

Efficient syntheses of new chiral peptidomimetic macrocycles through a configurationally driven preorganization

Miriam Bru, Ignacio Alfonso, M. Isabel Burguete and Santiago V. Luis*

Departamento de Química Inorgánica y Orgánica, UAMOA, Universidad Jaume I/CSIC, Campus del Riu Sec, Avenida Sos Bainat, s/n, E-12071 Castellón, Spain

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Abstract—A new family of 32-membered ring peptidomimetic macrocycles has been efficiently obtained in a simple one-pot two-step reductive amination reaction, from easily prepared precursors. The structural and stereochemical variables have been explored in order to rationalize the obtained selectivity. The formation of the [2A+2B] tetraimine intermediate has been explained in terms of a very favorable configurationally driven preorganization as detected by NMR, CD and molecular modeling.
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Macrocyclic peptidomimetics are a growing area of research due to their unique structural properties because of the combination of different functional groups in the cycle.¹ The diversity in functionalities of amino acid side chains (basic, acidic, polar, or nonpolar) and their availability from commercial sources make amino acid derivatives very versatile building blocks for the preparation of synthetic intermediates.² Moreover, amino acids are chiral entities, very suitable for the design of chiral selectors, ligands for asymmetric catalysis, molecular receptors or even chemosensors. Accordingly, these compounds are very attractive targets for supramolecular,³ medicinal,⁴ and bioorganic chemists.⁵ In the last few years, we have been interested in the syntheses of macrocyclic polyaza cyclophanes and the concomitant study of their properties for the molecular recognition of cationic and anionic species.⁶

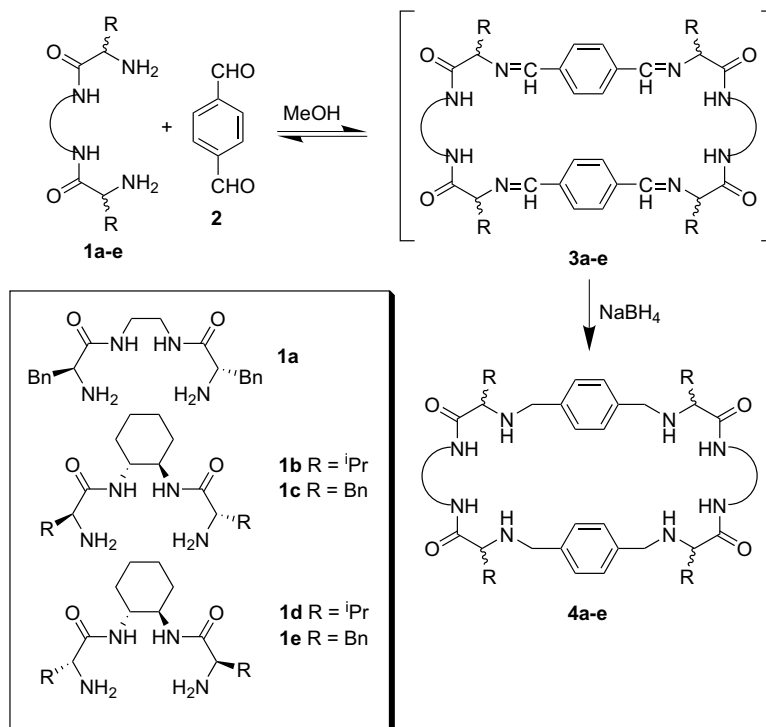
More recently, we have described a simple strategy for the synthesis of peptidomimetic macrocyclic cyclophanes. The key step is a macrocyclization process facilitated by a preorganization of the peptidomimetic moiety in a U-turn geometry. A deep structural study allowed us to find a combination of intramolecular H-bonding and solvophobic effects as the driving forces for this process.⁷ The compounds thus obtained have

been used in molecular recognition and sensing processes, as well as organogelators, with a very promising potential in supramolecular chemistry and materials science.⁸ Encouraged by these previous results, we envisioned to explore different synthetic approaches which would give us the tools for preparing similar and even more elaborated members of this family of synthetic receptors. In this regard, preliminary studies suggested the convenience of preparing larger cycles in order to increase the functionality of the host molecules for a molecular recognition event. Macrocyclization, especially for medium sized and large cyclic structures, is the key step for macrocycles syntheses, usually leading to low yields and requiring tedious purification steps.⁹ Here we report an easy one-pot two-step cyclization procedure, based on reductive amination reaction, to render 32-membered rings in good yields and from easily obtained synthons (Scheme 1). The reaction comprises the formation of four imino bonds with their subsequent reduction and it is strongly dependent on defined structural factors.

Initial experiments with ethylenebis(aminoamide) peptidomimetic **1a** and terephthaldehyde **2** (Scheme 1) were rather discouraging, leading to the formation of a mixture containing the corresponding [2+2] cycloadduct as a minor compound, accompanied by many non-identified peaks in the ESI-MS spectrum (entry 1 in Table 1). Nevertheless, the expected macrocyclic compounds **4b,c** were easily prepared from **1b,c** and **2** as preliminary modeling had suggested. The bis(aminoamide) compounds were prepared from activated amino acid esters

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*Corresponding author. Tel.: +34 964728239; fax: +34 964728214; e-mail: luis@qio.uji.es



Scheme 1.

Table 1.

Entry	Bis(aminoamide)	Dialdehyde	Yield ^a (%)
1	1a	2	— ^b
2	1b	2	67
3	1c	2	55
4	1b	Isophthalaldehyde	35
5	1d	2	— ^b
6	1e	2	— ^b

^a Isolated yields.^b Yield not determined because a complicated mixture of compounds were obtained by both ESI-MS and TLC.

and (*R,R*)-cyclohexane-1,2-diamine, following the previously described procedure for similar structures.⁷ The cyclohexane-1,2-moiety was selected in order to favor a rigid and well-defined spatial disposition of the bis(aminoamide) fragment. Aldehyde–amine condensation between **1b,c** and terephthalaldehyde **2** (MeOH, rt, 20 h) led to the macrocyclic tetraimine **3b,c**, which was in situ reduced with sodium borohydride to the corresponding macrocyclic tetraamine **4b,c** (Table 1, entries 2 and 3).¹⁰

Analysis of the mass spectrum of the crude product, after conventional work-up, revealed the presence of the [2+2] cyclic compound as the major product of the reaction. Simple silica gel purification procedure yielded the desired cyclic product with a 55–67% overall yield calculated from **1b,c**. The nature of the cyclic products have been unambiguously established by ESI-TOF mass spectrometry, showing a peak corresponding to the diprotonated [2+2] cyclic compounds (Fig. 1). Full isotopic pattern analysis was extremely useful for the clear

characterization of the obtained peaks. Chiral cyclohexane-1,2-diamine had been previously used for cyclization processes in a similar fashion leading to [3+3] or [2+2] cyclic products depending on the reaction conditions used.¹¹ However, the large differences observed for **1a** and **1b** are intriguing as much as **1a** is known to adopt a U-turn preorganization.⁷ Accordingly, we completed our study of the influence of other fragments of the cyclic structure by its change in a modular way. Some results are gathered in Table 1. As previously stated, the reaction can be performed either with aliphatic or aromatic side chains of the amino acid precursor, leading to similar final yields (Table 1, entries 2 and 3). The use of *meta* dialdehyde instead of the *para* derivative decreased the isolated yield, being the rest of the peptidomimetic recovered as the starting material or as open chain oligomers (entry 4). This result suggests that the geometrical disposition around the flat and rigid aromatic spacer is also important, most likely as a consequence of the higher symmetry of *para* compared to *meta* substitution of the aromatic dialdehyde.

The conformational restrictions provided by the cyclohexane-1,2-diamine moiety appear to be the most important factor. Strictly speaking, the appropriate preorganization seems to be regulated through a ‘match/mismatch’ of the configurations of the stereogenic centers of the diamine and the aminoacid subunits. Thus, compounds **1d,e** having (*R,R*) configuration in the diamine moiety but *D* configuration in the amino acid α carbon led, once again, to a mixture of compounds detected by ESI-MS, where the major ones corresponded to the starting material **1d,e**. This stereochemical mismatch effect is a very solid proof for the conformational and geometrical selectivity displayed in this process.¹²

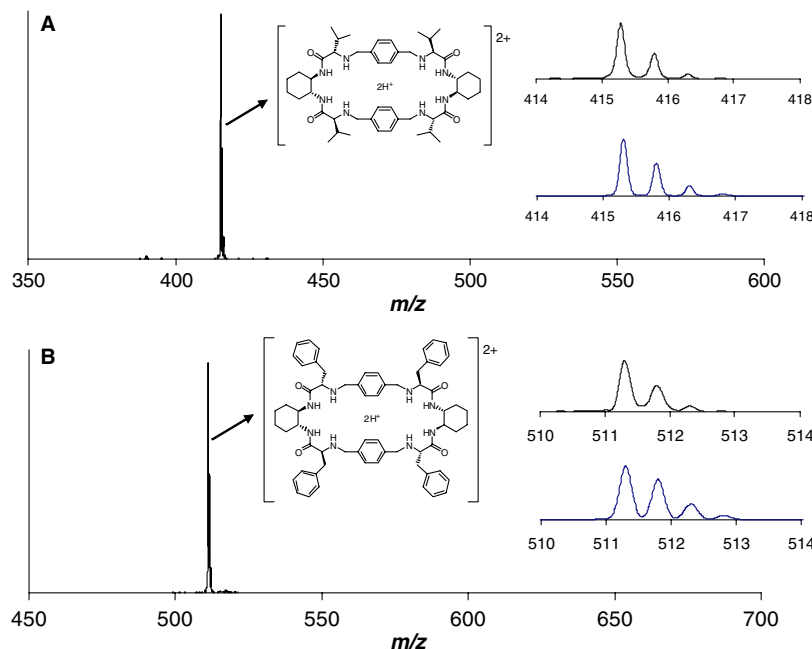


Figure 1. ESI-TOF mass spectra of (A) **4b** and (B) **4c** with experimental (black) and simulated (blue) isotopic pattern.

With the aim of getting more precise information about the reaction course, we followed the process for the formation of **3b** by ^1H NMR spectroscopy. Just a few minutes after mixing **1b** and **2**, the reaction started as observed by the gradual disappearance of aldehyde *CHO* signals (δ 9.99–10.11 ppm) and the growing of imino methyne signals (δ 8.07–8.34 ppm). In the first stage of the reaction, a complicated group of signals was formed, which simplified after 24 h. At that point, a major compound (ca. 70% from integration of the signals) was obtained with a highly symmetrical geometry, as shown by both ^1H and ^{13}C NMR signals.¹³ This major imine compound showed one singlet for the aromatic protons, which can be only explained by a fast rotation of the aromatic ring with respect to the macrocyclic main plane. Regarding the relative disposition between imine bonds, they must be all in the same *S-trans* configuration or again in a fast equilibrium between *S-cis* and *S-trans* to render an effective D_2 -symmetry in the NMR timescale. The presence of other minor imino signals and the fact that no other cyclic compounds were isolated after reduction suggest that this minor non-symmetrical imino groups came from the presence of different relative dispositions between $\text{C}=\text{N}$ double bonds and supports the assumption that the major compound is an all-*S-trans* isomer. All these imino signals also showed strong NOE effects with the C^αH protons of the peptidomimetic moiety, supporting the connectivity between both substructures, and a *syn* disposition between these protons in the major species, as depicted in Figure 2.

It must be pointed out that the presence of different isomers in the $\text{C}=\text{N}$ double bond is eliminated after reduction with sodium borohydride. Despite that, the high geometrical preference for the system to form the D_2 -symmetrical cyclic structure is to be noted. The compo-

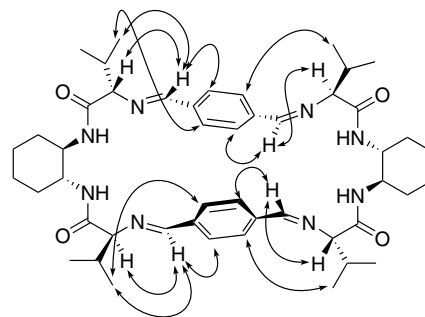


Figure 2. Selected NOE contacts in NOESY experiments on **3b**.

sition of this mixture does not change over a long period of time (>8 weeks) or by heating the sample up to 60 °C, supporting that it is the equilibrium mixture and the reaction occurs under thermodynamic control. It is also noteworthy that performing the same experiment with **1d** instead of **1b** led to a very complicated group of signals in the ^1H NMR and to the incomplete consumption of dialdehyde **2** even at very long reaction times (>3 days).

The formation of the tetraimine intermediate **3b** has been also ascertained by circular dichroism (CD). The CD of a mixture of **1b** and **2**, after 24 h of reaction time, clearly showed a bisigned curve [Fig. 3, UV: $\lambda_{\text{max}} = 279$ nm (59,600); CD: 296 nm (−3721)/267 nm (4467)]. The sign of the exciton coupling suggests that the chirality of the (*R,R*)-cyclohexane-1,2-diamine is transferred throughout the whole system, and the magnitude of the amplitude is in agreement with a highly chiral and ordered structure setting the corresponding chromophores, namely the aromatic diimines, in a close proximity one to each other.¹⁴ Accordingly, the corresponding experiment with the mismatch combination

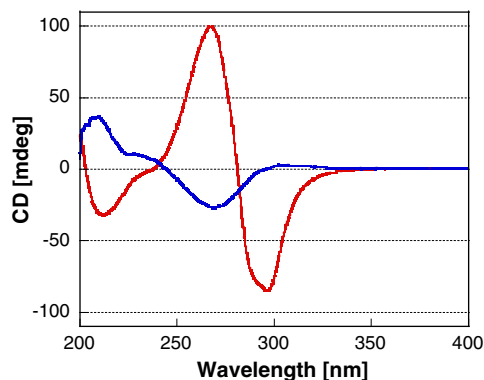


Figure 3. CD spectra of **3b** (red) and a mixture of **1d** and **2** (blue) in MeOH (conc. 23 μ M).

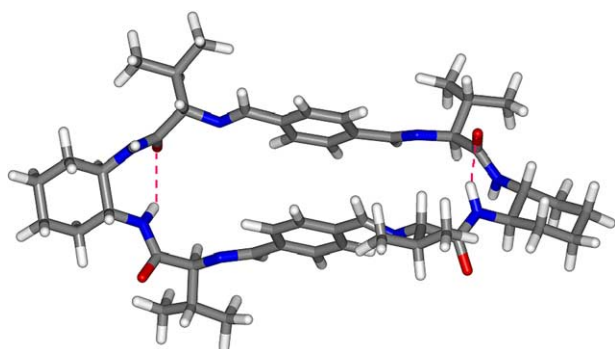


Figure 4. AM1 optimized structure of tetraimine intermediate **3b**. Hydrogen bonds are highlighted in red dashed lines.

of stereocenters yielded a less intense CD spectrum with no signs of exciton-split curves.

In order to illustrate the three-dimensional structure of the tetraimine intermediate **3b**, some molecular modeling has been also undertaken.¹⁵ The obtained minimum of energy is shown in **Figure 4**, presenting a pseudo- D_2 -symmetry and with interatomic distances, which nicely fit the experimentally observed NOE contacts. The smooth distortion from the D_2 -symmetry is due to the intramolecular averaged in solution and leading to the symmetry observed H-bonding between consecutive amide groups. The structure presents all *S-trans* relative disposition of imine bonds and an almost flat conformation for the aromatic diimine groups, maximizing the conjugation of the system.¹⁶ The isopropyl side chains set on equatorial position, pointing out of the macrocyclic structure. Thus, this conformation also gives us a clue for explaining the mismatch effect with the diastereomeric counterpart **1d**. Inversion of C^α configuration would set the side chain on axial disposition, increasing the bulkiness of the corresponding macrocyclic tetraimine and explaining the less favorable formation of the 32-membered ring cyclic compound. Actually, molecular modeling suggests that the steric repulsion in the hypothetical diastereomeric tetraimine **3d** would break both the aromatic imine conjugation and the intramolecular hydrogen bonds observed for **3b**, leading to a much less stable minimum of energy.¹⁵

In summary, here we report on a very efficient one-pot two-step procedure to prepare 32-membered ring peptidomimetic macrocycles in high yields and selectivity. This selectivity is the result of a conformational preorganization of the precursors and the formation of the most stable cyclic structure, allowing intramolecular H-bonding and imine conjugation in the intermediate. The final cyclic compounds have different functionalities (amine, amide, and aromatic rings) and eight chiral centers arranged in a highly symmetrical (D_2) structure. These characteristics make them very promising candidates for molecular recognition, catalysis and sensing purposes. Studies in that direction are underway in our laboratory.

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