203. Cyclodextrin Chemistry. Selective Modification of all Primary Hydroxyl Groups of α- and β-Cyclodextrins

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Summary

Two efficient methods are described for the selective modification of all six primary hydroxyl groups of α-cyclodextrin (α-CD, **1**). One, using an indirect strategy, involves protection of all 18 hydroxyl functions as benzoate esters, followed by selective deprotection of the six primary alcohol groups. The other, using a direct strategy, involves selective activation of the primary hydroxyl groups *via* a bulky triphenylphosphonium salt, which is then substituted by azide anion as the reaction proceeds. A number of modified α-cyclodextrin derivatives have been prepared and fully characterized, among which are: the useful intermediate α-cyclodextrin-dodeca(2,3)benzoate (**3**); hexakis(6-amino-6-deoxy)-α-cyclodextrin hexahydrochloride (**7**); hexakis(6-amino-6-deoxy)-dodeca(2,3)-*O*-methyl-α-cyclodextrin hexahydrochloride (**9**), hexa(6)-*O*-methyl-α-cyclodextrin (**13**). The direct substitution is shown to be even more efficient for β-cyclodextrin (**16**), giving the heptakis(6-azido-6-deoxy)-β-CD-tetradeca(2,3)acetate (**17**), while the indirect strategy fails. The compounds are characterized by extensive use of ^{13}C- and ^{1}H-NMR. spectroscopy. The steric and statistical problems of selective polysubstitution reactions for the cyclodextrins are discussed, and possible reasons for the observed differences in reactivity between α- and β-cyclodextrins are examined.

The dodecabenzoate **3** presents a very marked solvent effect on physical properties (IR. and NMR. spectra, optical rotation); the effects observed may be ascribed to an unusually strong intramolecular network of hydrogen bonds which severely distorts the α-cyclodextrin ring and lowers the symmetry from six-fold to three-fold.

Introduction. – The cyclodextrins are a family of cyclic α-(1–4)-linked oligo-D-glucoses of toroidal shape formed from starch by *Bacillus macerans.* Their ability to form inclusion complexes by insertion of a wide variety of organic molecules into their hydrophobic intramolecular cavity, together with the presence of numerous hydroxyl groups available for modification, have provided impetus to a large number of investigations aimed at the study of molecular complexation, molecular catalysis, and enzyme models [1–4].

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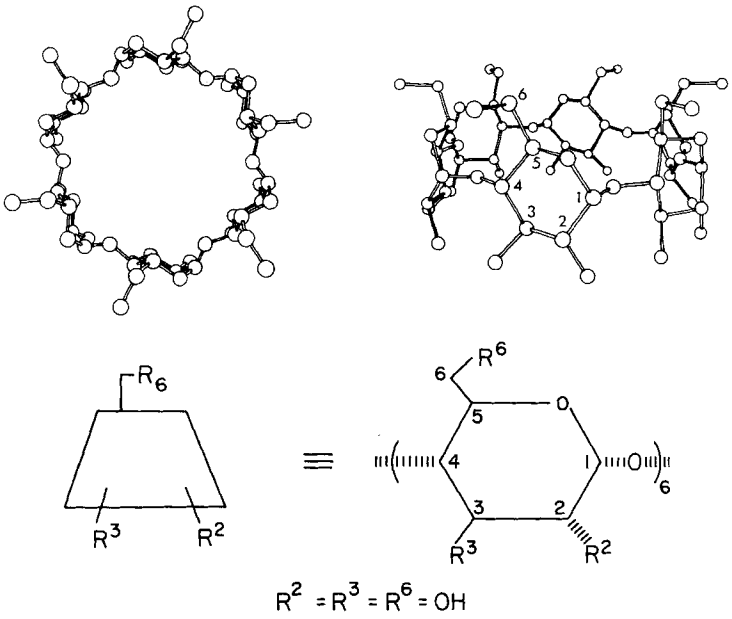

Fig. 1. *Schematic representation of α-cyclodextrin* (bottom); *view from the primary hydroxyl side* (top left) *and side view* (top right) *of the molecular structure of α-cyclodextrin* based on crystallographic results [5]; only carbon and oxygen atoms are shown.

The size of the intramolecular cavity, and therefore the complexation and catalytic properties, depends on the number of glucopyranose units forming the ring, with six and seven such units in α- and β-cyclodextrin respectively (α-CD and β-CD). Thus for α-CD the 'top' perimeter of the torus (~ 9 Å high and 13.5 Å in outside diameter) is lined with the six primary hydroxyl groups (at C(6) of the sugar molecules) and the slightly wider 'bottom' is ringed by the twelve secondary hydroxyl groups (at C(2) and C(3) [5]. The cavity, lined with a ring of C–H groups (C(3)), a ring of glycosidic oxygen atoms, and another ring of C–H groups (C(5)), is ~ 5 Å in diameter. For β-CD the intramolecular cavity is ~ 7 Å in diameter. *Figure 1* shows a drawing of α-CD and a schematic representation of the molecule.

Selective chemical modification of the hydroxyl groups in order to influence the complexation properties and/or to attach reactive functional groups is a major area of interest. The achievement of selective and efficient modification, especially polysubstitutions, is complicated by the statistical problem imposed by the large number of hydroxyl groups (18 for α-CD, 21 for β-CD). Furthermore, the geometry of the molecule is such that for selective polysubstitution, developing steric interactions may tend to reverse the initial selectivity ([6] and this communication). A number of modified cyclodextrins have been reported (see ref. in [1–4]) whose purity, however, has all too often not been subjected to sufficient critical scrutiny.

In the course of our investigations it became clear that methods of characterization of organic molecules like elemental analysis, thin-layer chromatography, IR. and UV.

spectroscopy *etc.* could not cope with the multiplicity of products, especially positional isomers, expected from reactions on these large, multi-functional substrates. Indeed, ^{1}H-NMR. spectroscopy proved to be of only limited utility, and we rely in this work on extensive use of ^{13}C-NMR. (with high signal/noise, routinely $>20/1$) as a most important tool for the control of purity as well as determination of structure. Further controls using high-pressure liquid chromatography were performed.

In view of our interest in the design of synthetic molecular receptors, carriers, and catalysts [7], the cyclodextrin unit, with its cavity, presented itself quite naturally as a substrate for further elaboration. For our purpose, as well as for the general interest of the problem, the first goal was the discrimination between the primary and the secondary hydroxyl groups of α- and β-CD, *i.e.* between the 'top' and 'bottom' of the two molecules. We report here our results on new selective and efficient reactions which lead to highly pure α- and β-cyclodextrin derivatives, where modification of all six or seven primary hydroxyl groups has been achieved.

We chose as a first target the hexa-amino derivative of α-CD in which the primary hydroxyl groups are replaced by primary amine groups. Such a compound should have several interesting features:

a) The six primary amine groups and twelve remaining secondary hydroxyl groups have very different chemical properties, allowing facile further selective modifications, *e.g.*, attachment of receptor sites or reactive groups;

b) Protonation of the amine groups should affect the complexation properties towards ionic substrates;

c) The 'top' *vs.* 'bottom' discrimination thus achieved could be further elaborated to give directional hydrophobic-hydrophilic derivatives which might act as complexing agents and carriers affecting membrane structure and transport.

Strategies for selective modification. – The problem of discriminating between one set of six primary hydroxyl groups and one set of twelve secondary hydroxyl groups raises the question of the strategy to be followed, either: 1) an *indirect* or reverse method based on non-selective reaction with all hydroxyl groups followed by selective deprotection of one set of functions, or 2) a *direct* approach involving selective reaction with only one set.

Reflection upon the problems of the direct approach reveals two major difficulties, statistical and steric. First, neglecting steric considerations, consider a reaction which has a 10:1 primary:secondary selectivity (*i.e.*, given *one* primary hydroxyl and *one* secondary hydroxyl, the reaction with the primary hydroxyl occurs in 91% yield). This hypothetical reaction applied to α-cyclodextrin does not give a $(0.91)^6 = 0.57 = 57\%$ yield of hexa-6-substituted product as one might think at first. The actual expected yield should be much lower. For hexa-6-substitution the first reaction would proceed with a selectivity of $(10\times 6):(1\times 12) = 5:1$ giving 83% yield. The second reaction on this first product would proceed with an apparent selectivity of $(10\times 5):(1\times 12) = 4.17:1$ giving 81%, *etc.* Thus, the yield would decline until the sixth and last reaction on the same molecule, where the selectivity would be $(10\times 1):(1\times 12) = 0.83:1$ giving a 45% yield for the last substitution. The

overall yield of the desired material is the product of these individual reaction yields and is only 11%[2]).

For α-cyclodextrin, the geometry of the molecule introduces another factor which will further lower the yields of selective direct reactions which rely on the local differences in steric hindrance. Since the primary hydroxyl groups are on one side of the molecule and the secondary ones are on the other, progressive reaction of bulky reagents with the primary hydroxyl groups must decrease the selectivity for steric reasons as the degree of substitution increases. Hence *Tsujihara et al.* ([6], see also references therein) showed in a careful study with β-cyclodextrin, that sulfonylation with *p*-toluenesulfonyl chloride did not proceed with sufficient selectivity to isolate a pure hepta-6-tosylate. With the potentially more selective mesitylenesulfonyl chloride the reaction proceeded rapidly to *hexa*-substitution with further reaction becoming very slow. Their final yield of a *hepta*-6-substituted product (the heptakis(6-azido-6-deoxy)-β-CD) was 1.2%. Independent work in our laboratory has confirmed this result with β-CD. With α-cyclodextrin we were not able to obtain the desired selectively substituted products in a pure state by either tosylation or mesitylene-sulfonylation following previous reports on hexa-(6-tosyl)-α-CD [8–10] and hepta-(6-tosyl)-β-CD [8] [9].

With smaller reagents the inherent reactivity difference between the sets of hydroxyl groups does not appear to be sufficient. It is thought that even in water there is a network of hydrogen bonds which links the hydroxyl groups at C(3) with the hydroxyl groups at C(2) on the contiguous glucose unit and lowers the pK_a of the secondary hydroxyls [11–14]. We have observed that for methylation with methyl iodide or dimethylsulfate, the secondary hydroxyl groups at position 2 react as fast or faster than the primary hydroxyl groups *(vide infra)*. Hence it would seem that the direct strategy requires a bulky reagent to first effect the discrimination.

The indirect strategy relies on the amplification of the steric difference between the two sets of hydroxyl groups. Since the ring of twelve secondary hydroxyl groups at the 'bottom' of the α-cyclodextrin is not substantially larger in diameter than the ring of six primary hydroxyl groups on the 'top', protection of all the hydroxyl functions should crowd the 'bottom' even more than the 'top'. Deprotection of the primary hydroxyl groups becomes easier and easier, *i.e.* if the first deprotection reaction proceeds with reasonably selectivity, then the subsequent reactions on the same molecule will be even more selective.

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[2]) The general formula for the % yield of the *i*-th substitution in a polysubstitution reaction where two groups of functions, *n* members in the preferred group and *m* members in the competing group, compete with a selectivity of x:y is given by equation (1):

$$\%\ \text{yield-}i\text{-th reaction} = 100\left[\frac{x(n-i+1)}{my+x(n-i+1)}\right] \tag{1}$$

The final overall yield for selective substitution at all *n* groups is the product given by equation (2):

$$\%\ \text{yield complete selective substitution} = 100\prod_{i=1}^{n}\frac{xi}{xi+my} \tag{2}$$

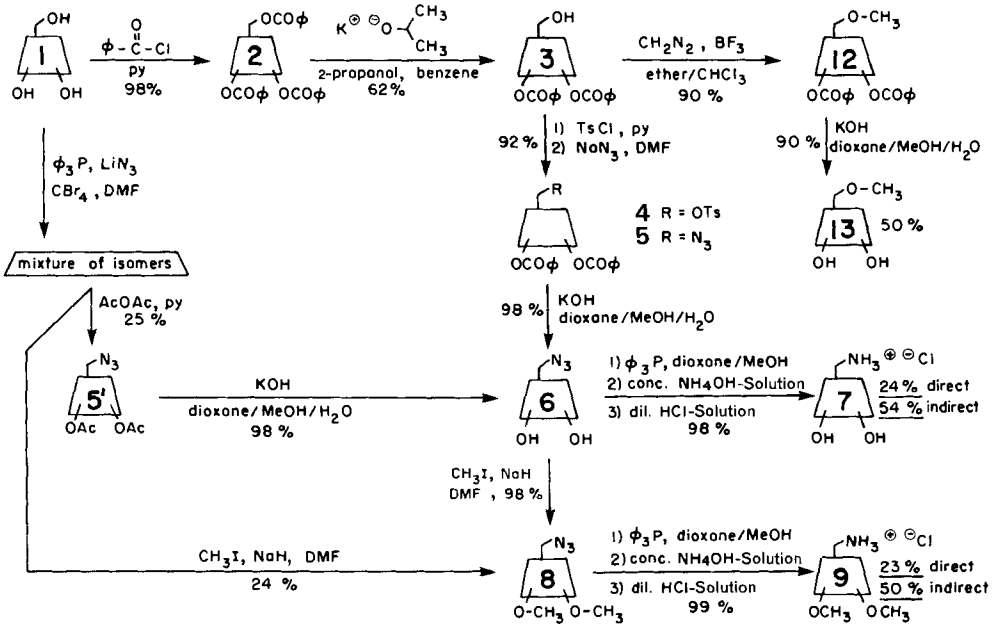
Neglecting other effects, this is the maximum possible overall yield.

Keeping in mind the requirements of each we chose to proceed with both strategies, and two methods were developed for α-cyclodextrin which led to the desired hexakis(6-amino-6-deoxy)-α-cyclodextrin (7, *Scheme 1*).

a) *The Dodecabenzoate Route* (indirect strategy) involving the selective deprotection of the primary hydroxyl groups.

b) *The Oxido-Reductive Substitution Route* (direct strategy) involving the selective reaction at the primary hydroxyl groups.

Scheme 1. *Reaction sequences for the selective modification of α-cyclodextrin* (see *Fig. 1* for α-CD representation)



The Dodecabenzoate Route: α-Cyclodextrin-dodeca(2,3)benzoate, 3, from Selective Deacylation of α-Cyclodextrin-octadeca(2,3,6)benzoate, 2. – The benzoyl group was considered to be a convenient acyl group since the corresponding esters should possess sufficient steric bulk and moderate reactivity. The octadecabenzoate of α-CD (**2**) was prepared by modification of the procedure of *Cramer et al.* [9]. Surprisingly, little or no hydrolysis was observed upon treatment of **2** with excess KOH in 90% dioxane at room temperature for 12 hours. However the addition of 6 equivalents of MeOH gave a rapid non-selective loss of all the benzoate esters in 15 minutes. Therefore anhydrous alcoholysis was explored using the potassium alkoxide in a mixture of the alcohol and benzene. Using methanol or ethanol rapid non-selective alcoholysis was observed, with thin layer chromatography (TLC.) revealing a multitude of products. At the other extreme, *t*-butyl alcohol showed only a few percent reaction after 19 hours at room temperature. However extremely selective and efficient cleavage of the primary esters

was achieved using potassium isopropoxide in 2-propanol and benzene under strictly controlled conditions. The reaction was followed by TLC. and showed remarkably few products with the desired α-cyclodextrin-dodeca(2,3)benzoate, (**3**) obtained in an estimated (by TLC.) 80% yield. The isolated yield after column chromatography was 62%. The product was identified by ^{1}H- and ^{13}C-NMR. spectroscopy, and showed the desired six-fold symmetry (See *Fig. 2* and *5*). The spectral results will be discussed below. The remarkably few products observed (by TLC.) during reaction suggests that, as discussed above, when one or two benzoate

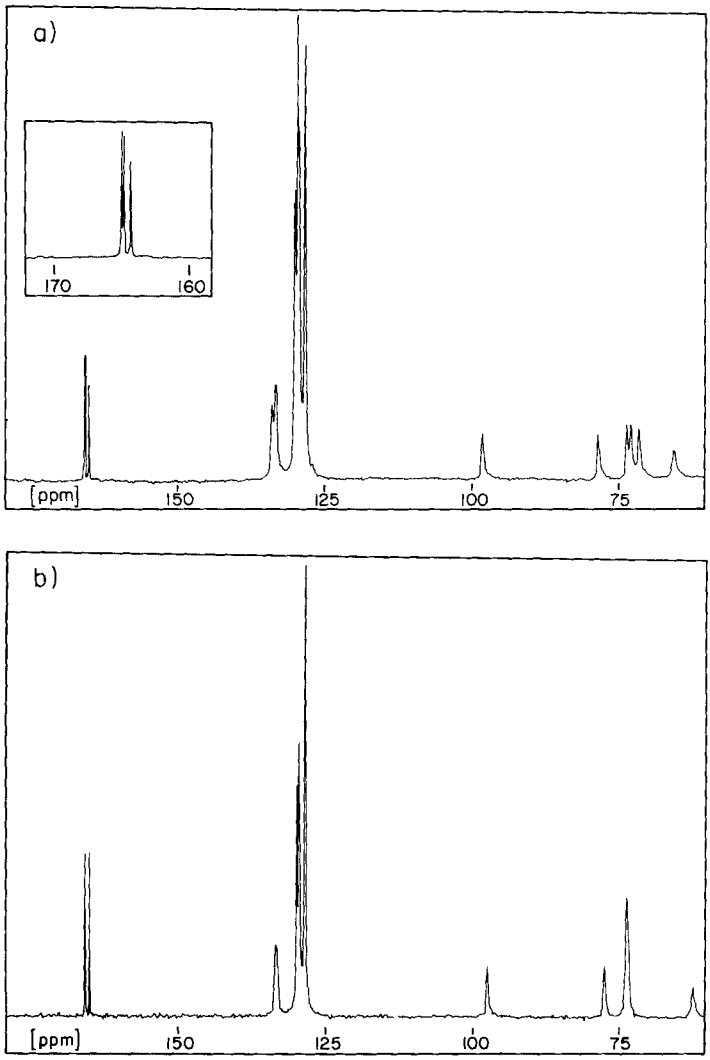


Fig. 2. *^{13}C-NMR. spectra of: a) α-cyclodextrin-octadeca(2,3,6)benzoate* (**2**); inset shows expansion of the three carbonyl carbon signals; b) *α-cyclodextrin-dodeca(2,3)benzoate* (**3**) (in DMSO-d_6; 25 MHz; shifts in ppm from internal TMS).

esters are removed from the primary side of the cyclodextrin, removal of the remaining benzoates on that side is rapid. Similarly, but less frequently, when a benzoate ester on the secondary site is cleaved, this is followed by rapid removal of several more secondary benzoates. The fact that one of the major side-products has fewer than twelve benzoate esters suggested that this might be α-CD-hexa(2)benzoate or α-CD-hexa(3)benzoate. However ^{13}C-NMR. analysis did not show the symmetry expected for these derivatives.

Attempts to optimize the reaction gave no improvement in yield. The alcoholysis was routinely run with *two* equivalents of isopropoxide (the reaction is catalytic with respect to base) for 12 hours at 0 °C simply to facilitate the careful following of the reaction by TLC. At room temperature with *six* equivalents of reagents the same result was obtained in 30 minutes. The use of other secondary alcohols showed no significant improvement: 2-butanol gave results similar to 2-propanol; cyclohexanol afforded a slightly better yield as estimated by TLC. but reaction work-up proved to be more difficult. Experiments with a more sterically hindered ester, α-CD-octadeca(2,3,6)-*o*-toluate, showed very slow reaction with isopropoxide: after 5 days at room temperature most of the products were more substituted than the desired dodeca-ester. Experiments on selective deacylation of the α-CD-octadeca-acetate (**15**)[3]) were unsuccessful.

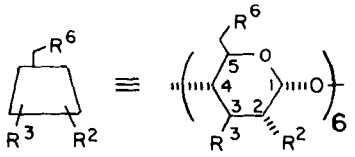
Hexakis(6-amino-6-deoxy)-α-cyclodextrin hexahydrochloride (**7**) *and derivatives.* Tosylation of the dodecabenzoate **3** followed by treatment with sodium azide in dimethylformamide (DMF) affords the hexakis(6-azido) derivative **5** *via* the hexa(6)tosylate **4**. Both reactions have very high isolated yields (> 95%). Again, ^{13}C-NMR. spectroscopy of each product confirmed the expected six-fold symmetry. Base hydrolysis of **5** removes quantitatively the twelve benzoate groups when performed with KOH in dioxane containing water and methanol. Additional water has to be added in the course of the reaction since the dissolution of the starting material and product requires different solvent decomposition. Hydrolysis does not occur upon treatment of **5** with KOH/dioxane/water in the absence of methanol at room temperature.

The reduction of the hexa(6-azido)-α-CD (**6**) to the hexa(6-amino) derivative was achieved very smoothly and in a very high isolated yield (> 98%) by treatment with triphenylphosphine in purified dioxane followed by addition of concentrated ammonium hydroxide [15] [16]. The compound was isolated as its hexahydrochloride **7**. This procedure was by far the best of a number of reactions which had also been tried. Thus, for instance, whereas it has been reported that a hexa-azido derivative of α-CD may be catalytically reduced in 4 hours with hydrogen and platinum oxide at low pressure [10], our pure hexa(6-azido) compound **6** showed no reduction under similar conditions after several days. Indeed, attempts to reduce the hexa(6-azido) compound **5'** (discussed below) required 218 atm of hydrogen for 20 hours at 70° using 20% by weight platinum oxide catalyst before complete reduction of the azides was seen. Reduction with lithium aluminium hydride yielded products that proved difficult to isolate while use of sodium borohydride in refluxing 2-propanol gave rapid reduction which was

[3]) Prepared by the method of *French* [49].

accompanied by formation of several unidentified side-products. Attempts to reduce the hexa(6-azido)-α-CD-dodeca(2,3)benzoate (**5**) with either of these catalytic or hydride methods gave no reduction or reduction accompanied by partial loss of benzoate. The reduction of **5** with chromous chloride led with a rapid and complete loss of azide to a compound containing chromium ions which could not be removed.

Methylation of the hexa(6-azido)-α-CD (**6**) in DMF by treatment with crystalline sodium hydride and purified methyl iodide gives a quantitative yield of the dodeca(2,3)-*O*-methyl derivative **8**[4]). Reduction of **8** with triphenylphosphine and ammonium hydroxide affords the hexakis(6-amino-6-deoxy)-dodeca(2,3)-*O*-methyl-α-CD, a hexa-amino derivative of cyclodextrin having a completely *O*-methylated 'bottom' isolated as its hexahydrochloride salt **9**. For the purpose



10 $R^2 = R^3 = -OMe$ $R^6 = -NHAc$
11 $R^2 = R^6 = -OMe$ $R^3 = -OH$
14 $R^2 = R^3 = R^6 = -OMe$
15 $R^2 = R^3 = R^6 = -OAc$

of further characterization and for the demonstration of the facility of further elaboration **9** was converted to **10** with acetic anhydride and six equivalents of triethylamine in dioxane at room temperature for two hours. The hexakis(6-acetamido)-dodeca(2,3)-*O*-methyl-α-CD (**10**) was very soluble in both water and chloroform. Attempted acetylation of **7** with acetic anhydride and pyridine does not afford a clean hexakis(6-acetamido)-dodeca(2,3)acetate derivative either by reaction at room temperature or at reflux. It is noteworthy that the *O*-acetylation of the hexa(6-azido)-α-CD is easy (see below). All products discussed show clean ^{13}C-NMR. spectra in accord with their six-fold symmetry (see below) and have been fully characterized.

Oxido-Reductive Substitution Route. – *Formation of Hexakis(6-azido-6-deoxy)-α-Cyclodextrin,* **6**, *and Derivatives* (Scheme 1). Several methods for selective substitution of primary hydroxyl groups in the presence of secondary hydroxyl groups have been developed, especially in sugar chemistry [17] [18]. For example, primary hydroxyl groups have been selectively reacted to form primary tosylates [19] [21], tritylethers [22], pivaloyl esters [23], and alkyl halides (using *Vilsmeier-Haack* type reagents) [24] [25]. Keeping in mind the special requirements, discussed above,

[4]) The use of sodium hydride from 50% oil emulsion caused the reaction to be incomplete, even when most of the oil was removed from the hydride by extraction. Further, with either impure methyl iodide or DMF the reaction had a tendency to develop a large amount of heat and to explode. Exclusion of light is necessary to prevent trace iodine formation which leads to a brown colored crude product difficult to purify. These difficulties could be avoided by using freshly distilled reagents and *crystalline* sodium hydride.

imposed by the goal of selective poly-substitution of cyclodextrins, it seemed that a recently developed oxido-reductive substitution method offered a good chance for success. The reaction involves the production of a phosphonium salt used to activate a primary hydroxyl function towards nucleophic displacement [26–29]. For example, tri-*n*-butylphosphine, dialkyl disulfide, plus a ribonucleoside gave from 26–90% yield of the 5′-*S*-alkylthio-5′-deoxyribonucleoside [30], and triphenylphosphine, carbon tetrabromide, lithium azide, plus a ribonucleoside gave 45–92% yield of the 5′-azido-5′-deoxyribonucleosides [31].

Because of the apparent selectivity of the reaction and of the large size of the triphenylphosphine (and the even larger reactive phosphonium salt) we could expect that treatment of *α*-CD with triphenylphosphine (6 equiv.), carbon tetrabromide (6 equiv.), and lithium azide (large excess) in DMF at room temperature would give a sufficiently selective reaction to allow substitution of six primary hydroxyl groups prior to reaction with the secondary ones. This reaction is especially attractive since it does not in principle require the formation of a very hindered hexa-*O*-phosphonium derivative, but rather could proceed by sequential activation followed by *in situ* nucleophilic displacement at each primary hydroxyl group independently. In fact, it leads to a mixture of azido-deoxy-*α*-CD derivatives. As *Castro et al.* [29] found for *α*-D-glucopyranoside itself, blocking of the unreacted hydroxyl groups was necessary to effect separation of products. Hence the crude azidodeoxy-*α*-CD mixture was acetylated with acetic anhydride in pyridine and the desired product was separated by 'short column' chromatography [32] allowing the clean isolation of hexakis(6-azido-6-deoxy)-*α*-CD-dodeca(2,3)diacetate (**5′**), which could be quantitatively hydrolyzed to the hexakis(6-azido-6-deoxy)-*α*-CD (**6**); the latter was identical to the product obtained by the dodecabenzoate route. Alternatively, the crude azido-*α*-CD mixture could be quantitatively *O*-methylated with crystalline sodium hydride and methyl iodide in DMF giving a mixture of four azido-*O*-methylated compounds which could be separated by 'short column' chromatography, affording the hexakis(6-azido-6-deoxy)-dodeca(2,3)-*O*-methyl-*α*-CD (**8**), which proved identical to the product obtained by the dodecabenzoate route. The overall yield of **6** or **8** by this direct substitution route is about 25% from *α*-CD as compared to an overall yield of about 55% by the dodecabenzoate route, which involves more steps. Attempts to improve the yields of the direct substitution reaction failed and in most cases actually lowered the yield. For example, replacement of lithium azide by sodium azide gave incomplete substitution of the primary hydroxyl groups. Lowering the temperature or preformation of the phosphoniumcarbon tribromide bromide salt led to lower yields. Variation in the order of addition of reagents was ineffective. The reaction without the addition of azide gave no isolable brominated products. The three isolated side-products (possibly each a mixture of isomers) from the *O*-methylation of the crude azido-CD mixture were analyzed by ^{13}C-NMR. spectroscopy. The spectra were consistent with the formation of one, two, and three secondary azido-deoxy groups. ^{1}H-NMR. spectra of these side products showed the corresponding one, two, and three 6-*O*-methyl singlets expected. No evidence was seen for the high field ^{13}C signal expected for bromine substitution at a primary or secondary center ($CH_2OH \sim 61$ ppm, $CH_2-N_3 \sim 52$ ppm, CH_2-Br

~30 ppm). The ^{13}C-NMR. spectra suggest that only the secondary hydroxyl groups at C(2) are involved, but they are rather inconclusive and difficult to interpret in detail. In retrospect, the 25% yield obtained is quite good in light at the statistical factors discussed above for selective polysubstitution reactions. Neglecting complicating steric effects (*i.e.*, assuming each successive substitution exhibits the same inherent selectivity), the apparent selectivity primary:secondary is ~20:1 for this direct substitution reaction.

Selective *O*-Methyl Derivatives of α-Cyclodextrin. – Selectively *O*-methylated derivatives might be interesting as complexing agents [33] [34] and as substrates for further transformation. *Casu et al.* [35] synthesized the per-*O*-methylated *α*- and *β*-CD using MeI and BaO in DMSO and further reported that treatment of either *α*- or *β*-CD with dimethyl sulfate and BaO in a mixture of DMF and DMSO gave the dodeca(2,6)-*O*-methyl-*α*-CD or the tetradeca(2,6)-*O*-methyl-*β*-CD. The position of substitution was assigned by degradation studies. However, experimental details were brief. *Bergeron et al.* [36] used an extension of this alkylation to obtain the hepta(3-*O*-methyl)-*β*-CD. Hence *β*-CD was selectively allylated using allyl bromide, BaO and $Ba(OH)_2$ in DMF/DMSO to give the tetradeca(2,6)-*O*-allyl-*β*-CD, followed by *O*-methylation at the remaining hydroxyl groups, isomerisation to the vinyl ethers, and vinyl ether cleavage to give the desired hepta(3-*O*-methyl)-*β*-CD.

We found that per-*O*-methylation could be achieved using CH_3I and crystalline NaH in DMF giving the octadeca(2,3,6)-*O*-methyl-*α*-CD (**14**) in 98% yield. Successful selective reaction of the twelve 2,6-hydroxyl groups of *α*-CD depended crucially on the ability to keep the reaction cool, as it tended to quickly develop a large amount of heat rather unpredictably in the course of methylation, causing 3-*O*-methylation to occur. Our detailed procedure for the production of dodeca(2,6)-*O*-methyl-*α*-CD (**11**) is included in the experimental section.

Several new selectively *O*-methylated derivatives of *α*-CD are accessible by the dodecabenzoate route. Hence, treatment of the dodecabenzoate **3** with a large excess of dry, alcohol free diazomethane in ether/chloroform with BF_3 as catalyst, followed by 'short column' chromatography, gives a 90% yield of the hexa(6-*O*-methyl)-*α*-CD-dodeca(2,3)benzoate (**12**), which can be quantitatively methanolyzed to hexa(6-*O*-methyl)-*α*-CD (**13**) with an overall yield of 50% from *α*-CD. This 6-*O*-methylated derivative **13** has only free secondary hydroxyl groups with a lipophilic primary side, and should have interesting complexing properties. Specifically, this compound would be useful to test the proposal that the primary hydroxyls play an important role in complexation. [34] [37]. Although the reaction sequence has not been completed, the dodeca(2,3)-*O*-methyl-*α*-CD, with now only the primary hydroxyl groups free, should also be accessible from the dodecabenzoate **3**. Preliminary results indicate that treatment of **3** with dihydropyran in chloroform (and *p*-toluenesulfonic acid as catalyst) gives a good yield of clean hexa(6-*O*-pyranyl)-*α*-CD-dodeca(2,3)benzoate, which after methanolysis of the benzoates, *O*-methylation of the secondary hydroxyl groups, and acid hydrolysis of the protecting pyranyl ethers, should give the dodeca(2,3)-*O*-methyl-*α*-CD in good yield. Similarly, from the hexa(6-*O*-pyranyl)-*α*-CD one should be able to

Table 1. ^{13}C-*NMR. Chemical Shifts*

Compound	Solvent	C(1)	C(2)	C(3)
α-CD (**1**)	D_2O	101.5	71.8	73.4
	DMSO-d_6	101.9	72.0	73.2
Peracetate (**15**)[b])	$CDCl_3$	96.5	70.9	70.9
Perbenzoate (**2**)	$CDCl_3$	98.5	71.7	72.6
	DMSO-d_6	97.1	71.2	72.0
2,3-Dodecabenzoate (**3**)	DMSO-d_6	96.7	72.3	72.3
	$CDCl_3$	98.5, 94.7	69.9*[d])	71.0*[d])
Hexatosyl(2,3)dodecabenzoate (**4**)	$CDCl_3$	98.6	71.2	71.9
Hexaazido(2,3)dodecabenzoate (**5**)	$CDCl_3$	98.3	71.3	71.9
Hexaazido(2,3)dodecaacetate (**5'**)	$CDCl_3$	96.9	71.2	71.2
Hexaazide (**6**)	DMSO-d_6	101.7	71.6	72.7
Hexaammonium (**7**)	D_2O	101.4	71.4	72.6
Hexaazido(2,3)dodecamethyl (**8**)	$CDCl_3$	99.8	78.4	81.1
Hexaammonium(2,3)dodecamethyl (**9**)	D_2O	98.7	80.1*	81.3*
Hexaacetamido(2,3)dodecamethyl (**10**)	D_2O	98.4	80.5*	80.9*
2,6-Dodecamethyl (**11**)	$CDCl_3$	101.5	82.2	73.4
Hexamethyl(2,3)dodecabenzoate (**12**)	$CDCl_3$	98.4	72.5*	72.7*
Hexa-6-*O*-methyl (**13**)	DMSO-d_6	101.9	71.8	73.2
Per-*O*-methyl (**14**)	$CDCl_3$	100.2	81.5	82.3*

[a])All shifts are downfield in ppm from TMS (see experimental section); (d): double intensity of similar peaks, (b): identification based upon relative peak broadness observed, *x*: *ipso* position on benzene ring. Assignments of peaks marked with asterisks (*) are tentative. Numbers in parentheses in the '$-O-CH_3$' column refer to carbon of sugar. [b])From [44]. [c])Aromatic: 130.0, 129.9, 129.8, 129.6, 128.6, 128.1(x, d)

selectively *O*-methylate only the six 2-hydroxyl groups (using dimethyl sulfate as described) followed by deprotection to give the hexa (2-*O*-methyl)-α-CD.

^1H- and ^{13}C-NMR. Spectroscopic Characterization of the α-Cyclodextrin Derivatives. – Whereas the ^1H-NMR. spectra are usually too complex and too similar to be of much use in determining the structure and purity of the α-CD derivatives described here, the ^{13}C-NMR. spectra are of great value. Indeed, because of the 6-fold rotational symmetry of the system, very simple ^{13}C-NMR. spectra are expected, containing a maximum of six signals for the sugar skeleton. With spectra determined with high signal/noise ratios (routinely > 20/1), the absence of other peaks becomes a good criterion of purity. ^{13}C-NMR. spectra were taken for all the derivatives reported here *(Table 1)* and no signals due to impurities were discernible. Assignments for the ^{13}C-NMR. spectra *(Table 1)* are based upon the

for α-Cyclodextrin Derivatives[a])

C(4)	C(5)	C(6)	$-O-CH_3$	C=O	C_{para}
81.3	72.1	60.5			
82.0	72.0	60.0			
77.2	69.5	63.9		170.6(d), 169.2	(20.6($-CH_3$))
78.9	70.7	63.4		166.2, 166.0, 164.6	133.1, 132.4[c]) 132.0
77.0	69.9	63.9		165.5, 165.3, 164.8	133.4, 132.9[d]), 132.8
76.5	72.3	60.7		165.8, 165.1	133.3, 133.0[e])
75.6, 73.0	69.2, 66.0	62.1, 56.1		166.2, 165.0, 164.9, 163.2	132.6, 132.5[f]), 132.1, 131.9
[g])	70/2	69.2(b)		166.0, 164.5	132.5, 132.2[h])
79.6	71.3	52.3		166.1, 164.5	132.6, 132.3[i])
77.7	70.5	51.9		170.5, 169.3	(20.7($-CH_3$))
83.4	70.4	51.4			
82.5	68.0	40.4			
83.4	71.2	52.0	61.8(2), 58.3(3)		
80.3*	68.2	40.5	60.9(2), 58.3(3)		
81.8*	70.7	40.4	60.7(2), 58.0(3)	174.0	(22.2($-CH_3$))
83.7	70.5	71.0(b)	60.4(2), 59.1(6)		
78.5	71.6	72.2(b)	59.8(6)	166.6, 164.9	132.9, 132.5[j])
82.4	70.3	71.0(b)	58.0(6)		
82.5*	71.3	71.5(b)	61.9(2), 57.9(3), 59.0(6)		

128.0(x), 127.6. [d])Aromatic: 129.5, 129.3, 129.0(d), 128.7, 127.7. [e])Aromatic: 129.5(x), 129.2, 128.1. [f])Aromatic: 130.7, 129.3, 129.2, 128.8, 127.9, 127.7, 127.6, 127.3. [g])Peak not resolved from $CDCl_3$ signals. [h])Benzoyl: 129.8, 129.5, 129.4(x), 128.0(x), 127.6(d); Tosyl: 145.4, 133.1, 130.3, 128.3, 21.8($-CH_3$). [i])Aromatic: 129.9, 129.6, 129.3(x), 128.0(x), 127.7(d). [j])Aromatic: 130.2(x), 130.0, 128.0.

convincing assignments for α- and β-CD's by *Colson et al.* [38], work on the ^{13}C-NMR. spectra of peracetylated and 6-deoxy-cyclodextrins [39], and the wealth of data available concerning other carbohydrates and their derivatives (*e.g.* [40–42]). In general, the resonance of the anomeric carbon atom C(1), appears at ~100 ppm downfield from the reference signal of tetramethylsilane (TMS), with the signal for C(4) usually appearing at 76–83 ppm, and the signal for the unsubstituted primary carbon atom, C(6), at ~60 ppm. The signals of the other carbon atoms, C(2), C(3), and C(5), lie between those of C(6) and C(4). The *O*-methylation of a hydroxyl group is expected to shift the α-carbon downfield by 8–11 ppm, while the β-carbon atoms undergo 0.5–1.0 ppm upfield shifts. The *O*-methyl groups appear in the range 56–62 ppm. Esterification of a hydroxyl group shifts the α-carbon atom only slightly, but may affect more the signals of C(1), C(4) or C(5). Identification of C(6) is often facilitated by its relatively

shorter spin-lattice relaxation time, which results in a slightly broader signal than for the other sugar backbone carbon atoms. It is often difficult to decide among the possible assignments for C(2), C(3), and C(5); where alternative assignments are possible the relevant shifts are marked in *Table 1* with an asterisk, and the indicated assignments should be regarded as tentative.

For the benzoate derivatives, the furthest downfield signals, at 160–170 ppm and usually very sharp, belong to the carbonyl carbon atoms, which prove to be highly sensitive to the position of acylation and the substitution pattern. The small signals just upfield, at 130–135 ppm, belong to C_{para} ($\equiv C_p$) carbon atom of each benzene ring and are also quite sensitive to the substitution environment.

Figure 2 shows the ^{13}C-NMR. spectra of the α-CD-octadecabenzoate (**2**) and the α-CD-dodeca(2,3)benzoate (**3**) in DMSO-d_6 solution. The expected *six* signals for the sugar carbon atoms are found for each derivative in the region 60–100 ppm, indicating that the symmetry of the α-CD ring has been preserved. (The signals for C(2), C(3), and C(5) coincide for **3**). It is the ester carbonyl-C signals which indicate the degree of substitution. In the octadecabenzoate there are three carbonyl-C signals at equal intensity, one for each kind of ester (*i.e.* at C(2), C(3), and C(6)). The dodeca(2,3)benzoate shows *two* carbonyl-C peaks of equal intensity. The C_p carbon atoms show the same multiplicity. Hexatosylation at C(6) causes an ~8 ppm downfield shift (from 61 ppm to 69 ppm) of the C(6) signal, with slight changes for other carbon atoms. Replacement by azide shifts the C(6) signal upfield by 17 ppm to 52 ppm. Removal of the benzoates gives the hexakis(6-azido-6-deoxy)-α-CD (**6**), the spectrum of which is shown in *Figure 3*. Conversion to the hexa-ammonium compound **7** shifts the C(6) resonance upfield to 40 ppm *(Fig. 3)*. Throughout these transformations the six-fold symmetry, denoting hexa(6-substitution), is preserved. The ^{13}C-NMR. of the hexakis(6-amino-6-deoxy)-dodeca(2,3)-*O*-methyl-α-CD hexahydrochloride (**9**) is also shown in *Figure 3*, with the C(2) and C(3) resonances now shifted downfield near C(4) and the two *O*-methyl groups appearing at 58 and 61 ppm. The *N*-acetylation of **9** to **10** causes only a small downfield shift of the C(5) signal, with all other resonances remaining in virtually the same position.

The *O*-methylation of α-CD-dodeca(2,3)benzoate (**3**) to **12** causes a ~12 ppm downfield shift of the C(6) signal, and the spectrum shows the expected two benzoate carbonyl groups and the two C_p signals. Removal of the benzoates gives hexa(6-*O*-methyl)-α-CD (**13**) whose spectrum is shown in *Figure 4*. Deacylation causes only small shifts for C(2) and C(3), with larger shifts for C(1) and C(4).

The ^{1}H-NMR. spectra are not as useful as the ^{13}C-NMR. spectra, but several clear features can be observed[5]). The anomeric proton, H–C(1), is seen as a doublet at 4.5–5.5 ppm with $J_{1,2} \simeq 3$ Hz. For the benzoate derivatives **2**, **3**, **4**, **5** and **12**, the H–C(3) signal is a doublet of doublets far downfield, ~6 ppm, with $J_{2,3} \sim J_{3,4} \sim 10$ Hz and the H–C(2) signal is somewhat less deshielded and appears as a doublet of doublets at ~4.8 ppm. The use of 250MHZ- and 360MHz-^{1}H-NMR.

[5]) Assignments are based on decoupling experiments for **2** and **3**, the assignments for α-CD at 220 MHz previously determined [12] [43] and work on cyclodextrin peracetates [44] and 6-bromo-6-deoxy peracetates [25].

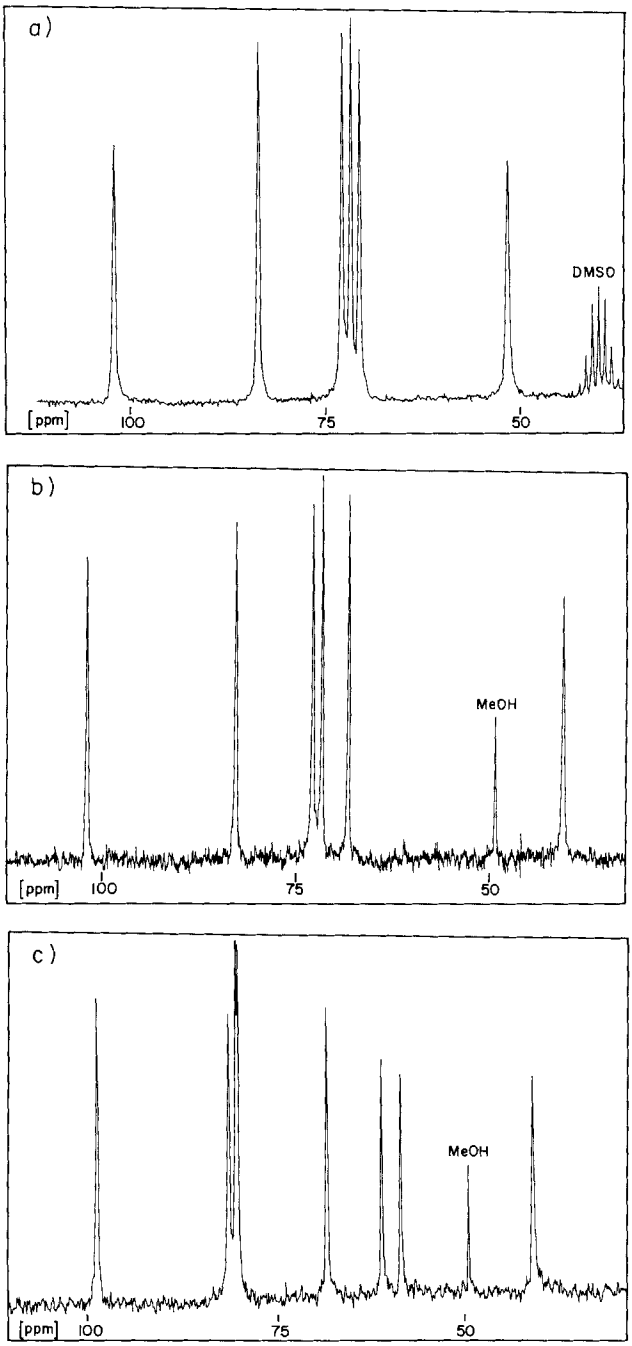


Fig. 3. *^{13}C-NMR. spectra of: a) hexakis(6-azido-6-deoxy)-α-cyclodextrin* (**6**) *in DMSO-d_6; b) hexakis(6-amino-6-deoxy)-α-cyclodextrin hexahydrochloride* (**7**) *in D_2O; c) hexakis(6-amino-6-deoxy)-dodeca-(2,3)-O-methyl-α-cyclodextrin hexahydrochloride* (**9**) *in D_2O* (25 MHz; shifts from TMS)

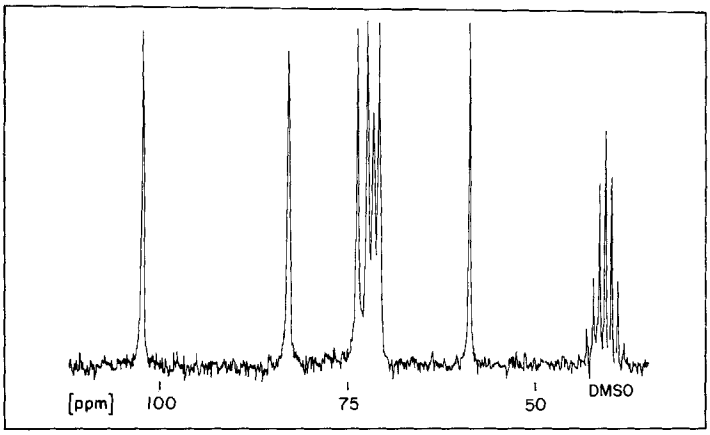


Fig. 4. *^{13}C-NMR. spectrum of hexa-6-O-methyl-α-cyclodextrin* (**13**) *in DMSO-d_6* (25 MHz)

for the perbenzoate **2** and the dodecabenzoate **3** reveals a different set of protons (*o*, *m*, and *p*) for each of the different positions of benzoate substitution (for **2**: C(2), C(3), and C(6); for **3**: C(2) and C(3). (See *Fig. 5* and also discussion below).

For the *O*-methyl derivatives **8**, **9**, **10**, **11**, **12** and **13** the positions of each *O*-methyl signal in the ^{1}H-NMR. spectra were found to be very close to those seen for per-*O*-methyl-α-CD itself, and the sharpness and singularity of each was a good indication of complete hexakis-substitution. Hence, for example, deliberately incomplete reduction of **8** was reflected in a multiplicity of signals for the *O*-methyl groups at C(2) and C(3).

Spectroscopic Properties of α-CD-dodeca(2,3)benzoate (3). – *Figure 5a* shows the 360MHz-^{1}H-NMR. spectrum of the α-CD-octadeca(2,3,6)benzoate (**2**) in $CDCl_3$ solution. All signals could be assigned by decoupling experiments. Of note are the very low field ortho-proton doublet (one of three sets of ortho-doublets, each twelve protons), the H–C(3) triplet at ~6.3 ppm (six protons), the H–C(1) doublet at ~5.5 ppm (six protons), and the H–C(2) doublet of doublets at ~5 ppm (six protons). In the 360MHz-^{1}H-NMR. spectrum of the dodecabenzoate (**2**) in $CDCl_3$ solution *(Fig. 5b)*, the six-fold symmetry is unexpectedly reduced to three-fold with two sets of signals observed for each sugar position. The spectrum has not been completely assigned, but some features are clear from decoupling experiments. The low field ortho doublet is now two doublets, each *six* protons. The large multiplet at ~6.3 ppm is a combination of a *m*-carbon-atom triplet from three upfield-shifted benzene rings (which show the *o*-doublet and *p*-triplet at ~6.7 and 6.9 ppm). The doublet at ~5.7 ppm is from *three* H–C(1), coupled to the dramatically deshielded H–C(2) doublet of doublets at ~5.6 ppm (*three* protons). The broad peak at ~5.5 ppm appears to be the other set of three H–C(1). None of the observed protons are exchangeable by prolonged shaking with D_2O. In contrast, the ^{1}H-NMR. spectrum (at 250 MHz) of **3** in DMSO-d_6 reveals the expected six-fold symmetry, shown in *Figure 5*. The H–C(3), H–C(1), H–C(2), and H–C(4) signals are shifted little from their positions seen for the

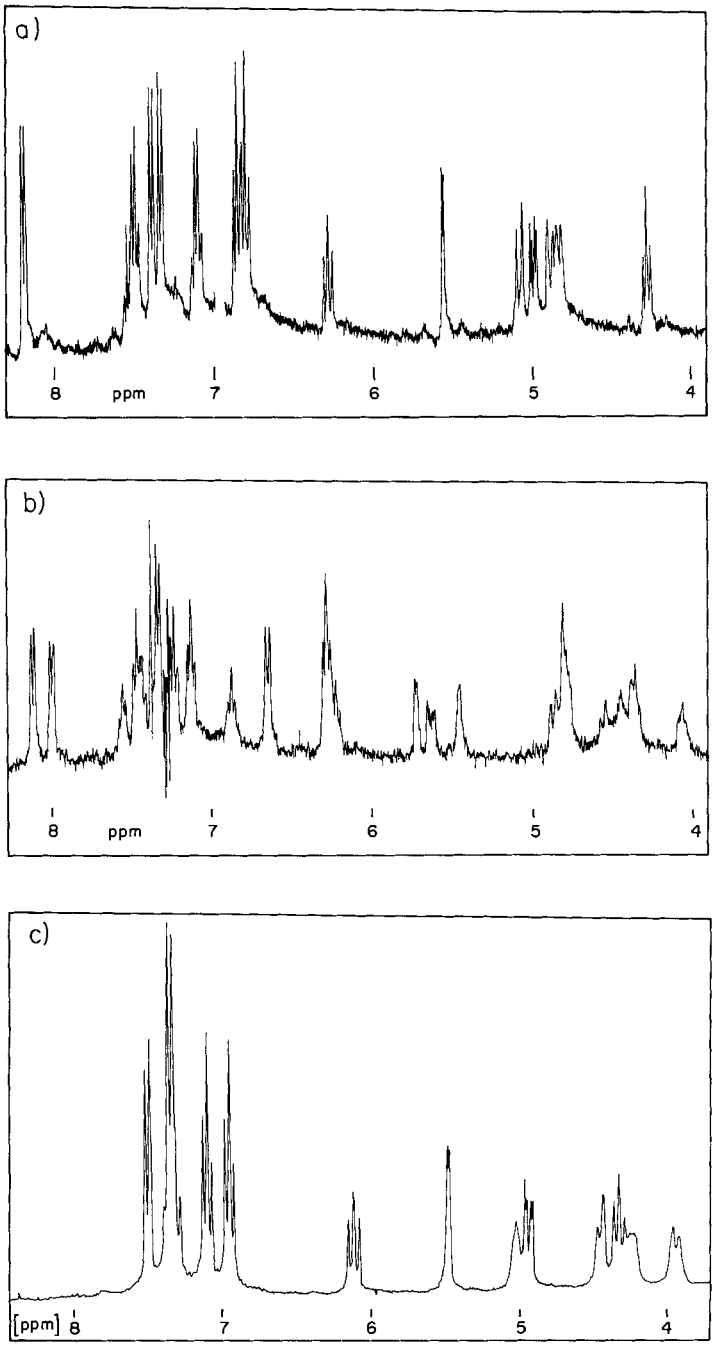


Fig. 5. ^1H-*NMR. spectra of: a) α-cyclodextrin-octadeca(2,3,6)benzoate* (**2**) ($CDCl_3$, 360 MHz); b) *α-cyclodextrin-dodeca(2,3)benzoate* (**3**) ($CDCl_3$, 360 MHz); c) *α-cyclodextrin-dodeca(2,3)benzoate* (**3**) (DMSO-d_6, 250 MHz, reference TMS)

perbenzoate **2** in $CDCl_3$. The H–C(5) and H–C(6) are shifted upfield as expected upon deacylation of the primary benzoates. The broadened signal at ~5 ppm is due to the six primary hydroxyl groups and is exchangeable with D_2O.

The ^{13}C-NMR. spectrum of the perbenzoate **2** in $CDCl_3$ is shown in *Figure 6a*. The expected three different carbonyl-C signals are seen at low field. The single peaks for each sugar carbon atom confirm the six-fold symmetry. For the dodecabenzoate **3** in $CDCl_3$ *(Fig. 6b) four* (instead of the expected two) carbonyl-C signals are seen. There are now two equal-sized signals for each sugar carbon

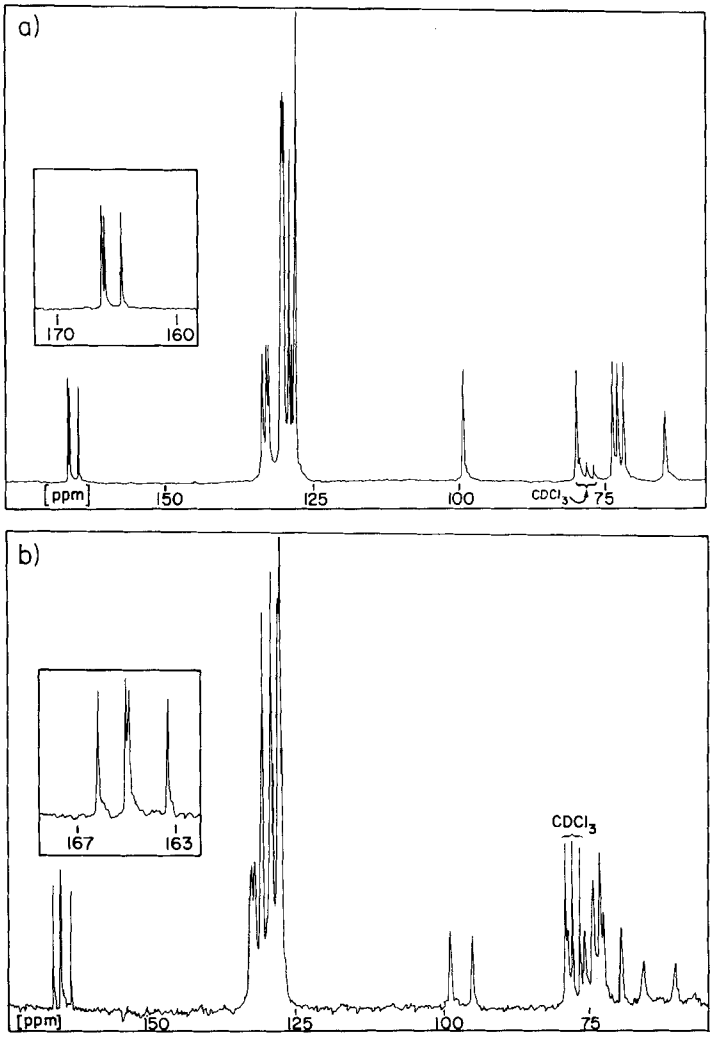


Fig. 6. ^{13}C-*NMR. spectra of:* a) *α-cyclodextrin-octadeca(2,3,6)benzoate* (**2**) in $CDCl_3$; inset shows expansion of the carbonyl carbon signals; compare to *Figure 2a;* b) *α-cyclodextrin-dodeca(2,3)benzoate* (**3**) in $CDCl_3$; inset shows expansion of the carbonyl carbon signals; compare to *Figure 2b* (25 MHz; reference: TMS)

atom position, *e.g.*, two C(1) peaks ~100 ppm, two C(4) peaks at ~75 ppm, and two C(6) peaks at ~60 ppm. In each of these cases one of these peaks is close to the position expected from the perbenzoate **2** spectrum, while the other is upfield. As with ^{1}H-NMR., the ^{13}C-NMR. of **3** in DMSO-d_6 *(Fig. 2b)* shows the expected six-fold symmetry. For both ^{1}H- and ^{13}C-NMR. spectroscopy, the reduction in apparent symmetry of **3** to three-fold in $CDCl_3$ is not concentration dependent over an order of magnitude in concentration.

The IR. spectra of the dodecabenzoate **3** in chloroform and DMSO suggests an explanation for the differences observed in the NMR. spectra. In DMSO the O–H stretching vibration gives a normal broad peak at ~3430 cm^{-1}. In chloroform however, it weakens by almost 200 cm^{-1} to 3260 cm^{-1}, a very low frequency for an O–H stretching vibration but close to that observed for strong, multiple hydrogen-bonds in the 'novolaks', polynuclear phenols which form strong cyclic donor acceptor hydrogen bonding systems [45]. The IR. spectra are not concentration dependent.

The dramatic 'doubling' of the ^{1}H- and ^{13}C-NMR. signals of **3** in $CDCl_3$, even for protons and carbon atoms remote from the primary hydroxyl groups, suggests that three of the six α-glucose units are in a significantly different environment from that in the perbenzoate **2**. The three-fold symmetry observed requires that these 'odd' glucose units be alternating units so as to maximise the hydrogen-bonding of three primary hydroxy groups, with the other three hydroxyl groups participating in a 'second shell'. It is possible that a few internally bound water molecules participate in this structure.

The optical rotations observed confirm some large conformational differences of **3** in the two solvents. While the rotations of **2** in chloroform and DMSO are virtually identical, the rotations of **3** in the two solvents (unchanged upon ten-fold dilution) differ by more than a factor of ten ($a_D^{22} = +9.0$, $c = 1.1$, $CHCl_3$; $a_D^{22} = +96$, $c = 1.3$, DMSO). This phenomenon is being further investigated.

Upon quantitative conversion of the dodecabenzoate **3** to the hexatosyl-dodecabenzoate **4** or to the hexa-*O*-methyldodecabenzoate **12**, the expected six-fold symmetry of the spectra is restored.

Selective Modification of β-Cyclodextrin. – Selective modification of β-CD might be expected to be easier than for α-CD. For example, whereas in a previously reported preparation of dodeca(2,3)-*O*-α-methyl-α-CD (**11**), *O*-methylation at C(3) was sometimes observed, no such tendency was found for the same reaction on β-CD [35]. This difference was ascribed to a stronger H-bond network for β-CD in the ring of secondary hydroxyl groups [35] [46]. Our work on selective primary tosylation or mesitylene sulfonylation of α- and β-CD's revealed that unwanted secondary sulfonylation was much more facile with α-CD than with β-CD. This tendancy was noted by *Pinter* [47] who was unable to isolate a polytosyl-α-CD derivative free of secondary tosylation, but who reported a polytosylated-β-CD free from secondary tosylation (by an ^{1}H-NMR. criterion).

There is then evidence to suggest than the direct strategy using the oxidoreductive substitution reaction might be even more effective for β-CD than for α-CD. Indeed, reaction of β-CD [16] in DMF with triphenylphosphine, lithium

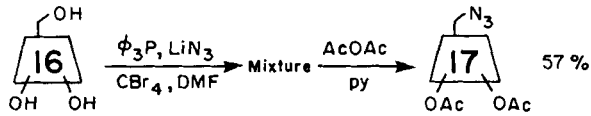
Table 2. ^{13}C-*NMR. Chemical Shifts*

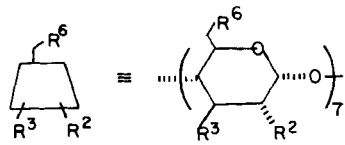
Compound	Solvent	C(1)	C(2)	C(3)
β-CD (**16**)	D_2O	101.9	71.9	73.1
	DMSO-d_6	103.1	74.3	73.6
Hepta-azido(2,3)tetradecaacetate (**17**)	$CDCl_3$	96.6	70.9	70.4
Peracetate (**18**)[b])	$CDCl_3$	96.8	70.9	70.4
Perbenzoate (**19**)	$CDCl_3$	97.7	71.7	71.7
	DMSO-d_6	97.5	71.2	71.2
2,6-Tetradecamethyl (**20**)	$CDCl_3$	101.0	81.9	70.6
3-Heptamethyl (**21**)[c])	D_2O	101.0	72.1	82.7[f])

[a])All shifts are downfield in ppm from TMS (see experimental section); (d): double intensity of similar peak, (b): identification based on relative peak broadness observed. Numbers in parentheses in the '$-O-CH_3$'

azide, and carbon tetrabromide gave a crude material which was acetylated and purified by 'short column' chromatography as in the α-CD case. This sequence gave a 57% yield of heptakis(6-azido-6-deoxy)-β-CD-tetradeca(2,3)acetate (**17**), over twice the yield for the α-CD reaction, representing a selectivity primary:secondary of 60:1 (*vs.* 20:1 for α-CD). The reaction sequence from this selectively hepta(6-substituted)-β-CD to the heptakis(6-amino-6-deoxy)-β-CD or the heptakis(6-amino-6-deoxy)-tetradeca(2,3)-*O*-methyl-β-CD has not been completed, but we anticipate no difficulties in the subsequent reactions, using conditions similar to those worked out for the corresponding α-CD derivatives. Therefore, these hepta(6-amino)-β-CD derivatives should be available in $>50\%$ yield from β-CD using the direct, oxido-reductive reaction sequence.

Scheme 2. *Selectively modified β-cyclodextrin derivatives*





18 $R^2 = R^3 = R^6 = -OAc$
19 $R^2 = R^3 = R^6 = -OCO\phi$
20 $R^2 = R^6 = -OMe$ $R^3 = -OH$
21 $R^2 = R^6 = -OH$ $R^3 = -OMe$

for β-Cyclodextrin Derivatives[a])

C(4)	C(5)	C(6)	$-O-CH_3$	C=O	C_{para}
81.1 82.7	72.1 73.2	60.4 61.2			
77.1	70.7	51.5		170.5, 169.5	(20.8($-CH_3$))
76.8	69.7	62.6		170.7, 170.4, 169.4	(20.8($-CH_3$))
78.0	70.2	63.7		166.2, 166.1, 164.6	133.5, 132.7, 132.3[e])
77.3	69.6	63.5		165.5, 165.2, 164.6	133.5, 133.1, 132.7[d])
83.6	73.6	71.3(b)	60.2(2), 59.3(6)		
77.8[f])	72.1	60.4	59.6(3)		

column refer to carbon of sugar skeleton. [b])From [44]. [c])Aromatic: 130.2, 129.8(d), 128.9, 128.5, 127.9, 127.8. [d])Aromatic: 129.6, 129.3, 129.2, 129.1, 129.0, 127.9. [e])From [36]. [f])Assignments are reversed in [36].

Application of the indirect strategy to β-CD did not give satisfactory results. Hence, attempts at selective deprotection of the β-CD perbenzoate using potassium isopropoxide in benzene/2-propanol failed to give isolable β-CD-tetradeca(2,3)benzoate, but rather showed a multitude of products indicating that initial selectivity of cleavage was not high, a possible reflection of a decrease in steric crowding at the secondary side due to the larger cyclodextrin ring size or of an increase in reagent accessibility to the inside of the β-cyclodextrin ring (see below). It is possible that with alcohols more hindered than 2-propanol selective cleavage for the β-CD-perbenzoate might be observed. The ^{13}C-NMR. data for the β-CD derivatives are given in *Table 2*. *Figure 7* shows the ^{13}C-NMR. spectrum for the heptakis(6-azido-6-deoxy)-β-CD-tetradeca(2,3)acetate (**17**).

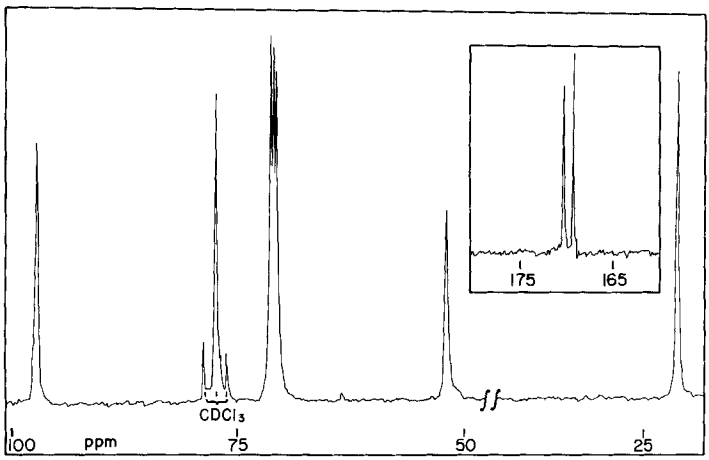


Fig. 7. *^{13}C-NMR. spectrum of heptakis(6-azido-6-deoxy)-β-cyclodextrin-tetradeca(2,3)acetate* (**17**); inset shows the two carbonyl carbon signals ($CDCl_3$, 25 MHz, reference TMS)

Conclusion. – Discrimination between the primary and secondary hydroxyl sides of the cyclodextrin molecule has been achieved for α-CD *via* an indirect strategy, whereas a direct strategy was preferable for β-CD. This contrasting behavior may be understood in terms of the difference in ring size (and perhaps in resulting flexibility) between α-CD and β-CD.

The success of the oxido-reductive substitution reaction (direct strategy) depends upon the sequential *in situ* activation and substitution of all primary hydroxyl groups. Apparently, for a monoglucopyranoside the activation step to form a bulky triphenylphosphonium ether is more rapid than subsequent substitution [29] so that with cyclodextrins these bulky groups might accumulate on the primary side. As a result steric hindrance to the subsequent substitution by azide anion increases faster for α-CD than for β-CD, since the latter has larger ring size. Thus, since substitution (as well as the later stages of activation) on the primary side is slower for α-CD than for β-CD, activation of the secondary side becomes more probable with α-CD than with β-CD. The indirect strategy depends more on steric effects which could include several contributions: 1) strain relieve which is greater in α-CD than in β-CD especially for removal of the first benzoyl group; this factor is even more important if the removal of the first group is rate determining; 2) the difference in accessability between the primary and secondary benzoate groups which is smaller for the somewhat less crowded β-CD perbenzoate; 3) the possible inclusion of the alcoholysis reagent which may be easier for the larger β-CD system; 4) the flexibility of the system which is lower for the smaller α-CD-perbenzoate thus increasing the difference in accessibility of the primary and secondary esters as compared to the more flexible β-CD-perbenzoate.

One may summarize these considerations as follows. For α-CD, primary/secondary selectivity may be achieved by *steric control* since the reactivity of the α-CD hydroxyl groups is more sensitive to steric effects, and these are more pronounced in the indirect method. On the other hand, β-CD is comparatively less affected by steric factors and selectivity is controlled by the *intrinsic functional reactivity* which is higher for primary than for secondary hydroxyl groups in the direct substitution process.

It is clear that successful selective polyfunctional substitutions on α- or β-cyclodextrins require the careful consideration of the geometry of the cyclodextrin molecule and the effects of statistical and steric factors on progressive reaction. The strategies and methods developed here provide efficient access to numerous selectivity functionalized cyclodextrins which should prove of interest in a wide variety of further studies on molecular receptors, transport, and catalysis.

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Experimental Part

General. – The ^{1}H-NMR. spectra were measured on the following spectrometers: *Varian* CFT-20 at 80 MHz, *Varian* XL-100 or *Varian* HA-100 at 100 MHz, *Cameca* THN-250 at 250 MHz, and

Bruker Spectrospin at 360 MHz. Chemical shifts for spectra take in $CDCl_3$ or DMSO-d_6 are given in ppm downfield from internal tetramethylsilane (TMS). Spectra taken in D_2O are referenced to internal sodium trimethylsilylpropanesulfonate (TSP), with the spectra being taken before and after addition to detect possible induced shifts caused by complexation of the reference salt. (None were observed). Coupling constants reported are based on first order analysis and are given in Hz. Abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet, br. = broad. The ^{13}C-NMR. spectra were measured at 25.1 MHz on a *Varian* XL-100 spectrometer operating in *Fourier*-Transform mode with complete proton decoupling. Spectra were typically accumulated with an acquisition time of 0.5 seconds, with no pulse delay, using a spectral width of 5 KHz and pulse width of 25 μs. (60° pulse). Accumulation times were 3–18 h (20,000–130,000 transients). Solutions were typically 15–50 mM. Chemical shifts for spectra taken in $CDCl_3$ or DMSO-d_6 are given in ppm downfield from internal TMS. Spectra taken in D_2O use methanol as an internal standard, which was determined to be 49.1 ppm downfield from external TMS in $CDCl_3$, and the shifts are referenced to TMS using this conversion. The internal methanol was shown not to effect the ^{13}C-NMR. spectra[6]). IR. spectra are reported in cm^{-1}, measured on a *Perkin Elmer* 457A grating spectrometer and are referenced to the polystyrene line at 1601.4 cm^{-1}. The microanalyses were performed at the *Service Central de Microanalyse* of the CNRS or by *Galbraith Laboratories* (Knoxville, Tennessee). Samples for analysis were rigorously dried under high vacuum at 30–100°[7]). The optical rotations (OR.) have been measured on a *Perkin-Elmer* 141 polarimeter using the 589 nm sodium line (D). Samples for OR. were rigorously dried. Thin layer chromatography (TLC.) was done on silica gel plates (*E. Merck* Silica G-60, 0,25 nm, glass) visualized with 50% sulfuric acid spray and heat. The Rf's reported refer to plates run for 10–15 cm, spotted with dilute solutions. For the detection of impurities, TLC. plates were run with several spottings using progressively higher concentrations of compound. The Rf's for such overloaded spots tended to be larger than for dilute samples. 'Short column' chromatography [32] was performed using TLC. grade silica gel (*E. Merck*, Silica G-60), which contains $CaSO_4$ (13%) as a binding agent. Other column chromatography was done using column grade silica gel (*E. Merck*, Silica G-60, 0.063–0.2 mm particle sizes). High pressure liquid chromatography (HPLC) was performed on a *Waters* M-6000 HPLC with differential UV. detection at 254 nm using a 50 cm × 2 mm column packed with *Waters* Porasil T (25–37 μ). Solvent systems for chromatography are *v/v*. All solvents and reagents used were carefully purified by standard methods. Dioxane was distilled from the Na/benzophenone ketyl. The azide salts were recrystallized from 2-propanol/ether and triphenylphosphine from ethanol. Carbon tetrabromide was sublimed at 0.1 mm, 40°, and stored in the dark. Crystalline sodium hydride was obtained from *Alfa-Ventron*. The cyclodextrins, α- and β-, obtained from *Aldrich Chemical Company*, were purified by the method of *French* [48], freeze-dried, and stored over P_2O_5 under HV. Other abbreviations: RT. = room temperature, i.V. = in vacuo, HV. = high vacuum.

Dodecabenzoate Route. – *α-Cyclodextrin-2,2′,2″,2‴,2⁗,2⁗′,3,3′,3″,3‴,3⁗,3⁗′,6,6′,6″,6‴,6⁗,6⁗′-octadecabenzoate* (**2**). This compound was prepared by modification of the method of *Cramer et al.* [9]. Purified and dried α-cyclodextrin (**1**), 9.73 g (10 mmol), was added with stirring to a solution of 160 ml distilled benzoyl chloride (~1.44 mol) in 240 ml dry pyridine. The bright pink solution was stirred at 50° for 72 h. The resulting mixture, now orange-brown with some precipitate, was evaporated under reduced pressure at 50° until about half volume. The solution was then cooled in an ice-bath, and 500 ml of anhydrous methanol were added very slowly with stirring. The solution was evaporated to a syrup i.V., and 1 l of dry methanol was added, followed by 100 ml of water. The copious white precipitate was filtered off, resuspended in 1 l of methanol, stirred for 1 h, and reprecipitated with 100 ml of water. The pure white α-CD-perbenzoate (**2**) was filtered off and

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[6]) The shifts for α-cyclodextrin thus referenced to internal methanol are uniformly 1.0 ppm smaller than those given by *Colson et al.* [38], who used external neat TMS as reference. We found the reference system using internal methanol gives better agreement between the shifts of spectra measured in D_2O and those measured in DMSO-d_6 and $CDCl_3$.

[7]) Some difficulty was encountered obtaining correct microanalyses for the polyazide compounds. For **5′**, **6**, and **17** correct analysis results were obtained for C and H, with the analysis results for N being consistently low. The hexakis(6-amino-6-deoxy)-α-CD hexahydrochloride (**7**) could not be completely dried without decomposition.

dried i.V. over P_2O_5 to give 28.0 g (98%). – TLC (benzene/ethanol 4:1): Rf = 0.80. – $a_D^{22} = +54$ ($c = 1.0$, $CHCl_3$). – $[a]_D^{22} = +66$ ($c = 1.0$, DMSO). – IR. (nujol): 1720 and 1740 (carbonyls); 1600, 1580, and 1450 (phenyl). – ^{1}H-NMR. ($CDCl_3$, 360 MHz): (see *Figure 5*): 4.29 (*t*, 6 H–C(4), $J_{3,4} = J_{4,5} = 9.5$); 4.85 ($d \times d$, 6 H–C(5), $J_{4,5} = 9.5$, $J_{5,6a} = 4$, $J_{5,6b} < 2$); 4.90 ($d \times d$, 6 H_a–C(6), $J_{gem} = -12.8$, $J_{5,6a} = 4$); 5,00 ($d \times d$, 6 H–C(2), $J_{1,2} = 3.4$, $J_{2,3} = 10.4$); 5.09 (*d*, 6 H_b–C(6), $J_{5,6b} < 2$, $J_{gem} = -12.8$); 5.57 (*d*, 6 H–C(1), $J_{1,2} = 3.4$); 6.81 (*t*, 12 H–C_m, $J_{o,m} = J_{m,p} = 8$); 6.86 (*t*, 12 H–C_m, $J_{o,m} = J_{m,p} = 8$); 7.10 (*d*, 6 H–C_p, $J_{m,p} = 8$); 7.12 (*d*, 6 H–C_p, $J_{m,p} = 8$); 7.33 (*d*, 12 H–C_o, $J_{o,m} = 8$); 7.39 (*d*, 12 H–C_o, $J_{o,m} = 8$); 7.49 (*t*, 12 H–C_m, $J_{o,m} = J_{m,p} = 8$); 7.55 (*d*, 6 H–C_p, $J_{m,p} = 8$); 8.18 (*d*, 12 H–C_o, $J_{o,m} = 8$).

$(C_{27}H_{22}O_8)_6$ (2846.83) Calc. C 68.35 H 4.67% Found C 68.21 H 4.67%

a-Cyclodextrin-2,2',2'',2''',2'''',2''''',3,3',3'',3''',3'''',3'''''-dodecabenzoate (**3**). Potassium isopropoxide solution in 2-propanol was prepared by adding carefully cleaned potassium metal (scraped clean under mineral oil of all gray residue, cut into small 1 cm^3 pieces, and washed free of all oil in dry heptane under nitrogen) to dry 2-propanol with stirring. The solution was titrated to determine the concentration of base. 8.54 g dried *a*-perbenzoate (**2**) (3 mmol) was added with stirring to 120 ml dry benzene, and 60 ml dry 2-propanol was added. The solution was then cooled to 0°, and 4.6 ml of 1.32M potassium isopropoxide solution in 2-propanol was added (6 mmol). The solution was stirred at 0° for 12 h and then neutralized with 0.1N HCl. The solution was evaporated under reduced pressure to a syrup, and the syrup was dissolved into 200 ml dry ethanol free chloroform. The chloroform solution was extracted three times with an equal volume of water, dried over magnesium sulfate, and filtered. To the chloroform solution was added hexane until the crude product precipitated out as a white powder. Yield of crude product: 5.64 g TLC. (benzene/ethanol 4:1) showed the product at Rf 0.44 and four other spots, at Rf's 0.61, 0.48 (very faint spot), 0.17 and 0.07. 5.64 g of this crude material was dissolved in 20 ml of benzene/ethanol 6:1 and layered carefully onto a silica gel column (4.8 × 95.0 cm, 850 g silica, prepared with benzene/ethanol 6:1) and eluted with the same solvent at a flow rate of *~ 1.0 l/h*. (Slower elution results in loss of most of the product). After the first 1300 ml (approximely 1.5 column volumes) 25 ml fractions were collected and monitored by TLC. The pure product (Rf: 0.44, benzene/ethanol 4:1) appeared in fractions 13–60. These fractions were combined and evaporated almost to dryness under reduced pressure. The product was then dissolved in a minimum of warm methanol, precipitated by the addition of water, filtered off, and dried i.V. over P_2O_5 to yield 4.06 g (61%) of *a*-CD-dodeca(2,3)benzoate (**3**). – TLC: (benzene/ethanol 4:1) Rf 0.44; (benzene/ethanol 6:1) Rf 0.23. – HPLC ($CHCl_3$/ethanol 6:1): one peak. – $[a]_D^{22} = +9.0$ ($c = 1.1$, $CHCl_3$), $[a]_D^{22} = +96$ ($c = 1.3$, DMSO). – IR. ($CHCl_3$): 3260 (br., hydroxyl); 1747 and 1725 (br., carbonyls); 1605, 1585, and 1500 (phenyl). – IR. (DMSO): 3430 (br., hydroxyl); 1735 and 1720 (carbonyl); 1600 (phenyl). – ^{1}H-NMR. ($CDCl_3$, 360 MHz): see *Figure 5* and discussion. – ^{1}H-NMR. (DMSO, 250 MHz) (see *Fig. 5*): 3.92 (br. *d*, 6 H–C5), $J \approx 10$); 4.2 (br. *d*, 6 H–C(6), $J \approx 10$); 4.31 (*t*, 6 H–C(4), $J_{3,4} \simeq J_{4,5} \simeq 9$); 4.4 (br. *d*, 6 H–C(6), $J = 10$); 4.93 ($d \times d$, 6 H–C(2), $J_{1,2} = 3.4$, $J_{2,3} = 10.5$); 5.02 (br. *t*, 6 H–O–C(6), $J \simeq 3$); 5.48 (*d*, 6 H–C(1), $J_{1,2} = 3.4$); 6.12 ($d \times d$, 6 H–C(3), $J_{3,4} = 9.5$, $J_{2,3} = 10.5$); 6.96 (*t*, 12 H–C_m, $J_{o,m} = J_{o,p} = 8$); 7.11 (*t*, 12 H–C_m, $J_{o,m} = J_{o,p} = 8$); 7.32 (*t*, 6 H–C_p, $J_{m,p} = 8$); 7.35 (*d*, 12 H–C_o, $J_{o,m} = 8$); 7.37 (*t*, 6 H–C_p, $J_{m,p} = 8$); 7.90 (*d*, 12 H–C_o, $J_{o,m} = 8$). – ^{13}C-NMR. ($CDCl_3$ and DMSO) see *Table 1* and *Figures 2* and *6*.

$(C_{20}H_{18}O_7)_6$ (2222.17) Calc. C 64.86 H 4.90% Found C 65.00 H 5.33%
„ 65.26 „ 5.06%

a-Cyclodextrin-2,2',2'',2''',2'''',2''''',3,3',3'',3''',3'''',3'''''-dodecabenzoate-6,6',6'',6''',6'''',6'''''-hexa-p-toluenesulfonate (**4**). 0.67 g a-CD-dodeca(2,3)benzoate (**3**) (0.3 mmol) was dissolved in 30 ml of dry pyridine. To this solution was added 5.7 g (30 mmol) distilled *p*-toluenesulfonyl chloride and the reaction was left at RT. for 18 h. The clear solution (with a fine precipitate of pyridine hydrochloride) was poured in a thin stream into 400 ml of rapidly stirring ice/water. The fluffy white product precipitated and was rapidly separated from the water solution by centrifugation. This product was twice suspended in 400 ml of cold water, stirred for a few minutes and centrifuged again. The dried product showed one charable spot on TLC. (Rf 0.77, benzene/ethanol 4:1), but on fluorescent TLC. plates showed a very faint additional spot at Rf 0.04. This could be removed easily by dissolving the product in a minimum of $CHCl_3$/ethyl acetate 1:1 and passing the solution

rapidly through a very small (4×1 cm) silica column. The eluted solution was evaporated to give the pure hexa(6-tosyl)-α-CD-dodeca(2,3)benzoate (**4**) with a yield of 0.90 g (95%). – $[\alpha]_D^{22} = +104$ ($c = 1.1$, $CHCl_3$). TLC.: (benzene/ethanol 4:1) Rf 0.77; ($CHCl_3$/ethyl acetate 1:1) Rf 0.66. – IR. (KBr): 1737 and 1728 (carbonyl); 1600, 1980, 1487, 1450 (phenyl); 1360, 1175 (sulfonate). – IR. ($CHCl_3$): 1745 and 1730 (carbonyl); 1600, 1585, 1490, 1450 (phenyl); 1364 (sulfonate). – ^{1}H-NMR. ($CDCl_3$, 100 MHz): 2.52 (*s*, 18 H, 6 CH_3); 4.02 (br. *t*, 6 H–C(4)); 4.3–4.9 (*m*, 24 H, H–C(2,6,5)); 5.12 (*d*, 6 H–C(1)); 6.01 (br. *t*, 6 H–C(3); 6.8–8.1 (*m*, 72 H-aromatic). – ^{13}C-NMR. ($CDCl_3$): see *Table 1*.

$(C_{27}H_{24}O_9S)_6$ (3147.31)	Calc.	C 61.82	H 4.61	S 6.11%	Found	C 61.54	H 4.63	S 6.13%
					,,	61.28	,, 4.61	,, 6.11%

6,6′,6″,6‴,6⁗,6⁗′-Hexaazido-6,6′,6″,6‴,6⁗,6⁗′-hexadeoxy-α-cyclodextrin-2,2′,2″,2‴,2⁗,2⁗′,3,3′,3″,3‴,3⁗,3⁗′-dodecabenzoate (**5**). To a solution of 0.787 g (0.25 mmol) hexa(6-tosyl)-α-CD-dodeca(2,3)benzoate (**4**) in 10 ml dry dimethylformamide (DMF) under N_2 was added 1 g (~15 mmol) dry sodium azide. The reaction was stirred under N_2 at 65° for 18 h, cooled to RT. and poured into 150 ml of ice water. The white precipitate was filtered off, resuspended in 150 ml of water, filtered off again, and dried i.V. over P_2O_5 to give 0.575 g (97%) of the pure hexakis(6-azido-6-deoxy)-α-CD-dodeca(2,3)benzoate (**5**). – TLC. (benzene/ethanol 4:1): Rf 0.63. HPLC. ($CHCl_3$/ethyl acetate 20:1): one peak. – $[\alpha]_D^{22} = +126$ ($c = 1.1$, $CHCl_3$). – IR. (KBr): 2100 (azide); 1740 and 1730 (carbonyl); 1600, 1580, 1485, 1450 (phenyl). No sulfonate. – IR. ($CHCl_3$): 2100 (azide); 1742 and 1727 (carbonyl); 1600 and 1450 (phenyl). No sulfonate. – ^{1}H-NMR. ($CDCl_3$, 250 MHz): 4.06 (*m*, 12 H–C(6)); 4.14 (br. *t*, 6 H–C(4), $J_{3,4} \approx J_{4,5} \approx 10$); 4.53 (*m*, 6 H–C(5)); 5.07 (*d*×*d*, 6 H–C(2), $J_{1,2} = 3$, $J_{2,3} = 10$); 5.46 (*d*, 6 H–C(1), $J_{1,2} = 3$); 6.18 (*t*, 6 H–C(3), $J_{2,3} \approx J_{3,4} = 10$); 6.8–7.5 (*m*, 60 H-aromatic). – ^{13}C-NMR. ($CDCl_3$): see *Table 1*.

$(C_{20}H_{17}N_3O_6)_6$ (2372.25)	Calc.	C 60.76	H 4.33	N 10.63%	Found	C 60.62	H 4.55	N 10.34%
					,,	60.75	,, 4.41	,, 10.37%

6,6′,6″,6‴,6⁗,6⁗′-Hexaazido-6,6′,6″,6‴,6⁗,6⁗′-hexadeoxy-α-cyclodextrin (**6**). 2.37 g (1 mmol) Hexakis(6-azido-6-deoxy)-α-CD-dodeca(2,3)benzoate (**5**) was dissolved in 300 ml of purified dioxane. To this solution was added 30 ml methanol, 10 ml water, and 1.6 g (~25 mmol) potassium hydroxide. The solution was stirred and became increasingly cloudy with a fine white precipitate. After 30 min an additional 25 ml water was added, which clarified the solution, and stirring was continued for an additional 1 h. The reaction was neutralized with 1N HCl and evaporated to dryness i.V. The white residue was extracted with 300 ml chloroform, filtered off, and stirred in a 200 ml fresh chloroform, filtered off and dried i.V. This chloroform insoluble material was suspended in 300 ml water, stirred for 30 min, filtered off, and washed with an additional 100 ml water. The pure product, chloroform and water insoluble, was dried extensively i.V. over P_2O_5 to yield 1.10 g (98%) of the pure hexakis(6-azido-6-deoxy)-α-CD (**6**). – TLC. (butanone/ethanol/water 7:1:1): Rf 0.32. – $[\alpha]_D^{22} = +88$ ($c = 1.1$, DMSO). – IR. (nujol): 3350 (br., hydroxyl); 2100 (azide); no carbonyl. – ^{1}H-NMR. (DMSO-d_6, 80 MHz): 3.2–3.9 (*m*, 36 H–C(2,3,4,5,6)); 4.86 (*d*, 6 H–C(1), $J_{1,2} = 2.5$); 5.42 (br. *s*, 6 H–O–C(3), $J_{3,OH} < 1$); 5.58 (*d*, 6 H–O–C(2), $J_{2,OH} = 6$). – ^{13}C-NMR. (DMSO-d_6): see *Table 1* and *Figure 3*.

$(C_6H_9N_3O_4)_6$ (1122.94)	Calc.	C 38.51	H 4.85	N 22.45%	Found	C 38.65	H 4.95	N 19.72%
					,,	38.92	,, 4.84	,, 19.56%

6,6′,6″,6‴,6⁗,6⁗′-Hexaamino-6,6′,6″,6‴,6⁗,6⁗′-hexadeoxy-α-cyclodextrin hexahydrochloride (**7**). 112 mg (0.1 mmol) hexakis(6-azido-6-deoxy)-α-CD (**6**) was suspended in a mixture of 10 ml purified dioxane and 2 ml distilled methanol. To the slightly milky solution was added, with stirring under N_2, 0.472 g (1.8 mmol) purified triphenylphosphine. Bubbles of gas were observed in the solution. Stirring was continued for 1 h and the solution became clear. To this solution was added 0.5 ml conc. NH_4OH-solution dropwise, and the mixture was stirred under N_2 for 12 h. The solvents were removed i.V., and the products were suspended in 25 ml water and neutralized with 1N and 0.1N HCl to pH 4. This water solution/suspension was washed three times with 50 ml benzene, the triphenylphosphine oxide going into the benzene layer, and the water solution was freeze dried and further dried i.V. over P_2O_5 to give 115 mg (97%) of the hexakis(6-amino-6-deoxy)-α-CD.

6 HCl (**7**). – $[\alpha]_D^{22} = +116$ ($c = 0.53$, H_2O). – IR. (KBr): 3400 (H_2O); 3300 (br., hydroxyl); 2900 (ammonium); 2000, 1610, 1490 (ammonium combination bands); no azide. – ^{1}H-NMR. (D_2O, 100 MHz): ~3.2 (*m*, 12 H–C(6)); 3.43 (*t*, 6 H–C(4), $J_{3,4} \simeq J_{4,5} \simeq 9$); 3.5 (*d*×*d*, 6 H–C(2), $J_{1,2} = 3$, $J_{2,3} = 10$); 3.85 (*d*×*d*, 6 H–C(3), $J_{2,3} = 10$, $J_{3,4} = 9$); ~4.0 (br. *m*, 6 H–C(5)); 5.01 (*d*, 6 H–C(1), $J_{1,2} = 3.1$). – ^{13}C-NMR. (D_2O): see *Table 1* and *Figure 3*.

$(C_6H_{12}ClNO_4)_6$ (1185.75)	Calc.	C 36.47	H 6.12	Cl 17.94	N 7.09%
$(C_6H_{12}ClNO_4)_6 \cdot 4\,H_2O$ (1257.78)	„	„ 34.38	„ 6.41	„ 16.91	„ 6.68%
	Found	„ 34.56	„ 6.70	„ 16.56	„ 6.30%

6,6′,6″,6‴,6⁗,6⁗′-Hexaazido-6,6′,6″,6‴,6⁗,6⁗′-hexadeoxy-2,2′,2″,2‴,2⁗,2⁗′,3,3′,3″,3‴,3⁗,3⁗′-dodeca-O-methyl-α-cyclodextrin (**8**). 0.561 g (0.5 mmol) hexakis(6-azido-6-deoxy)-α-cyclodextrin (**6**) was dissolved in 100 ml freshly-distilled dimethylformamide (DMF) in a flask fitted with a reflux condenser and placed under a positive pressure of nitrogen. The flask was placed in a stirring bath of ether (or dichloromethane) which serves to maintain the reaction at RT. To this solution was added 0.7 g (~30 mmol) *crystalline* sodium hydride and 3.8 ml (~60 mmol) *freshly distilled* methyl iodide. The reaction mixture was protected from light and stirred for 4 h. The mixture, a clear solution with solid excess sodium hydride, was evaporated under N_2 and protected from light, to about 100 ml. The suspension was rapidly filtered, and the clear solution was further evaporated to 50 ml, poured into 300 ml of rapidly stirring ice/water, and filtered. The precipitate was washed extensively with water, and dried i.V. over P_2O_5 to yield 0.594 g (92%) hexakis(6-azido-6-deoxy)-dodeca(2,3)-*O*-methyl-α-CD (**8**). – TLC.: (benzene/2-propanol 20:1) Rf 0.16; (benzene/2-propanol 10:1) Rf 0.33. – $[\alpha]_D^{22} = +169$ ($c = 0.57$, $CHCl_3$). – IR. ($CHCl_3$): 2100 (azide); 2925 (C–H); 2980 (CH_3-antisym.); 2830 (CH_3-sym.); no hydroxyl. – ^{1}H-NMR. ($CDCl_3$, 80 MHz): 3.1–3.9 (envelope, 36 H–C(2,3,4,5,6)); 3.49 (*s*, 6 H_3C–O–C(3)); 3.61 (*s*, 6 H_3C–O–C(2)); 4.98 (*d*, 6 H–C(1), $J_{1,2} = 3.0$). – ^{13}C-NMR. ($CDCl_3$): see *Table 1*.

$(C_8H_{13}N_3O_4)_6$ (1291.26) Calc. C 44.65 H 6.09 N 19.53% Found C 44.75 H 6.07 N 19.47%

6,6′,6″,6‴,6⁗,6⁗′-Hexaamino-6,6′,6″,6‴,6⁗,6⁗′-hexadeoxy-2,2′,2″,2‴,2⁗,2⁗′,3,3′,3″,3‴,3⁗,3⁗′-dodeca-O-methyl-α-cyclodextrin-hexahydrochloride (**9**). 400 mg (0.310 mmol) hexakis(6-azido-6-deoxy)-dodeca(2,3)-*O*-methyl-α-CD (**8**) was dissolved in 15 ml dry purified dioxane. To the stirring solution under N_2 was added 1.506 g (5.74 mmol) purified triphenylphosphine. After stirring for 1.5 h, 1.5 ml conc. NH_4OH-solution was added to the solution and stirring under N_2 was continued for 12 h. The solvents were removed i.V., and the white residue was suspended in 100 ml water, neutralized to pH 4 with 1N and 0.1N HCl, and washed with 3×50 ml benzene. The water solution was freeze-dried to give 415 mg (99%) of the hexakis(6-amino-6-deoxy)-dodeca(2,3)-*O*-methyl-α-CD hexahydrochloride (**9**). – $[\alpha]_D^{22} = +115$ (0.55, H_2O). – IR. (KBr): 3400 (H_2O); 2880 (br., ammonium); 2000, 1600, 1490 (ammonium combination bands); no azide. – ^{1}H-NMR. (D_2O, 100 MHz): 3.0–3.6 (envelope, 30 H–C(2,3,4,6)); 3.34 (*s*, 6 H_3C–O–C(2 or 3)); 3.43 (*s*, 6 H_3C–O–C(3 or 2)); 4.0 (br. *m*, 6 H–C(5)); 5.18 (*d*, 6 H–C(1), $J_{1,2} = 3$). – ^{13}C-NMR. (D_2O): see *Table 1* and *Figure 3*.

$(C_8H_{16}ClNO_4)_6$	Calc.	C 42.58	H 7.15	Cl 15.71	N 6.21%
(1354.07)	Found	„ 42.55	„ 7.30	„ 15.62	„ 6.02%

6,6′,6″,6‴,6⁗,6⁗′-Hexa-N-acetamido-6,6′,6″,6‴,6⁗,6⁗′-hexadeoxy-2,2′,2″,2‴,2⁗,2⁗′,3,3′,3″,3‴,3⁗,3⁗′-dodeca-O-methyl-α-cyclodextrin (**10**). 50 mg (0.037 mmol) Hexakis(6-amino-6-deoxy)-dodeca(2,3)-*O*-methyl-α-CD hexahydrochloride (**9**) was suspended in 1 ml dry purified dioxane and 30 µl (0.222 mmol) dry triethylamine was added, followed by 1 ml distilled acetic anhydride. The solution was stirred under N_2 for 2 h. The precipitate of triethylammonium chloride was filtered off and the solvent was evaporated i.V. Preparative TLC (butanone/methanol/water 7:1:3) gave the pure product (**10**) (free of triethylammonium chloride), freely soluble in both $CHCl_3$ and H_2O, which was freeze dried to give 47 mg (90%) hexakis(6-acetamido-6-deoxy)-dododeca(2,3)(*O*-methyl)-α-CD (**10**). – $[\alpha]_D^{22} = +98$ ($c = 1.0$, H_2O). – TLC. (butanone/methanol/water 7:1:3): Rf 0.34. – IR. (KBr): 3350, 3220 (N–H); 2900, 2800 (C–H); 1660 (carbonyl, amide I); 1550 (N–H band, amide II). – ^{1}H-NMR. (D_2O, 80 MHz): 1.92 (*s*, 6 H_3C–C=O); 3.1–3.9 (envelope, 36 H–C(2,3,4,5,6), 6 H–N); 3.44

(*s*, 6 H_3C–O–C(2 or 3)); 3.55 (*s*, 6 H_3C–O–C(3 or 2)); 5.18 (*d*, 6 H–C(1), $J_{1,2}=3$). – ^{13}C-NMR. (D_2O): see *Table 1*.

$(C_{10}H_{17}NO_5)_6$ (1405.65) Calc. C/N = 8.57 Found C/N = 8.65

Oxido-Reductive Route. – *6,6',6'',6''',6'''',6'''''-Hexaazido-6,6',6'',6''',6'''',6'''''-hexadeoxy-α-cyclodextrin-2,2',2'',2''',2'''',2''''',3,3',3'',3''',3'''',3'''''-dodecaacetate* (**5'**). To a solution of 0.973 g (1.0 mmol) α-cyclodextrin (**1**) in 25 ml dry DMF were added 1.47 g (30 mmol) purified lithium azide, 1.61 g (6.12 mmol) purified triphenylphosphine and 2.03 g (6.12 mmol) sublimed carbon tetrabromide. The addition of the later caused a mildly exothermic reaction and the solution turned yellow. The reaction was stirred under N_2 for 8 h. To the brown solution was added 5 ml methanol, and the volume was reduced to about half by rotary evaporation under reduced pressure. The solution was then poured into 250 ml water, and the precipitate was washed with water. The precipitate was rigorously dried i.V. over P_2O_5 for a minimum of 48 h and then suspended in 25 ml benzene, stirred for 30 min, filtered off, and washed with 10 ml benzene giving the crude azido-cyclodextrin mixture free of UV. absorbing materials. This benzene-insoluble crude product was then per-acetylated by heating in 15 ml pyridine with 6 ml acetic anhydride at 45° for 8 h. This reaction solution was diluted with benzene, washed twice with 10% chlorhydric acid, once with water, and dried over magnesium sulfate. TLC. on a 15 cm plates (benzene/ethanol 4:1) showed two products: Rf 0.48 and Rf 0.47. TLC. using butanone/ethanol/water 7:1:1, showed three products, Rf's: 0.32, 0.27 and 0.22. The desired product could be isolated by 'short column' chromatography (4.0 × 16 cm, 100 g silica gel, benzene/ethanol 15:1) and after precipitation from benzene/petroleum ether and prolonged drying i.V. gave 0.41 g (25%) hexakis(6-azido-6-deoxy)-α-CD-dodeca(2,3)acetate (**5'**). – TLC. (benzene/ethanol 4:1): Rf 0.48; TLC. (butanone/ethanol/water 7:1:1): Rf 0.32. – $[\alpha]_D^{22} = +133$ ($c = 1.1$, $CHCl_3$). – IR. ($CHCl_3$): 2900 (C–H); 2100 (azide); 1755 (carbonyl); 1250, 1050 (acetate). – ^{1}H-NMR. ($CDCl_3$, 100 MHz): 2.04 (*s*, 6 H_3C–C=O); 2.05 (*s*, 6 H_3C–C=O); 3.66 (br. *m*, 12 H–C(6)); 3.80 (*t*, 6 H–C(4), $J_{3,4} \sim J_{4,5} \sim 9$); 4.0 (br. *m*, 6 H–C(5)); 4.82 (*d* × *d*, 6 H–C(2), $J_{1,2}=3.5$, $J_{2,3}=10$); 5.04 (*d*, 6 H–C(1), $J_{1,2}=3.5$); 5.43 (*d* × *d*, 6 H–C(3), $J_{2,3}=10$, $J_{3,4}=9$). – ^{13}C-NMR. ($CDCl_3$): see *Table 1*.

$(C_{10}H_{13}N_3O_6)_6$ (1627.39)	Calc.	C 44.28	H 4.83	N 15.49%	Found	C 44.23	H 5.04	N 14.80%
						„ 44.59	„ 4.96	„ 14.54%

6,6',6'',6''',6'''',6'''''-Hexaazido-6,6',6'',6''',6'''',6'''''-hexadeoxy-α-cyclodextrin (**6**). The hexakis(6-azido-6-deoxy)-α-CD-dodecakis(2,3)acetate (**5'**) was quantitatively deacetylated to **6'** by the procedure described above for the debenzoylation of **5**. The yield was 98% and the product was identical by TLC. and ^{13}C-NMR. to that obtained by the dodecabenzoate route.

6,6',6'',6''',6'''',6'''''-Hexaazido-6,6',6'',6''',6'''',6'''''-hexadeoxy-2,2',2'',2''',2'''',2''''',3,3',3'',3''',3'''',3'''''-dodeca-O-methyl-α-cyclodextrin (**8**). 0.914 g of the crude azido-substituted-α-CD obtained as described above (from 0.69 g CD, 0.71 mmol) was per-*O*-methylated exactly as described for the pure hexakis(6-azido-6-deoxy)-α-CD (**6**) in the dodecabenzoate route. After work-up as described, 1.00 g of crude azido-per-*O*-methyl-α-CD was obtained which on TLC. (benzene/2-propanol 20:1) showed five spots, Rf's: 0.25, 0.20, 0.16, 0.14 and 0.0 with each of the first four being of approximately equal intensity, and the last was a minor product. This crude material was applied to a 'short column' (benzene/2-propanol 20:1, 3.4 × 12 cm, 55 g silica) and eluted with the same solvent. After 50 ml was eluted, 5 ml fractions were collected. The desired product, at Rf 0.16 (identified by ^{13}C-NMR. see discussion) was found cleanly separate in fractions 9–17, and was evaporated i.V., dissolved in 1 ml acetone, and precipitated by the addition of 30 ml water. After filtration, and drying i.V. over P_2O_5, hexakis(6-azido-6-deoxy)-dodeca(2,3)-*O*-methyl was obtained with a yield of 0.210 g (23%, from α-CD). This material proved identical to that obtained by the dodecabenzoate route as judged by TLC., ^{13}C-NMR., and ^{1}H-NMR.

***O*-Methyl Derivatives of α-Cyclodextrin.** – *2,2',2'',2''',2'''',2''''',6,6',6'',6''',6'''',6'''''-dodeca-O-methyl-α-cyclodextrin* (**11**)[8]). It was found necessary that all reagents for this reaction be of the highest purity (see foot-note 4 in discussion section). 0.97 g (1 mmol) α-cyclodextrin (**1**) was dissolved in 6 ml of distilled dimethyl sulfoxide. To this stirred solution 6 ml of freshly distilled dimethyl-

[8]) This compound has been previously reported [35] but some difficulties in synthesis were encountered by the authors and their experimental details were scarce.

formamide was added, and the solution was cooled to 0° in a large ice bath. Under N_2, 2 g (~6 mmol) of barium hydroxide ($Ba(OH)_2 \cdot 8\,H_2O$) and 2 g (~12 mmol) of *freshly ground* carbonate-free barium oxide was added. After several min 4 ml (~42 mmol) distilled dimethyl sulfate was added, and the mixture was stirred vigorously under N_2 for 48 h at 0°. To the white milky suspension 2 ml conc. NH_4OH-solution was added, stirred for 3 h, and the solution was evaporated rapidly i.HV. at a temp. not exceeding 90°. After cooling, the solid cake was extracted with 200 ml chloroform and twice again with 50 ml. The combined chloroform solution was washed 4 times with 100 ml water, dried over magnesium sulfate and evaporated to 10 ml. Addition of 100 ml hexane precipitated the crude product, which was washed with 200 ml petroleum ether (20–40°) and dried i.V. The crude material (0.93 g) showed three spots on TLC. (benzene/ethanol 4:1): Rf 0.28, 0.13, 0.06. The desired product (Rf 0.28) was purified on a silica gel column (1.9×55 cm) eluted with benzene/ethanol 20:1, evaporated i.V., recrystallized from chloroform/hexane, and dried i.V. at 80° over P_2O_5 to give 0.82 g (72%) of the dodeca(2,6)-*O*-methyl-*α*-CD (**11**). – TLC. (benzene/ethanol 4:1): Rf 0.28. – $[\alpha]_D^{22} = +120$ ($c = 0.93$, $CHCl_3$) (lit. [35] $[\alpha]_D^{20} = +130$). – IR. ($CDCl_3$) and ^{1}H-NMR. ($CDCl_3$) as previously described [35]. – ^{13}C-NMR. ($CDCl_3$): see *Table 1*.

$(C_8H_{16}O_5)_6$ (1141.19) Calc. C 50.52 H 7.42% Found C 50.31 H 7.37%
„ 50.43 „ 7.37%

*6, 6′, 6″, 6‴, 6⁗, 6⁗′-Hexa-*O*-methyl-α-cyclodextrin-2, 2′, 2″, 2‴, 2⁗, 2⁗′, 3, 3′, 3″, 3‴, 3⁗, 3⁗′-dodecabenzoate.* (**12**). 0.778 g (0.35 mmol) *α*-CD'-dodeca(2,3)benzoate (**3**) was dissolved in 100 ml dry, ethanol-free chloroform under N_2. The solution was cooled to 0° and 10 ml of 0.6M diazomethane (redistilled after drying over KOH for 48 h) in dry, alcohol-free ether was added. To the stirring yellow solution was added approximately 50 µl distilled BF_3 etherate. A vigorous evolution of N_2 was observed and 4 more 10 ml additions of diazomethane were made over the next 20 min. (Total diazomethane added was 50 ml of 0.6M = 30 mmol). The copious white polymethylene precipitate was filtered off, the ether removed under reduced pressure, and the chloroform solution washed once with hydrogen carbonate solution and twice with water. The chloroform layer was dried over sodium sulfate, filtered, and evaporated to dryness i.V. The crude white product was stirred in 100 ml methanol for 5 min, filtered, and precipitated from the methanol by the addition of 30 ml water. TLC. (benzene/ethanol 20:1) revealed one major product at Rf 0.34 and several very minor products at lower Rf's. There was in addition one very faint spot at Rf 0.36. Yield of crude material: 0.795 g. The product was purified by 'short column' chromatography eluting with benzene/ethanol 40:1. 0.500 g of the crude material was dissolved in 1 ml of solvent and applied to a 'short' silica column 3×15 cm (~55 g silica gel). After the elution of 150 ml, 5 ml fractions are collected and analyzed by TLC. The pure product was contained in fractions 6–14. The fractions were evaporated i.V. dissolved in methanol and precipitated with water to yield 0.466 g (90%). Hexa-6-*O*-methyl-*α*-CD-dodeca(2,3)benzoate (**12**). – TLC. (benzene/ethanol 20:1): Rf 0.34; TLC. (benzene/ethanol 4:1): Rf 0.73; TLC (butanone/ethanol/water 4:3:2): Rf 0.82. HPLC. ($CHCl_3$/ethyl acetate 25:1): one peak. – $[\alpha]_D^{22} = +79$ ($c = 0.6$, $CHCl_3$). – IR. ($CHCl_3$): 2975 ($-CH_3$, antisym.); 2950 (C–H), 2815 ($-CH_3$, sym.), 1746 and 1727 (shoulder), (carbonyls); 1600, 1580, 1450 (phenyl); no hydroxyl. – ^{1}H-NMR. ($CDCl_3$, 80 MHz): 3.55 (*s*, 6 H_3C–O–C(6)); 4.19 (br. *t*, 6 H–C(4), $J_{3,4} \sim J_{4,5} \sim 9$); 4.3 (*m*, 12 H–C(6)); 4.5 (*m*, 6 H–C(5)); 5.03 (*d*×*d*, 6 H–C(2), $J_{1,2} = 3.3$, $J_{2,3} = 11$); 5.44 (*d*, 6 H–C(1), $J_{1,2} = 3.3$); 6.16 (*d*×*d*, 6 H–C(3), $J_{2,3} = 11$, $J_{3,4} = 9$); 6.7–7.5 (*m*, 60 H, arom.). – ^{13}C-NMR. ($CDCl_3$): see *Table 1*.

$(C_{21}H_{20}O_7)_6$ (2306.33) Calc. C 65.62 H 5.24% Found C 65.74 H 5.13%

*6, 6′, 6″, 6‴, 6⁗, 6⁗′-Hexa-*O*-methyl-α-cyclodextrin* (**13**). 0.200 g (0.087 mmol) hexakis-6-*O*-methyl-*α*-cyclodextrin-dodeca(2,3)benzoate (**12**) was dissolved in 25 ml purified dioxane to which was added with stirring 2 ml ethanol and 2.1 ml 1N KOH (2.1 mmol KOH). The clear solution became cloudy. After 1 h 2 ml water was added to clarify the solution, and the stirring was continued for 30 min. To the clear solution was added 20 ml water, and the organic solvents were *carefully* removed under reduced pressure. The water phase was neutralized with 1N and 0.1N HCl, evaporated i.V. to ~10 ml, and 5 ml chloroform was added. The emulsion was *carefully* evaporated under reduced pressure until only one phase was apparent. The product thus precipitated and was centrifuged, washed with chloroform saturated water, and centrifuged again to give 82 mg slightly off-white material which reveals a small amount of methyl benzoate contamination in the ^{1}H-NMR. The

crude product was recrystallized twice from $CHCl_3$ and petroleum ether (40–60°) to give, after drying i.V., 80 mg (90% yield) hexa(6-*O*-methyl)-*α*-CD (**13**). – TLC. (butanone/ethanol/water 4:3:2): Rf 0.50; TLC. (butanone/ethanol/water 7:1:1): Rf 0.09. – $[\alpha]_D^{22} = +133$ ($c = 0.61$, DMSO). – IR. (nujol): 3320 (br., hydroxyl). – ^{1}H-NMR. (DMSO, 80 MHz): 3.24 (*s*, 6 H_3C–O–C(6)); 3.0→3.95 (envelope, 36 H–C(2,3,4,5,6)); 4.76 (*d*, 6 H–C(1), $J_{1,2} = 2.6$); 5.36 (*d*, 6 H–O–C(3), $J \simeq 1.5$); 5.44 (*d*, 6 H–O–C(2), $J \simeq 7$). – ^{13}C-NMR. (DMSO-d_6): see *Table 1* and *Figure 4*.

$(C_{17}H_{12}O_5)_6$ (1057.02) Calc. C 47.73 H 6.87% Found C 47.91 H 7.24%

*2,2′,2″,2‴,2⁗,2⁗′,3,3′,3″,3‴,3⁗,3⁗′,6,6′,6″,6‴,6⁗,6⁗′-Octadeca-*O*-methyl-α-cyclodextrin* (**14**). Previously reported synthesis required extensive purification [35] whereas methylation with methyl iodide and crystalline sodium hydride in DMF as described above for **8** gave a quantitative yield of the desired product without the need of chromatography. – $[\alpha]_D^{22} = +164$ ($c = 1.1$, $CHCl_3$), (lit. [35] $[\alpha]_D^{22} = +163$, $CHCl_3$). – IR. ($CDCl_3$) and ^{1}H-NMR. ($CDCl_3$) as reported [35]. – ^{13}C-NMR. ($CDCl_3$): see *Table 1*.

$(C_9H_{16}O_5)_6$ (1225.35) Calc. C 52.93 H 7.90% Found C 52.55 H 7.65%

Derivatives of β-cyclodextrin. – *β-Cyclodextrin-2,2′,2″,2‴,2⁗,2⁗′,3,3′,3″,3‴,3⁗,3⁗′,6,6′,6″,6‴,6⁗,6⁗′-heneicosabenzoate* (**19**). A procedure for β-CD-perbenzoate has been reported [9]. A modification of our procedure above for the α-CD-perbenzoate (**2**) gave a quantitative yield from β-cyclodextrin (**16**). – $[\alpha]_D^{22} = +22$ ($c = 1.1$, $CHCl_3$), (lit. [9] $[\alpha]_D$: $+18 \pm 2$ ($c = 0.1$, $CHCl_3$)). – ^{13}C-NMR. ($CDCl_3$ and DMSO): see *Table 2*.

$(C_{27}H_{22}O_8)_7$ (3321.30) Calc. C 68.35 H 4.67% Found C 68.34 H 4.49%
,, 68.37 ,, 4.68%

*2,2′,2″,2‴,2⁗,2⁗′,6,6′,6″,6‴,6⁗,6⁗′-tetradeca-*O*-methyl-β-cyclodextrin* (**20**). Prepared as previously reported [35] with the modifications reported here for the α-CD derivative **11**. – TLC. (benzene/ethanol 4:1): Rf 0.27. – $[\alpha]_D^{22} = +123$ ($c = 1.1$, $CHCl_3$), (lit. [35] $[\alpha]_D^{22} = +122$). – ^{1}H-NMR. ($CDCl_3$): as reported in [35]. – ^{13}C-NMR. ($CDCl_3$): see *Table 2*.

$(C_8H_{14}O_5)_7$ (1331.39) Calc. C 50.52 H 7.42% Found C 50.07 H 7.52%

6,6′,6″,6‴,6⁗,6⁗′-Heptaazido-6,6′,6″,6‴,6⁗,6⁗′-heptadeoxy-β-cyclodextrin-2,2′,2″,2‴,2⁗,2⁗′,3,3′,3″,3‴,3⁗,3⁗′-tetradecaacetate (**17**). Prepared as for **5′** above: 1.145 g (1.01 mmol) β-cyclodextrin, 1.716 g (36 mmol) lithium azide, and 1.871 g (7.13 mmol) triphenylphosphine were dissolved in 30 ml of dry DMF. To this solution 2.374 g (7.16 mmol) carbon tetrabromide was added, and a slightly exothermic reaction took place. The mixture was stirred for 8 h at RT. and 5 ml methanol was added to stop the reaction. After 15 min the volume was reduced to half under reduced pressure, and the yellow viscous solution was poured into 40 ml water. The precipitate which formed was isolated, washed with water, and air-dried. This crude material was dissolved in 150 ml warm methanol (dissolves with stirring overnight) and 50 ml petroleum ether was added. The precipitate (0.943 mg after drying over P_2O_5 i.V.) was dissolved in 15 ml dry pyridine, and 7 ml acetic anhydride was added. After stirring for 8 h at 50° under N_2, the solvents were removed under reduced pressure, and the residue was dissolved in 50 ml benzene. The benzene solution was washed three times with 10% HCl-solution and twice with water, dried over $MgSO_4$, filtered and evaporated i.V. Short column chromatography (benzene/ethanol 16:1, 100 g silica, 4×16 cm) gave 1.085 g (57%) heptakis(6-azido-6-deoxy)β-CD-tetradeca(2,3)acetate. – TLC. (benzene/ethanol 6:1): Rf 0.36. – IR. ($CHCl_3$): 2095 (azide); 1750 (carbonyl); no hydroxyl. – ^{1}H-NMR. ($CDCl_3$, 100 MHz): 2.07 (*s*, 7 H_3C–C=O); 2.08 (*s*, 7 H_3C–C=O); 3.66 (br. *m*, 7 H–C(6)); 3.8–4.2 (*m*, 14 H–C(4 and 5)); 4.81 (*d*×*d*, 7 H–C(2), $J_{1,2} = 3$, $J_{2,3} = 9$); 5.09 (*d*, 7 H–C(1), $J_{1,2} = 3$); 5.28 (*t*, 7 H–C(3), $J_{2,3} \sim J_{3,4} \sim 9$). – ^{13}C-NMR. ($CDCl_3$): see *Table 2* and *Figure 7*.

$(C_{10}H_{13}N_3O_6)_7$ (1898.62) Calc. C 44.28 H 4.83 N 15.49% Found C 44.46 H 4.81 N 14.58%

REFERENCES

[1] *F. Cramer*, «Einschlussverbindungen», Springer Verlag, Berlin 1954.
[2] *F. Cramer & H. Hettler*, Naturw. *54*, 625 (1977).
[3] *D. W. Griffiths & M. L. Bender*, Adv. Catalysis *23*, 209 (1973).

[4] *M. L. Bender & M. Komiyama*, 'Cyclodextrin Chemistry', Springer Verlag, Berlin 1978.
[5] *W. Saenger*, in 'Environmental Effects on Molecular Structure and Properties' (Editor B. Pullman), p. 265–305, D. Reidel Publishing Company, Dordrecht-Holland 1976.
[6] *K. Tsujihara, H. Kurita & M. Kawazu*, Bull. chem. Soc. Japan *50*, 1567 (1977).
[7] *J. M. Lehn*, Accounts chem. Res. *11*, 49 (1978); *J. M. Lehn*, Pure appl. Chemistry, in press (1978).
[8] *Von W. Lautsch, R. Wiechert & H. Lehmann*, Kolloid-Z. *135*, 134 (1954).
[9] *F. Cramer, G. Mackensen & K. Sensse*, Chem. Ber. *102*, 494 (1969).
[10] *S. Umezawa & K. Tatsuta*, Bull. chem. Soc. Japan *41*, 464 (1968).
[11] *B. Casu, G. Gallo & A. Vigevani*, Tetrahedron *22*, 3061 (1966).
[12] *M. St.-Jacques, P. R. Sundararajan, K. J. Taylor & R. H. Marchessault*, J. Amer. chem. Soc. *98*, 4386 (1976).
[13] *R. L. VanEtten, G. A. Clowes, J. F. Sebastian & M. L. Bender*, J. Amer. chem. Soc. *89*, 3253 (1967).
[14] *C. Van Hooidonk & C. C. Groos*, Rec. Trav. chim. Pays Bas *89*, 845 (1970).
[15] *W. C. Mungall, G. L. Green, G. A. Heavner & R. L. Letsinger*, J. org. Chemistry *40*, 1659 (1975).
[16] *T. Hata, I. Yamamoto & M. Sekine*, Chemistry Letters *1975*, 977.
[17] *A. H. Haines*, Adv. Carbohydrate Chemistry and Biochemistry *33*, 11 (1976).
[18] *B. J. Ball & F. W. Parrish*, Adv. Carbohydrate Chemistry *23*, 233 (1968).
[19] *R. S. Tipson*, Adv. Carbohydrate Chemistry *8*, 107 (1953).
[20] *J. Asselineau*, Bull. Soc. chim. France 937 (1955).
[21] *E. Hardegger, R. M. Montavon & O. Jucker*, Helv. *31*, 1863 (1948).
[22] *B. Helferich*, Adv. Carbohydrate Chemistry *3*, 79 (1948).
[23] *G. Weimann & H. G. Khorana*, J. Amer. chem. Soc. *84*, 4329 (1962).
[24] *D. Ikeda, T. Tsuchiya & S. Umezawa*, Bull. chem. Soc. Japan *44*, 2529 (1971).
[25] *K. Takeo, T. Sumimoto & T. Kuge*, Die Stärke *26*, 111 (1974).
[26] *J. B. Lee & M. M. El Sawi*, Chemistry & Ind. *1960*, 839.
[27] *J. B. Lee & T. J. Nolan*, Canad. J. Chemistry *44*, 1331 (1966).
[28] *J. P. H. Verheyden & J. G. Moffatt*, J. org. Chemistry *37*, 2289 (1972).
[29] *B. Castro, Y. Chapleur, B. Gross & C. Selve*, Tetrahedron Letters *1972*, 5001.
[30] *I. Nakagawa & T. Hata*, Tetrahedron Letters *1975*, 1409.
[31] *T. Hata, I. Yamamoto & M. Sekine*, Chemistry Letters *1975*, 977.
[32] *B. J. Hunt & W. Rigby*, Chemistry & Ind. *1967*, 1868.
[33] *R. Breslow, H. Kohn & B. Siegel*, Tetrahedron Letters *1976*, 1645.
[34] *R. J. Bergeron & M. P. Meeley*, Bioorganic Chemistry *5*, 197 (1976).
[35] *B. Casu, M. Reggiani, G. G. Gallo & A. Vigevani*, Tetrahedron *24*, 803 (1968).
[36] *R. J. Bergeron, M. P. Meeley & Y. Machida*, Bioorganic Chemistry *5*, 121 (1976).
[37] *P. C. Manor & W. Saenger*, J. Amer. chem. Soc. *96*, 3630 (1974).
[38] *P. Colson, H. J. Jennings & I. C. P. Smith*, J. Amer. chem. Soc. *96*, 8081 (1974).
[39] *K. Takeo, K. Hirose & T. Kuge*, Chemistry Letters *1973*, 1233.
[40] *T. Usui, N. Yamaoka, K. Matsuda, K. Tuzimura, H. Sugiyama & S. Seto*, J. chem. Soc. Perkin Transactions 1 *1973*, 2425.
[41] *J. B. Stothers*, 'Carbon-13 NMR Spectroscopy', p. 458–468 Academic Press, New York 1972.
[42] *E. Bretmaier & W. Voelter*, '^{13}C-NMR Spectroscopy', p. 223–242, Verlag Chemie, Weinheim/Bergstr., 1974.
[43] *D. J. Wood, F. E. Hruska & W. Saenger*, J. Amer. chem. Soc. *99*, 1735 (1977).
[44] *K. Takeo & T. Kuge*, Agricult. biolog. Chemistry *9*, 1416 (1970).
[45] *S. Kovac & G. Eglinton*, Tetrahedron *25*, 3599 (1969).
[46] *B. Casu, M. Reggiani, G. G. Gallo & A. Vigerani*, J. chem. Soc. Special Publication 23, p. 217–227, 1968.
[47] *A. Pinter*, Ph.D. Thesis, Columbia University 1973.
[48] *D. French*, J. Amer. chem. Soc. *71*, 353 (1949).
[49] *D. French*, Adv. Carbohydrate Chemistry *12*, 189 (1957).