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Self-assembly of a nucleotide-calixarene hybrid in a triangular supramolecule

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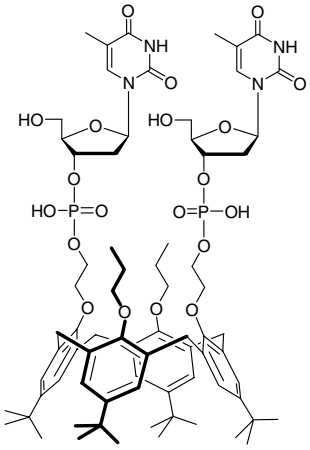
Abstract—The self-assembly of a thymine nucleotide-calixarene hybrid (**1**) in $CDCl_3$ as a solvent was investigated. FT-IR, ESI-MS, ^1H and DOSY-NMR spectra evidenced that compound **1** (ammonium or sodium salt) self-assembles in a triangular trimeric supramolecule by thymine–thymine hydrogen bonding. The saline form is crucial for the arrangement in the cyclic trimer as the protonation of the nucleotide phosphate groups leads the assembly toward a dimeric species.

Molecular self-assembly through specific interactions is a versatile tool for the controlled generation of higher-order structures.[1] In the last decade, the versatility of natural nucleobases as supramolecular motifs has inspired the development of a variety of self-assembled structures in both polar and apolar solvents.[2] These artificial systems represent interesting mimics of natural biomolecules, which self-organize in specific three-dimensional structures determining their biological activity. Attractive self-assembled structures have been produced introducing nucleobase, nucleoside, and nucleotide units into molecular platforms.[3,4] In these systems, the nucleobases drive the supramolecular assembly by non-covalent interactions, whereas the scaffold plays a role in controlling the three-dimensional array of the assembly that is formed.

In a previous Letter, we have reported the synthesis of di-nucleotide-calixarene conjugates and a preliminary study about their self-assembly in chloroform.[4] The nucleotide-calixarene derivatives bearing two 2′-deoxyadenosine, 2′-deoxycytidine, or 2′-deoxyguanidine nucleotide moieties, compatible with the presence of multiple hydrogen bonding sites per molecule, showed scarce solubility and ill-resolved ^1H NMR spectra. In contrast, the 2′-deoxythymidine-calixarene derivative (**1**) was completely soluble in $CDCl_3$ and provided enough resolved proton spectra. ^1H and VT-NMR experiments suggested that compound **1** (ammonium salt) self-assembles in a discrete species.[4]

Herein, we report a study aiming to better understand the structural features of the self-assembly of **1**.

FT-IR measurements showing two significant bands at 3395 and 3174 cm^{-1} due to the stretching vibration[6] of the non-H-bonded and H-bonded imido-NH, respectively, corroborated that T–T hydrogen-bonding, widely present in natural and artificial self-assembled or folded systems,[5] drives the self-assembly of **1**.



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To elucidate the size of the self-assembling aggregate, ESI-MS analysis of **1** was performed. The mass spectrum gave evidence that a trimeric species of **1** was present. In fact, it showed peaks at 1427.6 $[M-H]^-$ and 1449.5 $[M-2H+Na]^-$ relative to the monomeric form, and at 2174.5 $[3M+3Na-5H]^{2-}$ and 2184.5 $[3M+4Na-6H]^{2-}$corresponding to a doubly charged trimeric species. The absence of significant ions corresponding to multiply charged dimeric or higher-order aggregates and the range of trimeric adducts present in the mass spectrum for **1** suggested a trimeric cyclic structure. A few examples of self-assembly in trimeric cyclic structures have been reported for nucleoside[7] and calixarene derivatives.[8]

Molecular modeling proposed a triangular arrangement for the trimeric assembly of **1** (Fig. 1).

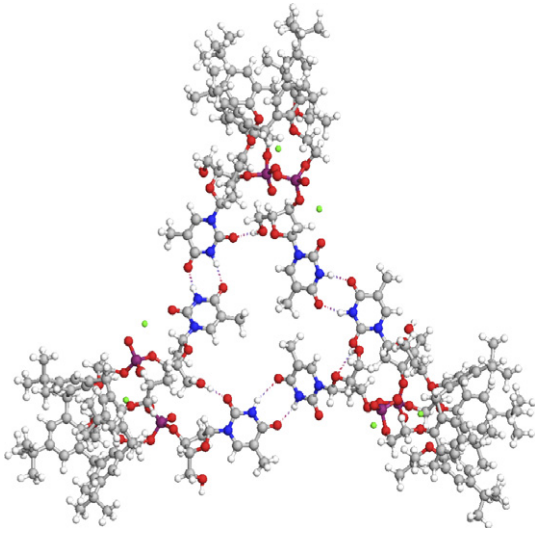

Figure 1. Computer-simulated structure of self-assembled compound **1**, sodium salt, in $CHCl_3$ as a solvent (MacroModel 7.2, Amber*, 10,000 steps).

It is reminiscent of the double rosette-type assembly reported by Reinhoudt et al. on calix[4]arene dimelamines mixed with two equivalents of cyanuric/barbituric acid in apolar solvent,[8] and by Hong et al. on calix[4]arene dicarboxylic acid mixed with tris(imidazoline) in polar solvent.[9] In these systems like in compound **1** the calix[4]arene platform promotes the exclusive formation of a cyclic structure in favor of other oligomeric assemblies.[10]

The identity of the assembly of **1** in solution was studied by diffusion-ordered NMR spectroscopy (DOSY), widely used for studying supramolecular aggregation.[11] The diffusion coefficients were used to calculate hydrodynamic radii by means of the Einstein–Stokes equation, and the obtained values (r_{exp}) were compared with the calculated average radii (r_{calc}) obtained from minimized structures. At 10 mM concentration, compound **1** (ammonium or sodium salt) showed a diffusion coefficient of $2.33 \pm 0.06 \times 10^{-10}$ m^2 s^{-1} resulting in r_{exp} of 15.9 ± 0.4 Å. This value was in good agreement with the radius ($r_{calc} = 15.5$ Å) calculated for the cyclic trimeric structure depicted in Figure 1.

To investigate the stability of the trimeric aggregate, NMR dilution experiments from 10 to 0.5 mM were carried out. Using acid free $CDCl_3$ as a solvent, the trimeric species persisted also at 0.5 mM concentration, whereas if commercial $CDCl_3$ was used the trimer progressively dissembled (Fig. 2) and compound **1** at 0.5 mM existed only as a monomeric species ($D = 4.56 \pm 0.10 \times 10^{-10}$ m^2 s^{-1}, $r_{exp} = 8.1 \pm 0.2$ Å, $r_{calc} = 8.2$ Å). These results evidenced that the self-assembly of **1** is affected by the residue acidity of the solvent.

^{1}H NMR spectra pointed out that the disassembly of **1** from trimeric to monomeric structure involves a conformational change of the calixarene skeleton (Fig. 2). In particular, the downfield shift of the CH_3 propyl groups and the upfield shift of the *t*-Bu and ArH protons indicated that in the monomeric species the rings bearing the propyloxy substituents are essentially parallel.[12] This implies that the monomer adopts a *pinched-cone* conformation as opposed to a *regular-cone* in the trimeric assembly.[13]

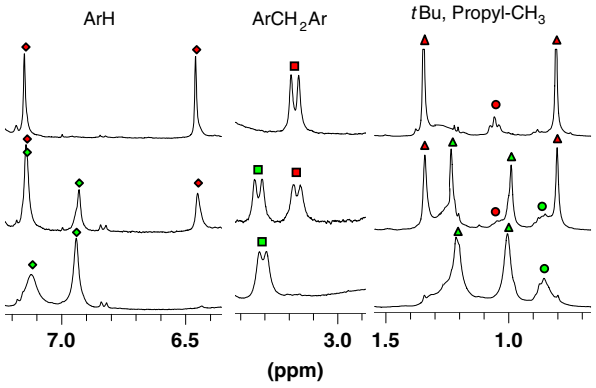

Figure 2. Portions of the ^{1}H NMR spectra of **1** at different concentrations (commercial $CDCl_3$, 297 K): (bottom) 10 mM, (medium) 1 mM, and (top) 0.5 mM. The disassembly by dilution generates a new signal pattern labeled in red.

The conformational change of the calixarene skeleton during the dilution experiments can be ascribed to the protonation of the phosphate groups due to the residue acidity of the $CDCl_3$.[14] As a confirmation, no conformational change was observed performing the same dilution experiments in $CDCl_3$ passed through a basic alumina column. In this case, ^{1}H NMR spectra pointed out that in both trimeric and monomeric species, the calix[4]arene skeleton adopts a *regular-cone* conformation (Fig. 3).

To further verify the effect of the acidity on compound **1**, apposite protonation of the phosphate groups was carried out by passing on an ion-exchange resin H^+. ^{1}H NMR spectra confirmed that compound **1** in its acid form adopts a *pinched-cone* conformation at both

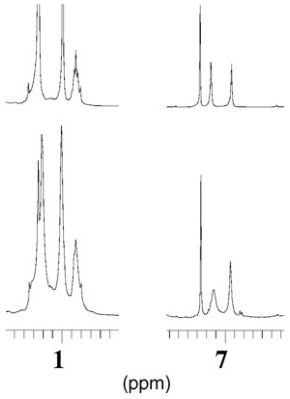

Figure 3. *t*-Bu and ArH regions of the ^{1}H NMR spectra of **1** in saline form (acid free $CDCl_3$, 297 K) at different concentrations: (bottom) 10 mM, trimeric species; (top) 0.5 mM, monomeric species.

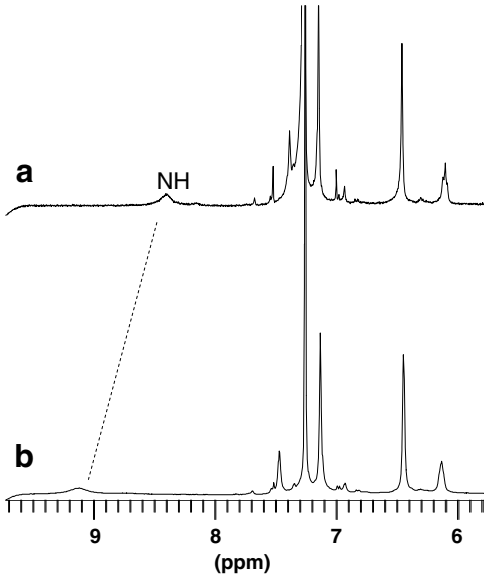

Figure 4. ^{1}H NMR spectra of compound **1** in acid form ($CDCl_3$, 297 K) at (a) 2 mM and (b) 10 mM concentrations. Downfield of the thymine NH-imido proton in the dimeric species is indicative of the presence of intermolecular hydrogen bonding.

10 and 0.5 mM. DOSY experiments showed that compound **1** at 10 mM self-assembles in a dimeric ($D = 3.20 \pm 0.08 \times 10^{-10}$ m^2 s^{-1}; $r_{exp} = 11.6 \pm 0.3$ Å, $r_{calc} = 11.3$) rather than in a trimeric form. At 2 mM the dimer is disassembled in monomer ($D = 4.53 \pm 0.09 \times 10^{-10}$ m^2 s^{-1}; $r_{exp} = 8.2 \pm 0.2$ Å). Thymine–thymine intermolecular hydrogen bonding drives the dimeric self-assembly of **1** as displayed by the downfield shift ($\Delta\delta = 0.73$ ppm) of the thymine NH-imido proton (Fig. 4).

To elucidate the different self-assembling of compound **1** in its acid and saline form, molecular modeling calculations were performed. They suggested that in the saline form, the cation coordinates not only the phosphate anions but also the phenol oxygens fixing the calixarene skeleton in a *regular-cone* conformation (Fig. 5 right), which promotes the trimeric assembly. In contrast, the protonation of the phosphate groups, through intramolecular hydrogen bonding, blocks the calixarene skeleton in a *pinched-cone* conformation (Fig. 5 left), and confers to the nucleotide moieties a preorganization favoring the dimeric aggregation.

In conclusion, we have shown how a T–T hydrogen-bonding motif drives the self-assembly of a thymine nucleotide-calixarene hybrid into a dimeric or trimeric structure and how the simple protonation–deprotonation of the nucleotide phosphate groups can determine the switching between the two aggregate types. This study highlights how it is possible to harness the calix[4]-arene platform and the nucleotide functionalities to construct novel self-assembled structures potentially useful for nanotechnogical applications.

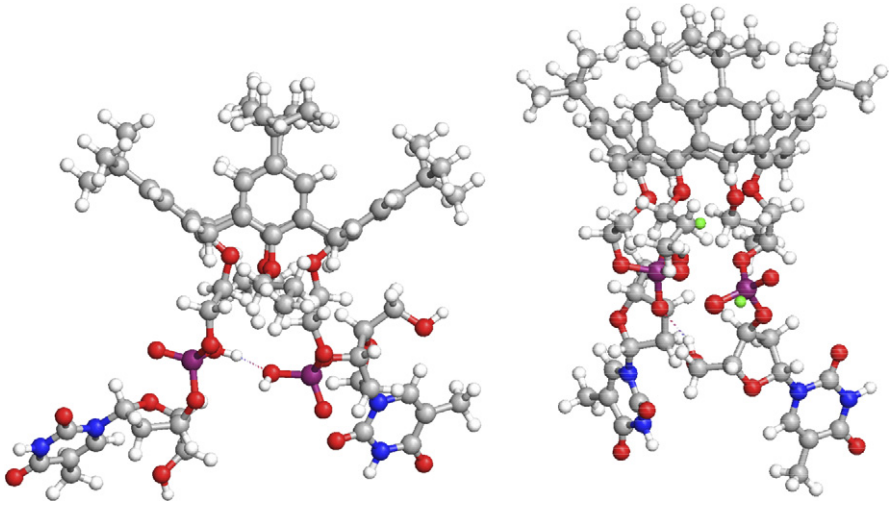

Figure 5. Minimized structures (MacroModel 7.2, Amber*, 10,000 steps, $CHCl_3$) of **1**: acid form in *pinched-cone* conformation (left) and saline form in *regular-cone* conformation (right). Sodium cations are colored in green.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.068.

References and notes

1. (a) Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **1996**, *35*, 1154–1196; (b) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382–2426; (c) Special Issue 'Supramolecular Chemistry and Self-Assembly': *Science* **2002**, *295*, 2400–2421; (d) Lehn, J.-H. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4763–4768.
2. (a) Sivakova, S.; Rowan, S. J. *Chem. Soc. Rev.* **2005**, *34*, 9–21; (b) Sessler, J. L.; Lawrence, C. M.; Jayawickramarajah, J. *Chem. Soc. Rev.* **2007**, *36*, 314–325; (c) Mezzina, E.; Mariana, P.; Itri, R.; Masiero, S.; Pieraccini, S.; Spada, G. S.; Spinozzi, F.; Davis, J. T.; Gottarelli, G. *Chem. Eur. J.* **2001**, *7*, 388–395; (d) Iwaura, R.; Yoshida, K.; Masuda, M.; Yase, K.; Shimizu, T. *Chem. Mater.* **2002**, *14*, 3047–3053; (e) Thibault, R. J.; Hotchkiss, P. J.; Gray, M.; Rotello, V. M. *J. Am. Chem. Soc.* **2003**, *125*, 11249–11252.
3. (a) Drain, C. M.; Fischer, R.; Nolen, E. G.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1993**, 243–245; (b) Schall, O. F.; Gokel, G. W. *J. Am. Chem. Soc.* **1994**, *116*, 6089–6100; (c) Bonaccio, S.; Capitani, D.; Segre, A. L.; Walde, P.; Luisi, P. L. *Langmuir* **1997**, *13*, 1952–1956; (d) Sessler, J. L.; Wang, R. *J. Org. Chem.* **1998**, *63*, 4079–4091; (e) Sidorov, V.; Kotch, F. W.; El-Kouedi, M.; Davis, J. T. *Chem. Commun.* **2000**, 2369–2370; (f) Kotch, F. W.; Sidorov, V.; Lam, Y.-F.; Kayser, K. J.; Li, H.; Kaucher, M. S.; Davis, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 15140–15150; (g) Kim, S. J.; Kim, B. H. *Nucleic Acids Res.* **2003**, *31*, 2725–2734.
4. Consoli, G. M. L.; Granata, G.; Cunsolo, F.; Galante, E.; Geraci, C. *Tetrahedron Lett.* **2006**, *19*, 3245–3249.
5. Keniry, M. A.; Owen, E. A.; Shaker, R. H. *Nucleic Acids Res.* **1997**, *25*, 4389–4392.
6. Kyogoku, Y.; Lord, R. C.; Rich, A. *J. Am. Chem. Soc.* **1967**, *89*, 496–504.
7. (a) Chen, H. C.; Ogo, S.; Fish, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 4993–5001; (b) Sessler, J. L.; Jayawickramarajah, J.; Sathiosatham, M.; Sherman, C. L.; Brodbelt, J. S. *Org. Lett.* **2003**, *5*, 2627–2630.
8. (a) Vreekamp, R.; van Duyhoven, H. J. P. M.; Hubert, M.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **1996**, *35*, 1215–1218; (b) Timmerman, P.; Vreekamp, R.; Hulst, R.; Verboom, W.; Reinhoudt, D. N.; Rissanen, K.; Udachin, K. A.; Ripmeester, J. *Chem. Eur. J.* **1997**, *3*, 1823; (c) Timmermann, P.; Weidmann, J.-L.; Joliffe, K. A.; Prins, L. J.; Reinhoudt, D. N.; Shinkai, S.; Frish, L.; Cohen, Y. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2077–2089; (d) Timmerman, P.; Prins, L. J. *Eur. J. Org. Chem.* **2001**, *17*, 3191–3205; (e) Kerckhoffs, J. M. C. A.; van Leeuwen, F. W. B.; Spek, A. L.; Kooijman, H.; Crego-Calama, M.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5717–5722.
9. Lee, H. Y.; Moon, D.; Lah, M. S.; Hong, J.-I. *J. Org. Chem.* **2006**, *71*, 9225–9228.
10. Timmermann, P.; Weidmann, J.-L.; Joliffe, K. A.; Prins, L. J.; Reinhoudt, D. N.; Shinkai, S.; Frish, L.; Cohen, Y. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2077–2089.
11. (a) Cohen, Y.; Avram, L.; Frish, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 520–554; (b) Kapur, G. S.; Cabrita, E. J.; Berger, S. *Tetrahedron Lett.* **2000**, *41*, 7178–7185.
12. Webber, P. R. A.; Cowley, A.; Beer, P. D. *Dalton Trans.* **2003**, 3922–3926.
13. (a) Gutsche, C. D. *Calixarene Revisited*; Royal Society of Chemistry: Cambridge, 1998; (b) *Calixarene 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, 2001.
14. The simple concentration of the diluted sample of **1** up to 10 mM did not return the initial *regular-cone* conformation, which was only replaced by basic treatment with diluted ammonia.