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Supramolecular Control for the Modular Synthesis of Pseudopeptidic Macrocycles through an Anion-Templated Reaction

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Abstract: The anion-templated synthesis of different pseudopeptidic macrocycles has been studied in detail by using a multidisciplinary approach. The reaction between an open-chain pseudopeptidic diamine and the appropriate dialdehyde is highly affected by the presence of the best fitting anionic template. The formation of the corresponding macrocyclic tetraimino-template supramolecular complex is demonstrated by NMR (ROESY and PGSE) and mass spectrometry (ESI-TOF). These supramolecular complexes can be easily reduced to the corresponding more stable tetraamine macrocycles. Accordingly, we have used this reaction to efficiently synthesize a family of new pseudopeptidic macrocycles in a one-pot two-steps anion-templated reductive amination reaction, which comprises a multicomponent macrocyclization through the selective formation of four chemical bonds to yield a unique macrocyclic structure. Different variables like the aliphatic spacer between amino acidic moieties, geometry of the dialdehyde, and structure of the amino acid side chains were thoroughly studied, and their effect in the formation and stability of the supramolecular complexes discussed. The conformational preorganization induced by the template has been monitored by circular dichroism, reflecting the differences observed in the isolated yields, as well as by NMR spectroscopy. This effect has been also supported by molecular modeling. All the experimental and theoretical techniques were strongly consistent and reflected the same trends by comparing the different structural variables introduced in the system.

Introduction

Amino acid derived macrocyclic compounds have recently drawn much attention in very different fields like synthetic,[1] bioorganic,[2] medicinal,[3] and supramolecular chemistry.[4] Their large ring structure restricts the conformational freedom and usually confers them a geometrical organization of the amino acid residues in a preferred disposition,[5] allowing them to host small molecules and ions,[6] with interesting potentials in molecular recognition. Besides, they are attractive scaffolds for the assembly of functional groups in a well defined three-dimensional geometry, for the mimicry of biological natural and non-natural tertiary structures.[7] Thus, they are excellent candidates as scaffolds for the design of relatively complex structures aiming the interaction with biological functions.[8] Another interesting property of peptide-like macrocycles is their ability

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to self-assemble into superior structures.[9] Accordingly, they can form supramolecular nanotubes[10] and gels[11] with very interesting biological properties as antibacterial or anti-HIV drugs,[12] delivery systems,[13] and nanomaterials.[14] The peptidic frame usually makes them highly biocompatible and also allows a broad range of molecular diversity through side-chain replacements. However, the key step for the chemical synthesis of this family of compounds is the macrocyclization reaction.[15] Apart from those systems showing a conformational preorganization for the cyclic structure,[16] this step usually requires high dilution techniques or the use of protecting groups which lead to low yields, mixtures of oligomers of different sizes, and tedious purification steps.[17] Several approaches to overcome this problem have been developed during the last decades,[18] and supramolecular techniques like templated synthesis seemed especially attractive within this context.[19] Although templation based on cationic species is a well-known process,[20] anion templation is still in its infancy, being in most cases restricted to inorganic spherical species.[21] As far as we know, only some remarkable examples dealing with tetrahedral[22] and octahedral[23] anions have been reported. The reason for the gap between the development of anion and cation templation techniques mainly relies on the intrinsically more complicated physicochemical nature of anions,[24] which makes their general coordination chemistry studies a bit tougher. During the last couple of years, anion templation has been successfully used for the synthesis of rotaxanes,[25] pseudorotaxanes,[26] catenanes,[27] (metalla)macrocycles,[28] and molecular cages,[29] but the use of this approach for peptide-like macrocycles is almost nonexistent.

On the other hand, we have recently synthesized and studied new pseudopeptidic macrocycles[30] with interesting properties as organogelators,[31] molecular receptors,[32] chemosensors,[33] or

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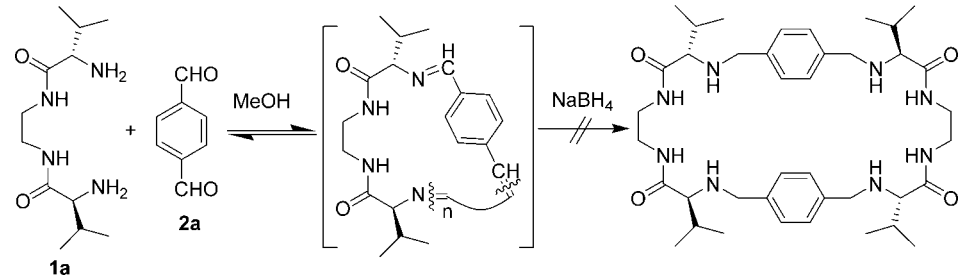
Scheme 1



molecular devices.[34] Within this research project, we envisioned the preparation of larger structures to expand the possibilities for the generation of a family of compounds by increasing the size and complexity of the substrates. To achieve this goal reductive amination between the corresponding bis(amidoamine) **1a** and dialdehyde **2a** seemed to be a reasonable option (Scheme 1). Unfortunately, we found that a well-defined conformational preorganization is mandatory for the formation of the desired [2 + 2] tetraimino intermediate.[35] In the absence of such preorganization, the reaction always led to a complex mixture of oligomers. Here we report on the use of anionic dicarboxylates to template[36] this process for the most flexible examples, bearing a linear aliphatic spacer between aminoacidic moieties. Different structural variables have been mapped on the macrocyclic framework and their effect on the templation procedure has been studied by different experimental and theoretical approaches.

Results and discussion

Design of the Anion Templation Approach. After the preliminary study of the configurationally driven preorganization necessary for the proposed [2 + 2] macrocyclization reaction, we decided to use a different method to promote such a conformational folding. According to the well-established binding modes between anions and NH amide groups,[37] we screened, by molecular modeling, several anions as templates for the desired process.[38] Starting from the modeled structure of the [2 + 2] tetraimino intermediate, we studied the possible noncovalent complexes between the proposed macrocycle and different anions. Monte Carlo analyses rendered terephthalate **3a** as the best candidate, showing an excellent structural complementarity with the macrocycle (Figure 1). According to the computer generated structure, this dianion would present four hydrogen bonds between its carboxylate groups and the amide hydrogen atoms of the bisamide moieties and also a possible π-stacking interaction with the aromatic rings of the macrocycle.[39] Besides, CPK inspection of this structure showed that the template perfectly fills the macrocyclic cavity, maximizing the entropic contribution due to the desolvation of the inner cavity of the cycle.

To check this proposal, we followed the reaction between the bis(aminoamide) **1a** and dialdehyde **2a** by different techniques. The ^{1}H NMR spectrum of the crude of the reaction between **1a** and **2a** (methanol-d_4, room temp, 3 h) showed a complicated group of signals (Figure 2a), indicative of a mixture of species in solution. The observation of aldehyde (9.9–10.2 ppm) and α-methoxyamine (at ca. 5.6 ppm) protons clearly demonstrates the existence of open-chain derivatives. The presence of other anions (as tetrabutylammonium -TBA- salts) had minor effects on the ^{1}H NMR spectra (Figure 2b−d). However, when terephthalate dianion **3a** was used, the spectrum after 3 h showed an almost quantitative conversion to a major

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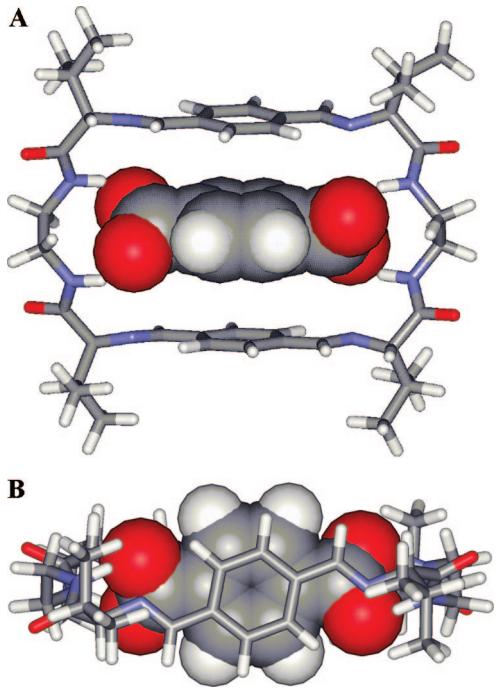

Figure 1. (A) Up and (B) side views of the optimized geometry for the proposed supramolecular complex between the tetraimino macrocycle (stick) and terephthalate dianion (space filling).

(>90%) imino compound with a remarkable D_2 symmetry (Figure 2e). The supramolecular species thus formed was completely characterized by a full set of NMR experiments (Supporting Information, Figures S1−S3), showing a good agreement with the proposed structure.[40] The macrocycle shows only one imine methyne signal and one single aromatic peak. Besides, the ^{13}C NMR chemical shift for the inimo C═N atom (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 (at 8.24 ppm) showed a strong ROE effect with the C$^{\alpha}$H (at 3.59 ppm) of the pseudopeptidic moiety (Supporting Information, Figure S3), supporting the connectivity between both substructures, and a syn disposition between these hydrogens in the major species (Figure 2, inset on the upper left), in good agreement with the computed geometry (Figure 1). By following the gradual increase of the imine signal (Figure 2, inset on the upper right), we observed that the formation of the imine bond in the presence of **3a**·2TBA was ca. 6-fold faster than in the absence of the template. These data suggest that the template also catalyzes the imine condensation.[41] The proposed inclusion of the anion within the macrocyclic polyimine was also demonstrated independently by additional techniques. For instance, intermolecular 1D ROESY enhancement was observed between ortho protons of the aromatic imine and the ortho protons from the template (see Figure 2f, and Figure S3 for the 2D ROESY), supporting a close proximity between both nuclei (3.6–3.8 Å in the computed structure). Moreover, PGSE NMR[42] experiments showed that signals from the macrocyclic imine and from the anion diffuse at the same rate, supporting that they form part of the same supramolecular entity. Quantitative analysis rendered a self-diffusion coefficient $D = 5.9 \pm 0.1 \times 10^{-10}$ $m^2 \cdot s^{-1}$, much smaller than that of the free solvated template ($6.4 \pm 0.1 \times 10^{-10}$ $m^2 \cdot s^{-1}$). Accordingly, the diffusion volume of the supramolecular complex was estimated to be 950 Å^3, while the computed volume of the minimized structure was 907 Å^3. This represents a very good agreement considering the number of approximations assumed.[43]

Definitive proofs for the existence of the proposed supramolecular structure were obtained by mass spectrometry. Thus, ESI-TOF mass spectra of the crude reaction mixture, at the negative detection mode, showed two major peaks at $m/z = 438.2$ and 877.5 corresponding to the dianionic and sodiated monoanionic complexes, respectively. Full isotopic analyses also confirmed these assignments (Figure S4) showing a perfect agreement between simulated and experimental mass spectra, and supporting the large stability of the proposed supramolecular complex, which resists the conditions of the mass spectrometry measurement. We also performed the ESI-TOF MS with the other assayed templates (chloride, acetate and benzoate). Interestingly, the supramolecular complexes formed by the macrocyclic tetraimine and the anions were detected as minor peaks. However, they were accompanied by major species where the imine bond has not been formed, namely of the type [**1a** + **2a** + **A**]$^-$ and [**1a** + (**2a**)$_2$ + **A**]$^-$ with **A** as the corresponding anion. This observation suggests a less specific association with a lower propensity to undergo condensation toward the corresponding macrocycles.

Thus, combination of NMR and ESI-TOF MS techniques unambiguously showed the anion templation effect on this system and also served to characterize the corresponding supramolecular species formed in solution. At that point, we wondered if this methodology would allow us to synthetically prepare the corresponding tetraamino derivative, by the in situ reduction of the four imine bonds on the intermediate. Satisfyingly, borohydride reduction of the supramolecular complex led to the expected compound in very good overall yield (60%) after chromatographic purification. The final compound was fully characterized by spectroscopic techniques and single crystal X-ray diffraction analysis of the corresponding tetrahydrochloride salt (see Supporting Information). We envisioned to extend this methodology to the preparation of a family of compounds by mapping different variables of the macrocyclic structure (Scheme 2, Table 1) such as the aliphatic spacer (n = 0–2), amino acid side chain (aliphatic, aromatic, branched, H-bonding), and dialdehyde geometry (para/meta). In all the cases, the corresponding macrocycles were obtained in good overall yields (Table 1), considering the difficulty of macrocyclization

(40) After the complete characterization of the [2 + 2] tetraimine macrocycle and the assignation of its ^{1}H NMR signals, we observed that this species was also present in the reactions templated by acetate and benzoate anions (see Figure 2). Acquisition of the corresponding NMR spectra of these samples after longer reaction times showed an increase of the signals of the intended macrocycle, but always mixed with other open-chain derivatives.

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(43) The exprimental molecular volume was calculate by approximating the shape of the molecul 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: $D = k_B T/6\pi h r_H$ where k_B is the Boltzmann constant and h is the viscosity of pure solvent. All these approximations could render a quantitative difference between the theoretical and experimental value of molecular volume. Additionally, counterions and salvation shell were not considered for the molecular modeling structure. These facts also would increase the experimentally obtained volume as compared with the theoretical one.

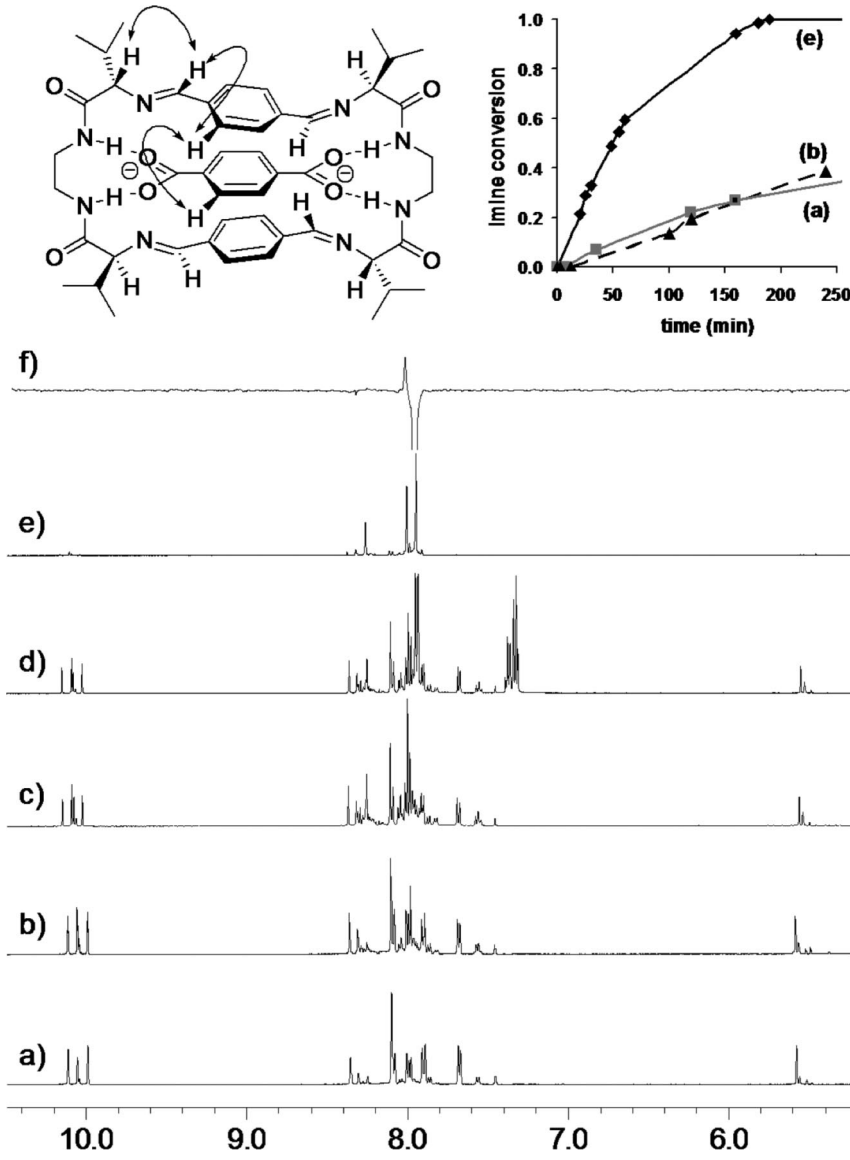
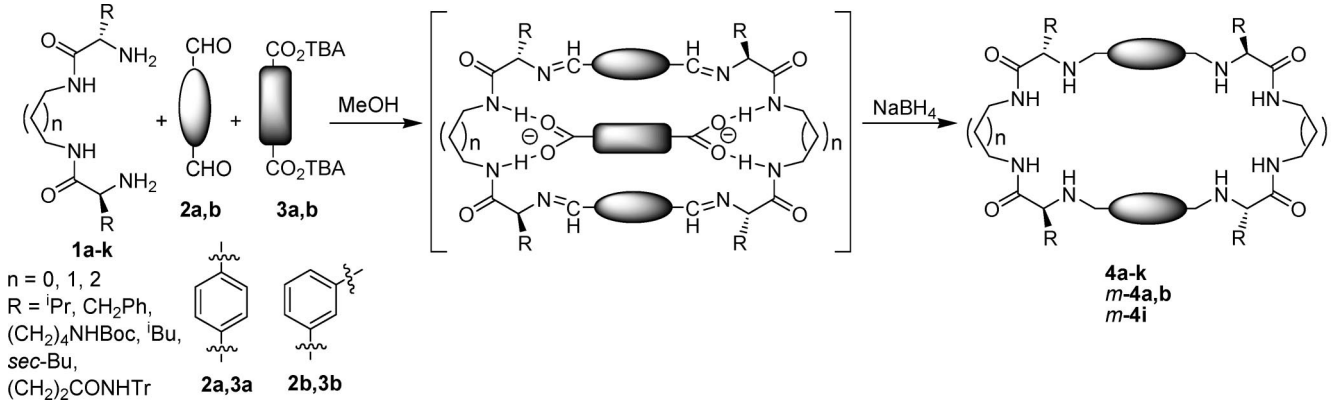


Figure 2. Partial ^{1}H NMR spectra (500 MHz, 303 K, after 3 h of reaction in CD_3OD) of a mixture of **1a** and **2a** (a) alone and in the presence of the corresponding TBA salts of (b) chloride, (c) acetate, (d) benzoate, or (e) **3a**; (f) 1D ROESY trace upon irradiation of the template **3a** signal. Other key ROE effects are shown with double-headed arrows in the structure on the upper left (see Figure S3 in the Supporting Information). The increment of overall imine conversion versus time is also plotted for spectra a, b, and e on the upper right corner.

Scheme 2. Synthesis of Pseudopeptidic Macrocycles through Anion-Templated Reductive Amination



processes, and the decrease in yields associated to a careful chromatographic purification. Besides, for the accurate evaluation of the yield, we have to take into account that four independent bonds in two-step processes have to be formed. Accordingly, for an overall 26% yield, we can estimate an 85% average theoretical yield for every step. However, some remark-

Table 1. Obtained Yields for the Synthesis of Pseudopeptidic Macrocycles through Anion-Templated Reductive Amination

entry	sust.	*n*	R	Aaa	dialdehyde	template	product	Yield (%)[a]
1	**1a**	0	iPr	Val	**2a**	**3a**	**4a**	60
2	**1b**	0	CH_2Ph	Phe	**2a**	**3a**	**4b**	65
3	**1c**	1	iPr	Val	**2a**	**3a**	**4c**	30
4	**1d**	1	CH_2Ph	Phe	**2a**	**3a**	**4d**	36
5	**1e**	2	iPr	Val	**2a**	**3a**	**4e**	26
6	**1f**	2	CH_2Ph	Phe	**2a**	**3a**	**4f**	33
7	**1a**	0	iPr	Val	**2b**	**3b**	*m*-**4a**	36
8	**1b**	0	CH_2Ph	Phe	**2b**	**3b**	*m*-**4b**	30 [17][b]
9	**1g**	0	$(CH_2)_4NHBoc$	Boc-Lys	**2a**	**3a**	**4g**	40
10	**1h**	0	iBu	Leu	**2a**	**3a**	**4 h**	50
11	**1i**	0	sec-Bu	Ile	**2a**	**3a**	**4i**	35
12	**1i**	0	sec-Bu	Ile	**2b**	**3b**	*m*-**4i**	26
13	**1j**	1	sec-Bu	Ile	**2a**	**3a**	**4j**	27
14	**1k**	0	$(CH_2)_2CONHTr$	GlnTr	**2a**	**3a**	**4k**	31

[a] Isolated overall yields after condensation, reduction, hydrolysis, workup, and chromatographic purification, calculated from the starting pseudopeptidic bis(amidoamine) **1a**−**k**. [b] The value between brackets shows the isolated yield of the corresponding [3 + 3] macrocyclic byproduct.

able differences in Table 1 must be pointed out.[44] For instance, the enlargement of the spacer by one methylene group led to an important decrease of the yield (compare entries 1 and 3 or 2 and 4), as expected considering the larger flexibility of the propylene moiety. Surprisingly, the decrease in the efficiency was not so large with an additional methylene group in the spacer (see entries 5 and 6). Regarding the dialdehyde geometry, we have found that para substitution is more efficient than meta, probably due to its higher symmetry and lower number of possible conformations of the open-chain intermediates. However, meta-derivatives were obtained in acceptable to good yields (entries 7, 8, and 12) by using the best fitting isophthalate **3b** template, which again highlights the important role played by the template. Interestingly, in the case of phenylalanine derivative **1b**, the reaction with the isophthaldehyde **2b** and the template **3b** produced the expected [2 + 2] macrocycle in 30% yield in addition to an important amount of the [3 + 3] macrocycle in 17% yield (entry 8 in Table 1). This surprising and remarkable result suggests that it is possible to obtain larger macrocycles by optimizing the size and topology of the template. Studies in that direction are currently under development and will be published in due course.

Regarding the effect of the side chain, the reaction works with aliphatic and aromatic residues, aromatic side chain being slightly better (entries 2, 4, and 6). In this regard, the benzyl side chain can prevent amide solvation in polar environments, favoring its interaction with the anionic template.[34] Among the aliphatic derivatives (deriving from amino acids Val, Leu, and Ile), some surprising differences were obtained since the observed trend (Val > Leu > Ile) is not trivial to rationalize (see below in text). Interestingly, two examples bearing H-bonding donor groups (amide and carbamate) were successfully assayed (entries 9 and 14), suggesting that the templated process is highly selective toward the backbone amide group.

Intrigued by some of these observations, we have characterized the tetraimine−dianion supramolecular complexes for some selected examples. To understand the differences due to the aliphatic spacer (*n*), we studied the templated reaction with **1c** ($n = 1$) and **1e** ($n = 2$) (see Supporting Information for details). Both the NMR and ESI-TOF MS data support the formation of the corresponding tetraimine−dianion supramolecular complexes, although with a slightly lower efficiency. The effect of the aldehyde geometry was also studied in a similar way, following the templated and nontemplated reactions between **1a** and **2b**. Although the supramolecular species was completely characterized also in this case (Figures S7−S9), its formation is slower and some other uncharacterized species remained detectable even after long reaction times. Finally, an example bearing a hydrogen-bonding side chain (**1g**) was also studied. Also in this case, the experimental data (Figures S10−S12) strongly support the formation of the intended supramolecular macrocycle−anion complex, despite the competing presence of H-bond donor groups in the side chain. However, NMR spectra showed broad signals implying a conformationally more flexible structure in solution (see Supporting Information). This fact would disfavor the templation effect, explaining the somehow lower final yield.

Anion Template Induced Preorganization: Circular Dichroism and Molecular Modeling Studies. The presence of the template must preorganize the system leading to the supramolecular tetraimino−dianion intermediate. Thus, the spatial disposition of aromatic bis(imine) chromophores must be well defined and highly determined by the template. This effect can be accurately measured by electronic circular dichroism (CD) spectroscopy.[45] Accordingly, CD spectra were acquired for the crude condensation reaction (40 mM in methanol, after 3 h at room temp) between **1a** and **2a** in the absence and in the presence of **3a**·2TBA. A more pronounced Cotton effect was found with the template (Figure 3), implying a more organized system due to the presence of the dicarboxylate. Besides, the observed negative sign of the Cotton effect clearly reflects the relative disposition of the chromophores in the computed geometry, as seen in Figure 1.

At that stage, we wondered if we could use this technique for the comparison of the differences observed with the side-chain nature or the aliphatic spacer. To do that, we selected some representative examples and performed the CD spectra of the crude of the condensation in the absence and in the

(44) The estimated loss of material due to chromatographic purification was around 5–10%. No important differences due to the structure of to the final compound were observed. The rest of the mass of the crude corresponded to a trace amount of open-chain oligomers (not fully characterized) and to the starting bis(amidoamine) **1a**−**k**. On the other hand, as the imine groups of the corresponding intermediates are electronically and sterically very similar, the observed differences in the yields are not expected to be due to the reduction step. Accordingly, there must be a direct correlation between the observed final yields and the formation and stability of the supramolecular tetraimino−dianion intermediate.

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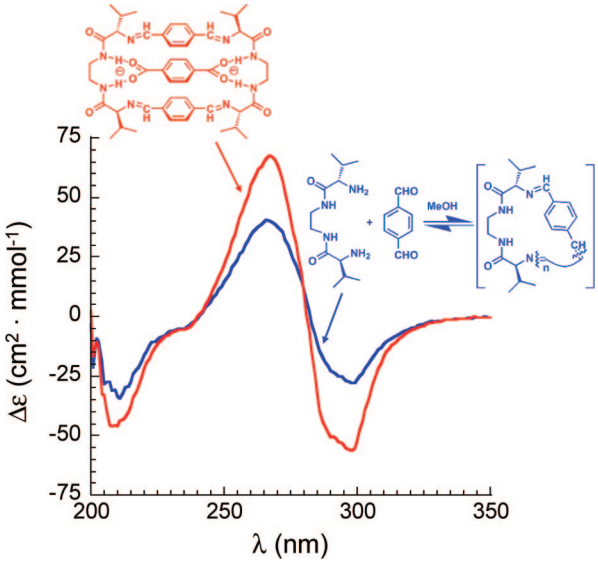

Figure 3. Normalized CD spectra (MeOH, 3 h of reaction at room temp) of a 1:1 mixture of **1a** and **2a** in the absence (blue trace) and in the presence (red trace) of 0.5 equiv of **3a**·2TBA.

presence of the template. To avoid problems comparing chromophores with different electronic transitions, we used the *p*-dialdehyde **2a** in all the cases. We also avoided interfering aromatic groups in the side chains. For the study of the effect of the aliphatic spacer (*n*), experiments with increasing lengths (**1a**, **1c**, **1e**) were carried out. To study the intriguing effect of the aliphatic side chain, the leucine derivative **1h** was also measured. For the right isolation of the effect of the template on the CD signal, we obtained the corresponding difference CD spectra (templated minus nontemplated) for every example. The results are shown in Figure 4A. Interestingly, the intensity of the template-induced Cotton effect increases in the order **1e** < **1c** < **1h** < **1a**, exactly with the same trend as for the isolated yields of the templated reaction. More remarkably, if we plot the intensities of the template-induced CD signal, either at the maximum or at the minimum wavelength, versus the isolated yield, we obtain a linear correlation with a similar slope (~0.6–0.7), obviously differing by the sign (Figure 4B). Our interpretation of these results is that the template effect causes a preorganization of the system, readily measurable by CD and proportional to the induced increase of the signal intensity. Accordingly, the larger is the induced preorganization (CD), the more efficient (higher yield) is the templated reaction.

We have also performed molecular modeling calculations to better understand the process, by studying the effect of the template in the hypothetical aminoaldehyde intermediates previous to the formation of the last C═N bond, which would complete the macrocyclization (Figure 5). At that point, the anion must induce a structural organization of the linear precursor to adapt it to the molecular shape and charge density of the template. Monte Carlo simulations of the corresponding open chain tris(imino)aminoaldehyde were carried out, in the absence (Figure 5A) and in the presence (Figure 5B) of the corresponding templates. The binding with the template dramatically increased the rigidity of the intermediate leading to a lower number of accessible local minima. In the absence of the template, the system behaved as a mixture of quite structurally different conformations, while the presence of the template clearly rigidified its conformational freedom.

A close inspection of the global minima of the open-chain intermediates gave additional clues about the templation process. The proposed stabilizing H-bonding interactions between the template and the macrocycle (Figure 1) are already present in the previous open-chain derivative (Figure 5B). Even more interestingly, the presence of the template approximates both ends of the linear molecule, with the correct geometry for the nucleophilic attack of the amine to the aldehyde carbonyl (see distances depicted in Figure 5). Moreover, the H-bonding pattern involving terephthalate also suggests that **3a** could act as a proton shuttle, explaining the observed acceleration of the templated cyclization process by general acid–base catalysis. Thus, an H-bond can be proposed between the nucleophilic amino NH and the COO of the template (1.71 Å). On the other hand, the aldehyde carbonyl is H-bonded to the amide NH (1.81 Å). This arrangement would facilitate the proton transfer from the amine NH to the aldehyde CO, through the participation of the carboxylate of the template (distance CHO···OOC = 3.28 Å). Therefore, the effect of the template could be double: thermodynamic and kinetic. On one hand, it favors the formation of the correct macrocycle by stabilizing its structure through noncovalent interactions. Additionally, it could accelerate the imine bond formation by acid–base catalysis and by setting the reacting groups at the correct geometry to undergo condensation. To break down thermodynamic and kinetic contributions seems

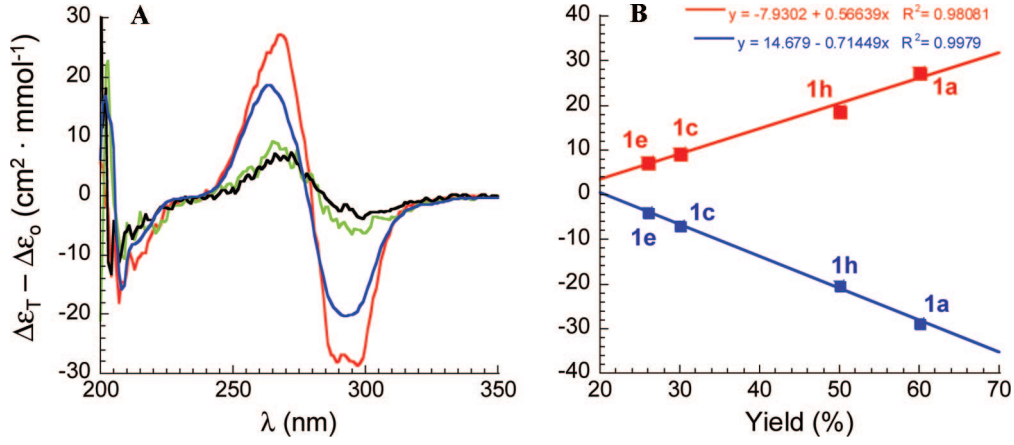

Figure 4. (A) CD difference spectra between the templated ($\Delta\varepsilon_T$) and nontemplated ($\Delta\varepsilon_o$) reaction of **2a** with **1a** (red), **1h** (blue), **1c** (green), and **1e** (black); (B) plot of the template-induced CD signal intensity ($\Delta\varepsilon_T - \Delta\varepsilon_o$) either at the maximum (red) or at the minimum (blue) wavelength versus the final yield of anion-templated reaction.

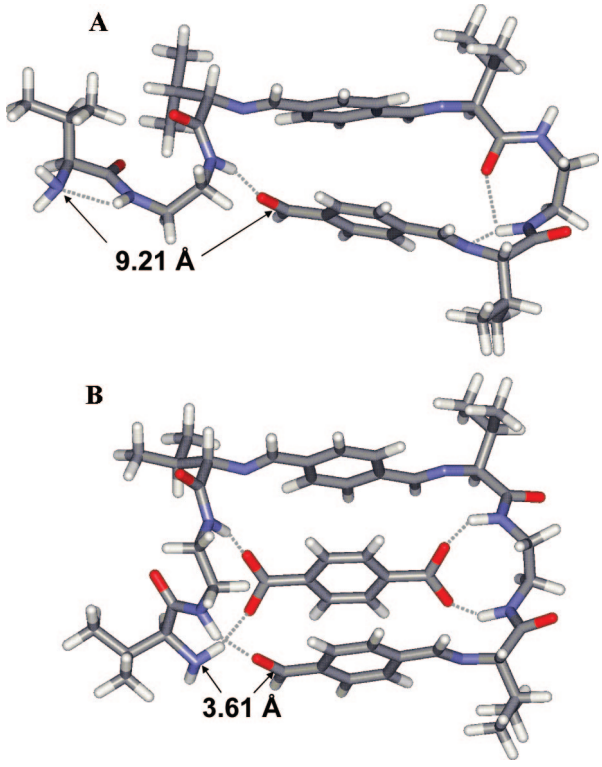

Figure 5. Global minima for the hypothetical aminoaldehyde intermediate of [**1a** + **2a**] (A) in the absence and (B) in the presence of the template **3a**. Hydrogen bonds are shown as gray dotted lines and computed distances between reacting aldehyde and amino groups are also displayed.

to be difficult in this case, as the macrocycle is formed at the expense of the template and both effects (thermodynamic and kinetic) would be acting at the same time.

Conclusions

In this paper, we have deeply studied the anion-templated synthesis of pseudopeptidic macrocycles, obtained upon multicomponent[46] reductive amination reaction between an open chain pseudopeptidic bis(amidoamine) and an aromatic dialdehyde in the presence of the corresponding aromatic dicarboxylate. Different structural variables on the macrocyclic framework have been mapped, such as the aliphatic spacer between amino acid moieties, geometry of the dialdehyde, or nature of the side chain. The effect of the dicarboxylate anion template has been clearly demonstrated by NMR (including intermolecular ROEs and self-diffusion rates) and ESI-TOF mass spectrometry.

The structural preorganization necessarily induced by the template has been studied by electronic CD spectroscopy. The presence of the template increased the negative Cotton effect, in agreement with the rearrangement of the aromatic bis(imine) chromophores in a more defined conformational disposition. Thus, we have used CD spectroscopy for comparing different derivatives. The anion-induced CD signal increase clearly correlates with the template effect and, ultimately, with the reaction yields. This trend was found for examples bearing different side chains and different aliphatic spacers. This anion-templated preorganization effect has been further supported by molecular modeling calculations.

In summary, a simple and highly efficient anion-templated synthesis of new pseudopeptidic macrocycles has been achieved. A wide structural diversity can be implemented in the reaction leading, in all the cases, to the desired compound. The differences observed in the isolated yields have been explained in terms of the flexibility and stability of the key supramolecular intermediate complexes. This new synthetic procedure demonstrates the success of applying concepts from the supramolecular chemistry field to face and solve synthetic challenges.

Experimental Details

General Procedure for the Anion-Templated Macrocyclization Reaction (Shown for 4a). Pseudopeptidic bis(amidoamine) **1a** (100 mg, 0.282 mmol) was dissolved in 2 mL of degassed CH_3OH, inside a flask under nitrogen. Terephthalate dianion **3a** (bis-TBA salt, 91.5 mg, 0.141 mmol) was dissolved in 1 mL of degassed CH_3OH and added over the solution of **1a**. Terephthaldehyde **2a** (37.8 mg, 0.282 mol) was dissolved in 1 mL of degassed CH_3OH, added over the solution mixture of **1a** + **3a**, and then 1.5 mL of CH_3OH was added until a final volume of 5.5 mL. The mixture was stirred overnight, then a large excess of $NaBH_4$ (87 mg, 2.257 mmol) was carefully added at 0 °C, and the mixture was allowed to react for 24 h before being hydrolyzed (conc. HCl, to acidity) and evaporated to dryness. The residue obtained was dissolved in water, basified with 1N NaOH, and extracted with $CHCl_3$. The combined organic layers were dried ($MgSO_4$) and the solvents were evaporated in vacuum. The product was purified by flash chromatography on silica gel using CH_2Cl_2 as eluent while slowly increasing the polarity with MeOH containing a few drops of aqueous ammonia.

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Supporting Information Available: Detailed experimental procedures, full spectroscopic data, selected 1D and 2D NMR spectra, copies of ^1H and ^{13}C NMR spectra of the final compounds and X-Ray crystallographic CIF file for **4a**·4HCl. This material is available free of charge via the Internet at http://pubs.acs.org.

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