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Shape selectivity in the synthesis of chiral macrocyclic amides

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ABSTRACT

Shape-persistent, optically-active arylamide macrocycles have been designed and approached by using a stepwise, convergent methodology. The source of chirality, an axially-chiral Binol scaffold, incorporates methoxy functionalities in the 2,2′ positions, and carboxylic functionalities in the external 3,3′ positions. The latter can be efficiently elaborated through aromatic amidation to introduce aromatic spacers of differing shapes. The peculiar arrangement of functionalities on the Binol skeleton functions as an element of rigidification of the covalent structure through the formation of stable intramolecular hydrogen bonds. When this element is counterbalanced by the use of a flexible 3,3′-diaminobiphenyl as a spacer, yields for the macrocyclization step increase to values higher than 50%. The recognition properties of this particular macrocycle have been exploited and, while they indicate modest binding affinities towards carboxylate anions, the additional stabilization of neighbouring amide functionalities suitably placed within the covalent framework induces detectable binding of proper difunctional carboxylates.

1. Introduction

Shape-persistent macrocyclic structures are of increasing interest for applications in the field of nanoscience.[1] This is especially true as the issue of conformational rigidity of a covalent cyclic structure is related both to the possibility of enhancing the recognition properties towards suitable inclusion guests, and to the formation via self-assembly of stable organic nanotubes by supramolecular organization in the third dimension. As to the latter, different cyclic units have been used, such as, for example, cyclic peptides,[2] carbon-rich,[3] or urea-based structures.[4] Recent examples have proven how chirality can be exploited as a tool for creating organization and function at the nanoscale.[5] Binol (1,1′-binaphthyl-2,2′-diol) based synthons are popular in the recent literature, given their robustness, their availability and their relative ease of derivatization, and they are becoming more and more attractive molecular modules also for applications in materials science[6] and molecular recognition.[7] The basic Binol moiety can be conveniently functionalized in various positions, frequent ones being the 4,4′ and 6,6′ positions; access to the 3,3′ positions is also well documented.[8] The role of amide functionalities as hydrogen-bonding tools for the stabilization of assembled nanostructures has been elegantly exploited in several contexts, for instance in the field of foldamers[9] or in the design of assembled architectures as artificial ion channel mimics.[10] In particular, by introducing additional intramolecular hydrogen-bonding interactions to reduce the conformational mobility of the molecular backbone, Gong et al. have elegantly developed high-yielding syntheses of cyclic aromatic oligoamides containing large cavities, which in some cases behave as artificial channels.[11] Amide functionalities are also important as they possess hydrogen-bonding capability in the context of anion complexation. Several macrocyclic systems capable of effective anion recognition and discrimination have been previously reported.[12]

In this paper, we report on the design, synthesis and characterization of novel rigid, optically-active tetraamidic macrocycles with recognition and discrimination capabilities towards carboxylate and dicarboxylate-containing substrates.

2. Results and discussion

2.1. Design, synthesis and spectroscopic characterization

The design of the building blocks was driven by the fulfilment of two key objectives: (a) the introduction of amide-containing functionalities in the external 3,3′ positions of the Binol skeleton, in order to define a suitable internal cavity into macrocyclic structures containing two or more axially-chiral units; (b) the use of rigid aromatic spacers of differing size to join the chiral fragments. Three different molecular modules have been envisaged as spacers (Scheme 1):

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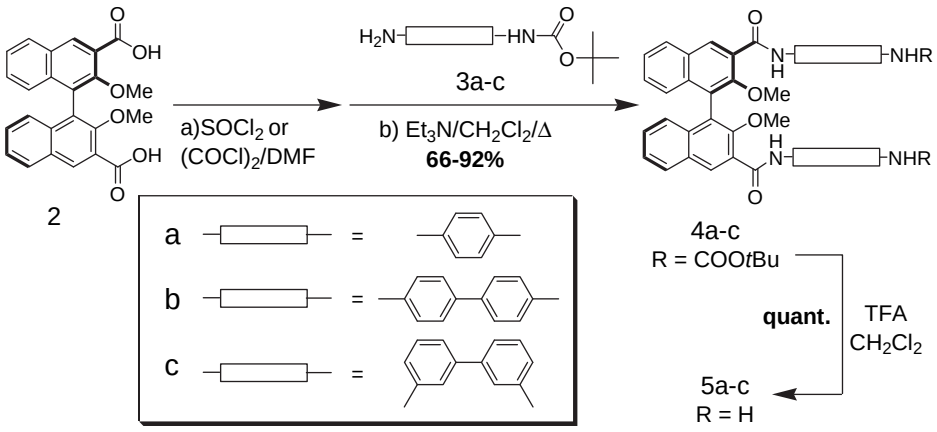
where the *p*-disubstituted phenyl and *p*-disubstituted biphenyl can be considered as shape-persistent, the *m*-biphenyl, given the fast unconstrained rotation around the aryl–aryl bond, can exist in different conformations possessing variable distances amongst the two ends, and it can be considered shape-unstable (Fig. 1).[13]

We turned our attention to compound **2**, which can be easily obtained from **1** under nonracemizing conditions,[16] and in which the competing phenol functionalities are protected as methyl ethers. Both (*R*)-**2** and (*S*)-**2** enantiomers were used routinely in the experiments described below. Direct generation of the carboxylic acid



Scheme 1. Synthesis of precursors **4** and **5**. (*R*)-Enantiomers only depicted for clarity.

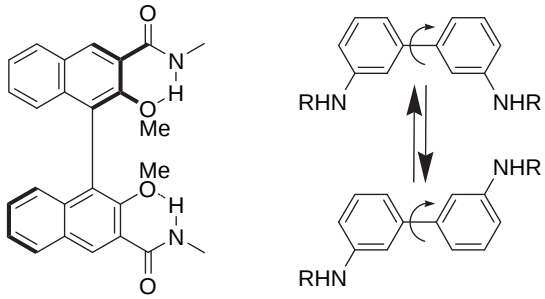
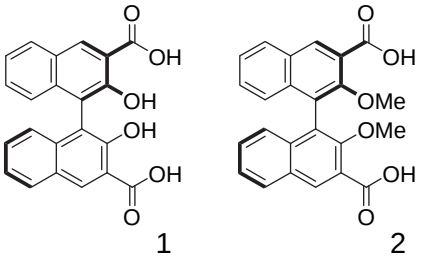
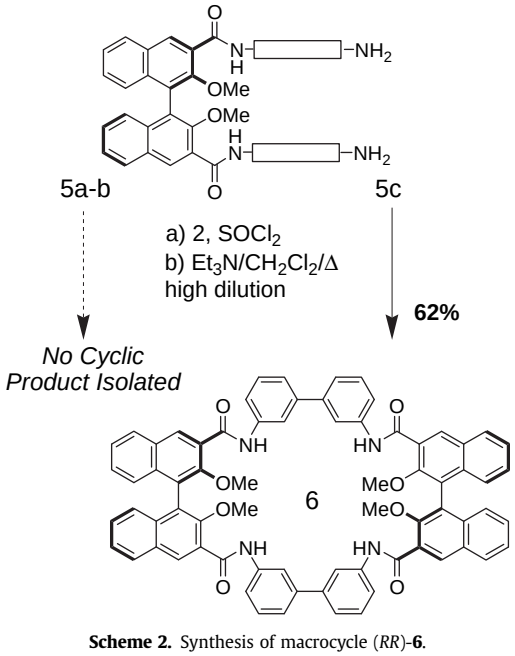


Figure 1. Representations (left) of the intramolecular hydrogen-bonding interaction as an element of internal rigidification, and (right) of the free rotation around the aryl–aryl bond that grants, only in the case of the 3,3′-biphenyl disubstituted spacers, an element of additional flexibility.

It was also deemed desirable to leave the possibility to further elaborate the internal 2,2′ positions, in order to insert guest-stabilizing functionalities, or moieties capable of inducing self-assembly in the third dimension. 3,3′-Dicarboxy-1,1′-binaphthyl-2,2′-diol **1** was therefore considered a convenient starting point, since its synthesis is well established and its resolution, to obtain both enantiomers in high purity, has been reported by several groups.[14] Our first attempts focused on the functionalization of **1** with aromatic amines via the formation of new amide bonds in the 3,3′ positions. We found that literature precedents for such aromatic amidation in the presence of vicinal (and competing) phenol moieties (which are comparable in nucleophilicity with aromatic amines) were rare,[15] and in our hands, test reactions on monofunctional model compounds gave disappointing results in terms of isolated yields of the desired products (see Supplementary data, model compound S1).



chloride (with $SOCl_2$, or oxalyl chloride and DMF) followed by reaction with the mono-BOC-protected aromatic amines **3a–c** in the presence of Et_3N as the acid scavenger gave compounds **4a–c** in good yields (82, 66 and 92% for **4a**, **4b** and **4c**, respectively), after purification by column chromatography. Alternative amidation procedures, performed directly with the aromatic carboxylic acid and anilines, using carbonyldiimidazole[17] or bis(2-oxo-3-oxazolidinyl)-phosphinic chloride and diisopropylethylamine[12b] were not as satisfactory. Deprotection under standard conditions (TFA, CH_2Cl_2) gave aromatic diamines **5a–c** in quantitative yields, which were used without further purifications in the subsequent cyclization step. Cyclization reactions were always attempted using fragments with the same chirality, in order to generate homochiral macrocycles such as **6**, as depicted in Scheme 2. When **5a** was subjected to cyclization conditions with equimolar amounts of the acyl chloride of **2** under high dilution conditions, in the presence of an excess of Et_3N as the



Scheme 2. Synthesis of macrocycle (*RR*)-**6**.

acid scavenger, a series of open-chain adducts could be identified, but no macrocyclic product could be isolated or even identified. When **5b** and the acyl chloride of **2** were subjected to cyclization under the same conditions, a small amount (4%) of a compound correctly identified as the [2+2] macrocycle by ESI-MS could be isolated after repeated column chromatography, but not completely purified. When diamine **5c** was reacted with the acyl chloride generated from **2**, again under the same conditions described above, substantial yields (50–60%) of macrocycle **6** could be isolated by column chromatography using medium polarity solvents. The macrocycle was found to be fully soluble in common organic solvents, including chlorinated solvents, THF, DMSO and acetone.

The much lower yields in the case of the cyclization reactions with *p*-phenyl and *p*-biphenyl substituted anilines, when compared to the 3,3′-diphenyl aromatic aniline, cannot be ascribed to a different electronic reactivity; for instance, the first amidation reaction to produce compounds **4a**–**c** worked for all the differently shaped amines equally well. Rather, it can be related to the mismatch in fit between the shape and dimensions of the aromatic spacers to be inserted, and the unavoidable bite angle of the two binaphthyl units locking the macrocycle. In addition, the rigidification through hydrogen bonding of the amide ends of both *p*-phenyl and *p*-biphenyl fragments brings the other ends far apart, so that cyclization becomes problematic. Instead, in the case of the 3,3′-subtituted diphenyl spacers the inherent shape flexibility associated with the aryl–aryl rotation compensates for the hydrogen-bonding rigidification and makes cyclization possible in good yields.

^{1}H NMR spectroscopy revealed for all compounds in $CDCl_3$ the presence of a sharp signal for the NH proton resonances of the amide functionalities, with very little variability in terms of chemical shifts (Table 1), as to indicate a structural similarity for precursors **4**, **5** and macrocycle **6**, with the NH group locked, at least on the NMR time-scale, in an S(6) type hydrogen bonded system with the neighbouring phenol ether in the 2,2′ positions.[18] The simplicity of the NMR spectra (see below, Fig. 4) reflects the structural symmetries found in precursors **4**–**5** and in macrocycle **6** (C_2 and D_2 molecular symmetries, respectively).

Table 1
Selected chemical shifts for compounds **4a**–**c**, **5a**–**c** and **6** in $CDCl_3$ (300 MHz, 25 °C)[a]

Entry	Compound	NH	Binol–H4[b]	OCH_3
1	(*R*)-**4a**	10.18	9.02	3.47
2	(*R*)-**5a**	9.76	8.98	3.47
3	(*S*)-**4b**	10.03	9.03	3.51
4	(*S*)-**5b**	10.03	9.03	3.51
5	(*R*)-**4c**	10.05	9.01	3.51
6	(*S*)-**5c**	10.07	9.04	3.51
7	(*RR*)-**6**	10.00	9.00	3.53

[a] All spectra were recorded at 5–10 mM sample concentration.
[b] Resonances related to the singlet corresponding to the proton in the 4,4′ positions of the Binol skeleton.

The UV/vis spectra of protected precursor **4c** and macrocycle **6** recorded in solvents possessing different solvating and hydrogen-bonding abilities (CH_2Cl_2, EtOH, THF), show little solvent dependence, with λ_{max} around 245 nm in all cases, and with a well-defined shoulder around 280 nm (see Figs. S1 and S2, see Supplementary data). Comparison with data available in the literature on parent chromophores[19] reveals that the spectra are not just the bare sum of those generated by the two major aromatic chromophoric components.

The CD spectra show a more marked activity for the macrocycle (*RR*)-**6**, with exciton couplet signals larger in intensity than the ones of precursor **4c** (Figs. S1 and S2). A significant solvent dependence was instead found for compound (*S*)-**4b** (Fig. 2): in the UV spectra, the λ_{max} tends to increase by going from THF to CH_2Cl_2, the latter

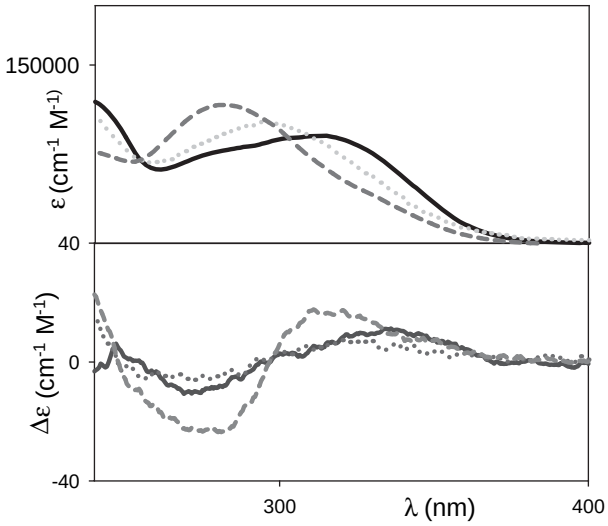


Figure 2. UV and CD (240–400 nm) solvent dependent behaviour of compound (*S*)-**4b** in CH_2Cl_2 (full line), EtOH (dotted line) and THF (broken line). Spectra were taken at $2.6–3.0\times10^{-6}$ M.

being the weakest competitor for the intramolecular hydrogen bond. In all solvents, furthermore, CD traces in Figure 2 show the exciton couplet signature typical of the Binol moiety.

2.2. Molecular modelling

Quantum chemical calculations on macrocycle **6** at the density functional B3LYP/6-31G(d) level of theory[20] were performed in order to gain further insight into its structural features and potential binding affinity.

A minimum-energy conformational search, carried out without any constraint, returned a C_2-symmetric structure in which the four carbonyl groups point outwards with respect to the well-defined cavity generated by the macrocycle (ca. 6–7 Å diameter), whereas the amide NH groups are oriented towards the interior of the cavity (Fig. 3). However, two of the four amide hydrogen atoms are involved in intramolecular hydrogen bonding with the methoxy oxygen atoms, making them less available for complexation of anionic species (vide infra).

Additional calculations at the same level of theory (DFT B3LYP/6-31G(d)) were carried out on the macrocycles, which would hypothetically result from the [2+2] cyclization reaction with the *p*-diaminophenyl and 4,4′-diaminobiphenyl spacers (**6A** and **6B**, see Supplementary data). The different outcome of the macrocyclizations could be rationalized by comparing the geometrical and energetic features of (*RR*)-**6** with those of **6A** and **6B**. Both these macrocycles present a significant distortion of the spacers, with their nitrogen atoms forced above the mean planes generated by the relative aromatic rings, with an offset of ca. 0.3 and 0.2 Å, respectively, whereas in the case of (*RR*)-**6** no distortion is observed, owing to the above-mentioned flexibility of the 3,3′-disubstituted spacer. On top of this, a direct comparison of the total energies obtained from geometry-optimization of the constitutional isomers (*RR*)-**6** and **6A**, shows a difference of 93.3 kJ/mol, which can confidently be ascribed to a higher macrocyclic ring strain in the latter compound.

2.3. Complexation studies

A ^{1}H NMR screening of the anion-binding abilities of macrocycle **6** was undertaken. A series of potential guests were selected, testing halides (Cl^-, I^-), aliphatic and aromatic mono- and di-carboxylates

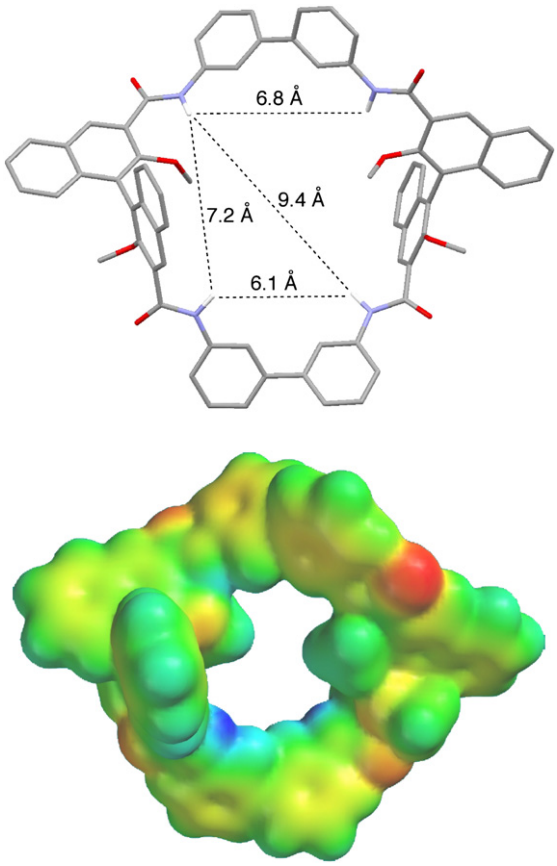


Figure 3. Top: minimum-energy conformation of macrocycle (*RR*)-**6** based on DFT B3LYP/6-31G(d) geometry optimizations. Bottom: electrostatic potential surface (contoured at a fixed 0.002 isovalue).

(acetate, benzoate, glutarate, *iso*-phtalate, (*R*)- and (*S*)-mandelate, see Supplementary data). A series of ^{1}H NMR titration experiments were carried out, in which the host concentration was kept constant (0.01 M) while the guest concentration was varied.[21] Addition of anionic guests, in the form of their of tetrabutylammonium salts, produced progressive downfield shifts of the signals of amide NH protons (Fig. 4), indicating that these groups were engaged in hydrogen bonding with the carboxylate guest, with a fast-exchanging equilibrium on the NMR time-scale. Glutarate was found to bind better to macrocycle **6** than the other candidates, as its length is ideal to span the cavity of **6** and interact simultaneously with two different NH groups (K_a=30±12 M^{-1}), possibly in a cooperative fashion.[22] The overall modest binding efficiency of macrocyle **6** is probably a consequence of the intramolecular NH···O hydrogen bonds.

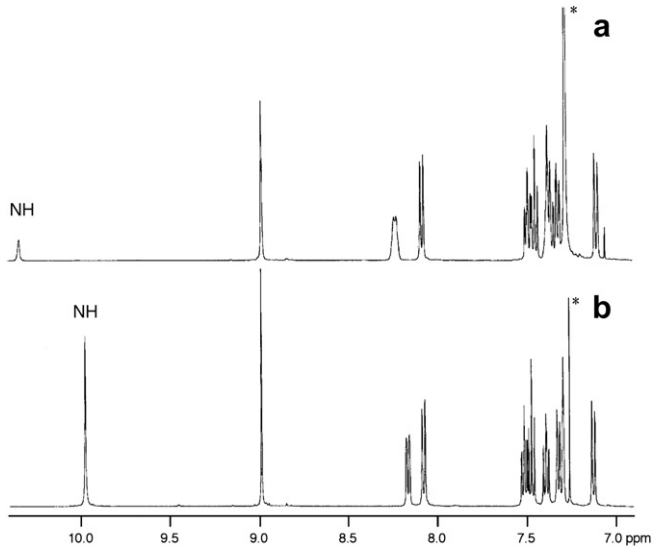


Figure 4. Partial ^{1}H NMR spectra (500 MHz, 25 °C, $CDCl_3$) of (a) [**6**]=0.01 M; (b) [**6**]=0.01 M, [$(OOCCH_2CH_2CH_2COO)^{2-}\cdot 2n$-$Bu_4N^+$]=0.06 M. *Residual solvent peak.

Their presence, which is confirmed also by the quantum chemical calculations, has a two-faced effect. On one hand, it contributes to the rigidification of the macrocyclic structure, while on the other it significantly reduces the tendency of such amide hydrogen atoms to interact with incoming guests,[23] as already been observed in similar compounds.[24]

3. Conclusions

We have presented the design and successful synthesis of a rigid, optically-active macrocycle, in which four amide functionalities are embedded into a 32-membered molecular backbone entirely comprised of sp^2 hybridized atoms. The synthesis is very efficient when the intrinsic presence of an element of structural rigidification, a strong intramolecular hydrogen bond, is compensated by the use of an aromatic spacer possessing a sufficient degree of flexibility. The anion recognition of carboxylate anions, probably as a consequence of the entropic difficulty in reorganizing the NH bond involved in this intramolecular hydrogen bond, and of steric hindrance of the vicinal methoxy group, is greatly reduced when compared with analogous systems reported in the literature. The recognition of suitable dicarboxylate anions, however, brings about detectable association constants in $CDCl_3$, and augurs well for the use of these molecular building blocks in nanoscale chiral assemblies.

4. Experimental section

4.1. General

All commercially available compounds (including **2a**) were used as received. Compounds (*R*)-**1** and (*S*)-**1**,[14] (*R*)-**2** and (*S*)-**2**,[16] **3b** and **3c**,[25] were prepared by following literature procedures. THF (CaH_2) and CH_2Cl_2 (CaH_2) were dried and distilled before use. ^{1}H and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ on 200, 300 or 500 MHz NMR spectrometers, using the residual solvent signal as the internal standard. Chemical shifts are reported in parts per million versus tetramethylsilane. 1D TOCSY NMR spectra were recorded at 500 MHz in $CDCl_3$, with arrayed spinlock times (15–150 ms). 1D NOESY NMR spectra were recorded at 500 MHz in $CDCl_3$, with a NOE mixing time of 500 ms. The UV/vis spectroscopic studies were conducted on a commercially available spectrophotometer. Mass spectra were recorded using an Electrospray Ionization spectrometer. Analytical thin layer chromatography was performed on silica gel, chromophore loaded, commercially available plates. Flash chromatography was carried out using silica gel (pore size 60 Å, 230–400 mesh). Optical rotations were measured on a polarimeter with a sodium lamp (λ=589 nm) and are reported as follows: $[\alpha]_D$ (c=g(100 mL)$^{-1}$, solvent). CD spectroscopy was performed using an appropriate spectropolarimeter; spectra were recorded at 25 °C at a scanning speed of 50 nm min^{-1} and were background corrected.

4.2. Synthetic procedures

*4.2.1. Compound (R)-**4a**.* A solution of (*R*)-**2** (150 mg, 0.37 mmol) in $SOCl_2$ (8 mL) was heated to reflux for 3 h. The solvent was removed in vacuo and the residue dissolved in dry CH_2Cl_2 (10 mL). A solution

of **3a** (233 mg, 1.12 mmol) and Et_3N (0.13 mL, 0.93 mmol) in dry CH_2Cl_2 (20 mL) was then added, and the mixture was heated under reflux overnight. After cooling to room temperature, the organic phase was washed with brine, dried (Na_2SO_4) and the residue purified by column chromatography (hexanes/AcOEt: 7/3) to yield (*R*)-**4a** (221 mg, 82%) as a white solid; [found: C, 70.42; H, 6.01; N, 7.03. $C_{46}H_{46}N_4O_8$ requires C, 70.57; H, 5.92; N, 7.16%]; $[\alpha]_D^{25}$ −98.1 (*c*=0.05, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.18 (s, 2H, N*H*CO), 9.02 (s, 2H, Binol–H4), 8.12 (d, 2H, *J*=8.1, Binol), 8.03 (d, 4H, *J*=8.7, aromatic), 7.82 (d, 4H, *J*=8.7, aromatic), 7.57 (t, 2H, *J*=6.6, Binol), 7.42 (t, 2H, *J*=6.6, Binol), 7.17 (d, 2H, *J*=8.7, Binol), 3.47 (s, 6H, OCH_3), 1.53 (s, 18H, *tert*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 163.1, 153.0, 141.8, 135.5, 134.8, 130.6, 130.4, 129.8, 129.1, 127.7, 126.2, 125.5, 125.3, 125.2, 119.2, 80.8, 62.0, 28.1; ESI-MS, *m*/*z* (%)=1527.2 $[2M+Na]^+$ (20%), 775.3 $[M+Na]^+$ (100%).

*4.2.2. Compound (S)-**4b**.* A solution of (*S*)-**2** (340 mg, 0.84 mmol) in $SOCl_2$ (5 mL) was heated to reflux for 3 h. The solvent was removed in vacuo and the residue dissolved in dry CH_2Cl_2 (10 mL). A solution of **3b** (400 mg, 1.69 mmol) and Et_3N (2 mL, excess) in dry CH_2Cl_2 (20 mL) was then added, and the mixture was heated under reflux overnight. After cooling to room temperature, the organic phase was washed with brine, dried (Na_2SO_4) and the residue purified by column chromatography (hexanes/AcOEt 9/1 to 7/3) to yield (*S*)-**4b** (510 mg, 66%) as a yellow solid; [found: C, 74.37; H, 5.93; N, 5.91. $C_{58}H_{54}N_4O_8$ requires C, 74.50; H, 5.82; N, 5.99%]; $[\alpha]_D^{25}$ +51.9 (*c*=0.007, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.03 (s, 2H, NHCO), 9.03 (s, 2H, Binol–H4), 8.12 (d, 2H, *J*=8.0, aromatic), 7.83 (d, 4H, *J*=7.8, aromatic), 7.6–7.4 (m, 16H, Binol and aromatic), 7.17 (d, 4H, *J*=7.8, aromatic), 6.64 (s, 2H, N*H*BOC); 3.51 (s, 6H, OCH_3); 1.53 (s, 18H, *tert*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0 (C═O), 153.0, 152.6, 137.5, 137.1, 136.7, 135.4, 135.1, 130.4, 125.8 (C_{quat}), 134.5, 129.7, 128.9, 127.2×2, 126.1, 125.3, 120.5, 118.8 (CH), 80.5 (–*C*(CH_3)$_3$), 62.1 (OCH_3), 28.2 (–C(*C*H_3)$_3$).

*4.2.3. Compound (R)-**4c**.* Oxalyl chloride (632 mg, 8 equiv) and a drop of dry DMF were added to a solution of (*R*)-**2** (250 mg, 0.62 mmol) in dry CH_2Cl_2 (15 mL). The solution was heated to reflux for 2 h. After a further 1 h stirring at room temperature, the solvent was removed in vacuo and the residue dissolved in dry CH_2Cl_2 (20 mL). A solution of **3c** (407 mg, 1.43 mmol) and Et_3N (200 mg, 3 equiv) in dry CH_2Cl_2 (20 mL) was added, and the mixture was heated under reflux for 2 h. After cooling to room temperature, the organic phase was washed with brine, dried (Na_2SO_4) and the residue purified by column chromatography (hexanes/AcOEt: 9/1 to 7/3) to yield (*R*)-**4c** as a yellow solid (536 mg, 92%). By following a synthetic protocol with $SOCl_2$ the yield was 63%; [found: C, 74.41; H, 5.90; N, 5.94. $C_{58}H_{54}N_4O_8$ requires C, 74.50; H, 5.82; N, 5.99%]; $[\alpha]_D^{25}$ +97 (*c*=0.017, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.05 (s, 2H, NHCO), 9.01 (s, 2H, Binol–H4), 8.11 (d, 2H, *J*=8.0, aromatic), 7.92 (s, 2H, aromatic), 7.78 (d, 2H, *J*=7.6, aromatic), 7.6–7.4 (m, 16H, Binol and aromatic), 7.22 (d, 2H, *J*=8.0, aromatic), 6.81 (s, 2H, N*H*BOC); 3.51 (s, 6H, OCH_3), 1.53 (s, 18H, *tert*-butyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.1, 153.0, 152.8, 141.8, 141.4, 138.8, 138.5, 135.4, 130.4, 125.9, 125.4 (C_{quat}), 134.5, 129.7, 129.4, 129.3, 128.9, 126.1, 125.3, 123.3, 121.8, 119.1, 118.8, 117.5, 117.1 (CH), 80.5 (*C*(CH_3)$_3$), 62.1 (OCH_3), 28.2 (–C(*C*H_3)$_3$).

*4.2.4. Compound (R)-**5a**.* A solution of (*R*)-**4a** (104 mg, 0.13 mmol) was stirred for 2 h at room temperature in trifluoroacetic acid/CH_2Cl_2 1/9 v/v (15 mL). The organic solution was washed with a satd solution of $NaHCO_3$, then with H_2O, dried over Na_2SO_4 and the solvent was removed in vacuo to afford a brown solid in quantitative yield, which was used without further purification. $[\alpha]_D^{25}$ −32.1 (*c*=0.01, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.76 (s, 2H, CON*H*), 8.98 (s, 2H, Binol–H4), 8.12 (d, 2H, *J*=8.0, Binol), 7.56 (m, 6H, Binol and aromatic), 7.35 (t, 2H, *J*=7.3, Binol), 7.12 (d, 2H, *J*=8.7, Binol), 6.58 (d, 4H, *J*=8.7, aromatic), 3.47 (s, 6H, OCH_3).

*4.2.5. Compound (S)-**5b**.* A solution of (*S*)-**4b** (370 mg, 0.40 mmol) was stirred for 2 h at room temperature in trifluoroacetic acid/CH_2Cl_2 1/9 v/v (20 mL). The organic solution was washed with a satd solution of $NaHCO_3$, then with H_2O, dried over Na_2SO_4 and the solvent was removed in vacuo to afford a brown solid in quantitative yield, which was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.02 (s, 2H, CON*H*), 9.03 (s, 2H, Binol–H4), 8.13 (d, 2H, *J*=7.8, Binol), 7.83 (d, 4H, *J*=8.0, aromatic), 7.6–7.4 (m, 12H, Binol and aromatic), 7.17 (d, 2H, *J*=8.1, Binol), 6.77 (d, 4H, *J*=8.0, aromatic), 3.51 (s, 6H, OCH_3).

*4.2.6. Compound (R)-**5c**.* A solution of (*R*)-**4c** (240 mg, 0.26 mmol) was stirred for 2 h at room temperature in trifluoroacetic acid/CH_2Cl_2 1/9 v/v (15 mL). The organic solution was washed with a satd solution of $NaHCO_3$, then with H_2O, dried over Na_2SO_4, and the solvent was removed in vacuo to afford a yellow solid in quantitative yield, which was used without further purification. $[\alpha]_D^{25}$ +86 (*c*=0.008, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.07 (s, 2H, CON*H*); 9.04 (s, 2H, Binol–H4), 8.12 (d, 2H, *J*=8.0, Binol), 7.96 (s, 2H, aromatic), 7.76 (d, 2H, *J*=8.0, aromatic), 7.6–7.0 (m, 16H, Binol and aromatic), 6.69 (d, 2H, *J*=7.2, aromatic), 3.51 (s, 6H, OCH_3).

*4.2.7. Macrocycle (RR)-**6**.* A solution of diacid (*R*)-**2** (121 mg, 0.3 mmol) was transformed into the diacyl dichloride as reported in the preparation of **4c**, then dissolved in dry THF (15 mL), and transferred into a pressure-equalized dropping funnel. A solution of diamine (*R*)-**5c** (210 mg, 0.29 mmol) in dry THF (15 mL) was put into a second pressure-equalized dropping funnel, and the two solutions were added dropwise over 1.5 h to a solution of Et_3N (88 mg, 0.87 mmol, 3 equiv) in dry THF (100 mL) under N_2. The stirring was continued at room temperature for a further 15 h, and the solvents removed in vacuo. The resulting solid was partitioned between CH_2Cl_2 and a satd $NaHCO_3$ solution, the organic layer separated, washed with brine, and dried (Na_2SO_4). The product was then purified by column chromatography (hexanes/AcOEt: 7/3) to yield (*RR*)-**6** as a white solid (195 mg, 62%); [found: C, 78.49; H, 4.88 N, 5.06. $C_{58}H_{54}N_4O_8$ requires C, 78.53; H, 4.76; N, 5.09%]; $[\alpha]_D^{25}$ +91 (*c*=0.002, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.98 (s, 4H, NH), 8.99 (s, 4H, Binol–H4), 8.16 (ddd, 4H, *J*=7.8, 2.0, 1.0, aromatic–H6′), 8.08 (d, 4H, *J*=8.2, Binol–H5), 7.51 (ddd, 4H, *J*=8.2, 6.9, 1.2, Binol–H6), 7.47 (t, 4H, *J*=7.8, aromatic–H5′), 7.39 (ddd, 4H, *J*=8.2, 6.9, 1.2, Binol–H7), 7.32 (dt, 4H, *J*=7.8, 1.0, aromatic–H4′), 7.29 (t, 4H, *J*=2.0, aromatic–H2′), 7.12 (dd, 4H, *J*=8.2, 0.8, Binol–H8), 3.52 (s, 12H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0 (C═O), 153.0, 142.0, 138.3, 135.5, 134.7 (CH), 130.3, 129.7, 129.7 (CH), 128.9 (CH), 126.1 (CH), 125.5, 125.3 (CH), 123.8 (CH), 119.9 (CH), 119.1 (CH), 62.2 (OCH_3); ESI-MS, *m*/*z* (%) 1123.4 $[M+Na]^+$ (100%).

4.3. Molecular modelling

The conformational analysis of macrocycles (*RR*)-**6**, **6A** and **6B** were carried out with the classical molecular mechanics force field (MMFF) by using the Monte Carlo method to randomly sample the conformational space. The equilibrium geometry obtained for the minimum-energy conformer of each macrocycle was refined at the PM3 semi-empirical level, and the data obtained were fully reoptimized without any constraint at the density functional level of theory (DFT, B3LYP functional) using the 6-31G(d) basis set.[20] All quantum mechanical calculations were performed using Spartan'08[26] on a Macintosh equipped with Intel Dual Quad Core CPUs at 3.2 GHz.

4.4. Determination of the binding constants by ^{1}H NMR spectroscopy

The K_a values for the complexation of (*RR*)-**6** with anions were assessed by Benesi–Hildebrand[27] linear treatment of the data obtained from ^{1}H NMR titration experiments. Samples were prepared by adding to a 0.7 mL solution of the host (0.01 M in $CDCl_3$) successive aliquots of stock solution of the guests (0.1 M in $CDCl_3$) to a final volume of 1.0 mL. Values of δ_{obs} for the NH resonances were collected by keeping the [host] to [guest] ratio in the 1/0.5–1/10 interval. The following stock solutions were used: [(*RR*)-**6**]=0.01 M in $CDCl_3$; [guest]=0.1 M in $CDCl_3$.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.03.102. This data include MOL files and InChIKeys of the most important compounds described in this article.

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