Synthesis of a 'Head-to-tail' Type Cyclodextrin Dimer Linked by a Disulfide Bridge

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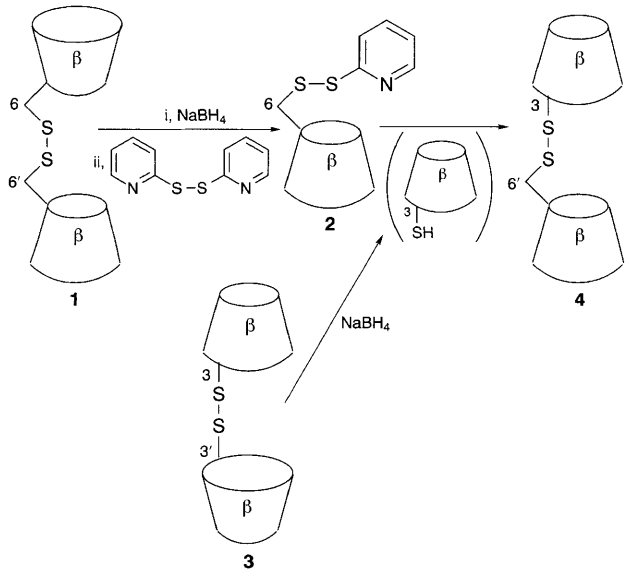
A 'head-to-tail' type cyclodextrin dimer, where C-3 of one cyclodextrin and C-6 of the other are linked by a disulfide bond, is synthesized using 2,2′-dipyridyl disulfide, which is widely applicable to the preparation of other dimers.

Cyclodextrins (CD) exhibit unique molecular recognition which resembles that of an enzyme or receptor,[1] but they bind guest molecule more weakly than does an enzyme or receptor. In order to improve binding ability, another cyclodextrin has been introduced as an additional binding site.

According to the linking position, 3 types of dimers are possible, namely 'head-to-head',[2] 'tail-to-tail,[3] and 'head-to-tail', where 'head' and 'tail' imply primary and secondary hydroxy sites of CD, respectively. In the case of the 'head-to-tail' dimer, for example, C-6 of one CD and C-2 or C-3 of the other CD are linked with a suitable linker. The dimers can also be classified into homo- and hetero-dimers composed of the same and the two different CD molecules, respectively. Synthesis of a heterodimer composed of α- and β-CD was reported by Wang *et al.*[4]

The previous studies[2b,e,g,3a,c] showed that a CD dimer which possesses suitable structure, binds a guest molecule as strongly as an antibody binds its antigen. It is noteworthy to create a novel dimer which shows stronger and more specific binding ability. We report here the first example of the synthesis of a 'head-to-tail' dimer, in which the two CD molecules are linked with a disulfide bridge. In the disulfide-bridged dimer, the two OH groups of each CD are replaced by a disulfide function. The 'head-to-tail' homodimer was synthesized starting from the corresponding 'head-to-head' and 'tail-to-tail' homodimers by the use of 2,2′-dipyridyl disulfide (Scheme 1).

The 'head-to-head' homodimer β-CD-6S-6′S-β-CD **1**†[2b] (50 mg, 2.17×10^{-5} mol) in H_2O (1 ml) was reduced by $NaBH_4$ (25 mg, 6.6×10^{-4} mol) for 1 h. The reaction mixture was acidified and made weakly basic, followed by addition of 2,2′-dipyridyl disulfide (240 mg, 1.1×10^{-3} mol) in pyridine (1 ml). It was stirred for 1 h and concentrated *in vacuo*. The residue was dissolved in H_2O, washed with diethyl ether, and concentrated *in vacuo*. The crude product was dissolved in 25% aq. MeOH (40 ml) and applied to a reversed-phase column. The 25% aq. MeOH (200 ml) elution gave 6S-(2′-pyridylthio)-6-thio-β-CD **2** (39 mg, 71%).‡



Scheme 1

The 'tail-to-tail' homodimer β-CD-3S-3′S-β-CD **3**[3a] (60 mg, 2.6×10^{-5} mol) was dissolved in H_2O (1 ml) and reduced with $NaBH_4$ (30 mg, 7.9×10^{-4} mol) for 1 h. This solution was acidified and made basic, followed by addition of the solution of **2** (320 mg, 2.5×10^{-4} mol) in pyridine (1 ml). After evaporation of solvent, the residue was dissolved in H_2O (5 ml) and purified by gel filtration column chromatography giving the 'head-to-tail' homodimer β-CD-3S-6′S-β-CD **4** (59 mg, 99%).

Compound **4** showed the expected pseudomolecular ion peak [M + Na^+] at *m/z* (FAB) 2321. Reduction of **4** using $NaBH_4$ yielded each component of 6-sulfanyl- and 3-sulfanyl-β-CD. It was also confirmed by HPLC quantification that **4** produced an equimolar amount of 6S-(2′-pyridylthio)-6-thio-β-CD and 3S-(2′-pyridylthio)-3-thio-β-CD by $NaBH_4$ treatment followed by reaction with 2,2′-dipyridyl disulfide.

The binding constant (*K*a) of **4** with methyl orange and ethyl orange were 1.8×10^4 dm^3 mol^{-1} and 6.0×10^4 dm^3 mol^{-1}, respectively. Compound **4** binds both guests *ca.* 6 times more strongly than β-CD. This is the result of cooperative binding of the two CD moieties but its effect is smaller than that in the case of **1**.[2b] However, there must be a guest molecule that fits **4** better, as Breslow suggested.[3a]

The method described here for the preparation of a 'head-to-tail' homodimer is also applicable to the synthesis of hetero-dimers of all three types, *i.e.* 'head-to-head', 'tail-to-tail', and 'head-to-tail'. For example, by use of X-CD-3S-3′S-X-CD and Y-CD-6S-6′S-Y-CD as starting materials, we can synthesis X-CD-3S-6′S-Y-CD, where X and Y are α, β, and/or γ. The case that X = Y = β is described here. If X-CD-6S-6′S-X-CD and Y-CD-6S-6′S-Y-CD are used, X-CD-6S-6′S-Y-CD is prepared. X-CD-3S-3′S-X-CD and Y-CD-3S-3′S-Y-CD give X-CD-3S-3′S-Y-CD.

A preliminary experiment showed that K_a of β-CD-6S-6′S-γ-CD **5** with 6-*p*-toluidinonaphthalene-2-sulfonate (TNS) was 3.2×10^4 dm^3 mol^{-1}, one third of that of β-CD-6S-6′S-β-CD **1**. However, compound **5** bound 8-anilinonaphthalene-1-sulfonate (ANS) with $K_a = 1.9 \times 10^3$ dm^3 mol^{-1}, 3 times as strong as **1**. Compounds **5** and **1** clearly discriminate TNS and ANS, although these two are not the optimized guest compounds.

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Footnotes

† '6S-6′S' stands for a disulfide bridge between C-6 of one CD and C-6 of the other CD in place of the OH groups.
‡ FAB *m/z* 1260 (M + H^+), ^{13}C NMR (25 MHz, [$^2H_6$]Me_2SO) 59.8 (C-6), 69.2, 72.0, 72.3 and 72.8 (C-2, C-3, and C-5), 80.5, 81.1 and 81.4 (C-4), 85.4 (C-4′), 101.0 and 101.9 (C-1), 118.9, 120.8, 137.6, 149.1 and 159.0 (aromatic carbons).

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