

Structural Study of Monosubstituted β -Cyclodextrins. Crystal Structures of Phenylthio- β -cyclodextrin and Phenylsulphinyl- β -cyclodextrin and Spectroscopic Study of Related Compounds in Aqueous Solution

Shigehiro Kamitori, Ken Hirotsu,* and Taiichi Higuchi

Department of Chemistry, Faculty of Science, Osaka City University, Sumiyoshi-ku, Osaka 558, Japan

Kahee Fujita,* Hatsuo Yamamura, and Taiji Imoto

Faculty of Pharmaceutical Science, Kyushu University, Higashi-ku, Fukuoka 812, Japan

Iwao Tabushi*

Department of Synthetic Chemistry, Kyoto University, Kyoto 606, Japan

The crystal structures of two monosubstituted β -cyclodextrins which have bulky hydrophobic groups instead of primary hydroxy groups were determined by *X*-ray diffraction. These compounds consist of the host (cyclodextrin moieties) and guest parts (hydrophobic groups), and have the ability to act as both host and guest at the same time. The crystal structures were solved by using Patterson maps, rotation functions, and trial-and-error methods combined with a rigid-body least-squares technique. The structures were refined by using a block-diagonal least-squares method to *R* values of 0.14 and 0.13. Hydrophobic groups are intermolecularly included in the cyclodextrin cavity of another molecule, and novel helical polymers are formed by repetition of this intermolecular inclusion. A spectroscopic study confirmed that this intermolecular inclusion occurs in aqueous solution.

Cyclodextrins are truncated, cone-shaped, cyclic oligosaccharides composed of six or more α -1,4 linked glucoses. They have hydrophobic cavities in the centres of molecules and primary hydroxy groups on the narrow sides of macrocycles and secondary hydroxy groups on the other sides. Since cyclodextrins are able to form stable complexes with a variety of organic compounds by inclusion within the hydrophobic cavities, they have received much attention as relatively low-molecular-weight models for biological macromolecules.^{1,2} Chemically modified cyclodextrins have been extensively studied to improve their inclusion and catalytic abilities.³⁻⁶ The structures of cyclodextrins⁷⁻⁹ and many inclusion complexes of them with various guest molecules⁹⁻¹⁹ have been determined by *X*-ray analyses, but few structures of modified cyclodextrins have been elucidated. There are several *X*-ray reports of methylated cyclodextrins,²⁰⁻²² where all hydroxy groups at the 2-, 3-, and 6-positions or the 2- and 6-positions are methylated to make the interior hydrophobic. However, to be useful as a model for enzymes, cyclodextrins require chemical modification, such as the introduction of bulky groups instead of hydroxy. Recently we have reported the crystal structure of a monosubstituted β -cyclodextrin, 6-deoxy-6-*t*-butylthio- β -cyclodextrin,²³ which was prepared by the replacement of a primary hydroxy group with a *t*-butylthio group. This compound is interesting because of its dual host (cyclodextrin moiety) and guest (*t*-butylthio group) character. Our *X*-ray study shows that the *t*-butylthio group is intermolecularly included in the cavity of the macrocycle of another molecule, giving the first inclusion complex formed by molecules of the same kind. Repetition of this hydrophobic interaction produces a novel helical polymer of the macrocycle. *X*-Ray analysis of the unsymmetrically disubstituted β -cyclodextrin 6A,6D-deoxy-6A-(*t*-butylthio)- β -cyclodextrin²⁴ showed this to have a similar helical polymeric structure.

These results suggest the possible formation of helical polymers in solid and dimer or higher complexes in solution by the same type of host-guest compounds. In order to elucidate the molecular interaction of these host-guest compounds in solid and in solution, phenylthio and phenylsulphinyl groups were selected as the guest parts. Here we report the *X*-ray crystallo-



R = SPh (1)

R = SOPh (2)

X = H (3)

X = CH₃ (4)

graphic study of two compounds, 6-deoxy-6-phenylthio- β -cyclodextrin (1), 6-deoxy-6-phenylsulphinyl- β -cyclodextrin (2), and a spectroscopic study of the related compounds, 6-deoxy-6-(*p*-hydroxy-*m*-nitrophenacyl)thio- β -cyclodextrin (3) and 6-deoxy-6-(4-hydroxy-5-methyl-3-nitrophenacyl)thio- β -cyclodextrin (4), in solution.

Experimental

Preparation of Monosubstituted Cyclodextrins.—6-Deoxy-6-phenylthio- β -cyclodextrin (1). A solution of thiophenol (640 mg, 5.28×10^{-3} mol) and 6-deoxy-6-*p*-tosyloxy- β -cyclodextrin (500 mg, 3.88×10^{-4} mol) in a degassed solvent of aqueous Na₂CO₃ (160 ml; pH 10.0) and ethanol (40 ml) was stirred at 50 °C for 2 days. After removal of the insoluble material by filtration, the filtrate was concentrated *in vacuo* and stirred vigorously with tetrachloroethylene (3 ml). The precipitate was collected by filtration and dissolved in aqueous ethanol. The solution was concentrated *in vacuo*. These procedures (dissolution and concentration) were repeated three times. The concentrated material was dissolved in 10% aqueous methanol (350 ml) and filtrated. The filtrate was applied on a reversed-phase column (Lobar Column LiChroprep RP-8, size A; Merck). After elution with water (100 ml), gradient elution from 10% aqueous methanol (500 ml) to 50% aqueous methanol (500 ml) was applied. The fractions of product (1) were easily monitored by u.v. absorption measurements. These fractions were collected, concentrated *in vacuo*, dissolved in water, and lyophilized (yield 246 mg, 52%), δ ([²H₆]DMSO) 7.1–7.5 (5 H, C₆H₅), 4.8 (7 H, 1-H of cyclodextrin), 3.0–4.0 (other protons of cyclodextrin);

Table 1. Fractional co-ordinates

| (1) | x | y | z | | x | y | z |
|--------|-------------|-------------|-------------|--------|-------------|------------|-------------|
| S(1)1 | -0.053 7(4) | 0.664 2(4) | 0.172 7(3) | O(4)4 | 0.252 5(8) | 0.432 5(9) | 0.056 7(6) |
| C(1)1 | -0.154(1) | 0.505(1) | 0.103(1) | O(5)4 | 0.350(1) | 0.563(1) | 0.069 3(7) |
| C(2)1 | -0.193(1) | 0.515(1) | 0.058(1) | O(6)4 | 0.351(2) | 0.495(2) | 0.149(1) |
| C(3)1 | -0.159(1) | 0.564(1) | 0.026 2(9) | C(1)5 | 0.263(1) | 0.789(1) | -0.032 9(9) |
| C(4)1 | -0.154(1) | 0.622(1) | 0.055 8(8) | C(2)5 | 0.299(1) | 0.756(1) | -0.070 4(9) |
| C(5)1 | -0.115(1) | 0.605(1) | 0.098 4(9) | C(3)5 | 0.299(1) | 0.687(1) | -0.059 8(9) |
| C(6)1 | -0.118(1) | 0.663(1) | 0.131(1) | C(4)5 | 0.321(1) | 0.675(1) | -0.010 0(9) |
| O(2)1 | -0.198 8(8) | 0.458 4(8) | 0.031 3(6) | C(5)5 | 0.276(1) | 0.712(1) | -0.023 8(9) |
| O(3)1 | -0.204 1(9) | 0.577 5(9) | -0.011 9(7) | C(6)5 | 0.291(1) | 0.705(1) | 0.078 2(9) |
| O(4)1 | -0.124 7(7) | 0.665 4(7) | 0.026 1(5) | O(2)5 | 0.272 3(8) | 0.765 5(8) | -0.117 1(6) |
| O(5)1 | -0.146 3(7) | 0.561 9(8) | 0.125 7(5) | O(3)5 | 0.339 5(9) | 0.655 3(9) | -0.093 2(6) |
| C(7)1 | -0.079(1) | 0.627(1) | 0.224(1) | O(4)5 | 0.313 6(8) | 0.608 5(8) | -0.002 4(6) |
| C(8)1 | -0.135(1) | 0.603(1) | 0.232(1) | O(5)5 | 0.283 0(8) | 0.772 7(8) | 0.011 5(6) |
| C(9)1 | -0.141(2) | 0.573(2) | 0.275(1) | O(6)5 | 0.353(1) | 0.714(1) | 0.084 2(8) |
| C(10)1 | -0.098(2) | 0.569(2) | 0.310(1) | C(1)6 | 0.028(1) | 0.862(1) | -0.039(1) |
| C(11)1 | -0.044(2) | 0.598(2) | 0.301(1) | C(2)6 | 0.067(1) | 0.854(1) | -0.087 1(9) |
| C(12)1 | -0.030(2) | 0.627(2) | 0.261(1) | C(3)6 | 0.116(1) | 0.803(1) | -0.083 4(8) |
| C(1)2 | 0.025(1) | 0.342(1) | 0.124 2(9) | C(4)6 | 0.159(1) | 0.824(1) | -0.043 8(8) |
| C(2)2 | -0.032(1) | 0.325(1) | 0.091 7(9) | C(5)6 | 0.124(1) | 0.829(1) | 0.003 7(9) |
| C(3)2 | -0.054(1) | 0.383(1) | 0.069 7(9) | C(6)6 | 0.160(1) | 0.856(1) | 0.042(1) |
| C(4)2 | -0.077(1) | 0.424(1) | 0.109 3(9) | O(2)6 | 0.021 9(8) | 0.834 0(8) | -0.122 9(6) |
| C(5)2 | -0.020(1) | 0.439(1) | 0.143(1) | O(3)6 | 0.151 7(9) | 0.804 5(9) | -0.126 8(6) |
| C(6)2 | -0.053(1) | 0.473(1) | 0.188(1) | O(4)6 | 0.201 3(7) | 0.773 8(7) | -0.039 3(5) |
| O(2)2 | -0.005 1(9) | 0.290(1) | 0.053 8(7) | O(5)6 | 0.073 8(8) | 0.877 2(8) | -0.005 1(6) |
| O(3)2 | -0.107 7(8) | 0.366 4(8) | 0.042 1(6) | O(6)6 | 0.188(1) | 0.912(1) | 0.030 5(7) |
| O(4)2 | -0.097 1(7) | 0.479 7(7) | 0.088 0(5) | C(1)7 | -0.155(1) | 0.719(1) | 0.017 3(8) |
| O(5)2 | 0.000 2(8) | 0.383 0(8) | 0.160 1(6) | C(2)7 | -0.153(1) | 0.735(1) | -0.037 3(9) |
| O(6)2 | -0.001(1) | 0.487(1) | 0.218 5(7) | C(3)7 | -0.085(1) | 0.747(1) | -0.049 5(9) |
| C(1)3 | 0.255(1) | 0.370(1) | 0.077(1) | C(4)7 | -0.057(1) | 0.794(1) | -0.020 2(8) |
| C(2)3 | 0.215(1) | 0.327(1) | 0.052(1) | C(5)7 | -0.065(1) | 0.776(1) | 0.033 5(9) |
| C(3)3 | 0.152(1) | 0.346(1) | 0.050(1) | C(6)7 | -0.043(1) | 0.825(1) | 0.066 2(9) |
| C(4)3 | 0.128(1) | 0.351(1) | 0.100 7(9) | O(2)7 | -0.172 0(8) | 0.683 0(8) | -0.063 0(6) |
| C(5)3 | 0.170(1) | 0.395(1) | 0.128 5(8) | O(3)7 | -0.084 4(8) | 0.768 8(8) | -0.099 6(6) |
| C(6)3 | 0.152(1) | 0.388(1) | 0.181(1) | O(4)7 | 0.006 5(7) | 0.800 1(7) | -0.029 8(6) |
| O(2)3 | 0.240(1) | 0.328(1) | 0.002 6(8) | O(5)7 | -0.130 6(8) | 0.765 8(8) | 0.041 7(6) |
| O(3)3 | 0.120 5(9) | 0.299 3(9) | 0.026 2(7) | O(6)A7 | -0.045(1) | 0.813(1) | 0.112 9(9) |
| O(4)3 | 0.068 4(8) | 0.373 0(8) | 0.097 3(6) | O(6)B7 | -0.066(2) | 0.882(2) | 0.061(2) |
| O(5)3 | 0.231 2(8) | 0.376 8(9) | 0.125 2(6) | OW1 | -0.286(1) | 0.469(1) | -0.041(1) |
| O(6)3 | 0.185 0(9) | 0.434 6(9) | 0.206 9(7) | OW2 | 0.118(2) | 0.542(2) | 0.188(1) |
| C(1)4 | 0.368(1) | 0.581(1) | 0.020(1) | OW3 | -0.013(2) | 0.157(2) | 0.057(2) |
| C(2)4 | 0.382(1) | 0.517(1) | -0.003(1) | OW4 | -0.315(2) | 0.618(2) | 0.025(1) |
| C(3)4 | 0.318(1) | 0.476(1) | -0.001(1) | OW5 | 0.502(3) | 0.543(2) | -0.084(2) |
| C(4)4 | 0.305(1) | 0.468(1) | 0.053(1) | OW6 | 0.127(2) | 0.165(2) | 0.073(1) |
| C(5)4 | 0.297(1) | 0.525(1) | 0.076(1) | OW7 | 0.156(3) | 0.340(3) | -0.079(2) |
| C(6)4 | 0.287(2) | 0.531(2) | 0.135(2) | OW8 | 0.258(3) | 0.416(3) | -0.118(2) |
| O(2)4 | 0.391(1) | 0.529(1) | -0.052 9(9) | OW9 | 0.179(3) | 0.942(3) | -0.143(2) |
| O(3)4 | 0.331(1) | 0.419(1) | -0.021 4(7) | | | | |
| (2) | | | | | | | |
| S(1)1 | 0.313 6(5) | -0.081 8(8) | 0.620(1) | O(2)4 | 0.227(1) | 0.408(2) | -0.044(2) |
| C(1)1 | 0.377(1) | -0.184(2) | 0.368(2) | O(3)4 | 0.333 9(9) | 0.356(1) | -0.039(2) |
| C(2)1 | 0.346(2) | -0.238(2) | 0.313(3) | O(4)4 | 0.369 1(8) | 0.327(1) | 0.132(2) |
| C(3)1 | 0.291(1) | -0.193(2) | 0.291(3) | O(5)4 | 0.270 8(8) | 0.474(1) | 0.178(2) |
| C(4)1 | 0.267(1) | -0.193(2) | 0.384(2) | O(6)4 | 0.368(1) | 0.492(2) | 0.272(2) |
| C(5)1 | 0.299(2) | -0.144(3) | 0.448(3) | C(1)5 | 0.059(1) | 0.339(2) | 0.220(3) |
| C(6)1 | 0.278(1) | -0.148(2) | 0.548(3) | C(2)5 | 0.066(1) | 0.358(2) | 0.122(2) |
| O(2)1 | 0.376 9(9) | -0.241(1) | 0.228(2) | C(3)5 | 0.126(1) | 0.354(2) | 0.098(2) |
| O(3)1 | 0.264 6(9) | -0.244(1) | 0.231(2) | C(4)5 | 0.154(1) | 0.410(2) | 0.156(3) |
| O(4)1 | 0.222 6(8) | -0.145(1) | 0.364(2) | C(5)5 | 0.147(1) | 0.390(2) | 0.257(3) |
| O(5)1 | 0.352 2(9) | -0.177(1) | 0.453(2) | C(6)5 | 0.172(1) | 0.446(2) | 0.315(3) |
| C(7)1 | 0.280(1) | -0.108(2) | 0.715(3) | O(2)5 | 0.039(1) | 0.298(2) | 0.073(2) |
| C(8)1 | 0.284(2) | -0.178(3) | 0.762(3) | O(3)5 | 0.126 3(9) | 0.380(2) | 0.005(2) |
| C(9)1 | 0.249(2) | -0.193(3) | 0.837(4) | O(4)5 | 0.206 8(8) | 0.393(1) | 0.135(2) |
| C(10)1 | 0.211(2) | -0.135(3) | 0.857(4) | O(5)5 | 0.091 0(9) | 0.391(1) | 0.274(2) |
| C(11)1 | 0.208(2) | -0.070(3) | 0.813(4) | O(6)5 | 0.166(1) | 0.411(2) | 0.412(3) |
| C(12)1 | 0.245(2) | -0.052(4) | 0.740(4) | C(1)6 | 0.039(1) | 0.053(2) | 0.369(3) |
| O(6)1 | 0.305(1) | -0.005(2) | 0.594(2) | C(2)6 | 0.009(2) | 0.075(2) | 0.278(3) |
| C(1)2 | 0.489(1) | 0.063(2) | 0.256(3) | C(3)6 | 0.036(1) | 0.136(2) | 0.229(3) |
| C(2)2 | 0.488(2) | -0.011(2) | 0.208(3) | C(4)6 | 0.046(1) | 0.217(2) | 0.283(3) |
| C(3)2 | 0.438(1) | -0.053(2) | 0.226(3) | C(5)6 | 0.073(1) | 0.190(2) | 0.371(2) |

Table 1. (continued)

| (2) | | | | | | | |
|-------|------------|-----------|-----------|-------|------------|-----------|----------|
| | x | y | z | | x | y | z |
| C(4)2 | 0.432(1) | -0.076(2) | 0.321(3) | C(6)6 | 0.080(1) | 0.256(2) | 0.446(3) |
| C(5)2 | 0.429(2) | 0.006(2) | 0.376(3) | O(2)6 | 0.000(1) | 0.006(1) | 0.225(2) |
| C(6)2 | 0.439(1) | -0.011(2) | 0.481(2) | O(3)6 | 0.008(1) | 0.159(1) | 0.150(2) |
| O(2)2 | 0.491 6(9) | 0.008(1) | 0.108(2) | O(4)6 | 0.077 8(8) | 0.264(1) | 0.236(2) |
| O(3)2 | 0.440 3(9) | -0.131(1) | 0.171(2) | O(5)6 | 0.044 8(9) | 0.125(2) | 0.420(2) |
| O(4)2 | 0.382 6(8) | -0.105(1) | 0.333(1) | O(6)6 | 0.033 8(9) | 0.288(1) | 0.461(2) |
| O(5)2 | 0.480 5(9) | 0.041(1) | 0.347(2) | C(1)7 | 0.179(1) | -0.165(2) | 0.414(2) |
| O(6)2 | 0.487(1) | -0.058(1) | 0.495(2) | C(2)7 | 0.137(2) | -0.176(2) | 0.337(3) |
| C(1)3 | 0.416(1) | 0.334(2) | 0.146(2) | C(3)7 | 0.122(1) | -0.099(2) | 0.297(3) |
| C(2)3 | 0.446(1) | 0.283(2) | 0.077(2) | C(4)7 | 0.107(1) | -0.052(2) | 0.382(2) |
| C(3)3 | 0.440(1) | 0.193(2) | 0.106(2) | C(5)7 | 0.152(1) | -0.037(2) | 0.439(2) |
| C(4)3 | 0.456(1) | 0.180(2) | 0.209(2) | C(6)7 | 0.137(2) | 0.013(3) | 0.519(3) |
| C(5)3 | 0.425(1) | 0.244(2) | 0.261(3) | O(2)7 | 0.152 2(9) | -0.226(1) | 0.270(2) |
| C(6)3 | 0.439(1) | 0.239(2) | 0.366(3) | O(3)7 | 0.074 2(9) | -0.116(1) | 0.248(2) |
| O(2)3 | 0.430 9(8) | 0.292(1) | -0.012(2) | O(4)7 | 0.087(1) | 0.018(1) | 0.342(2) |
| O(3)3 | 0.472 6(9) | 0.147(1) | 0.053(2) | O(5)7 | 0.164 1(9) | -0.107(1) | 0.476(2) |
| O(4)3 | 0.444 8(8) | 0.107(1) | 0.230(2) | O(6)7 | 0.185(2) | 0.047(3) | 0.549(3) |
| O(5)3 | 0.438 1(9) | 0.320(1) | 0.232(3) | OW1 | 0.747(1) | -0.109(2) | 0.718(2) |
| O(6)3 | 0.493 4(9) | 0.253(1) | 0.376(2) | OW2 | 0.931(1) | -0.066(2) | 0.987(2) |
| C(1)4 | 0.231(1) | 0.459(2) | 0.109(2) | OW3 | 0.088(1) | -0.479(2) | 0.948(2) |
| C(2)4 | 0.267(1) | 0.434(2) | 0.020(3) | OW4 | 0.868(1) | -0.120(2) | 0.848(3) |
| C(3)4 | 0.303(1) | 0.364(2) | 0.040(2) | OW5 | 0.580(1) | -0.288(2) | 0.899(3) |
| C(4)4 | 0.339(1) | 0.391(2) | 0.119(2) | OW6 | 0.759(1) | -0.314(2) | 0.932(3) |
| C(5)4 | 0.304(1) | 0.403(2) | 0.201(3) | OW7 | 0.661(2) | -0.363(3) | 0.948(3) |
| O(6)4 | 0.336(1) | 0.436(2) | 0.291(3) | OW8 | 0.768(2) | -0.150(3) | 0.974(4) |

f.a.b. m/z 1249 ($M + Na^+$). An aqueous solution saturated with (1) at 40 °C was kept at 4 °C to give crystals.

6-Deoxy-6-phenylsulphinyl- β -cyclodextrin (2). To a solution of (1) (110 mg, 8.97×10^{-5} mol) in ethanol (80 ml) was added aqueous H_2O_2 (11 ml, 88 mM). After being stirred at 50 °C for 6 days, the solution was concentrated *in vacuo* and lyophilized (yield 111 mg, 99.6%), $\delta(D_2O)$ 7.80 (5 H, C_6H_5), 5.0–5.3 (7 H, 1-H of cyclodextrin), 3.20–4.30 (other protons of cyclodextrin) (Found: C, 42.6; H, 6.1. Calc. for $C_{48}H_{74}O_{35}S \cdot 6H_2O$: C, 42.6; H, 6.4%). An aqueous solution saturated with (2) at 90 °C was cooled to room temperature and then stored at 4 °C to give crystals.

X-Ray Structural Analysis.—The crystals used for data collection, a rectangular block of $1.8 \times 0.4 \times 0.4$ mm for (1) and $0.5 \times 0.4 \times 0.3$ mm for (2), were sealed in glass capillaries with a drop of mother liquor to avoid decomposition. Diffraction intensities were measured on a Phillips PW1100 diffractometer with graphite-monochromated Mo- K_α radiation ($\lambda = 0.71069$ Å). Lattice constants were determined by least-squares methods using 20 reflections for both crystals. Then 4 690 independent reflections [$2 \leq I < 3\sigma(I)$] for (1) and 3 506 independent reflections [$1 \leq I < 3\sigma(I)$] for (2) were collected up to 44° in 2θ and 40° in 2θ , respectively, using the ω -scan mode. No correction was made for an absorption effect. Crystal data are as follows.

$C_{48}H_{74}O_{34}S \cdot nH_2O$ (1), $M = 1227.1$ (excluding water molecules). Tetragonal, $a = b = 21.915(1)$ Å, $c = 28.337(2)$ Å, $V = 13\,607$ Å³, space group $P4_12_12$, $Z = 8$, $D_m = 1.43$ g cm⁻³.

$C_{48}H_{74}O_{35}S \cdot nH_2O$ (2), $M = 1243.2$ (excluding water molecules). Orthorhombic, $a = 26.026(3)$ Å, $b = 17.232(2)$ Å, $c = 14.810(2)$ Å, $V = 6\,642$ Å³, space group $P2_12_12_1$, $Z = 4$, $D_m = 1.44$ g cm⁻³.

Cyclodextrin moieties of these compounds have a non-crystallographic seven-fold axis. The directions of these axes were determined by using Patterson maps and rotation functions.²⁵ The molecular positions in the unit cell were located on R maps which were calculated using the model structure of β -cyclodextrin having seven-fold symmetry except

for the primary hydroxy oxygens. The resultant structures were refined by rigid-body least-squares methods,²⁶ each glucose residue was fixed through refinement. After the refinement by the block-diagonal least-squares methods,²⁷ the phenylthio group, the phenylsulphinyl group, and the primary hydroxy oxygens were found by Fourier syntheses. The primary hydroxy O(6)7 atom of (1) occupies two positions. Nine positions for water molecules for (1) and eight positions for water molecules for (2) were located by difference Fourier syntheses with a site-occupancy factor varying from 0.5 to 1.0, since some of them are highly disordered. The structures were refined to $R = 0.14$ for (1) and 0.13 for (2) by a block-diagonal least-squares method, using isotropic temperature factors for all atoms. The quantity minimized was $\Sigma \omega(|F_o| - |F_c|)^2$ with $\omega = 1.0$. Final atomic coordinates are given in Table 1. Bond lengths and angles are in Supplementary Publication No. SUP 56647 (10 pp.).*

Association Constant between β -Cyclodextrin and Mono-substituted β -Cyclodextrin.—The difference electronic spectrum was taken between (3)²⁸ (6.56×10^{-5} M) alone and (3) (6.56×10^{-5} M) in the presence of β -cyclodextrin in phosphate buffer (pH 11.0) at 25 °C. The reciprocal of the difference absorption at 348 or 380 nm was plotted against the reciprocal of β -cyclodextrin concentration. From the slope and the intercept, the association constant was obtained. The concentration of β -cyclodextrin ranges from 5.30×10^{-4} to 1.56×10^{-3} M. A similar procedure was carried out to obtain the association constant between (4)²⁸ (4.88×10^{-5} M) and β -cyclodextrin (1.31×10^{-3} – 4.62×10^{-3} M) at 416 or 540 nm.

Results and Discussion

The Molecular Conformation.—The molecular structures of (1) and (2) are shown in Figure 1 and the geometrical data are given in Table 2. The macrocycle structure of (1) has an

* For details of Supplementary Publications see Instruction for Authors in *J. Chem. Soc., Perkin Trans. 2*, 1986, Issue 1.

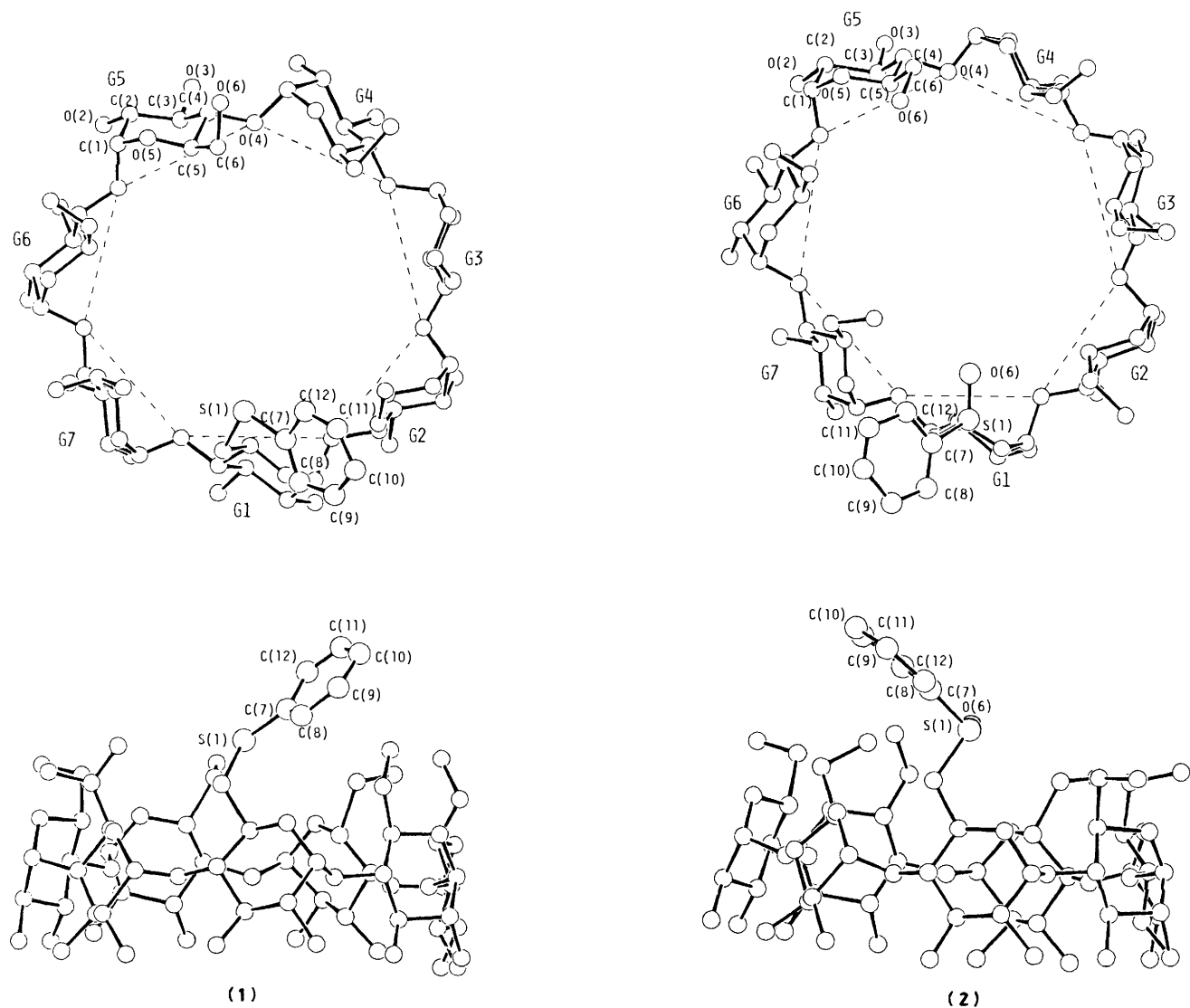


Figure 1. ORTEP molecular structures and numbering schemes of (1) and (2). The heptagons composed of seven O(4) atoms are drawn with dotted lines

approximate seven-fold axis and a round shape. All glucose residues have 4C_1 chair conformation. The secondary hydroxy groups between neighbouring glucose residues form intramolecular hydrogen bonds, which may maintain the round shape of cyclodextrin ring; O(2) n -O(3) n + 1 hydrogen bonds are in the range 2.79–3.02 Å. Seven glycosidic oxygen atoms [O(4) atoms] are coplanar within 0.11 Å. The heptagon composed of seven O(4) atoms is approximately regular since the side length and the radius of the heptagon are in the range 4.32–4.50 and 4.96–5.20 Å, respectively. The glucose residues are inclined to the perpendicular axis to the O(4) atoms plane to make the hydrophobic cavity small at the primary hydroxy site. The tilt angles¹⁵ of glucose residues are in the range 2.3–21.6°.

The structure of (2) also has glucose residues with 4C_1 chair conformation, and the secondary hydroxy groups form intramolecular hydrogen bonds, ranging from 2.58 to 2.93 Å. Seven O(4) atoms are coplanar within 0.21 Å, showing poor planarity compared with (1). The tilt angles of glucose residues are in the range 3.7–18.7°. The side length and the radius of the heptagon composed of seven O(4) atoms are in the range 4.25–4.51 and 4.93–5.26 Å, respectively, which are slightly wider than those of (1).

The conformations of substituent groups of (1) and (2) differ. The phenyl group of (1) is located just above the G1 glucose residue; the dihedral angle of C(5)–C(6)–S(1)–C(7) is –91.6°. On the other hand, the phenyl group of (2) is in the *trans*-conformation of C(5)–C(6)–S(1)–C(7), directing the outside of the cyclodextrin ring. The dihedral angles between the phenyl rings and the seven O(4) atoms planes of (1) and (2) are 51 and 35°, respectively.

The Host–Guest Interaction between Two Molecules.—The complex structures composed of two molecules of (1) and (2) are shown in Figure 2. Hydrophobic groups (guest parts) are intermolecularly included in hydrophobic cyclodextrin cavities (host parts) of another molecules.

In the case of (1), the phenylthio group enters the centre of the cavity from the side of secondary hydroxy groups, and the C(10) atom of molecule B almost reaches the C(5)H ring of molecule A. The dihedral angle between the phenyl ring of molecule B and the O(4) atom plane of molecule A is 53° (Figure 2). van der Waals contacts between the guest phenylthio group and the host cyclodextrin cavity are listed in Table 3; many contacts are found between the guest part and the glucose

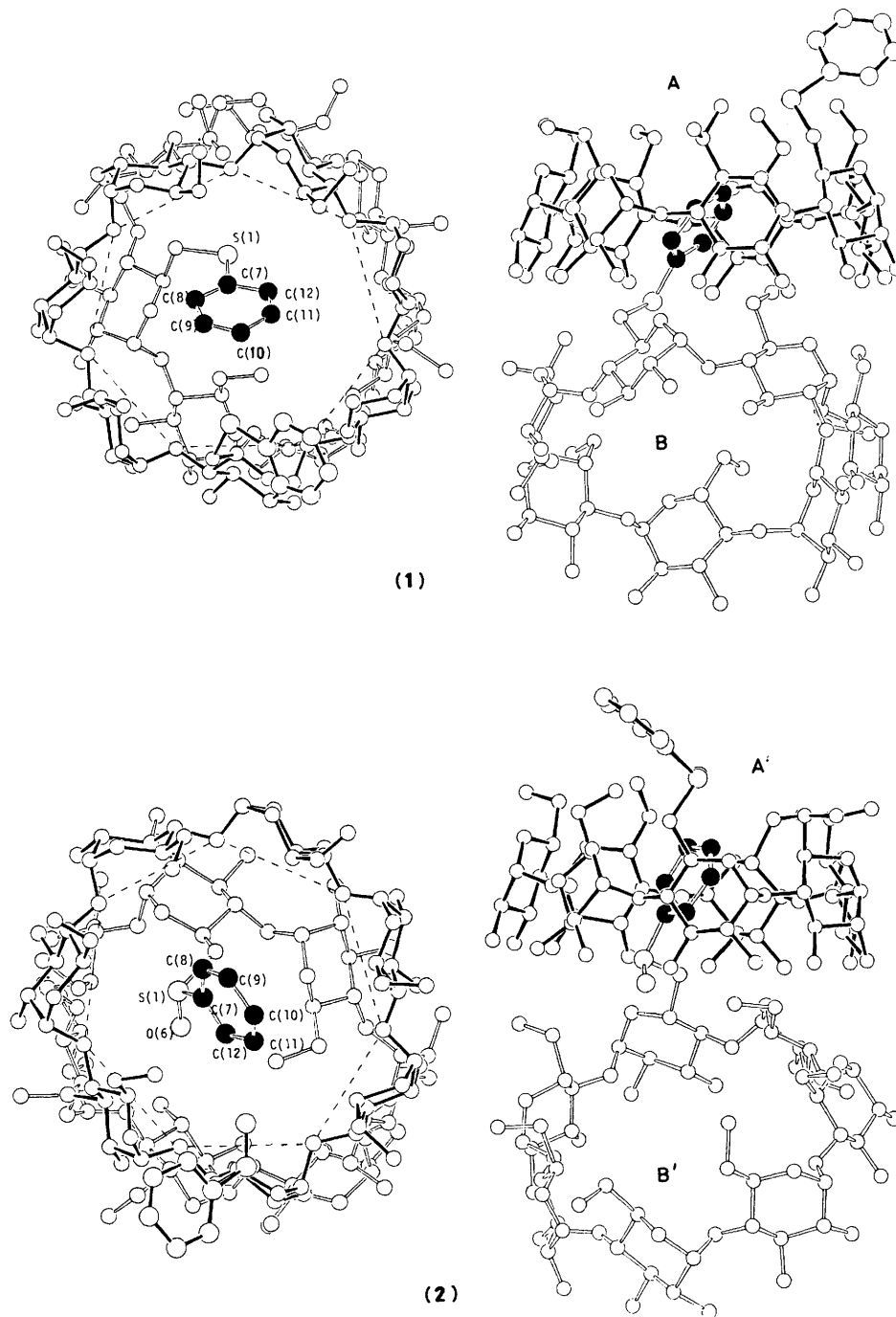


Figure 2. The complex structures composed of two molecules of (1) and (2). Phenyl rings of molecule B and B' are shown by filled circles

residues of G4 and G5. Two β -cyclodextrin macrocycles are connected by four hydrogen bonds between the primary hydroxy groups of molecule B and secondary hydroxy groups of molecule A. The distances of O(2)2–O(6)3, O(3)2–O(6)3, O(2)4–O(6A)7, and O(3)5–O(6A)7 are 3.09, 2.82, 2.97, and 2.78 Å, respectively.

In the case of (2), the guest phenylsulphonyl group is more deeply included in the host cyclodextrin cavity than that of (1), as the C(9)–C(10) bond is located above the C(5)H ring of molecule A' and almost parallel to the O(4) atom plane of molecule A'. The phenyl ring of molecule B makes a larger angle with the O(4) atom plane of molecule A', 68° in comparison

with 53° in (1). There is only one hydrogen bond between two molecules; the distance O(6)2–O(3)6 is 2.87 Å. The difference in the spatial arrangements of the guest parts in the cavities between (1) and (2) is related to the difference in the macrocyclic conformation between (1) and (2). Both the largest value and the average value of tilt angles in (1), where the phenyl ring is less deeply included than in (2), are larger than those of (2). The heptagon composed of O(4) atoms in (2), where the phenyl ring is relatively perpendicular to the O(4) atom plane, is slightly distorted to an elliptical form in comparison with that of (1) having approximately heptagonal symmetry,¹⁵ and the direction of the longer principal axis of the ellipse is almost

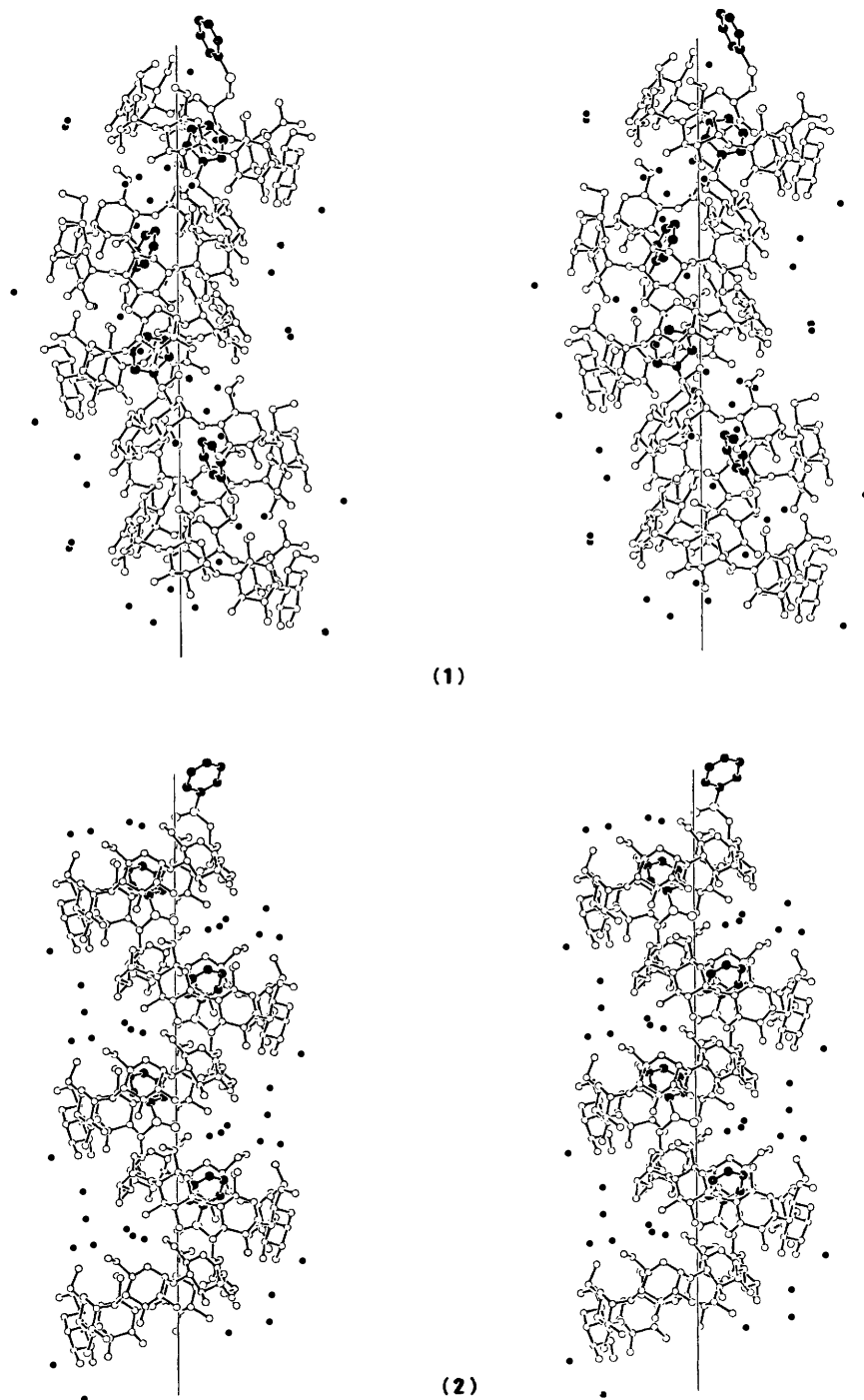


Figure 3. Stereodrawing of novel helical polymers related by the screw axes [4_1 for (1) and 2_1 for (2)] which are shown by long straight lines. Phenyl rings and water molecules are shown by filled circles

parallel to the phenyl plane (Figure 2). These relatively large tilt angles of (1) and the slightly elliptical distortion of (2) are induced in part by the above-mentioned van der Waals contacts and hydrogen bonds.

Polymeric Structure in Crystal.—In the crystalline state, as shown in Figure 3, the molecules are located around the screw axis to give the unique polymeric inclusion column structure formed from a single species acting both as a guest and as a host. The macrocycles in helical columns are related by a 4_1 screw

axis for (1) and 2_1 screw axis for (2). The macrocycles are inclined to these screw axes by 23° for (1) and 22° for (2). The phenylthio and phenylsulphonyl groups are spirally aligned in one direction through the columns following the macrocyclic arrangement and play roles as joints to bind the β -cyclodextrin rings. The distances between the guest part of molecule B or B' and the sulphur atom of molecule A or the sulphanyl oxygen atom of molecule A' are 4.43 \AA [C(10)1–S(1)1] for (1) and 4.28 \AA [C(10)1–O(6)1] for (2). These distances indicate that guest parts in polymeric inclusion columns might interact with

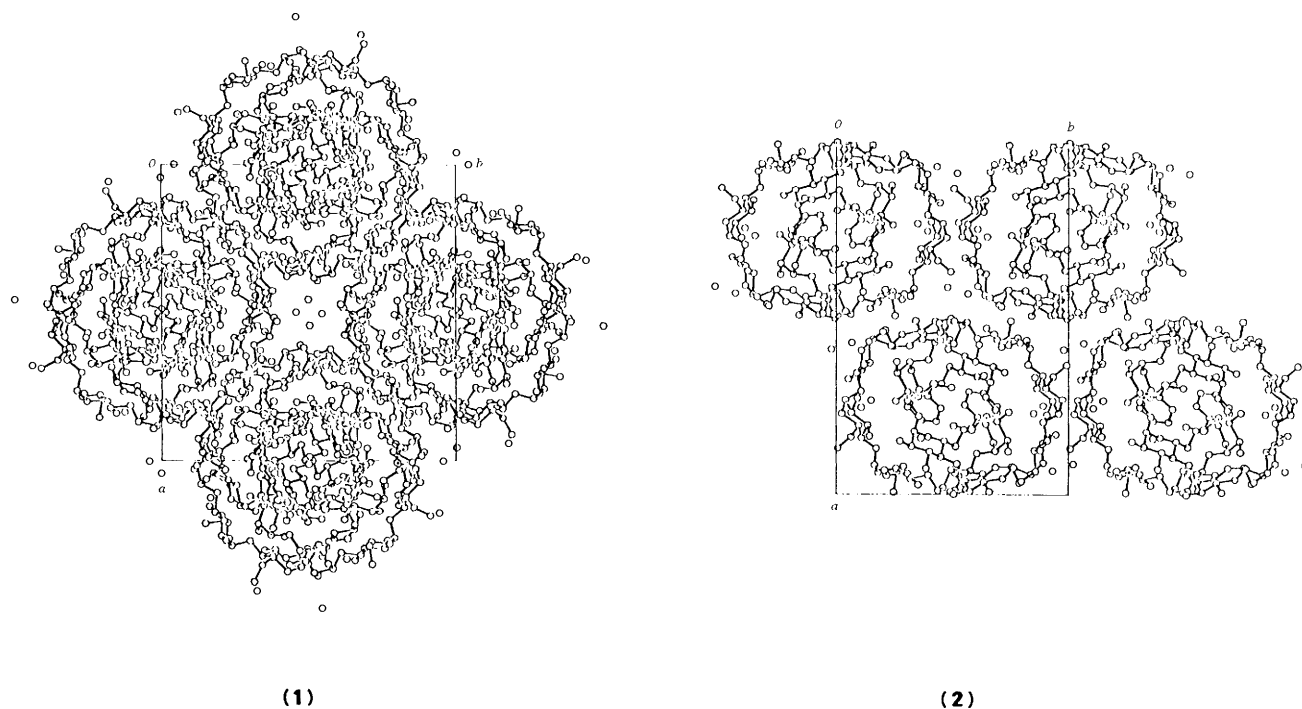


Figure 4. The crystal structures of (1) and (2) viewed down along the c axes

Table 2. Geometrical data

| Residue | Radius (Å) ^a | | Distance (Å) ^b | | Tilt angle (°) ^c | |
|---------|-------------------------|------|---------------------------|------|-----------------------------|------|
| | (1) | (2) | (1) | (2) | (1) | (2) |
| G1 | 4.96 | 4.97 | 4.47 | 4.25 | 19.2 | 3.7 |
| G2 | 5.03 | 5.26 | 4.32 | 4.27 | 12.8 | 8.9 |
| G3 | 5.17 | 4.94 | 4.39 | 4.52 | 2.6 | 17.6 |
| G4 | 5.05 | 4.93 | 4.41 | 4.38 | 21.5 | 6.4 |
| G5 | 5.02 | 5.13 | 4.50 | 4.30 | 21.6 | 9.8 |
| G6 | 5.09 | 5.24 | 4.32 | 4.51 | 12.3 | 17.9 |
| G7 | 5.20 | 4.93 | 4.41 | 4.52 | 3.8 | 18.7 |
| Average | 5.07 | 5.06 | 4.40 | 4.39 | 13.4 | 11.9 |

^a The radius is measured from the centre of gravity of the seven O(4) atoms to each O(4) atom. ^b The distance is defined as the O(4) n – O(4) n + 1 distance. ^c The tilt angle is defined as the angle made by O(4) atoms plane and the plane formed by O(4) n + 1, C(1) n , C(4) n , O(4) n of each glucose residue

each other. The introduction of a suitable functional group might be able to cause interactions, even chemical reactions, in the solid state.

The crystal structures of (1) and (2) are shown in Figure 4. Many water molecules fill the lattice space and form many hydrogen bonds with hydroxy groups in the cyclodextrin moieties.

Hybrid Dimerization in Aqueous Solution.—On the basis of the X-ray analysis, we might expect that monosubstituted β -cyclodextrins form dimers or higher complexes by the intermolecular host-guest interaction in aqueous solutions. In order to detect these phenomena, we studied the interaction between (3) or (4) and β -cyclodextrin because (1) and (2) showed too little change in their u.v. spectra on addition of β -cyclodextrin to allow an estimation of their associations and because (3) and (4) were very sensitive to their environments.²⁸ As expected,

Table 3. Main short contacts between guest part and host part

| Guest part atom | Host part atom | Short contact (Å) |
|-----------------|----------------|-------------------|
| (1) | | |
| S(1)1 | C(3)4 | 4.37 |
| S(1)1 | C(3)5 | 4.17 |
| S(1)1 | O(4)5 | 4.08 |
| C(8)1 | C(3)6 | 4.13 |
| C(8)1 | O(4)6 | 3.78 |
| C(10)1 | C(5)1 | 4.17 |
| C(12)1 | C(5)4 | 4.16 |
| C(12)1 | O(4)4 | 3.73 |
| (2) | | |
| S(1)1 | C(3)6 | 4.39 |
| C(8)1 | C(5)5 | 4.07 |
| C(8)1 | C(5)6 | 4.01 |
| C(8)1 | O(4)6 | 3.91 |
| C(11)1 | C(5)1 | 4.20 |
| C(11)1 | C(5)2 | 3.85 |
| C(11)1 | O(4)2 | 3.84 |
| C(12)1 | O(4)1 | 3.94 |
| O(6)1 | C(3)7 | 3.99 |

^a This Table lists distances less than 4.4 Å for S–C, 4.2 Å for S–O and C–C, and 4.0 Å for C–O.

the absorption spectra of (3) and (4) changed on addition of β -cyclodextrin in aqueous solutions. The difference spectra were treated by the Benesi–Hildebrand method²⁹ to give association constants of 282 and 15 l mol⁻¹ for 1:1 host-guest inclusion of (3) and (4) by β -cyclodextrin.³⁰ The association constants between (4) and β -cyclodextrin were smaller those that of (3), demonstrating the inclusion of the chromophore part by β -cyclodextrin.

Conclusions.—The present investigation suggests that these host-guest compounds, which have a hydrophobic group

servicing as a guest to the cavity of β -cyclodextrin, generally form a helical polymer by intermolecular inclusion in the crystal state. In aqueous solution, it is confirmed that these mono-substituted β -cyclodextrins form dimers or higher complexes by intermolecular interaction. Of course, in the presence of organic guest compounds for β -cyclodextrin, they form inclusion complexes with these organic compounds like β -cyclodextrin.²⁸ It should be noted that in aqueous solution they form inclusion complexes not only with another guest molecules but also among themselves because of their host-guest character.

Acknowledgements

We are indebted to the Crystallographic Research Centre, Institute for Protein Research, Osaka University, for computer calculation. This work was supported by Grant-in-Aid for the Special Project Research on the Properties of Molecular Assemblies (No. 59212039) from the Ministry of Education, Science and Culture.

References

- 1 M. L. Bender and M. Komiyama, 'Cyclodextrin Chemistry,' Springer-Verlag, Berlin, 1978.
- 2 W. Saenger, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 344.
- 3 I. Tabushi, *Acc. Chem. Res.*, 1982, **15**, 66.
- 4 I. Tabushi, *Tetrahedron*, 1984, **40**, 269.
- 5 R. Breslow, *Science*, 1982, **218**, 532.
- 6 A. P. Croft and R. A. Bartsch, *Tetrahedron*, 1983, **39**, 1417.
- 7 K. K. Chacko and W. Saenger, *J. Am. Chem. Soc.*, 1981, **103**, 1708.
- 8 K. Lindner and W. Saenger, *Carbohydr. Res.*, 1982, **99**, 103.
- 9 J. J. Stezowski, K. H. Jogun, E. Eckle, and K. Bartels, *Nature (London)*, 1978, **274**, 617.
- 10 M. M. Hording, J. M. MacLennan, and R. M. Paton, *Nature (London)*, 1978, **274**, 621.
- 11 R. Tokuoka, M. Abe, T. Fujiwara, K. Tomita, and W. Saenger, *Chem. Lett.*, 1980, 491.
- 12 R. Tokuoka, T. Fujiwara, and K. Tomita, *Acta Crystallogr., Sect. B*, 1981, **37**, 1158.
- 13 K. Harata, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 2315.
- 14 K. Harata, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 2596.
- 15 K. Harata, K. Uekama, M. Otagiri, F. Hirayama, and Y. Ohtani, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 1234.
- 16 K. Harata, K. Kawano, K. Fukunaga, and Y. Ohtani, *Chem. Pharm. Bull.*, 1983, **31**, 1428.
- 17 K. Uekama, F. Hirayama, T. Imai, M. Otagiri, and K. Harata, *Chem. Pharm. Bull.*, 1983, **31**, 3363.
- 18 J. A. Hamilton and M. N. Sabesan, *Carbohydr. Res.*, 1982, **102**, 31.
- 19 J. A. Hamilton and M. N. Sabesan, *Acta Crystallogr., Sect. B*, 1982, **38**, 3063.
- 20 M. Czugler, E. Eckle, and J. J. Stezowski, *J. Chem. Soc., Chem. Commun.*, 1981, 1291.
- 21 K. Harata, K. Uekama, M. Otagiri, and F. Hirayama, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 1732.
- 22 K. Harata, *Chem. Lett.*, 1984, 1641.
- 23 K. Hirotsu, T. Higuchi, K. Fujita, T. Ueda, A. Shinoda, T. Imoto, and I. Tabushi, *J. Org. Chem.*, 1982, **47**, 1143.
- 24 K. Fujita, A. Matsunaga, T. Imoto, K. Hirotsu, S. Kamitori, and T. Higuchi, *J. Am. Chem. Soc.*, 1985, **107**, 1790.
- 25 M. G. Rossmann and D. M. Blow, *Acta Crystallogr.*, 1962, **15**, 24.
- 26 ORFLS: W. R. Busing, K. O. Martin, and H. A. Levy, Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, 1965.
- 27 T. Ashida, 'HBLS V, The Universal Crystallographic Computing System-Osaka,' The Computation Centre, Osaka University, 1973, p. 55.
- 28 K. Fujita, T. Ueda, T. Imoto, I. Tabushi, N. Toh, and T. Koga, *Bioorg. Chem.*, 1982, **11**; (a) 72; (b) 108; (c) K. Fujita, T. Ueda, A. Matsunaga, and T. Imoto, *J. Chem. Soc. Jpn.*, 1983, 207.
- 29 H. A. Benesi and J. H. Hildebrand, *J. Chem. Soc.*, 1949, 2703.
- 30 A similar decrease in binding ability caused by the substitution of methyl for hydrogen has been reported, R. J. Bergeron, M. A. Channing, G. J. Gibeily, and D. M. Pillor, *J. Am. Chem. Soc.*, 1977, **99**, 5146.

Received 12th November 1985; Paper 5/1992