229. Synthesis and Properties of Chiral Macrotricyclic Ligands. Complexation and Transport of Chiral Molecular Cations and Anions[1])

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(9.VIII.78)

Summary

The optically active macrotricyclic cryptands **1** and **2**, containing the binaphthyl group as chiral unit, have been synthesized. These compounds contain lateral cavities which may serve as anchoring sites for polar groups of the substrates and a central, chiral cavity large enough for including more or less completely the bulk of a molecular ion. Their complexation properties towards molecular ions give evidence for the occurrence of two types of processes: a) direct complexation of primary ammonium cations, like phenylethyl ammonium chloride, occurs with either **1** or **2**; b) cascade binding, involving first complexation of an alkali cation followed by pairing with a molecular anion, takes place with **2**. Process b) may be considered as a *metallo-receptor* model system where binding of an anionic substrate is dependent on initial binding of a cation. In both cases a) and b) weak resolution of chiral racemic substrates has been observed by extraction and transport (through a bulk liquid membrane) experiments. This indicates that in the complex the bulk of the substrate should be located close to the chiral unit and therefore more or less in the central cavity. In the case of cryptand **2**, the resolution achieved for the (±)-mandelate anion is markedly affected by the nature of the complexed cation.

Molecular recognition, i.e. the ability of a ligand or *receptor molecule* to select and bind a substrate among a collection of molecules, can be achieved with a ligand containing an *intramolecular cavity* 1) of suitable size and shape for complete inclusion of the substrate, 2) lined with binding sites of appropriate nature and arrangement for strong attractive interaction with the substrate. Recognition thus requires the careful design of a receptor molecule presenting *intermolecular complementarity*. In particular, it involves discerning the proper interactions which will lead to substrate binding and inclusion, and building them into the walls which delineate the cavity of a synthetic receptor molecule.

[1]) Previous paper, see [1].

[2]) E.R.A. No. 265 of the C.N.R.S.

Hydrophobic effects may cause molecules to associate, and have been used as driving force for molecular complexation. However since they are thought to arise from the fact that the associated molecules disturb the solvent less than the separated ones we cannot expect a high directionality of complexation. That is to say that such association will probably lead to the existence in solution of complexes of similar energies but of different geometries. Thus, 'hydrophobic' type effects may provide stability but little selectivity. The binding of hydrophobic substrates by the cyclodextrins has yielded well defined examples of substrate inclusion in a molecular cavity [2]. Synthetic macrocycles [3–5] and macrotricycles [6] [7] containing cavities have also been shown to associate with hydrophobic substrates; to which extent the resulting molecular complexes are of the inclusion type is however less well defined at present than in the case of the cyclodextrins.

Polar cavities may serve as receptor sites for the binding of polar functional groups. The ability of macrocyclic polyethers to complex primary ammonium salts [8] has been extensively used to develop several classes of derivatives which display a number of interesting features [9–12]. The $-NH_3^+$ inserts into the [18]-crown-6 macrocyclic polyether by hydrogen bonding to alternate oxygen atoms, in agreement with the X-rays structure of a macrocyclic ammonium complex [14], although this is not the only possible binding geometry [15]. Using the macrocycle as *anchoring site* for the NH_3^+-groups of ammonium salts and lining its periphery with various structural units lead to molecular receptors which display various selectivity patterns of $R-NH_3^+$ complexation due to lateral interaction of the R-residue with the groups attached to the macrocycle [9–13]. Resolution of racemic ammonium salts has been achieved with chiral macrocyclic ligands [9] [11] [13] especially with crown ethers incorporating binaphthyl groups as chiral unit [9]. When reactive groups are attached to the macrocycle, enhanced rates of reaction with the bound substrates have been observed [16–19].

The work to be described here concerns the study of molecular receptors in which a macrocyclic subunit may serve as anchoring site for binding and inclusion of a substrate in the molecular cavity of the receptor.

As noted earlier [20–22], *cylindrical macrotricyclic* molecules possess *three cavities:* two lateral macrocyclic subunits which may bind NH_3^+-groups as well as alkali or alkaline-earth cations and a central cavity defined by the two macrocycles and the bridges linking them. When the central cavity is large enough, inclusion of substrates may become possible. Associations of such macrotricycles with fluorescent probes has indeed been detected [6] but it is not known at present to what extent inclusion of the probe occurs. However, a cylindrical macrotricyclic ligand provides the opportunity to use one (or both) of the lateral cavities for binding a functional group of a substrate and pull it into the central cavity, thus combining to some extent the features of the macrocyclic polyethers (lateral cavities) and of the cyclodextrins (central cavity). Two types of complexation may be envisaged with such substances: a) binding of primary ammonium *cations,* by fixation of the NH_3^+-group on one of the lateral macrocycles *(Fig. 1a);* b) *cascade binding,* in which a metal cation (alkali or alkaline-earth) is first bound by one of the macrocycles followed by binding of a *molecular anion* to this

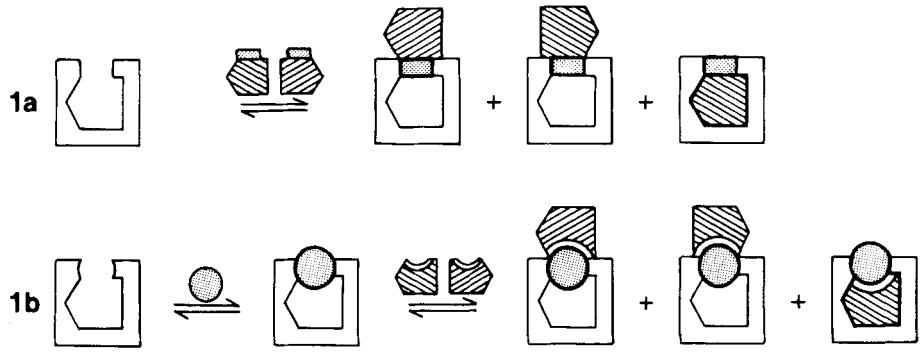


Fig. 1. *Schematic representation (in two dimensions) of two different association mechanisms between a substrate and a chiral ligand containing an internal cavity.* a) Direct interaction of a binding site of the substrate with an anchorage site on the ligand; b) cascade mechanism involving two successive steps: complexation of a metal cation to a binding site on the ligand followed by ion pair formation with a molecular anion. In both cases external and internal complexes may form; only the latter are expected to be appreciably affected by the properties (shape, size, chirality) of the intramolecular cavity of the ligand.

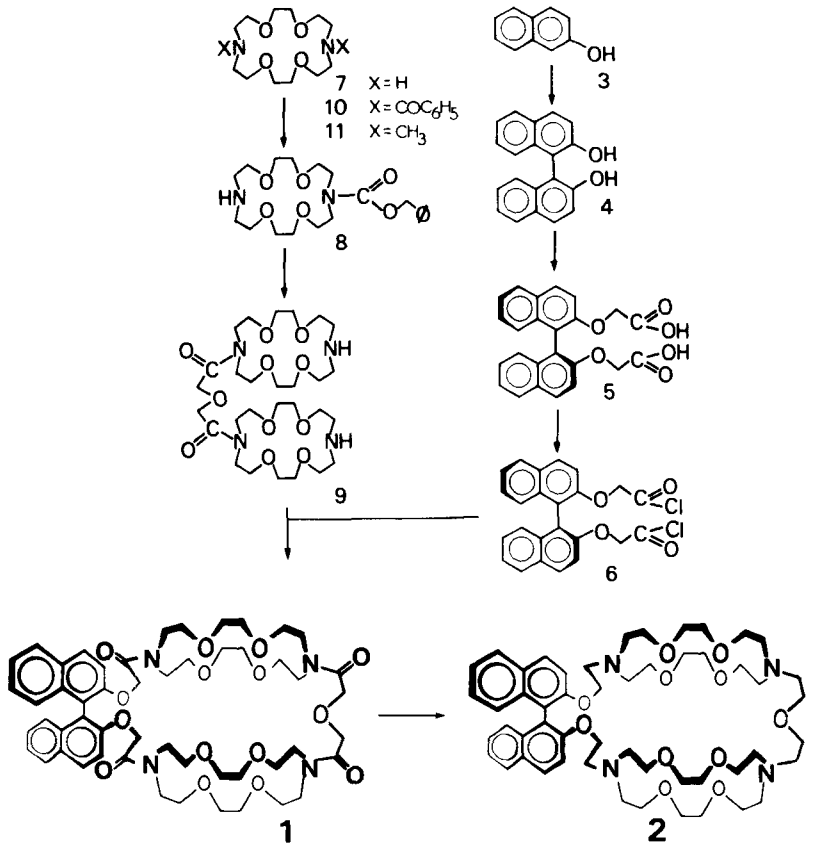
initially formed positively charged binding site *(Fig. 1b);* in this case the macrotricycle may be considered as an *apo-receptor* which is transformed into a *metallo-receptor* (or *holo-receptor*) prior to binding of the substrate[3]). In both cases, a macrocyclic subunit serves as (direct or indirect) anchoring sites for binding and orienting the substrate, thus limiting the number of possible geometries of the resulting molecular associate. However, the question still remains whether the bulk of the bound substrate (*i.e.* the R-group of $R-NH_3^+$ in case a) or the molecular anion in case b)) is outside or inside the central cavity of the macrotricycle.

When a chiral binaphthyl subunit (whose efficiency in chiral recognition is well documented [9]) is used as one of the bridges of a cylindrical macrotricycle, as in compounds **1** and **2**, the central cavity becomes chiral. Such a chiral cavity may help distinguishing between external and inclusion complexes. Indeed only in the latter case does one expect notable interaction of the bound substrate with the chiral unit; consequently, if the complexes formed with chiral substrates display *chiral discrimination*, they probably are *inclusion* complexes *(Fig. 1)*. We report here the synthesis and properties of ligands **1** and **2** *(Scheme)* and show that they indeed appear to form inclusion complexes (for a preliminary report on this work see [25]). The C_2-symmetry of the chiral binaphthyl groups of compounds **1** and **2** renders the two macrocyclic units equivalent and is also sufficiently lipophilic for extraction experiments (see below).

Synthesis of the Macrotricyclic Ligands **1** *and* **2**. The method followed for the synthesis of ligands **1** and **2** *(Scheme)* was the same as the general scheme described previously for other macrotricyclic ligands of cylindrical type [20].

[3]) This terminology follows that used in enzymology for metallo-enzymes: the holo-enzyme and its metal free apo-enzyme. We described earlier a similar process, *i.e.* the regulation of the binding of fluorescent probes to macrotricycles *via* prior binding of suitable metal cations [6]. The development of cyclodextrin derivatives bearing complexing sites for metal cation [23] [24] follows the same line of thought.

Scheme. *Reaction scheme for the synthesis of the macrotricyclic ligands* **1** *and* **2**.



Binaphthol [26] [27] was efficiently resolved *via* cyclic phosphate derivative [28]. The optically pure *S*-(−)-isomer **4** [29] [30] was converted into its diacetic derivative **5** in 98% yield using a suspension of potassium bromoacetate and potassium carbonate in methanol. We checked that this reaction, which is carried out at high temperature, did not lead to racemization. The transformation of **5** into the corresponding diacid dichloride **6** with oxalyl chloride was quantitative. The synthesis of the *N*-monoprotected diamine **8** and the bis-macrocyclic derivative **9** has been already described [20]. The diamine **9** was condensed under high dilution conditions [31] with **6** to give the optically active macrotricyclic tetramide **1** in 50% yield. The corresponding tetramine **2** was obtained by reduction with diborane in THF. The experimental details of the various steps and the physical characteristics of the synthesized compounds are described in the experimental section.

Complexation, Extraction and Transport of Primary Ammonium Salts by the Chiral Macrotricyclic Tetramide 1. – In order to avoid possible proton transfer between primary ammonium substrates $R-NH_3^+$ and the nitrogen sites of the ligand

we preferentially used the tetramide **1** rather than the tetramine **2** for studying the complexation properties of these macrotricyclic systems. However, the involvement of the nitrogen sites of **1** in amide functions is expected to decrease its complexation ability as compared to compound **2**. Indeed, whereas the diazatetraoxa macrocycle **11** complexes primary ammonium salts like [18]-crown-6 itself [32], the diamide model compound **10** is much less efficient (see below); furthermore the binding geometry is less well defined in the latter case.

The complexation of an optically active ammonium substrate (+)-S or (−)-S by a chiral ligand (−)-L is represented by the equations (1a) and (1b):

$$(-)\text{-L} + (+)\text{-S} \rightleftharpoons [(-)\text{-L}, (+)\text{-S}] \tag{1a}$$

$$(-)\text{-L} + (-)\text{-S} \rightleftharpoons [(-)\text{-L}, (-)\text{-S}] \tag{1b}$$

The two diastereoisomeric complexes obtained have in principle different association constants. The resulting chiral discrimination may be evaluated by the difference, in percentage, of the two diastereoisomers formed, *i.e.* the enantiomeric excess (**e.e.**).

A convenient way to determine the **e.e.** is to employ an *extraction method.* It consists in extracting an aqueous solution of a racemic substrate with an organic solution of the optically active ligand and analyzing the organic layer in order to determine the total amount of substrate extracted and the proportion of each diastereoisomer. The ligand must be lipophilic enough to remain in the organic layer and the substrate should not be extracted in the absence of the ligand; this was the case in the present work. Such extraction experiments have been extensively used in chiral discrimination studies involving binaphthyl-crown ethers and ammonium salts [9]. The extraction efficiency is greatly increased by using an appropriate anion of low charge density, like PF_6^- or BPh_4^-. We used instead the salting out effect of a large excess of the corresponding acid (HCl). In a typical experiment a 2 M solution of a primary ammonium salt (phenyl or naphthylethyl ammonium, phenylalanine methyl ester hydrochloride) in 6 N aqueous HCl was extracted with a 0.1 M solution of ligand **1** in chloroform. The following results were obtained: a) compound **1** is able to extract ammonium salts, therefore implying that complexation occurs in the organic phase; b) the extraction stoïchiometry does not exceed 1/1, although ligand **1** contains two potential binding sites for $R-NH_3^+$; c) under the same conditions no extraction was observed with the model compound **10**. These data indicate that the complexation of ammonium salts by ligand **1** probably involves the central cavity of the system since binding to the external faces of the macrocycles would not be expected to differ much from binding to **10**.

Further information about the nature of the complex formed was gained by making use of the chirality of the ligand. The ^{1}H-NMR. spectrum of the chloroform solution obtained by extraction of racemic α-naphthylethylammonium chloride displays two CH_3 doublets of unequal intensities arising each from one of the diastereoisomeric complexes [(−)-L, (+)-S] and [(−)-L, (−)-S]. Comparison

with the spectra of the solutions obtained with optically pure substrate, indicates an **e.e.** of about 15% for the [(−)-L, (−)-S] isomer in the organic layer.

Transport experiments through a liquid membrane [33] were performed following a procedure previously used for amino-acid [34] alkali cation transport [35] and chiroselective transport [36] [37]. It involves two aqueous layers separated by a non-miscible organic phase (chloroform in the present case); one aqueous phase *(IN phase)* contains the substrate studied; the organic phase contains the carrier **1** which extracts the substrate, carries it to the interface with the second aqueous phase *(OUT phase)* where the substrate is released and its rate of appearance is followed by UV. spectrometry and polarimetry. The rate of transport of D,L-*α*-naphthylethylammonium chloride was 0.35 mol/h with the set up used; the membrane contained 10% **e.e.** of the (−)-enantiomer and the *OUT phase* 13% **e.e.** of the same optical isomer. With *α*-phenylethylammonium chloride neither doubling of the NMR. signals for CH_3 nor chiroselective transport was observed.

These experiments indicate that the *structure* of the complex between the macrotricyclic ligand **1** and an ammonium salt involves at least partial inclusion into the central molecular cavity, probably *via* binding of the NH_3^+-groups to the internal face of one of the lateral macrocycles (see *Fig. 1*)[4]). Indeed, only in such internal complexes should the bound substrate interact appreciably with the chiral binaphthyl unit and therefore be subject to chiral discrimination. The smaller size of the phenyl as compared to the naphthyl group might account for the absence of chiral discrimination in the former case. The fairly low **e.e.** found may arise from unsufficient discriminating interactions and perhaps from some amount of external complexation.

Some complexation experiments were conducted with the *tetraamine* **2**. Complex formation of **2** with primary ammonium chlorides like ethylammonium; (±)-*α*-phenylethylammonium, (±)-*α*-naphthylethylammonium, $NH_3^+(CH_2)_nNH_3^+$ (n=4, 5, 8) may be observed by ^{1}H-NMR. spectroscopy in CD_3OD-solution; complexes of (1:1)-stoïchiometry are formed in all cases. However, extraction and transport experiments like those described above for the tetraamide **1** could not be performed because of protonation of **2** by proton exchange with the substrate without complexation. In the complexes formed in methanol solution the NH_3^+-group is probably bound to one of the lateral macrocycles as in the case of the model sub-unit **11** [32]; since ligand **2** forms only (1:1)-complexes with $R-NH_3^+$ but is able to bind two alkali cations (see below), the ammonium substrates may be expected to occupy the central cavity, thus hindering the complexation of a second species.

Chiral discrimination of molecular anions by ion pairing with alkali cation complexes of ligand 2. – The interaction of a salt of a chiral molecular anion (±)-A^- and a complexable cation M^+ with a chiral ligand (−)-L may lead to chiral discrimination *via* a two step, *cascade*, complexation process *(Fig. 1b)*

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[4]) The amide functions may also participate in substrate binding to some extent, since an acyclic chiral dioxa-diamid has been shown to extract and transport (±)-*α*-phenylethylammonium chloride [38].

involving: (i) complexation of the alkali metal cation by the optically active ligand *(apo-receptor)* yielding a cation inclusion complex:

$$(-)\text{-L} + M^+ \rightleftharpoons [M^+ \subset (-)\text{-L}] \tag{2}$$

(ii) ion pair formation between the resulting *metallo-receptor* and the racemic molecular anion $(\pm)$-A^-:

$$[M^+ \subset (-)\text{-L}] + (+)\text{-}A^- \rightleftharpoons \{[M^+ \subset (-)\text{-L}], (+)\text{-}A^-\} \tag{3a}$$

$$[M^+ \subset (-)\text{-L}] + (-)\text{-}A^- \rightleftharpoons \{[M^+ \subset (-)\text{-L}], (-)\text{-}A^-\} \tag{3b}$$

The preformation of a cation complex may allow some *regulation* of the chiral discrimination by the nature of the complexed cation. The second step requires a medium of low dielectric constant in order to favour strong cation-anion interactions. The *cation complexation properties* of cylindrical macrotricyclic ligands have been described in previous publications [21]. These ligands form mononuclear and binuclear cryptate cation inclusion complexes of 1:1 and 2:1 cation/ligand stoïchiometries with alkali and alkaline-earth cations. The crystal structure of a bis-sodium complex showed that the two Na^+ cations are located inside the central cavity and bound each to one of the lateral macrocyclic subunits [39]. However, the larger cations, Rb^+ and Cs^+, cannot entirely penetrate into the monocyclic subunit. In the corresponding complexes of the [18]-crown-6 ligand, which has a structure close to the two subunits in **2**, the Rb^+ and Cs^+ cations are situated outside the average plane formed by the six oxygen atoms (1.19 Å and 1.44 Å resp.) [40].

The *stability constants* for the complexes of ligand **2** with alkali cations have been measured in methanol/water 95:5 *(v/v)* using cation selective electrodes as in previous studies [21]. The following values have been obtained (at 25°):

Cation	Na^+	K^+	Rb^+	Cs^+
$\log K_1$	3.4	4.7	3.8	4.0
$\log K_2$	–	3.1	2.2	2.0

K_1 and K_2 correspond to the formation equilibria of the mono and binuclear complexes. The magnitude of the stability constants as well as the selectivity sequence are very similar to those obtained previously for other ligands of this type [21]. It is reasonable to assume that in the present case too, the cations were complexed by the two macrocyclic subunits. The complexed cation thus provides a charge precisely located inside the macrotricyclic ligand, which might serve for directing molecular complexation by ion pair formation, acting as an anchor site for inclusion of a molecular anion.

Cation complexation affects markedly the optical rotation of ligand **2**. In chloroform, $[\alpha]_D^{25}$ has the following values: $-68°$, $-25°$ and $0°$ for the free ligand, its Na^+ and K^+ complexes respectively. Chiral macrobicyclic cryptates also show optical rotations which gradually change as a function of cation

radius [25]. The same phenomenon has been observed in the case of cyclic peptides [41].

Extraction experiments were performed for testing the chiral discrimination ability of ligand **2** towards chiral anions following the processes in equations (2) and (3).

Aqueous solutions of alkali cation salts of racemic mandelic acid, (±) C_6H_5–CHOH–COOH, or of the corresponding naphthyl derivative (α-hydroxy-1-naphthaleneacetic acid), adjusted to pH 10 with the hydroxide of the cation studied, were extracted with a solution of ligand **2** in chloroform (0.07 M). In the case of the mandelate ion (0.75 M in water) the following substrate: ligand ratios were observed in the chloroform layer: M = Na^+ 0.6:1, K^+ 1:1, Rb^+ 1.2:1, Cs^+ 0.6:1, NH_4^+ 1.2:1 (error limit ±0.1). In presence of the tetraethylammonium cation $(NEt_4)^+$ which is known not to be complexed by ligand **2**, no extraction of mandelate in the organic layer could be detected. The stoïchiometry of the complex in the organic phase is in all cases close to 1:1. The driving force for extraction is the complexation of the cation (eq. 2).

With racemic (±) alkali mandelate the extraction experiments lead to diastereoisomeric complexes in the organic layer (eq. 3). The ^{1}H-NMR. spectra of the chloroform layer (Fig. 2) give the following results:

a) In the case of K^+, Rb^+ and Cs^+ mandelate two signals are observed for the benzylic proton, each arising from one diastereoisomer (eq. 3). This signal is not split with sodium mandelate;

b) Integration of the benzylic signals and identification by comparison with the spectra obtained with optically active mandelate, shows that with K^+, (−)-mandelate is extracted preferentially (**e.e.** ~ 15%), with Cs^+, (+)-mandelate is extracted preferentially (**e.e.** ~ 10%), with Rb^+ and NH_4^+ (which both have a radius ~ 1.40 Å, intermediate between K^+, 1.33 Å, and Cs^+, 1.67 Å) no chiral discrimination is observed *(Fig. 2)*. Extractions using aqueous solutions of mandelate salt twice diluted gave the same results, thus confirming that the effect was due to the complex and not to eventual effects of extraction stoïchiometries;

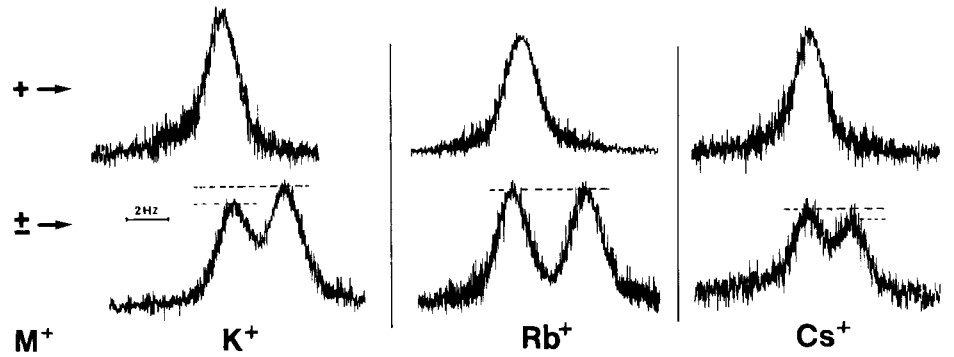

Fig. 2. *^{1}H-NMR. spectra of the organic layer obtained by extraction of aqueous solutions of the (+)-optically pure isomer and of the (±)-racemic mixture of the mandelate anion (3.3 M) with ligand* **2**, *0.07 M in $CDCl_3$.* Only the singlet due to the benzylic proton of the substrate is represented: C_6H_5–C*H*(OH)–COO^- M^+. The metal cation used is indicated below the corresponding spectrum.

c) With the larger anion, the naphthyl analog, the benzylic ^{1}H-NMR. signal is also split but no chiral discrimination is observed whichever cation is used. These findings, (i) that chiral discrimination is present, (ii) that it is influenced by both the cation and the anion, strongly *support the cohabitation of these ions in the central cavity of the ligand.* This agrees with the fact that the mandelate anion is extracted but no optical enrichment (**e.e.** $< 10\%$) is found when similar extraction experiments are performed with the alkali cation complexes of the chiral macrobicyclic ligand (**12**) [25]. With this system only the cation can be included in the molecular cavity, which is too small for anion inclusion, leading thus to a less structured complexed ion pair. Since the geometry of the ion pair inclusion complexes is not accurately known, it does not appear reasonable to try to explain either why a given isomer is preferentially complexed or the effect of the cations. However the reversal of chiral recognition between K- and Cs-mandelate (25%) indicate that the precise geometries of the ion pairs must be appreciably different, for instance cation size may affect the extend and direction of penetration of the mandelate anion in the central cavity. *Figure 3* illustrates the molecular shapes of the Rb^+ complex of ligand **2** and of the (R)-mandelate anion.

Transport experiments using ligand **2** for carrying alkali mandelate through a liquid chloroform membrane confirmed the results obtained by extraction. As expected, the rate of mandelate transport followed the extraction efficiencies as a function of the cation (rate = 0.6, 1.4 and 0.5 mmol/h for Na^+, K^+ and Cs^+ resp.). Also potassium-(−) mandelate (**e.e.** $\sim 10\%$ in the *OUT phase*) and (+) cesium mandelate (**e.e.** $\sim 1.5\%$) were transported preferentially, while no enrichment was observed with the sodium salt.

The ^{13}C-NMR. spectra of chloroform solutions of complexes between ligand **2** and potassium (+)- or (−)-mandelate show that the ^{13}C-shifts of the ligand are somewhat different when (+)- or (−)-mandelate is used. Small shifts are observed for the signals of the carbon atoms in the bridges linking the two macrocycles ($\Delta \sim 0.17$ ppm). One would indeed expect that if inclusion ion pairs are formed, the bridges defining the central cavity, should be more affected by the configuration of the anion than the macrocycles. The effect is however quite small and alone

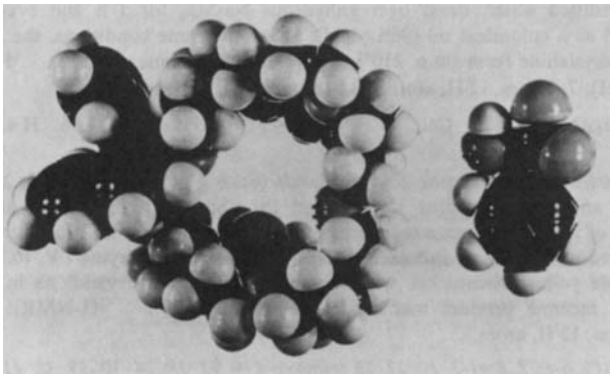

Fig. 3. *C.P.K. molecular models of the chiral macrotricyclic ligand* **2**, *containing a complexed rubidium cation, and of the mandelate anion.*

would not have much significance in itself. With (±)-mandelate averaged signals are observed, showing that anion exchange is fast, on the NMR. time scale.

Conclusion. – We have shown that cylindrical macrotricyclic ligands yield complexes by using a macrocyclic subunit as anchor site for binding the substrate. With primary ammonium salts the NH_3^+-group may bind directly to the macrocycle with or without participation of the amide functions; with alkali salts of organic anions, a cascade process is involved with first binding of the cation (yielding a *metallo-receptor*) followed by electrostatic pairing with the anion. When the substrates are chiral, *chiral discrimination* has been observed for *either a cationic or anionic chiral substrate* depending on the complexation mechanism. The occurrence of chiral discrimination, as well as other observations, may be ascribed to at least partial formation of inclusion complexes into the central molecular cavity of the macrotricyclic system. Higher chiral recognition might be obtained by incorporating a second chiral unit in the ligand and by introducing more binding sites so as to restrict the geometry of the complex and increase its structuration.

Experimental Part

^{1}H-NMR. spectra were measured on a *Varian* A-60 spectrometer, the chemical shifts are recorded in ppm downfield from internal TMS in $CDCl_3$, the usual symbols are used to describe NMR. spectra: *s* singlet, *d* doublet, *t* triplet, *m* multiplet, br. broad. ^{13}C-NMR. spectra were recorded on a *Fourier* Transform *Varian* XL-100 spectrometer. Melting points were taken on a *Kofler* block and are uncorrected. Elemental analysis were performed by 'Laboratoire de Microanalyse du CNRS, division de Strasbourg'. Optical rotation were measured on a *Perkin-Elmer* polarimeter.

Synthesis of the macrocyclic compounds 1 and 2. – The synthesis of the bis-macrocyclic derivative **9** has been previously described [20]. 1,1'-binaphthol was prepared [26] [27] and resolved [28] by literature methods, giving the optically pure *S*-(−)-isomer of **4**.

(S)-(−)-1,1'-Binaphtho-2,2'-diacetic acid (**5**). 6.8 g (23.7 mmol) of **4**, 34 g (245 mmol) of bromoacetic acid and 59 g (427 mmol) of anhydrous potassium carbonate were suspended in 200 ml anhydrous methanol. The mixture was heated under reflux for 6 h and evaporated to dryness. 100 ml distilled water were added and the pH was adjusted to 1 with 3N HCl, the solution was then extracted with 5×50 ml of benzene/ether 1:1. The combined organic phases were extracted with 3×100 ml distilled water, dried over anhydrous Na_2SO_4 for 1 h and evaporated to dryness giving compound **5** as a colourless oil (98% yield). Using the same conditions, the racemic compound was obtained in a crystalline form (m.p. 210°). – $[\alpha]_D^{25} = -36$ (acetone, $c = 0.22$). – ^{1}H-NMR.: 4.65 ppm (*s*, 4 H, 2 CH_2CO_2H); 7–8.1 (*m*, 12 H, arom.); 8.5 (br. *s*, 2 H, 2 CO_2H).

$C_{24}H_{14}O_6$ (398.08) Calc. C 71.63 H 4.51% Found C 71.66 H 4.56%

(S)-(−)-1,1'-Binaphtho-2,2'-diacetic acid dichloride (**6**). 6 g (15.1 mmol) of **5**, 20 g oxalyl chloride and one drop of anhydrous pyridine were stirred for about 1 h in 100 ml anhydrous benzene. The small amount of remaining unreacted starting material was filtered off, the filtrate was evaporated to dryness under reduced pressure and exclusion of moisture. After drying i.V. (0.1 Torr, 3 h at RT.) compound **5**, a pale yellow viscous oil, was obtained in quantitative yield. As in the previous case, the corresponding racemic product was crystalline (m.p. 73–75°). – ^{1}H-NMR.: 4.8 ppm (*s*, 4 H, CH_2COCl); 7–8.2 (*m*, 12 H, arom.).

1,1'-Binaphtho[5,6-e;7,8-g]-2,11,22,26-tetraoxo-4,9,15,18,24,30,33,38,41,46,49-undecaoxa-1,12,21,27-tetraaza-tricyclo[25,8,8,8^{12,21}]henpentaconta-5,7-diene (**1**). This compound was synthesized using the high dilution technique previously described [31]. The bis-macrocyclic compound **9** (6.8 g,

10.9 mmol) and triethylamine (5 g, 49 mmol) were dissolved in 500 ml anhydrous benzene. On the other hand 4.9 g (11.2 mmol) of **6** were dissolved in about 300 ml anhydrous benzene, rapidly filtered through glass wool to remove any possible unreacted carboxylic acid and the solution was adjusted to 500 ml with anhydrous benzene. The two solutions were simultaneously added dropwise over a period of 4–6 h to 2.5–3 l of benzene under vigorous stirring. The reaction mixture was filtered and evaporated to dryness to give a colourless oil which was purified by chromatography on alumina (*Merck*, activity II, III; eluent: $CHCl_3$). A white amorphous solid was obtained in 50% yield. – $[\alpha]_D^{25} = -42$ (acetone, $c = 0.23$). – UV. spectrum: $\lambda_{max} = 274$ nm ($17000 M^{-1}$), 331 nm ($5000 M^{-1}$). – ^{1}H-NMR.: 3.5 ppm (br. *s*, 48 H, OCH_2, $CONCH_2$); 4.3 (br. *s*, 4 H, OCH_2CO); 4.65 (br. *s*, 4 H, naphthyl-OCH_2CO^-); 7–8.1 (*m*, 12 H, arom.). –MS.: *988* (M^+).

$C_{52}H_{68}O_{15}N_4$ (989.144) Calc. C 63.14 H 6.93 N 5.66% Found C 63.03 H 6.97 N 5.62%

1, 1'-Binaphtho[5, 6-e; 7, 8-g]-4, 9, 15, 18, 24, 30, 33, 38, 41, 46, 49-undecaoxa-1, 12, 21, 27-tetraaza-tricyclo[25, 8, 8, $8^{12,21}$]henpentaconta-5, 7-diene (**2**). This compound was prepared by reduction of **1** with diborane according to the method previously described [20] [31] under a dry nitrogen atmosphere. 1.5 g (1.51 mmol) of **1** were suspended in 50 ml diborane in THF (0.5M). The reaction mixture was heated under reflux for 6 h. After cooling to RT. the excess of reagent was destroyed by dropwise addition of 15 ml distilled water. 100 ml 6N HCl and 50 ml THF were then added, the mixture was stirred at RT. for 3 h and evaporated to dryness under reduced pressure. The white residue obtained was suspended in 100 ml lithium hydroxide (5% in water) and the solution was extracted with 3 × 100 ml ether. The combined organic extracts were dried (anhydrous Na_2SO_4), and evaporated to dryness to give the crude tetramine **2** which was purified by chromatography on alumina (eluent: $CHCl_3$). This product contained about 4 water molecules which could be removed by freeze drying in anhydrous benzene. Yield: 90%. – $[\alpha]_D^{25} = -68°$ ($c = 0.17$, $CHCl_3$). – UV.: λ_{max} 277 nm ($9340 M^{-1}$), 333 nm ($5880 M^{-1}$). – ^{1}H-NMR.: 2.4-3 (*m*, 24 H, 12 NCH_2); 3.3–3.6 (br. *m*, 36 H, 18 OCH_2); 4.1 (*m*, 4 H, naphthyl-OCH_2); 7–8.1 (*m*, 10 H, arom.). – MS.: 933 (M^+).

$C_{52}H_{76}O_{11}N_4$ (933.208) Calc. C 66.93 H 8.21 N 6.00% Found C 66.98 H 8.34 N 5.86%

Extraction and Transport Experiments. – In a typical extraction experiment, 50 mg of compound **1** were dissolved in 0.5 ml $CDCl_3$ and shaken for about 1 min with 0.5 ml of a concentrated (naphthylethylammonium salt: 0.24M; phenylethylammonium salt: 2M) aqueous solution of the ammonium salt studied. The organic layer was decanted, dried over Na_2SO_4 and filtered through glass wool: ^{1}H-NMR. was used to obtain the stoïchiometry and the optical purity of the complexes formed.

The method and the experimental set up previously described [33] [35] was used to perform the transport experiments through a liquid membrane ($CHCl_3$). The temperature was maintained at 20 ± 0.5°. For the transport of the ammonium salts, the chloroform phase contained ligand **1** (10 mM), the left compartment of the cell (input side) the substrate (250 mM in 0.1N HCl), the right compartment (output side) 0.1N HCl. The appearance of the substrate in the right compartment was followed by UV. spectroscopy and the optical purities were determined by polarimetry. The transport of mandelate anion were performed under similar conditions; the left side contained the alkali salt of mandelate (2.9N) in water and the pH was adjusted to 12 with the hydroxide of the alkali cation studied. The chloroformic layer contained ligand **2** (5 mM), the right compartment was an ethanolamine buffer at pH 10.2. The transport rates depend of course on the geometry of the transport cell used; however, since only the relative rates of simultaneous transport of two enantiomers are of interest in the present context, the exact values of the total transport rates need not be discussed further.

The *stability constants* were determined at 25° in methanol/water 95:5 *(v/v)* using cation selective electrodes as described previously [21]; the ionic strength and the pH were kept constant with an aqueous solution of NEt_4Br (0.1M) and NEt_4OH (0.01M).

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