High-Pressure Synthesis of Cryptands via Double Amidation Reaction of Diazacoronands with Active Esters of α,ω-Dicarboxylic Acids

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Abstract: A general method for the synthesis of cryptands via the high-pressure double amidation reaction of seven diazacoronands with five various active esters (p-nitrophenyl and pentafluorophenyl) of dicarboxylic acids is described.

Key words: cryptands, diazacoronands, active esters, double amidation reaction, high-pressure technique

There has been a growing interest in the synthetic bimacrocyclic molecular receptors called ‘cryptands’ since Lehn’s discovery.1 The first synthesis of cryptands using the high-dilution technique2 stimulated a rapid research in this field due to their complexing behavior.3 It was soon recognized that they formed stable complexes with a wide range of species – from inorganic and organic ions to neutral molecules. Therefore, the studies aimed at rational design and synthesis of more elaborated cryptands with desired complexing properties are well advanced. A number of methods for the formation of cryptands is known; apart from the above-mentioned high-dilution technique,1,2 a quaternization-demethylation procedure,4 a template synthesis,5 and an imination reduction sequence6 seem to be the most useful ones. The quaternization-demethylation reaction has been greatly improved in our laboratory, using the high-pressure technique.7 Tailored synthesis of polyfunctional cryptands calls for further search for more efficient and selective methods. We now report a new high-pressure approach to the synthesis of cryptands via double N-acylation of diazacoronands with active diesters (Scheme 1).

Diazacoronands 1–7 were prepared according to our own procedure,8 based on the reaction of dimethyl esters of diglycolic, triglycolic, and tetruglycolic acids with appropriate α,ω-diamines carried out in methanol under ambient conditions and followed by reduction with BMS (borane–methyl sulfide).

The active p-nitrophenyl esters 8a, 9a, and 10 were obtained according to the procedure published by Zimmer et al.9 and modified by us, and the pentafluorophenyl esters 8b and 9b were prepared according to the procedure published recently by Liskamp and co-workers10 (Figure 1).

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Figure 1 Diazacoronands 1–7 and active esters 8–10.

Having in hand seven diazacoronands 1–7 and five active esters 8a, 8b, 9a, 9b, and 10, we commenced their macrocyclization reactions. The reactions were carried out in anhydrous nitromethane or acetonitrile, using the high-pressure technique.11 The results of macrocyclization reactions are listed in Table 1.
<table>
<thead>
<tr>
<th>Active Esters</th>
<th>8a</th>
<th>8b</th>
<th>9a</th>
<th>9b</th>
<th>10</th>
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<tr>
<td>Diaza coronands</td>
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<td>1</td>
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</table>

Table 1: Macrocyclization Reactions of Diaza coronands 1–7 with Active Esters 8–10
The reaction of the smallest diazacoronand 1 with \( p \)-nitrophenyl esters \( 9a \) and \( 10 \) gave the cryptands \( 11 \) and \( 12 \), respectively, in moderate yields. The use of the larger diazacoronand 2 afforded the corresponding cryptand 14 in a better yield (41\%) in the case of the active ester 10. A similar yield (42\%) was obtained for the macrocyclization reaction of diazacoronand 2 with pentafluorophenyl ester \( 9b \). The best results were obtained for the reactions of diazacoronand 3 with all the active esters used. In the case of larger diazacoronands 5, 6 and 7, the yields substantially dropped for all active esters applied (Table 1).

The cryptands were obtained usually in the form of pale-yellow glass. However, we were able to obtain a single crystal for compound 15 suitable for X-ray analysis. The X-ray structure confirms the formula of cryptand 15 monohydrate. In the solid state, the bicyclic cryptand exists in a ‘basket-like’ conformation (Figure 2).

![Figure 2](image)

**Figure 2**  X-ray structure of cryptand 15: a) ORTEP plot with atom labels; b) the crystal packing.

In summary, the high-pressure method for the synthesis of bicyclic cryptands presented here could be an alternative process to several known procedures, especially when substrates are sensitive to acids.

Melting points were determined on a Käfer hot-stage apparatus and are not corrected. All reported NMR spectra were recorded with Varian Unity plus 200 and 500 spectrometers at 200 and 500 MHz, respectively, \(^1H\ NMR\), and 50 and 125 MHz, respectively, \(^13C\ NMR\) in CDCl\(_3\). Chemical shifts are reported as \( \delta \) values relative to TMS peak defined at \( \delta = 0.00 \) \((^1H\ and\ ^{13}C\ NMR)\). The high-resolution mass spectrometry experiments were performed on a Quattro LC Micromass instrument using the ESI technique. The X-ray analysis was performed on a Kuma KM4 CCD x-axis diffractometer with graphite-monochromated MoK\(_\alpha\) radiation. All macrocyclization reactions were carried out in a piston-cylinder high-pressure apparatus at pressures of about 10 kbar. The main details of this apparatus have been published earlier.\(^{12}\) The analytical and preparative TLC separations were carried out on commercial Merck plates coated with 0.25 and 1.0 mm, respectively, of silica gel 60 F\(_{254}\). The reagent-grade solvents were dried and distilled prior to use under an inert atmosphere. Unless otherwise specified, all starting materials were purchased from commercial suppliers and were used without further purification.

\( p \)-Nitrophenyl ester \( 8a \) and pentafluorophenyl esters \( 8b \) and \( 9b \) were prepared according to the literature procedures.

### \( p \)-Nitrophenyl Esters

- **\( p \)-Nitrophenyl Ester 9a**
  
  \( 1H \) NMR (CDCl\(_3\), 200 MHz): \( \delta = 8.32–7.29 \) (m, 8 H), 4.49 (s, 4 H), 3.92 (s, 4 H).
  
  \( 13C \) NMR (CDCl\(_3\), 50 MHz): \( \delta = 168.0, 125.3, 122.2, 71.3, 68.5. \)
  
  HRMS (ESI): \( m/z \) calcd for \( C_{18}H_{16}N_2O_{10}Na [M + Na]^+ \): 443.0697; found: 443.0701.

- **\( p \)-Nitrophenyl Ester 10**
  
  Mp 86–88 °C (EtOH).
  
  \( 1H \) NMR (CDCl\(_3\), 200 MHz): \( \delta = 8.31–7.28 \) (m, 8 H), 4.46 (s, 4 H), 3.87–3.75 (m, 8 H).
  
  \( 13C \) NMR (CDCl\(_3\), 50 MHz): \( \delta = 168.1, 125.3, 122.2, 71.2, 70.7, 68.5. \)
  
  HRMS (ESI): \( m/z \) calcd for \( C_{20}H_{20}N_2O_{11}Na [M + Na]^+ \): 487.0959; found: 487.0960.

### Cryptands 11–23 by High-Pressure Macrocyclization; General Procedure

A solution of the respective active ester \( 8–10 \) (1 mmol) and the diazacoronand 1–7 (1 mmol) in nitromethane or MeCN (5 mL) was charged into a teflon ampoule. The ampoule was then placed in a high-pressure vessel, and the pressure was slowly increased to 10 kbar at 50 °C. After stabilization of the pressure, the reaction mixture was kept under these conditions for 72 h. After decompression, the solvent was evaporated and the residue was subjected to preparative TLC (CH\(_2\)Cl\(_2\)–MeOH, 87:13) to afford the desired cryptand. The characteristics of cryptand obtained are given in Table 2.

### X-Ray Structure Analysis of 15

Formula \( C_{16}H_{30}N_2O_8 \cdot H_2O \), M = 378.42; mp 172–174 °C (MeOH–Et\(_2\)O), monoclinic, \( a = 8.718(2) \), \( b = 11.657(2) \), \( c = 18.197(4) \) Å, \( \beta = 98.89(3) \) degrees, space group P2\(_1\)/c, \( V = 1827.1(6) \) Å\(^3\), \( Z = 4, \ D_\alpha = 1.376 \) Mg/m\(^3\), \( \mu (M_K) = 0.110 \) mm\(^-1\), \( T = 120(2) \) K, 10710 reflections collected, 2381 unique reflections collected, 2381 unique reflections (\( R_{	ext{Bragg}} = 0.0208 \)), which were used in all calculations: Data/parameters: 2381/244. The final \( R_1 = 0.0303 \) (all data), \( wR_2 = 0.0691 \).\(^{13–16}\)

### Acknowledgment

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<table>
<thead>
<tr>
<th>Product</th>
<th>$^1$H NMR $^a$ δ</th>
<th>$^1$C NMR$^b$ δ</th>
<th>ESI-HRMS m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>2.8–4.6 (m, 24 H)</td>
<td>46.3, 61.8, 67.9, 72.2, 170.8</td>
<td>calcd for C$<em>{22}$H$</em>{40}$N$_2$NaO$_9$ [M + Na]$^+$: 339.1527; found: 339.1547</td>
</tr>
<tr>
<td>12</td>
<td>2.8–4.5 (m, 28 H)</td>
<td>47.2, 49.3, 67.8, 69.8, 70.1, 170.0</td>
<td>calcd for C$<em>{20}$H$</em>{36}$N$_2$NaO$_8$ [M + Na]$^+$: 427.2051; found: 427.2077</td>
</tr>
<tr>
<td>13</td>
<td>2.7–4.9 (m, 28 H)</td>
<td>49.5, 50.6, 67.7, 68.1, 69.2, 69.6, 70.8, 170.0</td>
<td>calcd for C$<em>{20}$H$</em>{36}$N$_2$NaO$_9$ [M + Na]$^+$: 427.2051; found: 427.2077</td>
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<td>14</td>
<td>2.8–4.7 (m, 28 H), 4.41 (s, 4 H)</td>
<td>49.3, 49.5, 68.7, 69.0, 69.4, 70.2, 70.4, 71.1, 170.1</td>
<td>calcd for C$<em>{20}$H$</em>{36}$N$_2$NaO$_9$ [M + Na]$^+$: 427.2051; found: 427.2077</td>
</tr>
<tr>
<td>15</td>
<td>2.7–2.8 (m, 2 H), 2.9–3.0 (m, 2 H), 3.5–3.7 (m, 14 H), 3.8–4.0 (m, 4 H), 4.2–4.6 (m, 6 H)</td>
<td>48.9, 66.9, 70.28, 71.95, 169.9</td>
<td>calcd for C$<em>{22}$H$</em>{40}$N$<em>2$NaO$</em>{10}$ [M + Na]$^+$: 383.1789; found: 383.1799</td>
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<td>48.6, 69.1, 71.0, 71.8, 72.4, 169.6</td>
<td>calcd for: C$<em>{20}$H$</em>{36}$N$<em>2$NaO$</em>{9}$ [M + Na]$^+$: 427.2051; found: 427.2077</td>
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<td>17</td>
<td>2.5–2.8 (m, 2 H), 2.9–3.0 (m, 2 H), 3.5–4.0 (m, 26 H), 4.2–4.6 (m, 6 H)</td>
<td>47.7, 68.7, 70.2, 70.3, 70.4, 70.8, 169.7</td>
<td>calcd for: C$<em>{22}$H$</em>{40}$N$<em>2$NaO$</em>{9}$ [M + Na]$^+$: 427.2051; found: 427.2077</td>
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<td>18</td>
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<td>calcd for: C$<em>{22}$H$</em>{40}$N$<em>2$NaO$</em>{9}$ [M + Na]$^+$: 427.2051; found: 427.2077</td>
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<td>19</td>
<td>3.5–3.9 (m, 36 H)</td>
<td>49.6, 50.1, 69.9, 70.3, 70.7, 71.5, 71.9, 72.4, 170.3</td>
<td>calcd for: C$<em>{22}$H$</em>{40}$N$<em>2$NaO$</em>{9}$ [M + Na]$^+$: 427.2051; found: 427.2077</td>
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<td>20</td>
<td>2.9–3.0 (m, 4 H), 3.5–4.6 (m, 32 H)</td>
<td>48.0, 48.5, 69.6, 70.2, 70.4, 70.6, 70.9, 71.1, 171.6, 169.1</td>
<td>calcd for: C$<em>{22}$H$</em>{40}$N$<em>2$NaO$</em>{9}$ [M + Na]$^+$: 427.2051; found: 427.2077</td>
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<td>21</td>
<td>3.4–4.4 (m, 40 H)</td>
<td>49.7, 69.2, 70.1, 70.2, 70.4, 70.6, 169.7</td>
<td>calcd for: C$<em>{22}$H$</em>{40}$N$<em>2$NaO$</em>{9}$ [M + Na]$^+$: 427.2051; found: 427.2077</td>
</tr>
<tr>
<td>22</td>
<td>1.8–1.9 (m, 4 H), 3.3–4.3 (m, 32 H)</td>
<td>29.7, 49.2, 61.6, 69.7, 70.1, 72.3, 76.8, 77.1, 77.3, 169.3</td>
<td>calcd for: C$<em>{22}$H$</em>{40}$N$<em>2$NaO$</em>{9}$ [M + Na]$^+$: 427.2051; found: 427.2077</td>
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<tr>
<td>23</td>
<td>1.8–1.9 (m, 4 H), 3.3–4.5 (m, 36 H)</td>
<td>29.7, 46.7, 47.4, 69.9, 70.4, 70.7, 70.8, 76.8, 77.0, 77.3, 170.4</td>
<td>calcd for: C$<em>{22}$H$</em>{40}$N$<em>2$NaO$</em>{9}$ [M + Na]$^+$: 427.2051; found: 427.2077</td>
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**References**


(16) The crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 223757.