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Ion Pair Driven Self-Assembly of a Flexible Bis-Zwitterion in Polar Solution: Formation of Discrete Nanometer-Sized Cyclic Dimers

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The reversible self-association of individual molecules can lead to the formation of complex macroscopic assemblies with new and interesting properties.[1] For example, hydrogen bond-based self-assembly of self-complementary DDAA binding motifs[2] can lead to supramolecular polymers.[3,4] But the use of H-bonds limits the self-assembly to organic solvents. Only in addition with π-stacking[5] or metal−ligand[6] interactions is aggregation in even more polar solvents possible. There are very few reports for controlled self-assembly in aqueous solvents solely based on electrostatic interactions (H-bonds and ion pairs), in most cases limited to the heterodimerization of rather rigid molecules derived from calixarenes or cyclodextrins.[7] We present here a fully flexible self-complementary bis-zwitterion **1** that forms discrete nanometer-sized cyclic dimers in DMSO−water mixtures.

We could recently show that a guanidiniocarbonyl pyrrole carboxylate zwitterion forms extremely stable dimers even in water based on intermolecular ion pair formation.[8] Linking two such zwitterions via a spacer provides self-complementary bis-zwitterions capable, in principle, of both intra- and intermolecular self-assembly, depending on the nature of the spacer.[9] For the first example **1**, we chose a flexible and hydrophilic triethylene glycol chain as spacer. δ-Aminocaproic acid methyl ester **3** was thus attached to the pyrrole benzyl ester **2** via activation of the guanidino group by triflic anhydride (Scheme 1).[10] After hydrolysis of the methyl ester group in **4** the resulting free acid **5** was reacted with 0.5 equiv of diamino triethylene glycol **6**. Deprotection of **7** first with H_2/Pd and then TFA provided, after pH adjustment, the flexible bis-zwitterion **1** in 89% yield.

The self-association properties of **1** were first investigated by NMR dilution studies[11] in DMSO-d_6 in the concentration range of 0.5−50 mM (see Supporting Information [SI]). The NMR data revealed a concentration-dependent equilibrium of two different species in solution. However, in both species a fully associated ion pair is present according to the observed chemical shifts. The same results were also found for DMSO−water mixtures (DMSO-d_6/D_2O mixtures). To obtain more information about these two species, their corresponding hydrodynamic radii r_H were determined using DOSY experiments in DMSO-d_6.[12] The species predominating in dilute solutions (1 mM) has a similar molecular dimension (r_H = 0.73 nm) as the protected monomer **7**, which due to the lack of charges cannot self-assemble (r_H = 1.03 nm). The species present at higher concentrations (30 mM) is twice as large (r_H = 2.0 nm) pointing to a monomer/dimer equilibrium as also supported by MS experiments (Figure 1). Distinct signals for the monomer and a dimer (but no larger aggregates) were detected both in FAB and ESI-MS experiments. The triethyleneglycol spacer in **1** is long and flexible enough to allow an intramolecular ion pairing between the two zwitterionic moieties even in the monomer. With increasing concentration of **1**, the monomeric loops then dimerizes to form discrete spherical particles. The formation of such structures is supported by molecular mechanics calculations (see SI).

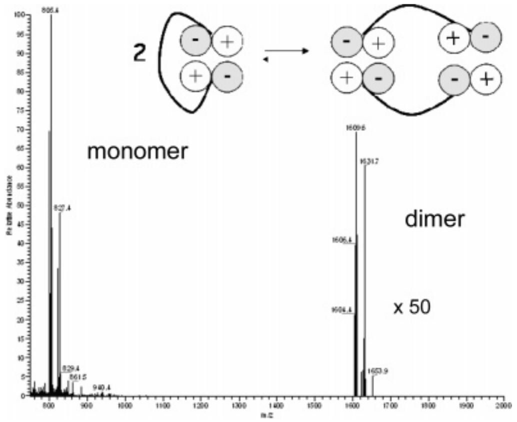
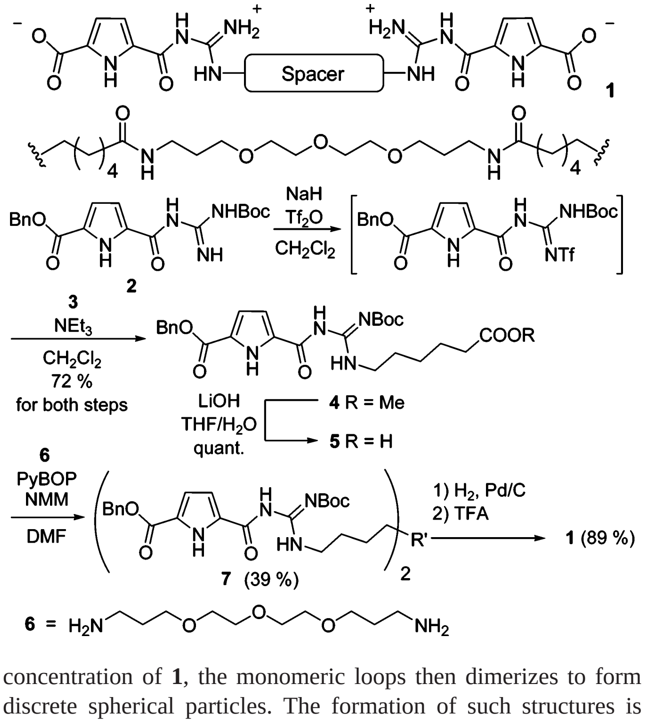


Figure 1. Schematic representation of the monomer/dimer equilibrium of **1** and the FAB-MS showing the coexistence of monomer and dimer in solution (c < 10 mM in DMSO).

Scheme 1. Flexible Bis-Zwitterion **1** and Its Synthesis



The formation of discrete particles of nanometer-sized dimension by self-assembly of **1** in DMSO could also be confirmed by dynamic light scattering (DLS) and small-angle neutron scattering studies (SANS). DLS shows the existence of a single diffusion mode corresponding to particles with a hydrodynamic radius of

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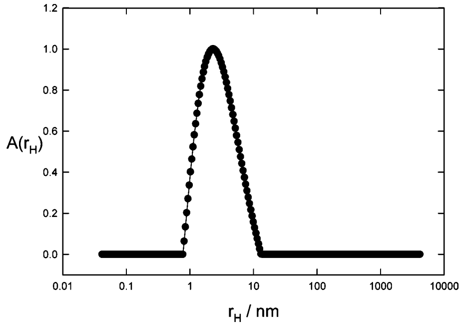

Figure 2. Intensity weighted distribution of hydrodynamic radii resulting from CONTIN analysis of the DLS data measured at a scattering angle of 90° ($c = 50$ mM in DMSO).

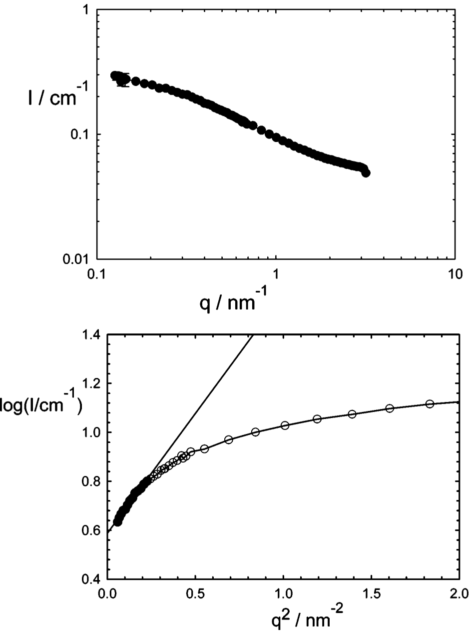

Figure 3. Scattering curve (top) and Guinier plot (bottom) resulting from the SANS experiments ($c = 45$ mM in DMSO).

$r_H \approx 3.0$ (± 0.1) nm at $c = 50$ mM in DMSO, in reasonably good agreement with the DOSY NMR experiments.[13] The size distribution as resulting from inverse Laplace transformation of the autocorrelation function is shown in Figure 2 and is characterized by a standard deviation of 50% (relative peak width).[14] Further information about particle size and shape of these aggregates were obtained from SANS measurements (Figure 3).[15] The linearity of the Guinier plot is consistent with a spherical particle shape. The radius of gyration extracted from Guinier extrapolation in the appropriate range of the scattering curve is $r_G = 2.9$ (± 0.2) nm, once more in good agreement with both the NMR and the DLS data.[16] The ratio of the average radius of gyration (from SANS) and hydrodynamic radius (from DLS) of is $r_G/r_H \approx 1.0$, which may point to a "hollow sphere" type structure.[17] This is in accordance with the expected structure for dimeric **1**. The "inner part" of the dimers only consists of the flexible polyether chains and most likely also contains a significant number of solvent molecules.

In conclusion, the fully flexible bis-zwitterion **1** presented here is, to the best of our knowledge, the first example for a homodimerization solely based on a H-bond-enforced ion pair formation which leads to stable nanometer-sized discrete particles in DMSO−water mixtures even without any structural bias within the molecule. We are currently exploring how the aggregation behavior of such bis-zwitterions (e.g., dimers vs oligomers and polymers) can be deliberately controlled by variation of the spacer between the two zwitterionic moieties.

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Supporting Information Available: Details on the synthesis, the NMR, DOSY, ESI-MS, DLS, and SANS experiments and the molecular mechanics calculations.

References

(1) (a) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, 1995. (b) Bowden, N. B.; Weck, M.; M.; Choi, I. S.; Whitesides, G. M. *Acc. Chem. Res.* **2001**, *34*, 231−238. (c) Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4763−4768. (d) Whitesides, G. M.; Boncheva, M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4769−4774.
(2) (a) Zimmerman, S. C.; Corbin, P. S. *Struct. Bonding* **2000**, *96*, 63−94. (b) Lüning, U.; Kuhl, C.; Uphoff, A. *Eur. J. Org. Chem.* **2002**, 4063−4070. (c) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382−2426. (d) Sijbesma, R. P.; Meijer, E. W. *Chem. Commun.* **2003**, 5−16.
(3) Reviews on supramolecular polymers: (a) Sherrington, D. C.; Taskinen, K. A. *Chem. Soc. Rev.* **2001**, *30*, 83−93. (b) Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W.; Sijbesma, R. P. *Chem. Rev.* **2001**, *101*, 4071−4097. (c) Schmuck, C.; Wienand, W. *Angew. Chem., Int. Ed.* **2001**, *40*, 4363−4369. (d) Lehn, J.-M. *Polym. Int.* **2002**, *51*, 825−839.
(4) Sijbesma, R. P.; Beijer, F. H.; Brunsveld, L.; Folmer, B. J. B.; Hirschberg, J. H. K. K.; Lange, R. F. M.; Lowe, J. K. L.; Meijer, E. W. *Science* **1997**, *278*, 1601−1604.
(5) (a) Moore, J. S. *Acc. Chem. Res.* **1997**, *30*, 402−413. (b) Wuerthner, F.; Yao, S.; Beginn, U. *Angew. Chem. Int. Ed.* **2003**, *42*, 3247−3250. (c) Arnaud, A.; Belleney, J.; Boué, F.; Bouteiller, L.; Carrot, G.; Wintgens, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 1718−1721.
(6) Selected references: (a) Seidel, S. R.; Stang, P. J. *Acc. Chem. Res.* **2002**, *35*, 972−983. (b) Cotton, F. A.; Lin, C.; Murillo, C. A. *Acc. Chem. Res.* **2001**, *34*, 759−771. (c) Caulder, D. L.; Raymond, K. N. *Acc. Chem. Res.* **1999**, *32*, 975−982. (d) Fujita, M. *Chem. Soc. Rev.* **1998**, *27*, 417−425.
(7) See for example: (a) Grawe, T.; Schrader, T.; Zadmard, R.; Kraft, A. *J. Org. Chem.* **2002**, *67*, 3755−3763. (b) Corbellini, F.; Flammengo, R.; Timmerman, P.; Crego-Calama, M.; Veslius, K.; Heck, A. J. R.; Luyten, I.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2002**, *124*, 6569−6575. (c) Fiammengo, R.; Timmerman, P.; de Jong, F.; Reinhoudt, D. N. *Chem. Commun.* **2000**, 2313−2314. (d) Hamilin, B.; Jullien, L.; Derouet, C.; Hervé du Penhoat, C.; Berthault, P. *J. Am. Chem. Soc.* **1998**, *120*, 8438−8447. (e) Bok Lee, S.; Hong, J.-I. *Tetrahedron Lett.* **1996**, *37*, 8501−8504.
(8) (a) Schmuck, C.; Wienand, W. *J. Am. Chem. Soc*. **2003**, *125*, 452−459. (b) Schlund, S.; Schmuck, C.; Engels B. *J. Am. Chem. Soc.* **2005**, *127*, 11115−11124.
(9) (a) ten Cate, A. T.; Kooijman, H.; Spek, A. L.; Sijbesma, R. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2004**, *126*, 3801−3808. (b) Gibson, H. W.; Yamaguchi, N.; Jones, J. W. *J. Am.* Chem. Soc. **2003**, *125*, 3522−3533.
(10) Schmuck, C.; Bickert, V. *Org. Lett.* **2003**, *5*, 4579−4581.
(11) Connors, K. A. Binding Constants; Wiley: New York, 1987.
(12) (a) Cohen, Y.; Avram, L.; Frish, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 520−554. (b) Johnson, C. S., Jr. *Prog. Nucl. Magn. Reson.* **1999**, *34*, 203−256.
(13) DLS cannot resolve monomers and dimers from small amounts of even larger oligomers probably also present at this high concentration. They all overlap in one averaged size distribution, giving rise to the slightly larger r_H value compared to the DOSY NMR experiments.
(14) Provencher, S. W. *Comput. Phys. Commun.* **1982**, *27*, 229−242.
(15) Lindner, P.; Zemb, T., Eds. *Neutron, X-rays and Light: Scattering Methods Applied to Soft Condensed Matter*; Elsevier: New York, 2002.
(16) A closer analysis of the SANS data showed that in addition to monomers and dimers a small amount of larger aggregates with a maximum diameter up to 11 nm is also present in solution under these conditions.
(17) Even though for such small particles (with size distribution) this analysis is accompanied by a relatively large error, coil-like or rodlike aggregate shapes can clearly be excluded. However, a homogeneous sphere structure might also be in accordance with experimental data within the experimental error range.

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