Tetrahedron Letters 51 (2010) 6521–6525

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis and characterization of hexasubstituted azacryptands

Nicolas De Rycke, Jérôme Marrot, François Couty, Olivier R. P. David *

UniverSud Paris, Institut Lavoisier, Université de Versailles St. Quentin-en-Yvelines, UMR 8180, 45 Avenue des Etats-Unis, 78035 Versailles, France

ARTICLE INFO

Article history:
Received 23 August 2010
Revised 28 September 2010
Accepted 4 October 2010
Available online 14 October 2010

Keywords:
Azacryptand
Nitrogen basicity
Imine condensation
Macrocyclic chemistry
Nitrogen ligand

ABSTRACT

Using an imine condensation strategy, hexaazacryptands were prepared from an aromatic triamine and various dialdehydes. The global shape of these cages can be modified by simple alkylation of the six nitrogen atoms. The cavity is thus elongated and rendered hydrophobic.

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Macrobicyclic azacryptands are long standing and well studied synthetic receptors.[1] In either their basic or protonated forms they display a very wide ability to host various species within the cavity formed by their three arms. Among the plethora of structures prepared, azabicyclic cyclophanes have demonstrated efficient and selective affinities for complex substrates, such as mono- or disaccharides.[2]

In addition to these impressive complexing properties, azacyclophanes **1** or **2** have the advantage of an extremely facile and scalable synthesis, which is crucial for further applications.[3]

Recently, Roelens,[3b] Ghosh,[3c] and Delgado[3d,e] reported the preparation of these sandwich-like cyclophanes which are prepared through reversible and thermodynamically driven imine condensation, allowing near quantitative formation of the receptor after a reduction step (see Fig. 1). Azacyclophane **1** was reported to be able to recognize β-glucopyranosides with exceptional selectivities,[3b] while **2** is able to encapsulate acetone in its neutral form or an iodide anion when fully protonated.[3c] The latter also showed good binding abilities toward phosphate[3e] and other tetrahedral anions.[3d]

Modulation of the cavity size and shape of this class of cryptands would offer some very interesting opportunities for tuning host–guest properties. Such modifications can be done in two different ways: an obvious one is to change the dialdehyde spacer while the other is to substitute the nitrogen atoms with the hope of influencing the global conformation of the azacyclophane. This approach would also allow functionalization of the azacyclophane and anchoring to a solid support or introduction of fluorogenic moieties. With this goal in mind, we first tested different dialdehydes of various lengths and angles between the two aldehydic moieties in the condensation with triamine **3**. As can be seen in Table 1, among the three isomers of diformylbenzene only the *meta*-substituted leads cleanly to cage compounds as previously reported. Next, we examined the reactivity of larger dialdehydes **6**[4] and **10**,[5] with geometrical characteristics close to those of m-**4**, (nearly parallel carbonyl groups). Surprisingly, intractable mixtures of incomplete condensation products were observed by TLC, evolving to polymeric material after 18 h, under various conditions. We were quite surprised by the outcome of diformylnaphthalene **6** condensation, since despite a longer distance between the two aldehydes, all geometrical parameters are identical to those of m-**4**. Only the decreased solubility of the condensation intermediates impairing the equilibration completion could account for this result. Finally, pyridine derivative **7** which rather closely overlaps the geometrical features of m-**4** reacted smoothly to give the corresponding cage **11** (entry 5). For future studies, we

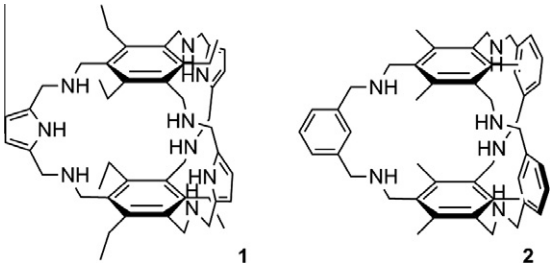

Figure 1. Structures of azacryptands **1** and **2**.

* Corresponding author.
E-mail address: odavid@chimie.uvsq.fr (O.R.P. David).

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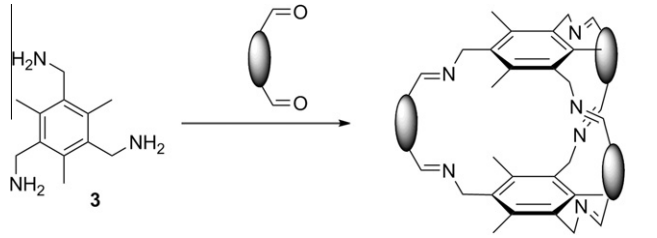
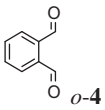
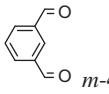
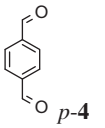
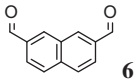
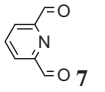
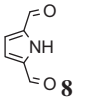
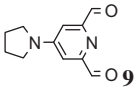
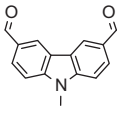
doi:10.1016/j.tetlet.2010.10.019

Table 1
Cage formation trials with various dialdehydes



Entry	Aldehyde	Yield of imine Cage
1	 *o*-**4**	Complex precipitate
2	 *m*-**4**	**5**, 99% (Refs. 3b,3c)
3	 *p*-**4**	Complex precipitate
4	 **6**	Complex precipitate
5	 **7**	**11**, 99%
6	 **8**	**12**, 99% (Ref. 3a)
7	 **9**	**13**, 95%
8	 **10**	Complex precipitate

also engaged DMAP derivative **9**[6] in the condensation, which gave cage **13** without complication.

Thus it appears that the formation of imine azacryptands like **5** can only be achieved when the reaction partners adhere to very strict geometrical parameters. We did not attempt to vary the nature of the tris-amine partner since Roelens[3b] had shown that hexasubstituted-triamino benzenes were mandatory to observe the cage formation, the alkyl substituents insuring the correct orientation of the aminomethyl branches.

It is noteworthy that all successful cage formations in this study were performed in solution. Roelens[3b] and recently Delgado[3e] synthesized cages by precipitation, respectively, from methanol and acetonitrile. In the latter case, the authors commented on the fact that such solubility issues could explain the rather low yields observed. The literature emphasizes the thermodynamic stability of such assemblies but in precipitation processes, one might consider the reaction to be kinetically controlled. In the case of Roelens, the cage precursor of **1** is formed in a quantitative yield. However, in the recent experiment of Delgado[3e] it appears that some 'polymer' is formed and precipitates, which thus cannot reverse back, in order to convert into the expected cage, thus leading to a 60% yield.

We then turned our attention toward the second option for tuning host affinities by inducing a global change through local modification. We thus tested the feasibility of hexafold reactions with the NH groups of azacryptand **2**. In the work of Roelens[3b] and of Ghosh,[3c] the donor H-bonding properties of the secondary amines were crucial to encapsulate different guests. We wanted to prepare modified azacryptands that would exhibit novel complexing properties due to the presence of tertiary amines. Concurrently, alkylation of the NH moieties would allow the introduction of functionalized side chains.

First, cage **2** was permethylated using standard Eschweiler-Clarke conditions.[7] In contrast to **2**, the hexamethylazacryptand **15** could be purified easily by flash chromatography, thus allowing its isolation in 79% yield, see Figure 2.

Next was attempted hexafold Michael additions with acrylates: without difficulty, cryptand **16** bearing six methyl esters was isolated after chromatography in 70% yield. Interestingly, the congener possessing *tert*-butyl esters could not be obtained, since the reaction stopped before completion and mass-spectrometry analysis showed the products to be three and fourfold Michael adducts, see Figure 3.

This can be rationalized by the fact that an incoming acrylate reactant has to enter the cavity in order to reach the nitrogen atom: the free space being reduced after each addition, hindered substrates are no longer able to make their way toward the remaining NH after four reactions.

Peracetylation was then tested, but even under forcing conditions (neat Ac_2O, AcCl under THF reflux, reaction time extended up to one month, all under basic conditions) full transformation could not be achieved.

Tosylation was more successful, since with an excess of tosyl chloride under basic conditions persulfonylation was reached after two days. Thus, cages **2** and **14** were converted into cryptands **17** and **18** in respective 38% and 26% yields after recrystallisation. See Figure 4.

All four substituted cryptands **15**–**18** are white, infusible, compounds, stable at room temperature, even if **16** shows slow degradation via retro-Michael reactions. The presence of the six substituents is supported by HRMS data.

Proton NMR data for cages **15**–**18** show in all cases broad signals due to the slow inversion of the nitrogen atoms, located in a very hindered and geometrically constricted environment. Recording proton NMR spectra at variable temperature allowed better resolution and full assignment. This led us to conclude that drastic

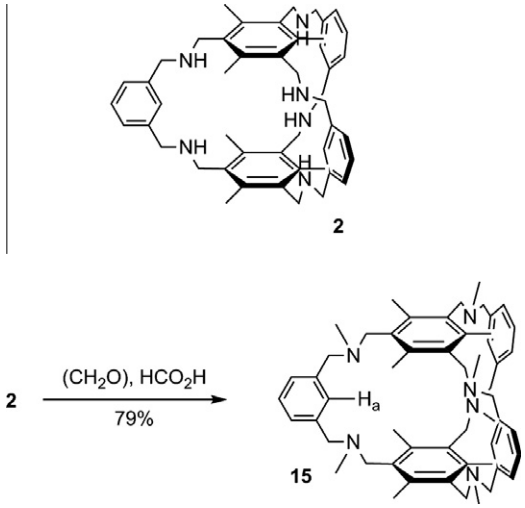


Figure 2. Permethylation of cage **2**.

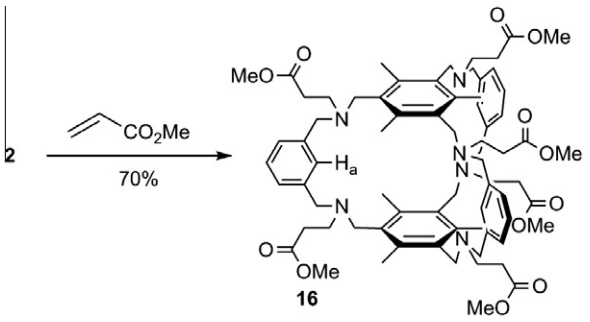


Figure 3. Hexafold Michael addition.

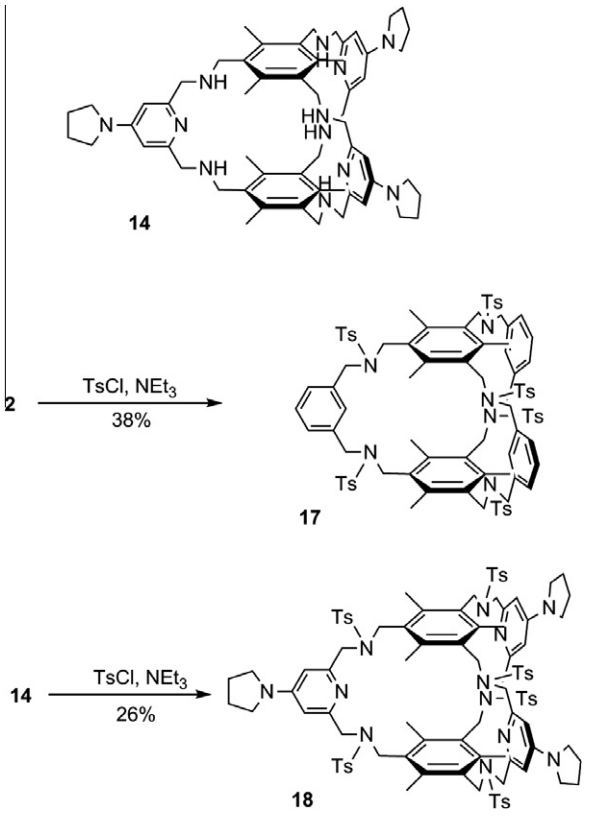


Figure 4. Tosylation of cages **2** and **14**.

conformational modifications took place upon N-substitution: the first clue was an important change in the chemical shift of the aromatic 'singlet' hydrogen, noted Ha in Figure 2. The chemical shift for this proton is recorded at 7.08 ppm in the hexaimine cage **5** and is shifted downfield to 7.46 ppm for the reduced cage **2**. In the alkylated and sulfonylated cages **15**-**17** the chemical shifts are, respectively, 6.67, 5.89, and 6.35 ppm, and these large upfield shifts suggest that the electronic environments are greatly modified in comparison with **2**. This could arise from a closer proximity of these protons to the π-orbitals of the adjacent aromatics. Additionally, proton NMR experiments performed at variable temperatures (from 213 to 343 K) showed significant modifications in the spectra of cages **15** and **16**. In particular, complication of the set of signals suggests the presence of several conformeric forms at low temperature. This indicates a relative flexibility of these azacrytpands.

These four compounds tend to crystallize as long, ultrathin needles in apolar solvents, but larger crystals could be obtained for **15** and **16** using mixtures of chlorinated solvents with acetone or acetonitrile. Unfortunately, we are as yet unable to grow suitable crystals of **17** for X-ray diffraction analysis. However, crystals of cage **18** obtained by tosylation of cage **14**, itself prepared by borohydride reduction of cage **13**, could nicely be crystallized and gave satisfactory diffraction results.

From X-ray data we could confirm the profound impact of nitrogen substitution on the overall conformation of the cryptand. As foreseen, cages **15** and **16** exhibit very distorted solid-state arrangements (Fig. 5). The three linking aromatics are strongly tilted, forming the faces of a regular prism. With this conformation, the central proton points toward the π-orbitals of the proximate aromatic ring. Interestingly, such a prismatic arrangement of aromatic moieties within a macrobicyclic structure can be found in a recently prepared octaprotonated azacryptand[8] bearing three thiophene rings. In compounds **15** and **16**, the two apical aromatics are taken away from each other, as compared to **2**, the distance increasing from 7.584 Å for **2** to 10.206 and 10.093 Å for **15** and **16**, respectively. Such an elongation along the C3 symmetry axis was also observed by Ghosh upon full protonation of **2**[3b] (with a distance of 9.357 Å).

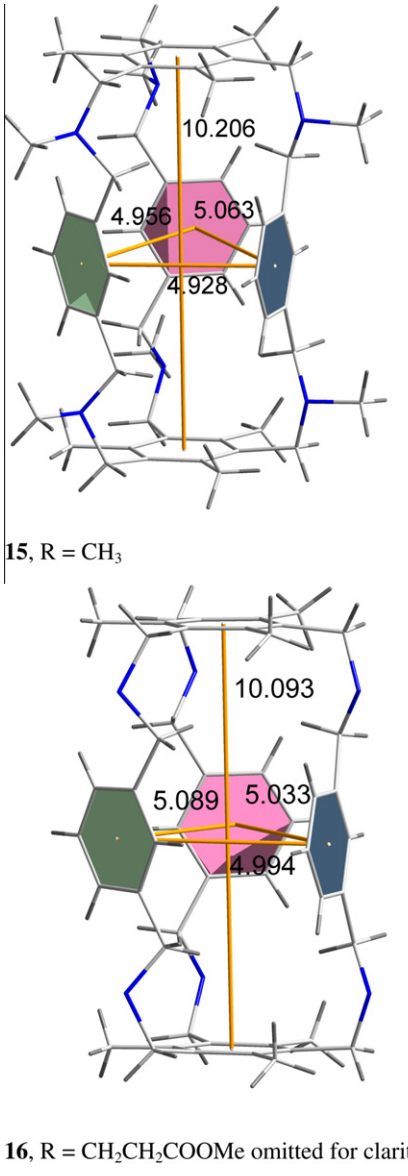


Figure 5. X-ray structures of cages **15** and **16**, **15**, R = CH_3, **16**, R = CH_2CH_2COOMe omitted for clarity.

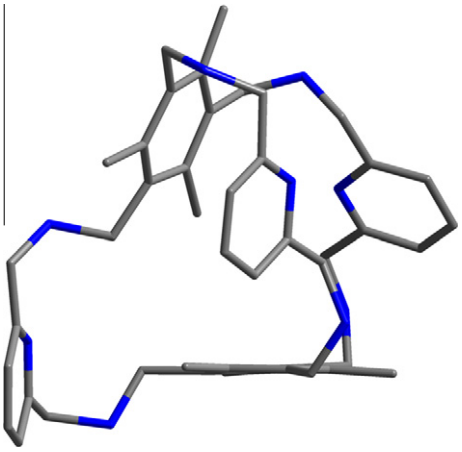


Figure 6. X-ray structure of cage **18**, tosyl and pyrrolidine groups omitted for clarity.

However, we believe that these elongations can be explained in these two cases by different molecular phenomena. Simple electrostatic repulsions can account for the longer distance between the 'floor' and 'roof' of the hexaammonium **2**·6H+ while more complex conformational constraints are responsible of the distortions observed in **15** and **16**. In cage **2**, the six NH bonds can easily point toward the center of the cavity, allowing the benzylic arms to radiate in the opposite direction. In cage **15**, the *N*-methyl group is now too bulky to point inside the cavity and this steric constraint drives it outside of the pocket. This forces the benzylic bond to rotate in consequence toward the inner space and, in a cascade response; the phenyl group accommodates this torsion by flipping almost perpendicular to its initial position in **2**. As a consequence, the π-orbitals are now exposed to the inner space of the cavity in place of the aromatic protons as in **2**. The mean distance between the centroids of two lateral phenyl rings was measured at 4.982 Å and 5.038 Å in cages **15** and **16**, respectively. As a point of comparison these distances were reported to be 11.161–11.277–9.315 Å in cage **2** incorporating acetone. One would notice that in **15** and **16** the nitrogen atoms are still pyramidal which is not the case anymore upon tosylation. Hence in **18** (and thus most likely also in **17**) the nitrogen atoms are strictly sp2 hybridized and planar. This, added to the important steric congestion imposed by the tosyl groups leads to the destruction of the regular shape of cage **18**. The two apical benzenes are no longer parallel, the cavity is considerably reduced and the architecture is no longer symmetrical as can be seen in Figure 6.

Precedent to these drastic modifications in cryptands conformation upon N-alkylation was observed with copper(II) and nickel(II) complexes, in which the metals are differently coordinated by the native versus the N-methylated ligand.[9]

We then turned our attention toward the protonation properties of these peculiar architectures. Thus cage **16**, which shows nicely resolved aromatic protons in its NMR spectrum, was chosen for titration experiments with various acids. Strong acids, such as $HClO_4$, H_2SO_4, HBr, and HCl expectedly induced protonation albeit in complex modes since the proton NMR spectra exhibited more than three aromatic resonances. On the contrary, titration with TFA showed a progressive shift downfield to finally lead to a unique protonated form as depicted in Figure 7. Importantly, the stoichiometric quantity of acid (i.e. 6 equiv) was insufficient to fully protonate cage **16**, only a large excess of the acid could assure a complete formation of the hexa-ammonium cage.

This suggests a drastic decrease of the amine basicity. This was further verified with the unexpected behavior of cage **16** toward acetic acid. We were quite surprised to observe that during titration of **16** with acetic acid, no change was detected in the NMR

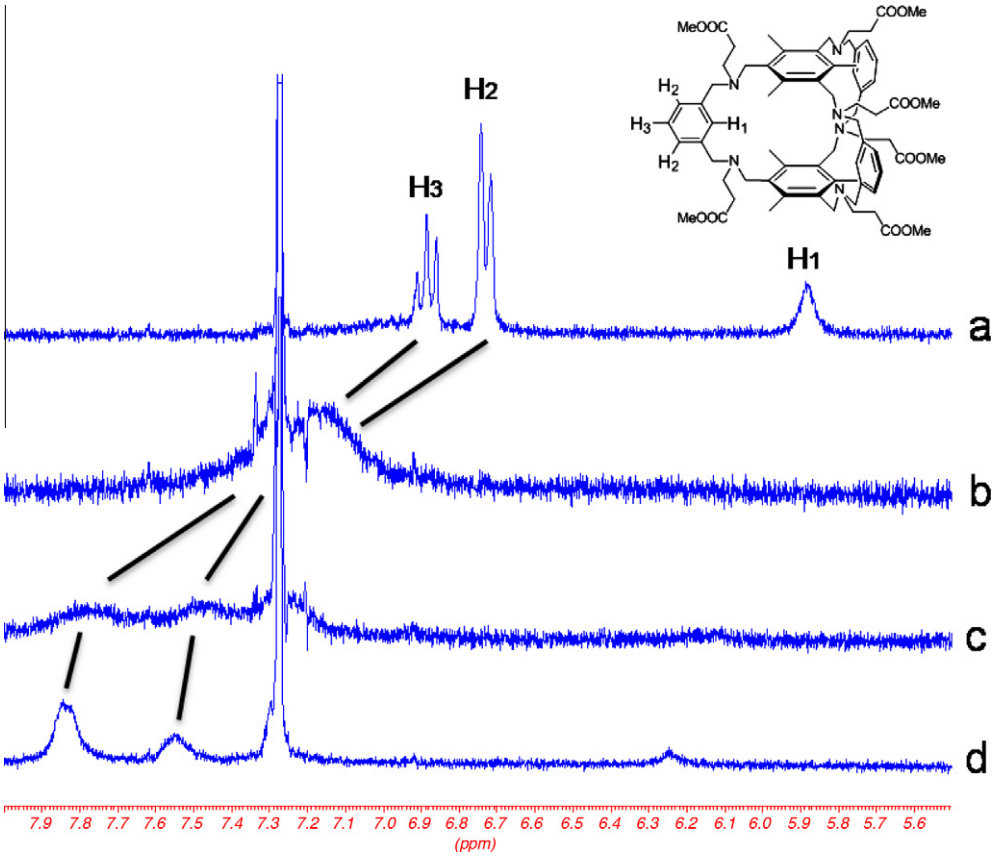


Figure 7. TFA titration of cage **16**, a: 0 equiv; b: 2 equiv; c: 6 equiv; d: 64 equiv in $CDCl_3/CD_3OD$, 300 MHz.

spectrum. Even in the presence of 400 equiv of this acid the hexaamine cage was still intact. It appears that tertiary amines of cage **16** are shielded against the approach of the organic acid. Hence, in an organic medium, a poorly dissociated carboxylic acid, such as AcOH is unable to promote proton transfer to **16** while substantially more acidic TFA[10] is operative in doing so, the respective bulkiness of these acids being almost equal in other respects. This reduced basicity could be explained by the demanding conformational changes that full protonation requires in such constrain cryptands. So far we were unable to demonstrate the encapsulation of small molecules within the cavity neither as the neutral cage nor in a protonated form, via crystallization or NMR detection of chemical shifts of hydrogen atoms of the potential guest. We believe that elongation of the bicycle is also reducing the accessibility of the cavity hence precluding encapsulation.

In conclusion, we explored the scope of the azacryptand one-step condensation. The direct hexa-imine assembly appears to be an all-or-nothing step, giving either intractable polymers or quantitative formation of the azacryptand. For this reason, the nature and form of the cavity cannot be varied at will by changing the initial reaction partners. Variation of the inner space and shape of these cages can, however, be achieved by local modification. Hence, simple N-alkylation induces a profound change in the overall conformation of cryptands **15** and **16**. These last undergo an elongation of a third of their initial height and the peripheral aromatic rings are brought closer to each other and strongly tilted. A drastic reduction in the amines' basicity was also observed as a consequence of the shielding of the nitrogen lone pairs.

Acknowledgment

N.D.R. thanks the French Ministry of Research for a graduate fellowship.

Supplementary data

Supplementary data (experimental details and copies of the proton and carbon NMR spectra, complete ORTEP diagrams) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.019.

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