Novel Podands and Macrocycles with Diacetal (Tetraoxadecalin) Cores: Synthesis, Structure, Stereochemistry and Cation Inclusion

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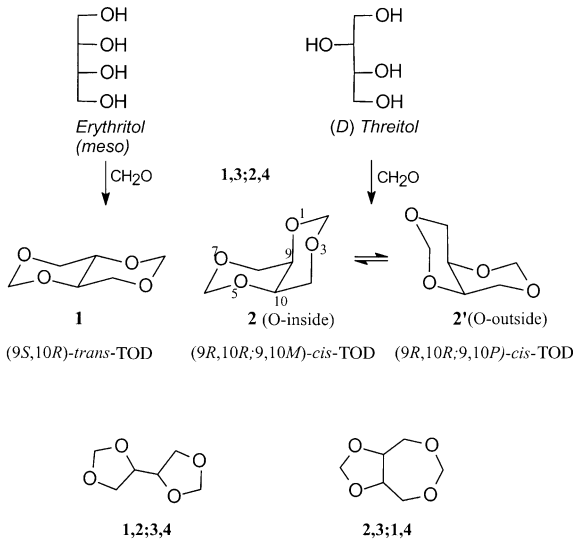
Abstract: A series of functionalized 2,6-dialkyl-*cis*-1,3,5,7-tetraoxadecalin podands (**3**–**10**, alkyl = hydroxy-, mesyloxy-, halo-, azido- and aminomethyl and -ethyl) were prepared, characterized, and used as precursors for a new and interesting class of macrocycles and cryptands (**12**–**21**), with the aim to use these as host–guest inclusion systems. Extensive spectroscopic work was performed, structural endorsement was obtained from X-ray diffraction analyses and further insight into the structures was obtained from theoretical/computational studies. A number of macrocycles in the series exhibited good complexation with alkaline-earth metal ions.

Keywords: cations · diacetals · diazacrowns · host–guest systems · macroheterocycles · tetraoxadecalins

Introduction

The 1,3,5,7-tetraoxadecalin (TOD) bicyclic system has long been known,[1] mainly from carbohydrate chemistry, and exists as diastereomeric chair–chair forms, as for example in *trans*- (**1**) and *cis*-TOD (**2**, **2′**) (Scheme 1). These diacetals are formed by the acid-catalyzed condensation of an aldehyde, in the simplest case formaldehyde, with either *threo*- or *erythro*-1,2,3,4-butanetetraol in a 1,3;2,4 mode. In fact, the above condensation is considerably more complex, in that it may also occur in a 1,2;3,4 mode (Scheme 1, bottom) to yield bi(4,4′-dioxolanyl), or in a 2,3;1,4 mode to form the tetraoxabicyclo[5,3,0]decane products, in any or all possible diastereomeric forms. Notably, *cis*-TOD can occur in two possible, interconvertible diastereomeric forms, namely O_{inside} (**2**) and $O_{outside}$ (**2′**). Moreover, when substituted aldehydes are used (Scheme 2), additional stereogenic centers are formed (in the acetal moiety), and the TOD products exhibit equatorial/axial isomerism as well (see *Stereochemistry and Conformational Analysis* section). We have recently dealt with these issues (isomerism, stereochemistry and relative stability) in some detail,[2] including a review of earlier related studies.[1] We also probed (computationally and experimentally) the structural and electronic characteristics of some of these isomeric systems.[3] The final conclusion drawn was that the six-membered isomers (TOD) in their



Scheme 1. The formation of the 1,3,5,7-tetraoxadecalin (TOD) diastereomers and the other possible bicyclic isomeric systems.

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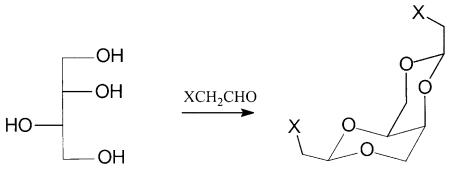


(*L*)-Threitol (2*R*,6*R*,9*S*,10*S*;9,10*P*)-2,6-bis(XCH_2)-*cis*-TOD

X	
Cl	3
Br	4
OH(R)	5
CH_2Br	6

a	b	c
R = Ms	Tos	Ac

Scheme 2. The 2,6-substituted *cis*-TOD podands (**3–6**) prepared from (*L*)-threitol.

O_{inside} form are indeed the thermodynamically preferred products, and the diequatorial isomers do (or can be made to) prevail.[2]

We aimed at preparing related macrocycles with diacetal cores, namely, *cis*-1,3,5,7-TOD in its O_{inside} form, in the hope that they would be capable of guest inclusion. The leading idea was to take advantage of the concave geometry of the *cis*-TOD system, with its built-in cavity bearing a high electron lone-pair concentration, to serve as a "core" in the synthesis of new host systems exhibiting ion and neutral (polar) molecule inclusion ability. Following our experimental and computational studies of the structural, stereochemical and conformational features of the basic TOD systems,[2,3] and an exploratory incursion in the realm of carbohydrate systems,[3e] we planned the synthesis and study of corresponding macrocyclic systems. We considered two approaches: 1) the condensation of terminal dialdehydes with threitol or 2) the reaction of *cis*-1,3,5,7-TOD podands, having judiciously functionalized substituents in 2 and 6 positions, and with spacers having terminal reactive groups for the preparation of the corresponding macrocycles, using mainly nucleophilic substitution reactions. The first approach resulted in disappointing yields, probably due to entropic effects, which we may later deal with using our recently developed transacetalation techniques.[4] Hence, we decided to take the second route. Some early results have been reported in preliminary form.[5] We describe now in detail the preparation of a series of key *cis*-TOD podands and, from this, our general approach to the preparation of novel *cis*-TOD macrocycles and accompanying oligomers.

Stereochemistry and conformational analysis: For the sake of clarity and consistency, we use the 1,3,5,7-tetraoxadecalin nomenclature, and not the carbohydrate designation, for example, **2** can be either 1,3:2,4-di-O-methylene-D-threitol or (cf. *Chem. Abs.*) (4aR)-(4ar,8ac)-tetrahydro[1,3]dioxino [5,4-d]-1,3-dioxin. In the same context, due to a peculiar omission of the CIP rules, one cannot assign configurations to the chiral (C_2) *cis*-decalin (and similar) systems, other than by 9,10-helicity specifications. Thus, the diastereoisomers **2** (O_{inside}) and **2′** ($O_{outside}$) are, in fact, (9*R*,10*R*;9,10-*M*)- and (9*R*,10*R*;9,10-*P*)-*cis*-1,3,5,7-tetraoxadecalin diastereoisomers, respectively.

The 1,3,5,7-TOD derivatives exist in the *trans* or *cis* configurations, depending on whether they originate from the reaction of an aldehyde with *erythro*- or *threo*-tetrahydroxy backbones. This stereospecificity has previously been discussed in the context of carbohydrates,[3e] where, in addition, one must pay attention to the relationship between the orientation of the terminal substituents in the starting tetraols and their orientation in the TOD products. Thus, if the two central carbons are (*R,S*), the acetalation product will be a *trans*-TOD (**1**), preserving the central *erythro* (S_2, *i*) symmetry in the TOD frame (Scheme 1); conversely, an (*R*,*R* or *S*,*S*) arrangement in the center of the (*threo*) tetraol, is compelled to yield a *cis*-TOD, preserving the C_2 symmetry in the TOD frame. In the latter configurational framework, the thermodynamically generally favored O_{inside} isomers are by now taken for granted,[2–5] with the understanding that an $O_{outside}$ isomer could be formed only if rendered thermodynamically more stable by judiciously effected substitution. Altogether, if the condensing aldehyde has a substituent such as CH_2–OR (or bulkier) on it, the latter will wind up on the 2,6-termini of the *cis*-TOD, most likely equatorially positioned. Finally, it should be stressed that all TOD diastereomers occur in double chair conformations (the twist-boat and half-chair forms being higher in energy) and that the two *cis*-TOD diastereomers are interconvertible (**2**⇄**2′**) either by conformational ring inversion (when possible), or by chemical isomerization (involving acetal opening and reclosure).

To illustrate the basics of this rather complex situation, we have depicted the formation of (9*R*,10*R*)-*cis*-TOD from D-threitol in Scheme 1. The reaction of L-threitol with substituted aldehydes, shown in Scheme 2, provides (9*S*,10*S*)-*cis*-TOD products with terminal equatorial substituents, that is, of (2*R*,6*R*) configuration.

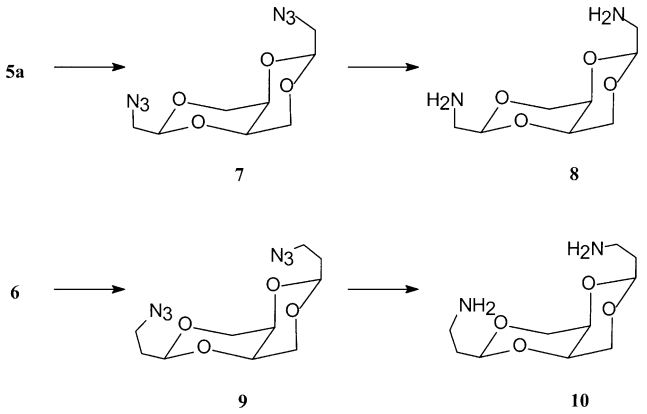
Results and Discussion

A series of 2,6-functionalized-dialkyl-*cis*-TOD compounds were prepared by the *para*-toluenesulfonic acid (PTSA)-catalyzed condensation of selected substituted aldehydes with (*rac.*), D- or L-threitol (Scheme 2), with the aim of using the terminal nucleophilic sites to assemble the macrocyclic structures. Thus, two sets of new compounds were synthesized and characterized, namely 2,6-bis(XCH_2)- and 2,6-bis(XCH_2CH_2)-*cis*-TOD podands. The previously investigated [2] bis(chloromethyl)-*cis*-TOD (**3**) and bis(bromomethyl)-*cis*-TOD (**4**) compounds, the important bis(hydroxymethyl)-*cis*-TOD (**5**) and its required derivatives (**5a**,**b**) belong to the first set. In the second (homologous) category, bis(2-bromoethyl)-*cis*-TOD (**6**) was prepared from threitol with 3-bromopropanal.

It should be noted that **5** is very hygroscopic and scarcely soluble in common solvents at room temperature, except in highly polar solvents such as H_2O, MeOH, and DMF. Thus, conversion to the corresponding dimesylate (**5a**) took

place best in DMF (at 0 °C), despite the known drawbacks of this solvent that is, high boiling point and difficulty of evaporation and, hence, of purification of the rather sensitive product. Interestingly, when the DMF solution was heated (150 °C), the main product was the bis(chloromethyl) derivative (**3**), most likely as a result of an S_Ni process.

The S_N2 reaction on the C–X centers of the 2,6-substituents in **3**, **4**, **5a** and **5b** was problematic and either failed or demanded drastic conditions. In spite of their good leaving-group character, all the above substituents showed intriguingly low reactivity towards common nucleophilic attack. However, some literature parallels to this sluggishness of leaving groups β to two oxygens could be found (if not yet well explained), for example, in the retardation of S_N2 rates in β-haloethylbromides.[6a] Thus, **3** was all but unreactive and the azidation of either **4** or **5a** (Scheme 3) had to be carried out in DMF (these reactions did not proceed in $CHCl_3$ or CH_3CN) and eventually led to the desired 2,6-bis(azidomethyl)-*cis*-TOD **7**.



Scheme 3. The preparation of 2,6-bis(aminomethyl)-*cis*-TOD (**8**) and 2,6-bis(2-aminoethyl)-*cis*-TOD (**10**).

In contrast to the above, a normal S_N2 azidation occurred on the homologous dibromide **6** (Scheme 3), readily providing the corresponding bis(2-azidoethyl)-*cis*-TOD **9**. Evidently, the nucleophilic substitution of the γ-positioned leaving group is normal in all respects.

The solubility of sodium azide also seems to play a significant role in these processes. The charge separation between Na^+ and N_3^- is greater in the aprotic solvent DMF, allowing N_3^- to acquire higher reactivity and to behave as a strong nucleophile.[6b]

Finally, reduction of the diazides **7** and **9** gave all but quantitatively the corresponding diamines, 2,6-bis(aminomethyl)-*cis*-TOD **8** and bis(2-aminoethyl)-*cis*-TOD (**10**).

Altogether, these transformations took place with good yields. The structures of the new podand systems were established by ^1H NMR, ^{13}C NMR, mass, IR spectra and elemental analyses. The NMR data are of particular interest and they are, therefore, presented collectively in Table 1 for appropriate comparative assessment. The chemical shifts and coupling constants in the TOD systems have certain general, structurally related, characteristic features. The most striking one is related to the 9,10 nuclei, $^1H_{9,10}$ and $^{13}C_{9,10}$, which resonate *at the highest field* in any and all of the measured NMR spectra. This is apparently due to the significant charge accumulation in the central, relatively short C9–C10 bond, which we had previously observed.[3a,b] We attributed this to the drain of electron density from the juxtaposed lone pairs on the relevant oxygen atoms into the O1–C9, C9–C10 and C10–O5 bond array. Furthermore, the 4/8-ax hydrogens usually turn up as a dd (geminal coupling and J(ax,eq) of 1.1–1.5 Hz) signal. The 4/8-eq protons however resonate as (geminal) doublets, apparently due to the slight flattening of the TOD system and increased H_{4eq}–H_{10eq} torsion angle, which reduces J(eq,eq) to almost zero. Furthermore, the 11,11′ protons in all the listed TOD compounds (**3–10**) are diastereotopic, but are nevertheless virtually isochronous, that is, little affected by the chirality of the

Table 1. ^1H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) data of 2,6-bis(XCH_2)-*cis*-TOD podands **3–10**.[a]

Item[b]	^1H in top row, ^{13}C in bottom row: positional assignments; δ in ppm (multipl., J in Hz)					
X	2.6	4.8 (eq)	4.8 (ax)	9.10	11.11′	Other
3	4.80 (t, 5.1)	4.23 (d, 12.5)	3.94 (dd 12.5;1.3)	3.70 (m)	3.60 (br d, 5.1)	
Cl	100.11		69.40	69.41	43.81	
4	4.83 (t, 5.0)	4.23 (d, 12.6)	3.93 (dd 12.6;1.2)	3.67 (m)	3.44 (bd, 5.0)	
Br	100.12		69.51	69.50	30.92	
5	4.76 (t, 4.7)	4.23 (d, 12.6)	3.93 (dd, 12.6;1.4)	3.71 (br s)	3.73 (bd, 4.7)	
OH	100.1		69.3 (dd)	69.6 (d)	63.7	
5a	4.90 (t, 4.0)	4.25 (d, 12.9)	3.95 (dd, 12.9;1.5)	3.71 (br s)	4.29 (dd, 4.2;1.2)	
OMs	99.11		69.07	69.07	50.04	
5b	4.86 (t, 4.7)	4.20 (d, 12.7)	3.91 (dd, 12.7;1.4)	3.68 (br s)	4.22 (bd, 4.7)	CH_3CO: 2.11, 170.7, 20.8
OAc	98.1		69.27	69.41	64.8	
7	4.71 (t, 4.7)	4.10 (d, 12.6)	3.89 (dd 12.6;1.25)	3.62 (br s)	3.33 (dd, 4.8;4.6)	
N_3	99.35		69.27	69.27	52.73	
8	4.60 (t, 4.6)	4.22 (d, 12.8)	3.94 (d, 12.8)	3.64 (br s)	2.92 (d, 4.6)	
NH_2	101.69		69.41	69.55	45.36	
6	4.83 (t, 5.4)	4.17 (d, 12.6)	3.90 (dd, 12.6;1.1)	3.65 (br s)	2.27 (dt, 6.4;5.4)	3.50 (t 6.4)
CH_2Br	99.5		69.7	69.6	28.0	37.3
9	4.76 (t, 5.4)	4.17 (d, 12.6)	3.88 (dd, 12.6,1.1)	3.63 (br s)	2.0 (dt, 6.6;5.4)	3.45 (t 6.6)
CH_2N_3	98.9		69.6	69.5	34.0	46.6
10	4.75 (t, 5.0)	4.14 (d, 12.3)	3.48 (dd, 12.3;1.4)	3.58 (br s)	1.87 (dt, 6.6;5.0)	2.87 (t 6.6)
CH_2-NH_2	100.4		69.5	69.4	37.3	38.0

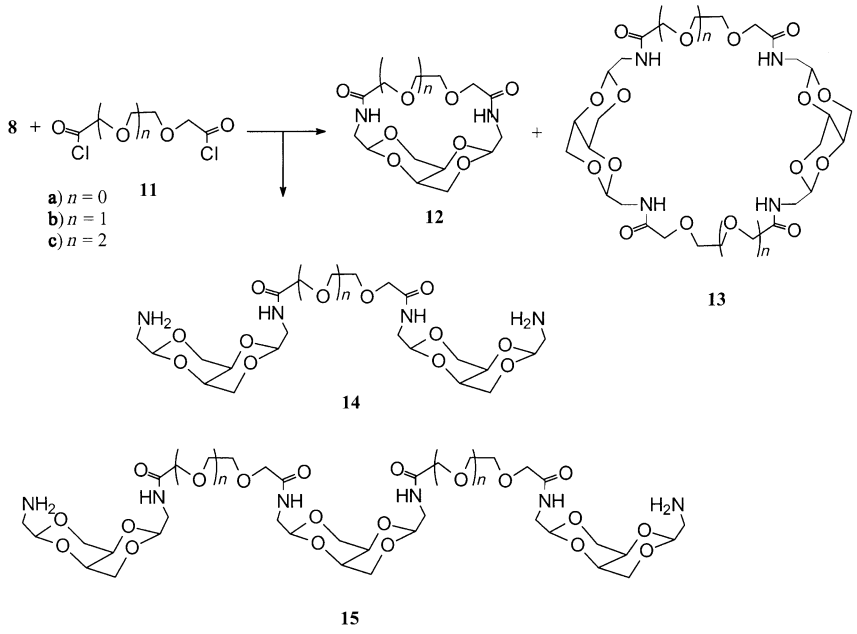
[a] See Scheme 2 and Scheme 3; [b] Compound number and the X-functional group.

system. The 12,12′ protons in **6**, **9** and **10** (triplets instead of ddd patterns) exhibit similar behavior.

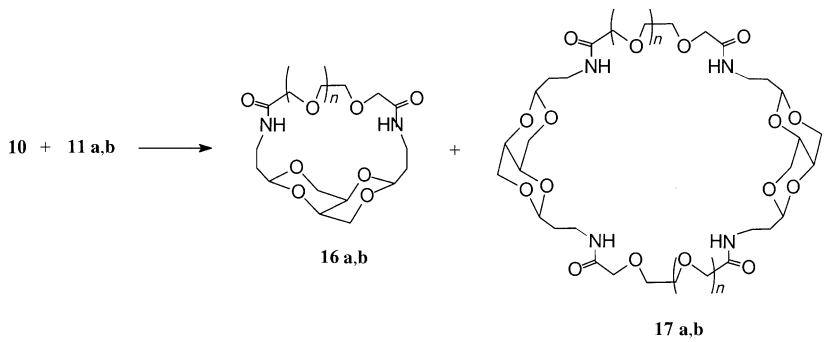
The next task consisted of using the above functionalized podands for the preparation of the desired macrocyclic systems. The most reasonable and general course to follow, after having ruled out nucleophilic substitution on β-acetalic centers, was the inverse one: namely, to have nucleophilic groups on the 2,6-TOD substituents attack the termini of any judiciously chosen spacer or bridging group, for example, of the (poly)glycolic acid dichloride type (**11**).[9–11] Thus, the reaction of 2,6-bis(aminomethyl)-*cis*-TOD (**8**) with di-, tri- and tetra-glycolic acid dichlorides (**11a–c**)[9] in DMF in presence of Na_2CO_3 afforded the macrocyclic dilactams (**12a–c**) in yields of 18–41% (Scheme 4). In a similar way, the reaction of 2,6-bis(aminoethyl)-*cis*-TOD (**10**) with **11a,b** in DMF, provided the corresponding macrocyclic dilactams **16a,b** (18–26%, Scheme 5).

Small (2–15%) amounts of macrocyclic tetralactams **13a,b** (in Scheme 4) and **17a,b** (in Scheme 5), resulting from [2+2] condensation modes, were isolated and identified by FAB-MS analyses. At the same time, approximately 2% of open chain oligomeric products **14** and **15**, as well as unidentifiable polymers, were isolated in the first instance (Scheme 4). Minute amounts of analogous oligomers and an appreciable quantity of polymers were observed in the homologous series.

Interestingly and disappointingly, no template effect was observed in the presence of various M_2CO_3 bases (M = Li, Na, K, Cs). In fact, the coexisting species formed in each of the processes depicted in Schemes 4 and 5 may be considered a dynamic combinatorial library (DCL),[7,8] and any of the products represents only one of these options (or a subset of the above DCL). To be sure, the framework can be more complex, namely, a dynamic combinatorial virtual library (DCVL), with additional [3+3], [4+4], etc., theoretically possible macrocyclic products. This would be comparable to our recent realizations of such complex DCVLs, involving similar systems, as for example, analogous macrocyclic thiacrown systems[5c] or related but tautomeric O–C–N systems.[8a] Further work is, however, under way to produce bias and template-induced forms.[8b]

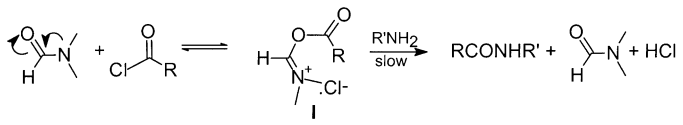


Scheme 4. The formation of the dilactams (**12a–c**) (**a**: $n=0$; **b**: $n=1$; **c**: $n=2$) and tetralactams (**13a–c**) (and accompanying open oligomers) from 2,6-diaminomethyl-*cis*-TOD (**8**) with di-, tri-, or tetraglycolic acid dichloride (**11a–c**), respectively.



Scheme 5. The formation of the dilactams (**16a,b**) (a: n = 0; b: n = 1) and tetralactams (**17a,b**) in the reaction of 2,6-diaminoethyl-*cis*-TOD (**10**) with di- or triglycolic acid dichloride (**11a,b**), respectively.

Notably and contrary to the earlier described favorable behavior of DMF, the reactions towards macrocyclic dilactams in DMF gave lower than expected yields, and no temperature effect was observed over the range 80–152 °C. We attribute this to a "spurious" reaction between DMF and the carboxylic acid dichlorides.[14,15] The amide molecule is an ambident base and the greater basic strength of the oxygen center has been demonstrated by protonation data of various amides.[15–17] Hence, the amide oxygen (hard) nucleophile is capable of interacting with the (hard) electrophilic center at the carbonyl group of the acylating reagent to form a reactive acylonium chloride intermediate (**I**) (Scheme 6). It is therefore suggested that in the above reactions carried out in DMF, the latter's interaction with di-, tri- and tetraglycolic acid dichlorides produced the corresponding acylonium salts (cf. Scheme 6′ in the Supporting Information). The salts, on interaction with the diamino podands, apparently provide pre-

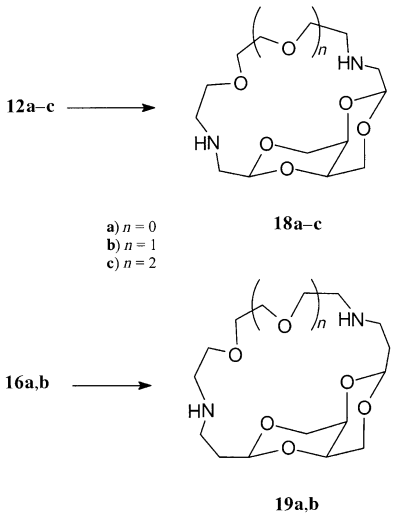


Scheme 6. The intermediacy of the acylonium ion (**I**) in the reaction of DMF with acyl chlorides (see also Supporting Information).

dominantly oligomeric and polymeric products that are difficult to isolate and characterize.

Indeed, when some of these reactions were carried out in acetonitrile, a remarkable enhancement of efficiency and ratio of products were observed. For example, the macrocyclic dilactams **12a,b** and **16a,b** were isolated in yields of 55–80%, apparently by having avoided the spurious reaction of the solvent with the acylchlorides in the process of macrocyclization.

Reduction of dilactams (**12a–c**) with $BH_3{\cdot}SMe_2$[12,13] yielded the corresponding 2′,8′-diaza-5′-oxanonalylidene-*cis*-1,3,5,7-TOD (**18a**), (2′,11′-diaza-5′,8′-dioxadodecanylidene)-*cis*-1,3,5,7-TOD (**18b**) and 2′,14′-diaza-5′,8′,11′-trioxapentadecanylidene)-*cis*-1,3,5,7-TOD (**18c**) in 75, 86, and 64% yields, respectively (Scheme 7). In the homologous series,



Scheme 7. The diazacrowns **18a–c** and **19a,b** obtained by $BH_3{\cdot}SMe_2$ reduction of the respective dilactams (**12a–c** and **16a,b**).

16a,b were similarly reduced to TOD-diazacrowns **19a,b** in 57 and 65% yields, respectively. As with the podands above, the NMR data of the macrocylic compounds are presented collectively in Table 2 and, on comparative assessment, are consistent with those shown in Table 1 and discussed above.

The structural assignments were confirmed by X-ray diffraction analysis of single crystals of the dilactams **12a** and **16a** and the diazacrown **18a**. Dilactams **12a** and **15a** were optically pure L-forms and their X-ray structures are shown in Figure 1 and Figure 2, supplemented by selected structural parameters in Table 3. Both occur in open conformations of these cyclic dilactams, which are stabilized by intramolecular N–H···O contacts (involving the NH groups which turn

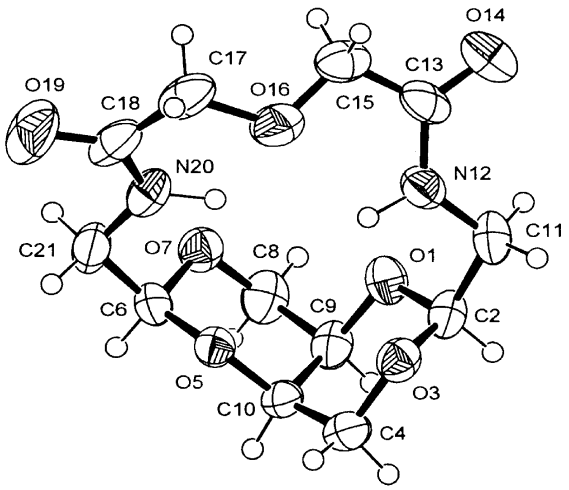


Figure 1. ORTEP drawing of dilactam **12a** with 50% probability thermal ellipsoids.

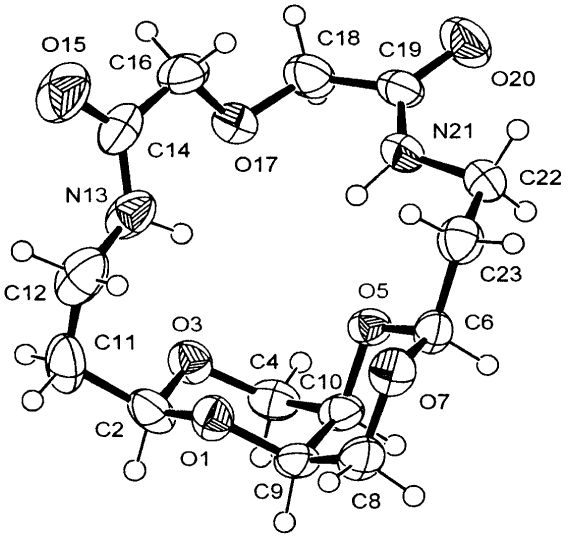


Figure 2. ORTEP drawing of dilactam **16a** with 50% probability thermal ellipsoids.

inward), as well as by intermolecular C=O···H–C contacts (involving the C=O groups which turn outward). The open conformation of macrocyclic dilactam **12a** is stabilized by six hydrogen bonds, whereas that of **16a** by four hydrogen bonds. Bearing the distances between hydrogen bonds in mind, the deviation of the molecule from C_2 symmetry becomes evident. Notably, the hydrogen bonds between the NH groups and the TOD oxygen atoms induce certain changes in the structural parameters characterizing the TOD molecule. These become evident when comparing the C4–C10, C8–C9, and C9–C10 bond lengths in compounds **12a** and **16a**, which are shorter (resulting in slight ring flattening) relative to those observed[3a] in *cis*-TOD itself (Table 3).

In the case of the racemic diazacrown **18a**, the crystal was not good enough to permit final refinement to reliable geometrical parameters beyond its structural proof (Figure 3). The latter, however, is valuable in so far that it

Table 2. ^{1}H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) data of 2,6-bis(XCH_2)-*cis*-TOD macrocycles **12**, **16**, **18** and **19**.[a]

Item[b] X	^{1}H in top row, ^{13}C in bottom row: positional assignments; δ in ppm (multipl., J in Hz) 2.6	4.8 (eq)	4.8 (ax)	9.10	11.11′	Other
12a $NHCOCH_2$-(O)-dilactam	4.98 (brs)	4.19 (d, 13.05)	3.90 (d, 13.05)	3.69 (brs)	3.50 (ddd, 15.58, 3.68, 1.75), 3.64 (ddd, 15.58; 5.82; 0.86)	4.12 (s, $H_{14,14'}$); 7.15 (NH);
	96.24		67.70	68.52	42.69	70.4 ($C_{14,14}$); 168.8 $(CO)_2$
12b $NHCOCH_2O$-CH_2-dilactam	4.82 (t, 1.92)	4.21 (d, 12.8)	3.96 (dd,12.8, 1.62)	3.72 (d, 1.62)	3.44 (ddd, 14.3, 3.5, 1.9), 3.84 (ddd 14.3, 6.65, 2.12)	4.04 (s,$H_{14,14'}$), 3.66 (brs, $H_{16,16'}$), 7.05 (NH);
	97.64		68.55	68.68	41.13 ($C_{11,11'}$), 69.13 ($C_{14,14'}$ and $C_{16,16'}$), 169.66 $(CO)_2$	
12c $NHCOCH_2OCH_2$-CH_2-(O)-dilactam	4.91 (t, 3.76)	4.13 (d, 12.0)	3.89 (d, 12.0)	3.43–3.84 (m, $H_{9,10,\ 11,11',\ 16,16',17,17'}$);4.04 (s, $H_{14,14'}$); 7.62 (brs,NH);		
	96.35		68.31	68.64	42.23 ($C_{11,11'}$), 71.07 ($C_{14,14'}$), 70.68 ($C_{16,16'}$), 70.37 ($C_{17,17'}$), 170.57 (CO)	
16a $CH_2NHCOCH_2$-(O)-dilactam	4.89 (t, 3.73)	4.17 (bd, 12.59)	3.89 (dd, 12.59; 1.29)	3.65 (brs)	1.87–1.99 (m, $H_{11,11'}$); 3.71 (dddd, 13.76; 6.94; 6.78; 3.05, $H_{12,12'}$); 3.49 (dddd, J=13.76; 7.02; 6.97; 3.16, $H_{12,12'}$), 4.08 (d, 15.19, $H_{15,15'}$)	
	100.35		69.54	69.62	32.84 ($C_{11,11'}$); 33.29 ($C_{12,12'}$); 70.82 ($C_{15,15'}$); 168.36 $(CO)_2$	
16b $CH_2NHCOCH_2$-OCH_2-dilactam	4.87 (t, 3.8)	4.13 (bd, 12.5)	3.88 (d, 12.5)	3.62 (brs)	1.93 (m, $H_{11,11'}$); 3.55 (dd, 10.5, 5.5, $H_{12,12'}$); 3.98 (d, 15.0, $H_{15,15'}$); 3.63 (d, 9.0, $H_{17',17}$); 3.76 (d, 9.0, $H_{17,17'}$); 7.57 (brs, NH)	
	100.87		67.46	66.91	33.39 ($C_{11,11'}$); 33.76 ($C_{12,12'}$); 68.43 ($C_{15,15?}$);68.10 ($C_{17,17'}$);168.90 $(CO)_2$	
18a $NHCH_2CH_2$-(O)-crown	4.84 (brs)	4.22 (d, 12.5)	3.89 (d, 12.5)	3.71 (brs)	3.03 (d, 1.6, $H_{11,11'}$); 3.09 (ddd, 11.4, 5.6, 5.6, $H_{13,13'}$); 3.31–3.2 (ddd, 11.4, 5.6, 5.6, $H_{14,14'}$)	
	98.82		68.59	68.80	50.47 ($C_{11,11'}$), 51.87 ($C_{13,13'}$), 69.18 ($C_{14,14'}$)	
18b $NHCH_2CH_2O$-CH_2-	4.79 (t, 3.0)	4.22 (d, 12.0)	3.80 (d, 12.0)	3.58 (brs)	2.92 (dd, 12.6, 1.6,$H_{11,11'}$); 3.00–3.13 (ddd, 12.3, 6.4, 4.2, $H_{13,13'}$); 3.65–3.72 (m, $H_{14,14',16,16'}$)	
	99.03		68.91	68.74	49.55 ($C_{11,11'}$), 52.30 ($C_{13,13'}$), 69.77 ($C_{14,14'}$), 68.99 ($C_{16,16'}$)	
18c $NHCH_2CH_2O$-CH_2CH_2-(O)-	4.71 (t, 3.65)	4.13 (d, 12.4)	3.67 (d, 12.4)	3.61 (brs, $H_{9,10}$), 2.87 (brs, $H_{11,11'}$); 2.85 (ddd, 12.9 6.1, 4.8, $H_{13,13'}$), 2.94 (ddd, 12.9, 6.1, 4.8 $H_{14,14'}$), 3.63 (m, $H_{16,16',17,17'}$)		
	99.80		69.19	69.13 ($C_{9,10}$), 48.70 ($C_{11,11'}$), 51.56 ($C_{13,13'}$), 69.99 ($C_{14,14'}$), 70.16 ($C_{16,16'}$), 70.59 ($C_{17,17'}$)		
19a CH_2NHCH_2-CH_2-(O)-	4.81 (t, 3.18)	4.13 (d, 12.6)	3.87 (d, 12.6)	3.58 (brs)	1.99 (dd, 4$H_{11,11'}$), 2.92 (t, 5.7 4H $_{12,12'}$), 3.6–3.7 (m, 8$H_{14,14',15,15'}$),	
	100.93		69.72	69.72	33.70 ($C_{11,11'}$), 49.77 ($C_{12,12'}$), 43.41 ($C_{14,14'}$), 69.7 ($C_{15,15'}$)	
19b CH_2NHCH_2-CH_2OCH_2-	4.79 (t, 4.15)	4.08 (d, 12.2)	3.82 (d, 12.2)	3.54 (brs)	1.90 (dd, 10.3, 5.8, 4$H_{11,11'}$), 2.81 (t, 5.8, 4$H_{12,12'}$), 2.78 (t, 5.2, 4H $_{14,14'}$), 3.56–3.7 (m, 8$H_{15,15',17,17'}$)	
	100.6		69.40	69.19	33.08 ($C_{11,11'}$), 48.76 ($C_{12,12'}$), 43.95 ($C_{14,14'}$), 70.02 ($C_{15,15'}$), 69.53 ($C_{17,17'}$)	

[a] See Scheme 2, Scheme 4, and Scheme 5. [b] Compound number and the X-functional group.

provides significant insight in its structure and behavior (see below).

An alternative, direct approach to the diazacrown **18c** has also been tried,[5] by reacting the diamine **8** with tetraethyleneglycol dimesylate (**20c**) in CH_3CN (Scheme 8). The diazacrown **18c** was indeed isolated, albeit in lower yields and with harder purification efforts.

We were interested at this point in securing TOD-cryptands by extending the bridging process to a double bridging one, that is, by a subsequent reaction of TOD-diazacrowns

Table 3. Selected X-ray structural parameters of TOD-dilactams **12a** and **16a** (see Figures 1 and 2) compared to those of *cis*-TOD[3a] (**2**).

	12a	**16a**	**2**
bond length [Å]			
O1–C2	1.412(5)	1.409(4)	1.411
O1–C9	1.433(4)	1.433(3)	1.436
C2–O3	1.418(5)	1.420(3)	1.413
O3–C4	1.436(5)	1.427(3)	1.434
C4–C10	1.504(6)	1.496(4)	1.510
C6–O7	1.410(5)	1.415(3)	1.413
O7–C8	1.422(5)	1.418(4)	1.434
C8–C9	1.507(6)	1.514(5)	1.510
C9–C10	1.508(6)	1.516(3)	1.529
torsion angles [°]			
C2-O1-C9-C10	54.3(4)	56.0(3)	55.8
C2-O1-C9-C8	174.1(3)	175.6(2)	176.4
C9-O1-C2-O3	−59.2(4)	−60.1(3)	−63.3
O1-C2-O3-C4	59.8(4)	58.9(3)	63.0
C2-O3-C4-C10	−56.9(4)	−54.7(3)	−56.5
O3-C4-C10-O5	−67.6(4)	−67.8(3)	−69.8
O3-C4-C10-C9	51.9(4)	51.3(3)	50.8
C6-O5-C10-C4	173.7(3)	179.4(2)	176.4
C6-O5-C10-C9	53.9(4)	59.0(3)	55.8
C10-O5-C6-O7	−58.2(4)	−62.7(2)	−63.3
O5-C6-O7-C8	59.5(4)	59.2(3)	63.0
C6-O7-C8-C9	−56.9(4)	−54.1(3)	−56.5
O7-C8-C9-O1	−67.3(4)	−68.8(3)	−69.8
O7-C8-C9-C10	52.3(4)	50.7(3)	50.8
O1-C9-C10-O5	67.3(4)	67.0(3)	69.6
O1-C9-C10-C4	−49.9(4)	−51.5(3)	−50.0
C8-C9-C10-O5	−50.4(4)	−52.1(3)	−50.0
C8-C9-C10-C4	−167.6(3)	−170.6(2)	−169.7

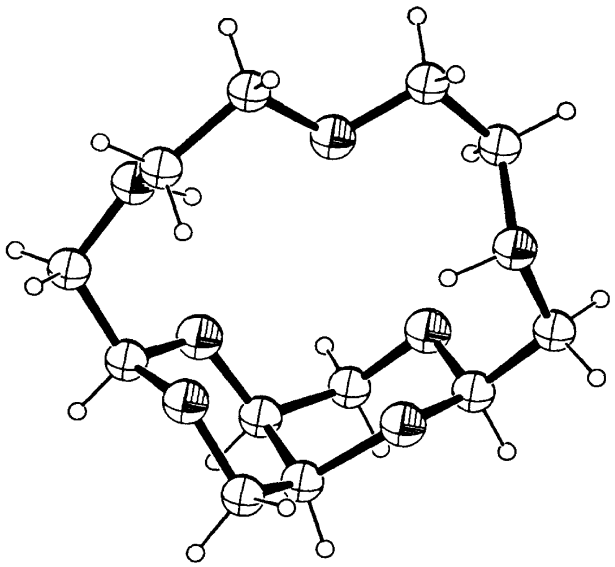
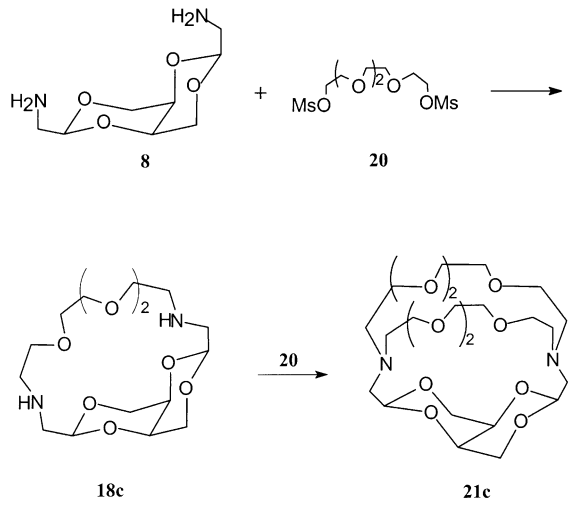


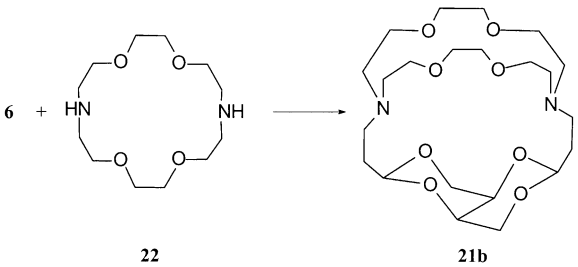
Figure 3. ORTEP drawing of diazacrown **18a**.

18a–c with either the polyglycolic acid dichlorides (**11**) (Scheme 4) or the mentioned polyethyleneglycol dimesylates (**20**) (Scheme 8). All attempts to realize this objective in the first case failed, while with the second method, the reaction of the diazacrown **18c** with **20c** provided the TOD-cryptand **21c** in rather poor yield (1.7%) (Scheme 8, bottom).



Scheme 8. An alternative route to the diazacrowns **18c** and to the crypt- and **21c**.

However, the lower member in the homologous series, the TOD-cryptand **21b**, was secured in 40% yield from the reaction of 2,6-bis(2-bromoethyl)-*cis*-TOD (**6**) with 1,4-diaza-6-crown-12 (**22**) (Scheme 9). FAB-MS revealed that it occurred as a TOD-cryptand–Na complex that undergoes decomplexation under weakly acidic conditions.



Scheme 9. The preparation of the cryptand **21b**.

The TOD-diazacrowns (**18**) were subjected to molecular mechanics and modeling calculations, in order to gain insight into their conformational behavior in a regime with energy control. We used Insight II[18], the SEARCH/COMPARE module for conformational search, and the energy minimization protocol implemented in the DISCOVER module for molecular dynamics. We also tried to understand the resistance of TOD-diazacrowns to the formation of an additional bridge. Compounds **18b** and **11b** were analyzed in this way, to find whether the range of the possible distances between the two electrophilic reaction sites of **11b** overlapped with those between the corresponding two nucleophilic sites of **18b**, so that after the first amidation reaction, a second reaction could take place, that is, lactam formation on the second site.

The conformational search for **18b** was done in two consecutive runs of MD: 800 ps at 300 K and 800 ps at 400 K. At every 10 ps a dynamic structure was sampled and minimized, thus giving 80 conformers in each run. At the same

time, the orientation of the lone pairs on the nitrogen atoms in the diazacrown ether **18b** was analyzed. It turned out that in all the lowest conformations of **18b**, the lone pairs on nitrogens were directed outward from the cavity, similar to that observed in the X-ray structure of **18a** (Figure 3). This apparently prevents the ready formation of the second bridge toward cryptand within the existing conformational array in addition to the steric and conformational restrictions in the **11** counterpart. Molecular dynamic calculations were also performed on the higher diazacrown **18c**, and the lowest symmetric form was molecular-mechanically optimized with either AMBER and MM3-GE (the latter is the MM3 force field,[20] which was parameterized for the *anomeric effect* in O–C–O systems. We have reparameterized[3b,20c] this for the *gauche effect* in O–C–C–O containing systems; evidently, all our systems contain both these types (O–C–O and O–C–C–O) of dioxa units.[3–5]).

These calculations provided a similar picture (Figure 4), with the MM3-GE treatment giving a somewhat better match of the TOD structural parameters with the X-ray

Figure 4. Stick model drawing of the diazacrown **18c** after AMBER optimization. TOD bond lengths after AMBER (MM3-GE) optimization: O1–C2 1.432 (1.422), C2–O3 1.434 (1.417), O3–C4 1.432 (1.434), C4–C10 1.525 (1.518), C9–C10 1.522 (1.519) (see also Supporting Information).

data. Both provided a structure with outward directed nitrogen lone pairs, analogous to the related X-ray structures (see above). This consistent feature is apparently due to the stabilization achieved in this open conformation by internal N–H···O hydrogen bonding. This provides little hope for the ability of some of these bridged *cis*-TOD system to complex ions. Nevertheless, several TOD-diazacrowns exhibited allosteric behavior, showed good complexation behavior with alkaline and earth-alkaline metal ions and excellent complexation with heavy metals. The macrocycle **19b** showed poor complexation behavior with both alkali and alkaline-earth metal ions.

The complexation behavior of TOD-diazacrowns **18a–c** and **19b** with alkali and alkaline-earth metal ions was studied, by using the well established NMR titration technique.[21,22] The latter is advantageous, since it requires only a small amount of sample, provides structural information and is less time consuming than other methods. However, it only provides accurate results for low complexation constant values of up to log $K \approx 4$. Indeed, the higher values of complexation constants with heavy metals have to be measured by electrochemical techniques and will be reported in due course.

None of the TOD-macrocyclic dilactams were found capable to complex alkali and alkaline-earth metal ions. TOD-diazacrown **18a** didn't complex alkaline metals, while TOD-diazacrowns **18b** and **18c** formed weak complexes (log $K \approx$ 2) with alkaline ions except K^+; but all three showed improved complexation with alkaline-earth metal ions. Table 4

Table 4. Complexation of TOD-diazacrowns **18a–c** and diazacrowns **22**,**23** with earth-alkaline metals.

Ligand	Ca^{2+} (0.99 Å)	Sr^{2+} (1.12 Å)	Ba^{2+} (1.34 Å)
18a	3.84 (ML)	3.24 (ML)	3.87 (ML)
18b	3.28 (ML)	4.24 (ML)	3.41 (ML)
18c	2.38 (ML)	3.39 (ML)	3.17 (ML)
22	3.87 (ML)	5.99 (ML_2)	6.12 (ML)
23	2.50 (ML)	3.50 (ML)	5.10 (ML)

shows the log K values of complexation of TOD-dizacrowns **18a–c** with alkaline-earth metal ions in MeOD:D_2O (4:1), in comparison with the known (determined by titration calorimetry[23]) 1,4-diaza-6-crown-12 (**22**) and 1,4-diaza-7-crown-14 (**23**). These compounds contain the same formal number of donor atoms as the TOD-diazacrowns **18b** and **18c**, respectively. A complete picture of the above complexation behavior is displayed in Figure 5.

Conclusion

We have prepared and studied a certain series of functionalized 2,6-dialkyl-*cis*-1,3,5,7-tetraoxadecalin podands (alkyl = hydroxy-, mesyloxy-, halo-, azido-, and aminomethyl and -ethyl) (**3**–**10**). These compounds were then used as precursors for a new class of oligomers, macrocycles and cryptands (**12**–**21**), which were to be applied as host–guest inclusion systems. NMR spectroscopic studies were performed and structural endorsement was obtained from X-ray diffraction analyses. Further insight was obtained from theoretical/computational studies. The diazacrowns **18a–c** were shown to complex alkaline-earth metal ions fairly well. These podands and macrocycles are projected to act as chiral ligands for heavy-metal–ion inclusion compounds and stereoselective catalysis.

Experimental Section

All reactions were carried out in purified dry solvents under Ar and monitored by TLC and/or by ^1H NMR spectroscopy. Column chromatography was performed on Merck silica gel (60, 0.040–0.063 mm). Melting points were determined on a Büchi capillary melting point apparatus and are not corrected. Elemental analyses (Microanalytical Laboratory, Hebrew University, Jerusalem) and/or high-resolution mass spectrometric analysis have been obtained for all new compounds. Mass spectra (EI-MS, CI-MS and FAB) and HRMS were recorded on a VG Autospec 250

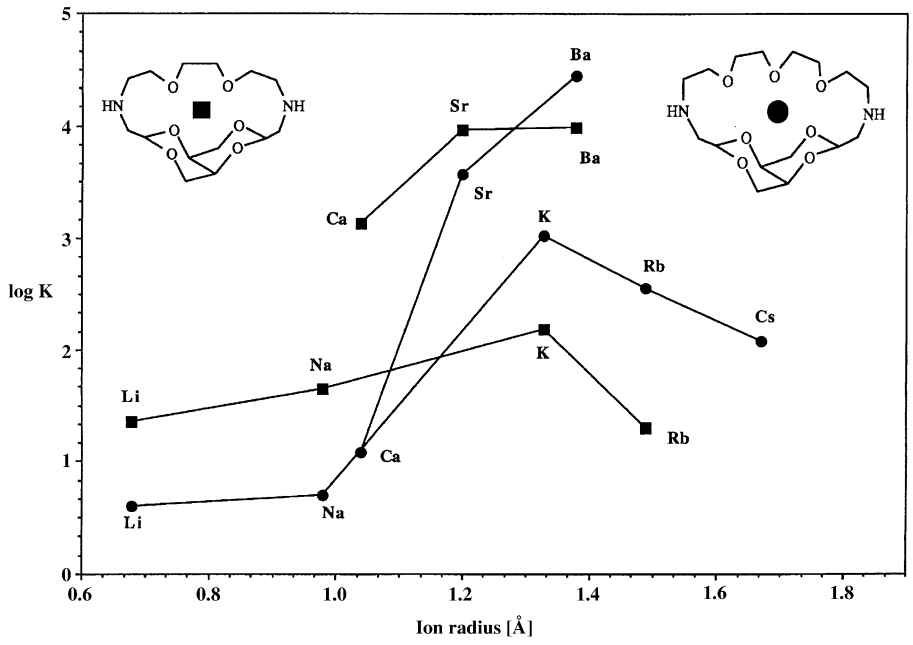


Figure 5. Stability constants of the complexes of the diazacrowns **18b** (squares) and **18c** (discs) with alkali and alkaline-earth metal ions versus their ionic radii.

mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded routinely on an AC-200 (supplemented when necessary by AM-360 or ARX-500) Bruker spectrometer in $CDCl_3$ with reference to TMS. IR spectra were recorded with a Nicolet 205 FTIR instrument in KBr pellets. Di-, tri-, and tetraglycolic acids dichlorides have been synthesized according to a known literature procedure.[9] Some of the products (in the X-methyl series) are stereochemically related to (L)-threitol (see Scheme 2), but others (in the X-ethyl series) are racemic; this is specified in the experimental procedures but is presented in the other scheme as belonging to the (D) series.

2,6-Bis(chloromethyl)-*cis*-1,3,5,7-tetraoxadecalin (3) and 2,6-bis(bromomethyl)-*cis*-1,3,5,7-tetraoxadecalin (4): These compounds were obtained as described earlier,[2] unless mentioned otherwise.

(2*R*,6*R*,9*S*,10*S*)-2,6-Bis(hydroxymethyl)-*cis*-1,3,5,7-TOD (5): (L)-Threitol (94 mg, 0.77 mmol) and glycolaldehyde (93 mg, 1.55 mmol) in 1N HCl (0.9 mL) were stirred for approximately 15 min until completely dissolved. HCl and water were removed in vacuo at approximately 40 °C. The colorless viscous residue still holds water, which was removed under high vacuum to constant weight, and crystallized afterwards on standing (all recrystallization attempts failed) to a white solid, m.p. 86–88 °C. Yield: 99%. EIMS (7 eV): *m*/*z* (%): 189 (7), 175 (100), 145 (27), 133 (71), 103 (25) [M^+/2]; $[\alpha]_D^{25}=18.9$ ($c=1$, methanol). The NMR spectra are given in Table 1. Compound **5** is very hygroscopic and therefore, after full spectroscopic characterization, were only its derivatives submitted to elemental analysis.

(2*R*,6*R*,9*S*,10*S*)-2,6-Bis(methanesulfonyloxymethyl)-*cis*-1,3,5,7-TOD (5a): Freshly distilled mesyl chloride (28.3 g, 246.8 mmol) was added carefully at 0 °C (with stirring under argon) to a solution of **5** (14.7 g, 71.3 mmol) and triethylamine (39.6 g, 390 mmol) in dry DMF (150 mL). The reaction was warmed up to room temperature during one hour and then a 10% $NaHCO_3$ solution (800 mL) was added. The reaction mixture was extracted with chloroform and the organic layer was washed with brine, dried over $MgSO_4$ and the solvent evaporated. Purification on silica gel gave **5a** (17.4 g, 67%), which crystallized on concentration m.p. 125 °C. $[\alpha]_D^{25}=23.3$ ($c=1$, chloroform); elemental analysis: calcd (%) for $C_{10}H_{18}O_{10}S_2$: C 33.15, H 5.01, S 17.14; found: C 33.32, H 4.93, S 17.69. The NMR spectra are given in Table 1.

In a different but related procedure, mesyl chloride (5.2 mL, 67.2 mmol) was added dropwise (0 °C) to a solution of **5** (4.0 g, 19.4 mmol) and triethylamine (15 mL) in absolute DMF (40 mL), and the reaction mixture heated to 150 °C for 45 min. The dark solution was cooled and washed with saturated $NaHSO_4$ (250 mL), and the mixture extracted three times with $CHCl_3$. The organic layer was washed twice with water, dried and evaporated, yielding a black residue. Silica gel chromatography provided a product (1.03 g, 24%, recrystallized from EtAc/PE) which was proven identical to 2,6-bis(chloromethyl)-*cis*-1,3,5,7-tetraoxadecalin (**3**), previously secured by a different route.[2] EIMS (7 eV): *m*/*z* (%): 241 [M^+], 193 [M^+-CH_2Cl]. The NMR spectra are given in Table 1. Small amounts of byproducts, such as the monochloro derivative were also obtained and not further dealt with.

(2*R*,6*R*,9*S*,10*S*)-2,6-Bis(azidomethyl)-*cis*-1,3,5,7-TOD (7): A solution of **5a** (4.1 g, 11.31 mmol) and sodium azide (5.5 g, 84.60 mmol) in dry DMF (25 mL) was stirred for 48 h at 85 °C under argon. After cooling, brine was added (200 mL) and the reaction mixture was extracted with $CHCl_3$. The organic layer was washed twice with brine, dried over $MgSO_4$ and the solvent evaporated. Purification on silica gel with PE/EA afforded **7** (2.17 g, 75%) as colorless crystals. M.p. 108 °C. EI-MS: *m*/*z*: 256 [M^+], 237, 200.1, 115, 69.0, 57.0; $[\alpha]_D^{25}=22.5$ ($c=1$, chloroform). The NMR spectra are given in Table 1. Elemental analysis: calcd (%) for $C_8H_{12}O_4N_6$: C 37.50, H 4.72, N 32.80; found: C 37.82, H 4.81, N 32.42.

(2*R*,6*R*,9*S*,10*S*)-2,6-Bis(aminomethyl)-*cis* 1,3,5,7-TOD (8): A solution of **7** (3.25 g, 12.68 mmol) in MeOH (80 mL) was stirred for 6 h in a Parrr aparatus under hydrogen (60 psi) in the presence of 5% Pd/C catalyst. The catalyst was filtered off and the solvent was evaporated to give **8** (2.73 g, 97%) as a colorless oil. FAB-MS: 205 [M^++H]; EI-HRMS: *m*/*z*: calcd for $C_8H_{16}O_4N_2$: 204.2238; found: 204.1110 [M^+]. $[\alpha]_D^{25}=31.8$ ($c=1$, methanol). The NMR spectra are given in Table 1.

(±)-2,6-Bis(2-bromoethyl)-*cis*-1,3,5,7-TOD (6): A solution of acrolein (2.3 mL, 34.4 mmole) and dicinamalacetone (indicator, 0.01 g) in toluene (100 mL) was put into a 250 mL three-necked reaction flask equipped with a Soxhlet extractor, thermometer and gas inlet tube to maintain an argon atmosphere. 1,2,3,4-Tetrahydronaphthalene (7.0 mL, 51.5 mmol) was added to a 25 mL three-necked generator flask equipped with a dropping funnel and a gas trap (containing tetrahydronaphthalene as well). The reaction flask was cooled (0–5 °C) in an ice bath and bromine (3.5 mL, 67.9 mmol) was added dropwise to the generator flask, liberating gaseous hydrogen bromide, which bubbled into the stirred solution until the indicator become deep red. The ice bath from the reaction flask was removed, *p*-toluenesulfonic acid monohydrate (0.05 g) and threitol (1 g, 8.2 mmole) were added and the red solution was then refluxed for 3 h. The reaction mixture was neutralized with dilute NaOH solution, washed with brine, dried ($MgSO_4$) and filtered. Removal of the solvents, followed by purification on silica gel ($CHCl_3$), afforded compound **6** (2.65 g, 90%) as a white solid. M.p. 86–87 °C. The NMR spectrum is given in Table 1. Elemental analysis: calcd (%) for $C_{10}H_{16}O_4Br_2$: C 33.53, H 4.50, Br 44.10; found: C 33.52, H 4.56, Br 44.43.

(±)-2,6-Bis(2′-azidoethyl)-*cis*-1,3,5,7-TOD (9): A solution of **6** (2.5 g, 6.9 mmol) and NaN_3 (7 g, 125 mmol) in CH_3CN (50 mL) was refluxed for 48 h. After the mixture was cooled down to room temperature and filtered, the solvent was evaporated and the residue was separated on silica gel ($CHCl_3$), to give **9** (1.8 g, 94%) as a yellow oil. The NMR spectra are given in Table 1. EI-MS: *m*/*z* (%): 284 (11) [M^+], 214 (100), 184 (13), 142 (13), 115 (75).

(±)-2,6-Bis(2′-aminoethyl)-*cis*-1,3,5,7-TOD (10): A catalytic amount of Pd/C (5%) was added to a solution of **9** (1.13 g, 3.98 mmole) in MeOH

(≈30 mL), and the mixture hydrogenated in a Parr apparatus (60 psi) overnight. After filtering off the catalyst and evaporating the solvent, the diamine **10** (0.8 g, 86%) was isolated as a colorless oil. The NMR spectra are given in Table 1. EI-MS: *m*/*z* (%): 232 (42) [M^+], 188 (85), 159 (52), 144 (100), 129 (31), 116 (68), 115 (31).

General procedure for preparing macrocyclic dilactams 12a–c and 16a,b in DMF: The diamine **8** or **10** (2.45 mmol) was added to a mixture of Na_2CO_3 (14 mmole, Li, K, or Cs carbonates can also be used) in dry DMF (50 mL), under argon. After the mixture had been stirred for 20 min at room temperature, the appropriate polyglycolic acid dichloride **11a–c** (2.45 mmol) was added and the reaction mixture was stirred for a further 10 min at room temperature and then at 90°C for seven days. After cooling down and addition of water (50 mL), the mixture was submitted to continuous extraction with chloroform for two days. The organic layer was dried over $MgSO_4$ and filtered, the solvent was evaporated and the crude residue was subjected to column chromatography on silica gel (EA/MeOH 5:2).

(2*R*,6*R*,9*S*,10*S*)-2,6-[1′,9′-(2′,8′-Diaza-3′,7′-dioxo-5′-oxanonalylidene)]-*cis*-1,3,5,7-TOD (12a): Recrystallization from MeOH/EA afforded **12a** (0.16 g, 21%) as a white solid. M.p. 225–227°C. The NMR spectrum is given in Table 2. FAB-MS: *m*/*z*: 303 [M^++H]; EI-HRMS: *m*/*z*: calcd for $C_{12}H_{18}O_7N_2$: 302.2806; found: 302.1114 [M^+]; elemental analysis: calcd for $C_{12}H_{18}O_7N_2$ (M_w 302.28): C 47.68, H 6, N 9.26; found: C 43.19, H 5.53, N 8.32.

(2*R*,6*R*,9*S*,10*S*)-2,6-[1′,12′-(2′,11′-Diaza-3′,10′-dioxo-5′,8′-dioxadodecanylidene)]-*cis*-1,3,5,7-TOD (12b): Recrystallization from MeOH/EA afforded **12b** (0.218 g, 26%) as a white solid. M.p. 230–232°C. The NMR spectrum is given in Table 2. FAB-MS: 347 [M^++H]; MS (DEI-HR): *m*/*z*: calcd for $C_{14}H_{22}O_8N_2$: 346.3332; found: 346.1376 [M^+]; elemental analysis: calcd for $C_{14}H_{22}O_8N_2$: C 48.55, H 6.4, N 8.08; found: C 47.03, H 6.27, N 7.73.

(2*R*,6*R*,9*S*,10*S*)-2,6-[1′,15′-(2′,14′-Diaza-3′,13′-dioxo-5′,8′,11′-trioxapentadecanylidene)]-*cis*-1,3,5,7-TOD (12c): Recrystallization from MeOH/EA afforded **12c** (0.390 g, 41%) as a colorless foam. The NMR spectrum is given in Table 2. $[\alpha]_D^{25}=26.6$ ($c=1$, chloroform). EI-MS: *m*/*z* (%): 390 (20.3) [M^+]; elemental analysis: calcd for $C_{16}H_{26}O_9N_2$: C 49.23, H 6.71, N 7.18; found: C 49.35, H 6.71, N 7.10.

(±)-2,6-[1′,11′-(3′,9′-Diaza-4′,8′-dioxo-6-oxaundecanylidene)]-*cis*-1,3,5,7-TOD (16a): Recrystallization from MeOH/EA afforded **16a** (0.148 g, 18%) as colorless crystals. M.p. 208–209°C. The NMR spectrum is given in Table 2. FAB-MS: 331 [M^++H].

(±)-2,6-[1′,14′-(3′,12′-Diaza-4′,11′-dioxo-6′,9′-dioxatetradecanylidene)]-*cis*-1,3,5,7-TOD (16b): Recrystallization from MeOH/EA afforded **16b** (0.237 g, 26%) as a pale yellow oil. The NMR spectrum is given in Table 2. EI-MS: *m*/*z* (%): 374 (41) [M^+], 84 (86); FAB-MS: 375 [M^++H].

General procedure for preparing macrocyclic di- and tetralactams in CH_3CN: A mixture of Na_2CO_3 (94 mmol) and **8** or **10** (5.8 mmol) in dry CH_3CN (250 mL) was refluxed under argon. The appropriate polyethyleneglycolic acid dichloride **11a,b** (5.8 mmol) in dry CH_3CN (250 mL) was added in one portion. The reaction mixture was refluxed for another 45 min., then cooled down and filtered. The carbonate precipitate was thoroughly and consecutively washed with chloroform, ethyl acetate and ethanol. The crude reaction mixture, contained unreacted starting materials and products. The crude compound was dissolved in 2.5% Na_2CO_3 solution (270 mL) and extracted with $CHCl_3$ (10×66 mL portions). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated. The water layer from the extraction was separately evaporated and the solid residue was triturated in hot chloroform, ethyl acetate, and acetonitrile. From the water layer, the macrocyclic tetralactams **13a,b** or **17a,b** were isolated, from **8** or **10** respectively. From the organic layer, the macrocyclic dilactams **12a,b** and **16a,b** were obtained. All physical data, including those of the open-chain di- and tetraamides **14** and **15** are given below.

(2*R*,6*R*,9*S*,10*S*)(2″*R*,6″*R*,9″*S*,10″*S*)-2,6;2″,6″-Bis[1′,9′-(2′,8′-diaza-3′,7′-dioxo-5-oxanonanylidene)]-di-*cis*-1,3,5,7-TOD (13a): The water phase contained a mixture of unreacted starting material **8** and the [2+2] macrocyclic tetralactam **13a**. The latter was isolated by trituration of the water phase in chloroform in 13.5% yield. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=7.86$ (t, $J=6.29$ Hz, 4H, NH), 7.73 (t, $J=6$ Hz, 4H, NH), 4.78 (t, $J=$ 4.8 Hz, 4H, H-2,2′,6,6′), 4.39–3.41 ppm (m, 26H, H-4,4′eq, 4,4′ax, 8,8′eq, 8,8′ax, 9,9′,10,10′,11,11′,12,12′,15,15′); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=$ 169.04 (CO), 98.23 (C-2,6), 70.26 (C-15,15′), 69.40 (C-4,8), 69.50 (C-9,10), 41.62 ppm (C-11,11′); FAB-MS: 605 [M^++H], 627 [M^++Na].

(2*R*,6*R*,9*S*,10*S*)(2″*R*,6″*R*,9″*S*,10″*S*)-2,6;2″,6″-[1′,12′-Bis(2′,11′-diaza-3′,10′-dioxo-5′,8′-dioxadodecanylidene)]-di-*cis*-1,3,57-TOD (13b): The [2+2] tetralactam **13b** was isolated by titration of the water phase in chloroform in 2% yield. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=7.18$ (t, $J=6$ Hz, 4H, NH), 4.80 (t, $J=5.38$ Hz, 4H, H-2,2′:6,6′), 4.17–3.65 ppm (m, 36H, H-4,4′eq, 4,4′ax, 8,8′eq, 8,8′ax, 9,9′, 10,10′, 11,11′, 15,15′, 17,17′); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=169.80$ (C=O), 97.53 (C-2,2′;6,6′), 70.46 (C-15,15′), 70.19 (C- 17,17′), 68.95 (C-4,4′,8,8′), 68.79 (C-9,9′,10,10′), 41.30 ppm (C-11,11′); FAB-MS: 693 [M^++H], 715 [M^++Na]; IR ($CHCl_3$): $\tilde{\nu}=895$, 1247, 1265, 1426, 1550, 1606, 1700, 2927, 2987, 3053 cm^{-1}.

(2*R*,6*R*,9*S*,10*S*)(2″*R*,6″*R*,9″*S*,10″*S*)-2,2″-Bis(aminomethyl)-6,6″-[1′,12′-(2′,11′-diaza-3′,10′-dioxo-5′,8′-dioxadodecanylidene)]-*cis*-1,3,5,7-TOD (14) and the homologous tetraamide (15): The open-chain diamide **14** was isolated by trituration of the water phase in chloroform in 1% yield. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=7.18$ (t, $J=6.16$ Hz, 2H, NH), 4.74 (m, 4H, H-2,2′,6,6′), 4.3 ppm (m, 28H, H-4,8eq,4′,8′eq,4,8ax,4′8′ax, 9,9′,10,10′,11,11′,12,12′, 15,15′,17,17′); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=$ 169.68 (CO), 98.50 (C-2,2′,6,6′), 70.90 (C-15,15′), 70.57 (C-17,17′), 69.28 (C-9,10), 68.48 (C-4,8), 42.85 ppm (C-11,11′,12,12′); FAB-MS: 553 [M^+ +H], 575 [M^++Na]; IR ($CHCl_3$): $\tilde{\nu}=753$, 896, 1118, 1272, 1423, 1677 cm^{-1}.

The open-chain tetraamide **15** was isolated by trituration of the water phase in chloroform in 2% yield. ^{1}H NMR(200 MHz, $CDCl_3$): $\delta=7.21$ (t, NH), 7.05 (t, NH), 4.75 (q, $J=4.44$ Hz, 6H, H-2,2′,2″,6,6′6″), 4.19–3.54 ppm (m, 46H); ^{13}CNMR (50 MHz, $CDCl_3$): $\delta=170.02$ (C=O), 169.71 (C=O)′, 96.57 (C-2,6), 98.28 (C-2′,6′), 97.61 (C2′,6′), 70.92 (14,17′), 70.77 (14′,17), 70.65 (C15,16′), 70.50 (C16,15′), 69.38 (C9,10,9′,10′,9′,10′), 69.23 (C4,8,4′,8′,4′,8′), 41.82 ppm (C11,12,11′,12′,11′,12′); FAB-MS: 899 [M^+ +H], 921 [M^++Na].

(±)-2,6;2″,6″-Bis[1′,11′-(3′,9′-diaza-4′,8′-dioxo-6′-oxaundecanylidene)]-di-*cis*-1,3,5,7-TOD (17a): The water phase contained a mixture of unreacted starting material (≈28%) and the [2+2] macrocyclic tetralactam **17a**. Pure **17a** was isolated in 5% yield. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=4.77$ (bd, 4H, H-2,2′,6,6′), 4.11 (d, $J=12.6$ Hz, 4H, H-4,4′,8,8′eq), 4.03 (brs, 8H, H-15,15′), 3.68 (d, $J=12.6$ Hz, 4H, H-4,4′,8,8′ax), 3.56 (brs, 4H, H-9,9′,10,10′), 3.53 (m, 8H, H-12,12′), 1.94 ppm (m, 8H, H-11,11′); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=168.90$ (CO), 100.23 (C-2,2′,6,6′), 71.02 (C-15,15′), 69.24 (C-4,8,9,10), 34.02 (C-12,12′), 33.78 ppm (C-11,11′); FAB-MS: 661 [M^++H], 683 [M^++Na], 699 [M^++K].

(±)-2,6;2″,6″-Bis[1′,14′-(3′,12′-diaza-4′,11′-dioxo-6′,9′-dioxatetradecanylidene)]-di-*cis*-1,3,5,7-TOD (17b): The water phase contained a mixture of some unreacted starting material (**10**) and of the [2+2] macrocyclic tetralactam **17b** (22%). ^{1}H NMR (200 MHz,$CDCl_3$): $\delta=4.74$ (brs, 4H, H-2,2′,6,6′), 4.13 (d, $J=12.6$ Hz, 4H, H-4,4′eq,8,8′eq), 3.98 (s, 8H, H-15,15′), 3.89 (d, $J=12.6$ Hz, 4H, H-4,4′ax,8,8′ax), 3.71 (s, H-17,17′), 3.62 (brs, 4H, H-9,9′,10,10′), 3.45 (brs, 8H, H-12,12′), 1.91 ppm (brs, 8H,H-11,11′); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=169.45$ (CO), 100.14 (C-2,2′,6,6′), 71.02 (C-15,15′), 70.54 (C-17,17′), 69.25 (C-4,8,4′,8′, 9,9′,10,10′), 34.02 ppm (C-11,11′,12,12′); FAB-MS: 748 [M^++H], 671 [M^++Na].

General procedures for preparing diazacrowns 18a–c: To a solution of macrocyclic dilactam **12a–c** (0.5 mmol) in dry THF (6 mL) under argon atmosphere, $BH_3{\cdot}SMe_2$ (2.0 M in THF, 3 ml, 6 mmol) was added and the solution was refluxed for two hours. The solvent was then evaporated, HCl (10%,14 mL) was added and the reaction mixture was heated for 90 min at 60°C, cooled down and basified (pH 11) with aqueous NaOH. This aqueous solution was subjected to continuous extraction with chloroform for a period of 20 h. The organic solution was dried ($MgSO_4$), filtered, and the solvent was evaporated. The crude product was dissolved in absolute MeOH (5 mL), filtered, and the solvent was evaporated. The product was purified by chromatography on silica gel MeOH/NH_4OH (30:1). The physical data of each diazacrown-TOD are given below.

(2*R*,6*R*,9*S*,10*S*)-2,6-[1′,9′-(2′,8′-Diaza-5′-oxanonalylidene)]-*cis*-1,3,5,7-TOD (18a): Chromatography as above afforded **18a** (0.104 g, 75%) as a colorless oil. The NMR spectrum is given in Table 2. FAB-MS: 275 [M^+ +H]; MS (DEI-HR): *m*/*z*: calcd for $C_{12}H_{22}O_5N_2$: 274.3142; found:

274.1528 [M^+]; elemental analysis: calcd (%) for $C_{12}H_{22}O_5N_2$ (M_w 274.31): C 50.54, H 8.25, N 10.20; found: C 50.89, H 8.41, N 9.65.

(2*R*,6*R*,9*S*,10*S*)-2,6-[1′,12′-(2′,11′-Diaza-5′,8′-dioxadodecanylidene)]-*cis*-1,3,5,7-TOD (18b): Chromatography as above afforded **18 b** (0.14 g, 86%) as a white solid (m.p. 168–170°C). The NMR spectrum is given in Table 2. EI-MS: *m*/*z* (%): 318 (87) [M^+], 273 (27), 172 (36), 120 (47), 118 (29), 102 (21), 71 (37), 44 (100); FAB-MS: 319 [M^++H]; MS (DEI - HR): *m*/*z*: calcd for $C_{14}H_{26}O_6N_2$: 318.1790; found: 318.1790 [M^+].

(2*R*,6*R*,9*S*,10*S*)-2,6-[1′,15′-(2′,14′-Diaza-5′,8′,11′-trioxapentadecanylidene)]-*cis*-1,3,5,7 TOD (18c): Chromatography as above afforded **18c** (0.300 g, 64%) as a colorless oil. The NMR spectrum is given in Table 2. EI-MS: *m*/*z* (%): 362 (58), 273 (15), 186 (41), 172 (44), 115 (26). $[\alpha]_D^{25}$ = 6.8 (*c* = 1, chloroform). Elemental analysis: calcd (%) for $C_{16}H_{30}O_7N_2$ (M_w = 362.43): C 53.02, H 8.34, N 7.73; found: C 52.73, H 8.43, N 7.59.

An alternative procedure for securing **18c** was to condense the diamine **8** with tetraethyleneglycol dimesylate (**20c**).[10] Compound **8** (0.3 mmol) in absolute acetonitrile (16 mL) was stirred with dry Na_2CO_3 (300 mg) for 10 min and after **20c** (0.31 mmol) was added, the mixture was stirred at 80°C for four days. After cooling to room temperature, the mixture was filtered and evaporated. The residue was purified on silica gel (MeOH/NH_4OH 30:1–15:1), to yield **18c** (17%).

When, in the above procedure, another portion of **20c** (0.3 mmol) was added and the reflux continued for another day and similarly worked-up, the cryptand 2,6-bi(2′,14′-diaza-5′,8′,11′-trioxapentadecanylidene)-*cis*-1,3,5,7 TOD (**21c**) was obtained in low yield (1.7%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.81–3.10 (m, 12H; CH_2N), 3.48–3.71 (m, 28H; CH_2OCH_2, CH_{ax}), 4.07 (d, *J* = 12.0 Hz, 2H; CH_{eq}), 4.81 ppm (m, 2H; OCH). EIMS: *m*/*z* (%): 520 (10) [M^+].

General procedure for preparing diaza crowns 19a,b: The macrocyclic dilactams (**16a,b**) were subjected to identical procedures to those described above for the lower homologues (**12**). The yields and physical data for each individual TOD-diazacrown are given below.

(±)-2,6-[1′,11′-(3′,9′-Diaza-6′-oxaundecanylidene)]-*cis*-1,3,5,7-TOD (19a): Chromatography as described above afforded **19a** (0.029 g, 56.8%) as an oil. The NMR spectral data is given in Table 2. FAB-MS: 303 [M^++H].

(±)-2,6-[1′,14′-(3′,12′-Diaza-6′,9′-dioxatetradecanylidene)]-*cis*-1,3,5,7-TOD (19b): Chromatography described as above afforded **19b** (0.024 g, 65%) as a colorless oil. The NMR spectral data is given in Table 2. FAB-MS: 347 [M^++H]; MS (DEI-HR): *m*/*z*: calcd for $C_{16}H_{31}O_6N_2$: 347.4283; found: 347.2182 [M^+].

Cryptand (±)-2,6-bis[1′,14′-(3′,12′-diaza-6′,9′-dioxatetradecanylidene)]-*cis*-1,3,5,7-TOD (23): A mixture of the dibromide **6** (0.0632 g, 0.017 mmol), of the diazacrown **22** (0.0461 g, 0.17 mmol) and of Na_2CO_3 (0.2 g, 1.88 mmol) in dry CH_3CN (20 mL) was refluxed for 12 days under argon with stirring in a 50 mL three-necked round bottom flask. The reaction mixture was then cooled down and filtered. The crude product was purified by chromatography on silica gel, using MeOH/NH_4OH (30:1) as eluent. The product **23** was obtained in 38% yield, as a complex with Na^+ (according to FAB-MS). It was taken up in $CHCl_3$ and washed with a 1% solution of HCl. The organic layer was dried over $MgSO_4$, filtered and evaporated. The cryptand thus obtained was analyzed by FAB-MS, which showed that it was successfully decomplexed. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.91 (t, *J* = 2.5 Hz, 2H, H-2,6), 4.12 (d, *J* = 12.1 Hz, 2H, H-4,8eq), 3.72 (m, 4H, H-4,8ax,9,10), 3.63 (m,12H, H-14,14′,15,15′,17,17′), 2.96 (m, 4H, H-12,12′), 1.79 ppm (m, 4H, H-11,11′); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 97.27 (C-2,6), 69.19 (C-4,8), 68.31 (C-9,10), 68.27 (C-15,15′), 65.71 (C-17,17′), 56.71 (C-12,12′), 43.60 (C-14,14′), 29.28 ppm (C-11,11′); FAB-MS: 361 [M^++H]; MS (DEI-HR): *m*/*z*: calcd for $C_{22}H_{40}O_8N_2$: 460.2862; found: 460.2862 [M^+].

Crystal structure analyses of dilactams 12a and 16a: The X-ray diffraction measurements were carried out at approximately 295 K on an automated CAD4 diffractometer equipped with a graphite monochromator, using $Mo_{K\alpha}$ (λ = 0.7107 Å) radiation. Intensity data were collected by the ω-2θ scan mode. Possible deterioration of the analyzed crystal was tested by detecting periodically the intensities of three reference reflections from different zones of the reciprocal space, and was found negligible during the experiment. No corrections for absorption and secondary extinction effects were applied. The structures were solved by direct methods (SHELXS-86)[19a] and refined by full-matrix least-squares (SHELXL-93).[19b] Non-hydrogen atoms were treated anisotropically. All hydrogen atoms were located on difference-Fourier maps; positions of those attached to carbon were adjusted to conform to standard bond lengths and angles.

Dilactam 12a: *Crystal data*: $C_{12}H_{18}N_2O_7$, formula weight 302.28, orthorhombic, space group $P2_12_12_1$, *a* = 7.603(3), *b* = 12.982(2), *c* = 13.846(2) Å, *V* = 1366.6 Å^3, *Z* = 4, ρ_{calcd} = 1.469 g cm^{-3}, *F*(000) = 640, $\mu(Mo_{K\alpha})$ = 1.22 cm^{-1}. *Data collection and refinement*: Diffraction data measured out to $2\theta_{max}$ = 50° with a constant scan rate of 3 deg min^{-1}. A total of 1320 unique reflections with positive intensities were recorded. The final refinement, based on F^2, converged at *R* = 0.041 for 1103 observations having $F_o > 4\sigma(F_o)$ and *R* = 0.051 (*wR*2 = 0.127) for 1320 unique data. At convergence, *S* = 0.86 and $|\Delta\rho|$ = 0.19 e Å^3.

Dilactam 16a: *Crystal data*: $C_{14}H_{22}N_2O_7$, formula weight 330.34, monoclinic, space group $P2_1$, *a* = 9.166(1), *b* = 8.293(2), *c* = 10.586(1) Å, β = 91.66(1)°, V = 804.3 Å^3, Z = 2, ρ_{calcd} = 1.364 g cm^{-3}, *F*(000) = 352, $\mu(Mo_{K\alpha})$ = 1.10 cm^{-1}. *Data collection and refinement*: Diffraction data measured out to $2\theta_{max}$ = 54° with a constant scan rate of 3 deg min^{-1}. A total of 1819 unique reflections with positive intensities were recorded. The final refinement, based on F^2, converged at *R* = 0.038 for 1617 observations having $F_o > 4\sigma(F_o)$ and *R* = 0.043 (*wR*2 = 0.120) for 1819 unique data. At convergence, *S* = 0.88 and $|\Delta\rho|$ = 0.20 e Å^3.

The open conformations of both these cyclic dilactams are stabilized by intramolecular N–H···O contacts (involving the NH groups which turn inward), as well as by intermolecular C=O···H–C contacts (involving the C=O groups which turn outward).

CCDC-206724 (**12a**) and -206725 (**16a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.can.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Centre, 12 Union Road, Cambridge CB21EZ, UK; Fax: (+44) 1223-336033; or deposit@ccdc.cam.ac.uk). These data, along with the atomic coordinates of the AMBER optimized structure of **18c**, are also given in the Supporting Information.

Complexation constant determination of TOD-diazacrowns with alkaline and alkaline-earth metal:

The ^{1}H NMR (200 MHz) titration technique was performed under fast exchange conditions using a solution of MeOD/D_2O (4:1). A sample containing a few milligrams of the TOD ligand (10 μM) in a known volume of solvent was loaded into the NMR tube and the spectrum measured. A known amount of the metal ion (50 μM), dissolved in a known volume of solvent, was added and another spectrum was taken, whereby a shift in the spectrum of the complexed ligand was observed. This process was repeated until no substantial change in NMR spectrum occurred. On the whole, 12 spectra were taken to calculate each log K value. Figure 6 in the Supporting Information shows a nonlinear curve describing the complexation of TOD-diazacrown **18c** with Ba(II). The inclusion of other alkaline-earth metals by diazacrowns **18a,b** followed the same pattern as that presented in Figure 6 in the Supporting Information.

Four parameters were included in the fitting function (the formalism is presented in the Supporting Information): the initial concentrations of the ligand and the metal salt (which are known and are not optimized during the fitting procedure), the complexation constant and the chemical shift of the complex (unknown and subject to optimization).

With a 120 μL volume of the metal salt, the ligand and the metal are at equimolar ratio. The inflection point on the graph (see Supporting Information; Figure 6), which is observed after addition of one equimolar amount of metal (120 μL) provides the evidence to the formation of a 1:1 metal to ligand complex.

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