220. Molecular Receptors. Functionalized and Chiral Macrocyclic Polyethers Derived from Tartaric Acid[1])

by **Jean-Paul Behr, Jean-Marc Girodeau, Rodney C. Hayward, Jean-Marie Lehn** and **Jean-Pierre Sauvage**[2])

Institut Le Bel, Université Louis Pasteur, 4, rue Blaise-Pascal, F-67000 Strasbourg

(11.VI.80)

Summary

A number of functionalized and chiral macrocyclic polyethers have been synthesized by condensation of the dithallium alcoholate of (*R*, *R*)-(+)-tartaric acid derivatives with α,ω-dihalides. In this way for instance, the tetracarboxylic [18]-O_6 macrocycle **3c** and its derivatives become readily available. They form complexes with various cationic substrates. NMR. and crystal-structure data provide information about the orientation of the side chains X in **3** with respect to the macrocycle. It is concluded that in the secondary amides like **3b** and in their complexes the four X-groups are preferentially in an axial orientation on the average. This property is of much significance for the design of molecular receptors and catalysts based on this macrocyclic structure. The preparation of a number of other macrocycles is also described.

Introduction. – Neutral macrocyclic polyethers form stable and selective complexes with alkali, alkaline-earth and primary ammonium cations [2–5]. The properties of this class of compounds are related to the behaviour of the natural neutral ionophore antibiotics like valinomycin and nonactin [6]. Developments in the chemistry of such macrocycles led to the design and synthesis of chiral and functionalized complexing agents [1] [7–12], which display enantiomeric recognition of organic primary ammonium cations [7] [12–14]. In our own approach to the design of receptor molecules for primary ammonium cations [1] [15] [16], an appropriate macrocyclic sub-unit had to be selected, which would display efficient binding properties towards primary ammonium cations, providing the anchoring site for the cationic $-NH_3^+$ head. In addition, lateral branching sites were required for attachment of secondary binding units and connection into macropolycyclic receptor molecules [15] [16]. Thus, the choice of the receptor unit followed three main criteria:

1) It should be an aliphatic 18-membered macrocyclic polyether of the [18]-crown-6 type which is suitable for complexing organic primary ammonium cations

[1]) Preliminary communication: [1].

[2]) ERA. 265 of the CNRS.

0018-019X/80/7/2096-16$01.00/0

[2] [7]. Crowns containing aromatic ethers (*e.g.* dibenzo and binaphthyl crowns) form less stable complexes than those containing only aliphatic ethers [2] [7] [17] owing, at least in part, to the weaker basicity of the aromatic ether O-atoms and to ring deformation introduced by the aromatic moiety;

2) It should bear functional groups enabling the attachment of side chains directly to the aliphatic C-atoms of the macrocycle in order to construct specific receptor molecules. Such modifications may involve the attachment of:

— other macrocyclic units, forming multisite receptors [16] [18];
— lipophilic side chains for carriers in membrane transport systems [16];
— reactive groups for developing catalytic systems [16].

The introduction of side chains confers a third dimension to the crown macrocycle, somewhat as in the macrobicyclic and macrotricyclic cryptands [16] [18] which display much stronger complexation towards alkaline, alkaline-earth and the ammonium cations than the crowns;

3) It would be desirable that the substituted macrocycle be *chiral with known absolute configuration.* Such chirality, present in the ring and possibly in the side chains, is necessary for the elaboration of a system enabling chiral recognition. An optically pure starting material was required to avoid tedious isomer separation and resolution steps.

L-(+)-Tartaric acid **1** appeared to be a highly suitable structural unit for incorporation into a crown ether system meeting our requirements, since it is a substituted ethylene glycol of known absolute configuration very readily available in optically pure form. This led to the one step synthesis of the 'bis-tartro-crown' macrocycles [1]. Other macrocycles containing similar fragments have been reported [19–21].

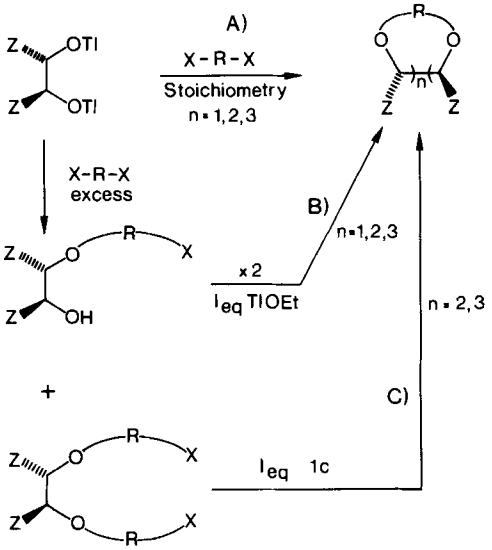
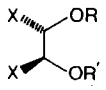


Fig. 1. *Synthetic paths for macrocycle synthesis.*

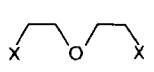
We now describe the synthesis and properties of our chiral macrocyclic core and some other macrocyclic derivatives of L-(+)-tartaric acid. The complexing properties of these new ligands will be reported in forthcoming papers.

Syntheses. – The synthesis of the present ligands is based on a modified *Williamson* synthesis of ethers derived from that described by *Seebach et al.* [22]. The dithallium alcoholate **1c** of the (*R*, *R*)-(+)-(*N*, *N*, *N'*, *N'*-tetramethyl) tartramide **1b** is alkylated in DMF or acetonitrile solution by an aliphatic diiodide or an activated dibromide. Three pathways have been considered *(Fig. 1)*. The one step procedure **A** in which four fragments are assembled into a macrocyclic structure, appears to be the most suitable; it gives the same overall yield as the two-steps routes **B** and **C** and has been used in the preparation of all macrocycles described. Depending on the nature of the dihalide, the major compound formed is the cyclic monomer (n = 1) or the cyclic dimer (n = 2). The cyclic trimer (n = 3) has been isolated in two cases. The nature of a given cyclic oligomer was determined using mass spectrometry.

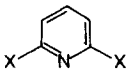
Aliphatic iodides give the best results in the alkylation of thallium alcoholates [22]. The amide derivatives of tartaric acid **1b** and **1d** were easily alkylated in this way whereas the diethyl ester **1a** did not react significantly.



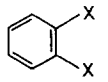
1 X = COOH, R = R' = H
1a X = COOEt, R = R' = H
1b X = $CONMe_2$, R = R' = H
1c X = $CONMe_2$, R = R' = Tl
1d X = CONHMe, R = R' = H
1e X = CONHMe, R = R' = Tl
1f X = $CONMe_2$, R = H, R' = $(CH_2)_2O(CH_2)_2I$
1g X = $CONMe_2$, R = R' = $(CH_2)_2O(CH_2)_2I$



2a X = I
2b X = OTs
2c X = OCH_2CH_2I



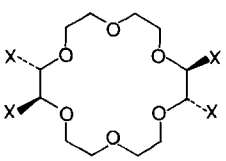
2d X = CH_2Br



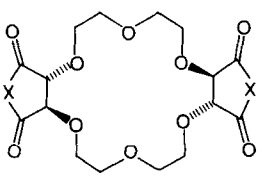
2e X = CH_2Br

Reaction of **1c** with **2a** gave a crude mixture from which the cyclic dimer [18]-O_6 **3a** may be easily isolated in about 20% yield by cristallization; the 27-membered ring [27]-O_9 **7a** was obtained in very low yield by careful chromatography of the residue and **10** was only present in traces. Compound **7a** has more recently been synthesized in higher yield [23] by a different route. When the di-*p*-toluenesulfonate **2b** was used in the synthesis of **3a** instead of the diiodide **2a**, the yield dropped from 20% to 10%, and with the corresponding dichloride no appreciable alkylation occured. When the diiodide **2c** was used in the cyclization with **1c**, the cyclic monomer [15]-O_5 **8a** and dimer [30]-O_{10} **9a** were obtained. With 2,6-bis(bromomethyl)pyridine (**2d**) only the cyclic dimer [18]-Py_2O_4 **6** was isolated. Finally the reaction of **1c** with α,α'-dibromo-*o*-xylene (**2e**) gave the cyclic cmopounds **11**, **12** and **13**.

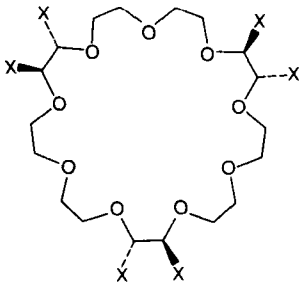
Similarly, treatment of the (*R*, *R*)-(+)-*N*, *N'*-dimethyltartramide (**1d**) with two equivalents TlOEt in DMF, gave **1e** which reacts with one equivalent **2a** to form **3b**. The latter cyclized to the bis-imide **5** in quantitative yield on attempted



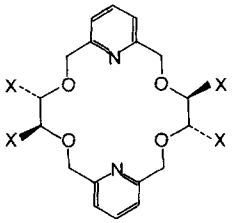
3a X = $CONMe_2$
3b X = CONHMe
3c X = COOH
3d X = COCl
3f X = $CON(n\text{-}Bu)_2$
3g X = H
4a X = CH_2NMe_2
4b X = CH_2OH
4c X = CH_2OTs
4d X = CH_2CN
4e X = CH_2COOH



3e X = O
5 X = NMe



7a X = $CONME_2$
7b X = COOH

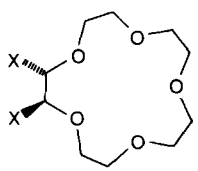


6 X = $CONMe_2$

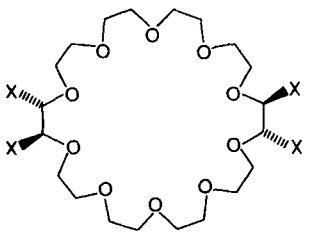
acidic hydrolysis or methanolysis. Reduction of **3a** by lithium aluminium hydride gave **4a**.

The most versatile substance, the tetracarboxylic acid **3c**, was obtained by acidic hydrolysis of **3a** or by treatment of the *N*-nitroso derivative of **3b** with mild base[3]). It can be activated either as the tetraacyl chloride **3d** or as the dianhydride **3e**. Treatment of **3d** with an amine [15] led to the corresponding tetracarboxamide (*e.g.* **3f**).

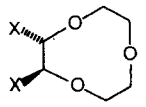
Reduction of **3c** by diborane in THF gave the tetrol **4b** together with other products apparently resulting from ring cleavage. Reduction with lithium aluminium hydride was even less satisfactory. The product **4b** obtained was difficult to purify and was converted to its more easily purified derivative **4c**. Compound **4b** has also been prepared independently in a different approach based on the use of sugar units [19]. The tetraacetic acid derivative **4e** has been obtained from **4b** by a series of straightforward reactions [24] *via* the tetratosylate **4c** and the



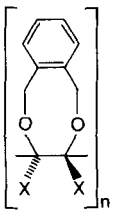
8a X = $CONMe_2$
8b X = COOH
8c X = COOMe



9a X = $CONMe_2$
9b X = H



10 X = $CONMe_2$



X = $CONMe_2$
11 n = 1
12 n = 2
13 n = 3

[3]) Procedure developed by *P. Vierling*, unpublished results.

tetranitrile **4d**. Acid hydrolysis of the [27]-O_9 hexaamide **7a** and of the [15]-O_5 diamide **8a** gave the corresponding polycarboxylic acid derivatives **7b** and **8b**; acid catalyzed methanolysis of **8a** yielded the diester **8c**.

For the synthesis of **3a** by the two-step routes *(Fig. 1)*, compounds **1f** and **1g** were synthesized by reaction of **1c** with a large excess of **2a**. The mono and the dialkylated derivatives are easily separated by solvent distribution. Treatment of **1f** and **1g** respectively with TlOEt and **1c** affords the macrocycle **3a** in about 20% yield.

Physical and spectral properties. The tartro-crowns obtained from the cyclizations are generally well crystallized with sharp melting points. They are soluble in polar solvents from chloroform to water; **3c** is soluble in polar solvents and **3f** is soluble in heptane. Being derived from (*R*,*R*)-(+)-tartaric acid, all compounds are chiral of known absolute configuration and optically active. Since some of the reactions performed might lead to isomerization, controls of optical purity were effected. The cyclization itself was performed in basic conditions but does not appear to cause racemization (see also [22]). A constant $[a]_D = 108 \pm 1°$ ($c = 1.6$,

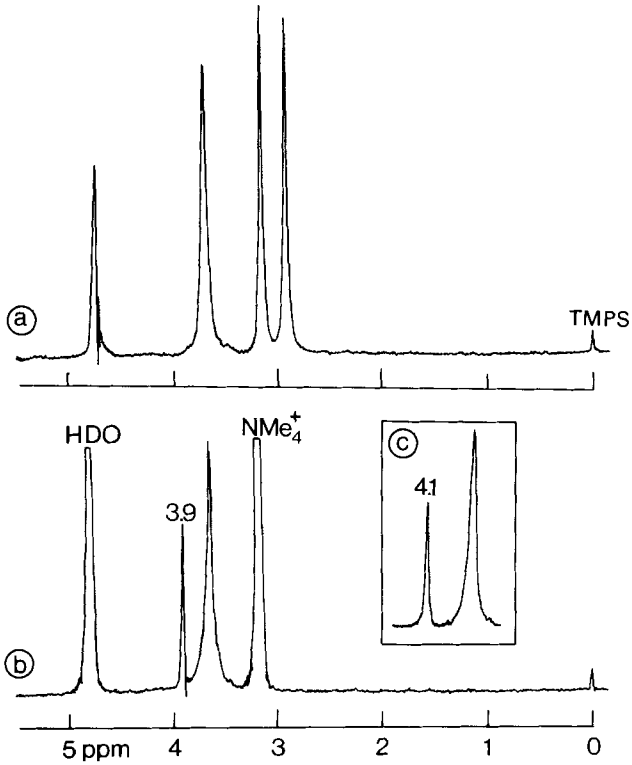


Fig. 2. *60-MHz-^{1}H-NMR. spectra of: a) the macrocyclic tetracarboxamide* **3a**; *b) NMe_4^+ salt of the tetracarboxylic acid* **3c** *at pH = 7.5; c) K^+ complex of* **3c** *obtained by addition of excess KCl, pH = 7.5;* the signals at 4.8 (a), 3.9 (b) and 4.1 (c) ppm are due to the protons at the asymmetric C-atoms; the signals at 3.7 (a), 3.65 (b), and 3.65 (c) ppm are due to OCH_2-protons; solvent D_2O, reference TMPS = sodium 3-trimethylsilylpropanesulfonate.

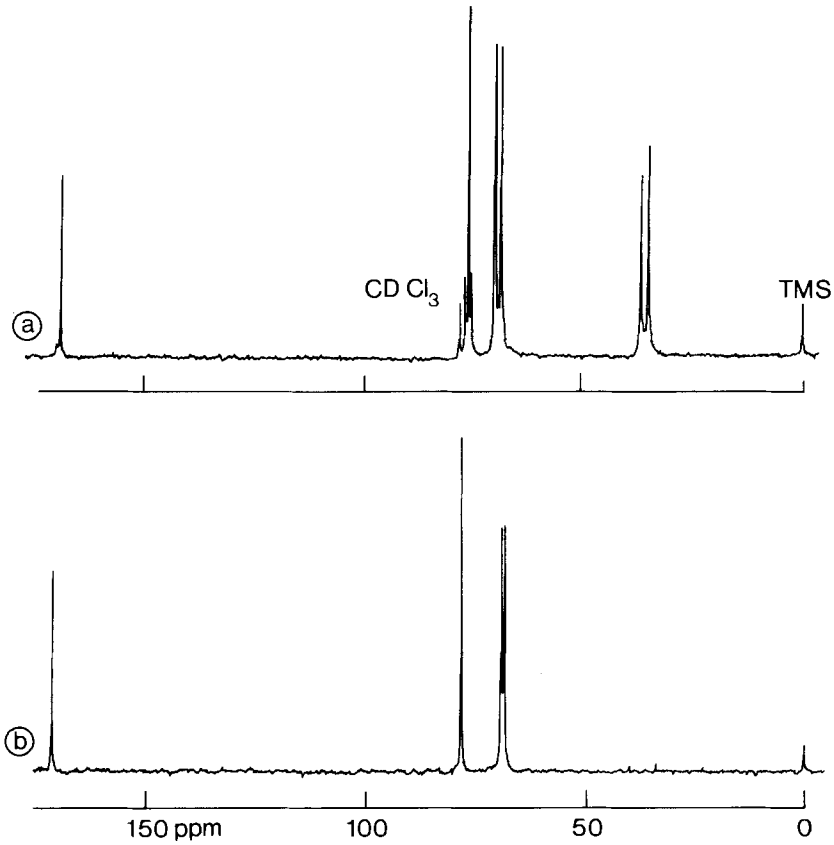


Fig.3. *^{13}C-NMR. spectra at 25 MHz of: a) the macrocyclic tetracarboxamide* **3a** *in $CDCl_3$; b) the tetracarboxylic acid* **3c** *in D_2O, reference TMPS.* The chemical shifts are listed in the experimental section.

$CHCl_3$) was measured for samples of the key compound **3a** obtained from numerous preparations and recrystallizations. The absence of any significant racemization on acid hydrolysis, conversion to acid chloride and reaction with an amine was confirmed by obtaining the same $[\alpha]_D$-values (within experimental error) for initial and final product **3a** along the sequence **3a**→**3c**→**3d**→**3a**. The ^{1}H- and ^{13}C-NMR. spectra are simple owing to the symmetry of the compounds and agree with the proposed structures. Some are shown in *Figures 2* and *3*. The OCH_2CH_2O signal is generally a single broad band, but is split into two well separated multiplets (by 0.37 ppm) in compounds **3e** and **5** containing a fused five-membered ring which is expected to distort the macrocycle [16]. Physical and spectral data are given in the experimental section. The structural and conformational properties of the compounds are discussed below together with those of their complexes.

Formation of cation complexes. – The formation of cation complexes was detected and followed conveniently by NMR. spectroscopy *(Fig. 2)*. Addition of a

complexable cation to a solution of the ligand led to appreciable shifts of the resonances. The effects observed depend on solvent, cation and stability of the complexes formed. The ligand/cation *stoichiometry*, determined from the shift observed as a function of the amount of cation added, is 1:1 in most cases. However a 1:2 complex of **9a** with KSCN was isolated. The crystal structure of the related dinuclear Na^+ complex of the parent [30]-crown-10 (**9b**) has been reported [25]. Ligand **3a** formed a 1:2 complex with Zn^{2+} in acetonitrile. In this case the cations are probably bound to the carbonyl and ether groups on each side of the molecule rather than situated in the cavity. The studied macrocycles complex many cations. For instance **3a** yields 1:1 complexes with Na^+, K^+, NH_4^+, Ca^{2+}, Sr^{2+}, Pb^{2+}, lanthanide (III) cations, and primary ammonium cations like $Ph\text{-}CH_2CH_2NH_3^+$ (see also [15]). More details will be reported together with the measurement of stability constants.

The formation of complexes may also be followed by polarimetry since it affects markedly the specific optical rotation. Thus, the following $[\alpha]_D$ values were measured in chloroform ($c = 1.5$) for the complexes formed by macrocycle **3a** in the presence of excess solid salt:

Cation	None	Na^+	K^+	Rb^+	NH_4^+
$[\alpha]_D^{20°}$	+108°	+33.5°	+69°	+76°	+50°

The first acidity of **3c** is lowered from $pK_a = 4.0$ to 3.2 by complexation of Na^+. The stability of the complex is very high and ^{13}C-NMR. experiments showed that it is formed even in 2N HCl. When a sodium salt was added to a dilute aqueous solution of **3c**, a Na^+ complex of composition **3c**, (3 CO_2H, CO_2^-), Na^+, 2 H_2O crystallized at pH = 0.

Furthermore when **3c** crystallized from concentrated HCl-solution, a compound of composition (**3c**, HCl, H_2O) was obtained, possibly the complex of the hydronium ion (**3c**, H_3O^+, Cl^-). The formation of an H_3O^+ complex of dicyclohexyl-[18]-crown-6 has been reported [26]. In these complexes the H_3O^+ species may be bound inside the ring in a way similar to the binding of NH_4^+ to [18]-crown-6 [27]. Titration of (**3c**, H_3O^+, Cl^-) with base (NMe_4OH) required five equivalents as expected. The species (**3c**, 2 H_2O) was isolated by crystallization from water.

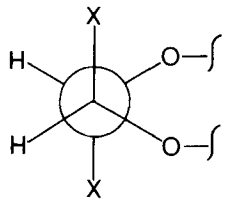
Structure and conformation of the macrocycles and of their complexes. – The macrocyclic structure of the ligands derive from their method of synthesis as well as from the analytical and spectral data.

By analogy with the numerous results reported for a large number of macrocyclic polyethers and related compounds [2–6], the complexes of the present macrocycles are expected to be of the inclusion type, with the cation bound to the oxygen sites and held in the macrocyclic cavity. Two recent crystal structure determinations confirm these expectations [28] [29]. Thus, in the complex of the dianion of the tetracarboxylic substance **3c** with the ethylenediammonium cation the ligand has the macrocyclic structure **3c** and the cation is bound by one of its NH_3^+ groups to the oxygen sites surrounding the molecular cavity [28].

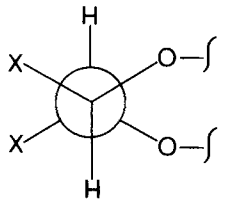
Finally, the orientation of the X substituents in compounds **3** is of importance since it should affect the complexation properties. Furthermore these groups serve

for attachment of branches and reactive groups providing macrocyclic receptors which display lateral recognition effects [15] and catalytic properties [16]. They may also be used for the incorporation of the basic macrocyclic unit into larger macropolycyclic structures.

In the crystal structures of the parent compound [18]-crown-6 (**3g**) [30], of its K^+ [31] and NH_4^+ [27] complexes, the orientation of the H-atoms which occupy the positions of groups X in **3** is diaxial for one (*R*)CHX–(*R*)CHX fragment (form *aa*) and diequatorial for the other (form *ee*), with respect to the average plane of the ring. On this basis one might expect that in compounds **3** the substituents X are oriented similarly, one CHX–CHX unit being of type *aa* and the other of type *ee*. In the first case (form *aa*), the groups X are approximately



aa



ee

vertical and may interact well with bound substrates; in the second case (form *ee*) they are inclined and directed outwards so that the chains which they bear interact less well with substrates, although of course they may bend back. This picture is, however, oversimplified since the nature of the X groups is expected to markedly affect their interaction with the remainder of the molecule and with a bound substrate.

The two crystal structures already mentioned support this view: in the ethylene diammonium-**3c**$^{2-}$ complex [28] as well as in the Sr^{2+} complex of a mixed function derivative of **3c** bearing two anilide groups above and two carboxylate groups below the ring [29], all four substituents X are found in an *axial orientation* (form *aa*). The strong carboxylate-cation interactions apparently more than compensate for the loss in stability which might result from a slight distortion of the ring conformation from the regular crown present in the K^+ and NH_4^+ complexes of **3g** [27] [31]. Furthermore in the second structure the amide groups are in H-bonding contact with the nearest ether O-atom in the ring.

Information about the orientation of the groups X in **3** may also be obtained in solution from the vicinal proton-proton coupling constants in the CHX–CHX fragment. From the usual angular dependence of vicinal coupling constants [32] $^3J_{H,H}$ is expected to be small in form *aa* (about 2–3 Hz) and large in form *ee* (about 8–10 Hz). $^3J_{H,H}$ in the CHX–CHX fragment of **3** may be obtained from the ^{13}C-satellite resonances of these protons. The following values were measured:

Compound (Solvent), **3a** ($CDCl_3$ or D_2O), **3b** ($CDCl_3$ or D_2O), **3a**/K^+ complex (D_2O), **3b**/K^+ complex (D_2O), **5** ($CDCl_3$); $^3J_{H,H} \pm 0.1$ Hz, 8.3 Hz, 2.0 Hz, 5.0 Hz, 2.0 Hz, 5.0 Hz.

In the bis(*N*-methylimide) **5** the fusion of the rigid five-membered ring imposes an angle of about 120° between the vicinal C–H bonds. In the other

flexible compounds the observed vicinal H,H-coupling may range from the coupling in form *aa* to that in form *ee* (see above). The large coupling observed for **3a** indicates a predominant *ee* conformation for the amide groups. On complexation of K^+, $^3J_{H,H}$ decreases, indicating a lesser contribution of the large *trans* coupling (form *ee*) and thus a distortion of the equatorial X groups towards axial orientation. In **3b**, the small $^3J_{H,H}$ shows that the conformation of the X groups in this compound is quite different from that in **3a**; in particular the contribution of ^3J *(trans)* (form *ee*) appears to be much smaller in **3b** than in **3a**. This favours a conformation in which on the average both CHX–CHX fragments in **3b** are of form *aa* or at least quite close to it, *i.e.* all four X groups are in axial type orientation. Complexation of K^+ does not much affect the conformation of **3b**, at least as far as may be judged from the $^3J_{H,H}$ values.

A possible interpretation of these data is as follows: in **3a** both CHX–CHX-units are close to type *ee* or at least form *aa* contributes little to the average orientation; on complexation, interaction of the amide groups with the centrally bound cation 'axializes' the X groups (smaller contribution of form *ee*); in **3b**, interactions due to the amide groups (possibly hydrogen bonding CONH···O with the nearby ring ether O-atom; see above) favour axial orientation of all four amide groups; complexation of K^+ does not affect much this conformer since the X groups are already in a position allowing interaction with the bound cation. These considerations seem to indicate that when the X groups are secondary amide functions and when a complex is formed, the most populated conformer has *all four X side chains on the average in an axial type orientation* extending above and below the ring, as pictured schematically in *Figure 4*. Furthermore, the preference for axial *versus* equatorial type orientation of the groups X depends on their nature, on their contribution to the relative energy of the *aa* and *ee* conformers and on their interaction with the remainder of the molecule, especially with the bound substrate in the complexes.

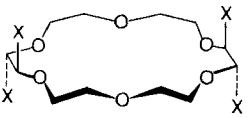


Fig. 4. *Schematic representation of the tetrasubstituted macrocycles* **3** *with axial type orientation of the substituents* (see discussion in text).

Side-chain substrate interactions are also affected by the orientation of the amide groups bearing the side chains with respect to the macrocyclic cavity, *i.e.* upon the conformation about the C(ring)–CON bond. The stereochemical dependence of the vicinal C*H*X–CO^{15}*N*H coupling constant may be used to determine the conformation of this fragment. Although this has recently been questioned [33], ^3J(H, ^{15}N) is expected to be large only for dihedral angles close to 180° [34]. The experimental value of this coupling in the NH_4^+ complex of the ^{15}N-enriched primary amide derivative (X=CO$^{15}NH_2$) of **3c** is less than 0.5 Hz (aqueous solution); this rules out a *trans* H, ^{15}N relationship, in agreement with the crystal structure of the Sr^{2+} complex where this dihedral angle is 130° [29].

The occurrence of observable short range interactions between labelled side chains and complexed ammonium substrates is a further illustration of their

spatial proximity. For instance when the hexamethylenediammonium cation is complexed by the 2-aminonaphthyl-6-sulfonate derivative of **3c** the methylene protons are shifted upfield by *ca.* 0.5 ppm owing to magnetic shielding by the aromatic groups. When **3** bears tryptophanate residues a charge transfer band is observed between the indole rings and a complexed pyridinium substrate [15].

All arguments developed above support the view that the lateral appendages X=CONHR effectively line the periphery of the central cavity, a conclusion which foreshadows their importance for the development of receptor molecules and catalysts based on the unit **3b**, in which the X groups may regulate complexation and/or react with the bound substrate.

Experimental Part

General. All melting points are uncorrected. IR. spectra were recorded on a *Perkin-Elmer* 337 spectrophotometer. Optical rotations ($[\alpha]_D$) were measured on *Perkin-Elmer* 141 and 241 MC polarimeters at 20°. The NMR. spectra were recorded using *Varian* A60 or *Varian* XL100 spectrometers. The NMR. data are expressed in ppm downfield from internal TMS. and are quoted as position, multiplicity (*s* singlet, *d* doublet, *t* triplet, *qa* quadruplet, *m* multiplet, br. broad), and assignment. Mass spectra were determined by the *Service de Spectrométrie de Masse* de Strasbourg on LKB 9005 and *Thomson* THN 208 instruments. Microanalyses were carried out by the *Service Central de Microanalyse* du CNRS, Strasbourg. Alumina for chromatography was *Merck*, standardized according to *Brockmann* at activity II–III. Ether refers to diethyl ether. Abbreviations: i.V. = *in vacuo*.

Preparation of starting materials. The following compounds were prepared following known procedures: thallous ethoxide [35], (*R,R*)-(+)-diethyl tartrate (**1a**) [36], (*R,R*)-(+)-*N,N,N',N'*-tetramethyltartramide (**1b**) [37], (*R,R*)-(+)-*N,N'*-dimethyltartramide (**1d**) [38], 1,5-diiodo-3-oxapentane (**2a**) [39], 2,6-bis(bromomethyl)pyridine (**2d**) [40]; *α,α'*-dibromo-*o*-xylene (**2e**) was commercially available.

1,11-Diiodo-3,6,9-trioxaundecane (**2c**) was obtained from the corresponding 1,11-dibromo-3,6,9-trioxaundecane [41] by treatment with a saturated solution of NaI in acetone. After stirring for 24 h at RT., the NaBr was filtered off, the solution again saturated with NaI and stirred for 48 h. After filtration and evaporation of the solvent, the crude product was dissolved in benzene, washed with water, then with aqueous $Na_2S_2O_3$-solution and again with water. The organic layer was dried ($MgSO_4$) and the solvent evaporated. The product obtained was pure as judged by its NMR. spectrum, and used without further purification. – ^{1}H-NMR. ($CDCl_3$): 3.19 (*t*, 4 H, CH_2I); 3.58 (*s*, 8 H, $O(CH_2)_2O$); 3.70 (*t*, 4 H, ICH_2CH_2O).

(2R,3R)-2-Hydroxy-3-(6-iodo-1,4-dioxahexyl)-N,N,N',N'*-tetramethylsuccinamide* (**1f**) *and (2R,3R)-2,3-bis(6-iodo-1,4-dioxahexyl)*-N,N,N',N'*-tetramethylsuccinamide* (**1g**). To a vigorously stirred solution of the diamide **1b** (14.0 g) in dry DMF (200 ml), thallous ethoxide (34.0 g) was added slowly at 20°. After stirring the fine suspension so formed for a further 30 min, 1,5-diiodo-3-oxapentane (**2b**) (100.0 g) was added. The temperature of the mixture was then raised to 70° and stirring continued for a further 3 h. Filtration and evaporation of the solvent gave an oil which was dissolved in CH_2Cl_2 (50 ml) and washed with water (4 × 150 ml). After drying and evaporating the organic phase, the residue was chromatographed on a short column of alumina (petroleum ether, toluene) to give the diiodide **1g** as an oil (12.0 g, 29%). – ^{1}H-NMR. ($CDCl_3$): 2.92 (*s*, 6 H, $CON(CH_3)_2$); 3.17 (*s+t*, 10 H, $CON(CH_3)_2$ and CH_2I); 3.72 (*m*, 12 H, OCH_2); 4.79 (*s*, 2 H, OCH). – ^{13}C-NMR. ($CDCl_3$): 2.8 (ICH_2); 35.7, 35.9, 37.1 (NCH_3); 68.9, 69.2, 70.1 (OCH_2); 71.8 (CHOH); 79.1 (OCH); 169.3, 170.5 (CO).

Concentration of the aqueous phase to 400 ml and extraction with $CHCl_3$ (4 × 100 ml) followed by chromatography on alumina (toluene/$CHCl_3$, 1:1) gave the monoiodide **1f** as an oil (11.0 g, 38%). – ^{1}H-NMR. ($CDCl_3$): 2.88 (*s*, 6 H, $CON(CH_3)_2$); 3.11 (2 *s+t*, 8 H, $CON(CH_3)_2$ and CH_2I); 3.66 (*m*, 6 H, OCH_2); 3.8–4.2 (1 H, HO); 4.48 and 4.60 (*d* × *d*, 2 H, OCH). – ^{13}C-NMR. ($CDCl_3$): 3.0 (CH_2I); 35.8, 37.4 (NCH_3); 69.0, 70.3, 71.9 (OCH_2); 77.0 (OCH); 169.3 (CO).

(2R, 3R, 11R, 12R)-(+)-(N, N, N′, N′, N″, N″, N‴, N‴-Octamethyl-1, 4, 7, 10, 13, 16-hexaoxacyclooctadecane-2, 3, 11, 12-tetracarboxamide) (**3a**). To dry DMF (4000 ml) contained in a 6 l three-necked flask with indented walls and stirred with a powerful mechanical stirrer, at RT. and under dry N_2, *(R, R)*-(+)-*N, N, N′, N′*-tetramethyltartramide (**1b**) (41.0 g) was added, followed, over a period of 15 min, by thallous ethoxide (3 × 10 ml; 105 g); the resulting white suspension was stirred for 30 min. 1,5-Diiodo-3-oxapentane (**2a**) (65.5 g) was added at once and the mixture stirred for a further 1 h. Then the temperature was raised to 65–70° in about 1 h and maintained at that temperature for 6–8 h. The finely powdered orange thallous iodide formed was removed by filtration through a pad of sand (3 cm height) over alumina (5 cm height) on a *Büchner* funnel, and the solvent was evaporated *i.V.* to give a light-brown pasty solid mass which was kept at 50° i.V. (0.5 Torr) overnight. This crude product was dissolved in CH_2Cl_2 (about 20 ml) and transferred on an alumina (*Merck*, activity II–III) column (7 × 15 cm). The product was eluted first with 1000 ml toluene and then with five portions (5 × 250 ml) of CH_2Cl_2 yielding 6 fractions which were evaporated. The first fraction contained the largest amount of material (about 25–30 g), the others only between 1–5 g. The middle fractions are already solid or pasty 'solid'. Each residue was separately triturated with ether (2 × 50 ml for the first fraction; 1 × 20 ml for the others) in order to remove the oily substances. The first fraction left only a small residue (*ca.* 3.5 g). The residues were separately dissolved in the minimum amount of hot acetone. On cooling the solutions to room temperature, the desired macrocycle **3a** separated as a white crystalline solid (*ca.* 10.5 g, 19%), m.p. 186°. $[\alpha]_D^{20} = +108°$ ($c = 1.5$, $CHCl_3$). – IR. (KBr): 2910, 1625, 1130–1110 cm^{-1}. – ^{1}H-NMR. ($CDCl_3$): 2.83 and 3.10 (2 *s*, 24 H, $CON(CH_3)_2$); 3.63 (*m*, 16 H, OCH_2); 4.68 (*s*, 4 H, OCH). – ^{13}C-NMR. ($CDCl_3$): 35.2, 37.0 (NCH_3); 68.9, 70.2 (OCH_2); 75.7 (OCH); 169.1 (CO). – MS.: M^+ 548; *m/z* 504, 491, 476.

$C_{24}H_{44}N_4O_{10}$ (548.5) Calc. C 52.54 H 8.08 N 10.21% Found C 52.56 H 8.37 N 10.32%

Crystallization of the mother-liquor residues from hot THF. raised the yield of **3a** to 20%.

The above procedure was developed from the initial one [1] over many preparations.

In a slightly different run, using double the quantity of reagents in the same volume of DMF, 18 g (*ca.* 16%) of **3a** were obtained. Preparations performed in acetonitrile in lieu of DMF gave lower yields. In a few cases where the preparation went wrong, the initial precipitate was not orange (the colour of pure thallous iodide) but yellow-green. No attempt was made to analyze this behaviour further.

(2R, 3R, 11R, 12R)-(+)-N, N′, N″, N‴-Tetramethyl-1, 4, 7, 10, 13, 16-hexaoxacyclooctadecane-2, 3, 11, 12-tetracarboxamide (**3b**). The method of preparation from *(R, R)*-(+)-*N, N′*-dimethyltartramide (**1d**) and isolation of the product was analogous to that described for **3a**. Satisfactory yields (16–20%) were obtained at 5 times the reactant concentrations used for **3a**. Compound **3b** crystallizes as needles, m.p. 255° (from CH_2Cl_2/THF); $[\alpha]_D^{20} = +66°$ ($c = 0.75$, $CHCl_3$). – ^{1}H-NMR. ($CDCl_3$): 2.76 and 2.85 (*d*, 12 H, $CONHCH_3$): 3.55 (*m*, 16 H, OCH_2); 4.32 (*s*, 4 H, OCH); 7.03 (br. *s*, 4 H, $CONHCH_3$). – ^{13}C-NMR. ($CDCl_3$): 26.1 (CH_3); 69.9, 72.3 (OCH_2); 81.8 (OCH); 170.7 (CO).

$C_{20}H_{36}N_4O_{10}, \frac{1}{2}H_2O$ (501.5) Calc. C 47.89 H 7.44 N 11.1% Found C 47.39 H 7.17 N 11.32%

(2R, 3R, 11R, 12R)-(+)-1, 4, 7, 10, 13, 16-Hexaoxacyclooctadecane-2, 3, 11, 12-tetracarboxylic acid (**3c**). Compound **3a** was heated in 2.5M HCl (100 ml of acid per 10.0 g of crown) at 80° for 24 h. The residue obtained on evaporation to dryness *i.V.*, was redissolved in water and evaporated to dryness 3 times more. The crystalline product was then dissolved in a minimum of water and passed through a column of ion exchange resin in the acid form (*Dowex*, 50 W × 8; 250 g of resin per 10 g of residue). The acid fractions (pH < 3) were evaporated and recrystallization of the residue from the minimum of boiling water gave the tetracid **3c** (> 95%) as needles, m.p. 213°; $[\alpha]_D^{20} = +67°$ ($c = 0.73$, H_2O). – ^{1}H-NMR. (D_2O): 3.66 (*m*, 16 H, OCH_2); 4.55 (*s*, 4 H, OCH). – ^{13}C-NMR. (D_2O): 68.4, 69.0 (OCH_2); 78.2 (OCH); 171.9 (CO). – MS.: M^+ 440 (0); *m/z* 332 (100).

$C_{16}H_{24}O_{14} + 2\,H_2O$ (476.4) Calc. C 40.34 H 5.92% Found C 40.52 H 5.83%

(a) Equimolar proportions of the tetracid **3c** and NaCl were dissolved in the minimum of water. The aqueous solution slowly deposited crystals of the sodium complex as needles, m.p. > 260°. – ^{1}H-NMR. (D_2O): 3.63 (*m*, 16 H, OCH_2); 4.35 (*s*, 4 H, OCH).

$C_{16}H_{23}NaO_{14} + 2\,H_2O$ (498.4) Calc. C 38.56 H 5.46 Na 4.61% Found C 38.75 H 5.46 Na 4.84%

(b) From a solution of the tetracid **3c** in a minimum of concentrated hydrochloric acid in the cold, crystals of composition (**3c**, HCl, H_2O) separated, m.p. >260°.

$C_{16}H_{27}ClO_{15}$ (494.9) Calc. C 38.83 H 5.50% Found C 38.43 H 5.50%

(2R,3R,11R,12R)-1,4,7,10,13,16-Hexaoxacyclooctadecane-2,3,11,12-tetracarbonyl tetrachloride (**3d**). The tetracid **3c** (1.0 g) was stirred in dry CH_2Cl_2 (15 ml) and freshly sublimed PCl_5 (1.67 g) was added portionswise. After stirring at RT. overnight, the clear solution was evaporated *i.V.* to afford the acid chloride **3d** (1.1 g, 95%), needles, m.p. 180° (dec.) (from CH_2Cl_2 at 0°). – ^{1}H-NMR.: 3.73 (*m*, 16 H, OCH_2), 5.50 (*s*, 4 H, OCH).

(2R,3R,11R,12R)-1,4,7,10,13,16-Hexaoxacyclooctadecane-2,3:11,12-tetradicarboxylic dianhydride (**3e**). The finely powdered tetracid **3c** (0.68 g) was refluxed in freshly distilled acetyl chloride (15 ml) until a clear solution was obtained. Refluxing was continued for a further 2 h and the excess acetyl chloride removed *i.V.* to give the crystalline anhydride **3e** (0.62 g, yield ~100%), m.p. 153–154°. – ^{1}H-NMR. ($CDCl_3$): 3.69 and 3.92 (2 *m*, 2×8 H, OCH_2); 4.77 (*s*, 4 H, OCH). – ^{13}C-NMR. (CD_2Cl_2): 71.1, 71.25 (OCH_2); 80.4 (OCH); 166.95 (CO).

(2R,3R,11R,12R)-(+)-N,N,N',N',N'',N'',N''',N'''-Octabutyl-1,4,7,10,13,16-hexaoxacyclooctadecane-2,3,11,12-tetracarboxamide (**3f**). With efficient stirring, a solution of the acid chloride **3d** (2.57 g) in dry CH_2Cl_2 (50 ml) was added dropwise to dibutylamine (3.20 g) and triethylamine (2.50 g) in dry CH_2Cl_2 (100 ml) chilled in an ice-salt bath. After stirring for a further 15 min, the mixture was evaporated to dryness, the residue partitioned between heptane and water, and the organic phase washed with dilute hydrochloric acid, water, then dried ($MgSO_4$). Removal of the solvent gave compound **3f** as a solid (95%), m.p. 81°; $[\alpha]_D^{20} = +49°$ ($c = 1.27$, $CHCl_3$). – ^{1}H-NMR. ($CDCl_3$): 0.93, 1.38 and 3.23 ($CON(C_4H_9)_2$); 3.70 (*s*, 16 H, OCH_2); 4.78 (*s*, 4 H, OCH). – ^{13}C-NMR. ($CDCl_3$): 13.3 (CH_3); 19.7 (CH_3CH_2); 29.2, 30.8 (NCH_2CH_2); 45.2, 47.1 (NCH_2); 67.7, 70.1 (OCH_2); 74.9 (OCH); 168.1 (CO).

(2R,3R,11R,12R)-1,4,7,10,13,16-Hexaoxacyclooctadecane-2,3,11,12-(15N)-tetracarboxamide (**3f-15N**). A mixture of $(^{15}NH_4)_2SO_4$ (0.13 g) and NaOH (0.19 g) was gently heated on a metal bath (80 to 200°) and the $^{15}NH_3$ produced was flushed with an argon stream. The dried ($CaCl_2$) gas was bubbled into a solution of **3d** (0.05 g) in CH_2Cl_2 (5 ml). When the outlet gas became basic, the precipitate formed was centrifuged, dried, dissolved in CD_3OD (0.4 ml) and used as such for the NMR. measurements. The expected structure of the product (**3**, $X = CO^{15}NH_2$) was confirmed by the spectral data. – ^{1}H-NMR.: 3.84 (*m*, 16 H, OCH_2); 4.45 (*s*, 4 H, OCH).

(2S,3S,11S,12S)-2,3,11,12-Tetrakis(dimethylaminomethyl)-1,4,7,10,13,16-hexaoxacyclooctadecane (**4a**). A solution of $LiAlH_4$ (0.50 g) in dry THF (15 ml) was added dropwise to a stirred suspension of compound **3a** (0.90 g) in dry THF (3 ml). After reflux under N_2 for 18 h, the mixture was cooled and the excess hydride destroyed by the dropwise addition of 5% aqueous LiOH. Following drying ($MgSO_4$) and solvent evaporation, the crude product was chromatographed on alumina (CH_2Cl_2) to give **4a** as a colourless oil (0.65 g, 80%). – ^{1}H-NMR. ($CDCl_3$): 2.23 (*s*, 24 H, $CH_2N(CH_3)_2$); 2.35 (br. *m*, 8 H, $CH_2N(CH_3)_2$); 3.63 (*m*, 20 H, OCH_2 and OCH). – ^{13}C-NMR. ($CDCl_3$): 45.1 (NCH_3); 59.8 (NCH_2); 68.9, 71.2 (OCH_2); 78.7 (OCH). – MS.: M^+ 492; *m/z* 448, 446, 435, 391.

(2S,3S,11S,12S)-1,4,7,10,13,16-Hexaoxacyclooctadecane-2,3,11,12-tetrakis(methanol) (**4b**). A solution of B_2H_6 in THF (80 ml; 0.7M in BH_3) was slowly added to a stirred solution of **3c** (3.3 g) in dry THF (50 ml) under argon. After stirring for 2 h at 25°, excess B_2H_6 was destroyed by adding dry methanol and the volatile borate removed by repetitive evaporation of methanolic solutions until the residue was of constant weight. Continuous extraction of an aqueous solution of the latter with $CHCl_3$ gave, on concentration of the aqueous phase, the crude tetrol **4b** (oil, 2.4 g), used without further purification for the next step. – ^{1}H-NMR. ($CDCl_3$): 3.10 (br., 4 H, HO); 3.65 (br. *m*, 28 H, OCH_2 and OCH). – ^{13}C-NMR. ($CDCl_3$): 61.5 (CH_2OH); 70.4, 70.8 (OCH_2); 80.9 (OCH).

(2S,3S,11S,12S)-(−)-2,3,11,12-Tetrakis(p-toluenesulfonyloxymethyl)-1,4,7,10,13-16-hexaoxacyclooctadecane (**4c**). Tosyl chloride (8.0 g) was added in small portions to a stirred solution of crude **4b** (2.0 g) in freshly distilled dry pyridine (50 ml) cooled in an ice-salt bath. After standing at 0° for 48 h, the pyridine was removed at 25° under reduced pressure. The residue in a minimum of CH_2Cl_2 was chromatographed on silica gel (benzene/CH_2Cl_2 gradient). The product **4c** crystallized slowly from CH_2Cl_2/ether as prisms (2.34 g, 45%), m.p. 122–123° (dec.). $[\alpha]_D^{20} = -9°$ ($c = 0.67$, $CHCl_3$). – ^{1}H-NMR. ($CDCl_3$): 2.36 (*s*, 12 H, aryl-CH_3); 3.15–3.78 (*m*, 20 H, OCH_2 and OCH); 4.0 (*m*, 8 H,

CH_2–OTs); 7.4 (*qa*, 16 H, $C_6H_4CH_3$). – ^{13}C-NMR. ($CDCl_3$): 21.6 (CH_3); 68.7 (CH_2SO_3); 71.0 (OCH_2); 77.1 (OCH); 128.1, 130.0, 133.2, 145.0 (aryl-C).

$C_{44}H_{56}O_{18}S_4$ (1000.9) Calc. C 52.80 H 5.64% Found C 52.63 H 5.50%

(2S,3S,11S,12S)-(+)-1,4,7,10,13,16-Hexaoxacyclooctadecane-2,3,11,12-tetrakis(acetonitrile) (**4d**). A mixture of the tetra-*p*-toluenesulfonate **4c** (1.0 g) and NaCN (0.24 g) in dry DMSO (20 ml) was stirred for 5 days at 25°. The clear brown solution was poured into water, extracted with CH_2Cl_2 (4 × 50 ml) and the combined extracts were washed with water; drying ($MgSO_4$) and removal of the solvent gave an oil which slowly solidified. Recrystallization from methanol gave **4d** (0.31 g, 75%), m.p. 136–137°; $[\alpha]_D^{20} = +19°$ ($c = 0.39$, $CHCl_3$). – ^{1}H-NMR. ($CDCl_3$): 2.68 (*m*, 8 H, CH_2CN); 3.43–4.12 (*m*, 20 H, OCH_2 and OCH).

$C_{20}H_{28}N_4O_6$ (420.5) Calc. C 57.13 H 6.71 N 13.32% Found C 56.55 H 6.57 N 13.27%

(2S,3S,11S,12S)-(−)-1,4,7,10,13,16-Hexaoxacyclooctadecane-2,3,11,12-tetrakis(acetic acid) (**4e**). A solution of **4d** (0.20 g) in dry methanol (15 ml) was saturated with gaseous HCl and refluxed for 5 h. Most of the methanol was then removed under reduced pressure, water (10 ml) was added and the mixture heated at 80° for a further 5 h. Removal of the solvents and passage of an aqueous solution of the crude product through an acid *Dowex* (50 W × 8) column yielded, on evaporation of the acidic fractions (pH < 4), a crystalline residue. Recrystallization from acetonitrile gave **4e** (0.22 g, 95%), m.p. 197–201°. $[\alpha]_D^{20} = -23°$ ($c = 0.42$, H_2O). – ^{1}H-NMR. (D_2O): 2.65 (br., 8 H, CH_2CO_2); 3.64 (*s*, 20 H, OCH_2 and OCH).

$C_{20}H_{32}O_{14}$ (496.4) Calc. C 48.38 H 6.49% Found C 48.58 H 6.62%

(2R,3R,11R,12R)-(+)-N,N'-Dimethyl-1,4,7,10,13,16-hexaoxacyclooctadecane-2,3:11,12-tetracarboximide (**5**). This was obtained in quantitative yield from attempted acid hydrolysis of **3b** by the procedure described for the conversion of **3a** into **3c**; needles, m.p. 128° (from toluene). $[\alpha]_D^{20} = +147°$ ($c = 1.0$, $CHCl_3$). – ^{1}H-NMR. ($CDCl_3$): 2.8 (*s*, 6 H, $CONCH_3$); 3.54 and 3.87 (*m*, 2 × 8 H, OCH_2); 4.26 (*s*, 2 H, OCH). – ^{13}C-NMR. ($CDCl_3$): 24.5 (NCH_3); 70.7, 71.2 (OCH_2); 80.8 (OCH); 172.6 (CO).

$C_{18}H_{26}N_2O_{10}$ (430.4) Calc. C 50.23 H 6.04 N 6.51% Found C 50.14 H 6.06 N 6.32%

(4R,5R,15R,16R)-(+)-N,N,N',N',N'',N'',N''',N'''-Octamethyl-3,6,14,17-tetraoxa-23,24-diazatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8,10,12(24),19,21-hexaene-4,5,15,16-tetracarboxamide (**6**). (*R,R*)-(+)-*N,N,N',N'*-tetramethyl)tartramide (**1b**) (2.04 g), 2,6-bis(bromomethyl)pyridine (4.98 g) and thallous ethoxide (5.0 g) were reacted in dry DMF (150 ml) as described for the preparation of **3a**. The crude product obtained after filtration and evaporation of the solvent was chromatographed on alumina ($CHCl_3$) to give **6** (0.44 g, 15%) which crystallized from acetone as needles containing solvent of crystallization, m.p. 224°. $[\alpha]_D^{20} = +107°$ ($c = 1.6$, $CHCl_3$). – ^{1}H-NMR. ($CDCl_3$): 2.92 and 3.17 (2 *s*, 24 H, $CON(CH_3)_2$); 4.62 (*s*, 8 H, OCH_2); 5.0 (*s*, 4 H, OCH); 7.11 (*m*, 6 H, C_5H_3N). – ^{13}C-NMR. ($CDCl_3$): 35.6, 37.5 (NCH_3); 71.4 (OCH_2); 75.9 (OCH); 120.5, 137.1, 157.6 (aryl. *C*); 169.7 (CO). – MS.: $M^+ + 1$ 615; *m/z* 584, 570, 542.

$C_{30}H_{42}N_6O_8$ (614.7) + ½ C_3H_6O Calc. C 58.77 H 7.05 N 13.05% Found C 58.73 H 6.93 N 12.95%

(2R,3R,11R,12R,20R,21R)-(+)-N,N,N',N',N'',N'',N''',N''',N'''',N'''',N''''',N'''''-Dodecamethyl-1,4,7,10,13,16,19,22,25-nonaoxacycloheptacosane-2,3,11,12,20,21-hexacarboxamide (**7a**). The oily mother liquors from the crystallization of **3a** were first chromatographed on alumina (30 g per g of oil). After elution with toluene, which yielded some more crystalline **3a**, the remaining compounds were removed from the column by adding 2% methanol to the eluant. These residues were further chromatographed on silica gel (4 g per g of oil) deactivated by 5% of water. The least polar compounds were removed with CH_2Cl_2 and then five 200 ml-fractions were taken by adding respectively 1, 2, 4, 10 and 20% methanol to the eluant. Thin layer chromatography (TLC.) showed the presence of **7a** in all 5 fractions. Both macrocycles **3a** and **7a** are easily revealed by I_2, showing up much *faster* on alumina TLC. plates than the other materials. A more careful chromatography of the residues was then undertaken on alumina (100 g per g of residue; CH_2Cl_2 and CH_2Cl_2/MeOH 98:2). The fractions containing **7a** were evaporated *i.V.* and finally chromatographed on silica for TLC. deactivated with 5% of water (CH_2Cl_2/MeOH 95:5). The last fractions collected contained the desired

compound as a colourless oil (1%)[4]; $[\alpha]_D^{20} = +111°$ ($c = 1.07$, $CHCl_3$). – ^{1}H-NMR. and ^{13}C-NMR.: identical with those of **3a**. – MS.: MH^+ 824.

Compounds **3a** and **7a** have very similar $[\alpha]_D$ and NMR. spectra (and identical elemental analysis). The purity of **7a** and the absence of any significant amount of **3a** may be checked by addition of a guanidinium salt to the corresponding polycarboxylate derivatives. This leads to different ^{1}H- and ^{13}C-NMR. spectra, since only the larger ring system yields a stable guanidinium complex (see [23]). A more detailed description of the preparation and properties of **7a** will be given elsewhere.

(2R, 3R)-(+)-(N, N, N′, N′-Tetramethyl-1, 4, 7, 10, 13-pentaoxacyclopentadecane-2, 3-dicarboxamide) (**8a**) and *(2R,3R,17R,18R)-(N,N,N′,N′,N″,N″,N‴,N‴-octamethyl-1,4,7,10,13,16,19,22,25,28-decaoxacyclotriacontane-2,3,17,18-tetracarboxamide* (**9a**). The tartramide **1b** (25.8 g), 1,11-diiodo-3,6,9-trioxaundecane (**2c**) (52.4 g) and thallous ethoxide (63.0 g) were treated in dry DMF (1200 ml) for 15 h at 60° as detailed for the synthesis of **3a**. After filtration and solvent evaporation, the crude material was chromatographed on alumina. Following elution of the non-polar materials with ether, elution with $CHCl_3$ gave fractions rich in a mixture of **8a** and **9a**. Compound **8a** was obtained by continuous benzene extraction of an aqueous solution of the mixture. Recrystallization from ether at 0° gave 6 g (12%) of **8a** as needles, m.p. 65°; $[\alpha]_D^{20} = +84°$ ($c = 0.7$, $CHCl_3$). – ^{1}H-NMR. (C_6D_6): 2.33 and 2.47 (2 *s*, 12 H, $CON(CH_3)_2$); 3.26 and 3.40 (*s* and *m*, 16 H, OCH_2); 4.67 (*s*, 2 H, OCH). – ^{13}C-NMR. ($CDCl_3$): 35.6, 37.3 (NCH_3); 69.0, 70.6, 71.0 (OCH_2); 76.7 (OCH); 169.7 (CO). – MS.: M^+ 362; *m/z* 318, 290.

$C_{16}H_{30}N_2O_7$ (362.4) Calc. C 53.02 H 8.34 N 7.72% Found C 53.06 H 8.36 N 7.77%

Compound **9a** was isolated as their KSCN complex, m.p. 235°. – ^{1}H-NMR. ($CDCl_3$): 2.93 and 3.23 (2 *s*, 24 H, $CON(CH_3)_2$); 3.55 (br. *s*, 32 H, OCH_2); 5.15 (*s*, 4 H, OCH). – MS.: M^+ 724 (free ligand).

$C_{32}H_{60}N_4O_{14} \cdot 2\,KSCN \cdot H_2O$	Calc.	C 43.58	H 6.66 N 8.96%
(937.2)	Found	„ 43.64	„ 6.39 „ 8.93%

Separation and purification of the compounds formed by the reaction of **2c** with **3a** has also been performed by liquid phase chromatography. After filtration and solvent evaporation, the crude reaction product (51.0 g) was subjected portionwise (5 g) to chromatography on a *Waters* Prep LC 500 apparatus, using a 5 × 122 cm gel permeation preparative column (*Styragel* 200 Å for MW 200 to 4000) with toluene as the eluant. The chromatogram (refractometric detection) showed monomeric, dimeric and higher molecular weight materials to be present in about equal amounts. After recycling until the separation was sufficient, 13 g of monomer fraction M and 11 g of dimer fraction D could be recovered; no attempt was made to further purify the higher molecular weight material. Removal of non-cyclic materials from fractions M and D was performed with the same equipment using a preparative *Waters* silica Prep PAK column and methanol/chloroform 8:2 as eluant. Fraction M and D yielded about 6.5 g (13%) of compound **8a** and 7.0 g (13%) of compound **9a** respectively.

(2R,3R)-(+)-1,4,7,10,13-Pentaoxacyclopentadecane-2,3-dicarboxylic acid (**8b**). The diamide **8a** was hydrolyzed with 2.5N aqueous HCl under reflux as described for **3a**. Work up and isolation as described for the latter gave, on recrystallization from water, the diacid **8b** (95%), m.p. 60–70° (dec.). On drying *i.V.*, the crystals changed into a colourless glass; $[\alpha]_D^{20} = +24°$ ($c = 0.61$, H_2O). – ^{1}H-NMR. (D_2O): 3.70 (*m*, 16 H, OCH_2); 4.37 (*s*, 2 H, OCH). – ^{13}C-NMR. ($CDCl_3$): 69.2, 69.9, 70.2, 70.5 (OCH_2); 79.8 (OCH); 170.9 (CO). – MS.: MH^+ 309.

$C_{20}H_{20}O_9$ (308.2) + 3 H_2O Calc. C 39.77 H 7.23% Found C 39.89 H 7.04%

(2R,3R)-(+)-1,4,7,10,13-Pentaoxacyclopentadecane-2,3-dicarboxylate (**8c**). The diamide **8a** (0.30 g) in dry methanol (10 ml) saturated with dry HCl gas, was heated under reflux for 72 h. The methanol was then evaporated *i.V.* and the residue was treated with water (10 ml) and extracted with CH_2Cl_2. The organic layer was washed with 10% aqueous K_2CO_3-solution, dried ($MgSO_4$) and

---

[4] Possibly this tedious procedure might be improved for isolation of **7a** but no attempts were made at this stage. Compound **7a** has also been obtained by a designed synthetic route [23] giving 18% yield in the final cyclization (improved over the 10% yield reported earlier [23]).

evaporated to give the diester **8c** as a colourless oil (0.23 g, 85%); $[\alpha]_D^{20} = +49°$ ($c = 0.41$, $CHCl_3$). – ^{1}H-NMR. ($CDCl_3$): 3.73 and 3.80 (2 *s*, 22 H, CO_2CH_3 and OCH_2); 4.28 (*s*, 2 H, OCH).

*(7*R*, 8*R*)-(+)-7, 8-(*N, N, N′, N′*-Tetramethyl-6, 7-benzo-1,4-dioxa-6-cyclooctene-(2*R, 3*R)-(+)-2, 3-dicarboxamide* (**11**), *(2*R, 3*R, 10*R, 11*R)-(+)-2, 3, 10, 11-(*N, N, N′, N′, N″, N″, N‴, N‴-octamethyl)-6, 7:14, 15-dibenzo-1, 4, 9, 12-tetraoxa-6, 14-cyclohexadecadiene-2, 3, 10, 11-tetracarboxamide* (**12**), *and (2*R, 3*R, 10*R, 11*R, 18*R, 19*R)-(+)-2, 3, 10, 11, 18, 19-(*N, N, N′, N′, N″, N″, N‴, N‴, N⁗, N⁗, N⁗′, N⁗′-dodecamethyl)-6, 7 : 14, 15 : 22, 23-tribenzo-1, 4, 9, 12, 17, 20-hexaoxa-6, 14, 22-cyclotetracosatriene-2, 3, 10, 11, 18, 19-hexacarboxamide* (**13**). The tartramide **1b** (4.08 g), *α,α′*-dibromo-*o*-xylene (**2e**) (5.28 g) and thallous ethoxide (2.9 ml) were treated in dry acetonitrile (250 ml) for 75 min at 70° as detailed for the synthesis of **3a**. After filtration and solvent removal, the residue was chromatographed on alumina. Elution with toluene followed by $CHCl_3$ allowed the monomer **11**, dimer **12** and trimer **13** to be separated. Compound **11** was recrystallized from ether (20%), m.p. 104–105°; $[\alpha]_D^{20} = +46°$ ($c = 1.6$, $CHCl_3$). – ^{1}H-NMR. ($CDCl_3$): 2.85, 3.1 (2 *s*, 2×6 H, $N(CH_3)_2$); 4.76 (*s*, 2 H, OCH); 5.02 (*s*, 4 H, OCH_2); 7.0 (*m*, 4 H, C_6H_4). – MS.: M^+ 306.

$C_{16}H_{22}N_2O_4$ (306.3) Calc. C 62.72 H 7.24 N 9.14% Found C 62.65 H 7.25 N 9.14%

Compound **12** was recrystallized from toluene (22%), m.p. 230°; $[\alpha]_D^{20} = +114°$ ($c = 1.5$, $CHCl_3$). – ^{1}H-NMR. ($CDCl_3$): 2.85, 3.02 (2 *s*, 2×12 H, $N(CH_3)_2$); 4.65 (*s*, 8 H, OCH_2); 4.82 (*s*, 4 H, OCH); 7.1 (*s*, 8 H, C_6H_4).

$C_{32}H_{44}N_4O_8$ (612.7) Calc. C 62.72 H 7.24 N 9.14% Found C 62.67 H 7.03 N 9.15%

The trimer **13** was a glass which could not be crystallized (12.5%); $[\alpha]_D^{20} = +76°$ ($c = 0.87$, $CHCl_3$). – ^{1}H-NMR. ($CDCl_3$): 2.76, 2.85 (2 *s*, 2×18 H, $N(CH_3)_2$); 4.63 (*s*, 18 H, OCH_2, OCH); 7.65 (*s*, 12 H, C_6H_4). – MS.: M^+ 918.

We thank *C. Sirlin* for his contribution to the improvement of the synthetic procedure of obtaining macrocycle **3a**, *C. Sirlin* and *P. Lix* for the preparation of **3b** and *P. Plumeré* for performing several preparations of **3a**.

REFERENCES

[1] *J.M. Girodeau, J.M. Lehn & J.P. Sauvage,* Angew. Chem. *87*, 813 (1975); Angew. Chem. Int. Ed. *14*, 764 (1975).
[2] *C.J. Pedersen & H.K. Frensdorff,* Angew. Chem. *84*, 16 (1972); Angew. Chem. Int. Ed. *11*, 16 (1972).
[3] *J.M. Lehn,* Structure and Bonding *16*, 1 (1973).
[4] *J.J. Christensen, D.J. Eatough & R.M. Izatt,* Chem. Rev. *74*, 351 (1974).
[5] 'Progress in Macrocyclic Chemistry', Vol.1 and Vol.2, Ed. R.M. Izatt & J.J. Christensen, John Wiley & Sons, New York 1979; 'Coordination Chemistry of Macrocyclic Compounds', Ed. G.A. Melson, Plenum Press, New York 1979.
[6] *Y.A. Ovchinnikov, V.T. Ivanov & A.M. Shkrob,* 'Membrane Active Complexones', Elsevier Scient. Pub. Comp., N.Y. 1974.
[7] *D.J. Cram & J.M. Cram,* Science *183*, 803 (1974); Acc. Chem. Res. *11*, 8 (1978).
[8] *F. Wudl & F. Gaeta,* Chem. Commun. *1972*, 107.
[9] *I.J. Burden, A.C. Coxon, J.F. Stoddart & C.M. Wheatley,* J.Chem. Soc. Perkin I *1977*, 220; *D.A. Laidler & J.F. Stoddart,* Carbohydrate Res. *55*, C1 (1977); Tetrahedron Lett. *1979*, 453; *R.B. Pettman & J.F. Stoddart,* Tetrahedron Lett. *1979*, 457, 461.
[10] *R.C. Hayward, C.H. Overton & G.H. Whitham,* J. Chem. Soc. Perkin I *1976*, 2413.
[11] *L. Töke, L. Fenichel, P. Bakó & J. Szejtli,* Acta Chim. Acad. Scient. Hungaricae *98*, 357 (1978); *M. Žinić, B. Bosnić-Kašnar & D. Kolbah,* Tetrahedron Lett. *1980*, 1365.
[12] *V. Prelog & D. Bedeković,* Helv. *62*, 2285 (1979).
[13] *W.D. Curtis, R.M. King, J.F. Stoddart & G.H. Jones,* Chem. Commun. *1976*, 284.

[14] *V. Prelog,* Pure Appl. Chem. *50*, 893 (1978); *A.P. Thoma, A. Viviani-Nauer, K.H. Schellenberg, D. Bedeković, E. Pretsch, V. Prelog & W. Simon,* Helv. *62*, 2303 (1979).
[15] *J.P. Behr, J.M. Lehn & P. Vierling,* Chem. Commun. *1976*, 621.
[16] *J.M. Lehn,* Pure Appl. Chem. *50*, 871 (1978); *51*, 979 (1979).
[17] *J.M. Timko, R.C. Hegelson, M. Newcomb, G.W. Gokel & D.J. Cram,* J. Am. Chem. Soc. *96*, 7097 (1974); *D.E. Kime & J.K. Norymberski,* J. Chem. Soc. Perkin I *1977*, 1048.
[18] *J.M. Lehn,* Acc. Chem. Res. *11*, 49 (1978).
[19] *W.D. Curtis, D.A. Laidler, J.F. Stoddart & G.H. Jones,* Chem. Commun. *1975*, 833.
[20] *N. Ando, Y. Yamamoto, J. Oda & Y. Inouye,* Synthesis *1978*, 688.
[21] *T. Matsui & K. Koga,* Tetrahedron Lett. *1978*, 1115.
[22] *H.O. Kalinowski, D. Seebach & G. Grass,* Angew. Chem. *87*, 812 (1975); Angew. Chem. Int. Ed. *14*, 763 (1975); and Chem. Ber., in press.
[23] *J.M. Lehn, P. Vierling & R.C. Hayward,* Chem. Commun. *1979*, 296.
[24] *A.C. Cope & A.S. Mehta,* J. Am. Chem. Soc. *86*, 5626 (1964).
[25] *J.D. Owen & M.R. Truter,* J. Chem. Soc. Dalton *1979*, 1831.
[26] *R.M. Izatt, B.L. Haymore & J.J. Christensen,* Chem. Commun. *1972*, 1308.
[27] *D. Nagano, A. Kobayashi & Y. Sasaki,* Bull. Chem. Soc. Jpn *51*, 790 (1978).
[28] *J.J. Daly & J.P. Behr,* unpublished results.
[29] *J.P. Behr, D. Moras & J.C. Thierry,* unpublished results.
[30] *J.D. Dunitz & P. Seiler,* Acta Crystallogr. *B30*, 2739 (1974).
[31] *J.D. Dunitz, M. Dobler, P. Seiler & R.P. Phizackerley,* Acta Crystallogr. *B30*, 2733 (1974).
[32] *J.B. Lambert,* Acc. Chem. Res. *4*, 87 (1971).
[33] *K.D. Kopple, A. Ahsan & M. Barfield,* Tetrahedron Lett. *38*, 3519 (1978).
[34] *V.F. Bystrov, Y.D. Gavrilov & V.N. Solkan,* J. Magn. Res. *19*, 123 (1975).
[35] *M. Fieser & L. Fieser,* 'Reagents for Organic Synthesis', J. Wiley & Sons, Inc., Volume 2, 1969.
[36] *P.W. Fiet,* J. Med. Chem. *7*, 14 (1964).
[37] *D. Seebach, H. Dörr, B. Bastani & V. Eyrig,* Angew. Chem. *81*, 1002 (1969); Angew. Chem. Int. Ed. *8*, 982 (1969).
[38] *M.H. Filippo,* Recl. Trav. Chim. Pays Bas *29*, 121 (1912).
[39] *C.H.S. Gibson & J.D.A. Johnson,* J. Chem. Soc. *1930*, 2525.
[40] *W. Baker, K.M. Buggle, J.F.W. McOmie & D.A.M. Watkins,* J. Chem. Soc. *1958*, 3594.
[41] *J.R. Dann, P.P. Chiesa & J.W. Gates, jr.,* J. Org. Chem. *26*, 1991 (1961).