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Self-Associating Cyclocholates

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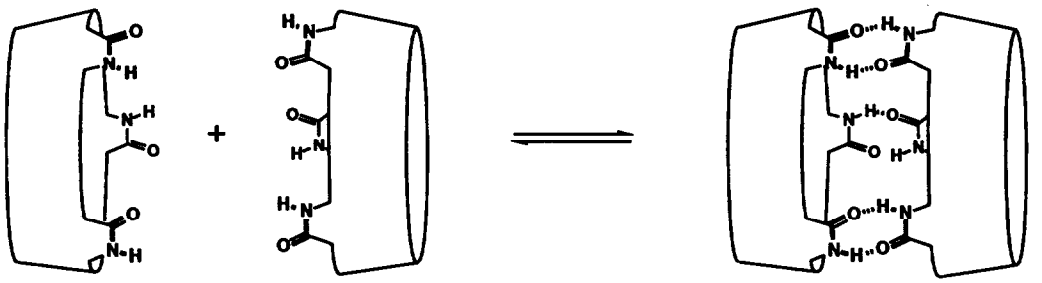
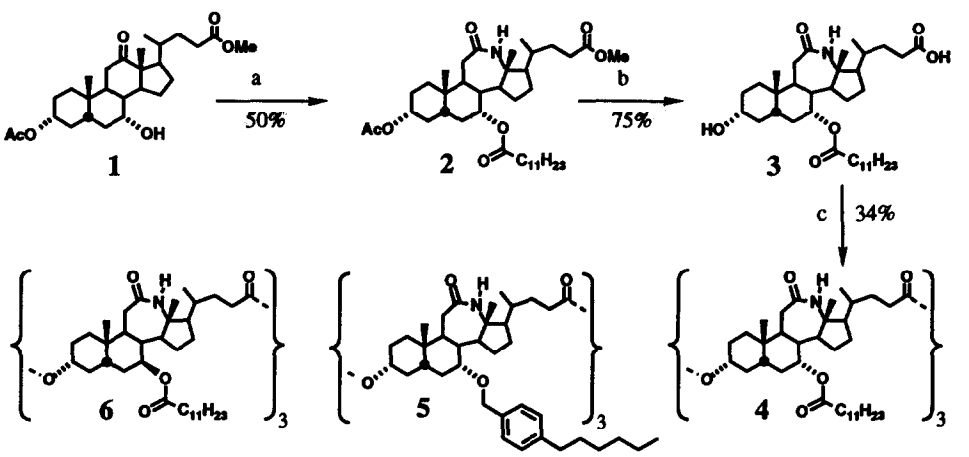
Abstract: Self-complementary steroidal triamides have been prepared and their reversible self-assembly into molecular cylinders demonstrated.

While the isolated hydrogen bond is an instrinsically weak interaction, cooperative formation of a series of hydrogen bonds can be a powerful driving force in molecular recognition, well known examples being the assembly of proteins and DNA in aqueous solution.[1] Multiple hydrogen bond formation has been the basis of numerous relatively low molecular weight synthetic host-guest systems in organic solution,[2] but only recently has the concept been extended to the assembly of larger well-defined supramolecular aggregates.[3] We report here on the synthesis and self-recognition properties of ring-shaped molecules designed to mutually hydrogen-bond in organic solution, forming short cylinders:



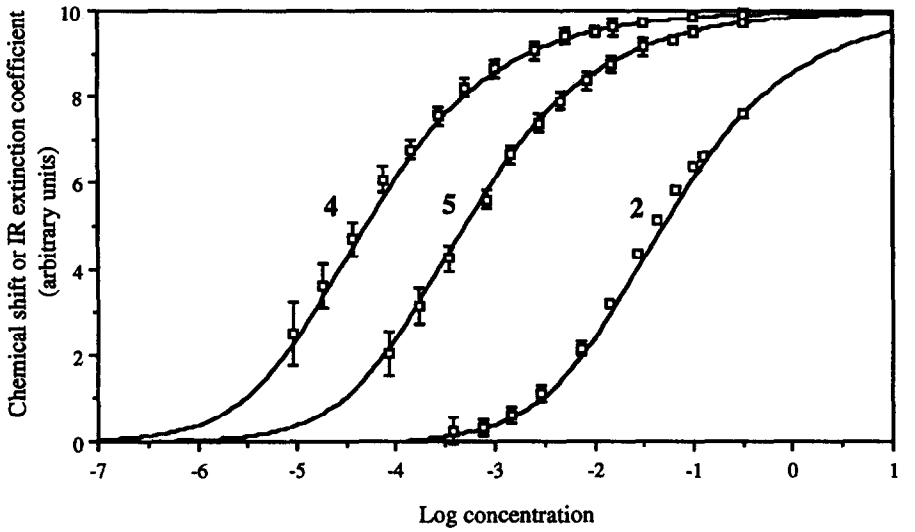
'Cyclocholates', macrolides prepared by head to tail condensation of cholic acid derivatives,[4,5] were used as the basic building blocks. These were rendered self-sticky by the introduction of simple cis-amides as complementary hydrogen bond donor/acceptor sites on one rim of the macrocycle.[6]

Three macrocycles **4**, **5**, and **6** (Scheme 1) differing only in the type and orientation of solubilizing group were prepared by similar routes. The synthesis of **4** is given as an example. Starting from readily available ketone **1**,[7] esterification of the free hydroxyl group with dodecanoic acid, followed by Beckmann ring expansion[8] provided amide **2**. Selective hydrolysis of the terminal ester protecting groups, and then macrolactonization of hydroxy acid **3** under modified Yamaguchi conditions[9] afforded, after chromatography, a moderate yield of cyclotrimer **4**.[10] The cyclotrimer was the main product (ca. 50% as judged by ^{1}H NMR of the crude reaction mixtures) in the synthesis of all three macrolides **4** (34% isolated), **5** (40%) and **6** (31%). Decreasing amounts of higher oligomers up to cyclooctamer were detectable by FAB mass spectrometry, but were not isolated.



Scheme 1. (a) (i) Dodecanoic acid, 2,6-dichlorobenzoyl chloride, DMAP (ii) $NH_2OH.HCl$, NaOAc (iii) p-TsCl, Py (b) aq NaOH (c) 2,6-dichlorobenzoyl chloride, DMAP, 4Å sieves, 2 mM in CH_2Cl_2 at RT.

Equilibrium constants for dimerization of amides **2**, **4**, **5** and **6** were determined by ^1H NMR and/or FT IR spectra over the concentration range 5×10^{-6} to ca. 0.5 M in dry carbon tetrachloride at 23–25°C. Experimental data along with best-fit theoretical curves are given below for **2**, **4**, and **5**:



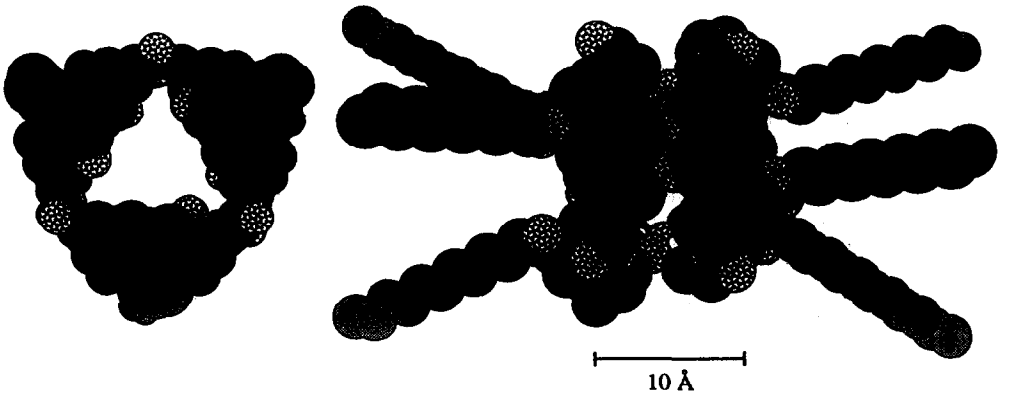
In the determination of equilibrium constants by the NMR method, the position of the fast exchange averaged NH resonance as a function of concentration provided the most accurate results, due to the large difference in chemical shift of this resonance between the free and hydrogen bonded forms ($\Delta\delta = 2.3$ ppm). IR equilibrium constants were derived from the relative and absolute intensities of bands due to monomeric NH stretch (sharp, 3425 cm^{-1}) and dimeric NH stretch (broad multiple absorbances around 3200 cm^{-1}) as a function of concentration.

The monomeric reference compound **2** dimerizes quite weakly, $K = 18$ l mol^{-1}, compared to a simple seven membered amide such as caprolactam, $K = 100$ l mol^{-1}.[11] Molecular models suggest that this is probably due to steric hindrance around the NH group. Triamides **4** and **6** self-associate strongly in CCl_4, with $K = 3 (\pm 2) \times 10^4$ and $2 (\pm 1) \times 10^4$ l mol^{-1} respectively. The binding in these cases was most accurately determined by IR, since in the ^{1}H NMR spectra the NH resonances were very broad due to intermediate exchange on the NMR timescale.[12] Triamide **5** dimerized somewhat less strongly with $K = 2 (\pm 1) \times 10^3$ l mol^{-1} as determined by both IR and NMR.

A qualitative study of the self-association of **6** by molecular mechanics[13] suggested that a face to face arrangement is the most likely geometry for the dimer, since only in this orientation can enough hydrogen bonds be formed (between four and six) to account for the stability of the complex. It was apparent however that the relative orientation of the amide groups was less than ideal. Energy minimization of monomer **2** shows that the amide group does not lie in the plane of the steroid, but is angled downwards (into the page as drawn) by about 20°. Thus when two cyclocholate rings come together the steroid subunits have to rotate somewhat to produce more nearly planar amide-amide bridges or form distorted hydrogen bonds, or both. It seems that despite the flexible nature of cyclocholate rings, the strain induced in this process more than offsets the advantage of forming all six possible hydrogen bonds. Indeed the IR spectra of fully associated triamides **4**, **5** and **6** showed a monomer-like NH stretch at 3430 cm^{-1}, in addition to the more intense dimer bands, implying that there are one or more unbound NHs or 'free ends' present in the dimeric complex. An alternative explanation for this apparent monomer peak was considered; namely that instead of simple dimerization, non-specific oligomerization was occurring, producing a broad distribution of species containing free ends.[3d,14] This possibility was eliminated by direct measurement of molecular weight in solution using vapour pressure osmometry. At a concentration of 38 mM the apparent molecular weight of triamide **4** was 3600 (± 400) which is, within experimental error, that of a dimer (3510, $MW_{monomer}$ = 1755), and is very much lower than would be expected for multiple aggregation models.[15]

At present we rationalize the weaker association of benzyl-solubilized triamide **5** compared to long-chain-solubilized **4** by invoking unfavourable steric interactions among the converging and relatively bulky phenyl rings, which tend to open up the outside face, rotating the steroid subunits so as make the amide–amide bonding less favourable. A space-filling representation of a low energy conformer of **6** is given below to give an idea of the shape of these molecules.

Ulimately we hope to be able to extend the work described above to generate larger and kinetically more stable molecular containers and tubes.



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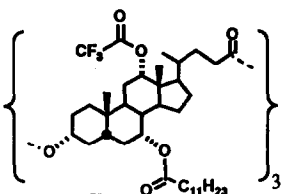
14. Indeed computer simulation of various aggregation possibilities suggested that dilution curves which are experimentally rather close to a simple dimerization curve can be generated by postulating eg a linear polymerization of cyclocholate subunits. For an early analysis of this type of problem see Saunders M.; Hyne J.B. *J. Chem. Phys.* **1958**, *29*, 1319.
15. Schrier E.E. *J. Chem. Education* **1968**, *45*, 176. Apparent molecular weight was calculated over the concentration range 3 to 38 mM by comparison with a calibration curve determined over the same concentration range with the non-associating cyclocholate **7** (MW = 2004) using a Wescor 5500 osmometer operating at 35°C. The aggregation state of **4** was also checked by freezing point depression measurements in benzene. At 6 mM **4** had an apparent molecular weight of 2460 (± 180) compared to the theoretical value of 2440 calculated from NMR and IR dilution data in benzene at 25°C. For comparison, reference **7** gave a value of 2070 (± 150) at 8 mM in benzene.



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