Self-Organization of Spheroidal Molecular Assemblies in Polar Solvents
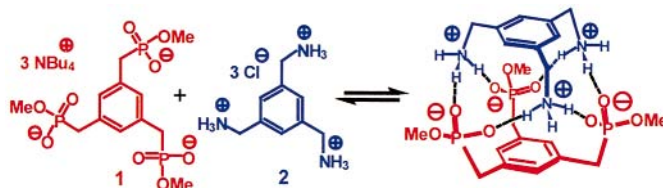
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Received September 27, 1999

ABSTRACT

We report a number of 1:1 noncovalent complexes composed of a symmetrical trisphosphonate and various symmetrical trisammonium or trisamidinium compounds. The spheroidal complexes show high thermodynamic stability, with association constants K_a reaching 10^6 M^{-1} in methanol and in some cases even exceeding 10^3 M^{-1} in water. The observed K_a values correlate well with the different degree of preorganization of the complexation partners.

Self-organization of complementary moieties into new functional structures represents a fundamental process that is used extensively by Nature. Among others, the DNA double helix is formed spontaneously by the template-directed dimerization of complementary nucleic acid strands.[1] Chemists have recently designed various types of molecular capsules which self-assemble from smaller components by virtue of multiple noncovalent interactions.[2] However, most of these model systems rely on weak directed hydrogen bonds and are hence restricted to nonpolar solvents (for the few exceptions, see ref 3). We now report on a simple and versatile access to capsule-like complexes, which display a pronounced complex stability even in water. These non-covalent complexes are composed of highly charged complementary building blocks based on ammonium (or amidinium) and phosphonate ions.[4]

Molecular mechanics simulations reproducibly revealed a favorable symmetrical complex between trisphosphonate

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(1) (a) Pörschke, D.; Eigen, M. *J. Mol. Biol.* **1971**, *62*, 361−381. (b) Craig, M. E.; Crothers, D. M.; Doty, P. *J. Mol. Biol.* **1971**, *62*, 383−401.

(2) For an excellent review, see: (a) Conn, M. M.; Rebek, J. *Chem. Rev.* **1997**, *97*, 1647−1668. Some very recent work on self-organized molecular capsules based on hydrogen bonds: (b) Heinz, T.; Rebek, J. *Nature* **1998**, *394*, 764−767. (c) Martin, T.; Obst, U.; Rebek, J. *Science* **1998**, *281*, 1842−1845. (d) Mammen, M.; Simanek, E. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1996**, *118*, 12614−12623. (e) Kikuchi, Y.; Tanaka, Y.; Sutarto, S.; Kobayashi, K.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1991**, *114*, 10302−10306. (f) Vreekamp, R. H.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 4282−4288. (g) Mogck, O.; Böhmer, V.; Vogt, W. *Tetrahedron* **1996**, *52*, 8489−8496. (h) Sessler, J. L.; Wang, R. *J. Am. Chem. Soc.* **1996**, *118*, 9808−9809. (i) Prins, L. J.; Huskens, J.; de Jong, F.; Timmermann, P.; Reinhoudt, D. N. *Nature* **1999**, *398*, 498−502.

(3) Exceptions include the following. Molecular capsules in water using the hydrophobic effect: (a) Zhao, S.; Luong, J. H. T. *J. Chem. Soc., Chem. Commun.* **1995**, 663−664. (b) Harada, A.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1988**, 1352−1353. (c) Boulas, P.; Kuntner, W.; Jones, M. T.; Kardish, K. M. *J. Phys. Chem.* **1994**, *98*, 1282−1287. (d) Venema, F.; Rowan, A. E.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1996**, *118*, 257−258. Metal chelates: (e) Lehn, J. M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1347−1360. (f) Lee, J.; Schwabacher, A. W. *J. Am. Chem. Soc.* **1994**, *116*, 8382−8383. (g) Klüfers, P.; Schuhmacher, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1863−1865. (h) Saalfrank, R. W.; Burak, R.; Reihs, S.; Löw, N.; Hampel, F.; Stachel, H.-D.; Lentmaier, J.; Peters, K.; Peters, E.-M.; von Schnering, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 993−995. (i) Takeda, N.; Umemoto, K.; Yamaguchi, K.; Fujita, M. *Nature* **1999**, *398*, 794−796. (j) Olenyuk, B.; Whiteford, J. A.; Fechtenkötter, A.; Stang, P. J. *Nature* **1999**, *398*, 796−798.

(4) A relatively vague self-organization of a molecular capsule based on flexible ammonium carboxylate ion pairs has been described: Lee, S. B.; Hong, J.-I. *Tetrahedron Lett.* **1996**, *37*, 8501−8504.

1 and trisammonium ion **2** that exhibits a cyclic arrangement of alternating positive and negative charges interconnected by a regular network of linear hydrogen bonds.[6] These structures were calculated to be far more stable than the respective simple ion pairs.[7] The idea of generating a compact spheroidal assembly with an alternating order of molecular arms coming from the top and bottom unit seemed to be very encouraging (Figure 1).
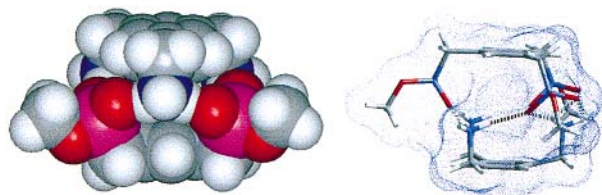

Figure 1. Force-field-optimized structure of the complex from trisphosphonate **1** and its complementary analogous trisammonium salt **2**. Left: side view of a CPK model. Right: calculated Connolly surface[5] (dotted line represents the solvent accessible area around the complex).

Trisphosphonate **1** was prepared in two steps by a Michaelis–Arbuzov reaction from 1,3,5-tris(bromomethyl)-benzene, followed by hydrolysis of the trisphosphonate hexamethyl ester with aqueous tetrabutylammonium hydroxide. Complexes composed of **1** and symmetrical trisammonium and trisamidinium compounds gave rise to sharp signals in ^{1}H, ^{13}C, and ^{31}P NMR spectra (Figure 2). Upfield shifts for ^{1}H NMR signals were indicative of complexation. Job plots supported a perfect 1:1 stoichiometry.[8] Evaluation of NMR titration curves with nonlinear regression methods revealed a large thermodynamic stability, with association constants K_a reaching 10^6 M^{-1} in methanol (Figure 3, Table 1).[9]

This was an interesting result considering our initial experiments with α,ω-diammonium ions and xylylene bis-phosphonates, which also formed 1:1 complexes in solution. However, their association constants were several orders of magnitude lower than those of their C_{3v}-symmetrical counterparts investigated in this paper.[13] Even with shorter hydrogen bond lengths and two additional charges in the trisphosphonate complexes, the drastic increase in binding energy can be best explained by a network of alternating
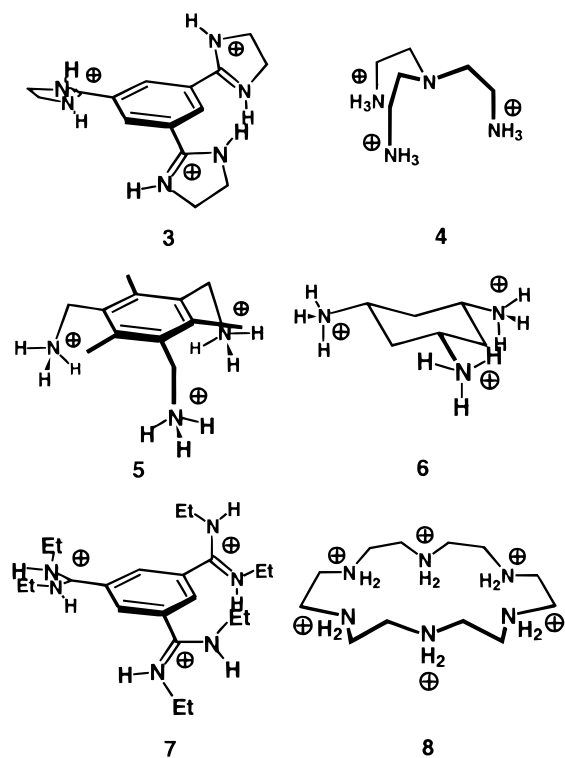
(5) (a) Connolly, M. L. *Science* **1983**, *221*, 709–713. (b) Connolly, M. L. *J. Appl. Crystallogr.* **1983**, *16*, 548.

(6) Molecular Modelling Program: CERIUS^2 by Molecular Simulations Inc. Force field: Dreiding 2.21.

(7) For flat structures, which form simple ion pairs, see: Schneider, H.-J.; Schiestel, T.; Zimmermann, P. *J. Am. Chem. Soc.* **1992**, *114*, 7698–7703.

(8) (a) Job, P. *Ann. Chim.* **1928**, *9*, 113–203. (b) Blanda, M. T.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 4626–4636.

(9) (a) Schneider, H. J.; Kramer, R.; Simova, S.; Schneider, U. *J. Am. Chem. Soc.* **1988**, *110*, 6442–6448. (b) Wilcox, C. S. In *Frontiers in Supramolecular Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds; VCH: Weinheim, 1991; pp 123–143. (c) Macomber, R. S. *J. Chem. Educ.* **1992**, *69*, 375–378.

(10) Kraft, A.; Fröhlich, R. *Chem. Commun.* **1998**, 1085–1086.

(11) Bowen, T.; Planalp, R. P.; Brechbiel, M. W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 807–810.

Figure 2. Symmetrical trisammonium and trisamidinium cations and hexazacrown **8** used for the NMR titrations with trisphosphonate **1**. All structures are depicted in the C_{3v}-symmetrical conformation necessary for complexation.

charges described in Figure 1. Such a combination of weak multipoint interactions is reminiscent of many natural, selective, and strong recognition processes.[14]

Molecular mechanics simulations of the complex between **1** and **2** soaked in a solvent shell of explicit water molecules
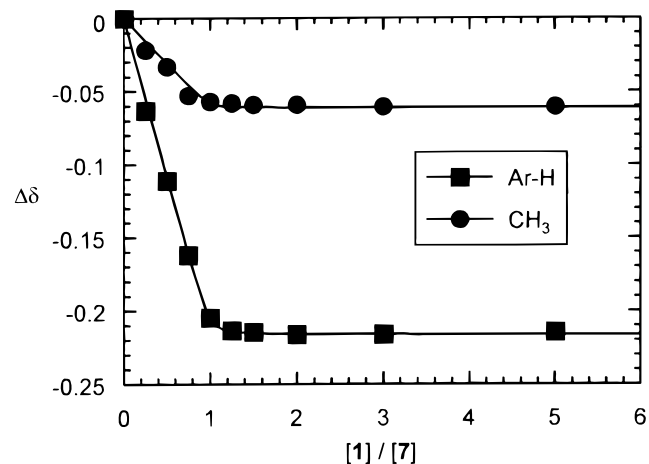

Figure 3. Typical NMR titration curve showing the change in the chemical shift $\Delta\delta = \delta_{observed} - \delta_0$ for two ^{1}H NMR signals of trisamidine **7** ($c = 0.1$ mM) on addition of trisphosphonate **1** in CD$_3$OD.

Table 1. Association Constants K_a [M^{-1}] for 1:1 Complexes between Symmetrical Trications and **1** Determined by NMR Titrations in Methanol and Water at 20 °C

trication[a]	K_a [M^{-1}] in CD$_3$OD	K_a [M^{-1}] in D$_2$O[c]
trisimidazoline **3**[10]	$3.0 \times 10^3 \pm 16\%$[b]	
tren **4**	$4.8 \times 10^4 \pm 48\%$	
mesitylenetriamine **5**	$8.0 \times 10^4 \pm 34\%$	$2.6 \times 10^3 \pm 13\%$
mesitylenetriamine **2**	$1.4 \times 10^5 \pm 11\%$	$4.0 \times 10^3 \pm 6\%$
cyclohexanetriamine **6**[11]	$9.9 \times 10^5 \pm 32\%$	$1.1 \times 10^3 \pm 15\%$
trisamidine **7**[12a]	$1.1 \times 10^6 \pm 8\%$	$1.0 \times 10^3 \pm 9\%$

[a] Ammonium and amidinium chlorides except for **6** which was used as a bromide. [b] Errors are standard deviations. [c] pD $\cong$ 7.0.

(layer thickness: 5 Å) employing a more sophisticated energy minimization approach (quasi Newton−Raphson algorithm[15a]) also indicated a high stability for the 1:1 complex even in a highly competitive solvent environment. The calculations starting from different hydrogen bond patterns converged toward the proposed hydrogen bond network that is characterized by a staggered orientation of the substituents and regularly bridging hydrogen bonds.[15b]

It is well known that a self-organization process is governed by a delicate balance between enthalpic gain and entropic cost. Both starting materials are flexible molecules with various rotatable bonds that need to be conformationally fixed in the final complex. In this respect, the required entropy loss for the self-organization process lies between Rebek's tennisball (composed of rigid halfs) and Whitesides's rosette (composed of highly flexible components).[16] Because in our example the three binding sites are all covalently linked to an aromatic core, only torsional degrees of freedom contribute to the free binding energy (Figure 4).

Figure 4. Schematic presentation of the self-organization process involved in the formation of a 1:1 complex from a mixture of **1** and a trisammonium or trisamidinium ion (**2**−**7**).

The varying number of flexible bonds within the trisammonium ions should therefore reflect their total difference in torsional entropy.[17] This correlation has indeed been found

in complexes of **1** with **6**, **2**, and **4**, which contain three, six, and nine freely rotating bonds, respectively. Thus, the K_a values in Table 1, spanning several orders of magnitude, convincingly reflect the different degree of preorganization of the complexation partners. The smallest value for tris-imidazoline **3** probably originates from the fact that the trication prefers an almost planar conformation but has to be strongly twisted for complexation.[18] Trisamidine **7**, on the other hand, is already ideally preoriented prior to complexation as a result of the congestion of three bulky N,N′-diethyl-substituted amidinium groups at the 1,3,5-positions of the benzene ring.[12] This preorganization of **7** (similar to **6**) explains the remarkably high association constants with **1** in organic solvents, where hydrogen bonds considerably contribute to the overall binding strength. It would be interesting to check if the transition from three methyl groups in **5** to the corresponding triethyl-substituted triamine leads to increased binding due to preorganization as Anslyn demonstrated with his citrate receptor.[19]

In contrast to most molecular capsules known to date, several of our trisammonium trisphosphonates form strong complexes even in water, with K_a values varying between 10^3 and 10^4 M^{-1} (Table 1). In water, however, the dominating electrostatic interaction of the hard ammonium cation is superior to that of the delocalized amidinium cation. Therefore, here the distribution of association constants becomes much more uniform.

Preliminary experiments in the direction of defined higher aggregates were already very promising. Thus, a Job plot proved unambiguously that, even in water, a 2:1 complex was formed between two half-spheres of **1** and a belt of hexaza-18-crown-6 **8** (Figure 5). This shows that our
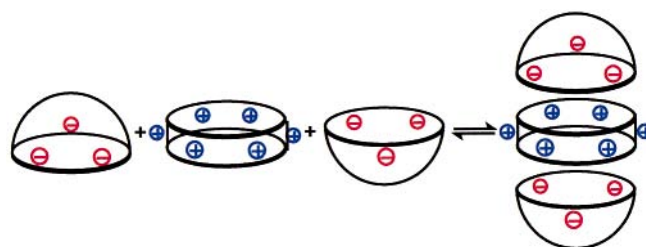

Figure 5. Schematic presentation of the self-organization process involved in the formation of a neutral 2:1 complex from a mixture of **1** and hexaza-18-crown-6 (**8**).

approach for the design of molecular capsules, by using a combination of preorientation and an array of alternating charges, can be effectively transferred to systems with more

(12) (a) Kraft, A. J. Chem. Soc., Perkin Trans. 1 **1999**, 705−714. Two crystal structures of bulky N,N′-disubstituted aromatic amidines confirm the strong twist of the amidine moieties: (b) Tinant, B.; Dupont-Fenfau, J.; Declercq, J.-P.; Podlaha, J.; Exner, O. Collect. Czech Chem. Commun. **1989**, 54, 3245−3251. (c) Boeré, R. T.; Klassen, V.; Wolmershäuser, G. J. Chem. Soc., Dalton Trans. **1998**, 4147−4154.

(13) K_a values typically range from 10^1 to 10^2 M^{-1} in methanol: Grawe, T.; Schrader, T. Unpublished results.

(14) Mammen, M.; Choi, S.-K.; Whitesides, G. M. Angew. Chem., Int. Ed. **1998**, 37, 2754−2794.

(15) (a) Mackay, D. H.; Cross, A. J.; Hagler, A. T. In Prediction of Protein Structure and the Principles of Protein Conformation; Fasman, G. D., Ed.; Plenum Press: New York, 1989; pp 317−358. (b) INSIGHT II, version 98.0, 1999, MSI, San Diego, CA.

(16) (a) Wyler, R.; de Mendoza, J.; Rebek, J. Angew. Chem., Int. Ed. Engl. **1993**, 32, 1699−1700. (b) Branda, N.; Wyler, R.; Rebek, J. Science **1994**, 263, 1267−1268. (c) Seto, C. T.; Whitesides, G. M. J. Am. Chem. Soc. **1993**, 115, 905−916. (d) Seto, C. T.; Whitesides, G. M. J. Am. Chem. Soc. **1993**, 115, 1330−1340.

than two components. At present we are devising larger, highly preorganized capsules with the aim of testing their abilities to accommodate guests in polar media. The transport of drugs, sensors, markers, or reagents by such artificial container molecules would, especially in physiological solution, open the door for a wide range of possible applications.[2]

(17) For an application of Whitesides's entropy model to our complexes, see the Supporting Information. (a) Mammen, M.; Shakhnovich, E. I.; Whitesides, G. M. *J. Org. Chem.* **1998**, *63*, 3168−3175. (b) Mammen, M.; Shakhnovich, E. I.; Whitesides, G. M. *J. Org. Chem.* **1998**, *63*, 3821−3830.

(18) NMR chemical shift data indicate a preference for a planar conformation of **3** prior to complexation as supported by two crystal structures: (a) ref 10. (b) Kraft. A.; Osterod, F.; Fröhlich, R. *J. Org. Chem.* **1999**, *64*, 6425−6433.

(19) Metzger, A.; Lynch, V. M.; Anslyn, E. V. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 862−865.

Supporting Information Available: Experimental procedures and full characterization for compounds **1**, **2**, and **5**, entropy estimations, NMR titration curves, Job plots, and force-field calculations of complex geometries for selected complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9910924