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Note

Direct synthesis of a sandwich-type molecule involving porphyrin and two molecules of cyclomaltoheptaose

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In biomimetic chemistry based on cyclomalto-oligosaccharides (cyclodextrins, CDs), it is essential to develop syntheses of CDs with the desired functional groups at appropriate positions. We have described[1] a new type of derivative (**1**) comprising a porphyrin sandwiched between two CD molecules and prepared by coupling $6^A,6^D$-dideoxy-$6^A,6^D$-di-iodo-βCD (**3**) with tetrakis(2-mercaptophenyl)-porphyrin and have characterized the five possible isomers (**1a–1e**, Fig. 1).

We now report an alternative route (Scheme 1) which gives three (**1a–c**) of

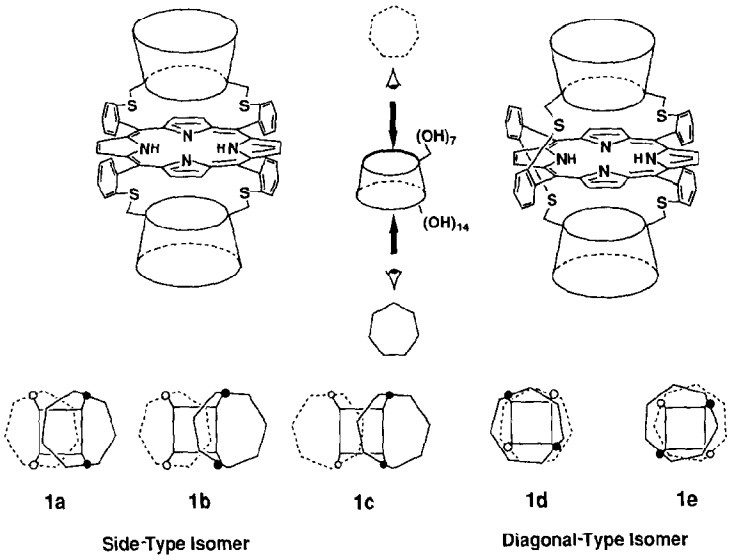

Fig. 1. Two types of CD-sandwiched porphyrins and their isomers. Heptagons represent the edge of the primary-OH side of βCD (one side = one glucose residue), and dashed and full lines indicate views from primary- and secondary-OH sides, respectively. Squares represent the porphyrin and each corner corresponds to the position of the phenyl thio-ether bond.

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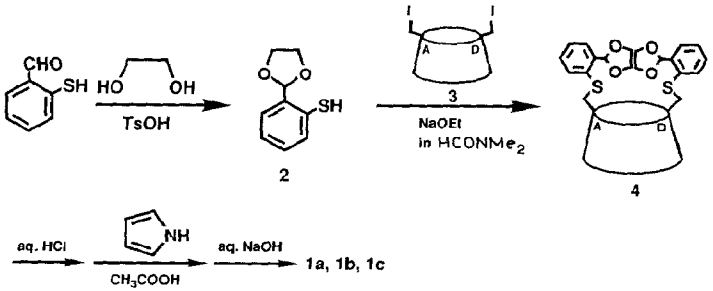
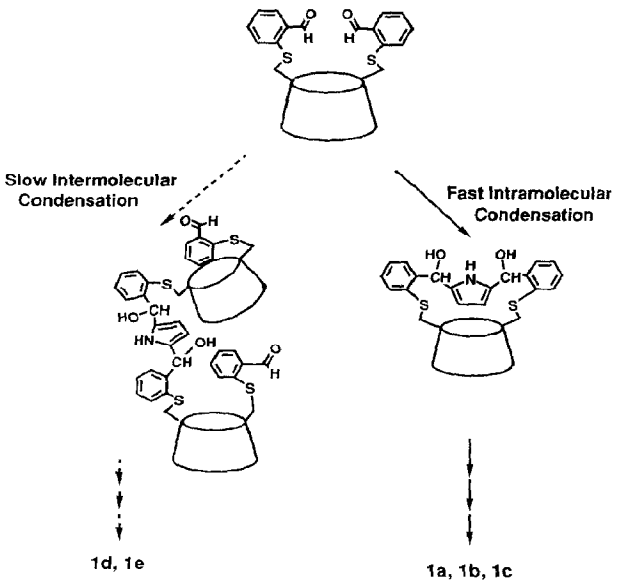
the isomers of **1**. The key CD derivative (**4**) involved in the synthesis was prepared by the reaction of **3** with a five-fold excess of 2-mercaptobenzaldehyde ethylene acetal (**2**) under the usual basic conditions[2]. Treatment of **4** with aqueous HCl regenerated the aldehyde groups, and the product was treated directly with pyrrole in acetic acid. H.p.l.c. of the mixture of products revealed only the three side-type isomers (**1a–c**) of **1** in the ratios 1:9:5 (combined yield, 0.2%); the diagonal-type isomers **1d** and **1e** were not detected. The n.m.r. spectra, f.a.b.-mass spectra (M^+ at *m/z* 2940), and retention times in h.p.l.c. of the isomers **1a–c** were identical with those of the corresponding isomers obtained[1] previously.



Scheme 1. The synthetic route for **1a–1c** via the bis-aldehyde derivative of the βCD derivative **4**.



Scheme 2. Two possible condensations of **4** with pyrrole.

CPK space-filling models of **1** show that the formation of diagonal-type isomers requires no special strain. The reaction[1] of **3** with the $\alpha\beta\alpha\beta$ atropisomer of tetrakis(2-mercaptophenyl)porphyrin gives **1d** and **1e** in reasonable yields. The reaction of **3** with the $\alpha\alpha\beta\beta$ atropisomer also gives **1a–c** in a combined yield similar to that noted above, but with a different distribution of products (ratios 1:2:1). Thus, the present results indicate that, in the step-wise condensation of the aldehyde moieties of **3** with pyrrole, the intramolecular condensation step is much faster[3] than the intermolecular reaction which affords the diagonal-type products (Scheme 2) and that the product distribution is determined kinetically.

Since the CD-sandwiched porphyrins are water-soluble and offer a (chiral) hydrophobic pocket at the axial positions of porphyrin, they may have value in heme-mimetic chemistry.

EXPERIMENTAL

Electronic and ^{1}H-n.m.r. spectra were recorded on a Hitach U-3410 and a JEOL FX-90Q spectrometer, respectively. H.p.l.c. was performed on a Waters Model 6000 instrument.

2-Mercaptobenzaldehyde ethylene acetal (**2**). — A solution of 2-mercaptobenzaldehyde[4] (10 g, 0.073 mol) and *p*-toluenesulfonic acid (6 g, 0.035 mol) in benzene (760 mL) and ethylene glycol (200 mL) was boiled under reflux at 90° for 2 h under N_2 with the removal of water by a Dean–Stark apparatus. The mixture was then washed with water, dried ($MgSO_4$) and concentrated. Chromatogaphy (hexane–AcOEt, 5/1) of the residue afforded **2** (13 g, 98%). ^{1}H-N.m.r. data (90 MHz, $CDCl_3$): δ 7.12–7.62 (m, 4 H, benzene H), 6.01 (s, 1 H, acetal H), 4.05–4.22 (m, 4 H, ethylene H), 3.77 (s, 1 H, SH). Mass spectrum: *m/z* 182.0397 (M^+) (calc. for $C_9H_{10}O_2S$: 182.04010).

6^A,6^D-Bis[2-(1,3-dioxolan-2-yl)phenylthio]cyclomaltoheptaose (**4**). — To a solution of **2** (14 g, 0.077 mmol) in dry *N,N*-dimethylformamide (170 mL) was added NaOEt (6.5 g, 0.096 mol) under Ar. After 10 min, **3**[2] (19 g, 0.014 mol) was added, and the mixture was stirred for 3 h at room temperature under Ar and then concentrated. The residue was washed with EtOH and then eluted from a reversed-phase column (Merck RP-8) with aqueous 40% methanol, to yield **4** (17 g, 83%) as a white powder. ^{1}H-N.m.r. data (90 MHz, D_2O): δ 7.03–7.55 (m, 8 H, benzene H), 6.03 (s, 1 H, acetal H), 6.00 (s, 1 H, acetal H), 4.93–5.17 (b, 7 H, H-1 of βCD), 3.02–4.17 (m, 50 H).

CD-sandwiched porphyrins **1a–c**. — A suspension of **4** (17 g, 0.012 mol) in M HCl (300 mL) was stirred vigorously for 1 h at room temperature and then concentrated under reduced pressure. To a solution of the residue in acetic acid (1000 mL) at 95°, pyrrole (1.6 g, 0.024 mol) was added quickly. The mixture was kept at 95° for 6 h and then concentrated to dryness. The residue was treated with M NaOH (100 mL) for 12 h at room temperature. The solution was neutralized and concentrated, and the product was eluted from Bio-Gel P-4 (Bio-Rad, 100–200 mesh) with

H_2O at 50°. The fractions having absorption (λ_{max} 425 nm) for porphyrin were collected, combined, and purified by h.p.l.c. on a column (2 × 30 cm) of ODS-AQ (Yamamura) by elution with a gradient (88:12 → 88:15) of H_2O–MeCN during 90 min. Retention time (min) **1a**, 35; **1b**, 45; **1c**, 48 (see ref. 1 for physicochemical data on **1a–1c**).

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