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Chemoenzymatic syntheses of new optically active C_2-symmetrical macrocyclic polyazacyclophanes

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Abstract—The syntheses of new C_2-symmetrical optically active macrocyclic polyazacyclophanes have been achieved from a common synthetic precursor, which has been prepared in enantiopure form by means of a chemoenzymatic pathway. The effect of the aromatic spacer on the flexibility of the systems is also discussed.

1. Introduction

Polyazacyclophanes are highly interesting systems in supramolecular chemistry as they can be used for the binding of both organic and inorganic ions.[1] The presence of an aromatic ring in their structure confers on them some chemical peculiarities[2] related to their molecular recognition and metal binding properties, and even biological activity.[3] These particular abilities are usually related to face-to-face or edge-to-face interactions with the host molecule. Thus, these systems exhibit special features when used in supramolecular constructions, presenting the aromatic unit as an additional point of interaction for the binding of the host molecule[4] or even for the self-assembling of the azamacrocycle itself.[5] Furthermore, the geometrical restrictions imposed by the rigid flat aromatic ring have led to the discovery of a new metal-binding behaviour.[6] These metal complexes displayed new reactivity, which can be compared with enzyme mimics[7] or exploited for the selective monofunctionalisation of one of the secondary amino groups of the azacrown.[8] Moreover, the aromatic moiety can act as an antenna, broadening the applications of these macrocyclic polyamines for the development of new molecular sensors.[9]

Despite the importance of this family of compounds, examples describing the preparation of optically active polyazacyclophanes are scarce in the literature.[10] For many of them, the source of the chirality arises from natural products, such as amino acids.[10c,d] Considering the potential applications of these systems and our previous work in this area,[11] we decided to tackle the syntheses of new optically active polyazacyclophanes. As in previous studies, we have used chiral *trans*-cyclohexane-1,2-diamine to obtain C_2-symmetrical optically active structures (Fig. 1). Optically active *trans*-cyclohexane-1,2-diamine has been efficiently used in catalysis and molecular recognition showing, in many cases, a high degree of enantiodiscrimination.[12]

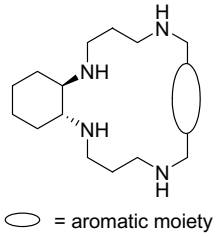

Figure 1. General structure of the optically active polyazacyclophanes.

2. Results and discussion

Previously, we reported the enzymatic sequential kinetic resolution of *trans*-cyclohexane-1,2-diamine **1**.[13] The

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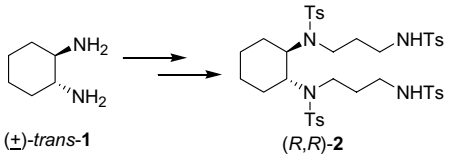
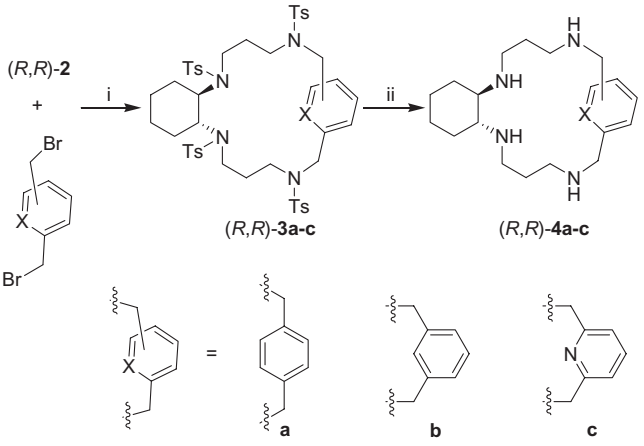
corresponding bis(amidoester) derivatives thus obtained were used for the syntheses of different optically active aza[11] and oxaazamacrocycles[14] in enantiopure forms, using modifications of the Richman–Atkins[15] general procedure. These compounds showed selective binding properties towards biologically interesting chiral anions in water.[14,16] The key intermediate for some of the described systems was the enantiopure tosylated polyamine (*R*,*R*)-**2** (Scheme 1). Based on these previous results, we considered it of interest to synthesise analogues bearing an aromatic moiety in their structure. We envisioned that the presence of the aromatic ring could add interesting properties in molecular recognition events.



Scheme 1.

Reaction of (*R*,*R*)-**2** with the appropriate bis(electrophile) under Richman–Atkins reaction conditions (excess K_2CO_3 in refluxing CH_3CN) led to the macrocyclic tetratosylated polyamines (*R*,*R*)-**3a**–**c** (Scheme 2). We selected *para* and *meta* disubstituted bis(bromomethyl)benzene (**a** and **b**, respectively) and 2,6-bis(bromomethyl)pyridine (**c**) as electrophiles to get different aromatic spacers, and no significant differences in yields or reaction times were found. Final acidic hydrolysis of tosyl groups afforded the corresponding polyazacyclophanes (*R*,*R*)-**4a**–**c**, in 40–45% overall yields calculated from (*R*,*R*)-**2**. These yields are in the range of the reported ones in structurally related systems.[2b] It must be pointed out that the final compounds were shown to be impure by traces of the corresponding monotosylated macrocycles (clearly detectable by ESI-MS experiments). We tried their purification by recrystallisation and, finally a very pure material was obtained in every case after careful flash chromatography, although the efficiency of the process was somewhat low (15–30%).



Scheme 2. Syntheses of the optically active polyazacyclophanes. Reagents and conditions: (i) K_2CO_3, CH_3CN, reflux; (ii) HBr (48% in water), PhOH, reflux.

Regarding the structural characterisation of the tosylated macrocyclic polyamines (*R*,*R*)-**3a**–**c**, both ^1H and ^{13}C NMR spectra showed a very broad and complicated group of signals. This suggests a dynamic process, probably related to the rotational barrier of the N–S bond of sulfonamides which, in this case, would produce a mixture of interconverting diastereomers. This hypothesis was confirmed after deprotection of the Ts groups, which produced a simplification of the NMR spectra of (*R*,*R*)-**4a**–**c**. Accordingly, the ^{13}C NMR spectra showed the expected number of signals for C_2-symmetrical structures in solution. These results support that there were no racemisation processes during the synthetic sequence, as epimerisation of a stereogenic centre would have led to a *cis*/*trans* diastereomeric mixture.

Comparison of the NMR spectra of the HCl salts of (*R*,*R*)-**4a** and (*R*,*R*)-**4b** (300 MHz, acidic D_2O, room temperature) showed some interesting features, which must be pointed out. For instance, the diastereotopicity of the benzylic protons differs from *meta* to *para* substituted derivatives. Thus (*R*,*R*)-**4a** showed an AB quartet for these protons ($|^2J_{AB}| = 13.2$ Hz, $\delta_A = 4.37$ ppm and $\delta_B = 4.43$ ppm) while in (*R*,*R*)-**4b**, the same methylenes appeared as a slightly broad singlet at 4.39 ppm. This experimental observation suggests a higher flexibility for the *meta* derivative. Interestingly, the diastereotopicity of benzylic protons of (*R*,*R*)-**4a** implies an efficient transference of chirality throughout the whole macrocyclic structure, a fact also observed in other azamacrocycles bearing the same chiral moiety.[17] In addition to that, the relative disposition between the aromatic ring and the main macrocyclic plane is also of interest. Semi-empirical PM3 theoretical calculations[18] of (*R*,*R*)-**4a**·$4H^+$ showed that the most favoured conformer is the one with the aromatic ring perpendicular to the macrocyclic main plane (Fig. 2).

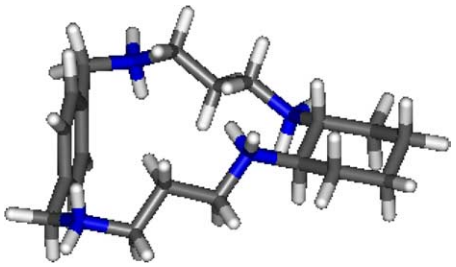


Figure 2. PM3 optimised geometry for (*R*,*R*)-**4a**·$4H^+$.

This conformation would set the propylene moiety on top of the anisotropy cone of the benzene ring. Accordingly, the protons of that moiety in (*R*,*R*)-**4a** resonate at a higher field ($\Delta\delta \sim 0.2$ ppm)[19] than those of both (*R*,*R*)-**4b** and the corresponding linear polyamine precursor. These data support the presence of a conformation like the one represented in Figure 2, which is in agreement with the reported data for related systems.[20]

However, the actual situation in solution is dynamic and, consequently, a bit more complicated. A conformer such as the one shown in Figure 2 exclusively has an element of symmetry: a binary axis passing through the centre of the aromatic ring (Fig. 3). Then, the spin system for the aromatic protons should be AA′BB′. Despite that, its ^{1}H NMR showed a clear singlet for those signals. Regarding the ^{13}C NMR, only two signals were observed for the aromatic carbons: one methyne and one quaternary carbon at 131.8 and 131.4 ppm, respectively. All these data support the idea that the rotation of the aromatic ring with respect to the macrocyclic main plane is fast in the NMR time scale, making all the aromatic CH's chemically equivalent. Therefore, the source for the lower flexibility of (*R*,*R*)-**4a** with respect to (*R*,*R*)-**4b** is not due to a high rotational barrier but, most likely, to a larger strain energy imposed by the *para* substitution.

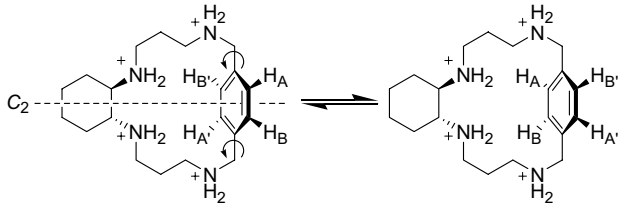


Figure 3. Proposed conformational behaviour of (*R*,*R*)-**4a**·4H^{+}.

The structural differences produced by the aromatic substitution could be a crucial topic if these compounds are used as receptors for the molecular recognition of chiral anions in water. Related to this, the acid–base properties of (*R*,*R*)-**4a** have been preliminarily studied. Thus, potentiometric titration of the corresponding tetrahydrochloride in aqueous Me_4NCl yielded log*K* values of 9.57, 8.43, 6.80, and 3.59 for the successive protonation of nitrogen atoms. These values show that (*R*,*R*)-**4a** exists as di- and triprotonated species close to neutral pH, in good agreement with reported data of the parent compound lacking the cyclohexane fused moiety.[2] The existence of polycationic forms in water at pH values close to neutrality opens the applicability of these systems for the binding of biologically interesting anions, whose many are chiral in nature. Studies in that direction are currently in progress and will be published in due course.

3. Conclusions

In summary, we have carried out the efficient syntheses of three different C_2-symmetrical optically active polyazacyclophanes, bearing either *para* or *meta* benzene or 2,6-pyridine units. The chirality of the systems arises from biocatalytically prepared (*R*,*R*)-cyclohexane-1,2-diamine moiety. Structural studies revealed conformational preferences of the corresponding protonated forms in water, showing differences depending on the aromatic substitution. All these facts suggest the potential of these systems for the molecular recognition of biologically interesting chiral anions.

4. Experimental

4.1. General

All reagents were purchased from commercial suppliers and used without further purification. Solvents were distilled over an adequate desiccant and stored under nitrogen. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh), except for the final polyamines which have been purified by column chromatography on ICN Ecochrom silica gel 60 (32–63 mesh) pH = 7. Melting points were taken using a Gallenkamp apparatus and are uncorrected. Optical rotations were measured using a Perkin–Elmer 241 polarimeter and specific rotations are quoted in units of 10^{-1} deg cm^2 g^{-1}. NMR spectra were obtained with TMS (tetramethylsilane) as internal standard using a Bruker AC-200 (^{1}H, 200 MHz and ^{13}C, 50.3 MHz) or a Bruker AC-300 (^{1}H, 300 MHz and ^{13}C, 75.5 MHz) spectrometer. Mass spectra were recorded on a Hewlett-Packard 1100 LC/MSD. For hydrochloride salts, the samples were basified by the addition of 1 M NaOH before acquiring the ESI-MS spectra. For the pH-metric titrations of (*R*,*R*)-**4a** Metrohm-702 titrimeter was used, 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 performed under nitrogen. The protonation constants were determined by titration with 0.1 M NaOH of a solution containing 10^{-3} M of the HCl salt of the polyazacyclophane in the presence of Me_4NCl (0.1 M). The measurements were carried out twice and the data analysis performed with the computer program SUPERQUAD. The titration curves were treated either as separated entities or as a single set without significant variations in the stability constants.

4.2. General procedure for the cyclisation reactions of (*R*,*R*)-*N*,*N*′-(cyclohexane-1,2-diyl)-*N*,*N*′,*N*″,*N*‴-tetrakis(*p*-toluenesulfonyl)bis(propane-1,3-diamine)

Dry acetonitrile (30 mL) was added to a flask containing (*R*,*R*)-**2** (844 mg, 1.0 mmol) and K_2CO_3 (1.38 g, 10.0 mmol) under a nitrogen atmosphere. The mixture was refluxed for 30 min and then a solution of the adequate electrophilic reagent (1.0 mmol) in dry acetonitrile (20 mL) added dropwise. The reaction mixture was kept at reflux for 2 days. After this time, the solvent was removed and the crude residue purified by filtration on silica gel eluted with ethyl acetate, to give the corresponding tosylated azamacrocycle.

4.2.1. (7*R*,8*R*)-7,8-(Butane-1,4-diyl)-*N*,*N*′,*N*″,*N*‴-tetrakis(*p*-toluenesulfonyl)-2,6,9,13-tetraaza[14]paracyclophane. Yield 96%; white solid, mp 123–1235 °C; $[\alpha]_D^{20} = -5.8$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.75–1.75 (bm, 12H), 1.90–2.25 (br, 2H), 2.40 (br s, 12H), 2.60–3.45 (br, 6H), 3.75 (m, 2H), 4.10–4.75 (m, 4H), 6.75–8.15 (br m, 20H); MS (EI, *m*/*z*): 791 (M−Ts) (12%). Anal. Calcd for $C_{48}H_{58}N_4O_8S_4$: C, 60.86; H, 6.17; N, 5.91. Found: C, 60.75; H, 6.30; N, 5.62.

4.2.2. (7*R*,8*R*)-7,8-(Butane-1,4-diyl)-*N*,*N*′,*N*″,*N*‴-tetrakis(*p*-toluenesulfonyl)-2,6,9,13-tetraaza[14]metacyclophane. Yield: 98%; white solid, mp 116–117 °C; $[\alpha]_D^{20} = -27.8$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 0.80–2.20 (bm, 12H), 2.45 (br s, 12H), 2.65–3.95 (br, 10H), 4.10–4.75 (m, 4H), 6.90–7.90 (br m, 20H); MS (EI, *m*/*z*): 791 (M−Ts) (12%); 637 (M−2Ts) (35%). Anal. Calcd for $C_{48}H_{58}N_4O_8S_4$: C, 60.86; H, 6.17; N, 5.91. Found: C, 60.69; H, 6.35; N, 5.81.

4.2.3. (7*R*,8*R*)-7,8-(Butane-1,4-diyl)-*N*,*N*′,*N*″,*N*‴-tetrakis(*p*-toluenesulfonyl)-2,6,9,13-tetraaza[14]-(2,6)-pyridinophane. Yield: 98%; white solid, mp 116–117 °C; $[\alpha]_D^{20} = -1.3$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 0.85–2.20 (bm, 12H), 2.40 (br s, 12H), 2.65–3.95 (br, 10H), 4.10–4.75 (m, 4H), 6.75–8.15 (br m, 20H); MS (EI, *m*/*z*): 792 (M−Ts) (60%). Anal. Calcd for $C_{47}H_{57}N_5O_8S_4$: C, 59.53; H, 6.06; N, 7.39. Found: C, 59.70; H, 6.30; N, 7.25.

4.3. General procedure for the hydrolysis of the tetratosylated azamacrocycles

A reaction mixture containing the tetratosylated azacrowns (0.5 mmol), phenol (0.58 g, 6.2 mmol) and 48% aqueous HBr (6.6 mL) was heated to reflux for 3.5 days. After this time, the mixture was allowed to cool down to room temperature and then, water and dichloromethane added and the aqueous layer repeatedly washed with dichloromethane. The organic layer was discarded and the aqueous layer, previously basified with 1 M NaOH, was extracted again with dichloromethane. The combined organic phases were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (MeOH/aqueous NH_3 9:1). The polyamine was dissolved in a minimum amount of methanol and concentrated HCl added until pH $\leqslant$2. The acid solution was evaporated to dryness to afford the corresponding azamacrocycle as its hydrochloric salt.

4.3.1. (7*R*,8*R*)-7,8-(Butane-1,4-diyl)-2,6,9,13-tetraaza[14]-paracyclophane tetrahydrochloric salt. Yield: 46% (23%); white hygroscopic solid, decomposes without melting; $[\alpha]_D^{20} = -19.0$ (*c* 0.5, MeOH) ^1H NMR (D_2O) δ (ppm): 1.04–1.60 (several m, 4H), 1.75 (m, 2H), 1.85–2.15 (several m, 6H), 2.80–3.25 (m, 6H), 3.27–3.43 (several m, 4H), 4.26–4.48 (qAB, $|^2J_{AB}| = 13.2$ Hz, $\delta_A = 4.37$ ppm, $\delta_B = 4.43$ ppm, 4H), 7.60 (s, 4H); ^{13}C NMR (D2O) δ (ppm): 22.3 (CH_2), 22.8 (CH_2), 26.4 (CH_2), 42.5 (CH_2), 42.6 (CH_2), 50.4 (CH_2), 58.1 (CH), 131.4 (C), 131.8 (CH); MS (ESI^+, *m*/*z*): 353 $(M+Na)^+$. Anal. Calcd for $C_{20}H_{38}Cl_4N_4$: C, 50.43; H, 8.04; N, 11.76. Found: C, 50.70; H, 8.35; N, 11.45.

4.3.2. (7*R*,8*R*)-7,8-(Butane-1,4-diyl)-2,6,9,13-tetraaza[14]-metacyclophane tetrahydrochloric salt. Yield: 44% (28%); white hygroscopic solid, decomposes without melting; $[\alpha]_D^{20} = -31.0$ (*c* 0.37, H_2O); ^1H NMR (D_2O) δ (ppm): 1.20–1.66 (several m, 4H), 1.71–1.98 (m, 2H), 2.02–2.40 (m, 6H), 2.99–3.53 (m, 10H), 4.39 (s, 4H), 7.54–7.81 (m, 4H); ^{13}C NMR (D_2O) δ (ppm): 22.6 (CH_2), 22.7 (CH_2), 27.1 (CH_2), 42.0 (CH_2), 43.1 (CH_2), 50.2 (CH_2), 57.7 (CH), 130.6 (C), 130.8 (CH), 131.9 (CH), 133.4 (CH); MS (ESI^+, *m*/*z*): 353 $(M+Na)^+$. Anal. Calcd for $C_{20}H_{38}Cl_4N_4$: C, 50.43; H, 8.04; N, 11.76. Found: C, 50.27; H, 8.42; N, 11.30.

4.3.3. (7*R*,8*R*)-7,8-(Butane-1,4-diyl)-2,6,9,13-tetraaza[14]-(2,6)-pyridinophane tetrahydrochloric salt. Yield: 45% (15%); white hygroscopic solid, decomposes without melting; $[\alpha]_D^{20} = -7.8$ (*c* 0.5, H_2O); ^1H NMR (MeOH-d_4) δ (ppm): 1.35–1.56 (m, 2H), 1.60–1.98 (several m, 4H), 2.21–2.61 (m, 6H), 3.36–3.98 (m, 10 H), 4.40–4.65 (qAB, $|^2J_{AB}| = 14.9$ Hz, $\delta_A = 4.50$ ppm, $\delta_B = 4.61$ ppm, 4H), 7.47 (d, $^3J_{HH} = 7.8$ Hz, 2H), 7.93 (t, $^3J_{HH} = 7.8$ Hz, 1H); ^{13}C NMR (D_2O) δ (ppm): 23.9 (CH_2), 24.1 (CH_2), 28.1 (CH_2), 42.8 (CH_2), 46.4 (CH_2), 52.2 (CH_2), 58.1 (CH), 123.4 (CH), 140.1 (CH), 152.3 (C); MS (ESI^+, *m*/*z*): 354 $(M+Na)^+$. Anal. Calcd for $C_{19}H_{37}Cl_4N_5$: C, 47.81; H, 7.81; N, 14.67. Found: C, 47.67; H, 8.02; N, 14.35.

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19. ^{1}H ^{13}C HMQC and ^{1}H ^{13}C HMBC heteronuclear correlation experiments allowed the assignation of the signals of the propylene substructure. For (*R*,*R*)-**4a**, CH_2 in α to the nitrogens showed a multiplet centred at 3.00 ppm while CH_2 in β appeared as a multiplet centred at 2.00 ppm. On the other hand, (*R*,*R*)-**4b** showed the corresponding signals, also as multiplets, at 3.25 and 2.13 ppm, respectively. Finally, the linear polyamine precursor showed those groups of signals as two multiplets at 3.25 and 3.50 ppm for N–CH_2 protons and at 2.25 ppm for the hydrogens of the centre of the propylene.
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