CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201104045

Efficient Synthesis of Pseudopeptidic Molecular Cages

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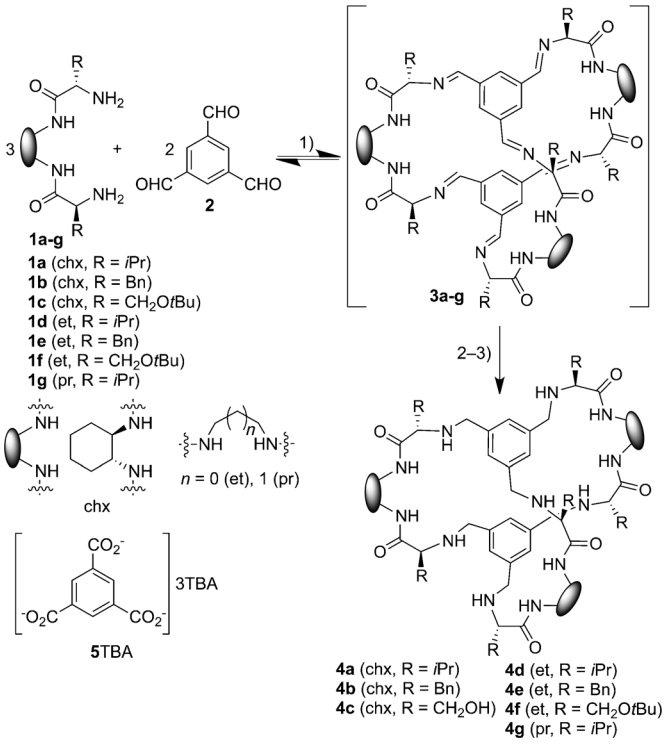
The construction of new molecular structures through the programmed assembly of building blocks in a predictable and selective way is a major challenge in modern chemistry.[1] To this aim, the understanding of the structural rules governing the assembly allows the suitable design of increasingly complicated scaffolds. Among the de novo designed chemical entities recently prepared, molecular cages[2] are fascinating architectures with important applications in molecular recognition,[3] catalysis,[4] and biomimetic chemistry.[5] Their three dimensional hollow structures, leaving a well-defined inner space, make them promising candidates for the inclusion of interesting guests,[6] even for elusive[7] or unstable[8] species. In connection with the biochemical world, they can mimic the solvent-excluded binding sites of natural receptors.[9] Moreover, they have been described as nanoreactors, because the molecular confinement of the reactants inside the macrobicyclic cavity can largely enhance kinetics or dramatically change the final reaction outcome.[10] Inspired by the seminal works in macrobicyclic peptides,[11] we reasoned that the introduction of amino acid derived chemical moieties (peptide-like or pseudopeptides) would increment the functional variability and would be beneficial for future biological applications. However, one of the main drawbacks for the practical use of molecular cages is the possibility of preparing them in an easy and modular way, in reasonable yields and with enough structural diversity.[12] Besides, the presence of different competing pathways in the cyclization process and the use of multistep syntheses, often lead to complex final mixtures, requiring to be separated, which also limits the application of those procedures.[13] Recently, we have shown that an efficient synthesis of pseudopeptidic macrocycles can be carried out taking advantage of a designed preorganization and a dynamic covalent procedure,[14,15] which is able to self-select the favored structures by chemical exchange.[16] To this aim, we used two approaches for inducing the needed preorganization: a configurationally driven conformational bias[14] or an anion templation procedure.[15] In this regard, although anion templation is a well-known phenomenon,[17] most of the examples found in the literature are based on inorganic anions,[17b–g] while the use of more elaborated organic anionic templates is scarce.[15,17a] These two methods (preorganization and anion templation) allowed us to prepare a diverse family of pseudopeptidic macrocycles in enough quantity for further supramolecular chemistry studies.[18] Considering the success of these methods in the macrocyclic field, we envisioned to apply them to develop a versatile synthetic protocol for pseudopeptidic molecular cages. The retrosynthetic analysis considered a [3+2] reductive amination reaction between three molecules of a C_2 symmetrical pseudopeptidic bis(amidoamine) (**1a–g**) and two molecules of a flat and simple trialdehyde (**2**) as depicted in Scheme 1. These [3+2] imine



Scheme 1. Synthesis of pseudopeptidic cages: 1) equilibration at RT either in the absence or in the presence of **5**TBA. 2) BH_3·py. 3) HCl.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201104045.

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condensations are highly challenging, since usually lead to larger oligomers,[19] interlocked structures,[20] polymeric materials,[21] or dynamic mixtures.[22] Besides, in our case, the overall process comprises the formation of six covalent bonds in two steps each, which should be equivalent to carry out twelve reactions in one pot. Accordingly, in order to obtain a good selectivity towards the intended D_3 symmetric cage, the starting material must be appropriately preorganized.

The key step for the success of the reaction is the formation of the hexaimine intermediate (**3**), through a dynamic covalent process that is able to self-correct the wrong species in the dynamic equilibrium. Initially, we used the bis(amidoamine) derived from the (*R*,*R*)-1,2-diaminocyclohexane (chx) spacer and L-Valine (R = *i*Pr) amino acid (**1a**). Based on previous studies, this compound is preorganized in a U-shaped conformation when the right combination of chiral centers ((*R*,*R*)-diamine and (*S*)-amino acid) is implemented in the molecule.[14] Thus, we monitored the reaction between **1a** and **2** by ^{1}H NMR (500 MHz, RT, 10 mM of **1a** in CD_3OD).[23] We observed the decrease of the aldehyde methyne signals (at 10.0–10.2 ppm) and the raise of the imine-type protons (at ca. 8.3 ppm), until reaching an almost complete conversion to a D_3 symmetric imine compound. The ^{1}H and ^{13}C NMR signals of this species were consistent with the proposed hexaimine cage (**3a**), and also in full agreement with the model structure (Figure 1 A).[23] For instance, the NOESY spectrum showed a cross peak between the imine methyne and both the aromatic CH and the Cα–H of the pseudopeptide moiety (see double-headed arrows in Figure 1 A). These data imply the connectivity between the fragments with an *S-trans* arrangement of the conjugated imines, and a *syn* disposition between the imine C–H and the Cα–H, as obtained by molecular modeling. Other additional nOes were consistent with a diequatorial chair conformation of the cyclohexane moiety (Figure 1 A).[23] To our delight, the in situ reduction of this intermediate led to the pseudopeptidic hexamine cage **4a** in very good overall isolated yield from **1a** (47 %) considering the number of bonds formed in a one-pot two-steps process, the necessary acidic hydrolysis, the work-up and a reverse-phase chromatographic purification to obtain an analytically pure material.[24] Remarkably, no other cyclic oligomers were isolated, supporting the excellent selectivity of the reaction. Further studies showed that the reaction is also efficient with aromatic (**4b**, R = Bn, 30 % isolated yield) and polar (**4c**, R = CH_2OH, 59 % isolated yield) side chains on the pseudopeptidic moiety.[23,24] The yield obtained with the Ser cage (**4c**) is highly remarkable, especially considering that it includes the step for the deprotection of the O–*t*Bu groups, performed on the crude reaction before the final chromatographic purification.

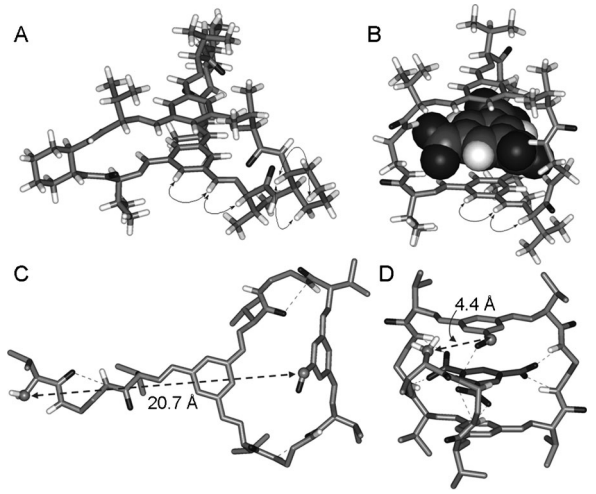

Figure 1. Optimized geometries for: A) the hexaimine cage **3a**, B) the supramolecular complex formed by **3d** and **5** (in CPK representation). Observed nOes are shown in curved double-headed arrows. C,D) Hypothetical amino aldehyde intermediate previous to the macrobicycle formation (for **3d**) in the absence C) and in the presence D) of the template. For simplicity, in C and D, nonpolar hydrogen atoms have been omitted.

With the aim of generalizing our synthetic procedure, the less rigid derivative with an ethylene (et) spacer and L-Val (R = *i*Pr) as the starting amino acid (**1d**) was also studied. Despite the flexibility of **1d**, the use of the suitable anion template during the imine formation had largely improved the process in the case of macrocycles.[15] Accordingly, we also aimed to study the anion template effect in the synthesis of the pseudopeptidic cages. Molecular modeling studies showed that benzene-1,3,5-tricarboxylate (**5**) should be a suitable template for the formation of the hexaimine cage **3d**, perfectly filling the macrobicyclic cavity and forming up to six hydrogen bonds between the carboxylate anions and the amide groups of the pseudopeptidic moieties (Figure 1 B). Taking into account these results, we monitored the condensation between **1d** and **2** by ^{1}H NMR (500 MHz, RT, 10 mM of **1d** in $CDCl_3/CD_3OH = 9:1$) in the absence and in the presence of the trianion **5** as its tris(tetrabuthylammonium) salt (**5**TBA). The evolution of the corresponding spectra showed marked differences due to the presence of the template (Figure 2 A).[23]

Strikingly, in the presence of **5**TBA, the system rapidly evolved towards the formation (>80 % as observed by ^{1}H NMR)[23] of a highly symmetric imine compound in only 3 h of reaction. The chemical shifts and nOes (Figure 1 B.) are consistent with the presence of the D_3 symmetric hexaimine cage **3d**.[23] Moreover, DOSY NMR spectra (Figure 2 B) showed the same self-diffusion rate ($D = 6.49 \times 10^{-6}$ cm^2 s^{-1}) for the signals corresponding to the pseudopeptidic cage and those assigned to the template (both the aromatic tricarboxylate and the TBA cation) suggesting that they are forming part of the same non-covalent species. Estimation of the molecular volume of this supramolecular species by DOSY[23] rendered a value of 2210 Å^3, in reasonably good agreement with the one obtained for [**3d**+**5**+3TBA] by modeling (2183 Å^3). A definitive proof for the formation of this supramolecular complex was obtained by ESI-TOF mass spectrometry (Figure 2 C).[23] The mass spectrum of the reaction mixture in the anion detection mode showed the

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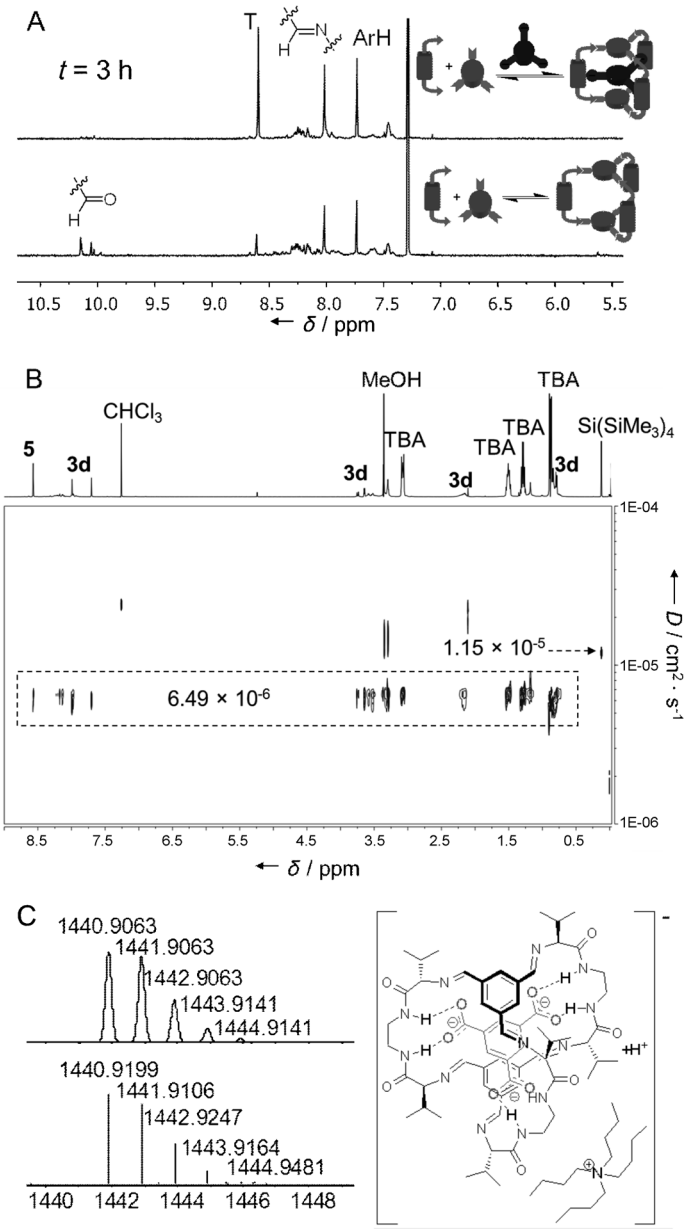

Figure 2. A) Partial ^{1}H NMR spectra of the crude reaction mixture of **1d** and **2** (500 MHz, RT, 10 mM of **1d** in $CDCl_3/CD_3OH = 9:1$ after 3 h of reaction) in the absence (lower trace) and in the presence (upper trace) of **5**TBA. B) DOSY NMR spectrum of the templated reaction (500 MHz, 298 K, in $CDCl_3/CD_3OD = 9:1$) using $Si(SiMe_3)_4$ as an internal standard for the diffusion scale. C) Selected signals (calculated and experimental) for the high resolution ESI-TOF mass spectrum of the $[\mathbf{3d}+\mathbf{5}+TBA+H]^-$ complex (see also the Supporting Information).[23]

peaks for the corresponding supramolecular species: $[\mathbf{3d}+\mathbf{5}+H]^{2-}$ ($m/z = 599.3$, doubly charged), $[\mathbf{3d}+\mathbf{5}+2H]^-$ ($m/z = 1199.6$, monoanionic) and $[\mathbf{3d}+\mathbf{5}+TBA+H]^-$ ($m/z = 1440.9$, singly charged). On the other hand, the reaction performed in the absence of the template required up to 27 h to reach the imine conversion observed for the templated reaction in 3 h. This difference suggested a remarkable acceleration of the formation of the cage by the anion template.[25] To visualize the source of this kinetic effect, molecular modeling studies were performed with the hypothetical amino aldehyde previous to the formation of the last imine bond leading to the cage, in the absence (Figure 1C) and in the presence (Figure 1D) of the template. The results clearly showed the preorganization effect induced by the template, which is able to fold the intermediate into the suitable conformation (with the pseudopeptide wrapping the template) and with the right geometry for the reaction to take place (compare the distances between the amino nitrogen and the aldehyde carbon in Figure 1C and D). Besides, the anionic template could act as a proton shuttle accelerating the reaction by acid–base catalysis.

For the experimental support of this anion-induced preorganization, circular dichroism (CD) has proved to be a very valuable technique, since the CD signal reflects the spatial organization of the UV chromophores in chiral molecules.[26] Thus, we monitored the reaction between **1d** and **2**, with and without template, by CD (Figure 3). The imine cage formation was accompanied by the growth of an intense negative split Cotton effect in the CD spectrum, characterized by a negative minimum at 278 nm and a positive maximum at 255 nm, in agreement with both the proposed model structure and our previous studies in macrocyclic related systems.[15] The formation of the cage is strongly favored by the presence of the template as observed by the comparison of the corresponding CD spectra at 4 h of reaction (Figure 3) or by the plots of the time evolution of the CD signal at 255 nm (Figure 3, inset). The results suggested that the reaction is approximately 4-fold faster in the presence of **5**, implying a remarkable kinetic template effect of the anion.

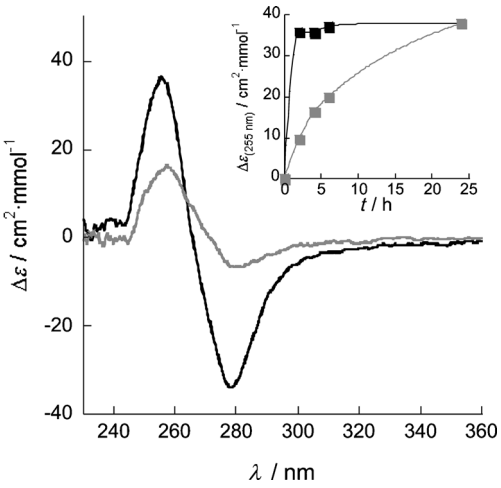

Figure 3. CD spectra for the mixture of **1d** and **2** in the absence (gray) and in the presence (black) of template (**5**TBA) after 4 h of reaction. Inset: time evolution of the CD signal at 255 nm with (black) or without (gray) template.

The in situ reduction of each reaction after 24 h of equilibration showed important differences, despite both of them initially contained **3d** as the main compound. The analytical HPLC analysis of the crude of the templated reaction

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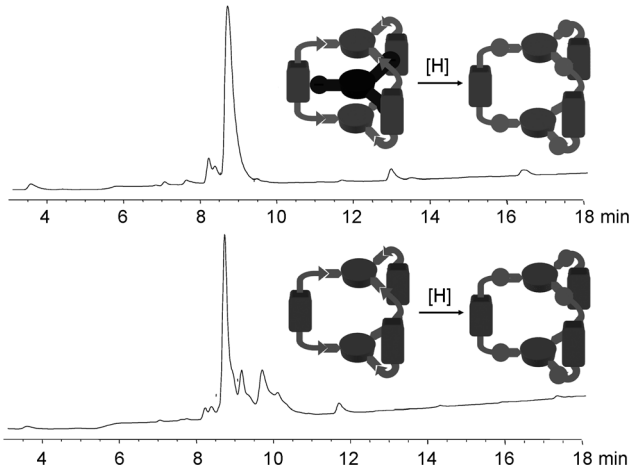

Figure 4. Analytical reverse phase HPLC traces of the crude reactions (24 h of equilibration and subsequent reduction with BH_3·py) between **1d** and **2** in the absence (lower trace) and in the presence (upper trace) of **5**TBA.

showed the presence of **4d** practically as a single product, while in the absence of the anion other peaks were readily observed (Figure 4). This selectivity was also expressed in a higher isolated yield of **4d** from the templated reaction (24% versus 15%).[23,24]

These results suggest that the tricarboxylate anion also stabilizes the cage structure during the reduction process, acting as a thermodynamic template. Therefore, the anion templated process is more efficient in terms of the reaction time, the selectivity and the yield. Besides, this anion templation method allows the synthesis of other pseudopeptidic cages bearing different side chains (R = Bn, CH_2OtBu[27] **4e**–**f**, respectively) or a longer aliphatic spacer like propylene (pr, $n=1$, R = *i*Pr, **4g**).[23]

In summary, we have demonstrated that modular pseudopeptidic molecular cages can be easily prepared in a selective and efficient process, thanks to a delicate molecular/supramolecular design and the self-correction capability of a dynamic covalent system. The key feature for the success of the reaction is the correct preorganization of the pseudopeptidic precursors, which can be accomplished by a conformational bias or by anion templation. Our results represent a definitive generalization of the use of organic anion templates for the preparation of pseudopeptidic molecules with different topologies. Thus, we have demonstrated that the molecular rules operating in the macrocyclic field can be applied in more complicated and structurally demanding systems. The modularity of our approach allows us to envision the preparation of highly diverse pseudopeptidic cages displaying different polarity, flexibility, molecular sizes, and functions. The extensive generalization of our synthetic method to a larger variety of cages, and their applications in molecular recognition and catalysis are underway.

Acknowledgements

Financial support from the Spanish MICINN (CTQ2009-14366-C02 project) is gratefully acknowledged. A. M. and I. A. also thank Prof. Angel Messeguer for continuous support.

Keywords: anion templates · cage compounds · preorganization · pseudopeptides · supramolecular chemistry

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[23] See the Electronic Supporting Information for Details.

[24] For a fair evaluation of the yields obtained in these processes, we must bear in mind that six covalent bonds are formed in two steps each (12 steps in one-pot). Accordingly, the average yield for each step can be estimated as the *n*-th root of the overall yield, being *n* the number of steps. Thus, a 47% isolated yield would correspond to an average 97% yield per step.

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[27] The problems encountered during the purification of this serine derivative prompted us to isolate it as the *O*-protected form (**4f**, R = CH_2O*t*Bu). Besides, during the chromatographic purification of **4f**, some undesired partial *O*-deprotection was detected that lowered the final (non-optimized) yield.

Received: December 24, 2011
Revised: February 24, 2012
Published online: March 29, 2012

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