Optically Active Dioxatetraazamacrocycles: Chemoenzymatic Syntheses and Applications in Chiral Anion Recognition

Ignacio Alfonso, Francisca Rebolledo, and Vicente Gotor*[a]

Dedicated to Professor José Elguero on the occasion of his 65th birthday

Abstract: Two new C_2 and D_2 symmetrical dioxatetraaza 18-membered macrocycles [(*R*,*R*)-**1** and (*S*,*S*,*S*,*S*)-**2**] are efficiently synthesized in enantiomerically pure forms by a chemoenzymatic method starting from (±)-*trans*-cyclohexane-1,2-diamine. The protonation constants and the binding constants with different chiral dicarboxylates are determined in aqueous solution by means of pH-metric titrations. The triprotonated form of (*S*,*S*,*S*,*S*)-**2** shows moderate enantioselectivity with malate and tartrate anions ($\Delta\Delta G = 0.62$ and 0.66 kcal mol^{-1}, respectively), being the strongest binding observed in both cases with the L enantiomer. Good enantiomeric discrimination is obtained with tetraprotonated (*R*,*R*)-**1** and *N*-acetyl aspartate, the complex with the D-enantiomer being 0.92 kcal mol^{-1} more stable than its diastereomeric counterpart. Despite the lack of enantioselectivity of tri- and tetraprotonated (*R*,*R*)-**1** for the tartrate anion, a very good diastereopreference for *meso*-tartrate is found. All these experimental results allow us to propose a model for the host–guest structure based on coulombic interactions and hydrogen bonds.

Keywords: chiral anion recognition · enantiomeric resolution · host–guest chemistry · macrocycles · molecular recognition

Introduction

Oxaazamacrocycles are attractive molecules with a variety of applications in the fields of supramolecular chemistry and catalysis.[1] The presence of two kinds of heteroatoms (nitrogen and oxygen) in the macrocyclic ring confer hybrid properties, between those of azacrowns and crown ethers, on these structures.[2] Thus, depending on structural factors like size of the ring or number and disposition of the heteroatoms, these systems are able to form kinetically and thermodynamically stable complexes with different metals.[3] Furthermore, when protonated, they are excellent anion binders.[4] For instance, some of these compounds are receptors for biologically important anions like nucleotides and nucleic acids. The complexation affects the reactivity of the anion, leading to interesting applications in supramolecular catalysis. Therefore, 24- to 36-membered-ring oxaazamacrocycles have been extensively studied for their ATPase,[5] phosphorylase[6], and enolase[7] activities in comparison with the normal enzymatic catalysis.

However, the design and synthesis of selective receptors for optically active polyanions still constitutes a difficult task facing chemists. Although cyclodextrins have proved to be excellent ligands for the recognition of helicity,[8] only low selectivities have been obtained with compounds bearing chiral centers.[9] Recently, sapphyrin-based receptors[10] have been successfully used for the recognition and transport of aspartate and glutamate derivatives; these are the first receptors capable of the selective recognition of dianionic dicarboxylates with chiral centers.

Taking into account the interest and scarcity of suitable optically active macrocycles that act as selective receptors of chiral anions,[11] in this work we aimed at the synthesis of optically active oxaazamacrocycles **1** and **2**, with C_2 and D_2 symmetry, respectively, by a chemoenzymatic method. In addition, we studied their protonation and their chiral anion recognition properties in aqueous solution, since this is the natural environment of biologically important anions.

Results and Discussion

Design and synthesis: Structural complementarity in molecular recognition is crucial for the success of a given receptor.[12] Coulombic attractions and hydrogen-bond for-

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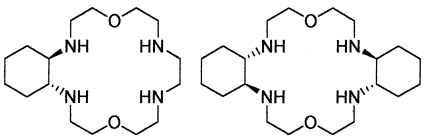

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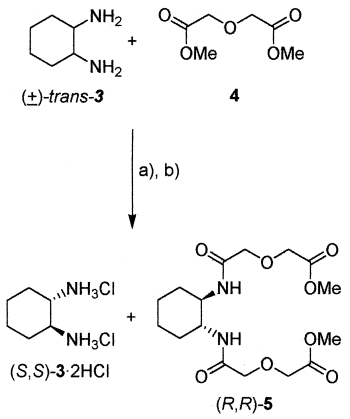
mation play a dominant role in the anion complexation of polyammonium macrocycles.[13] The strongest binding usually occurs with the fully protonated form of the azamacrocycle and when substrate and receptor are preorganized into complementary shapes. In addition, compounds containing an optically active *trans*-cyclohexane-1,2-diamine moiety have proved to be very useful in both asymmetric synthesis[14] and enantiomeric and diastereomeric recognition of peptides.[15] These were the reasons we believed compounds **1** and **2** would be good candidates for the recognition of optically active α,ω-dicarboxylates. Both oxaazamacrocycles are 18-membered rings, a convenient size for the complexation of 1,2-dicarboxylates.[16] They have two ether units separating the N–C–C–N fragments, which increase the pH values for full protonation and, furthermore, may cooperate in the binding as hydrogen-bond acceptors. Compound **1** has C_2 symmetry, and **2** possesses three orthogonal binary axes to give it overall D_2 symmetry.

Racemic *trans*-cyclohexane-1,2-diamine [(±)-**3**] is an interesting substrate for lipase-catalyzed kinetic resolutions. The presence of two amine groups of the same configuration allows us to carry out a sequential kinetic resolution.[17] Recently, we applied this methodology to the resolution of (±)-**3** with dimethyl malonate using lipase B from *Candida antarctica* (CAL) as catalyst.[18] Now, with the structure of azamacrocycles **1** and **2** in mind, we focused on extending this biocatalytic process to the resolution of (±)-**3** with dimethyl 3-oxapentanedioate (**4**). Reactions were carried out in 1,4-dioxane as solvent and with the molar ratio diamine:diester varied depending on the required conversion. Thus, when equimolecular amounts of (±)-**3** and **4** were used, a mixture containing the double aminolysis compound bis(amidoester) (*R*,*R*)-**5** and the remaining (*S*,*S*)-**3** was obtained (Scheme 1),



(±)-*trans*-**3** **4**

a), b)

(*S*,*S*)-**3**·2HCl (*R*,*R*)-**5**

Scheme 1. Enzymatic resolution of (±)-**3**. a) CAL, 1,4-dioxane, 30 °C; b) HCl (g).

the product of the monoacylation of the diamine being undetected. After the elimination of the lipase from the medium, the remaining diamine (*S*,*S*)-**3** was transformed into the corresponding dihydrochloride by treatment with dry hydrogen chloride in order to facilitate separation and isolation of the compounds. The enantiomeric excess of (*R*,*R*)-**5** was determined by chiral HPLC (see the Experimental Section), whereas the diamine (*S*,*S*)-**3** was determined as previously described.[18] As is indicated in Table 1 (entry 1),

Table 1. Enzymatic resolution of (±)-**3**.

Molar ratio (±)-**3**:**4**	*t* [h]	*ee* (*S*,*S*)-**3** [%]	*ee* (*R*,*R*)-**6** [%]
1:1	9	92	> 99
1:1.3	15	97	> 99
1:1.5	39	> 99	> 99

enantiomeric excesses were very high for both compounds, (*R*,*R*)-**5** being in fact enantiopure. In order to improve the *ee* of (*S*,*S*)-**3**, the conversion degree of the enzymatic reaction has to be improved and, consequently, an excesss of diester **4** must be used. Enantiopure (*S*,*S*)-**3** was obtained when a 1:1.5 molar ratio of **3**:**4** was used for a longer reaction time. Large amounts of monoacylation product (ca. 30 %) and enantiopure (*R*,*R*)-**5** were also isolated in this process. These compounds [(*R*,*R*)-**5** and (*S*,*S*)-**3**] have been used in this work for the syntheses of the oxaazamacrocycles (*R*,*R*)-**1** and (*S*,*S*,*S*,*S*)-**2**, respectively.

The oxaazamacrocycle (*R*,*R*)-**1** was synthesized from (*R*,*R*)-**5** following a modification of the Richmann – Atkins[19] procedure, which mainly involves the coupling of a tosylated polyamine (*R*,*R*)-**8** with a doubly electrophilic reagent in the presence of a base (Scheme 2). The ester functions of (*R*,*R*)-**5** were quantitatively transformed into amides by conventional ammonolysis (ammonia in metha-

Abstract in Spanish: *Se han sintetizado dos nuevos dioxatetraazamacrociclos de 18 eslabones [(R,R)-**1** y (S,S,S,S)-**2**] enantioméricamente puros y con simetría C_2 y D_2, a partir de la (±)-trans-ciclohexano-1,2-diamina mediante un método quimioenzimático. Además, se han determinado tanto las constantes de protonación como las de complejación con diferentes dicarboxilatos quirales en disolución acuosa mediante valoraciones potenciométricas. La forma triprotonada de (S,S,S,S)-**2** muestra una enantioselectividad moderada con los aniones malato y tartrato ($\Delta\Delta G = 0.62$ y $0.66\ kcal\,mol^{-1}$, respectivamente), apareciendo en ambos casos la interacción más fuerte con el enantiómero* L. *Se obtiene una buena discriminación enantiomérica con (R,R)-**1** en su forma tetraprotonada y N-acetil aspartato, siendo el complejo con el enantiómero* D *$0.92\ kcal\,mol^{-1}$ más estable que con su correspondiente enantiómero. A pesar de la ausencia de enantioselectividad de (R,R)-**1** tri- y tetraprotonados con el anión tartrato, se encuentra una diastereopreferencia importante hacia el mesotartrato. Todos estos resultados experimentales nos permiten proponer un modelo para la estructura supramolecular, basado en interacciones culombianas y enlaces por puente de hidrógeno.*

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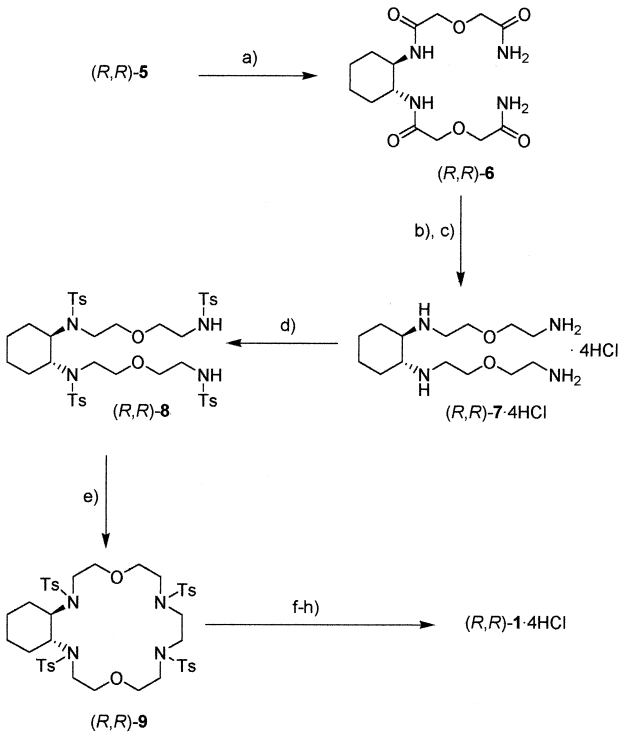


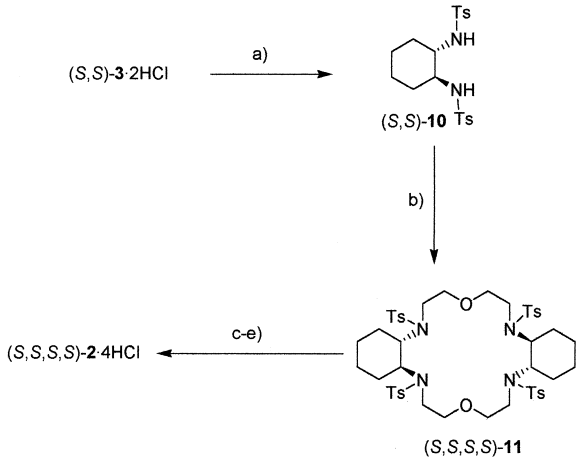
Scheme 2. Synthesis of (*R*,*R*)-**1**. a) NH_3 in MeOH; b) $BH_3 \cdot THF$; c) HCl (6 N); d) TsCl, K_2CO_3, THF, H_2O; e) Cs_2CO_3, CH_3CN, $MsOCH_2CH_2OMs$; f) HBr, PhOH; g) NaOH (aq)/CH_2Cl_2; h) HCl in MeOH.

nol). Subsequent reduction (BH_3/THF) of the tetraamide (*R*,*R*)-**6** led to the tetraamine (*R*,*R*)-**7**, which was isolated and used in the next step as its tetrahydrochloride. Tosylation of (*R*,*R*)-**7** · 4HCl with tosyl chloride was efficiently carried out in a biphasic system formed by tetrahydrofuran and aqueous potassium carbonate.

The coupling of (*R*,*R*)-**8** with ethylene glycol dimesylate was accomplished with an excess of cesium carbonate in refluxing acetonitrile (Scheme 2). Under these conditions, the tetratosylated oxaazamacrocycle (*R*,*R*)-**9** was obtained with 87% yield after purification by flash chromatography. The cyclic structure was unambiguosly demonstrated by fast atom bombardment (FAB) mass spectrometry: the spectrum showed peaks at *m*/*z* values of 931 and 953, corresponding to $[M+H]^+$ and $[M+Na]^+$, respectively. Hydrolysis of the sulfonamide functions of (*R*,*R*)-**9** with 48% HBr and an excess of phenol yielded the desired dioxatetraazamacrocycle (*R*,*R*)-**1**, isolated as its tetrahydrobromide. The unprotonated species can be easily obtained as a colorless oil by addition of 4 N sodium hydroxyde and extraction with dichloromethane. Considering that the asymmetric centers do not participate in any reaction step, no racemization is expected in this synthesis. In confirmation, ^1H and ^{13}C NMR spectra of (*R*,*R*)-**1** and of its precursors [(*R*,*R*)-**7** and (*R*,*R*)-**8**] showed the expected signals for an effective C_2 symmetry (see experimental data). These facts demonstrate that in the above synthetic routes epimerization of the chiral centers has not taken place, since epimerization would lead to the formation of *cis*/*trans* diastereomeric mixtures and thus to an increase of the number of signals in the spectra.

In order to facilitate the purification of the macrocyclic salt and for the potentiometric measurements, (*R*,*R*)-**1** · 4HCl was manufactured by the addition of concentrated HCl to a methanolic solution of (*R*,*R*)-**1** and subsequent evaporation to dryness. The resulting solid was easily recrystallized in ethanol to give (*R*,*R*)-**1** · 4HCl with a 56% overall yield from (*R*,*R*)-**5**.

For the synthesis of the macrocycle (*S*,*S*,*S*,*S*)-**2**, we started from the enantiopure (*S*,*S*)-**3** · 2HCl (see Table 1, entry 3), following a modification of the Biernat and Luboch[20] procedure. It is well known that the formation of nine-membered rings is kinetically disfavored[21] and that 18-membered rings are the ones most easily obtained by means of the Richman–Atkins procedure.[19b] With these antecedents we envisioned the possibility of preparing the macrocycle (*S*,*S*,*S*,*S*)-**2** by a [2+2] cyclization reaction in which two molecules of the nucleophile react with two molecules of the electrophile (Scheme 3). Thus, the reaction of the bis(sulfonamide) (*S*,*S*)-**10**, obtained from (*S*,*S*)-**3** · 2HCl,[22] with diethylene glycol dimesylate led to the tosylated oxaazamacrocycle (*S*,*S*,*S*,*S*)-**11** in 80% yield after chromatographic purification. The reaction was carried out in refluxing acetonitrile and with an excess of alkaline carbonate as a base. No significant differences were observed when cesium or potassium salts were used, but with the former, the reaction time was shorter. Compound (*S*,*S*,*S*,*S*)-**11** showed a clear melting point (200–202 °C) and a single spot on TLC in a variety of eluents. The FAB mass spectrum showed peaks at *m*/*z* values of 985 and 1007, corresponding to $[M+H]^+$ and $[M+Na]^+$, respectively. These facts demonstrated again the 18-membered cyclic structure for the product and revealed the success of the [2+2] cyclization strategy in this synthesis. Hydrolysis of the resulting sulfonamide (*S*,*S*,*S*,*S*)-**11** was carried out under the conditions already described for (*R*,*R*)-**10**, yielding compound (*S*,*S*,*S*,*S*)-**2** · 4HBr, which was also converted into the corresponding tetrahydrochloride salt to facilitate its purification. Again the analysis of (*S*,*S*,*S*,*S*)-**2** · 4HCl by NMR spectroscopy revealed the expected symmetry. For example, the ^{13}C NMR spectrum showed only five signals corresponding to an effective D_2 symmetry in solution, demonstrating that epimerization procceses had not taken place.



Scheme 3. Synthesis of (*S*,*S*,*S*,*S*)-**2**. a) TsCl, K_2CO_3, THF, H_2O; b) Cs_2CO_3, CH_3CN, $MsOCH_2CH_2OCH_2CH_2OMs$; c) HBr, PhOH; d) NaOH (aq)/CH_2Cl_2; e) HCl in MeOH.

Protonation behavior: For the study of anion recognition by oxaazamacrocycles in aqueous solution, a preliminary knowledge of the protonation constants is necessary. The behavior of (*R*,*R*)-**1** and (*S*,*S*,*S*,*S*)-**2** towards protonation has been studied in 0.1 mol dm^{-3} NMe_4Cl solution at 298 K in the pH range 2–11.5. The values of the logarithm of the basicity constant for each protonation step of these macrocycles are shown in Table 2, together with the one previously reported

Table 2. Logarithms of the protonation constants measured by pH-metry in NMe_4Cl (0.1 mol dm^{-3}) at 298 K.

	trans-18-ane-N_4O_2[b]		(*R*,*R*)-**1**		(*S*,*S*,*S*,*S*)-**2**	
Reaction[a]	log *K*	Δ	log *K*	Δ	log *K*	Δ
L + H = HL	9.36		9.06(3)[c]		10.19(2)	
HL + H = H_2L	8.40	0.96	7.97(3)	1.09	9.10(1)	1.09
H_2L + H = H_3L	6.27	2.13	5.53(3)	2.44	5.29(2)	3.81
H_3L + H = H_4L	5.23	1.04	3.88(4)	1.65	4.26(2)	1.03

[a] Charges are omitted for clarity. [b] 7,16-Dioxa-1,4,11,13-tetraazacyclooctadecane; log *K* taken from ref. [3], measured in 0.1N $NaNO_3$ as supporting electrolyte. [c] Values in parentheses are standard deviations on the last significant figure.

for the structurally related *trans*-18-ane-N_4O_2 (7,16-dioxa-1,4,11,13-tetraazacyclooctadecane).[3] In this table we also present the difference between successive protonation constants for each compound (Δ), which can be interpreted as the ease with which a protonated species accepts the next proton: the higher the Δ value, the less favorable the protonation process. The common characteristic of both systems is that the third protonation step is the most difficult, as expected from the reported general protonation properties of macrocyclic polyamines.[23] However, some differences in the value of Δ are due to the presence of the cyclohexane. So, when the second proton is attached to the monoprotonated cyclohexane-1,2-diamine moiety, the Δ value is increased (see Table 2). This effect is shown in the fourth step for (*R*,*R*)-**1** and in the third for (*S*,*S*,*S*,*S*)-**2** compared with *trans*-18-ane-N_4O_2, and is in accordance with the previously reported protonation constants of ethylenediamine (Δ = 2.87)[24] and *trans*-cyclohexane-1,2-diamine (Δ = 3.17).[25]

Chiral anion recognition: As previously stated, chiral anion recognition is a nearly unexplored field in supramolecular chemistry.[1, 4a, 13] There are many polyanions with important biological activities; for instance, malate or succinate are intermediates in the citric acid and glyoxylate cycles,[26] and aspartate and glutamate have been thoroughly studied as excitatory aminoacid neurotransmitters.[27] We have studied the complexation of some of these derivatives with the protonated forms of macrocycles (*R*,*R*)-**1** and (*S*,*S*,*S*,*S*)-**2**.

The stability constants of the complexes of (*R*,*R*)-**1** and (*S*,*S*,*S*,*S*)-**2** with some chiral anions were measured in a 0.1 mol dm^{-3} NMe_4Cl solution at 298 K by pH-metric titrations; they are listed in Table 3. The enantioselectivity is shown as the difference between the logarithms of the binding constants obtained for both enantiomers of the anion. Some general conclusions can be extracted from these experimental results. Although all the anions form stable complexes with

Table 3. Logarithms of stability constants[a] for the interaction of (*R*,*R*)-**1** and (*S*,*S*,*S*,*S*)-**2** with chiral dicarboxylate anions, determined at 298 K in aqueous NMe_4Cl (0.1 mol dm^{-3}).

		$n^{[b]} = 4$		$n^{[b]} = 3$	
Macrocycle	Anion	log K_s	Δlog K_s[c]	log K_s	Δlog K_s[c]
(*R*,*R*)-**1**	D-tartrate	2.59(1)[d]		1.92(1)	
(*R*,*R*)-**1**	L-tartrate	2.56(1)	0.03	1.85(1)	0.07
(*R*,*R*)-**1**	*meso*-tartrate	3.92(1)		2.73(1)	
(*R*,*R*)-**1**	D-malate	2.96(2)		2.14(1)	
(*R*,*R*)-**1**	L-malate	–	n.a.[e]	2.21(1)	−0.07
(*R*,*R*)-**1**	*N*-Ac-D-Asp	4.21(1)		3.40(1)	
(*R*,*R*)-**1**	*N*-Ac-L-Asp	3.54(3)	0.67	3.26(1)	0.14
(*R*,*R*)-**1**	*N*-Ac-D-Glu	3.52(3)		3.12(2)	
(*R*,*R*)-**1**	*N*-Ac-L-Glu	–	n.a.[e]	3.12(2)	0.00
(*R*,*R*)-**1**	(*R*)-Me-succ	5.43(2)		4.31(2)	
(*R*,*R*)-**1**	(*S*)-Me-succ	5.42(2)	0.01[f]	4.20(2)	0.11[f]
(*S*,*S*,*S*,*S*)-**2**	D-tartrate	–		1.68(3)	
(*S*,*S*,*S*,*S*)-**2**	L-tartrate	–		2.16(1)	−0.48
(*S*,*S*,*S*,*S*)-**2**	*meso*-tartrate	2.69(2)		1.94(2)	
(*S*,*S*,*S*,*S*)-**2**	D-malate	2.47(3)		1.91(3)	
(*S*,*S*,*S*,*S*)-**2**	L-malate	2.80(3)	−0.33	2.36(2)	−0.45
(*S*,*S*,*S*,*S*)-**2**	*N*-Ac-D-Asp	–		2.49(3)	
(*S*,*S*,*S*,*S*)-**2**	*N*-Ac-L-Asp	–		2.53(3)	−0.04
(*S*,*S*,*S*,*S*)-**2**	*N*-Ac-D-Glu	–		2.72(3)	
(*S*,*S*,*S*,*S*)-**2**	*N*-Ac-L-Glu	–		2.80(3)	−0.08
(*S*,*S*,*S*,*S*)-**2**	(*R*)-Me-succ	–		3.00(2)	
(*S*,*S*,*S*,*S*)-**2**	(*S*)-Me-succ	–		3.01(2)	−0.01[f]

[a] As defined by the equation: $A^{2-} + LH_n^{n+} = [ALH_n]^{(n-2)+}$. [b] Number of protons accepted by the complex. [c] Δlog K_s = log K_s(D) − log K_s(L). [d] Values in parentheses are standard deviations on the last significant figure. [e] Not applicable. [f] Δlog K_s = log K_s(*R*) − log K_s(*S*).

some protonated form of both oxaazamacrocycles, recognition is less effective with compound (*S*,*S*,*S*,*S*)-**2**, probably due to the more rigid structure and less suitable preorganization of this receptor. Thus many of the anions form no complexes with $\mathbf{2}\cdot 4H^+$. In contrast, a very good chain selectivity is observed for (*R*,*R*)-**1** if binding constants with the acetyl derivatives of D-aspartate and D-glutamate are compared. Tri- and, particularly, tetraprotonated (*R*,*R*)-**1** bind the shorter *N*-Ac-D-aspartate more strongly, as would be expected for the cavity size of the macrocycle.

Concerning enantioselectivity, a general tendency is observed for (*S*,*S*,*S*,*S*)-**2** to be L-selective and (*R*,*R*)-**1** to be mainly D-selective, as a consequence of the different absolute configuration of the oxaazamacrocycles. Two significantly different binding constants were found for the two diastereomeric complexes obtained from $\mathbf{2}\cdot 3H^+$ and tartrate and malate anions (Δlog K_s = 0.48 and 0.45, corresponding to Δ(Δ*G*) = 0.66 and 0.62 kcal mol^{-1}), representing a binding enantioselectivity of ≈75:25. The selectivity of (*R*,*R*)-**1** towards malate and *N*-Ac-glutamate is manifested in the absence of stable complexes of $\mathbf{1}\cdot 4H^+$ with the L enantiomers. However, this significant result lacks practical applicability because $\mathbf{1}\cdot 4H^+$ and $\mathbf{1}\cdot 3H^+$ species are present together in solution in a narrow pH range and the latter does not discriminate enantiomerically. The best result was obtained with (*R*,*R*)-$\mathbf{1}\cdot 4H^+$ and *N*-Ac-aspartate, for which enantioselectivity was quite high (Δlog K_s = 0.67, ΔΔ*G* = 0.92 kcal mol^{-1}), leading to a binding enantioselectivity of ≈82:18, although the presence in solution of the complex with the less selective $\mathbf{1}\cdot 3H^+$ would decrease this ratio.

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In spite of the lack of enantioselectivity shown by (*R*,*R*)-**1** towards the two enantiomers of the tartrate anion, the excellent diastereoselectivity (see Table 3) exhibited by this receptor both in its tri- and tetraprotonated forms is surprising. Comparison of the $\log K_s$ values obtained for the complexes of $\mathbf{1}\cdot 4H^+$ with, for example, D-tartrate and *meso*-tartrate gives $\Delta\Delta G = 1.8$ kcal mol^{-1}, meaning a very high diastereoselective discrimination. This fact, which must be an effect of the geometry of the complex, was an essential clue to the host–guest structure that would allow us to explain the results.

In order to test the effect of the macrocyclic ring, we measured the binding constants between all these anions and (*S*,*S*)-cyclohexane-1,2-diamine as a control compound. The stability constants of the complexes formed are shown in Table 4. No complexation with tartrate isomers was detected under the experimental conditions (0.1 mol dm^{-3} NMe_4Cl and 298 K), while the other anions interact with the diprotonated diamine. It must be pointed out that the higher the hydrophobicity of the anion, the larger the binding constant is. In addition to this, the lack of enantiomeric and diastereomeric discrimination ($\Delta\log K_s$ very close to experimental error) clearly implies the importance of the crown ring in supramolecular chiral recognition.

Table 4. Logarithm of stability constants[a] for the interaction of (*S*,*S*)-**3**·$2H^+$ with chiral dicarboxylate anions, determined at 298 K in aqueous NMe_4Cl (0.1 mol dm^{-3}).

Anion	$\log K_s$	$\Delta\log K_s$[b]
D-tartrate	–	
L-tartrate	–	–
meso-tartrate	–	
D-malate	1.45(6)[c]	
L-malate	1.59(3)	– 0.14
N-Ac-D-Asp	2.07(2)	
N-Ac-L-Asp	1.97(2)	0.10
N-Ac-D-Glu	2.30(2)	
N-Ac-L-Glu	2.32(2)	– 0.02
(*R*)-Me-succ	2.60(1)	
(*S*)-Me-succ	2.42(1)	0.18[d]

[a] As defined by the equation: $A^{2-} + LH_2^{2+} = [ALH_2]$. [b] $\Delta\log K_s = \log K_s(D) - \log K_s(L)$. [c] Values in parentheses are standard deviations on the last significant figure. [d] $\Delta\log K_s = \log K_s(R) - \log K_s(S)$.

Another independent proof of the macrocycle–anion interaction was obtained from NMR experiments carried out with the anion that forms the most stable complex (see Supporting Information). The ROESY spectrum of a 1:4 mixture of (*R*,*R*)-$\mathbf{1}\cdot 4H^+$:(*R*)-Me-succ shows a cross-peak between CH_2N protons of the macrocycle and CH_3 protons of the anion, evidence supporting the formation of the complex in solution. Unfortunately, it was not possible to obtain similar data for the other anions.

Taking into account all these experimental results, we have proposed a model for the host–guest complex structure. It is well known that for high enantioselectivity (or diastereoselectivity), a receptor must have three points of interaction with the substrate, and at least one of them must be stereochemically dependent.[28] Molecular dynamic simulations of tetraprotonated *trans*-18-ane-N_4O_2[29] in solution revealed a flat conformation for the cycle, with all the ethylene groups in a *gauche* disposition and the ammonium groups towards the inner macrocyclic cavity. This conformation settles one lone pair of each oxygen in an *endo* position to the macrocyclic ring, leaving the other one free for possible hydrogen-bond interactions, as in the conformation shown in Figure 1a. The other two binding points must be due to carboxylate–diammonium coulombic interactions. Concerning the conformation of the anion, previous studies of the complexation of achiral dicarboxylates with 18-membered-ring hexaazamacrocycles revealed that they recognize maleate but not fumarate,[16] and a *gauche* conformation (*syn*-type) is favored compared with the *anti* conformation of the aliphatic dicarboxylate anions. With all these data in hand, we propose the model shown in Figure 1a, which allows two carboxylate–diammonium interactions and an additional hydrogen bond with the oxygen of the macrocycle. With this model, we can explain the diastereomeric preference for the tartrate anion. The *meso* derivative can form two cooperative hydrogen bonds (see Figure 1b), whereas for both D and L enantiomers only one bond is possible. Besides, the importance of the hydrogen bond in enantiomeric recognition is supported by the results obtained with methylsuccinate, where no enantiodiscrimination was observed (see Table 3).

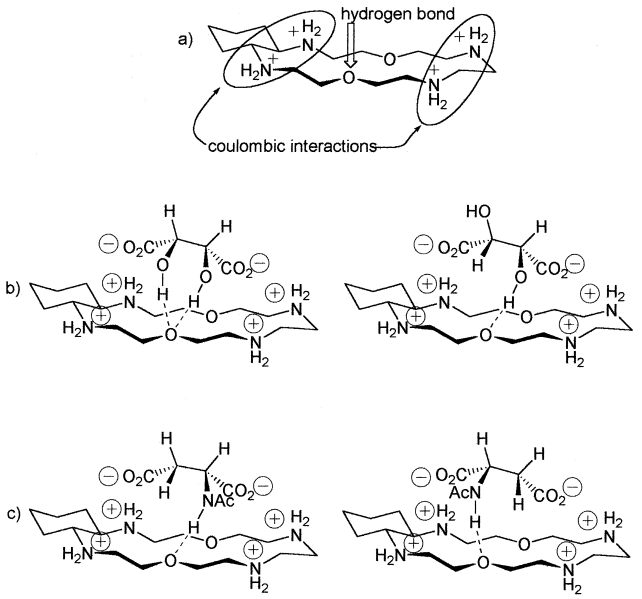
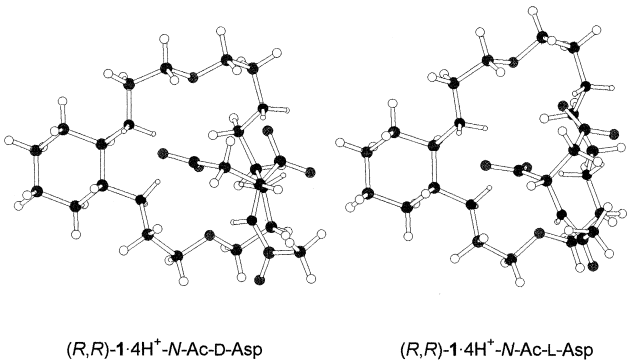


Figure 1. Proposed model for the host–guest structure: a) schematic representation of the interactions; models for the complexes of (*R*,*R*)-**1**·$4H^+$ with b) *meso*- and L-tartrate; c) D- and L-*N*-Ac-aspartate.

Furthermore, we used this model to explain the enantioselectivity exhibited by $\mathbf{1}\cdot 4H^+$ towards the aspartate derivative. Figure 1c shows the possible structures of the diastereomeric complexes formed with the pair of enantiomers of this anion. Both of them can, a priori, achieve the three proposed interactions, although the relative disposition of the anion in each is obviously different. In order to give an explanation of the results obtained with this anion, molecular mechanics calculations[30] have been undertaken. Figure 2 shows the



(*R*,*R*)-**1**·4H$^+$-*N*-Ac-D-Asp (*R*,*R*)-**1**·4H$^+$-*N*-Ac-L-Asp

Figure 2. MMX force-field minimized structures for the diastereomeric complexes of (*R*,*R*)-**1**·4H$^+$ and D- and L-*N*-Ac-aspartate.

optimized structures of both diastereomeric complexes of **1**·4H$^+$ and *N*-Ac-aspartate enantiomers. MMX force-field calculations predict a $\Delta\Delta H_f$ of 0.66 kcal mol^{-1} favorable to the D enantiomer, which is in good agreement with the experimental results (see Supporting Information). Inspection of the different contributions to the calculated energy shows a large difference in the torsional energy of both diastereomeric complexes. This fact and the comparison of the optimized geometries (see Figure 2) suggest that the complex with the L enantiomer is less stable owing to greater folding of the macrocycle upon complexation. Besides, the distortion of the structure is more important in the ethylene fragment than in the cyclohexane moiety. This could also explain the lower binding constants of **2** compared with **1**; the presence of the second six-membered ring in **2** would increase its rigidity and, therefore, would disfavor the binding with the dianion. Although entropically driven electrostatic forces have been identified as the most important contributions in anion binding,[31] other interactions like hydrogen bonds[32] and π-stacking[33] have been discussed, mainly in the context of selectivity.

In summary, we have described a simple and efficient chemoenzymatic method for the synthesis of two new 18-membered-ring oxaazamacrocycles from racemic *trans*-cyclohexane-1,2-diamine. Their protonation behavior and their binding constants with different chiral anions have been studied. These compounds show enantiomeric and diastereomeric molecular recognition properties depending on the structure of the anion added. From the experimental results we propose a model for the complexation based on two coulombic and additional hydrogen-bond interactions. It must be pointed out that, as far as we know, (*R*,*R*)-**1**·4H$^+$ seems to be the best receptor for the recognition of an anion with a chiral center in aqueous solution.

Experimental Section

General: All reagents were purchased from Aldrich Chemie. Solvents were distilled over an adequate desiccant and stored under nitrogen. Flash chromatography was performed with Merck silica gel 60 (230–240). Melting points were taken on a Gallenkamp apparatus and are uncorrected. Optical rotations were measured by means of a Perkin–Elmer 241 polarimeter. IR spectra were recorded on a Perkin–Elmer 1720-X FT IR spectrometer. Mass spectra were recorded on a VG Autospec. Microanalyses were performed on a Perkin–Elmer 240B elemental analyser. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker AC-300 (^{1}H, 300 MHz, and ^{13}C, 75.5 MHz), a Bruker AC-200 (^{1}H, 200 MHz, and ^{13}C, 50.3 MHz), or a Bruker AMX-400 (^{1}H, 400 MHz, and ^{13}C, 100.7 MHz) spectrometer. For the pH-metric titrations a Metrohm-702 titrimeter was used, the reference electrode was an Ag/AgCl electrode in saturated aqueous KCl, the cell was thermostated at 298 ± 0.1 K, the solution stirred, and all measurements were perfomed under nitrogen. The protonation constants were determined by titration with 0.1N NaOH of a solution typically containing 10^{-3}M of the HCl salt of the oxaazamacrocycle in the presence of Me_4NCl (0.1M). The log K_s values of the complexes were determined by titration with 0.1N NaOH of a solution containing 10^{-3}M of the HCl salt of the polyamine and 5×10^{-3}M of the desired dianions in the presence of 0.1M NMe_4Cl. All the measurements with each system were carried out at least twice and the data analysis was performed with the computer program SUPERQUAD.[34] The titration curves for each system were treated either as separated entities or as a single set without significant variations in the stability constants.

Dimethyl 3-oxapentanedioate (4): Diglycolyl chloride (5 mL, 40 mmol) was added dropwise at 0 °C to a vigorously stirred solution of triethylamine (12 mL) in dry methanol (20 mL). The reaction mixture was allowed to reach room temperature, then 3N HCl was added and extracted with dichloromethane (3 × 30 mL). The organic layers were dried and evaporated to dryness, giving an oily substance which solidified at 0 °C. The solid thus obtained was washed with hexane, yielding compound **4** (6.423 g, 94% yield). M.p. 39–40 °C; IR (nujol) 1754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.77 (s, 6H; CH_3), 4.25 (s, 4H; CH_2); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ = 51.7 (CH_3), 67.8 (CH_2), 169.9 (C=O); HRMS calcd for $C_5H_6O_4$ [*M* – MeOH] 130.0266609, found 130.026352.

Typical procedure for the enzymatic reaction: (±)-*trans*-Cyclohexane-1,2-diamine ((±)-**3**, 0.60 mL, 5.0 mmol), dimethyl 3-oxapentanedioate (**4**, 0.86 g, 5.0 mmol), and 1,4-dioxane (20 mL) were added to an Erlenmeyer flask containing lipase B from *Candida antarctica* (0.30 g) under nitrogen. The reaction mixture was shaken at 30 °C and 250 rpm until no traces of the diester were detected by TLC (acetone:diethyl ether:propan-2-ol 10:20:0.2). Afterwards, the enzyme was separated by filtration and washed with dichloromethane. Dry HCl was bubbled through the organic solution until a white precipitate was formed. Then the solvents were evaporated to dryness and the residue extracted with dichloromethane and 3N HCl. The organic layer was dried and evaporated, yielding the bis(amidoester) (*R*,*R*)-**5.** The aqueous layers contained a mixture of the monoamidoester and the diamine (*S*,*S*)-**3** as their hydrochloride salts, which can be separated by precipitation of (*S*,*S*)-**3**·2HCl with ethanol.

(*R*,*R*)-*N*,*N*′-(Cyclohexane-1,2-diyl)bis(methyl 4-carbamoyl-3-oxabutanoate) [(*R*,*R*)-5]: White solid (560 mg, 30% yield). M.p. 82–84 °C; $[\alpha]_D^{20} = +38.3$ ($c = 0.65$ in $CHCl_3$); *ee* > 99%; IR (nujol): 3295 (NH), 1754 (C=O), 1640 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.35 (br d, *J* = 4.9 Hz, 4H; $2CH_2$), 1.78 (br s, 2H; CH_2), 2.05 (br s, 2H; CH_2), 3.75 (s, 8H; 2CH + $2CH_3$), 3.92–4.14 (AB q, J_{AB} = 15.1 Hz, δ_A = 3.97, δ_B = 4.09, 4H; $2CH_2$), 7.08 (br s, 2H; NH); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 24.9 (CH_2), 32.5 (CH_2), 52.4 (CH), 53.1 (CH_3), 68.9 (CH_2), 71.3 (CH_2), 169.6 (C=O), 170.6 (C=O); MS (10 eV, E.I.) *m*/*z* (%): 374 (< 5) [*M*]$^+$, 227 (100); $C_{16}H_{26}N_2O_8$ (374.4): calcd C 51.33, H 7.00, N 7.48; found C 51.46, H 6.99, N 7.36; HPLC conditions for the determination of the enantiomeric excess: Chiralcel OD column, isocratic conditions, hexane:ethanol 90:10, sample conc: 0.5 mg mL^{-1}, flow rate: 0.8 mL min^{-1}, retention times (min): 15.7 (*R*,*R*), 19.8 (*S*,*S*), R_S = 2.75.

(*R*,*R*)-*N*,*N*′-(Cyclohexane-1,2-diyl)bis(4-carbamoyl-3-oxabutanamide) [(*R*,*R*)-6]: Bis(amidoester) (*R*,*R*)-**5** (1.87 g, 5.0 mmol) was added to a solution of NH_3 in methanol (10%, 150 mL) and stirred at 7 °C over 12 h. Then the solvent was removed and (*R*,*R*)-**6** was obtained quantitatively as a white solid. M.p. 96–97 °C; $[\alpha]_D^{20} = +16.1$ ($c = 0.28$ in MeOH); IR (nujol) 3505 (NH), 3295 (NH), 3151 (NH), 1682 (C=O), 1646 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.35 (br s, 4H; $2CH_2$), 1.83 (br s, 2H; CH_2), 2.1 (br s, 2H; CH_2), 3.78 (br s, 2H; 2CH), 3.92–4.08 (AB q, J_{AB} = 14.7 Hz, δ_A = 3.97, δ_B = 4.02, 4H; $2CH_2$), 3.95–4.16 (AB q, J_{AB} = 15.3 Hz, δ_A = 4.00, δ_B = 4.11, 4H; $2CH_2$), 5.65 (br s, 2H; NH), 7.00 (br s, 2H; NH), 7.10 (br s, 2H; NH); ^{13}C NMR ([D_6]DMSO, 50.3 MHz): δ = 24.5 (CH_2), 31.5 (CH_2), 52.2 (CH), 70.0 ($2CH_2$), 169.0 (C), 171.2 (C); MS (FAB$^+$, nitrobenzyl alcohol matrix) *m*/*z* (%): 345 (76) [*M*+H]$^+$, 367 (100) [*M*+Na]$^+$; $C_{14}H_{24}N_4O_6$ (344.4): calcd C 48.83, H 7.03, N 16.27; found C 48.53, H 6.99, N 16.36.

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(*R*,*R*)-*N*,*N*′-(Cyclohexane-1,2-diyl)bis(3-oxa-pentane-1,5-diamine) tetrahydrochloride [(*R*,*R*)-7·4HCl]: A solution of 1M BH_3·THF (100 mL) was added dropwise to a suspension of (*R*,*R*)-**6** (1.72 g, 5.0 mmol) in dry tetrahydrofuran (200 mL) under nitrogen. The mixture was refluxed for 7 h. After this time, the reaction mixture was treated at 0 °C with water (20 mL) and evaporated to dryness. The solid thus obtained was refluxed in 6N HCl (200 mL) for 4 h and then the water was removed in vacuo. The residue was dissolved in the minimum amount of H_2O, passed over Dowex 1 (basic form), and eluted with deionized water. The aqueous solution containing (*R*,*R*)-**7** was acidified to pH = 2 with conc. HCl and the solvent evaporated, and (*R*,*R*)-**7**·4HCl (2.08 g, 96%) was obtained as a highly hygroscopic solid after recrystallization in MeOH/$CHCl_3$. $[\alpha]_D^{20} = -32.0$ ($c = 1.0$ in MeOH); ^{1}H NMR (D_2O, 300 MHz): $\delta = 1.32$ (br m, 2H; 2*H*CH), 1.52 (br s, 2H; 2*H*CH), 1.73 (br s, 2H; 2*H*CH), 2.24 (br d, $J = 13.1$ Hz, 2H; 2*H*CH), 3.16 (t, $J = 5.0$ Hz, 4H; $2CH_2$), 3.24 (m, 2H; 2CH), 3.47 (m, 4H; $2CH_2$), 3.71 (t, $J = 4.6$ Hz, 4H; $2CH_2$), 3.79 (t, $J = 4.2$ Hz, 4H; $2CH_2$); MS (FAB^+, nitrobenzyl alcohol matrix) *m*/*z* (%): 289 (100) $[M+1]^+$, 311 (10) $[M+Na]^+$; $C_{16}H_{36}N_4Cl_4$ (458.4): calcd C 38.72, H 8.36, N 12.90; found C 38.46, H 8.12, N 13.10. The unprotonated species may be obtained by addition of sodium hydroxide to the aqueous solution of the corresponding tetrahydrochloride to pH = 13. Extraction with dichloromethane and subsequent evaporation of the solvent yielded (*R*,*R*)-**7** as an oily substance unsuitable for storage; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 1.05$ (m, 4H, 4NH), 1.10 (t, $J = 7.1$ Hz, 2H; 2NH), 1.24 (br t, $J = 9.0$ Hz, 2H; 2*H*CH), 1.73 (br d, $J = 8.2$ Hz, 2H; 2*H*CH), 2.04 (br s, 2H; 2CH), 2.14 (br d, $J = 11.4$ Hz, 2H; 2*H*CH), 2.58–2.69 (m, 2H; 2*H*CH), 2.85 (t, $J = 5.2$ Hz, 4H; $2CH_2$), 2.87–2.98 (m, 2H; 2*H*CH), 3.48 (t, $J = 5.2$ Hz, 4H; $2CH_2$), 3.52–3.60 (m, 4H; 2*H*CH), 4.80 (br s, 2H, NH); ^{13}C NMR ($CDCl_3$, 50.3 MHz): $\delta = 25.3$ (CH_2), 31.8 (CH_2), 41.9 (CH_2), 46.6 (CH_2), 61.8 (CH), 71.0 (CH_2), 73.1 (CH_2).

(*R*,*R*)-*N*,*N*′-(Cyclohexane-1,2-diyl)-*N*,*N*′,*N*″,*N*‴-tetrakis(*p*-toluenesulfonyl)bis(3-oxapentane-1,5-diamine) [(*R*,*R*)-8]: Tetrahydrochloride (*R*,*R*)-**7**·4HCl (700 mg, 1.61 mmol), diethyl ether (13 mL), and *p*-toluenesulfonyl chloride (1.71 g, 9.02 mmol) were added to a suspension of K_2CO_3 (12.5 g) in water (36 mL). The resulting biphasic system was vigorously stirred for 12 h. Water and ethyl acetate were then added to the mixture. The organic layer was washed with 3N HCl, dried, and evaporated to give (*R*,*R*)-**8** in 76% yield after flash chromatography (ethyl acetate/hexane 2:3). M.p. 86–88 °C; $[\alpha]_D^{20} = +6.7$ ($c = 0.51$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta =$ 1.10–1.40 (several m, 8H; $4CH_2$), 1.60 (br s, 2H; 2*H*CH), 2.38 (s, 6H; $2CH_3$), 2.46 (s, 6H; $2CH_3$), 3.09–3.20 (m, 8H; $4CH_2$), 3.38–3.48 (m, 2H; 2*H*CH), 3.52–3.62 (m, 2H, 2*H*CH), 3.78 (t, $J = 7.3$ Hz, 4H; $2CH_2$), 3.90 (br s, 2H; 2CH), 5.37 (t, $J = 5.8$ Hz, 2H, NH), 7.20 (d, $J = 8.2$ Hz, 4H; 4CH arom), 7.35 (d, $J = 8.2$ Hz, 4H; 4CH arom), 7.71 (d, $J = 8.2$ Hz, 4H; 4CH arom), 7.74 (d, $J = 8.2$ Hz, 4H; 4CH arom); ^{13}C NMR ($CDCl_3$, 50.3 MHz): $\delta = 21.4$ (CH_3), 21.5 (CH_3), 24.9 (CH_2), 29.6 (CH_2), 42.5 (CH_2), 42.8 (CH_2), 59.4 (CH), 69.1 (CH_2), 69.8 (CH_2), 127.0 (CH), 127.4 (CH), 129.6 (CH), 129.8 (CH), 136.7 (C), 137.0 (C), 143.1 (C), 143.8 (C); MS (FAB^+, nitrobenzyl alcohol matrix) *m*/*z* (%): 905 (43) $[M+H]^+$, 927 (100) $[M+Na]^+$, 749 (61) $[M-Ts]^+$; $C_{42}H_{56}N_4O_{10}S_4$ (905.2): calcd C 55.73, H 6.24, N 6.19; found C 55.59, H 6.60, N 5.81.

(1*R*,18*R*)-2,8,11,17-Tetrakis(*p*-toluenesulfonyl)-5,14-dioxa-2,8,11,17-tetraazabicyclo[16.4.0]docosane [(*R*,*R*)-9]: Dry acetonitrile (25 mL) was added to a flask containing (*R*,*R*)-**8** (765 mg, 0.85 mmol) and Cs_2CO_3 (2.76 g, 8.46 mmol) under nitrogen. The mixture was refluxed for half an hour and then a solution of ethylene glycol dimesylate (184 mg, 0.85 mmol) in dry acetonitrile (17 mL) was added dropwise. The reaction mixture was kept under reflux for 4 days. After this time, the solvent was removed and the residue subjected to flash chromatography (ethyl acetate:hexane 2:3) to yield (*R*,*R*)-**9** (87%) as a white solid. M.p. 198–200 °C; $[\alpha]_D^{20} = -11.2$ ($c =$ 0.50 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 1.00-1.50$ (br m, 4H; $2CH_2$), 1.50–1.80 (br m, 4H; $2CH_2$), 2.44 (m, 12H; $4CH_3$), 3.10–4.00 (several m, 22H; $10CH_2 + 2CH$), 7.31 (m, 8H; 8CH arom), 7.73 (m, 8H; 8CH arom); MS (FAB^+, nitrobenzyl alcohol matrix) *m*/*z* (%): 931 (28) $[M+H]^+$, 953 (96) $[M+Na]^+$, 775 (39) $[M-Ts]^+$; $C_{44}H_{58}N_4O_{10}S_4$ (931.2): calcd C 56.75, H 6.28, N 6.02; found C 56.54, H 6.24, N 5.74.

(*S*,*S*)-Cyclohexane-1,2-diylbis(sulfonamide) [(S,S)-10] was prepared from (*S*,*S*)-**3**·2HCl as previously described.[22]

(1*S*,9*S*,14*S*,22*S*)-2,8,15,21-Tetrakis(*p*-toluenesulfonyl)-5,18-dioxa-2,8,15,21-tetraazatricyclo[20.4.0.0^{9,14}]hexacosane [(*S*,*S*,*S*,*S*)-11] was obtained from (*S*,*S*)-**10** and diethylene glycol dimesylate as described for (*R*,*R*)-**9.** Yield: 80%; white solid; m.p. 200–202 °C; $[\alpha]_D^{20} = +5.2$ ($c = 0.65$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.95-1.40$ (several m, 8H; $4CH_2$), 1.50–1.75 (several m, 8H; $4CH_2$), 2.43 (s, 12H; $4CH_3$), 2.85–4.10 (several m, 18H; $8CH_2 + 2CH$), 4.91 (br s, 2H; 2CH), 7.31 (d, $J = 7.9$ Hz, 8H; 8CH arom), 7.84 (br s, 4H; 4CH arom), 8.02 (br s, 4H; 4CH arom); MS (FAB^+, nitrobenzyl alcohol matrix) *m*/*z* (%): 985 (3) $[M+H]^+$, 1007 (10) $[M+Na]^+$, 775 (5) $[M-Ts]^+$; $C_{48}H_{64}N_4O_{10}S_4$ (985.3): calcd C 58.51, H 6.55, N 5.69; found C 58.64, H 6.25, N 5.74.

General procedure for the hydrolysis of the tetratosylated azamacrocycles 9 and 11: Tetratosylated azamacrocycle (0.70 mmol) and an excess of phenol (1.14 mL, 13 mmol) were dissolved in 48% aqueous HBr (21 mL), and the solution was heated under reflux for 4 days. Water and dichloromethane were then added and the aqueous layer was repeatedly washed with dichloromethane. The organic layer was discarded and the aqueous one was evaporated under reduced pressure. The residue was treated with 4N NaOH (5 mL) and extracted several times with dichloromethane. The combined organic layers were dried and evaporated to dryness, yielding the desired azamacrocycle as a colorless oil. For the potentiometric measurements and for storage, the tetrahydrochloride was prepared by dissolution of the free amine in methanol, addition of conc. HCl and evaporation of the solvents. The residue was recrystallized in EtOH to yield the tetrahydrochloride of the corresponding dioxatetraazamacrocycle as a highly hygroscopic white solid, which is dried in vacuo and kept in a desiccant.

(1*R*,18*R*)-5,14-Dioxa-2,8,11,17-tetraazabicyclo[16.4.0]docosane tetrahydrochloride [(*R*,*R*)-1·4HCl]. Yield: 88%; decomposes at 250 °C; $[\alpha]_D^{20} = -35.6$ ($c = 0.50$ in H_2O); ^{1}H NMR (D_2O, 300 MHz): $\delta = 1.10-1.55$ (m, 4H; $2CH_2$), 1.65 (m, 2H; 2*H*CH), 2.05–2.45 (m, 2H; 2*H*CH), 3.10–3.90 (m, 22H; $10CH_2 + 2CH$); MS (FAB^+, nitrobenzyl alcohol matrix) *m*/*z* (%): 315 (39) $[M+1]^+$; $C_{16}H_{38}N_4O_2Cl_4$ (460.4): calcd C 41.74, H 8.32, N 12.17; found C 41.42, H 8.38, N 12.41. Spectral data for the free amine (*R*,*R*)-**1**: ^{1}H NMR ($DCCl_3$, 300 MHz): $\delta = 0.90-1.35$ (m, 6H; $2CH_2 + 2H$CH), 1.72 (br d, $J =$ 11.3 Hz, 2H; 2*H*CH), 2.10 (br d, $J = 10.9$ Hz, 2H; 2*H*CH), 2.24 (m, 2H; 2CH), 2.30–2.50 (b, 4H, 4NH), 2.61 (ddd, $J = 12.6$, 6.54, and 2.62 Hz, 2H; 2*H*CH), 2.79 (s, 4H; $2CH_2$), 2.80 (m, 4H; $2CH_2$), 2.97 (ddd, $J = 12.6$, 6.54, and 2.62 Hz, 2H; 2*H*CH), 3.48–3.66 (m, 8H; $4CH_2$); ^{13}C NMR ($DCCl_3$, 100.7 MHz): $\delta = 23.1$ (CH_2), 26.9 (CH_2), 44.9 (CH_2), 46.0 (CH_2), 48.4 (CH_2), 58.7 (CH), 65.9 (CH_2), 66.0 (CH_2).

(1*S*,9*S*,14*S*,22*S*)-5,18-Dioxa-2,8,15,21-tetraazatricyclo[20.4.0.0^{9,14}]hexacosane tetrahydrochloride [(*S*,*S*,*S*,*S*)-2·4HCl]: Yield: 75%; decomposes at 245 °C; $[\alpha]_D^{20} = -33.2$ ($c = 0.50$ in H_2O); ^{1}H NMR (D_2O, 200 MHz): $\delta = 1.28$ (m, 4H; 4*H*CH), 1.58 (br m, 4H; 4*H*CH), 1.70 (m, 4H), 2.07 (br d, $J =$ 12.9 Hz, 4H; 4*H*CH), 3.20 (m, 4H; 4*H*CH), 3.40 (m, 4H; 4*H*CH), 3.64 (m, 4H; 4CH), 3.85 (br d, $J = 6.46$ Hz, 8H; $4CH_2$); ^{13}C NMR (D_2O, 75.5 MHz): $\delta = 23.5$ (CH_2), 28.9 (CH_2), 42.1 (CH_2), 56.2 (CH), 63.3 (CH_2); MS (ES^+, 25 V) *m*/*z* (rel. intensity): 369.2 (2) $[M+1]^+$, 387.2 (2) $[M+1+H_2O]^+$, 405.2 (2.6) $[M+1+H^{35}Cl]^+$, 407.2 (1.3) $[M+1+H^{37}Cl]^+$; $C_{20}H_{44}N_4O_2Cl_4$ (514.5): calcd C 46.69, H 8.62, N 10.89; found C 46.42, H 8.38, N 11.01.

Acknowledgements

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