>
<tr>
<th>amine</th>
<th>$pK_a$</th>
<th>$K_{diss}$ (M$^{-1}$)</th>
<th>$\log(K_{eq})$ (kcal/mol)</th>
<th>$\Delta \mu$ (kcal/mol)</th>
<th>effective basicity ($pK_{eq}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>10.7</td>
<td>130</td>
<td>2.1</td>
<td>2.9</td>
<td>12.8</td>
</tr>
<tr>
<td>7</td>
<td>10.7</td>
<td>500</td>
<td>2.7</td>
<td>3.7</td>
<td>13.4</td>
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<tr>
<td>9</td>
<td>10.8</td>
<td>2510</td>
<td>3.4</td>
<td>4.6</td>
<td>14.2</td>
</tr>
<tr>
<td>10</td>
<td>8.5</td>
<td>2080</td>
<td>3.3</td>
<td>4.5</td>
<td>11.8</td>
</tr>
<tr>
<td>12</td>
<td>8.3</td>
<td>25100</td>
<td>4.4</td>
<td>6.0</td>
<td>12.7</td>
</tr>
<tr>
<td>13</td>
<td>8.1</td>
<td>31600</td>
<td>4.5</td>
<td>6.1</td>
<td>12.6</td>
</tr>
<tr>
<td>14</td>
<td>6.4</td>
<td>1590</td>
<td>3.2</td>
<td>4.4</td>
<td>9.6</td>
</tr>
<tr>
<td>15</td>
<td>10.6</td>
<td>650</td>
<td>2.8</td>
<td>3.8</td>
<td>13.4</td>
</tr>
<tr>
<td>17</td>
<td>9.1</td>
<td>1260</td>
<td>3.1</td>
<td>4.2</td>
<td>12.2</td>
</tr>
<tr>
<td>18</td>
<td>9.8</td>
<td>6310</td>
<td>3.8</td>
<td>5.2</td>
<td>13.6</td>
</tr>
<tr>
<td>19</td>
<td>9.8</td>
<td>6450</td>
<td>3.8</td>
<td>5.2</td>
<td>13.6</td>
</tr>
<tr>
<td>20</td>
<td>9.8</td>
<td>12600</td>
<td>4.1</td>
<td>5.6</td>
<td>13.9</td>
</tr>
<tr>
<td>24</td>
<td>10.8</td>
<td>31600</td>
<td>3.5</td>
<td>4.8</td>
<td>14.3</td>
</tr>
</tbody>
</table>

Table 1. Self-Exchange Rates and $pK_a$'s for Selected Encapsulated Amines

<table>
<thead>
<tr>
<th>amine</th>
<th>$pK_a$</th>
<th>$k_{277}$ (s$^{-1}$)</th>
<th>amine</th>
<th>$pK_a$</th>
<th>$k_{277}$ (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6$^{57}$</td>
<td>10.7</td>
<td>469(9)</td>
<td>15$^{58}$</td>
<td>10.6</td>
<td>1.05(5)</td>
</tr>
<tr>
<td>7$^{59}$</td>
<td>10.7</td>
<td>0.31(4)</td>
<td>17$^{60}$</td>
<td>9.1</td>
<td>479(9)</td>
</tr>
<tr>
<td>9$^{61}$</td>
<td>10.8</td>
<td>173(3)</td>
<td>18$^{62}$</td>
<td>9.8</td>
<td>1.01(2)</td>
</tr>
<tr>
<td>10$^{63}$</td>
<td>8.5</td>
<td>5.3(3)</td>
<td>19$^{64}$</td>
<td>9.8</td>
<td>0.24(3)</td>
</tr>
<tr>
<td>12$^{65}$</td>
<td>8.3</td>
<td>5.4(6)</td>
<td>20$^{64}$</td>
<td>9.8</td>
<td>1.9(3)</td>
</tr>
<tr>
<td>13$^{66}$</td>
<td>8.1</td>
<td>4.4(6)</td>
<td>24$^{67}$</td>
<td>10.8</td>
<td>0.13(2)</td>
</tr>
<tr>
<td>14$^{68}$</td>
<td>6.4</td>
<td>1.1(1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stabilization of Imminium Ions by Encapsulation

Encapsulated imminium ions remained stable for months at RT

Cage 1 has been used to stabilize phosphonium, diazonium ions, & tropylium ions

Acid Catalysis in Basic Solution: Acetal Hydrolysis

Addition of organic solvents decreased the rate of hydrolysis.
- saturation in substrate is observed
- 1st order in [H+] and [1]
- $\Delta S^\ddagger = -9$ cal mol$^{-1}$K$^{-1}$
- $k(H_2O)/k(D_2O) = 0.62$

Mechanism

Rate Accelerations:

\[
\begin{align*}
\text{MeO}_\text{Me} &\quad 190 x \\
\text{EtO}_\text{Et} &\quad 980 x
\end{align*}
\]

Orthoformate Hydrolysis

$\text{HC(OR)}_3 + \text{H}_2\text{O} \xrightarrow{1 \text{ mol} \% 1, \text{pH} = 11} \text{H}_2\text{O} + \text{2 ROH}$

Hydrolyzed by 1
R = Me (2), Et (3), Pr (4), i-Pr (5), Bu (6), i-Bu (7)

Not Hydrolyzed by 1
R = n-pentyl (8), Ph (9)

- $\Delta S^\circ = -5 \text{ cal mol}^{-1}\text{K}^{-1}$
- S.I.E. = 1.6
- addition of organic solvents led to product inhibition
- saturation in substrate
- no saturation in $[\text{H}^+]$ at $8 < \text{pH} < 13$

$$\frac{d[P]}{dt} = \frac{k_{\#}k_\#[S][\text{H}^+][1]}{k_{\#} + k_\#[S]} \quad 8 < \text{pH} < 13$$

Question(s)?
- What is the operative mechanism?
- derive the above rate law with $8 < \text{pH} < 13$
- Is the mechanism different than for acetal hydrolysis? Why or why not?

Solution

\[ S + 1 \overset{k_1}{\underset{k_{-1}}{\rightleftharpoons}} S \subset 1 \rightarrow P + 1 \]

Steady-State to \([S \subset 1]\) resting state:

\[ \frac{d[P]}{dt} = k_2[S \subset 1][H^+] \]

\[ [1]_t = [1] + [S \subset 1] \]

\[ [S \subset 1] = \frac{k_1[S][1]_t}{k_1[S] + k_{-1} + k_2[H^+]} \]

rate = \[ \frac{k_1k_2[S][H^+][1]_{tot}}{k_{-1} + k_1[S] + k_2[H^+]} \]

Saturation consequence: \(k_1[S] \gg k_2[H^+]\)

\[ k_{cat} = k_2[H^+] \quad ; \quad v_{max} = k_{cat}[1]_t \]

\[ v = \frac{k_{cat}[S][1]_t}{K_M + [S]} = \frac{v_{max}[S]_o}{K_M + [S]_o} \]

\[ \frac{1}{v} = \frac{1}{v_{max}} + \left( \frac{K_M}{v_{max}} \right) \frac{1}{[S]_o} \]
Michaelis-Menten kinetics

Table 1. Tabulation of Kinetic Parameters for Hydrolysis of Orthoformates in 1 at 50 °C, pH = 11.0

<table>
<thead>
<tr>
<th>Substrate</th>
<th>R</th>
<th>$K_M$ (mM)</th>
<th>$k_{cat}/k_{uncat}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Me</td>
<td>24.0</td>
<td>150</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>21.5</td>
<td>560</td>
</tr>
<tr>
<td>4</td>
<td>Pr</td>
<td>19.6</td>
<td>3900</td>
</tr>
<tr>
<td>5</td>
<td>i-Pr</td>
<td>7.69</td>
<td>890</td>
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</tbody>
</table>

Aza-Cope Rearrangement

Table 2. Rate Constants for Free ($k_{\text{free}}$) and Encapsulated ($k_{\text{encaps}}$) Rearrangements (Measured at 50 °C in D$_2$O) and Their Acceleration Factors

<table>
<thead>
<tr>
<th>compound</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_3$</th>
<th>$k_{\text{free}}$ ($\times 10^5$ s$^{-1}$)</th>
<th>$k_{\text{encaps}}$ ($\times 10^5$ s$^{-1}$)</th>
<th>acceleration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Br</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>3.49</td>
<td>16.3</td>
<td>5</td>
</tr>
<tr>
<td>2-Br</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>7.61</td>
<td>198</td>
<td>26</td>
</tr>
<tr>
<td>3-Br</td>
<td>Me</td>
<td>Et</td>
<td>H</td>
<td>3.17</td>
<td>446</td>
<td>141</td>
</tr>
<tr>
<td>4-OT's</td>
<td>Me</td>
<td>Et</td>
<td>H</td>
<td>1.50</td>
<td>135</td>
<td>90</td>
</tr>
<tr>
<td>5-OTs</td>
<td>H</td>
<td>$n$-Pr</td>
<td>H</td>
<td>4.04</td>
<td>604</td>
<td>150</td>
</tr>
<tr>
<td>6-OT's</td>
<td>Me</td>
<td>Et</td>
<td>$n$-Pr</td>
<td>1.69</td>
<td>74.2</td>
<td>44</td>
</tr>
<tr>
<td>7-OT's</td>
<td>Me</td>
<td>$n$-Pr</td>
<td>H</td>
<td>0.37</td>
<td>316</td>
<td>854</td>
</tr>
<tr>
<td>8-OTs</td>
<td>$n$-Bu</td>
<td>Me</td>
<td>H</td>
<td>3.97</td>
<td>222</td>
<td>56</td>
</tr>
<tr>
<td>9-OTs</td>
<td>TMS</td>
<td>Me</td>
<td>H</td>
<td>0.033</td>
<td>1.17</td>
<td>35</td>
</tr>
<tr>
<td>10-Br</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>6.3</td>
<td>331</td>
<td>53</td>
</tr>
</tbody>
</table>

Mechanism

Solvent Dependence:

\[(k_{D_2O} = 3.49 \times 10^{-5} \text{ s}^{-1}, k_{MeOD} = 3.62 \times 10^{-5} \text{ s}^{-1}, k_{CDCl_3} = 3.84 \times 10^{-5} \text{ s}^{-1})\].

Eyring Analysis:
- No cat: \(\Delta S^\ddagger = -8 \text{ eu}, \Delta H^\ddagger = 23.1 \text{ kcal/mol}\)
- w/ cat: \(\Delta S^\ddagger = +2 \text{ eu}, \Delta H^\ddagger = 23.0 \text{ kcal/mol}\)
- more sterically hindering substrates result in a more pronounced decrease in \(\Delta H^\ddagger\) (1-2 kcal/mol)

Cycloadditions ([4+2])

\[ \text{16} + \text{17} \xrightarrow{k_2 = 0.54 \text{ M}^{-1}\text{day}^{-1}} \text{18} \]

\[ \text{S_n} 1-1 + \text{4} \xrightarrow{} \text{5} + nS \]

- 200 fold acceleration
- No reaction with 15a or 2s

Catalyst Turnover


\[
\frac{dp}{dt} \text{(cat)} = 10 \frac{dp}{dt} \text{(uncat)}
\]
[4+2] regioselectivity

Fujita, M. et. al. Science 2006, 312, 251
Crystal structure and Modeling support

Fujita, M. et. al. Science 2006, 312, 251
[4+2] on Unreactive Substrate

[2+2] cycloadditions


In benzene, anti dimer is favored 21:2

>98% yield
Crystal Structure

Cross-Photodimerization [2+2]

\[
1\cdot(2\cdot3a) + 1\cdot3a + \text{free 3a} \quad \xrightleftharpoons{H_2O} \quad 2 \cdot 1\cdot(2\cdot3a)
\]

\[
1 + 2 + 3 \quad \xrightarrow{H_2O} \quad 1\cdot(2\cdot5a) + 1\cdot4 + 1\cdot6a
\]

<table>
<thead>
<tr>
<th>R</th>
<th>1\cdot(2\cdot3a)</th>
<th>1\cdot4</th>
<th>1\cdot6a</th>
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</thead>
<tbody>
<tr>
<td>OEt</td>
<td>0%</td>
<td>92%</td>
<td>0%</td>
</tr>
<tr>
<td>OMe</td>
<td>6%</td>
<td>44%</td>
<td>22%</td>
</tr>
<tr>
<td>H</td>
<td>21%</td>
<td>35%</td>
<td>14%</td>
</tr>
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</table>

Alkane Oxidation

Peroxide/alcohol = 4:1 (24%)

Selective Singlet Oxygen Oxidation

## Selectivities

![Chemical structures and spectra]

<table>
<thead>
<tr>
<th>$n$</th>
<th>CH$_3$CN / Rose bengal</th>
<th>Octaacid / Rose bengal</th>
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<tbody>
<tr>
<td>1</td>
<td>4%</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>5%</td>
</tr>
<tr>
<td>2</td>
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<td>20%</td>
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<td>10%</td>
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</tr>
<tr>
<td></td>
<td>5%</td>
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</tr>
<tr>
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<td>48%</td>
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<tr>
<td></td>
<td>5%</td>
<td>5%</td>
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</table>

**Rose bengal**
Conclusions

- The typical nano-space within these vessels ranges from 300-500 Å³ which is sufficient for encapsulation of 1 large or a number of small molecules.

- A nano-reactor may promote any one of the following:
  - rate acceleration
    - effective concentration
    - lower activation parameters
  - novel regio- and chemoselectivities
  - reactivity with otherwise unreactive substrates
  - stabilization of highly reactive intermediates
  - potential enantioselective catalysis where other methods are lacking

Reviews: