JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2000; **13:** 670–673

Self-organized ball-shaped molecular assemblies in water

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Received 27 August 1999; revised 9 April 2000; accepted 19 April 2000

ABSTRACT: A trisphosphonate and various triammonium and trisamidinium compounds, all containing a C_3 axis of symmetry, form strong 1:1 complexes in methanol and water. The structural information about these complexes is best explained in terms of self-assembly by means of a cyclic array of alternating charges resulting in the geometrical shape of a molecular capsule. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: self-organization; molecular capsules; trisphosphonates; trisamidines

Chemists have recently imitated Nature by designing molecular capsules which self-assemble from smaller components by virtue of multiple non-covalent interactions (for a review, see Ref. 1a; for recent work on self-organized molecular capsules based on hydrogen bonds, see Refs 1a–i). A prominent example is the supramolecular tennisballs created by Rebek and co-workers, which spontaneously self-assemble from self-complementary building blocks (Fig. 1).[2] Multiple hydrogen bonds lead to formation of a closed architecture, which can accommodate guest molecules with the right size and polarity. However, most of these model systems rely on weak directed hydrogen bonds, and are hence restricted to non-polar solvents. Other approaches make extensive use of hydrophobic interactions (as, e.g., in cyclodextrin dimers) (exceptions: molecular capsules in water using the hydrophobic effect[3]) or generate metal complexes with multifunctional bidentate ligands, which are able to include certain counterions (metal chelates[4]). We now report on a simple and versatile access to self-organized spheroidal molecular assemblies, which also strongly hold together in water. These are composed of highly charged complementary building blocks based on ammonium and phosphonate ions (a relatively vague self-organization of a molecular capsule based on flexible ammonium carboxylate ion pairs has been described.[5]). Multiple salt bridges enforced by an alternating array of oppositely charged functional groups should lead to strong binding even in highly polar solvents such as methanol or water. This could ultimately open a new dimension for the selective transport of guest molecules by such molecular containers in physiological solution (Fig. 1).

The parent trianion was synthesized in five steps from benzenetricarboxylic acid. After an Arbuzow reaction in the penultimate step the respective trisphosphonate was generated by alkaline hydrolysis with tetrabutylammonium hydroxide furnishing directly the C_{3v} symmetrical trisphosphonate salt.[6] The corresponding trication was prepared as a set of various triammonium und trisamidinium salts all of C_3 symmetry in their complex conformation, but with a different degree of flexibility (Fig. 2). Thus, the new concept of combining complementary half-spheres offers a substantial improvement over the self-complementary ‘one subunit–one complex’ strategy, in that the number of possible complexes is multiplied by simple variation of the structure of either subunit. Most C_{3v} symmetrical triammonium compounds were synthesized by established procedures; however, for the trisamidinium derivatives, Kraft developed new entries[7] (Two crystal structures of bulky *N*, *N*′-disubstituted aromatic amidines confirm the strong twist of the amidine moieties [7c,d]).

A first hint at the desired complex formation came from Job’s method of continuous variations.[8] Job plots for mixtures of the respective trications with the above-described trianion revealed a perfect 1:1 stoichiometry (Fig. 3a). The changes in chemical shift for several C*H* protons surpassed 0.3 ppm even in methanol, indicating a strong interaction in the complex. Since all NMR signals remained sharp throughout the entire series of NMR experiments, the existence of oligomers or even polymers seems unlikely.

We performed NMR titrations with both complex partners and plotted the dependence of the change of the

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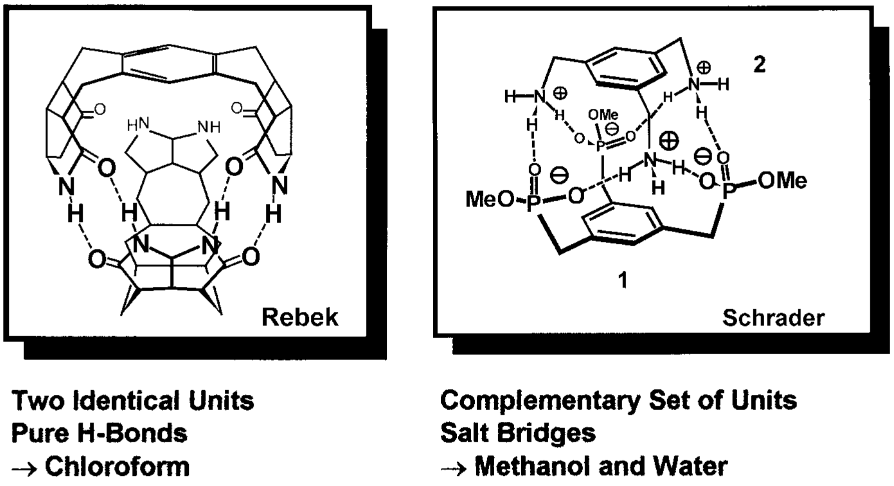
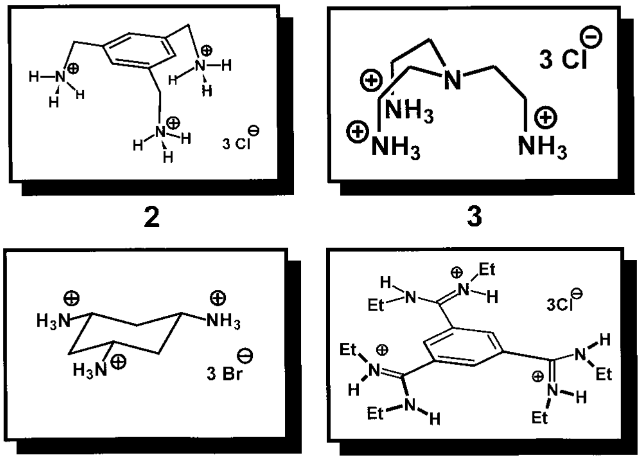


Figure 1. Hydrogen-bonded self-assemblies for solvents of different polarity

chemical shift of 'guest' protons on the amount of added 'host' molecule (the choice of the name guest and host is certainly arbitrary in this case). The resulting binding curves showed an extremely sharp curvature and were analyzed by non-linear regression methods (Fig. 3b).[9] In all cases a good fit of the experimental to the calculated curves for 1:1 stoichiometry was found. In methanol, the respective association constants range from 10^4 up to $10^6\ \mathrm{M}^{-1}$. In water, binding is still strong, in the range of $(1–4) \times 10^3\ \mathrm{M}^{-1}$ (Table 1). These extraordinarily high binding constants constitute a strong argument for the spheroidal structure of the complex. Even in DMSO (which is much less polar than methanol) the single ammonium–phosphonate interaction is not stronger than $10^3\ \mathrm{M}^{-1}$.

No chemically induced shifts (CIS) could be detected for the tetrabutylammonium counterions. However, we cannot rule out the possibility that counterions influence the aggregation behaviour. It is conceivable, for example, that even before complexation the chloride counterions of the trisammonium ions occupy those places which are later taken over by the phosphonate moieties. Hence they might produce a network of alternating positive and negative charges with a certain degree of pre-orientation. Such high binding constants give a good basis for the design of container molecules in protic solvents. Although we could not prepare crystals of the complex suitable for an x-ray structure analysis because of the strongly hygroscopic character of the trisphosphonate, we were able to detect a molecular ion peak for the **1 –2** complex with chemical ionization, but no peaks for higher oligomers.



2 3

4 5

Figure 2. C_{3v}-symmetrical triammonium und trisamidinium cations **2–5** in their complex conformation used for the NMR titrations with trisphosphonate **1**

The geometric parameters governing the complex formation between trisphosphonate **1** and triammonium pendant **2** were investigated by thorough molecular mechanics simulations employing the cff91 force-field as implemented in the DISCOVER simulation package.[10] The simulations were carried out under explicit treatment of an aqueous solvent environment. A series of energy minimizations using the VA09A algorithm (a variant of an iterative Newton–Raphson method)[10] conducted over 5000 iterations started from different mutual complex geometries. Interestingly, all simulations convergently revealed the same final complex geometry characterized by the alternating array of three positive and three negative charges interconnected by a network of stable hydrogen bonds. The convergent conformational outcome of these simulations, irrespective of the initial orientation and conformation of both complex partners, clearly supports the relevance and energetic stability of the resulting structural hypothesis depicted in Fig. 1. Detailed conformational searches prove this array to be far more stable than any respective simple ion pairs, even in a water surrounding[10] (for flat structures, which form simple ion pairs, see Ref. 11). It forces all the flexible

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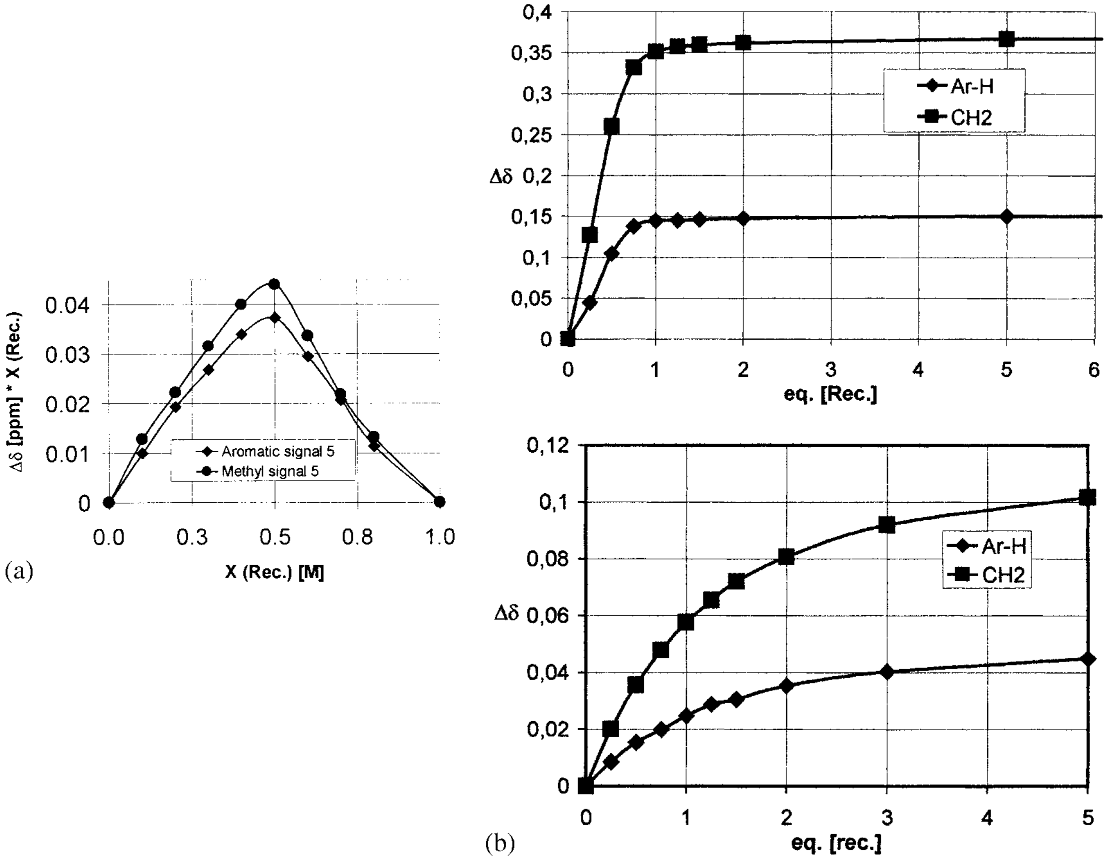

(a)

(b)

Figure 3. (a) Job plot of the complex between trisamidinium compound **5** and trisphosphonate **1** in CD_3OD; during the ^1H NMR experiment the signals of the aromatic and methyl group of **5** were detected. (b) Typical NMR titration curves plotted as the dependence in the change of the chemical shift of selected C*H* protons of triammonium salt **2** on the addition of trisphosphonate **1**: (top) in methanol; (bottom) in water

arms of each molecule to point in the same direction like the fingers of a claw or like an open mouth. Both complex partners are locked together similarly to gear wheels and thus form a molecular capsule. Calculations of its van der Waals surface reveal an internal cavity of approximately the size of a diatomic molecule. Even the Connolly surface, i.e. the water-accessible area around the complex, reveals a small cavity (Fig. 4).[12] However, inclusion of HF, CO or other diatomic molecules leads to a small destabilization and widening of the capsule; these spheroidal aggregates may be just too small for a favorable inclusion of diatomic guests. So far, we have not been able to prove any inclusion of small guests such as methanol or water.

Table 1. Association constants $K_{a(1:1)}$ (M^{-1}) for the 1:1 complexes between C_3 symmetrical trications and **1** determined by NMR titrations in deuterated methanol and water ($pD \cong 7.0$) at 20 °C (errors in K_a were estimated as standard deviations of $\leq 50\%$ for $K_a \leq 10^6$ M^{-1})

	$K_{a(1:1)}$ (M^{-1})	
Compound	In CD_2OD	In D_2O
2	1.4×10^5	4.0×10^3
3	4.8×10^4	3.8×10^3
4	9.9×10^5	1.2×10^3
5	1.1×10^6	1.1×10^3

It is well known that most self-organization processes are governed by a delicate balance between enthalpic gain and entropic cost. In our case, the three flexible arms of host and guest molecules have to be frozen simultaneously in the productive claw-like conformation. Since they are all covalently attached to a central core, the entropy change can be reduced to a (drastic) loss in torsional entropy. We are currently increasing both the rigidity and individual size of the half-spheres. With highly pre-organized complementary building blocks avoiding entropy-costly bonds, we hope to achieve strong binding to give molecular capsules under physiological conditions. The transport of drugs, sensors or reagents by such artificial container molecules would pave the way for a wide range of possible applications.[1]

EXPERIMENTAL

General protocol for the NMR titrations. Ten NMR

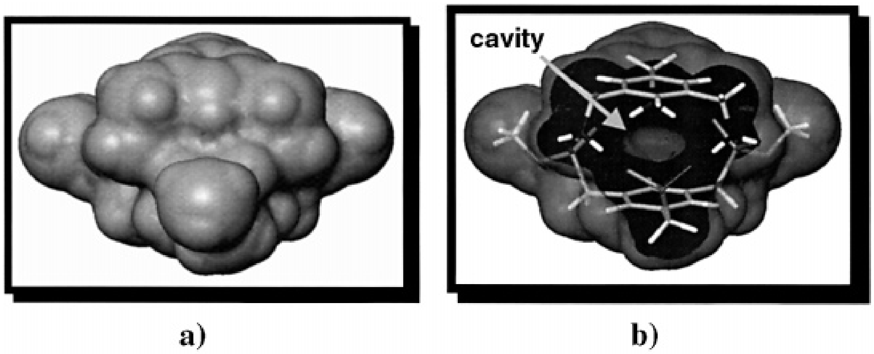

Figure 4. (a) Calculated Connolly surface for the complex between **1** and **2** (solvent-accessible area around the complex. (b) View into the 1:1 complex of **1** and **2** with internal cavity

tubes were each filled with 0.8 ml of a solution of the guest compound (c_{guest} = 0.5–4 mM) in a deuterated solvent (methanol-d_4 or D_2O). The host compound (1.525 equiv. corresponding to the guest) was dissolved in 0.61 ml of the same solvent, and the resulting solution was added in increasing volumes from 0–5 equiv. to the guest solution in 10 NMR tubes. Owing to its strong hygroscopicity, the tetrabutylammonium phosphonate solution contained ca 0.3–0.6% of water. Volume and concentration changes were taken into account during analysis. The association constants were calculated by non-linear regression methods.[9]

General protocol for the Job plots. Equimolar solutions (10 mmol in 10 ml, ca. 10 μM) of trication and trisphosphonate were prepared and mixed in various amounts. ^{1}H NMR spectra of the mixtures were recorded, and the chemical shifts were analysed by Job's method modified for NMR results.[8]

Acknowledgements

M.G. thanks the Land Nordrhein-Westfalen for a Lise-Meitner-Habilitationsstipendium.

REFERENCES

1. (a) Conn MM, Rebek J. *Chem. Rev.* 1997; **97**: 1647–1668; (b) Heinz T, Rebek J. *Nature (London)* 1998; **394**: 764–767; (c) Martin T, Obst U, Rebek J. *Science* 1998; **281**: 1842–1845; (d) Mammen M, Simanek EE, Whitesides GM. *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 RH, Verboom W, Reinhoudt DN. *J. Org. Chem.* 1996; **61**: 4282–4288; (g) Mogck O, Böhmer V, Vogt W. *Tetrahedron* 1996; **52**: 8489–8496; (h) Sessler JL, Wang R. *J. Am. Chem. Soc.* 1996; **118**: 9808–9809; (i) Prins LJ, Huskens J, de Jong F, Timmermann P, Reinhoudt DN. *Nature (London)* 1999; **398**: 498–502.
2. (a) Wyler R, de Mendoza J, Rebek J. *Angew. Int. Ed. Engl.* 1993; **32**: 1699–1700; (b) Branda N, Wyler R, Rebek J. *Science* 1994; **263**: 1267–1268; (c) Wyler R, de Mendoza J, Rebek J. *Angew. Chem., Int. Ed. Engl.* 1993; **32**: 1699–1700; (d) Branda N, Wyler R, Rebek J. *Science* 1994; **263**: 1267–1268.
3. (a) Zhao S, Luong JHT. *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 MT, Kardish KM. *J. Phys. Chem.* 1994; **98**: 1282–1287; (d) Venema F, Rowan AE, Nolte RJM. *J. Am. Chem. Soc.* 1996; **118**: 257–258.
4. (a) Lehn JM. *Angew. Chem. Int. Ed. Engl.* 1990; **102**: 1347–1360; (b) Lee J, Schwabacher AW. *J. Am. Chem. Soc.* 1994; **116**: 8382–8383; (c) Klüfers P, Schuhmacher J. *Angew. Chem. Int. Ed. Engl.* 1994; **33**: 1863–1865; (d) Saalfrank RW, 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; (e) Takeda N, Umemoto K, Yamaguchi K, Fujita M. *Nature (London)* 1999; **398**: 794–796; (f) Olenyuk B, Whiteford JA, Fechtenkötter A, Stang PJ. *Nature* (London) 1999; **398**: 796–798.
5. Lee SB, Hong J-I. *Tetrahedron Lett.* 1996; **37**: 8501–8504.
6. Schrader T. *J. Org. Chem.* 1998; **63**: 264–272.
7. (a) Kraft A, Fröhlich R. *Chem. Commun.* 1998; 1085–1086; (b) Bowen T, Planalp RP, Brechbiel MW. *Bioorg. Med. Chem. Lett.* 1996; **6**: 807–810; (c) Kraft A. *J. Chem. Soc., Perkin Trans. I* 1999; 705–714; (c) Tinant B, Dupont-Fenfau J, Declercq J-P, Podlaha J, Exner O. *Collect. Czech Chem. Commun.* 1989; **54**: 3245–3251; (d) Boeré RT, Klassen V, Wolmershäuser G. *J. Chem. Soc., Dalton Trans.* 1998; 4147–4154.
8. (a) Job P. *C. R. Acad. Sci.* 1925; **180**: 928; (b) Blanda MT, Horner JH, Newcomb M. *J. Org. Chem.* 1989; **54**: 4626–4636.
9. (a) Schneider HJ, Kramer R, Simova S, Schneider U. *J. Am. Chem. Soc.* 1988; **110**: 6442; (b) Wilcox CS. In *Frontiers in Supramolecular Chemistry and Photochemistry*, Schneider, H-J, Dürr H. (eds). VCH: Weinheim, 1991; 123; (c) MacComber RS. *J. Chem. Educ.* 1992; **69**: 375–378.
10. (a) Insight II, version 98.0 MSI: San Diego, CA, 1999; (b) Mackay DH, Cross AJ, Hagler AT. In *Prediction of Protein Structure and the Principles of Protein Conformation*, Fasman GD. (ed). Plenum Press: New York, 1989; 317–358.
11. Schneider H-J, Schiestel T, Zimmermann P. *J. Am. Chem. Soc.* 1992; **114**: 7698–7703.
12. (a) Connolly ML. *Science* 1983; **221**: 709; (b) Connolly ML. *J. Appl. Crystallogr.* 1983; **16**: 548.

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