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CHEMISTRY OF A HEPTANE-SOLUBLE CYCLODEXTRIN DERIVATIVE

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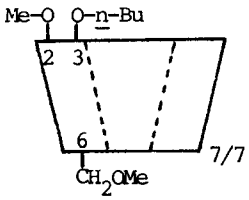
Summary. It is thought that β-cyclodextrin binds guest molecules in water because the cavity is less polar than the solvent. This communication describes a β-cyclodextrin derivative which binds guest molecules in heptane because the cavity is more polar than the solvent.

The vast literature on cyclodextrin chemistry[1,2] deals almost exclusively with systems in polar solvents. Two exceptions have appeared recently. Komiyama et al.[3] reported that per-acylated β-cyclodextrin forms complexes with salts of 2,4,6-trinitrophenol in chloroform and benzene. Nakai et al.[4] found that partitioning of 4-nitrophenol from water into chloroform is favored by the presence of permethylated β-cyclodextrin in the latter solvent. We now disclose our own results with a new peralkylated cyclodextrin derivative, heptakis (3-O-butyl-2,6-di-O-methyl)-β-cyclodextrin (I).[5] Attachment of 14 methyls and 7 butyls has three important



I

consequences: (1) The cyclodextrin is rendered heptane-soluble; compound I in heptane provides a polyether-like cavity within which polar solutes can adsorb. (2) The bottom side of cyclodextrins is compressed by polyalkylation;[6] this creates a "floor" known to benefit the complexation process.[7] (3) The volume of the toroidal cavity, in which guest molecules reside, is extended by the 7 butyl groups.

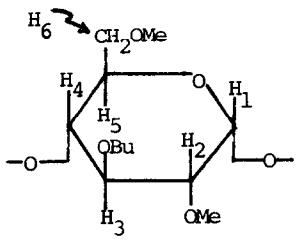
Synthesis of I was accomplished by fully butylating the known[8] heptakis (2,6-di-O-methyl)-β-cyclodextrin at the 3-position. Since the 3-position tends to resist alkylation (owing in part to an internal hydrogen bond),[9] it is worthwhile to describe our procedure in detail. The product from methylating β-cyclodextrin at all 2 and 6 positions[8] was dried 3 hours over P_2O_5 in a vacuum desiccator. This material (1.0 g, 0.75 mmol) plus sodium hydride (1.26 g powder, 52.5 mmol) were added to a magnetically stirred 50 ml flask containing 20 ml dimethylformamide (distilled over calcium hydride under reduced pressure). Neat n-butyl iodide (12 ml, 105 mmol)

was then added immediately to the mixture over 15 minutes followed by continued stirring for 24-30 hours at room temperature. Workup consisted of quenching with 20 ml cold water, extracting with 3 x 25 ml hexane, drying the extract with sodium sulfate, evaporating the hexane, and chromatographing the residue (100-200 mesh silica, 40% hexane/60% chloroform to 80% chloroform/20% ethyl acetate). The product, after decolorization with charcoal, was a clear glass (T_g = 59-65°; T_m = 96-100°) having the expected ^1H and ^{13}C NMR spectra. Our best yield of final product was 83%; it is not known whether equivalent yields can be obtained with substantially reduced levels of sodium hydride and n-butyl iodide. Anal. Calcd for $C_{84}H_{154}O_{35}$: C, 58.50; H, 9.02. Found: C, 58.76; H, 9.01.

The binding constant between p-nitrophenol and I in heptane (determined by the Benesi-Hildebrand method at 310 nm) equals 2.6 x 10^3 M^{-1}. In contrast, no binding between p-nitrophenol and I was evident in acetonitrile. These results may be compared with the aqueous association constants of 660 M^{-1} between p-nitrophenolate and ß-cyclodextrin and 341 M^{-1} between p-nitrophenol and α-cyclodextrin.[10,11] The lesson is clear: Binding occurs only when the polarity of the cavity differs substantially from that of the solvent from which the guest partitions. In water, guests with hydrophobic character seek the less polar polyether-like cavity; in heptane, guests seek the more polar cyclodextrin interior. Apparently, acetonitrile simulates the cyclodextrin cavity sufficiently to deter binding of p-nitrophenol.

Binding between I and aromatics in heptane was also studied by the newly developed Armstrong method.[12] p-Nitrophenol (pNP) and o-nitrophenol (oNP) were chromatographed on Brinkmann Polygram-6 sheets using 0.01-0.10 M I in heptane as the mobile phase. Only the para isomer showed enhanced migration over and above that with heptane alone. We conclude, in agreement with spectrophotometric work, that oNP does not bind to I in heptane. Since oNP but not pNP can engage in intramolecular hydrogen-bonding, we surmise that intermolecular hydrogen-bonding contributes to the stability of host-guest interactions in apolar media. This speculation was substantiated by chromatographic investigations of indole, 2,3-dimethylindole, and 1,2-dimethylindole. Although the first two compounds displayed large increases in R_f with the I content of the heptane, the third indole was actually "anti-binding".[12] Lack of an NH in 1,2-dimethylindole seems to impair dramatically the complexation process.

Decoupling experiments along with literature data[9] permitted our assigning all peaks in a



360 MHz ^{1}H NMR spectrum of I in C_6D_6 (Table I). When excess p-nitrophenol is added to solutions of I, significant upfield shifts are observed with H_3 and H_5 but not H_2 and H_4 (Table I); the former are inside the cavity whereas the latter are outside. Proximity of the aromatic guest to the glycosidic oxygens lining the cavity may account for the H_1 shift. Interestingly, the $-OCH_2$ of the 3-butoxy group consists of two magnetically non-equivalent protons (both with and without the presence of a guest). The fact that binding of p-nitrophenol displaces the multiplets for these protons by 25 and 37 Hz (compared to only 6 and 8 Hz for the two methoxy groups) suggests that the butyl groups, but not the methyls, are directed inwardly. This minimizes steric repulsion between the alkoxy groups on carbons 2 and 3, maximizes van der Waals interactions among the butyl groups, and may account in part for the difficulty in derivatizing the 3-hydroxyl when the 2-hydroxyl already bears a methyl.

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Table I

Proton	δ, ppm[a]	Form	Δ, Hz[b]
H_1	5.44	d	31→
H_2	3.24	d of d	6→
H_3	4.00	m	26→
H_4	4.16	m	17→
H_5	4.24	m	37→
H_6	3.81	m	←11
$-OCH_2$ of Bu	4.24	m	37→
	3.91	m	25→
C_2OCH_3	3.39	s	8→
C_6OCH_3	3.38	s	6→
CH_3 of Bu	0.98	t	←7

[a]Relative to TMS in C_6D_6; [b]Shift caused by excess pNP with arrow pointing to right indicating an upfield displacement.

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5. The schematic representation illustrates a convenient method for depicting cyclodextrin structure: The 2,3, and 6 indicate which hydroxyl is derivatized; the first 7 indicates that there are 7 sugars in the ring, whereas the second 7 indicates that all 7 sugars are derivatized as shown.
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