Supramolecular tapes formed by a catanionic cyclodextrin in water

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A β-cyclodextrin substituted with amino and carboxymethyl groups on the primary and secondary side respectively, has a positively charged primary face and a negatively charged secondary face at neutral pH, and self-assembles in water into supramolecular tapes that are 50–300 nanometres wide and up to 20 micrometres long.

'Janus' cyclodextrins are cyclodextrins with distinctly different primary and secondary faces.[1] The preparation of such cyclodextrins is not trivial since it requires synthetic differentiation of the primary and secondary sides of the cyclodextrin molecule.[2] However, several types of Janus cyclodextrins have been prepared to date, all of which show interesting self-assembling properties. The largest class of Janus cyclodextrins comprises amphiphilic molecules in which one face of the cyclodextrin has been substituted with large hydrophobic groups while the other face is substituted with polar or ionic groups, or is left unsubstituted. Many of these cyclodextrins are very hydrophobic and insoluble in water. However, recent reports describe micelles as well as bilayer vesicles composed entirely of amphiphilic cyclodextrins.[3,4] A second group of Janus cyclodextrins contains thiol or sulfide substituents exclusively on one face of the molecule, which induce assembly into monolayers on gold surfaces.[5] Yet another class contains small hydrophobic substituents on one face and polar or ionic substituents, or none, on the other face. These molecules form dimers in several solvents.[6] Finally, cyclodextrins with polar or ionic substituents on one face of the molecule (and no substituents on the other face) can form dimers in polar solvents,[7] and even specific heterodimers between ionic cyclodextrins of opposite charge in water.[8] We now report a new Janus β-cyclodextrin **3** bearing amino groups on the primary face and carboxymethyl groups on the secondary face, to give a cyclic oligo-aminoacid structure designed to assemble in water by multiple ion-pairing.

Heptakis(6-azido-6-deoxy)-β-cyclodextrin **1**[9] was reacted with sodium iodoacetate in the presence of potassium *tert*-

OR = [(OH)$_2$, (OCH$_2$COOH)$_5$]
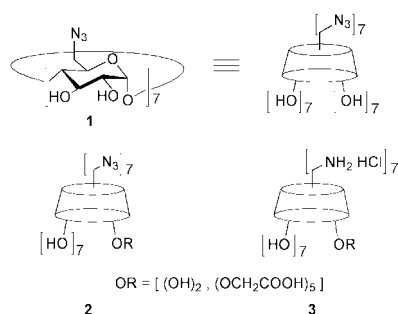
butoxide at 80 °C in DMF to yield 6-azido-6-deoxy-2-*O*-carboxymethyl-β-cyclodextrin **2**. This product was isolated by precipitation from water at pH 2. ^{1}H NMR (300 MHz, d$_6$-DMSO) showed a signal for the methylene protons of the carboxymethyl group at 4.35 ppm and separate signals for H$_1$′ at 5.15 and H$_1$ at 4.92 ppm. According to the relative integration of these ^{1}H NMR signals, a reproducible average of five carboxymethyl groups was introduced in **2**. The resolution of the NMR spectra of **2** is poor due to a combination of

aggregation and loss of molecular symmetry. Cyclodextrin **2** was then reduced to 6-amino-6-deoxy-2-*O*-carboxymethyl-β-cyclodextrin **3** by conventional phosphine reduction.[10] Product **3** was isolated by precipitation in water at pH 2 and purified by size exclusion chromatography. Despite our best efforts, the final product retained traces of phosphines. The structure of **3** (with five carboxymethyl groups on O-2) was confirmed by NMR. ^{1}H NMR (300 MHz, D$_2$O) shows a signal for the methylene protons of the carboxymethyl group at 4.28 ppm and signals for H$_1$′ at 5.07 as well as H$_1$ at 5.30 ppm. ^{13}C NMR (500 MHz, D$_2$O) shows the carbonyl and the methylene carbon of the carboxymethyl group at 174.4 and 69.1 ppm, respectively, as well as C$_2$′ at 80.0 and C$_2$ at 68.0 ppm. No shift was observed for C$_3$′ relative to C$_3$, confirming substitution at O-2 instead of O-3, as anticipated for this type of reaction at the secondary side of cyclodextrins.[2] As for **2**, the resolution of the NMR spectra of **3** is poor due to a combination of aggregation and loss of molecular symmetry.

Cyclodextrin **3** readily dissolves in 10 mM HEPES buffer (pH 7.4) upon gentle agitation at rt. The solution (0.1–1.0 mg mL^{-1}) is not completely transparent. Using transmission electron microscopy (with either uranyl acetate or phospho-tungstic acid as negative stain)[11] we observed that cyclodextrin **3** self-assembles into elongated tape-like structures (Figs. 1 and 2). The tapes are between 50 and 300 nanometres wide and up to 20 µm long, yet only several nanometres thick. They seem quite flexible, since multiple twists, bends and folds are observed. However, the tapes are also rather fragile, and readily break into smaller fragments during the preparation of samples for electron microscopy. A significant fraction of the cyclodextrin is present as amorphous aggregates. As expected, no tapes but only amorphous aggregates are observed when the pH is either reduced from 7.4 to 4, or increased from 7.4 to 10, or when 0.5 M NaCl is added to the cyclodextrin solution. At high and low pH, and also in the presence of more than 0.1 M NaCl,
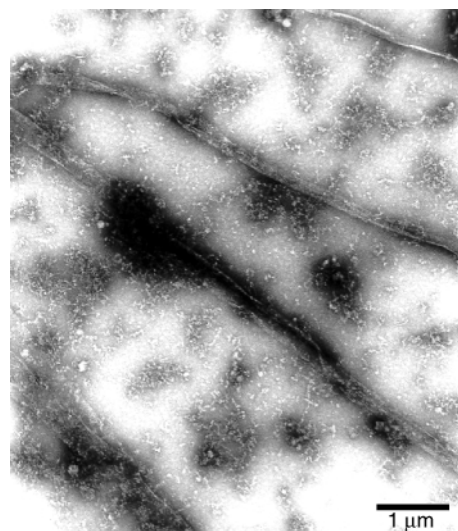

Fig. 1 Electron micrograph of cyclodextrin **3** in HEPES buffer (pH 7.4). Negative staining with 1% uranyl acetate.
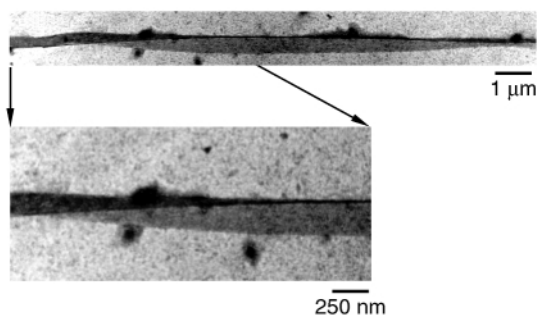
Fig. 2 Electron micrograph of cyclodextrin **3** in HEPES buffer (pH 7.4). Negative staining with 1% phosphotungstic acid.
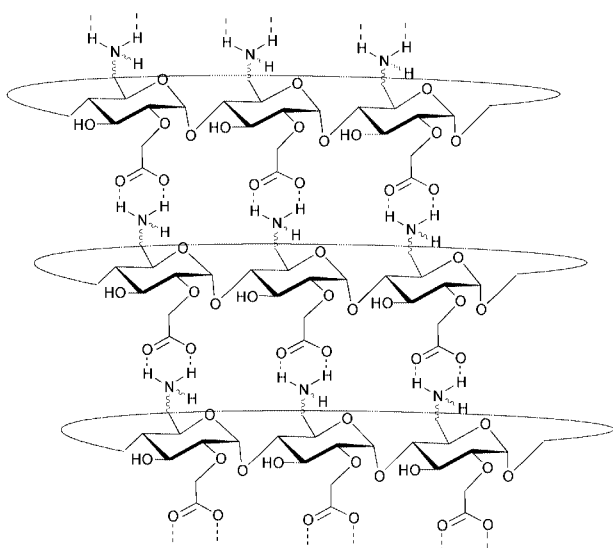

Fig. 3 Schematic illustration of the self-assembly of cyclodextrin **3**.

the solution of cyclodextrin **3** becomes completely transparent. Clearly, the elongated tapes at neutral pH and low ionic strength scatter visible light much more than the smaller, amorphous aggregates present at high and low pH, and at high ionic strength. The intensity of the scattered light at 400 nm as a function of NaCl concentration is constant up to 40 mM of added NaCl, and rapidly decreases at higher ionic strength. This demonstrates that the elongated tapes only form in aqueous solution of low ionic strength.

We propose that the elongated tapes result from ion-pairing of the catanionic cyclodextrin **3**. At neutral pH and low ionic strength, molecules of **3** assemble face to face, similar to the heterodimers described in the literature,[8] except that here each molecule has oppositely charged faces, so that the molecular pairing can continue indefinitely in two directions. The cyclodextrins can form an efficient intermolecular hydrogen bond network, with each molecule providing multiple NH hydrogen bond donor sites and CO hydrogen bond acceptor sites (Fig. 3). In this way they imitate the self-assembly of certain cyclic peptides to form nanotubes in water,[12] although here the protonated amino and carboxylate groups operate each on one side of the molecule, rather than alternately on the same side as do the hydrogen bonding NH and CO groups in the case of the peptides. The supramolecular structure adopted by cyclodextrin **3** is fundamentally different from previous examples of cyclodextrin self-assembly in polar solvents (including water), which have been induced by elongated guest molecules, namely the poly(rotaxanes)[13] and diphenylhexatriene inclusion compounds.[14]

The molecular faces of **3** may not perfectly superimpose. In crystal structures, cyclodextrins not only form channel structures, but also each molecular face can overlap with more than one other face to form cage structures.[15] Here, the molecules apparently assemble in three directions, two of which seem to be favoured over the third, as when bricks are used to form a wall. This would result in the formation of elongated tapes of variable width, but constant thickness. Further structural and computational investigations, as well as synthetic modifications, will contribute to a better understanding of the self-assembly of this novel catanionic Janus cyclodextrin.

Notes and references

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