# Macrocyclic Polylactams of Mirror Symmetry: Preparation and Structure

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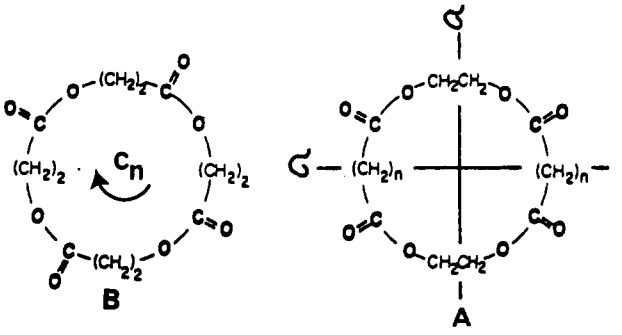
The synthesis and structure of a series of macrocyclic lactams possessing reflection symmetry are described. The synthesis involves condensation of diazasilolidines **1** and **2** with diacyl dihalides **3** to give either exclusively macrocyclic dilactams **4** or tetralactams **5**. The high product selectivity of these reactions is attributed to noncovalent interactions between silicon and carbonyl oxygen. The structures of the macrocyclic lactams prepared are analyzed by high-resolution $^1H$ and $^{13}C$ NMR spectrometry as well as by X-ray diffraction studies. The observed conformational regularities are discussed and compared with those of macrocyclic lactams of rotational symmetry.

Naturally occurring macrocyclic molecules are a large group of compounds that exhibit many different biological activities and may function as antibiotics, hormones, antitumor agents, or ion carriers.[1,2] The actinomycins are, for example, antibiotics, the peptides oxytocin and vasopressin are hormones, the spermine and spermidine alkaloids are antitumor agents, and the depsipeptides enniatin and valinomycin are ion carriers.

Although, this family of compounds may vary greatly in composition, ring size, ring symmetry, nature of the side chains, and chiral residues, their biological functions are believed to be largely determined by their three-dimensional arrangements in space. Establishing the relationship between molecular structure and conformation might therefore assist in the design of artificial compounds with similiar properties and in the identification of natural products that exert similar functions.

Upon inspection of the naturally occurring macrocyclic compounds, it becomes apparent that they often incorporate lactone and lactam functions in their ring skeletons. The abundance of these functional groups in the natural products attracted our attention, and we wondered if and to what extent the carbonyl dipoles might be responsible in shaping these molecules overall geometry. In an attempt to examine this possibility, we decided to synthesize several macrocyclic polycarbonyl compounds as model systems and to screen their conformational regularities. Within this framework we recently examined macrocyclic polylactones with emphasis on tetralactones and found that their conformations greatly depend on the ring symmetry: reflection symmetry (structure A) vs. rotational symmetry (structure B).



In this publication we describe the synthesis and structures of macrocyclic polylactams with reflection symmetry. We report on a novel template method for the efficient preparation of these compounds[9] and on their conformations in solution and in the solid state and compare their structures with those of macrocyclic polylactams with rotational symmetry (cyclic peptides), for which ample data are available.[4,6-8]

**Table I. Yields of Dilactams 4 and Tetralactams 5**

| starting matls | | yield,[a] % | |
|---|---|---|---|
| Si compd | acyl halide | dilactams 4 | tetralactams 5 |
| 1 ($m$ = 2, R = $CH_2CH_3$) | 3 ($n$ = 3) | | 24 |
| 1 ($m$ = 2, R = $CH_2Ph$) | 3 ($n$ = 3) | | 31 |
| 1 ($m$ = 2, R = $CH_2Ph$) | 3 ($n$ = 4) | 15 | |
| 1 ($m$ = 2, R = $CH_2Ph$) | 3 ($n$ = 5) | | 12 |
| 1 ($m$ = 2, R = $CH_2Ph$) | 3 ($n$ = 6) | 17.5 | |
| 1 ($m$ = 2, R = $CH_2Ph$) | 3 ($n$ = 7) | | 40.5 |
| 1 ($m$ = 2, R = $CH_2Ph$) | 3 ($n$ = 8) | 24.5 | |
| 2 ($m$ = 3, R = $CH_2CH_3$) | 3 ($n$ = 4) | | 21 |
| 2 ($m$ = 3, R = $CH_2CH_3$) | 3 ($n$ = 6) | | 15 |

[a] The remaining products were higher polymers.

## Synthesis

The preparation of macrocyclic polylactams from diamines and activated diacids requires to direct condensation reactions to form ring products in favor of polymers. In an attempt to achieve this goal, many different cyclization procedures have been developed. Early high-dilu-

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**Table II. Spectroscopic Properties of Dilactams 4 and Tetralactams 5**

| compd | IR (KBr): $\nu$, cm$^{-1}$ | mp, °C | $^1$H NMR ($CDCl_3$): $\delta$ Ph | $PhCH_2N$ | $CH_2NCH_2Ph$ | $CH_2CO$ | $CH_2(CH_2)$ |
|---|---|---|---|---|---|---|---|
| 4 ($m$ = 2, $n$ = 4) | 1610–1620, 1450, 1430 | 95–97 | 7.12–7.37 (m, 10 H) | 5.48 (d, $J$ = 14 Hz), 4.92 (d, $J$ = 16 Hz), 3.89 (d, $J$ = 16 Hz), 3.98 (d, $J$ = 14 Hz, 4 H) | 4.82–4.19 (m, 4 H) | 3.23–2.59 (m, 4 H) | 1.69–2.43 (m, 4 H) |
| 4 ($m$ = 2, $n$ = 6) | 1630, 1470, 1410 | 128–130 | 7.16–7.34 (m, 10 H) | 4.79–4.86 (d, $J$ = 18 Hz, 2 H), 4.55–4.62 (d, $J$ = 18 Hz, 2 H) | 4.83–4.79 (d, 2 H), 2.51–2.49 (d, $J$ = 10 Hz, 2 H) | 1.97–2.10 (m, 2 H), 2.54–2.68 (m, 2 H) | 1.36–1.70 (m, 8 H) |
| 4 ($m$ = 2, $n$ = 8) | 1635, 1450, 1420 | 110–112 | 7.19–7.38 (m, 10 H) | 8.03–4.31 (m, 4 H) | 5.03–4.31 (m, 2 H), 2.01–2.75 (m, 2 H) | 2.01–2.75 (m, 4 H) | 1.05–1.94 (m, 12 H) |

| compd | mp, °C | IR (KBr): $\nu$, cm$^{-1}$ | $^1$H NMR ($CDCl_3$): $\delta$ R′ = Me, Ph | R′$CH_2N$ | $CH_2NCH_2R'$ | $NCH_2CH_2CH_2N$ | $CH_2CO$ | $CH_2(CH)_2CH_2$ |
|---|---|---|---|---|---|---|---|---|
| 5 (R = Et; $m$ = 2, $n$ = 3) | 218–221 | 1625, 1470, 1420 | 1.12 (two overlap t, $J$ = 7 Hz, 12 H) | 3.24–3.40 (m, 8 H) | 3.24–3.40 (m, 8 H) | | 2.36 (m, 8 H) | 1.80 (m, 4 H) |
| 5 (R = $CH_2Ph$; $m$ = 2, $n$ = 3) | 231–234 | 1630, 1470, 1420 | 7.1–7.4 (m, 20 H) | 4.39 (s), 4.47 (s), 4.70 (s) (8 H) | 3.38 (t, $J$ = 8 Hz), 3.47 (br t), 3.57 (t, $J$ = 8 Hz) (8 H) | | 2.42 (t, $J$ = 8 Hz), 2.48 (br t), 2.57 (t, $J$ = 8 Hz, 8 H) | 2.01 (m, 4 H) |
| 5 (R = $CH_2Ph$; $m$ = 2, $n$ = 5) | 199–201 | 1630, 1445, 1410 | 7.2–7.4 (m, 20 H) | 4.34 (s), 4.47 (s), 4.53 (s), 4.66 (s) (8 H) | 3.61 (s), 3.35 (m, 8 H) | | 2.28 (m, 8 H) | 1.50 (m, 12 H) |
| 5 (R = $CH_2Ph$; $m$ = 2, $n$ = 7) | 199–204 | 1640, 1470, 1420 | 7.05–7.48 (m, 20 H) | 4.44 (s), 4.50 (s), 4.55 (s), 4.68 (s) (8 H) | 3.38 (m), 3.61 (s) (8 H) | | 2.36 (m, 8 H) | 1.51 (m, 20 H) |
| 5 (R = Et; $m$ = 3, $n$ = 4) | 127–129 | 1625, 1465, 1425 | 1.13 (m, 12 H) | 3.14–3.39 (m, 8 H) | 3.38–3.39 (m, 8 H) | 1.67–1.91 (m, 4 H) | 2.11–2.41 (m, 8 H) | 1.67–1.91 (m, 8 H) |
| 5 (R = Et; $m$ = 3, $n$ = 6) | 138–140 | 1630, 1460, 1440 | 1.06–1.35 (m, 12 H) | 3.07–3.44 (m, 8 H) | 3.07–3.44 (m, 8 H) | 1.7–1.87 (m, 4 H) | 2.15–2.34 (m, 8 H) | 1.23–1.45 (m, 8 H), 1.47–1.87 (m, 8 H) |

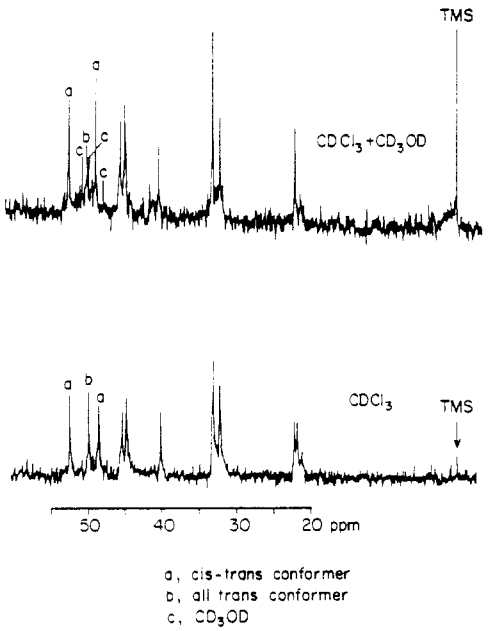
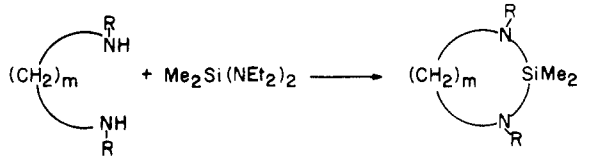



**Figure 1.** $^{13}$C NMR of tetralactam **5** ($m$ = 2, $n$ = 3).

tion techniques[10–13] have been complemented by various double-activation methods[14–17] and by a series of consecutive "zipper-type" reactions.[18] In most of these methods the macrocyclic lactams and polylactams are obtained by cyclization of a polyfunctional, linear precursor to a ring product. We report here on an alternative approach that makes use of silicon derivatives as covalent templates.[9] The method relies on converting acyclic diamines to cyclic diazasilolidines, wherein the silicon element functions as template. Subsequent condensation with activated diacids, either diacyl dihalides or diesters, provides macrocyclic polylactams with concurrent expulsion of silicon.

The cyclic diazasilolidine intermediates **1** ($m$ = 2) and **2** ($m$ = 3) were prepared by reacting the corresponding diamines, *N*,*N*′-dibenzylethylenediamine, *N*,*N*′-diethylethylenediamine, and *N*,*N*′-diethyl-1,3-diaminopropane with bis(diethylamino)dimethylsilane as described by Abel.[19]




1. R = Et, m = 2
   R = $PhCH_2$–, m = 2
2. R = Et, m = 3

Treating either of the cyclic diazasilolidine derivatives **1** or **2** with diacyl dihalide **3** resulted in the formation of macrocyclic polylactams **4** and **5**, which were isolated by

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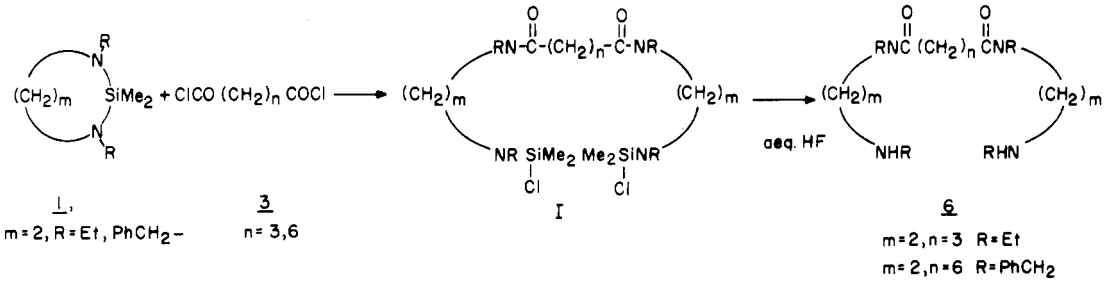
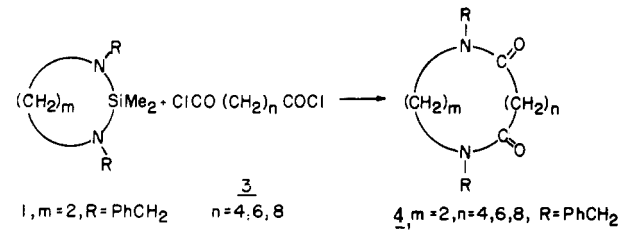
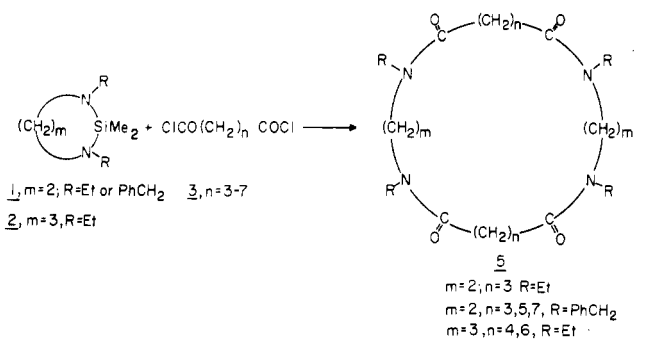



**Table III. Effect of Reaction Conditions on Yields**

| reactn product | solvent | reactn time, h | reactn temp, °C | yield, % |
|---|---|---|---|---|
| **5**, R = Et | $CH_3CN$ | 17.75 | 82 | 14.5 |
| $m = 2$ | DMF | instantaneous | 153 | 15.8 |
| $n = 3$ | xylene | 0.5–3.5 | 144 | 17.4–24.3 |
| | neat | instantaneous | rt | 0 |
| **5**, R = $CH_2Ph$ | $ClCH_2CH_2Cl$ | 16 | rt | 17.08 |
| $m = 2$, | $ClCH_2CH_2Cl$ | instantaneous | 146 | 30.6 |
| $n = 3$ | | | | |

extraction and subsequent chromatography on silica gel (Table I).




The spectroscopic and analytical properties of the macrocyclic products are given in Table II and Table VII (supplementary material). All macrocyclic lactams are characterized by a carbonyl absorption at 1610–1640 $cm^{-1}$, give rise to a molecular ion peak in the mass spectrum, and show a proton NMR pattern that is compatible with the presence of cyclic lactams (see following section).

The specific reaction conditions (temperature, solvent, concentration) are summarized in Table III. Inspection of Table III shows that temperature and solvent polarity have a negligable effect on the yields of the macrocyclic products. The nature of the products formed, macrocyclic dilactams **4** vs. macrocyclic tetralactams **5**, does however depend on the nature of the reactants, i.e. the length of the methylene chain in the amines and the acyl derivatives (Table I). If macrocyclic dilactams with an even number of ring members may be formed, they are obtained as sole ring products. If, on the other hand, the macrocyclic dilactams would be odd numbered, the corresponding macrocyclic tetralactams are obtained. The specificity of these reactions was demonstrated by thin-layer chromatography (silica gel 60, Merck, chloroform as mobile phase); which could readily distinguish between dilactams ($R_f$ 0.60 for **4**, $n = 7$) and tetralactams ($R_f$ 0.13 for **5**, $n = 7$). The specificity encountered here is exclusive and exceeds the specificity of any analogous cyclization reaction reported so far.[9-16] Control reactions carried out with free diamine, *N,N'*-dibenzylethylenediamine, and diacyl dihalide **3** ($n = 7$) under high-dilution conditions did provide different products than the corresponding silylated derivative **1** ($m = 2$) and diacyl dihalide **3** ($n = 7$): the macrocyclic dilactam **4** ($n = 7$) was obtained as sole macrocyclic product instead of the macrocyclic tetralactam **5** ($n = 7$). That the tetralactam **5** ($n = 7$) is not a secondary product (thermodynamically controlled product) formed from the dilactam **4** ($n = 7$) under the given reaction conditions was demonstrated experimentally: dilactam **4** was recovered unchanged when treated with dimethylsilyl dichloride in boiling xylene for 24 h. The silyl group thus exerts a genuine template effect.

In order to gain insight into the pathway of this reaction, its progress was followed by measuring the consumption of the acylating agent with time. It was found that the first 0.5 equiv is consumed faster than the second, indicating that this reaction occurs in a two-step process. This was confirmed when linear glutaroyl- and sebacoylamides **6** ($n = 3, 6$) were obtained in 72.9 and 59.7% yields, respectively, upon treatment of 1 equiv of diazasilolidine **1** (R = $PhCH_2$, $m = 2$) with 0.5 equiv of diacyl dihalide **3** (odd, $n = 3$; even, $n = 6$).

This stepwise process may be attributed to the diminished reactivity of the residual silicon–nitrogen bond in intermediate I due to the presence of the electronegative chlorine substituent. It may be used to selectively transform diamines to monoamides[20] or mixed diamides.[21]

The high yields of macrocyclic products obtained without the use of high-dilution techniques and through the intermediacy of linear I would be difficult to explain without the presence of conformations that are prone to ring formation. Since silicon derivatives are known to undergo noncovalent interactions with carbonyl oxygens of amide groups by expanding their coordination number from 4 to 5[22,23] it is likely that such interactions also take place in intermediate I.

The following reaction pathway may accordingly be suggested for the formation of macrocyclic polylactams via the silicon method. Reaction of cyclic diazasilolidines **1** ($m = 2$) and **2** ($m = 3$) with diacyl dihalide **3** ($n$ = even or odd) may provide four types of intermediates, Ia–d. When the diacyl dihalides contain an even number of methylene groups, the carbonyl groups are likely to assume an anti configuration (Ia,b), and when the diacyl dihalides contain an odd number of methylene groups, they are likely to assume a "syn" configuration (Ic,d). Noncovalent interactions between the carbonyl oxygen and the silicon atom may then stabilize specific conformations and direct sub-

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(21) E. Schwartz and A. Shanzer, unpublished results.
(22) J. F. Klebe, *Acc. Chem. Res.*, **3**, 299 (1970).
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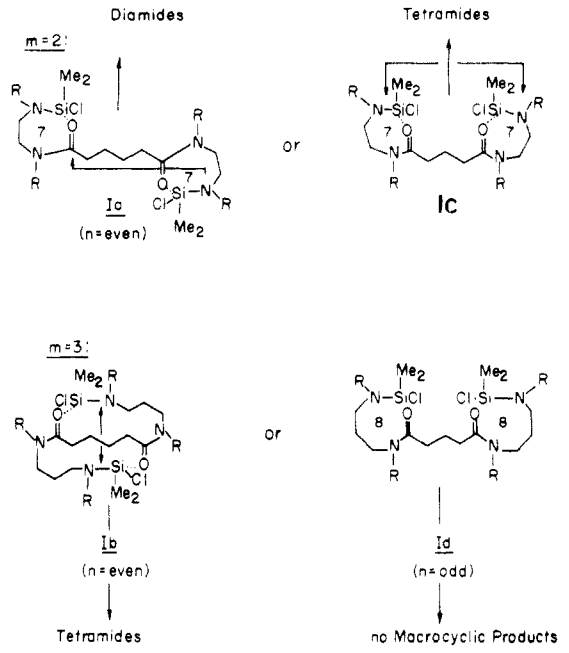
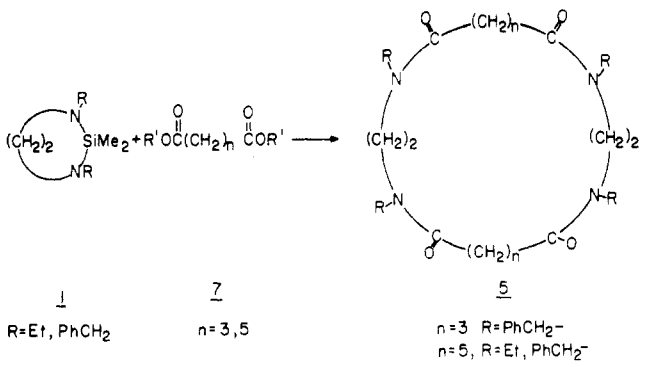


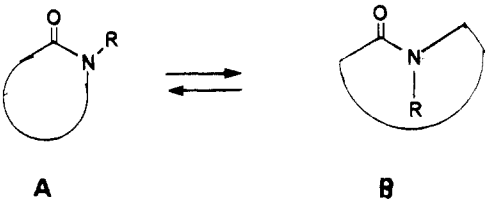

sequent cyclization reactions. When the diazasilolidine **1** contains two methylene groups ($m$ = 2), such interactions may occur between the proximate carbonyl oxygen and silicon atom to form seven-membered rings, Ia and Ic. Translactamation in Ia then provides the "even" dilactams **4** ($m$ = 2; $n$ = 4, 6, 8); condensation of Ic with a second diacyl dihalide yields the corresponding tetralactams **5** ($m$ = 2; $n$ = 3, 5, 7). When the diazasilolidine **2** contains three methylene groups ($m$ = 3), interactions between the proximate carbonyl oxygen and silicon atom would provide an unfavorable eight-membered ring and is therefore unlikely to occur. Intermediate Id may thus not be stabilized and fails to provide any macrocyclic product. In intermediate, Ib, on the other hand, noncovalent interactions between the distant carbonyl oxygen and silicon atom are possible and condensation with a second diacyl dihalide molecule may give the corresponding tetralactams **5** ($m$ = 3; $n$ = 4, 6).




Since acyl halides of functionalized acids are difficult to prepare, it was thought that the use of activated diesters instead of diacyl dihalides might be advantageous in these cases. Two major families of active esters are known; those derived from phenols and those derived from thiophenols.[24,25] Considering the pronounced affinity of silicon for oxygen, activated phenol esters were selected, since these derivatives would form silicon–oxygen compounds as byproducts. Replacement of diacyl dihalides by activated diesters, nitrophenolates, or pentochlorophenolates proved to be successful and led to macrocyclic tetralactams **5** in comparable yields.

## Structure

Amides derived from secondary amines where the two groups linked to the nitrogen are different can exist in two different amide configurations. In the case of cyclic monolactams, the preferred configuration depends on the nature of the ring and the substituents. In small rings, the cis configuration (A) is preferred, while in larger rings the trans configuration (B) may predominate.[26]




The energy barrier for this isomerization is usually high enough to result in a rate of interconversion that is slow relative to the NMR time scale.

In an attempt to elucidate the preferred configuration of the macrocyclic polylactams prepared above, proton NMR and particularly carbon-13 NMR spectrometry were selected as analytical tool.

In a first set of experiments, high-resolution proton NMR spectra (270 MHz) of both tetralactams **5** and dilactams **4** were recorded in chloroform solution at ambient temperatures. The data are summarized in Table II. Inspection of the table indicates that these macrocyclic compounds assume either a highly nonsymmetric conformation or several slow interconverting conformations. [The tetralactam **5** ($n$ = 3), for example, gave rise to three sets of signals that could be clearly distinguished; each of these sets coalesces at ca. 80 °C.]

In order to differentiate between these two possibilities and to single out the number and nature of the preferred conformers of the macrocyclic polylactams prepared, a thorough carbon-13 NMR analysis was undertaken. Due to the wider chemical shift range of carbon-13 relative to proton NMR spectra, components of faster equilibrating mixtures were anticipated to be distinguishable. In addition, the possible counting of each carbon signal was hoped to help identify the overall symmetry of the conformer. In order to correctly assign each carbon-13 signal of the macrocyclic products, the carbon-13 NMR spectra of three model compounds were first measured: *N*-benzyl-N-pentylamine, *N*-benzyl-*N*-pentylbutyramide, and the acyclic diamide derived from pimelic acid and *N*-benzyl-*N*-pentylamine. The carbon-13 NMR data of these compounds are summarized in Table IV. Inspection of these data shows that in the acyclic compounds the isomers with the higher field benzylic $CH_2$ signals ($\delta$ 48 vs. 51) are slightly favored. Consultation of available literature data[27] indicates that this higher field signal may be attributed to the syn configuration. Due to the large chemical shift difference for this carbon in the syn and in the anti configuration, it is of particular diagnostic value and was used in the present work to differentiate between the cis and the trans configurations in the macrocyclic products. It is also worthwhile to note that in the acyclic model compounds derived from pimelic acid only two sets of signals

(24) G. Wendelberger in "Houben Weyl, Methoden der Organischen Chemie", Vol, 15/2, E. Mueller, Ed., 4th ed., Verlag Georg Thieme, Stuttgart, 1974, p 12.
(25) G. Wendelberger, Reference 24, Vol. 15/2, p 275.
(26) W. E. Stewart and T. H. Siddall, *Chem. Rev.*, **70**, 517 (1970) and references therein.
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**Table IV. $^{13}C$ NMR Data of Model Compounds**

| carbon | | δ value | | | | |
|---|---|---|---|---|---|---|
| | | | *N*-benzyl-*N*-pentylbutyramide | | *N*-benzyl-*N*-pentylpimelate | |
| | | *N*-benzyl-*N*-pentylamine | major (syn) | minor (anti) | major (syn) | minor (anti) |
| NCO | | | 173.0 | 173.2 | 173.6 | 174.0 |
| *Ph*$CH_2$NH | $C_i$ | 140.6 | | | 140.1 | 139.9 |
| | o | 128.2 | | | 128.0 | 128.0 |
| | m | 128.4 | | | 128.5 | 128.5 |
| | p | 126.9 | | | 127.0 | 127.1 |
| *Ph*$CH_2$NCO | $C_i$ | | 137.4 | 138.2 | 137.1 | 138.0 |
| | o | | 128.0 | 126.2 | 128.2 | 126.3 |
| | m | | 128.5 | 128.9 | 128.6 | 128.9 |
| | p | | 127.2 | 127.5 | 127.3 | 127.5 |
| Ph*C*$H_2$NH | | 54.1 | | | 53.7 | 53.9 |
| Ph*C*$H_2$NCO | | | 48.2 | 51.0 | 48.6 | 51.8 |
| N*C*$H_2C$$H_2$ | | | | | 47.4, 47.1 | 46.1, 47.2 |
| NH*C*$H_2$ | | 49.5 | | | | |
| HN*C*$H_2C$$H_2$ | | 29.8 | | | | |
| HN*C*$H_2C$$H_2C$$H_2$ | | 29.6 | | | | |
| HN*C*$H_2C$$H_2C$$H_2C$$H_2$ | | 22.7 | | | | |
| HN$(CH_2)_4CH_3$ | | 14.1 | | | | |
| *C*$H_2$NCO | | | 47.1 | 46.2 | | |
| *C*$H_2C$$H_2$NCO | | | 28.3 | 27.3 | | |
| *C*$H_2$$(CH_2)_2$NCO | | | 29.1 | 29.2 | | |
| *C*$H_2$$(CH_2)_3$NCO | | | 22.4 | 22.4 | | |
| *C*$H_3$$(CH_2)_4$NCO | | | 14.0 | 14.0 | | |
| *C*$H_2$CON | | | 35.0 | 35.3 | 33.2 | 33.2 |
| *C*$H_2C$$H_2$CON | | | 19.0 | 18.8 | 25.3 | 25.4 |
| *C*$H_2$$(CH_2)_2$CON | | | 14.0 | 14.0 | 29.2 | 29.2 |

**Table V. $^{13}C$ NMR Data of Macrocyclic Dilactams 4**

| carbon | | δ of dilactam 4 | | | | |
|---|---|---|---|---|---|---|
| | | *m* = 2, *n* = 4 | | *m* = 2, *n* = 6: trans–trans (major) | *m* = 2, *n* = 8 | |
| | | trans–trans (minor) | cis–trans (major) | | trans–trans (major) | cis–trans (minor) |
| N*C*O | | 174.4 | 174.4, 176.3 | 174.8 | 175.2 | |
| Ph*C*$H_2$N | $C_i$ | 138.0 | 137.8, 136.7 | 137.6 | | |
| | o | | 126.9, 128.3 | 126.4 | 126.4 | |
| | m | | 128.8, 129.0 | 128.9 | 129.0 | 127.7–129.0 |
| | p | 127.4 | 128.0, 127.6 | 127.5 | 127.5 | |
| Ph*C*$H_2$NCO | | 51.9 | 55.0, 48.4 | 50.7 | 49.5 | 53.5, 47.0 |
| N*C*$H_2C$$H_2$ | | 41.8 | 43.1, 43.5 | 40.3 | 39.8 | 45.2, 44.8 |
| *C*$H_2$CO | | 34.2 | 35.5, 27.6 | 31.5 | 32.5 | 32.5, 30.2 |
| *C*$H_2C$$H_2$CO | | 21.7 | 23.1, 24.7 | 22.5 | 24.0 | |
| *C*$H_2C$$H_2C$$H_2$CO | | | | 25.3 | 25.1 | 22.8–26.6 |
| *C*$H_2C$$H_2C$$H_2C$$H_2$CO | | | | | | 25.6 |

**Table VI. $^{13}C$ NMR Data of Macrocyclic Tetralactams 5 (R = $CH_2Ph$)**

| carbon | | δ of tetralactam 5 | | | | | |
|---|---|---|---|---|---|---|---|
| | | *m* = 2, *n* = 3 | | *m* = 2, *n* = 5 | | *m* = 2, *n* = 7 | |
| | | trans–trans (minor) | cis–trans (major) | trans–trans (major) | cis–trans (minor) | trans–trans (major) | cis–trans (minor) |
| NCO | | 174.1 | 172.3, 174.2 | 174.3 | 173.3, 173.9 | 174.5 | |
| Ph*C*$H_2$N | $C_i$ | 136.8 | 136.4, 137.6 | 137.1 | 136.8, 137.5 | 137.3 | |
| | o | 126.5 | 128.0, 126.3 | 126.3 | | 126.4 | |
| | m | 129.1 | 128.7, 129.0 | 128.9 | 127.9–129.1 | 129.0 | |
| | p | 127.5 | 128.0, 127.5 | 127.4 | | 127.5 | |
| Ph*C*$H_2$NCO | | 49.5 | 48.2, 52.2 | 49.9 | 48.4, 52.7 | 50.0 | 52.8, 48.0 |
| N*C*$H_2C$$H_2$N | | 40.1 | 44.6, 45.1 | 40.4 | 45.1, 45.6 | 40.5 | 45.4, 45.0 |
| *C*$H_2$CO | | 33.1 | 32.0, 32.9 | 33.5 | | 33.9 | |
| *C*$H_2C$$H_2$CO | | 20.9 | 21.7, 22.0 | 25.6 | | 26.0 | |
| *C*$H_2C$$H_2C$$H_2$CO | | | | 29.6 | | 29.9 | |
| *C*$H_2C$$H_2C$$H_2C$$H_2$CO | | | | | | 29.9 | |

are observed, although three species (syn-syn, anti-anti, syn-anti) are likely to exist in solution. The observation of only two sets of signals indicates that the configuration of the first amide moiety does not affect the chemical shifts around the second one.

Having established the spectral pattern for the model compounds, the carbon-13 NMR spectra of both the macrocyclic dilactams **4** and tetralactams **5** were determined. The NMR data are summarized in Tables V and VI.

Among the macrocyclic dilactams, dilactam **4** ($n$ = 6) (Table V) gave rise to the simplest spectrum with only 10 signals, indicating the presence of a symmetric conformation with both lactam groups assuming the trans configuration, as indicated by the ca. 51 ppm resonance of the benzylic carbon. The spectra of the dilactams **4** ($n$ = 4,

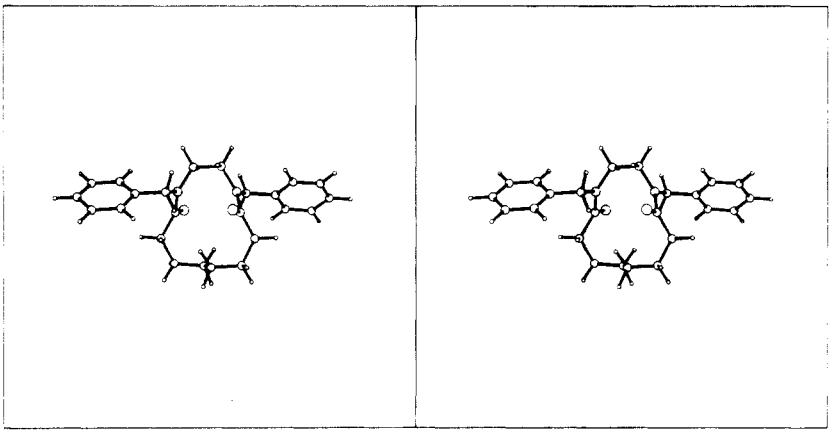

Figure 2.

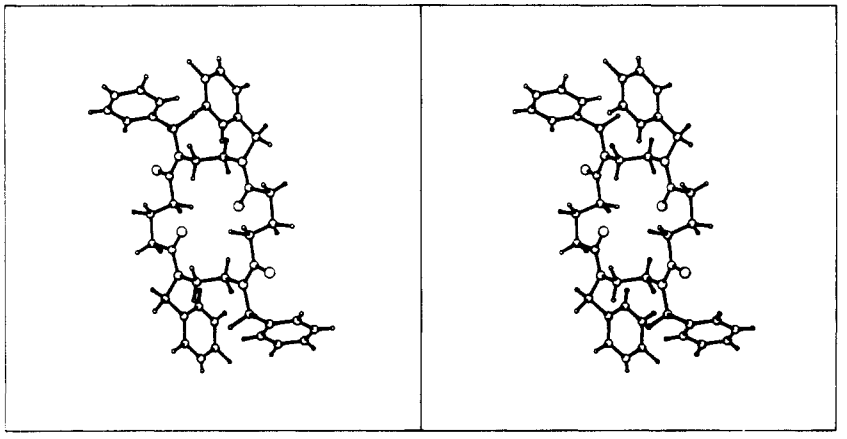

Figure 3.

8) were more complex, indicating the presence of more than one isomer. For dilactam 4 ($n$ = 4), signals similar to those observed for dilactam 4 ($n$ = 6) corresponding to the symmetric trans-trans configuration can still be seen. Yet, an additional set of signals belonging to a nonsymmetric conformation with one trans and one cis lactam bond can be recognized. The equilibrium constant between the two conformations is estimated to be 4.3 in favor of the nonsymmetric one. For the larger dilactam 4 ($n$ = 8), the symmetric conformation with two trans lactam bonds predominates ($K$ = 2.5). Yet, an additional set of signals corresponding to the nonsymmetric trans-cis configuration is also apparent.

For the tetralactams **5** three carbon-13 signals were observed for each carbon type, probably corresponding to the superposition of a highly symmetric ($D_2$) and a lower symmetry conformation. In the tetralactam **5** ($n$ = 3) (Table VI; Figure 1) the three sets of signals are of equal intensity in chloroform solution. Upon addition of methanol, however, one set of signals loses intensity while the other two remain equal, indicating the less symmetric conformer to become predominant. Relying on the chemical shift of the diagnostic benzyl carbon, the higher symmetry conformer is assigned to have all lactam bonds in a trans configuration, the second, lower symmetry conformer, to have two trans and two cis bonds. The sequence of these bonds, i.e. trans-trans-cis-cis or trans-cis-trans-cis, is difficult to deduce since the two ethylene moities do not affect each other (see data of the acyclic model compound). The presence of three methylene signals ($COCH_2CH_2CH_2CO$) of different intensities however suggests at least some conformational heterogeneity. The tetralactams **5** ($n$ = 5, 7) show similarly three sets of signals in chloroform solution, with the $D_2$ conformation with all trans lactam bonds dominating. For **5** ($n$ = 7) upon addition of methanol the equilibrium shifts in favor of the lower symmetry conformation with both trans and cis lactam bonds, as was the case for the tetralactam **5** with $n$ = 3.

The NMR data represented above indicate that in the larger rings highly symmetric conformations with all trans lactam bonds become favored, but not exclusively, while in the smaller rings lower symmetry conformations with both trans and cis lactam bonds may compete. In the dilactams, rings equal or larger than 12-membered show a preponderance of the trans-trans conformer.[28] In the tetralactams, rings equal or larger than 22-membered preferentially assume the conformation with all trans lactam bonds. Moreover, the all-trans conformation becomes less favored in polar solvents, as also has been observed in cyclic hexapeptides.[7]

Although NMR data allow us to distinguish conformers of different overall symmetry, they do not enable establishment of the orientation of the carbonyl groups relative to each other and relative to the ring plane. In order to establish this point, X-ray diffraction analyses were performed on two representatives: a dilactam 4 (R = $PhCH_2$; $m$ = 2; $n$ = 6) and a tetralactam **5** (R = $PhCH_2$; $m$ = 2; $n$ = 3). The stereoscopic views of each of the two compounds are given in Figures 2 and 3.

Figure 2 shows that in the dilactam 4 both lactam groups assume a transoid conformation with the carbonyl oxygens in an anti orientation, pointing above and below the mean

(28) One of the reviewers correctly pointed out that the predominant trans-trans conformation of dilactam 4 ($m$ = 2, $n$ = 6) is inconsistent with a continuous sequence from $n$ = 4 to $n$ = 6. This may be attributed to the nature of the 12-membered ring that can assume a cenformation with all rotamers anti or trans.

plane of the ring. Analogous conformations have earlier been suggested for certain macrocyclic dilactams.[29] Figure 3 shows that the tetralactam **5** contains two transoid and two cisoid lactam bonds that alternate around the ring. The carbonyl oxygens of the transoid lactams assume an anti orientation, pointing above and below the average plane of the ring. The carbonyl oxygens of the cisoid lactams are both in the mean plane of the ring and point toward its interior.

The structures found in the crystals are thereby identical with the preferred conformations observed in solution. Force field calculations on these two compounds confirmed that the conformations found in the crystal are the energetically favored ones.[30] It is also interesting to compare the conformation of the tetralactam **5** with that of the analogous tetralactone, which has recently been prepared.[5] While the lactone has all its functional groups in a transoid conformation, the lactam has both transoid and cisoid bonds. Yet, the conformations of both the tetralactam **5** and tetralactone possess an inversion center.

## Summary and Conclusion

We have introduced a novel method for the preparation of macrocyclic lactams that is based on the use of silicon as covalent template. The method is characterized by high product specificity, providing either macrocyclic dilactams or macrocyclic tetralactams as sole ring products. This high selectivity is attributed to noncovalent intramolecular interactions between silicon and carbonyl oxygen that stabilize specific conformations of the reaction intermediates and thereby determine the nature of the products.

The conformations of the macrocyclic di- and tetralactams have been examined both in solution and in the solid state. In solution most of these compounds show two major conformers: a highly symmetric conformer incorporating all trans lactam bonds and a lower symmetry one with both trans and cis lactam bonds. The former is preferred in the larger rings, and the latter, in the smaller ones. In the solid state these compounds assume the conformation that is the preferred one in solution and, on the basis of force field calculations, is the energetically favored one.

It is interesting to compare the macrocyclic tetralactams with a head-to-head arrangement and those with a head-to-tail arrangement, i.e., cyclic peptides. Extensive conformational studies on cyclic tetrapeptides[7,31] and depsipeptides[32,33] have shown that these compounds have two cis and two trans bonds that alternate around the ring. Yet, the carbonyl groups of the cisoid lactam bonds tend to be directed toward the exterior of the ring, in both peptides and depsipeptides. In the tetralactams described here the carbonyl groups of the cisoid bonds are directed toward the interior of the ring. This convergent arrangement of the cisoid lactam groups might be of particular relevance in the design of artificial ion carriers. Nocardamin,[34] a naturally occurring carrier for $Fe^{3+}$, is similarly characterized by a head-to-head arrangement of its lactam and hydroxamate groups. The hydroxamate groups that serve as bidentate binding sites assume a cisoid configuration and are directed toward the interior of the ring.[35] Should macrocyclic polylactams with a head-to-head arrangement be considered as artificial ionophores with bidentate binding sites? Experiments toward this direction are in progress as are forces field calculations to guide the selection of molecules to be synthesized.

## Experimental Section

**Preparation of Cyclic Diazasilolidines 1 and 2.** Melting points were determined and are uncorrected. IR spectra were obtained as KBr disks with a Perkin-Elmer Model 467.

The known cyclic diazasilolidine 1 (R = Et; $m$ = 2)[19] and the new cyclic diazasilolidines 1 (R = Bz; $m$ = 2) and 2 (R = Et; $m$ = 3) were prepared by reacting the parent diamines with bis(diethylamino)dimethylsilane in the presence of ammonium sulfate as described by Abel et al.[19] All compounds were distilled before use in high vacuum. They exhibited bp 145–147 °C (0.5 mmHg) for 1 (R = Bz; $m$ = 2) and bp 75–78 °C (0.3 mmHg) for 2 (R = Et; $m$ = 3).

**Preparation of Macrocyclic Dilactams 4 and Tetralactams 5.** Solutions of diazasilolidines 1 (0.0042 mol) and of diacyl dihalides **3** (0.0042 mol), in 20 mL of dry solvent each, were added simultaneously with a syringe pump at a speed of 0.15 mL/min to dry refluxing solvent (70 mL). After the addition had been completed, reflux was continued until IR analysis indicated consumption of all acyl halide by disappearance of the carbonyl absorption at 1800 $cm^{-1}$. Then, the mixture was concentrated in vacuo to half of its volume, washed with 5% aqueous $NaHCO_3$ and then with water, dried, and concentrated. Chromatography on silica gel (Woelm, 60–130) provided the macrocyclic dilactams **4** and tetralactams **5**, respectively. The yields of the products and their properties are summarized in Tables I–III and Tables VII and VIII (supplementary material). The reactions between diazasilolidine 1 (R = Bz, Et; $m$ = 2) and pimeloyl bis(2,4,5-trichlorophenyl) ester or glutaroyl bis($p$-nitrophenyl) ester were performed analoguously, to give the macrocyclic tetralactams in 30 and 15% yields, respectively.

**Isolation of Reaction Intermediates.** Solutions of diazasilolidines 1 (R = Et, $m$ = 2; R = Bz, $m$ = 2) (0.006 mol) in 25 mL of dry tetrahydrofuran were placed in a polyethylene bottle and treated at room temperature dropwise with solutions of diacyl dihalides **3** ($n$ = 3, 6) (0.003 mol) in 10 mL of dry tetrahydrofuran. Then, the mixtures were cooled in an ice bath, and 1 mL of 40% aqueous hydrogen fluoride was added. Stirring was continued for 30 min, and then the mixtures were washed with 5% aqueous $NaHCO_3$ and water, dried, and concentrated. Chromatography of the residues on an ion-exchange column (AG MP-50) and elution with methanol and with 0.5% NaOH in methanol provided the linear diamides **6** (R = Et, $n$ = 3; R = Bz, $n$ = 6) in 72.9 and 59.7% yields, respectively. The properties of these compounds are summarized in Table VIII (supplementary material).

**Structure Determination and Refinement.** The structures were solved by means of direct method using SHELX76. Refinement proceeded by anisotropic block-diagonal least-squares calculations. The H atoms were indicated in $\Delta F$ synthesis and introduced into refinement. The final $R$ values for 1577 (respectively 2918) observed reflections $F_0 > 3\sigma(F_0)$ were 0.073 (respectively 0.071).

**Crystal and Intensity Data for Dilactam 4 ($n$ = 6):** orthorombic, $a$ = 22.404 (3), $b$ = 8.744 (1), $c$ = 10.444 (1) Å; space group $Pbcn$, $Z$ = 4; 2430 reflections ($\theta \leq 70°$) measured on a NONIUS CAD4 single-crystal diffractometer using Ni-filtered Cu K$\alpha$ radiation.

**Crystal and Intensity Data of Tetralactam 5 ($n$ = 3):** monoclinic, $a$ = 18.867 (3), $b$ = 10.413 (2), $c$ = 9.740 (1) Å; $\beta$ = 104.24 (1)°; space group $P2_1/n$, $Z$ = 2; 3915 reflections ($\theta < 70°$) measured on a NONIUS CAD4 single crystal diffractometer using Ni-filtered Cu K$\alpha$ radiation.

**Acknowledgment.** We thank the US–Israel Binational Science Foundation for support.

**Registry No.** 1 ($m$ = 2, R = $CH_2CH_3$), 1005-84-1; 1 ($m$ = 2, R = $CH_2Ph$), 79265-18-2; 2 ($m$ = 3, R = $CH_2CH_3$), 36929-94-9; 3 ($n$ = 3), 2873-74-7; 3 ($n$ = 4), 111-50-2; 3 ($n$ = 5), 142-79-0; 3

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($n$ = 6), 10027-07-3; **3** ($n$ = 7), 123-98-8; **3** ($n$ = 8), 111-19-3; **4** ($m$ = 2, R = $CH_2Ph$, $n$ = 4), 99129-14-3; **4** ($m$ = 2, R = $CH_2Ph$, $n$ = 6), 99129-15-4; **4** ($m$ = 2, R = $CH_2Ph$, $n$ = 8), 99129-16-5; **5** ($m$ = 2, R = $CH_2CH_3$, $n$ = 3), 79265-23-9; **5** ($m$ = 2, R = $CH_2Ph$, $n$ = 3), 79265-20-6; **5** ($m$ = 2, R = $CH_2Ph$, $n$ = 5), 79265-21-7; **5** ($m$ = 2, R = $CH_2Ph$, $n$ = 7), 79265-22-8; **5** ($m$ = 3, R = $CH_2CH_3$, $n$ = 4), 99129-17-6; **5** ($m$ = 3, R = $CH_2CH_3$, $n$ = 6), 99129-18-7; **6** (R = Et, $n$ = 3), 99129-19-8; **6** (R = Bz, $n$ = 6), 99129-20-1; *N,N'*-diethylethylenediamine, 111-74-0; *N,N'*-dibenzylethylenediamine, 140-28-3; *N,N'*-diethyl-1,3-diaminopropane, 10061-68-4; bis(diethylamino)dimethylsilane, 4669-59-4; pimeloyl bis(2,4,5-trichlorophenyl) ester, 79265-19-3; glutaroyl bis(*p*-nitrophenyl) ester, 33109-59-0.

**Supplementary Material Available:** Analytical data and some physical properties of the compounds prepared (Tables VII and VIII (2 pages). Ordering information is given on any current masthead page.

# Template Synthesis, Structure, and Binding Properties of Macrocyclic *S,O*-Lactones

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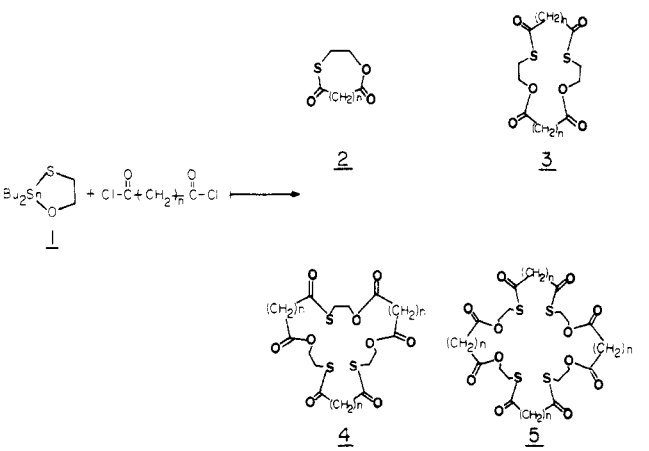
The synthesis, structures, and binding properties of mixed *S,O*-lactones, a new family of macrocyclic carbonyl compounds, are described. The synthesis involves the use of cyclic stannoxathiane (**1**) as a templated mercapto alcohol, which reacts with diacyl dihalides to provide monomeric **2**, dimeric **3**, trimeric **4**, and tetrameric **5** macrocyclic products in good overall yields and high stereospecificity. The dimeric derivatives **3** bind silver nitrate via their thiolactone groups when $n$ is even but do not bind when $n$ is odd. These regularities follow the conformational regularities of these compounds and demonstrate the relationship between conformation and binding. In addition, evidence is provided (crystal structures) that the conformation of the ligating molecule is preserved upon binding. The implications of these findings for the use of carbonyl groups in adjusting the conformation and binding properties of macrocyclic compounds are indicated.

Extensive studies on the crown ethers and related compounds have shown that their binding selectivities may be enhanced by imparting geometric constraints to these molecules. One approach involved the introduction of transannular bridges resulting in the tricyclic cryptands developed by Lehn.[1] Another approach relied on the incorporation of aromatic residues along the ring as exemplified in the spherands introduced by Cram.[2] Considering the abundance of carbonyl groups in naturally occuring ionophores such as the depsipeptides[3] and actins,[4] and the pronounced structural regularities of synthetic macrocyclic polylactones,[5] it occurred to us that carbonyl groups might similarly be used to reduce the conformational mobility. Reduced conformational mobility should then manifest itself by minimal conformational changes upon complexation. In order to examine the feasibility of this approach, we synthesized a new family of macrocyclic carbonyl compounds composed of thiolactone and lactone groups and screened their structures and binding properties. The thiolactone groups were selected to serve as binding sites for heavy metal ions by virtue of their donating sulfur atoms,[6-10] while the carbonyl groups of both lactones and thiolactones were anticipated to impart geometric constraint. In this publication we describe the synthesis of the novel macrocyclic *S,O*-lactones via the tin template method[5] and report on their metal binding properties. The pronounced binding selectivity of some of the compounds is suggested to derive from their defined conformation that is preserved upon binding.

## Results and Discussion

**Synthesis and Structure.** The preparation of macrocyclic polycarbonyl compounds represents a difficult synthetic problem since it requires direct condensation reactions to provide ring compounds in preference to

**Scheme I**



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