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Novel water soluble molecular clips. Towards nanostructures with controlled shape

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A novel water soluble clip, which forms 'razor blade-like' aggregates in water, is described.

Molecular structures and assemblies of molecules with dimensions in the nanometer range are currently of great interest.1 Practical application of these systems in various areas i.e. catalysis, material science and sensor development can be expected.2 Molecular self-assembly is recognized as being a useful synthetic strategy for the construction of nano-sized structures.3 Control over the shape and size of the structures that are formed remains a challenge.4 Relatively few self-assembly processes are known to lead to structures with finite shapes.5 Vesicles, and some of the aggregates formed from melamine and cyanuric acid are recognized examples.5 Here we report the self-assembling behaviour of novel water soluble clips, one of which was shown to form well defined 'razor blade-like' nanostructures when dispersed in water.

Clip molecules 4, 6 and 8 were synthesised according to standard procedures and procedures reported previously (Scheme 1).6f

Compound 4 was found to form dimers when dissolved in water at a concentration >2 mmol dm–3.1H NMR studies demonstrated that the cleft of one clip molecule was filled by the side wall of another molecule and vice versa. This dimerization process is caused by hydrophobic effects and favourable π–π stacking interactions. From 1H NMR dilution experiments the self association constant of clip 4 was calculated to be $K_s = 300$ dm3 mol–1. The 1H NMR experiments also suggested that the pyridine part of 4 was not involved in the association process. Clip 4 did not show any additional aggregation behaviour other than self-association.

Clip molecule 6 contains a larger hydrophobic cleft than 4 and was expected to form stronger dimeric complexes.1H NMR dilution studies (0.1–3 mmol dm–3 of 6) confirmed that the self-association constant of clip 6 was $K_s > 5000$ dm3 mol–1. It was surprising, however, that not only the 1H NMR signals of the protons of the naphthalene side walls of 6 shifted upon dilution but also the pyridine protons at the convex side of the glycoluril framework. This suggests that in solution two self-association geometries are possible: a 'head-to-head' and a 'head-to-tail' geometry (Fig. 1). In the latter case a favourable overlap between the electron rich 1,4-dimethoxynaphthalene side wall of one molecule and the electron poor pyridinium group of the other can be envisaged. In the other case self-association is based purely upon hydrophobic effects. When more concentrated samples (1–3 mmol dm–3) of 6 were allowed to stand for several hours, a pearly, milk-like dispersion was formed gradually. This suggested that large aggregates had been formed in solution. The addition of acetone or methanol to the suspension caused complete disaggregation and a clear solution was obtained which contained monomeric species only (1H NMR). Scanning electron microscopy showed that the surfaces of the superstructures were also slightly convex. According to freeze fracture electron microscopy [Fig. 2(c)] the 'razor blades' were constructed from a limited number of layers (ca. 50). Electron diffraction experiments proved that the aggregates were not crystals. Samples of the pearly suspension were investigated by powder diffraction measurements, which revealed a strong reflection corresponding to a repeating distance of 16.8 Å. Based on these results we propose that the formation of the 'razor blades' of 6 starts from head-to-head dimers, which act as initiators for further growth. Monomers can attach themselves

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\begin{align*}
\text{II, IV} & \quad \text{III, IV} \\
\end{align*}
\]

Scheme 1. Reagents and conditions: i, 1,4-Dimethoxybenzene, TFA, Ac2O, 85%; ii, pyridine, THF, CH2Cl2, 75%; iii, 1,4-dimethoxynaphthalene, TFA, Ac2O, 70%; iv, pyridine, THF, CH2Cl2, 50%; v, KOH, DMSO, 2,3-bis-(bromomethyl)napthalene, 20%

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onto the pyridinium units in a head-to-tail fashion, eventually forming a multilayer structure (Fig. 1) of which the outside

![Fig. 1 Computer generated picture showing the middle section of a 'razor blade-like' aggregate of 6. 'Head-to-tail' dimers A (repeating unit 17 Å). Central layer of 'head-to-head' dimers B (thickness 32 Å).](image)

surface is hydrophilic on all sides. Molecular modelling suggested a layer thickness of 17 Å, which is in good agreement with the results from the X-ray powder diffraction experiment.

The effect of guest molecules upon the aggregation process was then examined in order to investigate further the nature of the self-association of 6. 1H NMR binding studies were performed in water using 4-nitrophenol, 1,3-dihydroxybenzene and caffeine as guests. The first two molecules were surprisingly not bound in the cavity of 6, probably because of the strength of the dimeric complexes of this host. Caffeine was found to form quite strong complexes ($K_d = 8400 \text{ dm}^3 \text{ mol}^{-1}$) with clip 6 in water. 1H NMR spectroscopy showed, however, that this substrate binds between adjacent clip molecules and not in the cavities of the clips themselves. The addition of caffeine to 6 (1:1) resulted in a change in the shape of the aggregates: in place of 'razor blade-like' structures, spherical aggregates were formed. Powder diffraction revealed that approximately the same repeating distance, 17.1 Å, was present in these spheres. This suggested that they were still composed of head-to-tail type of dimers. The presence of the caffeine molecules between adjacent clip molecules apparently induces a larger curvature and hence a more bent, i.e. a sphere shaped, nanostructure (diameter 80–300 nm).

1H NMR experiments revealed that the oxidised form of riboflavine can also be bound in aggregates of 6. The flat structure of riboflavine can be changed reversibly into a bent structure with an angle of ca. 30°, by reducing the molecule with Na2S2O4. Dispersing 6 in the presence of the oxidised form of riboflavine, yielded spherical aggregates, comparable with those induced by caffeine [Fig. 2(d)]. The reduced form of riboflavine, however, induced the formation of infinite multilayer structures (not shown). Currently it has not been possible to modify the system in a way such that it can be switched reversibly between the two states.

Clip molecule 8, which has two 2-pyridyl groups at the convex side of the glycoluril framework, is water soluble after protonation of the pyridine groups. The aggregation behaviour of 8 was also studied by electron microscopy. Transmission and scanning electron micrographs showed that at pH = 1 long fibres were formed from 8 with lengths up to 10 μm. The thickness of these fibres varied from approximately 65 Å, which is twice the size of a dimer, to approximately 330 Å (bundle of 5 fibres). The interaction between the naphthalene moieties and the protonated pyridine groups in molecules of 8 is expected to be relatively small due to sterical reasons. Clip molecules 8 are expected therefore to form only 'head-to-head' type of dimers as found in the X-ray structure of the diphenyl glycoluril analogue.7 The fact that 8 has only one recognition site (the cavity) and not two, leads to simple fibres instead of 'razor blade-like' structures as in the case of 6.

In conclusion, it has been shown that rigid clip molecules with water soluble pyridyl functions can form interesting nanometer-sized aggregates, which can be modified by the addition of guest molecules. The 'razor blade-like' structures, which are obtained from clip molecule 6, are of special interest. They can be considered as being a first step toward the construction of aggregates which have controlled shape and dimension.

Footnote

† All new compounds were fully characterised by 1H NMR, FABMS and elemental analysis. Selected data for 4: 1H NMR (D2O), δ 8.74 (d, 4 H, PyrH, J 5.8 Hz), 8.50 (t, 2 H, PyrH, J 7.0 Hz), 8.00 (t, 4 H, PyrH, J 5.8 Hz), 7.74 (d, 8 H, ArH), 6.19 (s, 4 H, ArH), 5.59 (s, 4 H, ArCH2Py), 5.22 and 3.74 (2d, 8 H, NCH2Ar, J 16.0 Hz), 3.54 (s, 12 H, OMe); FABMS m/z 881 and 883 [M − Br]+. For 6: 1H NMR (CDCl3) δ 8.94 (d, 4 H, PyrH, J 5.60 Hz), 8.66 (t, 2 H, PyrH, J 8.00 Hz), 8.14 (t, 4 H, PyrH, J 5.80 Hz), 7.58 (m, 8 H, ArH), 7.50 and 6.79 (2m, 8 H, ArH), 5.80 (s, 4 H, ArCH2Py), 5.64 and 4.32 (2d, 8 H, NHCOCH3R, J 15.60 Hz), 3.95 (s, 12 H, OMe); FABMS m/z 902 [M − 2Br]+. For 8: 1H NMR (CDCl3) δ 8.55 (d, 2
H, PyrH, J 5.73 Hz), 7.78–6.89 (m, 14 H, ArH and PyrH), 7.67 (s, 4 H, ArH), 5.05 and 4.24 (2d, 8 H, NCH/HA, J 16.4 Hz); FABMS m/z 601 [M + H]⁺.

References

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