Macrocyclic Systems

Anion-Templated Syntheses of Pseudopeptidic Macrocycles**

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The design of molecular systems with programmable properties is a major challenge in modern chemistry. Among these properties, a key issue is the development of new procedures for the preparation of complex molecules based on the efficient programmed assembly of the corresponding structural components.[1] Supramolecular approaches to this problem have been developed over recent decades,[2] and templated synthesis, mainly based on cationic templates, is a well-

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known process.[3] However, anion templation is still in its infancy, as it is restricted to inorganic spherical species in most cases.[4] Recently, we synthesized and studied new pseudo-peptidic macrocycles[5] with interesting properties as organo-gelators,[6] molecular receptors,[7] chemosensors,[8] or molecular devices.[9] During this ongoing research, we envisioned the preparation of larger structures to increase the size and complexity of the substrates within the molecular recognition event. To achieve this goal, reductive amination between the corresponding bisamidoamine **1** and dialdehyde **2** seemed to be a reasonable option (Scheme 1). Unfortunately, we found that a well-defined configurational preorganization is mandatory for the formation of the desired [2+2] tetraimino intermediate.[10] In the absence of such preorganization, the reaction always led to a complex mixture of oligomers.

In the light of those results, we applied a rational approach to overcome this problem. According to the well-established binding modes between anions and NH amide groups,[11] we screened several anions as templates for the desired process in silico.[12] Starting from the modeled structure for the [2+2] tetraimino intermediate, we studied the possible non-covalent complexes between the proposed macrocycle and different anions. Monte Carlo analyses rendered terephthalate (**3**) the best candidate, as it shows an excellent structural complementarity with the macrocycle (Figure 1). According to the computer-generated structure, this dianion would present four hydrogen bonds between the carboxylate groups and the amide hydrogen atoms of the bisamide moieties and a π-stacking interaction with the aromatic rings of the macrocycle.
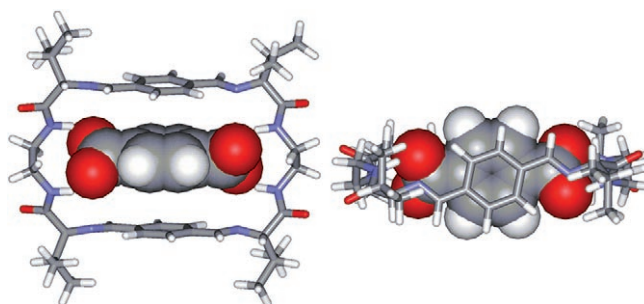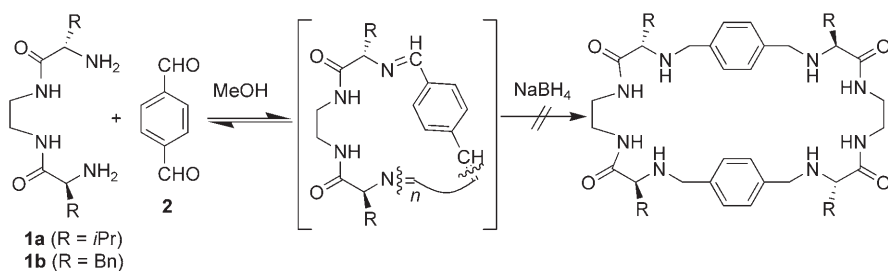

Figure 1. Top and side views of the optimized geometry for the proposed supramolecular complex between the tetraimino macrocycle (stick representation) and terephthalate dianion (space-filling representation). O red, N violet, C gray, H white.

The ¹H NMR spectrum of the crude product from the reaction between **1a** and **2** ([D₄]methanol, room temperature, 3 h) showed a complicated group of signals (Figure 2a). An observation of the aldehyde ($\delta = 9.9$–$\delta = 10.2$ ppm) and α-methoxyamine ($\delta \approx 5.6$ ppm) protons clearly demonstrates the existence of open-chain derivatives. The presence of different anions (as tetrabutylammonium (TBA) salts) had minor effects on the ¹H NMR spectra (see Figure 2b for chloride ions). However, when the terephthalate dianion (**3**) was used, the spectrum after 3 hours showed an almost quantitative conversion to a major (> 90%) imino compound

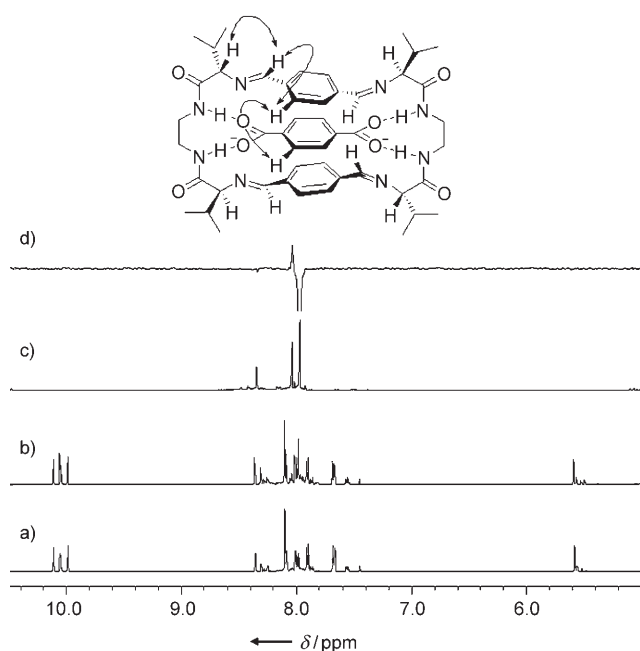**Scheme 1.** Proposed reductive amination macrocyclization reaction. Bn = benzyl.

Figure 2. Partial ^{1}H NMR spectra (500 MHz, 303 K, CD$_3$OD) of a mixture of **1a** and **2** (a) and in the presence of either TBACl (b) or **3**-(TBA)$_2$ (c). d) A 1D ROESY trace upon irradiation of the template signal. Key ROE effects are also shown with double-headed arrows.

the imine condensation.[13] The proposed inclusion of the anion within the macrocyclic polyimine was also demonstrated by different techniques. For example, intermolecular 1D ROESY enhancement was observed between the *ortho* protons of the aromatic imine and the *ortho* protons from the template (see Figure 2d), thus supporting a proximity between both nuclei (3.6–3.8 Å in the computed structure). Moreover, pulsed-field gradient spin-echo (PGSE) NMR[14] experiments showed that signals from the macrocyclic imine and the anion diffuse at the same rate, thus supporting that they form part of the same supramolecular entity. Quantitative analysis rendered a self-diffusion coefficient $D = 5.9 \pm 0.1 \times 10^{-10}$ m^{2}s^{-1}, which is much smaller than that of the free solvated template ($6.4 \pm 0.1 \times 10^{-10}$ m^{2}s^{-1}). Accordingly, the diffusion volume of the supramolecular complex was estimated to be 950 Å^3, whereas the computed volume of the minimized structure was 907 Å^3.[12] This finding represents a very good agreement considering the number of approximations assumed.[15]

Definitive proof for the existence of the proposed supramolecular structure was obtained by ESI-TOF mass spectra (negative detection mode) of the reaction mixture, which showed two major peaks at *m/z* 438.2 and 877.5, which correspond to the dianionic and sodiated monoanionic complexes, respectively. Full isotopic analyses also confirmed these assignments (Figure 3).
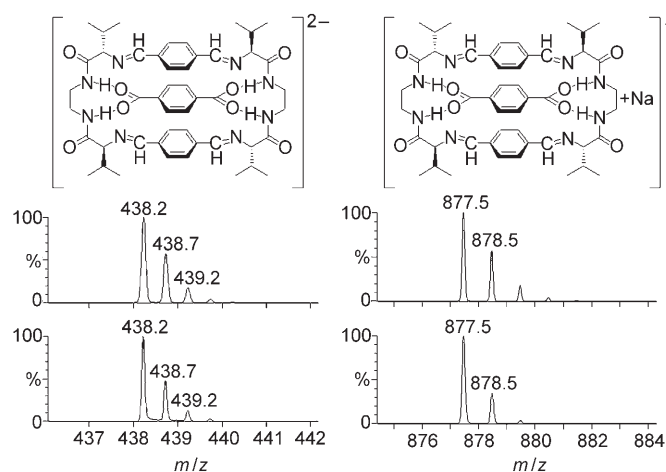

Figure 3. Experimental (lower trace) and simulated (upper trace) ESI-TOF mass spectra for the dianionic (left) and the sodiated monoanionic (right) supramolecular complexes.

with a remarkable D_2 symmetry (Figure 2c). The supramolecular species thus formed was completely characterized by a full set of NMR experiments, thus showing a good agreement with the proposed structure. The macrocycle shows only one imine methyne signal at $\delta = 8.24$ ppm and one single aromatic peak at $\delta = 7.99$ ppm. Besides, the ^{13}C NMR chemical shift for the inimo C=N atom ($\delta = 162.7$ ppm) suggests a conjugated aromatic diimine moiety. The high symmetry of the spectra implies an *S–trans* configuration of the diimino moieties. The imino proton signal showed a strong rotating-frame nuclear overhauser effect (ROE) effect with the C$_\alpha$H proton of the pseudopeptidic moiety. This finding supports the connectivity between both substructures, and a *syn* disposition between these hydrogen atoms in the major species (Figure 2), which is in good agreement with the computed geometry. By following the gradual increase of the imine signal, we observed that the formation of the imine bond in the presence of **3**-(TBA)$_2$ was approximately sixfold faster than in the absence of the template. These data suggest that the template also catalyzes

For the formation of a highly ordered complex as shown in Figure 1, the spatial disposition of aromatic chromophores must be well defined. This effect can be also accurately studied by circular dichroism (CD) spectroscopy. Thus, CD spectra were acquired for the crude condensation reactions in the presence and absence of **3**. A more pronounced cotton effect was found in the presence of the template (Figure 4), thus suggesting a more organized system. Moreover, the
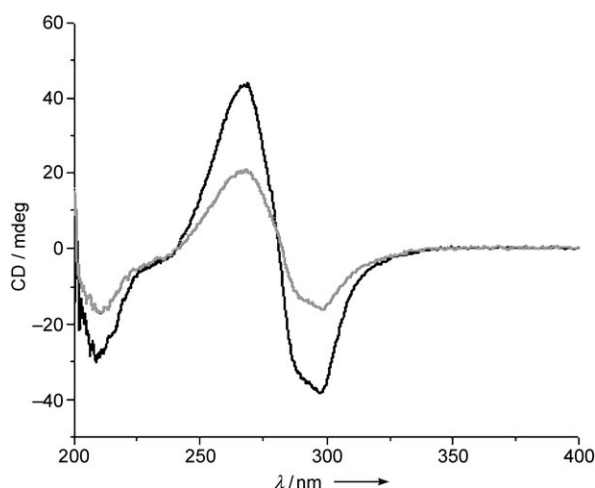
Figure 4. CD traces of a mixture of **1a** and **2** (MeOH, 3 h, 0.04 M, final concentration = 25 μM) in the absence (gray) and presence (black) of 0.5 equivalents of **3**-(TBA)$_2$.

Moreover, the hydrogen-bonding pattern involving terephthalate also suggests that **3** could act as a proton shuttle, thereby explaining the observed acceleration of the templated cyclization process by general acid–base catalysis.

We also wondered if the template-induced molecular organization would be operative in the presence of different configurations of the chiral centers of the open-chain precursors. As control experiments, we carried out the templated condensation reaction using either (*R,R*)-**1a** or (*S,S*)-**1b** (Figure 6 a, b, respectively) in separate experiments,

observed negative sign also reflects the relative disposition of the chromophores in the computed geometry.[16]

In such a supramolecular species, the anion must induce a structural organization to adapt the macrocyclic imine group to the molecular shape and charge density of the template. To understand that process, we studied the effect of the template in the hypothetical intermediate previous to the formation of the last C=N bond, which would lead to the final macrocycle. Monte Carlo simulations of the corresponding open-chain tris(imino)aminoaldehyde precursor were carried out, both in the absence and presence of **3** (Figure 5).[12] Binding with **3**
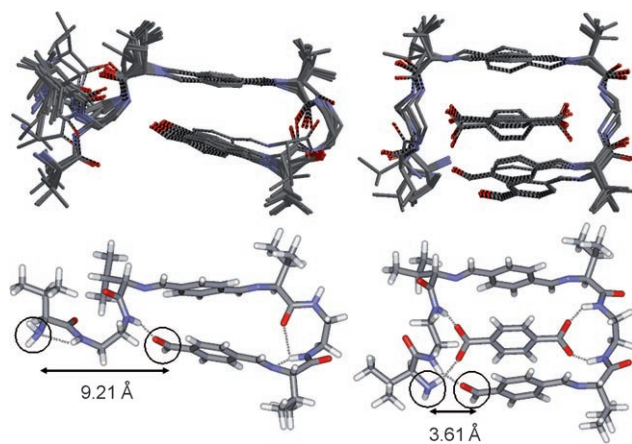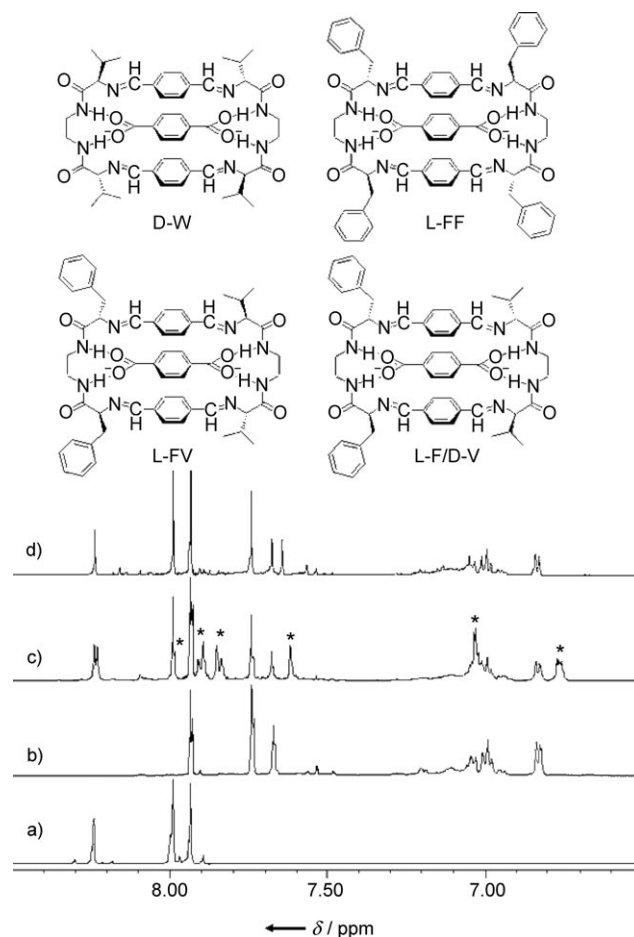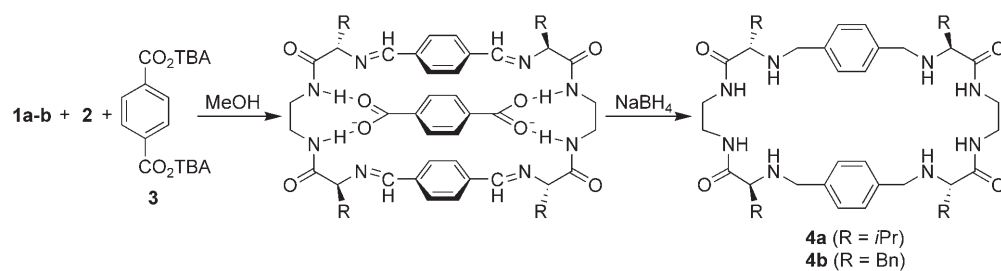

Figure 5. Superimposed structures within a energy gap of 2 kcal mol^{-1} (upper view) and global minima (lower view) for the hypothetical aminoaldehyde intermediate in the absence (left) and presence (right) of the template (hydrogen bonds indicated as gray dotted lines).

increases the rigidity of the intermediate (lower number of accessible local minima) and approximates the extremes of the molecule with the correct geometry for the nucleophilic attack of the amine on the aldehyde carbonyl functionality (see the distances between the encircled groups in Figure 5).

Figure 6. Partial ^{1}H NMR spectra (500 MHz, 303 K, CD$_3$OD) for a) D-VV, b) L-FF, c) L-FF + L-FV + L-VV (1:2:1 molar ratio), and d) L-FF + D-V. Signals corresponding to mixed nonsymmetrical L-FV are marked with an asterisk in (c).

thereby allowing the assignment of the corresponding signals for D-VV and L-FF complexes (see Figure 6 for the assumed terminology). Moreover, the spectrum obtained by mixing **2**, **3**-(TBA)$_2$, (*S,S*)-**1a**, and (*S,S*)-**1b** (2:1:1:1 molar ratio) showed the statistical formation of pure and mixed macrocycles (L-FF/L-FV/L-VV complexes in a 1:2:1 molar ratio; Figure 6 c), thus supporting that there are no detectable side-chain effects on the macrocyclization. Strikingly, when mixing equivalent amounts of **2** and the corresponding (*R,R*)-**1a** and (*S,S*)-**1b** bisamidoamines in the presence of the template, no mixed macrocycle was detected by NMR spectroscopic analysis

Scheme 2. Anion-templated syntheses of pseudopeptidic macrocycles.

(Figure 6d), thus implying that entities bearing the same side chain (and concomitantly, the same configuration) were exclusively formed. These results showed that anion templation induces a highly stereoselective molecular self-recognition, as only homochiral macrocycles were formed within the detection limit of ^{1}H NMR spectroscopy.[17]

Although the dynamic nature of the supramolecular complexes and imine-bond formation equilibria can make the isolation of these complexes difficult,[18] reduction of the corresponding C=N bonds in situ allowed us to obtain macrocycles **4a,b** in 60–65% overall yield from **1a,b** after chromatographic purification (Scheme 2) in a one-pot two-step process with synthetic utility. Besides, preliminary studies with systems derived from open-chain derivatives related to **1a,b**, but bearing larger aliphatic spacers, also confirm the trends described herein.

In summary, we have reported an unprecedented anion-templated reaction designed for the syntheses of new macrocycles. The formation of the intermediate supramolecular complex has been studied by different experimental and theoretical approaches and shows a perfect structural host–guest complementarity. This molecular organization is even expressed through a remarkable homochiral self-recognition. Further investigations on different templates and synthetic applications of this methodology are underway and will be published in due course.

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[15] The experimental molecular volume was calculated by approximating the shape of the molecule to a sphere ($V = 4/3\pi r^3$) of a radius equal to the hydrodynamic radius r_{H}, which was estimated using the Stokes–Einstein equation: $D = k_{\mathrm{b}} T/6\pi\eta r_{\mathrm{H}}$ where k_{b} is the Boltzmann constant and η is the viscosity of pure solvent. All these approximations could render a quantitative difference between the theoretical and experimental value of molecular volume. Additionally, one referee nicely drew our attention to the fact that the counterions and solvation shell were not considered for the molecular modeling structure. These factors also would increase the experimentally obtained volume relative to the theoretical one.

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[17] ESI mass-spectrometric experiments showed similar trends, although in this case a small amount of the mixed nonsymmetrical L-F/D-V complex was also detected, which can be a consequence of the very different conditions for the measurements and could destabilize the supramolecular complex in the mass spectrometer.

[18] Until now many attempts to obtain crystals suitable for X-ray diffraction analysis have been unsuccessful, probably as a result of the dynamic nature of the supramolecular complexes.