Novel water soluble molecular clips. Towards nanostructures with controlled shape

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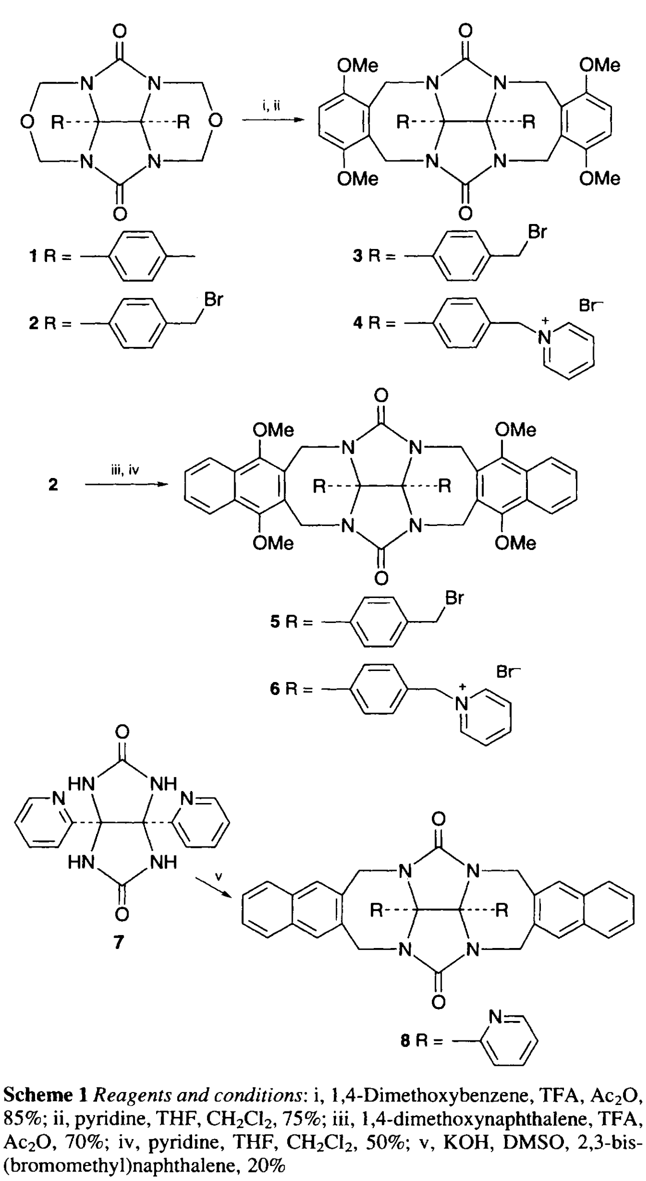
A novel water soluble clip, which forms 'razor blade-like' aggregates in water, is described.

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. 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).[6]†

Compound **4** was found to form dimers when dissolved in water at a concentration >2 mmol dm^{-3}. ^{1}H 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 ^{1}H NMR dilution experiments the self association constant of clip **4** was calculated to be K_s = 300 dm^3 mol^{-1}. The ^{1}H 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. ^{1}H NMR dilution studies (0.1–3 mmol dm^{-3} of **6**) confirmed that the self-association constant of clip **6** was K_s > 5000 dm^3 mol^{-1}. It was surprising, however, that not only the ^{1}H 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 (^{1}H NMR). Investigation of the pearly dispersion by electron microscopy [platinum shadowing technique, Fig. 2(*a*)] revealed the presence of well defined 'razor blade-like' aggregates which were stacked back-to-back to give long chains [Fig. 2(*b*)]. The 'razor blades' all had approximately the same proportions (1.2 × 8 μm) and rounded corners, with the same curvature. 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



Scheme 1 *Reagents and conditions*: i, 1,4-Dimethoxybenzene, TFA, Ac$_2$O, 85%; ii, pyridine, THF, CH$_2$Cl$_2$, 75%; iii, 1,4-dimethoxynaphthalene, TFA, Ac$_2$O, 70%; iv, pyridine, THF, CH$_2$Cl$_2$, 50%; v, KOH, DMSO, 2,3-bis-(bromomethyl)naphthalene, 20%

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

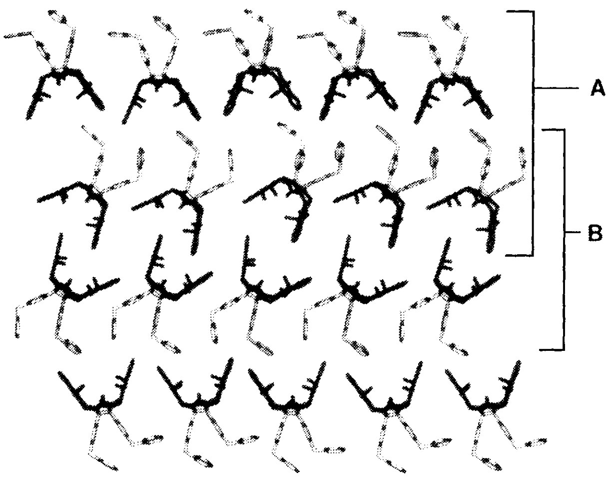


Fig. 1 Computer generated picture showing the middle section of a 'razor blade-like' aggregate of **6**. 'Head-to-tail' dimers A (repeating unit 17 Å). Central layer of 'head-to-head' dimers B (thickness 32 Å).

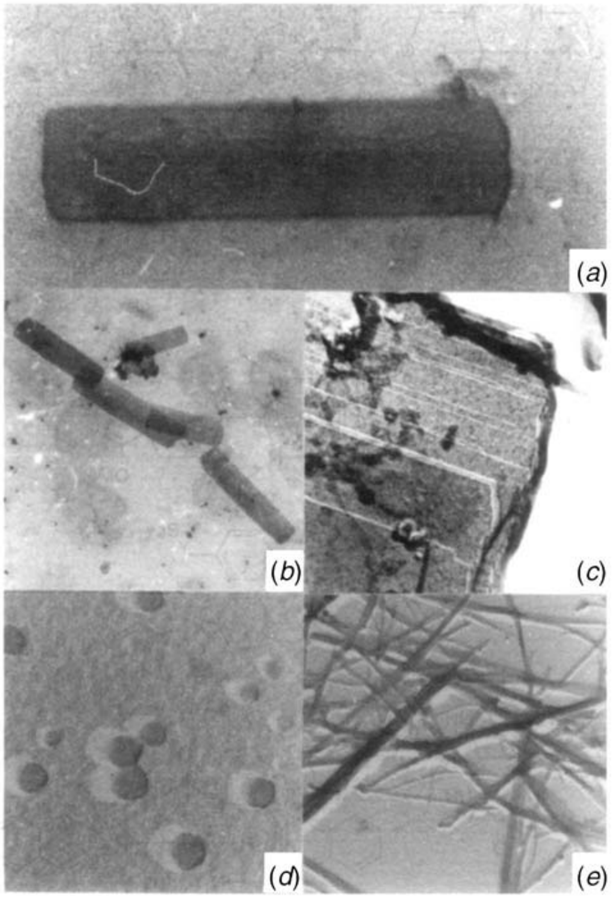


Fig. 2 Electron microscopic pictures of 'razor blade-like' aggregates formed in water by clip **6**: platinum shadowing technique, for (*a*) 1 cm = 0.8 μm, for (*b*) 1 cm = 3.2 μm. Freeze fracture electron micrograph of a 'razor blade-like' aggregate (*c*) 1 cm = 0.08 μm. Sphere-like structures formed from **6** by the addition of the oxidized form of riboflavine, platinum shadowing technique, (*d*) 1 cm = 0.16 μm; a similar structure is generated in the presence of caffeine. Fibres formed from **8** in water (*e*) pH = 1, platinum shadowing technique, 1 cm = 0.16 μm.

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**. ^{1}H 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_a = 8400 dm^3 mol^{-1}) with clip **6** in water. ^{1}H 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).

^{1}H 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 $Na_2S_2O_4$. 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 steric 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 ^{1}H NMR, FABMS and elemental analysis. *Selected data* for **4**: ^{1}H NMR (D_2O) 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), 7.24 (q, 8 H, ArH), 6.19 (s, 4 H, ArH), 5.59 (s, 4 H, ArCH_2Pyr), 5.22 and 3.74 (2d, 8 H, NC*H*HAr, *J* 16.0 Hz), 3.54 (s, 12 H, OMe); FABMS *m*/*z* 881 and 883 [M − Br]$^+$, 723 [M − 2Br − Pyr]$^+$. For **6**: ^{1}H NMR (D_2O) 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* 5.6 Hz), 7.58 (m, 8 H, ArH), 7.50 and 6.79 (2m, 8 H, ArH), 5.89 (s, 4 H, ArCH_2Pyr), 5.64 and 4.32 (2d, 8 H, NHC*H*HAr, *J* 15.60 Hz), 3.95 (s, 12 H, OMe); FABMS *m*/*z* 902 [M − 2Br]$^+$. For **8**: ^{1}H NMR ($CDCl_3$) 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, NC*H*HAr, *J* 16.4 Hz); FABMS *m/z* 601 $[M + H]^+$.

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