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SYNTHESIS OF CHEMICALLY MODIFIED CYCLODEXTRINS

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CONTENTS

I. INTRODUCTION

A. *Scope of review*

Cyclodextrins and their chemically modified derivatives have been the subject of numerous investigations. Recent interest in the use of chemically modified cyclodextrins for various purposes has generated a number of papers containing information pertinent to the syntheses and reactions of these useful compounds. However, since these compounds have found applications in many areas, it is difficult for a researcher who is not intimately acquainted with the field to keep abreast of recent developments. Therefore, a review of the synthesis of the various chemically modified cyclodextrins is warranted. The goal of this review is to provide a summary of the available information concerning the synthesis of chemically modified cyclodextrins in such a form that a reader can easily see what has been done and readily locate the appropriate references to the primary literature. In cases where chemically modified cyclodextrins have been the objects of detailed spectral investigations, brief descriptions of these studies and citations are included along with the synthetic descriptions.

The general subject of cyclodextrins has been reviewed previously.[1-7,172] However, the emphasis of these reviews has usually been to survey the properties and applications of the parent cyclodextrins, with little or no attention being given to the area of chemically modified cyclodextrins. Although one review was focused specifically on the area of chemically modified cyclodextrins,[8] the coverage is quite limited. In several reviews some information on chemically modified cyclodextrins has been included. Areas reviewed which fall in this category include enzyme modeling,[9-13] biomimetic petrochemistry,[14]

and cyclodextrin utilization in food.[15] A comprehensive examination of chemically functionalized cyclodextrins has not been previously attempted.

This review will examine the syntheses and applications of the derivatives of α-, β- and γ-cyclodextrin which have appeared in the chemical literature from the initial report of the discovery of cyclodextrins by Villiers[16] through June 1981. A few selected articles, which have been published subsequently, are also included. In order to provide the maximum insight into the complex array of cyclodextrin derivatives, the area of cyclodextrin polymers will not be reviewed, except for brief excursions into the area necessitated by the examination of the chemically modified cyclodextrins which are monomers for subsequent polymerization reactions. The entire area of cyclodextrin polymers is the subject of a recent review,[17] and the area is also examined in some depth as a subsection of another summary.[6]

Since the functionalizing groups, which have been attached to the parent cyclodextrins, vary from the simplest of alkyl groups to complex "arms" which may include several functionalities, a truly systematic organization for this review has not been attempted. Instead, an organization based upon the type of functionality is employed, with a particular derivative occasionally being mentioned under more than one category and listed in more than one table. This approach, while producing some fragmentation, allows for what the authors believe will be an easier access to pertinent information by grouping molecules of similar functionalities together. The subsections for different functionalities are presented in approximately the order of the appearance of the first examples of a type in the literature. Thus, the products of simple alkylations and acetylations are discussed early (together with the more recent work in these areas), while the more recent "capped" cyclodextrins are discussed in a later subsection. It is hoped that this method of organization will maximize the usefulness of this work.

B. *Nomenclature, structure and physical properties*

Cyclodextrins are cyclic oligosaccharides consisting of at least six glucopyranose units which are joined together by α(1→4) linkages. Although cyclodextrins with up to 12 glucose residues are known,[3] only the first three homologs have been studied extensively (Fig. 1). The oligosaccharide ring forms a torus (Fig. 2) with the primary hydroxyl groups of the glucose residues lying on the narrow end of the torus. The secondary glucopyranose hydroxyl groups are located on the wider end. For the purpose of this review, the value of *n* in structures and tables will indicate the number of glucopyranose residues in the cyclodextrin.

The initial discovery of cyclodextrins is attributed to Villiers,[16] who isolated them as degradation products of starch. In 1904, Schardinger[18] demonstrated that these compounds could be obtained by the action of *Bacillus macerans* amylase upon starch. That these compounds are often described in the older literature as Schardinger dextrins is attributed to the fact that Schardinger was the first to describe their

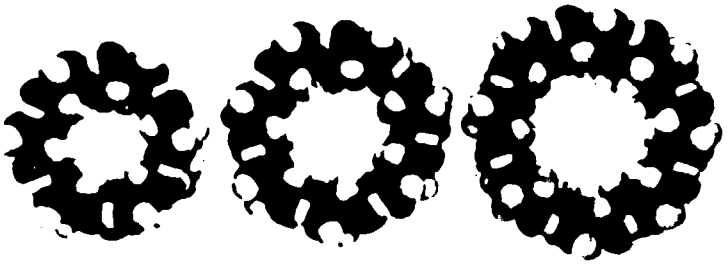


Fig. 1. Corey-Pauling-Koltun molecular models of α-, β-, and γ-substituted cyclodextrins viewed from the secondary hydroxyl side of the torus. (Photograph courtesy of M. L. Bender.)

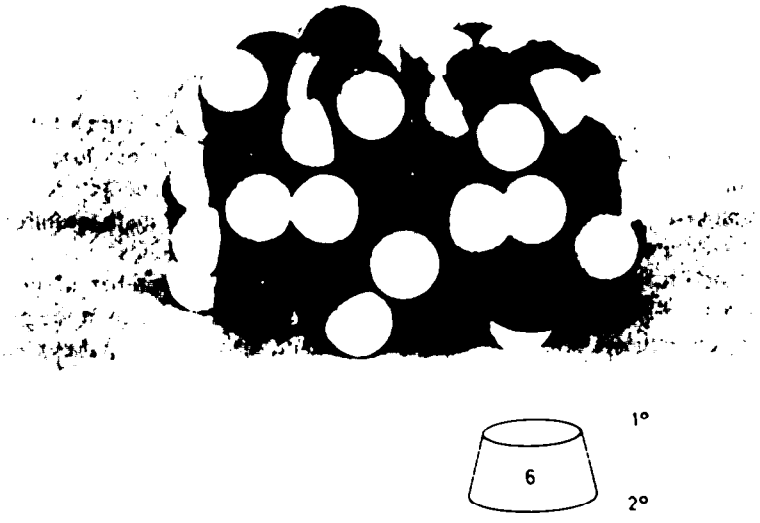
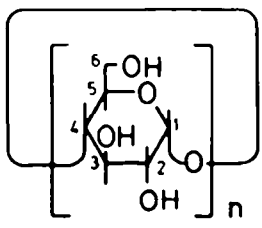


Fig. 2. Corey-Pauling-Koltun molecular model and structural representation of α-cyclodextrin-a side view of cyclodextrin torus. (The CPK model was provided by R. J. Bergeron.)

preparations and properties in detail.[1] Comprehensive accounts of the progress toward characterization and improvements in synthesis of the parent cyclodextrins are given elsewhere.[1,6] The reader is also referred to a number of excellent reviews in which detailed chemical and physical data for the unsubstituted parent cyclodextrins can be found.[1-7] The six-glucose unit containing cyclodextrin is specified as α-cyclodextrin (1), while the cyclodextrins with seven and eight glucose residues are designated as β-cyclodextrin (2) and γ-cyclodextrin (3), respectively (Table 1). There are, however, other names for these compounds. They are often referred to as Schardinger dextrins in the early literature.[1] These compounds have occasionally been called cycloglucans. Perhaps the most common alternative to the cyclodextrin nomenclature is the naming of these compounds as cycloamyloses.[3] This nomenclature has been used extensively from 1930 to the present. One might question if these compounds might not more correctly be named using such nomenclature, which appears to have great historical preference. However, *Chemical Abstracts* has adopted the cyclodextrin nomenclature, and we shall follow their convention.

As the complexity of the derivatives of cyclodextrins has grown, the need for higher precision in the nomenclature has also increased. Thus, a highly trivial name can be applied to a per substituted

Table 1. The parent cyclodextrins



Compound No.	n	Reference
1	6	7
2	7	7
3	8	7

cyclodextrin. However, as synthetic and characterization methods improved, it became necessary to specify not only which type of hydroxyl group has been substituted, but also on which glucopyranose residue(s) the substitution(s) had taken place. *Chemical Abstracts* specifies these glucose residues with capital letters in the name. However, this nomenclature system is rather cumbersome.

In this work, trivial names are used to provide unambiguous designations for the chemically modified cyclodextrins. A trivial nomenclature system is utilized which is a standardized form of the trivial nomenclatures most often found in the primary references. Substituents will be named in alphabetical order using the standard IUPAC group prefixes, with the few exceptions which follow. Acetyl will be used in preference to ethanoyl since the former name appears to be more firmly entrenched in the organic nomenclature. Also, in the interest of brevity, the following generally recognized contracted prefixes will be employed: tosyl for 4-methylbenzenesulfonyl; mesyl for methanesulfonyl; and trityl for triphenylmethyl. Substituents and substitution positions on a given glucose residue will be specified within parentheses or brackets. A multiplying prefix, indicating the number of glucose residues so substituted will precede the portion of the name in parentheses, with the name of the parent cyclodextrin following the closing parenthesis. Although perhaps redundant, the multiplying prefix *mono* will be used, since confusion might arise as to whether a name indicates substitution at only one glucose residue in the cyclodextrin or at all residues.

As an example of the use of this nomenclature system, an α-cyclodextrin derivative in which all the hydroxyl groups have been acetylated would be named as hexakis (2, 3, 6 - tri - *O* - acetyl) - α - cyclodextrin.

In cases where the point of substitution on the glucopyranose residue is unspecified, all possibilities will be designated in the name. Thus, α-cyclodextrin which has one hydroxyl group in the molecule acetylated (but *which* hydroxyl group has not been determined) would be named in this trivial system as mono [2 (3) (6) - *O* - acetyl] - α - cyclodextrin.

At times, this trivial nomenclature system will be insufficient to completely designate the structure of certain very complex cyclodextrin derivatives. When this is the case, the nomenclature of *Chemical Abstracts* (9th Collective Index period) will be used.

Within this review, liberal use of structures has been undertaken in the interest of clarity.

C. *Uses of cyclodextrins*

As was mentioned earlier, cyclodextrins and their derivatives have found application in several areas. Certainly a principal application has been the area of enzyme modeling and catalysis.[3,7,13] The relative ease with which a cyclodextrin may be appropriately substituted to synthesize models for enzymes and other macrocyclic molecules has promoted their use in this area. A considerable amount of excellent research in the area of catalysis by the unsubstituted cyclodextrins has been reported elsewhere.[3,7,13] In the present review, examples of enzyme modeling and catalysis will only be cited in connection with covalent intermediates that are of a more than transitory nature. The reader is referred to excellent summaries elsewhere[3,7,13] for more detailed discussions of this very important cyclodextrin application.

The advent of phase transfer catalysis, and the recognition of the role of "host-guest" chemistry in such compounds as zeolites, crown ethers and cryptands has accelerated research in the area of cyclodextrin inclusion compounds.[6] In fact, early observations of the behavior of cyclodextrins in the presence of iodine—an inclusion complex—assisted in the further characterization of these compounds.[19] The topic of cyclodextrin inclusion compounds has been reviewed.[6] The concept of microencapsulation (placing some "guest" compound within the cavity of the "host" cyclodextrin) has led to a number of industrially attractive uses for cyclodextrins. Applications include, but are not limited to: drug stabilization, foodstuff preservation and enhancement, plant protection, and use in the manufacture of toilet articles. A detailed discussion of these areas is outside the confines of this review. However, examples of such applications have been given elsewhere.[6]

Certain other applications of selected derivatives of cyclodextrins will be discussed under the specific functionality subsections. It should be noted that other applications, which are unmentioned here, also exist for these versatile compounds. New uses are being discovered at an accelerating rate.

II. SYNTHESIS OF CHEMICALLY MODIFIED CYCLODEXTRINS

A. *Acylated cyclodextrins*

1. *Introduction.* One of the first types of cyclodextrin derivatives to appear in the literature was the acylated cyclodextrins.[20] The category of acylated cyclodextrins includes numerous examples which

range in complexity from mono-substitution to the completely peracylated derivatives. Examples of acylated cyclodextrins are also known which involve various other functional groups, including halides, tosylates, mesylates, as well as various alkylated derivatives.

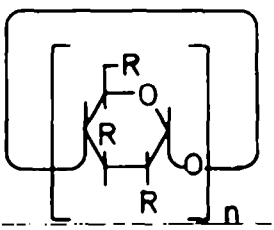
Many of these acyl derivatives were synthesized for purification purposes. Thus, peracetylated cyclodextrins were used in the early purification of the parent cyclodextrins which were obtained from starch digests.[20-23] Other acylated cyclodextrins were synthesized as intermediates for synthetic sequences in which the acyl groups functioned as protecting groups. A number of monoacylated derivatives were also prepared in connection with the work of Bender and others concerning cyclodextrins as acylation catalysts.[3,7]

In the following treatment, the peracylated cyclodextrins—that is, those derivatives in which all hydroxyl groups in the parent cyclodextrin have been acylated—will be examined first. Then those derivatives that contain other functionalities in addition to the acyl groups will be discussed. Finally, attention will be focused upon the monoacyl derivatives of cyclodextrins.

2. *Peracyl derivatives.* The peracyl derivatives of the cyclodextrins (Table 2) are perhaps the simplest synthetic, chemically modified cyclodextrins and appear early in the literature in the form of the peracetylated cyclodextrins, hexakis (2, 3, 6 - tri - *O* - acetyl) - α - cyclodextrin (**4**), heptakis (2, 3, 6 - tri - *O* - acetyl) - β - cyclodextrin (**5**) and octakis (2, 3, 6 - tri - *O* - acetyl) - γ - cyclodextrin (**6**). Freudenberg and Jacobi[20] reported in 1935 prior to the resolution of the conflict concerning the exact number of glucopyranose residues in the parent cyclodextrins, what appears to be the preparation of **4** and **5** by the treatment of the parent cyclodextrins with acetic anhydride in pyridine for 2 days at 40°. The crude products were then recrystallized from toluene to give what was reported to be **4** and **5**. Melting points and specific rotation data were also given. Since in this and other early work which employed acetylation for the purposes of purification mixtures were more often the rule rather than the exception, the purity of the acetylated derivatives might be questioned and care must be exercised in using the data provided in these pioneering reports. The peracetate **5** was also prepared by McClenahan *et al.*[21] by both the acetic anhydride–pyridine method and by employing powdered zinc chloride as the acetylation catalyst with acetic anhydride, as part of the procedure for obtaining pure β-cyclodextrin for specific rotation measurements.

In a further attempt to resolve the question of the number of glucopyranose residues in the parent cyclodextrins, Freudenberg *et al.*[22,23] undertook the synthesis of **4**, **5** and **6** using acetic anhydride–

Table 2. Peracylated cyclodextrins



Compound No.	R	n	Reference
4	-OAc	6	24
5	-OAc	7	24
6	-OAc	8	24
7	$-O\overset{O}{\overset{\|\|}{C}}CH_2CH_3$	7	27
8	$-O\overset{O}{\overset{\|\|}{C}}(CH_2)_2CH_3$	7	27
9	$-O\overset{O}{\overset{\|\|}{C}}(CH_2)_3CH_3$	7	27
10	$-O\overset{O}{\overset{\|\|}{C}}CF_3$	7	29
11	$-O\overset{O}{\overset{\|\|}{C}}Ph$	6	37
12	$-O\overset{O}{\overset{\|\|}{C}}Ph$	7	29

pyridine, as part of a quite complex purification scheme which had the goal of producing very pure α-, β- and γ-cyclodextrins (**1**, **2**, **3**) for molecular weight determinations. Since this work was used to support the claim (incorrect) that α-cyclodextrin (**1**) consisted of five glucopyranose residues and β-cyclodextrin (**2**) six residues, the purity of these derivatives is in doubt.

French *et al.*[24,25] again in the context of purification, reported the syntheses of **4**, **5** and **6** by treatment of the parent cyclodextrins with boiling acetic anhydride containing sodium acetate, followed by treatment with water and subsequent recrystallization from an appropriate solvent. Solubilities of these cyclodextrin peracetates in toluene, methanol, ethyl acetate and *n*-butyl acetate are given.[24]

Following the initial syntheses of these peracetylated derivatives, many applications have been reported. The peracetylated α- and β-cyclodextrins **4** and **5** have been used by Sand and Schlenk[26-28] as polar stationary phases in gas–liquid chromatography. Also, in an investigation of the conformation of the glucopyranose residues in oligo- and polysaccharides, Cramer *et al.*[29] measured the optical rotatory dispersion (ORD) spectra of **4** and **5**. In another conformational study,[30] the 100 MHz ^{1}H NMR and IR spectra of **4** and **5** are recorded. Takeo and Kuge[31] have also reported 100 MHz ^{1}H NMR data in their conformations study of the peracetylated cyclodextrins **4**, **5** and **6**. Hirauo,[32] in probing the characteristics of the 100 MHz NMR signal from the acetate–methyl groups protons in various peracetyl derivatives of oligo- and polysaccharides, includes data for **5**. The ^{13}C NMR spectra of **4**, **5** and **6** are reported by Takeo *et al.*[33,34] and the proton coupled ^{13}C NMR spectrum of **4** is available.[168] Acetyl substituent effects on the ^{13}C chemical shifts in oligo- and polysaccharides have been investigated by Gagnaire *et al.*[35] using **5**. Compound **5** has also been used as a reactant in an aceto brominolytic cleavage reaction for the synthesis of acetylated glycosyl bromide derivatives of higher maltooligosaccharides.[36]

Other nonacetyl peracyl derivatives have been synthesized. Heptakis (2, 3, 6 - tri - *O* - propanoyl) - β - cyclodextrin (**7**), heptakis (2, 3, 6 - tri - *O* - butanoyl) - β - cyclodextrin (**8**), and heptakis (2, 3, 6 - tri - *O* - pentanoyl) - β - cyclodextrin (**9**) were prepared and used as polar stationary phases in gas-liquid chromatography.[26,27] The trifluoroacetylated analog of **5**, heptakis (2, 3, 6 - tri - *O* - trifluoroacetyl) - β - cyclodextrin (**10**) was obtained as colorless, but very hygroscopic crystals.[29,83] The perbenzoylated analogs of **4** and **5**, hexakis (2, 3, 6 - tri - *O* - benzoyl) - α - cyclodextrin (**11**) and heptakis (2, 3, 6 - *O* - benzoyl) - β - cyclodextrin (**12**) have been utilized by Boger *et al.*[37] as intermediates in the selective modification of all primary hydroxyl groups in the parent cyclodextrins. Compound **12** was first prepared by Cramer, Mackensen and Sensse[29] using benzoyl chloride and pyridine.

3. *Acylated cyclodextrins with other functional groups.* In addition to the peracylated derivatives, a number of acylated cyclodextrins which also contain other functional groups have been synthesized (Table 3). There are numerous examples in which all primary hydroxyl groups in the cyclodextrin are substituted by other functional groups, while the remaining secondary hydroxyl groups are acetylated. Examples of this type include the 6-mesyl derivatives, hexakis (2, 3 - di - *O* - acetyl - 6 - *O* - mesyl) - α - cyclodextrin (**13**) and heptakis (2, 3 - di - *O* - acetyl - 6 - *O* - mesyl) - β - cyclodextrin (**14**), which were first reported by Lautsch *et al.*[38] Compounds **13** and **14** were prepared by stepwise reactions of the parent cyclodextrins, first with methanesulfonyl chloride and then with acetic anhydride-pyridine. These compounds were used as substrates for the complexation of iodine in which cyclodextrin–iodine complexes were examined by visible (420–600 nm) spectroscopy. Compound **14** was also prepared by Cramer *et al.*[29] as a synthetic intermediate.

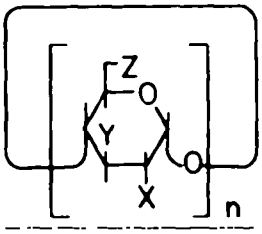
The tosyl analogs of **13** and **14** are also known. Hexakis (2, 3 - di - *O* - acetyl - 6 - *O* - tosyl) - α - cyclodextrin (**15**) was reported by Lautsch and Wiechert[39] in studies preliminary to an attempt to form a cyclodextrin polymer. Both **15** and the analogous β-cyclodextrin - based derivative, heptakis (2, 3 - di - *O* - acetyl - 6 - *O* - tosyl) - β - cyclodextrin (**16**), were synthesized by Cramer *et al.*[29] as synthetic intermediates in the preparation of other cyclodextrin derivatives. The ORD and UV spectra of **15** and **16** have also been reported.[29]

Heptakis (2, 3 - di - *O* - acetyl - 6 - *N* - acetylamino - 6 - deoxy) - β - cyclodextrin (**17**), an analog of **5** with the acetyl groups at the primary positions linked to the cyclodextrin via nitrogen rather than oxygen, is known.[39]

The mesylate **14** was treated with NaI to obtain the iodoacetate, heptakis (2, 3 - di - *O* - acetyl - 6 - deoxy - 6 - iodo) - β - cyclodextrin (**18**).[29] Further transformation of **18**, by reaction with potassium ethylxanthate (EtO–$\overset{\overset{S}{\|}}{C}$–SK) yielded[29] heptakis (2, 3 - di - *O* - acetyl - 6 - deoxy - 6 - ethoxythiocarbonylmercapto) - β - cyclodextrin (**19**).

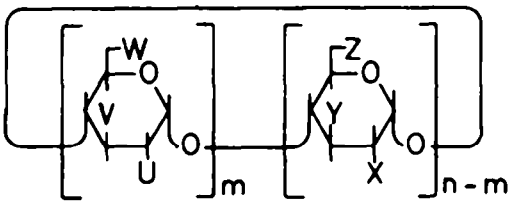
Acetylated 6-deoxy cyclodextrins, in which the primary hydroxyl groups have all been replaced by hydrogens, have also been synthesized:[33,40] hexakis (2, 3 - di - *O* - acetyl - 6 - deoxy) - α - cyclodextrin (**20**); heptakis (2, 3 - di - *O* - acetyl - 6 - deoxy) - β - cyclodextrin (**21**); and octakis (2, 3 - di - *O* - acetyl - 6 - deoxy) - γ - cyclodextrin (**22**).

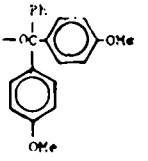
Table 3. Acylated cyclodextrins with other functional groups



Compound No.	X	Y	Z	n	Ref.
13	-OAc	-OAc	$-OS(=O)(=O)-CH_3$	6	38
14	-OAc	-OAc	$-OS(=O)(=O)-CH_3$	7	38
15	-OAc	-OAc	$-OS(=O)(=O)-C_6H_4-CH_3$	6	29
16	-OAc	-OAc	$-OS(=O)(=O)-C_6H_4-CH_3$	7	29
17	-OAc	-OAc	$-NH-C(=O)-CH_3$	7	39
18	-OAc	-OAc	-I	7	29
19	-OAc	-OAc	$-SC(=S)OEt$	7	29
20	-OAc	-OAc	-H	6	40
21	-OAc	-OAc	-H	7	40
22	-OAc	-OAc	-H	8	40
23	-OAc	-OAc	-Br	6	40
24	-OAc	-OAc	-Br	7	40
25	-OAc	-OAc	-Br	8	40
26	-OAc	-OAc	$-N_3$	6	37
27	-OAc	-OAc	$-N_3$	7	37
28	$-OC(=O)Ph$	-OH	$-OC(=O)Ph$	6	41
29	$-OC(=O)Ph$	-OH	$-OC(=O)Ph$	7	42
30	-OMe	-OH	$-OC(=O)Ph$	7	44
31	$-OC(=O)Ph$	$-OC(=O)Ph$	-OH	6	37
32	$-OC(=O)Ph$	$-OC(=O)Ph$	-OTs	6	37
33	$-OC(=O)Ph$	$-OC(=O)Ph$	-OMe	6	37
34	$-OC(=O)Ph$	$-OC(=O)Ph$	$-N_3$	6	37

Table 3 (*Contd*)



Compound No.	U	V	W	X	Y	Z	n	m	Ref.
35	-OAc	-OAc	-OAc	-OAc	-OAc	$-OC(Ph)_3$	7	3	29
36	-OAc	-OAc	-OAc	-OAc	-OAc		7	3	29
37	-OAc	-OAc	-OTs	-OAc	-OAc	-I	6	1	29
38	-OAc	-OAc	-OTs	-OAc	-OAc	-I	7	1	29
39	-OAc	-OAc	-OAc	-OAc	-OAc	-SCOEt	7	1	29
40	-OCOPh	-OCOPh	2/3 -OCOPh 1/3 -OH	-OCOPh	-OCOPh	$-OC(Ph)_3$	7	3	43
41	-OCOPh	-OCOPh	-OCOPh	-OCOPh	-OCOPh	-OMe	7	2	43

Compound **21** was first reported as a model compound by Takeo *et al.*[33] in their ^{13}C NMR investigations of cyclodextrins and their peracetates. Compounds **20–22** were prepared by Takeo *et al.*.[40] by the selective reductive debromination of the 6-bromo analogs, hexakis (2, 3 - di - *O* - acetyl - 6 - bromo - 6 - deoxy) - α - cyclodextrin (**23**), heptakis (2, 3 - di - *O* - acetyl - 6 - bromo - 6 - deoxy) - β - cyclodextrin (**24**), and octakis (2, 3 - di - *O* - acetyl - 6 - bromo - 6 - deoxy) - γ - cyclodextrin (**25**). Conformational studies of **20–25** have been conducted using ^1H NMR.[40]

Cyclodextrins with azide functions at all primary sites, and the remaining secondary hydroxyl groups having been acetylated, are known.[37] Boger *et al.*[37] have synthesized hexakis (2, 3 - di - *O* - acetyl - 6 - azido - 6 - deoxy) - α - cyclodextrin (**26**) and heptakis (2, 3 - di - *O* - acetyl - 6 - azido - 6 - deoxy) - β - cyclodextrin (**27**) by reaction of the parent cyclodextrins **1** and **2** with lithium azide, triphenyl phosphine and carbon tetrabromide in dry DMF, followed by treatment with acetic anhydride–pyridine. Proton and ^{13}C NMR spectral data are reported for these compounds.[37]

In addition to the mixed cyclodextrin derivatives that contain acetyl and other functional groups, the mixed benzoylated cyclodextrin derivatives, hexakis (2, 6 - di - *O* - benzoyl) - α - cyclodextrin (**28**) and heptakis (2, 6 - di - *O* - benzoyl) - β - cyclodextrin (**29**), in which only part of the available hydroxyl groups are benzoylated have been prepared. In these derivatives all hydroxyl groups except those at position 3 on the glucose residues are benzoylated. Ogawa and Matsui[41] synthesized **28** using a regioselective acylation technique which involved the initial trialkylstanylation of the polyhydroxyl compound. ^{13}C NMR shifts are reported for **28**, along with other physical data.[41] Kondo and Takeo[42] prepared [29] by treating the parent cyclodextrin **2** with benzoyl chloride at $-40°$. However, the product was shown by GLC to be a mixture of benzoyl substituted β- cyclodextrins with a 52% replacement of hydroxyl functions by benzoyl groups. In an ensuing series of oxidation–reduction reactions, this mixture was converted into a mixture of cyclic oligosaccharides in which some of the constituent D-glucose residues had been converted into D-allose residues by inversion of configuration at a secondary hydroxyl group site. A methyl-benzoyl derivative, heptakis (6 - *O* - benzoyl - 2 - *O* - methyl) - β - cyclodextrin (**30**), was utilized by Takeo and Kuge[44] as a synthetic intermediate.

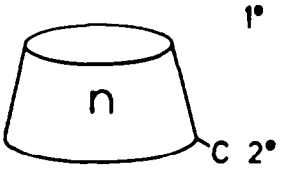
There are a number of benzoyl derivatives in which substitution of other functional groups has occurred at the primary hydroxyl groups, while the remaining secondary hydroxyl groups have been

esterified to form benzoate esters. The simplest example of this type is hexakis (2, 3 - di - *O* - benzoyl) - α - cyclodextrin (**31**), in which the primary hydroxyl functions remain unmodified. Derivatives **31** was prepared by Boger *et al.*[37] as an intermediate in a reaction scheme which was designed to provide selective modification of all primary hydroxyl groups in α-cyclodextrin (**1**). The perbenzoylated derivative **12** was treated with potassium isopropoxide in 2-propanol–benzene solvent to give **31**. Compound **31** was then further modified[37] by reaction with tosyl chloride in pyridine to produce the 6-tosyl derivative, hexakis (2, 3 - di - *O* - benzoyl - 6 - *O* - tosyl) - α - cyclodextrin (**32**). Derivative **31** was also modified[37] to give the 6-methyl analog, hexakis (2, 3 - di - *O* - benzoyl - 6 - *O* - methyl) - α - cyclodextrin (**33**), by treating **31** with diazomethane and boron trifluoride etherate in ether–chloroform solvent at 0°. Further reaction[37] of the 6-tosyl derivative **32** with sodium azide in DMF yielded hexakis (6 -azido - 2, 3 - di - *O* - benzoyl - 6 - deoxy) - α - cyclodextrin (**34**). ^{1}H and ^{13}C NMR data for these compounds are reported.[37]

Several asymmetrically functionalized acyl cyclodextrins have been prepared. Cramer, Mackensen and Sensse[29] have, in the course of ORD and UV spectral based conformational studies of glucose residues in cyclodextrins, prepared a tetra - 6 - trityl derivative, tetrakis (2, 3 - di - *O* - acetyl - 6 - *O* - trityl) - tris (2, 3, 6 - tri - *O* - acetyl) - β - cyclodextrin (**35**) and its 4, 4'-dimethoxytrityl analog, tetrakis [2, 3 - di - *O* - acetyl - 6 - *O* - (4, 4' - dimethoxytrityl)] - tris(2, 3, 6 - tri - *O* - acetyl) - β - cyclodextrin (**36**). Compounds **35** and **36** resulted from an attempt to tritylate all primary sites in β-cyclodextrin. That only four of the seven primary hydroxyl groups could be substituted was attributed to steric crowding at the primary hydroxyl side of the cyclodextrin torus[29] (Fig. 1). It should be noted that the structures given for **35** and **36** in Table 3 represent only two of a number of possible isomers which are presumably produced. Attempts by the same authors[29] to completely transform the 6-tosyl acetate **15** and its β-cyclodextrin analog **16** into derivatives which have all primary hydroxyl groups replaced by iodine and all secondary hydroxyl groups acetylated led to derivatives with iodine at all but one of the primary sites (the remaining group being tosylate) with acetate groups at all secondary sites. Thus, treatment of **15** and **16** with sodium iodide gave mono (2, 3 - di - *O* - acetyl - 6 - *O* - tosyl) - pentakis (2, 3 - di - *O* - acetyl - 6 - deoxy - 6 - iodo) - α - cyclodextrin (**37**) and hexakis (2, 3 - di - *O* - acetyl - 6 - deoxy - 6 - iodo) - mono (2, 3 - di - *O* - acetyl - 6 - *O* - tosyl) - β - cyclodextrin (**38**), respectively. Further reaction[29] of **38** with potassium ethylxanthate gave hexakis (2, 3 - di - *O* - acetyl - 6 - deoxy - 6 - ethoxythiocarbonylmercapto) - mono (2, 3, 6 - tri - *O* - acetyl) - β - cyclodextrin (**39**). Bergeron *et al.*[43] have reported the synthesis of tetra - 6 - trityl derivative, somewhat analogous to **35**, but involving benzoate groups instead of the acetyl groups of **35**. Thus, initial tritylation of the parent cyclodextrin **2**, followed by benzoylation, gave bis (2, 3, 6 - tri - *O* - benzoyl) - mono (2, 3 - di - *O* - benzoyl) - tetrakis (2, 3 - di - *O* - benzoyl - 6 - *O* - trityl) - β - cyclodextrin (**40**), a derivative in which four of the seven primary hydroxyl groups were tritylated, two of the seven primary hydroxyl groups were benzoylated and one of the primary hydroxyl groups remained unmodified. All secondary hydroxyl groups in **40** were benzoylated. Following removal of the trityl groups of **40**, the four regenerated hydroxyl groups together with the single unmodified hydroxyl group were methylated with diazomethane to give[43] bis (2, 3, 6 - tri - *O* - benzoyl) - pentakis (2, 3 - di - *O* - benzoyl - 6 - *O* - methyl) - β - cyclodextrin (**41**). Structures given in Table 3 for **40** and **41** represent only two of the several isomers that were presumably produced by these reactions.

4. *Monocylated cyclodextrins.* In addition to the acyl cyclodextrin derivatives previously described, in which several of the hydroxyl groups have been acylated, there are also known several monoacylated cyclodextrins (Table 4). The existence of these compounds may be attributed to the work of Bender[7] and others on the mechanism of covalent catalysis by cyclodextrins in the hydrolysis of aryl esters and related substrates. It had been shown[7] that the first step in the catalytic mechanism for hydrolysis of a cyclodextrin-complexed aryl ester substrate is nucleophilic attack by a secondary hydroxyl group of the cyclodextrin which ultimately results in a monoacyl cyclodextrin (Fig. 3). Under the reaction conditions, the monoacyl cyclodextrin usually undergoes subsequent reaction to give the parent cyclodextrin and the carboxylic acid as products. However, it is possible, at least in some cases,[7] to isolate an intermediate monoacyl cyclodextrin. Thus, it has been possible to prepare and characterize a number of monoacyl cyclodextrins which have an ester linkage at a secondary site. The simple monoacetyl derivative, mono [2 (3) - *O* - acetyl] - α - cyclodextrin (**42**) was prepared by Bender *et al.*[45] from *m*-nitrophenyl acetate in a carbonate buffer. Earlier, Bender's group[46] reported the preparation of an analogous monobenzoate, mono [2 (3) - *O* - benzoyl] - β - cyclodextrin (**43**) using *m*-nitrophenyl benzoate in a carbonate buffer. Separation of **43** from the reaction mixture was accomplished by gel filtration chromatography.[46] Harada *et al.*[47–49] synthesized a number of monoacyl cyclodextrins with unsaturated sidechains. Using the

Table 4. Monoacylated cyclodextrins



Compound No.	C	n	Ref.
42	-OAc	6	45
43	-OCPh	7	46
44	-OC-CH=CH$_2$	6	47
45	-OC-CH=CH$_2$	7	47
46	-OC-(CH$_2$)$_5$-NH-C-CH=CH$_2$	6	47
47	-OC-(CH$_2$)$_5$-NH-C-CH=CH$_2$	7	47
48	-OC-C=C(H)-Ph	6	45
49	-OC-C=C(H)-Ph	7	45
50	-OC-C=C(H)-Fe	7	52

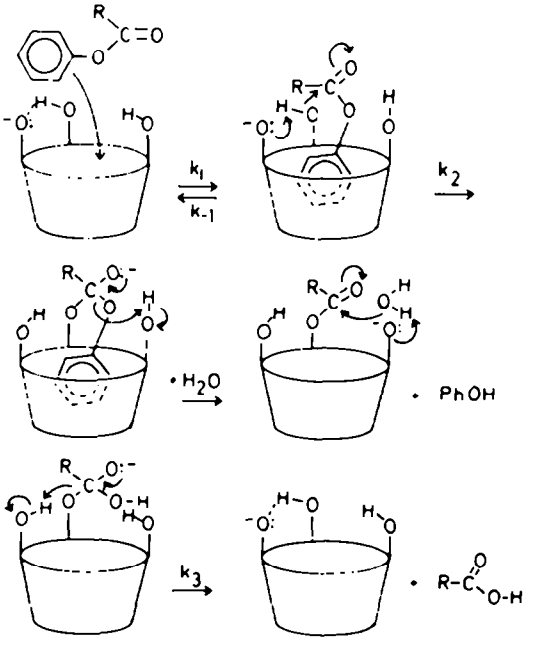


Fig. 3. Schematic representation of the hydrolysis of phenyl acetate to acetic acid and phenol as catalyzed by cyclodextrin. Modified scheme of W. Saenger, *Angew. Chem. Int. Ed. Engl.*, **19**, 344–62 (1980).

method developed by Bender,[46] mono [2 (3) - *O* - propenoyl] - α - cyclodextrin (**44**) and mono [2 (3) - *O* - propenoyl] - β - cyclodextrin (**45**) were prepared[47,48] from the respective parent cyclodextrins **1** and **2** and *m*-nitrophenyl acrylate. Analogous compounds with longer unsaturated side chains were prepared[47,48] by Bender's method[46] from *m*-nitrophenyl *N*-acrylyl - 6 - aminohexanoate and the parent cyclodextrins **1** and **2** which gave mono [2 (3) - *O* - (*N* - acrylyl - 6 - aminohexanoyl)] - α - cyclodextrin (**46**) and mono [2(3) - *O* - (*N* - acrylyl - 6 - aminohexanoyl)] - β - cyclodextrin (**47**), respectively. Derivatives **44–47** were characterized, and then polymerized[47] by radical initiation. The effectiveness of the resulting polymers as catalysts for the hydrolysis of several *p*-nitrophenyl esters was compared to that of the parent cyclodextrins **1** and **2**.[47] ^{13}C NMR data for **44** and **45** are also available.[48] The monomers **44–47** were also copolymerized with a variety of co-monomers.[48] Interactions of the monomeric derivatives **44–47** with fluorescent compounds are also reported.[49] Bender *et al.*[45] isolated the cyclodextrin monocinnamates, mono [2 (3) - *O* - *trans* - cinnamoyl] - α - cyclodextrin (**48**), and mono[2 (3) - *O* - *trans* - cinnamoyl] - β - cyclodextrin (**49**), which were prepared from the parent cyclodextrins **1** and **2** and *m*-nitrophenyl cinnimate. Compounds **48** and **49** were used to obtain[45] the rates of deacylation to form the parent cyclodextrins **1** and **2**, which is presumed to be the final step in the covalent catalysis of ester hydrolysis by cyclodextrins.[7] The rates of deacylation of **48** and **49** by amine catalysis were also determined[50] with the goal of utilizing such cyclodextrins as enzyme models. Komiyama and Bender[51] further investigated the nucleophilic acceleration of the cleavage of **49** by amines such as piperidine and quinuclidine. A cyclodextrin derivative which is analogous to the monocinnimates **48** and **49** but with a ferrocenyl moiety replacing the phenyl group has been reported by Czarniecki and Breslow.[52] Following the Bender[46] method, the parent β-cyclodextrin **2** was acylated by complexation and reaction with the *p*-nitrophenyl ester of ferrocinnamic acid to give mono [2 (3) - *O* - ferrocenylpropenoyl] β-cyclodextrin (**50**). The acylation of β-cyclodextrin to form **50** showed a 50,000-fold rate acceleration over the hydrolysis of the *p*-nitrophenyl ferrocinnamate ester by buffer alone. The magnitude of this acceleration is comparable to that noted for the acylation of the enzyme chymotrypsin by *p*-nitrophenyl acetate.[52] Thus, the cyclodextrin enzyme model exhibits both reaction selectivity and rate acceleration.[52] Further investigation in this area has been recently reported by Trainor and Breslow.[53]

A special application of the Bender[46] method has been utilized by Harada *et al.*[54] to prepare β-cyclodextrin dimers (Table 5) having β-cyclodextrin moieties attached at both ends of a dicarboxylic acid. Thus, bis - β - cyclodextrin succinate (**51**) was prepared by the reaction of bis (*m*-nitrophenyl) succinate with a large excess of β-cyclodextrin. Similarly, bis - β - cyclodextrin glutarate (**52**) was prepared from bis (*m*-nitrophenyl) glutarate and β-cyclodextrin. The interactions of **51** and **52** with potassium 2 - *p* - toluidinylnaphthalene - 6 - sulfonate were studies by a fluorescence technique.[54]

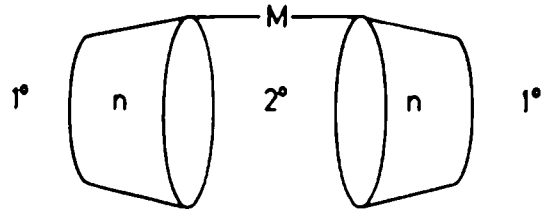
5. *Poorly characterized acyl cyclodextrin derivatives.* While many of the cyclodextrin derivatives which have been prepared are well-characterized single compounds, mixtures of cyclodextrin derivatives have been prepared and used in some cases. Mixtures of this sort, while not well-characterized, often possess considerable industrial utility. Mixtures of acyl cyclodextrins of this sort have been reported.[55] These syntheses of unspecified long chain and unsaturated esters of cyclodextrins are represented by a specific example.[55] The reaction of lauric acid and β-cyclodextrin in the presence of *p*-toluenesulfonic acid has led to a water-insoluble product with a degree of substitution of 0.077. Such long-chain acyl derivatives are reported[55] to find application as clathrating agents, soaps, detergents and plasticizers.

B. *Alkylated cyclodextrins*

1. *Introduction.* Alkyl derivatives of the cyclodextrins appeared early in the literature.[1] In analogy to the peracetylated derivatives, the permethylated cyclodextrins were initially synthesised for purification purposes, or alternately, for molecular weight or structure determination studies of the parent cyclodextrins. Subsequent to the initial preparations of these permethylated derivatives, other partially or fully alkylated cyclodextrin derivatives, some containing other functional groups, were prepared. The majority of these more complex alkyl derivatives were used as synthetic intermediates in schemes designed to produce even more highly functionalized cyclodextrins, while some of these fully or partially alkylated cyclodextrins were the subject of spectral investigations. In addition, a number of monoalkylated cyclodextrins are known, some of which have sulfide linkages to the cyclodextrins.

In this treatment, the results of the early research dealing with the permethylated cyclodextrin derivatives will be presented first, followed by discussion of the more recent research in this area. Subsequent to that, partially and fully alkylated cyclodextrins, some with other functionalities, will be examined. Finally, the monoalkylated cyclodextrins will be discussed.

Table 5. Duplex acylated cyclodextrins

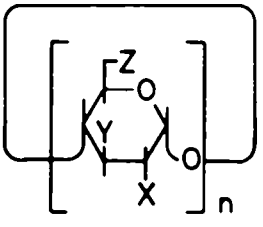


Compound No.	M	n	Ref.
51	$-O-\overset{O}{\overset{\|}{C}}-(CH_2)_2-\overset{O}{\overset{\|}{C}}-O-$	7	54
52	$-O-\overset{O}{\overset{\|}{C}}-(CH_2)_3-\overset{O}{\overset{\|}{C}}-O-$	7	54

2. *Permethylated cyclodextrins.* Early reports of research in the area of cyclodextrins—their nature and structure—contain references to the permethylated derivatives, hexakis (2, 3, 6 - tri - *O* - methyl) - α - cyclodextrin (**53**), and heptakis (2, 3, 6 - tri - *O* - methyl) - β - cyclodextrin (**54**) (Table 6). Irvine *et al.*[56] first reported in 1924 what is, apparently, the synthesis of **54** from the parent cyclodextrin **2** by repetitive treatment of **2** with dimethyl sulfate and sodium hydroxide. This lengthy process[56] required over twenty repetitions of the methylation procedure to yield, ultimately, a crystalline material of m.p. 102–105°. As has been noted previously in this work, the result of early research in the area of the synthesis of these cyclodextrin derivatives must be held in question. The early work often involved the use of impure parent cyclodextrins as starting materials for these preparations. French[1] also pointed out that the lengthy reaction process required to obtain a completely methylated product might result in structural alterations—a result which would have contributed to the then present controversy over the exact structural nature of the cyclodextrins.

Freudenberg and Rapp[57] employed a method different from that of the Pringsheim group[56] to obtain **54** and its α-cyclodextrin analog **53**. Treatment of the parent cyclodextrins, **1** or **2** with potassium metal in liquid ammonia resulted in formation of the corresponding potassium salts. These salts were then treated with methyl iodide in ethyl ether to give the crude products. Remethylation by treatment of the crude material with sodium in liquid ammonia followed by methyl iodide and subsequent recrystallization gave **53** or **54**. The solubilities of **53** and **54** in common solvents have been determined.[58] Specific rotation data[57,58] are also given for **53** and **54**. Since these permethyl derivatives were used to support the incorrect hypothesis[58] that α-cyclodextrin (**1**) contained five rather than six glucopyranose residues and that β-cyclodextrin (**2**) was formed from only six such residues, the purities of these compounds must be questioned. However, later work by Freudenberg and Cramer[59,60] in which freezing point depressions of mixtures consisting of **53** or **54** and cyclohexanol in various concentrations were determined, led to the

Table 6. Permethylated cyclodextrins



Compound No.	X	Y	Z	n	Reference
53	-OMe	-OMe	-OMe	6	37
54	-OMe	-OMe	-OMe	7	67

correct assignment of six glucopyranose residues for α-cyclodextrin (**1**) and seven for β-cyclodextrin (**2**).

Casu *et al.*[61] in the course of a conformational study of the parent cyclodextrins **1** and **2** and amylose, prepared **53** and **54** from reaction of the parent cyclodextrins with methyl iodide and barium oxide in DMSO maintained at 40° for five days. ^{1}H NMR and IR data for **53** and **54** are reported.[61] In another conformational study, the ORD spectra of **53** and **54** were measured by Cramer *et al.*[29] Compounds **53** and **54** were prepared[29] in this case by the action of methyl iodide and silver oxide upon the parent cyclodextrins in DMF. Recently, Szejtli *et al.*[67] have re-examined the synthesis and structure of **54**. They conclude, from ^{1}H and ^{13}C NMR studies that the previously-assigned structure for **54** is correct.

Following the initial syntheses of the permethyl derivatives **53** and **54**, several studies involving these compounds have appeared. Bergeron *et al.*[43] permethylated the parent cyclodextrin **2** in order to enhance the hydrophobic character of the cyclodextrin cavity and promote complex formation of the resulting permethyl derivative **54** and palmitoyl coenzyme A. The partial molar volume of **54** in water at 25° was determined by Shahidi *et al.*[62] In a study of substituent effects on the ^{13}C NMR chemical shifts of various oligo- and polysaccharides, the ^{13}C NMR spectra of **54** is reported.[35] High purity **53**, prepared from the parent cyclodextrin **1** with methyl iodide and sodium hydride in DMF, was utilized by Boger *et al.*[37] in research aimed at producing cyclodextrin derivatives with selective modification of all primary hydroxyl groups. Compound **54** has also been prepared[63] and the α(1→4) linkages hydrolyzed to give trimethylated glucopyranose units which were subsequently used as co-monomers in various polymeric processes. The complexing characteristics of **53** and **54** were investigated by Casu *et al.*[64] using ^{1}H NMR, UV and IR spectroscopy. These workers[64] also employed **53** and **54** as stationary phases for the GLC separation of saturated hydrocarbon mixtures. Complexation by **53** of 4-biphenylcarboxylate or *p*-methylcinnamate anions in aqueous solution was studied by Gelb *et al.*[65] using conductometric methods and ^{13}C NMR spectrometric analyses and values of the equilibrium constants are reported. Nalai *et al.*[66] prepared mixtures of **54** and various medicinals by grinding. X-ray diffraction analysis and IR spectral studies indicated that the medicinal molecules were "monomolecularly" dispersed in the ground mixtures.

3. *Fully and partially alkylated cyclodextrins—some with other functionalities.* In addition to the permethylated cyclodextrins previously discussed, several alkyl cyclodextrin derivatives are reported in which only a portion of the hydroxyl groups of the original cyclodextrin have been alkylated. In some cases, the remaining unalkylated hydroxyl groups have been functionalized by substitution of various other functional groups for hydroxyl. Other derivatives have been prepared wherein the remaining unalkylated hydroxyl groups of the partially alkylated cyclodextrin have been further alkylated by a reagent containing alkyl groups different from those of the original alkylating reagent. Thus, several completely alkylated cyclodextrins are known which contain more than one type of alkyl group.

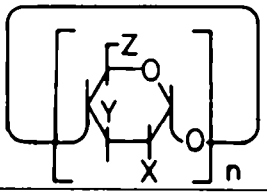
In the following listing and discussion of these compounds, symmetrically substituted alkyl cyclodextrin derivatives—those with the same pattern of functional groups on each glucopyranose residue—will be treated first (Tables 7 and 8). Subsequently, asymmetrically substituted derivatives will be examined (Table 9).

The 2, 6 - methyl substituted derivatives of **1** and **2**, hexakis (2, 6 - di - *O* - methyl) - α - cyclodextrin (**55**) and heptakis (2, 6 - di - *O* - methyl) - β - cyclodextrin (**56**) were first incorrectly reported by Staerk and Schlenk[68] to be the 3, 6-methylated derivatives. However, subsequent investigations[44,64] demonstrated that these derivatives are in fact the 2, 6-methylated compounds. A sample of **55** prepared by Staerk and Schlenk[68] was utilized by Bender *et al.*[46] to test the role of secondary hydroxyl groups in the cyclodextrin-catalyzed cleavage of phenyl esters. Compound **55** is uniquely suited for such a test since the derivative has all of its primary and half of its secondary hydroxyl groups "blocked" from participation in the cleavage reaction.

The 2, 6-dimethyl derivatives **55** and **56** were prepared from the parent cyclodextrins **1** and **2** by treatment[61] with dimethyl sulfate and barium oxide in a 1 : 1 mixture of DMF–DMSO, followed by recrystallization. Both **55** and **56** were employed by Casu *et al.*[61] in their conformational studies of cyclodextrins. Thus, the IR and ^{1}H NMR spectra of **55** and **56** are available.[61] ^{13}C NMR spectral data for **56** have been reported.[67]

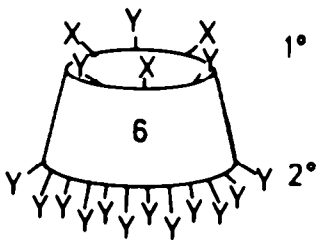
Bergeron *et al.*[69] utilized these partially methylated derivatives (**55** and **56**) to mimick the stimulatory effects of certain mycobacterial polysaccharides on the activity of a fatty acid synthetase. In a related enzyme modeling study, Bergeron *et al.*[43] have shown that alkylated cyclodextrins **55** and **56** mimick the action of these same mycobacterial polysaccharides in effectively complexing palmitoyl coenzyme A. Breslow *et al.*[70] utilized **55** in a test of a proposed mechanism for the cyclodextrin-catalyzed selective

Table 7. Symmetrical fully and partially alkylated cyclodextrins, and symmetrically alkylated cyclodextrins with other functional groups



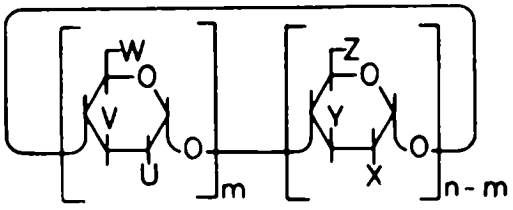
Compound No.	X	Y	Z	n	Reference
55	-OMe	-OH	-OMe	6	37
56	-OMe	-OH	-OMe	7	37
57	-OPr	-OH	-OPr	7	43
58	-OBz	-OH	-OBz	7	43
59	-OBz	-OMe	-OBz	7	43
60	-OH	-OMe	-OH	7	71
61	$-OCH_2CH=CH_2$	-OH	$-OCH_2CH=CH_2$	7	71
62	$-OCH_2CH=CH_2$	-OMe	$-OCH_2CH=CH_2$	7	71
63	$-OCH=CH-CH_3$	-OH	$-OCH=CH-CH_3$	7	71
64	$-OCH=CH-CH_3$	-OMe	$-OCH=CH-CH_3$	7	71
65	-OMe	-OH	-OH	7	44
66	-OMe	-OH	-Br	7	44
30	-OMe	-OH	-OCPh (O above C)	7	44
67	-OMe	-OMe	$-N_3$	6	37
68	-OMe	-OMe	$-NH_3^+Cl^-$	6	37
69	-OMe	-OMe	-NHAc	6	37
33	-OCPh (O above C)	-OCPh (O above C)	-OMe	6	37
70	-OH	-OH	-OMe	6	37

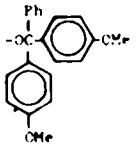
Table 8. Permethylated $6^A, 6^C, 6^E$ - trisubstituted - α - cyclodextrins and the related unsubstituted compound



Compound No.	X	Y	Reference
71	$-NH_3^+Cl^-$	-OMe	73
72	$-OC(Ph)_3$	-OH	73
73	$-OC(Ph)_3$	-OMe	73
74	-OH	-OMe	73
75	$-OSO_2CH_3$	-OMe	73
76	$-N_3$	-OMe	73

Table 9. Asymmetrically alkylated cyclodextrins and asymmetrically alkylated cyclodextrins with other functional groups



Compound No.	U	V	W	X	Y	Z	n	m	Reference
77	-OH	-OH	-OH	-OH	-OH	$-OC(Ph)_3$	7	3	29
35	-OAc	-OAc	-OAc	-OAc	-OAc	$-OC(Ph)_3$	7	3	29
36	-OAc	-OAc	-OAc	-OAc	-OAc		7	3	29
40	-OCPh	-OCPh	2/3 -OCPh 1/3 -OH	-OCPh	-OCPh	$-OC(Ph)_3$	7	3	43
41	-OCPh	-OCPh	-OCPh	-OCPh	-OCPh	-OMe	7	2	43
78	-OH	-OH	-OH	-OH	-OH	-OMe	7	2	43
79	-OMe	-OMe	$-NH_3^+Cl^-$	-OMe	-OMe	-OMe	6	1	73

chlorination of anisol by hypochlorous acid. Both **55** and **56** were prepared by Boger *et al.*[37] in connection with their synthetic efforts to synthesize derivatives of the parent cyclodextrins **1** and **2** with total modification of all primary hydroxyl groups. Casu *et al.*[64] also employed **55** and **56**, the 2, 6-methylated derivatives, in their study of the inclusion characteristics of methylated cyclodextrins.

Other 2, 6-alkylated cyclodextrins also appear in the literature. Heptakis (2, 6 - di - *O* - propyl) - β - cyclodextrin (**57**) was prepared[43,69] by the dialkylsulfate-barium oxide method. Compound **57** was used[43,69] to mimick the action of the mycobacterial polysaccharides as was discussed earlier for compounds **55** and **56**. The 2, 6-benzylated derivative, heptakis (2, 6 - di - *O* - benzyl) - β - cyclodextrin (**58**), was reported with little synthetic detail being given.[43] Subsequent alkylation of **58** with methyl iodide yielded[43] heptakis (2, 6 - di - *O* - benzyl - 3 - *O* - methyl) - β - cyclodextrin (**59**). Removal of the benzyl groups in **59** with lithium in ethylamine gave[43] the 3-methyl compound, heptakis (3 - *O* - methyl) - β - cyclodextrin (**60**). Derivative **60** was also used in the enzyme modeling experiment[43] previously described for compounds **55–57**. The synthetic strategy of blocking the 2, 6 - hydroxyl groups by alkylation, subsequent further alkylation of the 3-hydroxyl groups by a different alkylating agent, and then cleavage of the 2, 6 - ether linkages to give a 3-alkylated product has also been utilized in an alternative synthesis of **60**. Thus, Bergeron *et al.*[71] treated β-cyclodextrin (**2**) with 3-bromopropene in the presence of barium oxide-barium hydroxide octahydrate in DMF–DMSO to give the 2, 6-diallyl derivative, heptakis (2, 6 - di - *O* - allyl) - β - cyclodextrin (**61**). Reaction of the diallyl ether **61** with excess methyl iodide in DMF in the presence of sodium hydride yielded the 2, 6 - diallyl - 3 - methyl derivative, heptakis (2, 6 - di - *O* - allyl - 3 - *O* - methyl) - β - cyclodextrin (**62**) which was isomerized with potassium *t*-butoxide in DMSO to the 2, 6 - divinyl ether, heptakis (3 - *O* - methyl - 2, 6 - di - *O* - prop - 1 - enyl) - β - cyclodextrin (**64**). Cleavage of the vinyl ether groups of **64** gave the 3-methyl derivative **60**. Alternately, the 2, 6-diallyl derivative **61** could be first isomerized to the 2, 6-divinyl ether, heptakis (2, 6 - di - *O* - prop - 1 - enyl) - β - cyclodextrin (**63**). Analogous treatment of **63** with excess methyl iodide in DMF yielded **64** which was converted into the 3-methyl derivative, **60**. ^{1}H NMR spectra are reported for compounds **60–64**.[71] ^{13}C NMR data are available[71] for derivative **60** and IR data for compound **62** have been published.[71]

The 2-methyl analog of **60**, heptakis (2 - *O* - methyl) - β - cyclodextrin (**65**) was prepared by Takeo and Kuge.[44] Treatment of heptakis (6 - bromo - 6 - deoxy - 2 - *O* - methyl) - β - cyclodextrin (**66**) in hexamethylphosphoramide (HMPA) with sodium benzoate at 90° gave heptakis (6 - *O* - benzoyl - 2 - *O* - methyl) - β - cyclodextrin (**30**). Cleavage of the benzoyl group by reaction of **30** with sodium methoxide in methanol, followed by treatment with an ion exchange resin gave the 2-methyl derivative **65**. The ^{1}H NMR spectrum of **65** was utilized[44] in the structure proof of compound **56**.

Cyclodextrin derivatives with all secondary hydroxyl groups alkylated, and all primary hydroxyl groups substituted by other functional groups are also known.[37] As synthetic intermediates in an overall scheme to selectively modify all primary hydroxyl groups in cyclodextrins, Boger *et al.*[37] synthesized a number of these compounds. Thus, hexakis (6 - azido - 6 - deoxy - 2, 3 - di - *O* - methyl) - α - cyclodextrin (**67**) was prepared from the parent cyclodextrin **1** by two methods which involved a series of reaction and purification steps. Further treatment of **67** with triphenylphoshine in dioxane followed by addition of concentrated aqueous ammonia and workup gave hexakis (6 - amino - 6 - deoxy - 2, 3 - di - *O* - methyl) - α - cyclodextrin hexahydrochloride (**68**). Acetylation of compound **68** gave hexakis (6 - *N* - acetylamino - 6 - deoxy - 2, 3 - di - *O* - methyl) - α - cyclodextrin (**69**).

Boger *et al.*[37] also reported the synthesis of 6-methylated derivatives. The 2, 3-benzoylated α-cyclodextrin **31** was treated with diazomethane and boron trifluoride etherate in chloroform at 0° to give the 3-methyl analog hexakis (2, 3 - di - *O* - benzoyl - 6 - *O* - methyl) - α - cyclodextrin (**33**). Removal of the benzoyl protecting groups from **33** by treatment with potassium hydroxide gave the desired 6-methyl compound, hexakis (6 - *O* - methyl) - α - cyclodextrin (**70**). These authors[37] also report spectral data (^{13}C and ^{1}H NMR, IR) for derivatives **33**, **67–70**. The syntheses of several α-cyclodextrin derivatives which contain three symmetrically disposed functional groups by replacing three of the six primary hydroxyl groups has also been performed by Boger *et al.*[72,73] The remaining hydroxyl groups were methylated (Table 8). The 6^A, 6^C, 6^E-triammonio α-cyclodextrin derivatives, 6^A, 6^C, 6^E-triamino-6^A, 6^C, 6^E-trideoxy-2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^E, 3^F, 6^B, 6^D, 6^F-pentadeca - *O* - methyl - α - cyclodextrin trihydrochloride (**71**) has been studied as an enzyme model which is capable of stabilizing the trigonal bipyramidal transition state required for an in-line displacement at the phosphate group of a phosphate monoester.[72,74] Compound **71** was prepared by the following reaction sequence.[73] α-Cyclodextrin (**1**) was treated with excess trityl chloride in pyridine to give a mixture of di-, tri- and tetra-trityl derivatives. A short silica gel chromatography column was employed to obtain the desired tri-trityl derivative, 6^A, 6^C, 6^E-tri - *O* - trityl - α - cyclodextrin (**72**). Methylation of the fifteen remaining hydroxyl groups of **72** was accomplished using methyl iodine and crystalline sodium hydride in DMF to give 2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^E, 3^F, 6^A, 6^C, 6^E-pentadeca - *O* - methyl - 6^B, 6^D, 6^F - tri - *O* - trityl - α - cyclodextrin (**73**). The three trityl groups of **73** then were removed by concentrated hydrochloric acid to give a derivative containing 3 symmetrically disposed primary hydroxyl groups, 2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^E, 3^F, 6^A, 6^C, C^E - pentadeca - *O* - methyl - α - cyclodextrin (**74**). Further reaction of **74** with methanesulfonyl chloride in pyridine produced the 6-trimesylate, 6^A, 6^C, 6^E - tri - *O* - mesyl - 2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^E, 3^F, 6^B, 6^D, 6^F - pentadeca - *O* - methyl - α - cyclodextrin (**75**), which, when treated with sodium azide in DMF, yielded the 6-triazido compound, 6^A, 6^C, 6^E - triazido - 6^A, 6^C, 6^E - trideoxy - 2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^E, 3^F, 6^B, 6^D, 6^F - pentadeca - *O* - methyl - α - cyclodextrin (**76**). Compound **71** was obtained by the reduction of **76** with triphenylphosphine-ammonia. Derivatives **71–76** were characterized by their ^{1}H and ^{13}C NMR spectra.[73]

In addition to the symmetrical alkyl cyclodextrin derivatives discussed to this point, a number of asymmetric cyclodextrin derivatives containing alkyl groups are known (Table 9). During their conformational study of the glucopyranose residues in and the ORD spectra of cyclodextrins, Cramer *et al.*[29] prepared tetrakis (6 - *O* - trityl)) - β - cyclodextrin (**77**) by treating the parent cyclodextrin **2** with trityl chloride and pyridine. Substitution of the primary hydroxyl groups in **2** occurred only at four of the seven possible sites, probably due to steric interactions. A derivative containing four trityl groups with the remaining hydroxyl groups having been acetylated was prepared by an analogous reaction of **2** with trityl chloride in pyridine, followed by addition of acetic anhydride to the reaction mixture. Thus, tetrakis (2, 3 - di - *O* - acetyl - 6 - *O* - trityl) - tris (2, 3, 6 - tri - *O* - acetyl) - β - cyclodextrin (**35**) and an analogous compound (from 4, 4'-dimethoxytrityl chloride, pyridine and acetic anhydride), tetrakis - [2, 3 - di - *O* - (4, 4' - dimethoxytrityl)] - tris (2, 3, 6 - tri - *O* - acetyl) - β - cyclodextrin (**36**) were synthesized.[29] Compound **77** has also been prepared by other workers.[75] Physical data, and ORD and UV spectra are reported[29] for derivatives **35**, **36**, and **77**.

Bergeron *et al.*[43] prepared a benzoylated analog of the peracetylated 6-tetratrityl derivative **35** by

benzoylation of the 6-tetratrityl derivative **77**. The resulting material was a β-cyclodextrin derivative in which four of the seven primary hydroxyl groups were tritylated, two of the seven primary hydroxyl groups were benzoylated, one primary hydroxyl group remained unmodified, and all of the secondary hydroxyl groups were benzoylated: bis (2, 3, 6 - tri - *O* - benzoyl) - mono (2, 3, - di - *O* - benzoyl - 6 - *O* - trityl) - β - cyclodextrin (**40**). Following removal of the four primary trityl groups with dilute acid, methylation of the resulting *five* unprotected primary hydroxyl groups gave bis (2, 3, 6 - tri - *O* - benzoyl) - pentakis (2, 3 - di - *O* - benzoyl - 6 - *O* - methyl) - β - cyclodextrin (**41**). Removal of the benzoyl groups of **41** by treatment with sodium methoxide in methanol gave pentakis (6 - *O* - methyl) - β - cyclodextrin (**78**), in which only five of the seven primary hydroxyl groups were methylated. It should be noted that the reactions which produce compounds **35**, **36**, **40**, **41**, **77** and **78** give mixtures of isomers (i.e. although four of the seven primary hydroxyl groups have been tritylated, *which* four of the seven possible sites undergo reaction has not been specified). The structures given in Table 9 for these compounds represent only six of the possible isomeric variations.

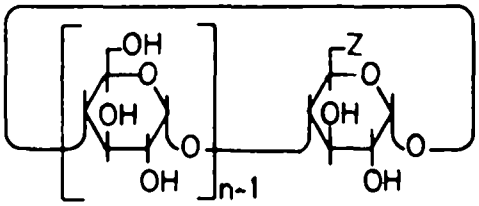
Other authors[76] have prepared benzyl cyclodextrin derivative mixtures by treating cyclodextrins with bis (trialkyltin) oxides and allowing the resulting cyclodextrin trialkyltin alkoxides to react with benzyl chloride.

In a series of reactions analogous to those used to prepare **71**, Boger *et al.*[73] synthesized mono (6 - amino - 6 - deoxy - 2, 3 - di - *O* - methyl) - pentakis (2, 3, 6 - tri - *O* - methyl) - α - cyclodextrin hydrochloride (**79**) from mono (6 - *O* - trityl) - α - cyclodextrin (**80**).[77]

4. *Monoalkylated cyclodextrins.* To this point, cyclodextrin derivatives with six or more alkyl groups have been examined. Several monoalkyl cyclodextrin derivatives with sulfur or oxygen linkages are also known (Table 10). The mono - 6 - trityl derivative, mono (6 - *O* - trityl) - α - cyclodextrin (**80**) was prepared by Melton and Slessor[77] from the parent cyclodextrin **1** and trityl chloride in pyridine. This material was utilized[73] in the synthesis of the permethylated monoamino cyclodextrin derivative **79**. The monotrityl derivative **80** was subjected[78] to *Aspergillus oryzae* amylase (Taka-amylase) in an attempt to form 6'-trityl substituted maltose. However, the attempted hydrolysis of **80** was found to be slow and complicated by side reactions.

Several monoalkyl derivatives in which the alkyl group is linked to the parent cyclodextrin by a sulfide rather than an ether linkage have been reported. Fujita, Shinoda and Imoto[79] prepared the mono - 6 - methylthio derivative, mono (6 - deoxy - 6 - methylthio) - β - cyclodextrin (**81**) from the parent cyclodextrin via a monotosyl intermediate. Similarly, the mono - 6 - *n* - propyl,[80] mono - 6 - *t* - butyl[79] and mono - 6 - neopentyl[80] sulfide derivatives were synthesized: mono (6 - deoxy - 6 - propylthio) - β - cyclodextrin (**82**), mono (6 - *t* - butylthio - 6 - deoxy) - β - cyclodextrin (**83**) and mono (6 - deoxy - 6 - neopentylthio) - β - cyclodextrin (**84**), respectively. Compounds **81**–**84** were studied as enzyme-like

Table 10. Monoalkylated cyclodextrins



Compound No.	Z	n	Reference
80	$-OC(Ph)_3$	6	77
81	-SMe	7	79
82	-SPr	7	80
83	$-SC(CH_3)_3$	7	79
84	$-SCH_2C(CH_3)_3$	7	80

catalysts in the cyclodextrin-catalysed hydrolysis of *meta*- and *para*-substituted phenyl acetates.[79,80] A recent X-ray analysis of **83** indicates that the *t*-butylthio group resides within the hydrophobic cavity of the cyclodextrin.[81]

C. *Cyclodextrin tosylates, mesylates and related derivatives*

1. *Introduction.* Following the early research in the area of cyclodextrins, which led to the synthesis (for purification or other purposes) of a large number of acyl and alkyl cyclodextrin derivatives, interest was focused on the preparation of more complex derivatives of cyclodextrins. As the nature of the parent cyclodextrins became better known, it was recognized that these versatile compounds, and their derivatives, might be utilized in several chemical applications, including enzyme modeling studies. Often, the requirements of these proposed applications included the need for very pure and well-characterized cyclodextrin derivatives. It also became apparent that cyclodextrin derivatives with a variety of other functional groups would be required for many of the proposed applications. The desirability of preparing cyclodextrins with such groups as amino, azido, or halo led to the preparation of a series of cyclodextrin derivatives containing tosyl (4-methylbenzenesulfonyl), mesyl (methanesulfonyl), or other related arylsulfonyl groups, which were then employed as intermediates in the synthesis of other cyclodextrin derivatives. In this treatment, the symmetrical cyclodextrin derivatives containing multiple tosyl, mesyl or related groups will be examined initially. Thereafter, the asymmetrically substituted cyclodextrin derivatives containing arylsulfonyl groups shall be surveyed. Finally, monotosyl cyclodextrins and related compounds will be discussed. In addition to the compounds listed in this subsection, several "capped" cyclodextrins involving arylsulfonyl linkages are known. Discussion of such derivatives will be postponed until subsection R.

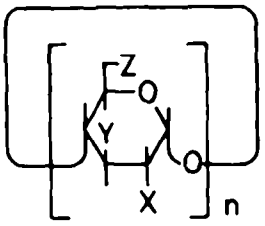
2. *Symmetric cyclodextrin derivatives containing multiple tosyl, mesyl or related groups.* Lautsch, Weichert and Lehmann,[38] in 1954, reported the first syntheses of the cyclodextrin tosylates (Table 11) hexakis (6 - *O* - tosyl) - α - cyclodextrin (**85**), and the analogous heptakis (6 - *O* - tosyl) - β - cyclodextrin (**86**). Compounds **85** and **86** were prepared from the parent cyclodextrins **1** and **2** by treatment with six (derivative **85**) or seven (derivative **86**) mole equivalents of tosyl chloride (*p*-toluenesulfonyl chloride) in pyridine. Reaction at room temperature, followed by recrystallization, gave the primary tosylates **85** and **86**. Umezawa and Tatsutu,[82] using a refinement of the procedure of Lautsch *et al.*[38] prepared **85** utilizing a low temperature reaction followed by chromatography. The purity of the sample of **85** prepared by Lautsch *et al.*[38] was questioned by these researchers,[82] since the initial preparation had not involved chromatography. Cramer *et al.*[29] in their UV and ORD spectral study of the conformations of the glucopyranose residues in cyclodextrins, produced **85** and **86** by the reaction of **1** and **2**, respectively, with a 50% excess of tosyl chloride in pyridine. Breslow *et al.*[84,85] employing a modification of the method of Lautsch *et al.*[38] prepared **86**. Specific rotation data for **85** and **86** and the reflectance spectra (420–600 nm) of the iodine complexes of **85** and **86** are reported.[38] Derivative **86** has been utilized[39] as a synthetic intermediate in the preparation of a cyclodextrin polymer. Compounds **85** and **86** have been converted into azido and amino cyclodextrins,[82] and other cyclodextrin derivatives.[29] Cramer and Mackensen[83],[119] also employed **85** and **86** as intermediates in the synthesis of cyclodextrin derivatives containing pendant imidazole moieties. Emert and Breslow[84] utilised **86** as a synthetic intermediate in the synthesis of a flexibly "capped" β-cyclodextrin in an attempt to improve the catalytic ability of β-cyclodextrin as an enzyme model. In further research, which was aimed at preparing cyclodextrin enzyme models that mimic the action of serine acylase enzymes, Breslow *et al.*[85] used **86** as a synthetic intermediate. Breslow[120] also employed **86** in the preparation of a hepta - 6 - substituted cyclodextrin imidazole derivative.

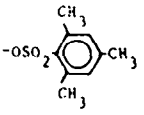
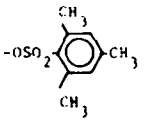
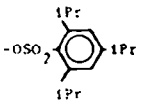
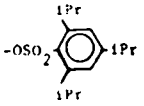
Analogs of **85** and **86**, in which the secondary hydroxyl groups have been acylated, are known. The acetyl analogs of **85** and **86**, hexakis (2, 3 - di - *O* - acetyl - 6 - *O* - tosyl) - α - cyclodextrin (**15**) and heptakis (2, 3 - di - *O* - acetyl - 6 - *O* - tosyl) - β - cyclodextrin (**16**) were prepared by Cramer *et al.*[29] by the reaction of **85** and **86** with acetic anhydride in pyridine. An earlier preparation of **16** was reported by Lautsch and Wiechert.[39] The ORD and UV spectra of **15** and **16** have been published.[29]

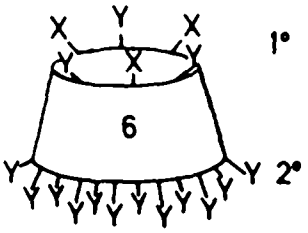
The benzoylated analog of **15**, hexakis (2, 3 - di - *O* - benzoyl - 6 - *O* - tosyl) - α - cyclodextrin (**32**), was synthesized by Boger *et al.*[37] Compound **32** was prepared[37] from the 2, 3-benzoylated material **31** by treatment with tosyl chloride in pyridine at room temperature followed by workup and column chromatography.

In addition to the series of 6-tosyl cyclodextrin derivatives just discussed, a number of analogous 6-mesyl derivatives have also been prepared. Lautsch *et al.*[38] report the preparation of hexakis (6 - *O* -

Table 11. Symmetric cyclodextrin derivatives containing multiple tosyl, mesyl, or related groups



Compound No.	X	Y	Z	n	Reference
85	-OH	-OH	-OTs	6	38
86	-OH	-OH	-OTs	7	85
15	-OAc	-OAc	-OTs	6	29
16	-OAc	-OAc	-OTs	7	29
32	-OCPh (O)	-OCPh (O)	-OTs	6	37
87	-OH	-OH	$-OSO_2CH_3$	6	38
88	-OH	-OH	$-OSO_2CH_3$	7	38
13	-OAc	-OAc	$-OSO_2CH_3$	6	38
14	-OAc	-OAc	$-OSO_2CH_3$	7	38
89	-OH or $-OSO_2CH_3$	$-OSO_2CH_3$ or -OH	$-N_3$	6	86
90	-OH or $-OSO_2CH_3$	$-OSO_2CH_3$ or -OH	$-N_3$	7	87
91	-OH or $-OSO_2CH_3$	$-OSO_2CH_3$ or -OH	$-OSO_2CH_3$	7	87
92	-OH	-OH	$-OSO_2Ph$	6	83
93	-OH	-OH		6	88
94	-OH	-OH		7	92
95	-OH	-OH		6	93
96	-OH	-OH		7	93



Compound No.	X	Y	Reference
75	$-OSO_2CH_3$	-OMe	73

mesyl) - α - cyclodextrin (87) and heptakis (6 - O - mesyl) - β - cyclodextrin (88), the mesyl analogs of 85 and 86. Derivatives 87 and 88 resulted from treatment of the parent cyclodextrins 1 and 2 with mesyl chloride (methanesulfonyl chloride) in pyridine at low temperature. Due to apparent difficulties encountered in the attempted recrystallization of 87 and 88, these workers[38] acetylated the compounds with acetic anhydride–pyridine and obtained hexakis (2, 3 - di - O - acetyl - 6 - O - mesyl) - α - cyclodextrin (13) and heptakis (2, 3 - di - O - acetyl - 6 - O - mesyl) - β - cyclodextrin (14), the mesyl analogs of 15 and 16.

Bender *et al.*[46] prepared 87 and 88 as a portion of their research on the mechanism of cyclodextrin-catalyzed cleavage of phenyl esters. Compound 88 is reported[46] to be as effective a catalyst in the cleavage of phenyl esters as is the parent β-cyclodextrin. This result is consistent with the proposed involvement of a secondary hydroxyl group of the cyclodextrin in the catalysis. The 6 - mesyl - β - cyclodextrin 88 was also synthesized by Cramer *et al.*[29] from 2 and mesyl chloride in pyridine. Acetylation of 88 with acetic anhydride–pyridine yielded[29] 14, the acetylated analog of 88. Cramer and Mackensen[83] employed 88 as an intermediate in preparing cyclodextrin derivatives with pendant imidazole moieties.

A symmetrical cyclodextrin trimesylate, 6^A, 6^C, 6^E - tri - O - mesyl - 2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^E, 3^F, 6^B, 6^D, 6^F - pentadeca - O - methyl - α - cyclodextrin (75), a compound with mesyl groups substituted for three symmetrically disposed primary hydroxyl groups and the remaining primary and secondary hydroxyl groups replaced by methoxy functions, has been reported.[73] Compound 75 was obtained[73] via compounds 72–74 (Table 8) from the parent cyclodextrin 1. Azido and amino analogs (76 and 71, respectively) were obtained by the further reactions[73] of 75.

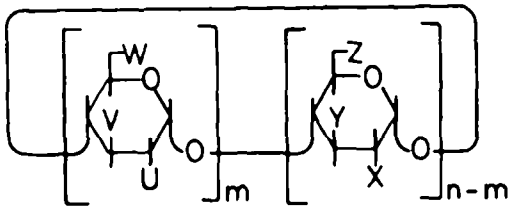
Cyclodextrin mesyl derivatives, with the mesyl groups attached at secondary hydroxyl sites, are also known. Hexakis [6 - azido - 6 - deoxy - 2 (3) - O - mesyl] - α - cyclodextrin (89) and heptakis [6 - azido - 6 - deoxy - 2 (3) - O - mesyl] - β - cyclodextrin (90) were utilized as synthetic intermediates in the preparation of modified cyclodextrins possessing antibacterial activity.[86] Compound 90 was produced[87] in a two step synthesis via the tetradecamesylate, heptakis [2 (3), 6 - di - O - mesyl] - β - cyclodextrin (91). Thus, reaction of the parent cyclodextrin 2 with mesyl chloride (2.15 mole equivalents per glucopyranose residue) in pyridine gave 91 in 98% yield. Further reaction of 91 with sodium azide in DMF at 85° for 7 hours produced 90 in 96% yield.

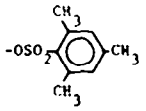
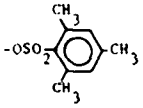
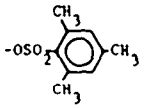
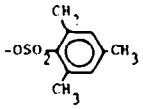
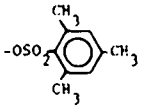
In addition to the 6-tosyl and 6-mesyl derivatives described above, a number of 6-arylsulfonyl cyclodextrin derivatives appear in the literature. Hexakis (6 - O - benzenesulfonyl) - α - cyclodextrin (92) was prepared by Cramer and Mackensen[83] as an intermediate in their syntheses of cyclodextrin imidazole derivatives. Kurita *et al.*[88–92] report the synthesis of the 6-mesitylsulfonyl cyclodextrin derivatives, hexakis [6 - O - (2, 4, 6 - trimethylbenzenesulfonyl)] - α - cyclodextrin (93) and heptakis [6 - O - (2, 4, 6 - trimethylbenzenesulfonyl)] - β - cyclodextrin (94). Certain amino cyclodextrin derivatives derived from 93 and 94 are reported to possess serum cholesterol-lowering activity.[88–91] Compound 94 resulted[92] from the action of mesityl chloride (2, 4, 6 - trimethylbenzenesulfonyl chloride) on 1 in dry pyridine. Other serum cholesterol-lowering-amino cyclodextrin derivatives were prepared[93] from hexakis [6 - O - (2, 4, 6 - triisopropylbenzenesulfonyl)] - α - cyclodextrin (95) and heptakis [6 - O - (2, 4, 6 - triisopropylbenzenesulfonyl)] - β - cyclodextrin (96).

3. *Asymmetric cyclodextrin derivatives containing tosyl or related groups.* Several asymmetric cyclodextrin derivatives containing tosyl or other arylsulfonyl groups have appeared in the literature (Table 12). An attempt by Cramer *et al.*[29] to prepare a hepta - 6 - iodo derivative of β-cyclodextrin by treating the 6-tosylate 86 with sodium iodide resulted in a mixture of compounds 97 which had 5.5 iodo groups and 1.5 tosyl groups per cyclodextrin molecule. In a related attempt[29] to synthesize the hexa - 6 - iodo peracetate from 15 and the hepta - 6 - iodo peracetate from 16, chemically modified cyclodextrins were prepared in which all but one primary tosyloxy group had been replaced by iodo groups and all secondary hydroxyl groups had been acetylated. Thus, mono (2, 3 - di - O - acetyl - 6 - O - tosyl) - pentakis (2, 3 - di - O - acetyl - 6 - deoxy - 6 - iodo) - α - cyclodextrin (37) and hexakis (2, 3 - di - O - acetyl - 6 - deoxy - 6 - iodo) - mono (2, 3 - di - O - acetyl - 6 - O - tosyl) - β - cyclodextrin (38) are known.[29]

Hexakis [6 - O - (2, 4, 6 - trimethylbenzenenesulfonyl)] - β - cyclodextrin (98) was prepared[94,95] and found to possess antibacterial activity. Compound 98 is closely related to 94. However, one primary hydroxyl group in 98 remains unsubstituted. Hexakis [6 - O - (2, 4, 6 - trimethylbenzenesulfonyl)] - β - cyclodextrin (99) was formed[92] as a coproduct in the preparation of 94 from the parent cyclodextrin 2. When a mixture of the hepta - 6 - mesitylsulfonyl derivatives 99 and 94 were treated with sodium azide

Table 12. Asymmetric cyclodextrin derivatives containing tosyl or related groups



Compound No.	U	V	W	X	Y	Z	n	m	Reference
97	-OH	-OH	-OTs	-OH	-OH	-I	7	1.5	29
37	-OAc	-OAc	-OTs	-OAc	-OAc	-I	6	1	29
38	-OAc	-OAc	-OTs	-OAc	-OAc	-I	7	1	29
98	-OH	-OH	-OH	-OH	-OH		7	1	95
99		-OH	-OH	-OH	-OH		7	1	92
100		-OH	-OH	-OH	-OH	$-N_3$	7	1	92
101		-OH	-OH	-OH	-OH	$-NH_2$	7	1	92

in DMF, a mixture of products including the hexa - 6 - azido - mono - 2 - mesitylsulfonyl compound, hexakis (6 - azido - 6 - deoxy) - mono [2 - *O* - (2, 4, 6 - trimethylbenzenesulfonyl)] - β - cyclodextrin (**100**), was produced. Catalytic hydrogenation (PtO_2 in methanol) of **100** yielded a mixture of positional isomers of hexakis (6 - amino - 6 - deoxy) - mono [2 - *O* - (2, 4, 6 - trimethylbenzenesulfonyl)] - β - cyclodextrin (**101**) (isolated as the hexahydrochloride). IR Spectral data for derivatives **98–101** are reported.[92]

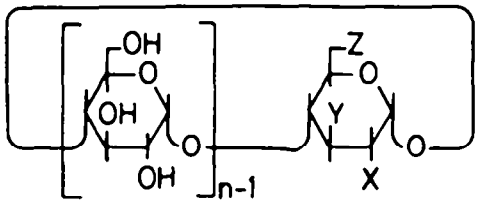
Other unspecified tosyl and mesyl derivatives of cyclodextrins, are reported[76] to have been prepared by treatment of trialkyl tin alkoxides of cyclodextrins with tosyl or mesyl chloride.

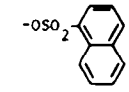
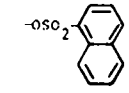
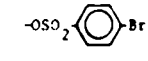
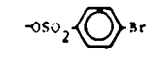
4. *Monotosyl cyclodextrin derivatives and related monosubstituted compounds.* Monotosyl derivatives and other related monoarylsulfonyl cyclodextrin derivatives are listed in Table 13. The earliest known monotosyl cyclodextrin derivative is the 6-tosyl derivative of **1**, mono (6 - *O* - tosyl) - α - cyclodextrin (**102**). Melton and Slessor[77] reported the preparation of **102** as a key intermediate in the synthesis of several monosubstituted α-cyclodextrin derivatives. Compound **102** was prepared[77] from freeze-dried **1** and tosyl chloride in pyridine. After reaction for 40 minutes at room temperature, water was added to terminate the process. Analysis showed a 67% conversion of **1** to **102**. Workup and chromatography yielded pure **102**, for which specific rotation data are given.[77]

The cyclodextrin derivatives prepared from **102** and **102** itself were treated with *Aspergillas oryzae* amylase (Taka-amylase) to prepare 6'-substituted maltoses.[78] Polyamino cyclodextrin derivatives have also been synthesized from **102**.[96] Onozuku *et al.*[107] prepared **102** using Melton and Slessor's method[77] and compared its ^{13}C NMR spectrum to that of a suspected mono - 3 - tosyl cyclodextrin derivative.

The 6-tosyl β-cyclodextrin analog of **102**, mono (6 - *O* - tosyl) - β - cyclodextrin (**103**), was first reported by Matsui, *et al.*[97] as a synthetic intermediate in the preparation of a copper-amino cyclodextrin complex. Compound **103** was tosylated with a 0.5 equivalent of tosyl chloride in pyri-

Table 13. Monotosyl cyclodextrins and related compounds



Compound No.	X	Y	Z	n	Reference
102	-OH	-OH	-OTs	6	77
103	-OH	-OH	-OTs	7	97
104	-OH	-OTs	-OH	6	107
105	-OH	-OTs	-OH	7	107
106	-OH	-OH		6	96
107	-OH	-OH		7	96
108	-OH	-OH		6	96
109	-OH	-OH		7	96

dine, followed by recrystallization from water.[97] Tabushi *et al.*[98] utilized derivative **103** to synthesize a cyclodextrin which was flexibly capped with a metal ion. Compound **103** was also employed in the preparation of polyamine cyclodextrin derivatives[96] and the metal complexes of those polyamine derivatives.[99] Matsui and Okimoto[100] used **103** in the preparation of a quaternary amino cyclodextrin—a simple enzyme model. Compound **103** was converted into several mono - 6 - halo cyclodextrin derivatives by Omichi and Matusshima.[101] These mono - 6 - halo cyclodextrins were then transformed into 6-halomaltotrioses, which were employed as substrates in hydrolysis studies using Taka-amylase A. Derivative **103** was utilized by Tabushi *et al.*[102] in the preparation of an amino cyclodextrin monomer, which was subsequently condensed with chloromethylated polystyrene to give a cyclodextrin-containing polymer. In an alternative polymer preparation method,[103] the mono - 6 - tosyl derivative **103** was condensed with triethylenetriamino-substituted polystyrene, to form the desired cyclodextrin polymer. Metal complexes of the polymers produced from **103** are reported to be especially effective in the extraction of organic anions from aqueous solutions.[170] Siegel[104] has employed **103** in the synthesis of a tetrameric iron–sulfur complex, which contains thiocyclodextrin ligands. Fujita *et al.*[79,80] used **103** in the synthesis of the 6-alkylthio derivatives **81–84**. A β-cyclodextrin–pyridoxamine artificial enzyme derived from **103** was reported by Breslow, Hammond and Lauer.[105] Hirotus *et al.*[81] converted **103** into the mono - 6 - *tert* - butylthio cyclodextrin, **83**. Breslow *et al.*[121] have utilized **103** in the preparation of cyclodextrin with a pendant imidazole moiety.

Other monotosyl derivatives of cyclodextrins have appeared. The mono - 3 - tosyl compounds, mono(3 - *O* - tosyl) - α - cyclodextrin (**104**) and mono (3 - *O* - tosyl) - β - cyclodextrin (**105**) are known. Iwakura *et al.*[106] prepared **104** by the treatment of α-cyclodextrin (**1**) with 10 equivalents of tosyl chloride in pH 11 buffer at 25° for 1 hr. Ion exchange chromatography yielded the pure α-cyclodextrin 3-tosylate **104**. UV and ^{1}H NMR data are reported[106] for **104**. Onozuku *et al.*[107] achieved the regiospecific tosylation of the parent cyclodextrins **1** and **2** to give **104** and **105**, respectively. The parent cyclodextrin (**1** or **2**) was treated with tosyl chloride in a highly basic medium (pH 12 carbonate buffer or a pH 13 sodium hydroxide solution) followed by ion exchange chromatography. Compounds **104** and **105** were obtained following purification of the crude products. Compound **105** was also utilized[112] in the synthesis of cyclodextrin nicotinamide derivatives.

In addition to the 3- and 6-monotosylated cyclodextrins discussed to this point, four mono - 6 - arylsulfonyl cyclodextrins are also known. Tabushi and Shimizu[96] prepared the mono - 6 - α - naphthalenesulfonyloxy derivatives, mono [6 - *O* - (1 - naphthalenesulfonyl)] - α - cyclodextrin (**106**) and mono [(6 - *O* - (1 - napthalenesulfonyl)] - β - cyclodextrin (**107**), and the mono - 6 - brosylates, mono [6 - *O* - (4 - bromobenzenesulfonyl)] - α - cyclodextrin (**108**) and mono [6 - *O* - (4 - bromobenzenesulfonyl)] - β - cyclodextrin (**109**). Compounds **106–109** were utilized in the synthesis of polyamino cyclodextrin derivatives.[96]

D. *Amino and azido derivatives of cyclodextrins*

1. *Introduction.* Following the initial preparations of the synthetically simpler cyclodextrin derivatives, which were usually alkylated or acetylated compounds, synthetic methods were developed (often employing cyclodextrin tosylates or related compounds) which enabled amino cyclodextrin derivatives to be prepared. While other methods have been utilized, the general synthetic strategy is to generate the amino derivatives from the corresponding cyclodextrin tosylates of mesylates via nucleophilic displacement of the sulfonate group by azide ion. The azido derivatives are subsequently converted into amino compounds by reduction. Examples of these azido and amino cyclodextrins are very prolific. In addition to numerous primary journal citations for these cyclodextrin derivatives, they are focal compounds or at least mentioned in many patents. Since much of the patent literature is only available to the authors of this review is abstract form, the discussion of cyclodextrin amine or azide derivatives given in patents will be confined to those compounds which are specifically listed in the patent abstract published by *Chemical Abstracts.*

The amino and azido cyclodextrins will be discussed in the following order: symmetrically substituted amine and azide cyclodextrin derivatives—those derivatives with two or more amino or azido groups symmetically disposed on the cyclodextrin skeleton—will be considered first. Thereafter, asymmetrically substituted amine and azide cyclodextrin derivatives will be examined. Subsequently, monosubstituted amino or azido cyclodextrins will be discussed. Finally, selective bifunctionalized cyclodextrin derivatives with amine, azide and related groups which have been prepared from "capped" cyclodextrins will be surveyed. In addition to the amino cyclodextrin derivatives discussed in this subsection, some other cyclodextrin amines will not be examined at this time. Specifically, cyclodextrins with pendant imidazolyl or substituted pyridyl moieties will be treated separately in later subsections of this work.

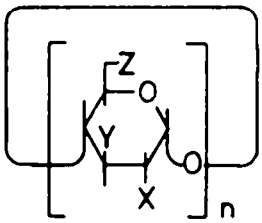
2. *Symmetrically substituted amino and azido cyclodextrin derivatives.* The earliest reported amino cyclodextrins are the 6-amino derivatives of the parent cyclodextrins **1** and **2**, hexakis (6 - amino - 6 - deoxy) - α - cyclodextrin (**110**) and heptakis (6 - amino - 6 - deoxy) - β - cyclodextrin (**111**) (Table 14). Compound **110** was first obtained by Umezawa and Tatsuta[82] from the reaction of the hexa - 6 - tosyl derivative **85** with sodium azide in DMF to give the hexa - 6 - azide, hexakis (6 - azido - 6 - deoxy) - α - cyclodextrin (**112**), which was hydrogenated (PtO_2 in methanol) to give **110**. IR data are reported[82] for **110** and **112**. In a later preparation, Boger *et al.*[37] synthesized **110** as its hexahydrochloride from **112** by reaction with triphenylphosphine in dioxane-methanol, followed by addition of aqueous ammonia and then acidification with hydrochloric acid. ^1H and ^{13}C NMR and IR spectral data for **110** and **112** are reported by these authors.[37] Compound **111**, the β-cyclodextrin analog of **110**, was first prepared by Lautsch and Wiechert[39] as a monomer for subsequent polmerization to form a cyclodextrin polymer. Derivative **111** was obtained from the hepta - 6 - tosyl analog **86** by an extended treatment with methanolic ammonia in a steel bomb. Reflection spectra of the iodine and the *p*-nitrophenol complexes of **111** are available.[39] Cramer and Mackensen[83] report an attempted further transformation of **111** to form an imidazole-substituted cyclodextrin. Compound **111**, prepared[86,90,92] from the hepta - 6 - mesitylsulfonyl derivative **94** via the corresponding azide, heptakis (6 - azido - deoxy) - β - cyclodextrin (**113**) is reported[89,90] to possess serum cholesterol-lowering activity. The hepta - 6 - amino derivative **111** was similarly produced[93] from the hepta - 6 - triisopropylbenzenesulfonyl derivative **96** via the hepta - 6 - azide **113**. Tsujihara, Kurita and Kawazu[92] report ^1H NMR and IR data for derivatives **111** and **113**, which were synthesized from the mesitylenesulfonyl derivative **94**.

A number of *N*-substituted amino cyclodextrins are known. Compound **110** was treated[82] with acetic anhydride in methanol to give the hexa - 6 - acetamido cyclodextrin, hexakis (6 - *N* - acetylamino - 6 - deoxy) - α - cyclodextrin (**114**). IR and ^1H NMR data for **114** are available.[82] The *N*-methyl and *N*-ethyl substituted amino cyclodextrins, heptakis (6 - deoxy - 6 - *N* - methylamino) - β - cyclodextrin (**115**) and heptakis (6 - deoxy - 6 - *N* - ethylamino) - β - cyclodextrin (**116**) have been reported. Derivative **115** was

prepared by Kurita *et al.*[88,89,91,93] from the hepta - 6 - mesitylsulfonyl compound **94** and the triisopropylbenzenesulfonyl compound **96** by treatment with methylamine in an autoclave at 60–70°C. Breslow *et al.*[84,85] report the preparation of **115** and the ethylamino analog **116** by treating the hepta - 6 - tosylate **86** with either methyl- or ethylamine. Further reaction[84,85] of **115** and **116** with formic anhydride yielded the *N*-formyl derivatives, heptakis (6 - deoxy - 6 *N* - formyl - *N* - methylamino) - β - cyclodextrin (**117**) and heptakis (6 - deoxy - 6 - *N* - formyl - *N* - ethylamino) - β - cyclodextrin (**118**). ^{1}H NMR spectral data for **115–118** are available.[85] The substituted amino groups of **117** and **118** would be expected to cluster together to form a "floor" on what was the primary hydroxyl group side of the cyclodextrin. It was suggested that such "flexible capping" would enhance the binding characteristics of the cyclodextrin. Therefore, Emert and Breslow[84] studied these derivatives (**117** and **118**) as reagents for acetyl transfer reactions from *m*-nitrophenyl acetate and *m-tert*-butylphenyl acetate to the secondary hydroxyl groups of the cyclodextrins. Reported data show rate enhancements. However, these authors[84] conclude that the "floor" either weakens or does not affect the overall binding—due probably to the now too-shallow cavity of the cyclodextrin. Compounds **117** and **118** have been utilized in other mechanistic studies.[85]

The hexa- and hepta - 6 - dimethylaminocyclodextrins, hexakis (6 - deoxy - 6 - *N*, *N* - dimethylamino) - α - cyclodextrin (**119**) and heptakis (6 - deoxy - 6 - *N*, *N* - dimethylamino) - β - cyclodextrin (**120**) were prepared[88,89,93] for use as serum cholesterol-lowering agents from either the corresponding mesitylsulfonates **93** or **94** or the triisopropylbenzene sulfonates **95** or **96**. Similarly produced were a number of other *N* - substituted amino cyclodextrins: heptakis [6 - deoxy - 6 - (1 - piperidino)] - β - cyclodextrin (**121**);[88,89,93] heptakis [6 - deoxy - 6 - (4 - methyl - 1 - piperdino)] - β - cyclodextrin (**122**);[89] heptakis [6 -

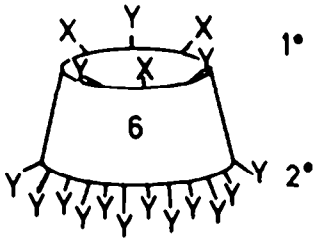
Table 14. Symmetrically substituted amino and azido cyclodextrin derivatives and related compounds



Compound No.	X	Y	Z	n	Reference
110	-OH	-OH	$-NH_2$	6	37
111	-OH	-OH	$-NH_2$	7	92
112	-OH	-OH	$-N_3$	6	37
113	-OH	-OH	$-N_3$	7	92
114	-OH	-OH	-NHAc	6	82
115	-OH	-OH	$-NHCH_3$	7	93
116	-OH	-OH	-NHEt	7	85
117	-OH	-OH		7	85
118	-OH	-OH		7	85
119	-OH	-OH	$-N(CH_3)_2$	6	89
120	-OH	-OH	$-N(CH_3)_2$	7	89
121	-OH	-OH		7	89
122	-OH	-OH		7	89
123	-OH	-OH		7	88

Table 14 (*Contd*)

Compound No.	X	Y	Z	n	Reference
124	-OH	-OH		6	89
125	-OH	-OH		7	89
90	-OH or $-OSO_2CH_3$	$-OSO_2CH_3$ or -OH	$-N_3$	7	87
26	-OAc	-OAc	$-N_3$	6	37
27	-OAc	-OAc	$-N_3$	7	37
34	-OCPh	-OCPh	$-N_3$	6	37
67	-OMe	-OMe	$-N_3$	6	37
68	-OMe	-OMe	$-NH_3^+Cl^-$	6	37
69	-OMe	-OMe	-NHAc	6	37
17	-OAc	-OAc	-NHAc	7	39



Compound No.	X	Y	Reference
71	$-NH_3^+Cl^-$	-OMe	73
76	$-N_3$	-OMe	73

deoxy - 6 - (4 - methyl - 1 - piperazinyl)] - β - cyclodextrin (**123**);[88,93] hexakis [6 - (9 - adenyl) - 6 - deoxy] - α - cyclodextrin (**124**)[88,89,93] and heptakis [6 - (9 - adenyl) - 6 - deoxy] - β - cyclodextrin (**125**).[88,89,93]

A number of symmetric azido and amino cyclodextrin derivatives, which also contain other functional groups, have been reported. A mixed azidomethanesulfonyl cyclodextrin derivative, heptakis [6 - azido - 6 - deoxy - 2 (3) - *O* - mesyl] - β - cyclodextrin (**90**) was prepared[86,87] from the hepta - 2 (3), 6 - dimesyl, compound **91** by treatment with sodium azide in DMF at 85° for 7 hr. The IR spectrum of the resulting compound **90** is reported.[87] Mixed acetylazides, hexakis (2, 3 - di - *O* - acetyl - 6 - azido - 6 - deoxy) - α - cyclodextrin (**26**) and heptakis (2, 3 - di - *O* - acetyl - 6 - azido - 6 - deoxy) - β - cyclodextrin (**27**), were reported by Boger *et al.*[37] Compounds **26** and **27** were synthesized from the parent cyclodextrins by an initial treatment of **1** or **2** with lithium azide, triphenylphosphine and carbon tetrabromide in DMF, followed by acetylation of the crude product (acetic anhydride–pyridine). Compound **26** was deacetylated with potassium hydroxide in methanol-dioxane to give the hexa - 6 - azide **112**. The benzoyl analog of **26**, hexakis (6 - azido - 2, 3 - di - *O* - benzoyl - 6 - deoxy) - α - cyclodextrin (**34**), was also prepared[37] by treatment of the hexa - 6 - tosylate **85** with sodium azide in DMF. The hexa - 6 - azide **112** was also obtained from **34** by the potassium hydroxide treatment[37] already described for compound **26**. Boger *et al.*[37] also prepared three permethylated azido and amino α-cyclodextrins.

Hexakis (6 - azido - 6 - deoxy - 2, 3 - di - *O* - methyl) - α - cyclodextrin (**67**) resulted from treating the hexa - 6 - azide **112** first with crystalline sodium hydride in DMF and then methyl iodide. The amino analog of **67**, hexakis (6 - amino - 6 - deoxy - 2, 3 - di - *O* - methyl) - α - cyclodextrin (**68**) was prepared from **67** by reaction with triphenylphosphine in dioxane, followed by addition of concentrated aqueous ammonia. Subsequent acidification gave the hexahydrochloride of **68**. Compound **68** was further transformed by reaction with acetic anhydride–triethylamine in dioxane to give hexakis (6 - *N* - acetylamino - 6 - deoxy - 2, 3 - di - *O* - methyl) - α - cyclodextrin (**69**). Spectral data (IR, ^1H and ^{13}C NMR) are reported[17] for compounds **26**, **27**, **34**, **67–69**. The acetyl β-cyclodextrin analog of **69** was synthesized by other workers.[39] Thus, heptakis (2, 3 - di - *O* - acetyl - 6 - *N* - acetylamino - 6 - deoxy) - β - cyclodextrin (**17**) was converted into the hepta - 6 - amine **111** by acetylation with acetic anhydride–pyridine

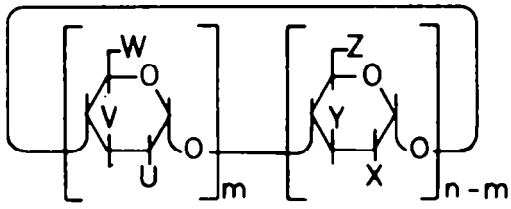
Two tri-substituted permethylated amino or azido cyclodextrins appear in the literature. The 6^A, 6^C, 6^E - triamino - 6^A, 6^C, 6^E - trideoxy - 2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^E, 3^F, 6^B, 6^D, 6^F - pentadeca - *O* - methyl - α - cyclodextrin trihydrochloride (**71**) was designed[72] to stabilize trigonal bipyrimidal transition states, such as that envisioned for an in-line displacement at the phosphorus atom of a phosphate monoester. Compound **71** was prepared[73] from the corresponding triazido derivative, 6^A, 6^C, 6^E - triazido - 6^A, 6^C, 6^E - trideoxy - 2^A, 2^B, 2^C, 2^D, 2^E, 2^F, 3^A, 3^B, 3^C, 3^D, 3^E, 3^F, 6^B, 6^D, 6^F - pentadeca - *O* - methyl - α - cyclodextrin (**76**) by reduction of **76** with triphenylphosphine and ammonia in dioxane. ^1H and ^{13}C spectra of **71** and **76** are reported.[73] Compound **71** has been investigated as a host molecule for phosphate esters. [74]

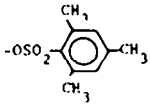
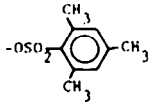
3. *Asymmetrically substituted amino and azido cyclodextrin derivatives.* Several asymmetrical substituted azido and amino cyclodextrin derivatives have been reported (Table 15). Often attempts to prepare amino derivatives of cyclodextrins in which all of the primary hydroxyl groups have been replaced by amino groups result in formation of partially substituted (at the 6-position) amino and azido cyclodextrin derivatives. In addition, other such derivatives are known, some of which contain a single primary mesitylsulfonyl group in addition to the nitrogen functional groups. The penta - 6 - amine, pentakis (6 - amino - 6 - deoxy) - α - cyclodextrin (**126**) was reported by Cramer *et al.*[29] to result from the reaction of the hexa - 6 - tosylate **85** and ammonia. Similarly, pentakis (6 - amino - 6 - deoxy) - β - cyclodextrin (**127**) was obtained as the monohydrochloride by the same workers[29] from the reaction, in a steel bomb, of methanolic ammonia and the hepta - 6 - tosylate **86**. The structure given for compound **127** in Table 15 represents one of a number of possible isomeric forms. Compound **126** and the hexa - 6 - amino analog, hexakis (6 - amino - 6 - deoxy) - β - cyclodextrin (**128**) are novel antimicrobial agents.[94] The researchers[94] prepared **126** and **128** as polyhydrochlorides from the corresponding penta- or hexa - 6 - mesitylsulfonates **98** and **99** and methanolic ammonia by sealed tube reactions. Compound **128** has also been synthesized[92] from the hexa - 6 - mesitylsulfonyl β- cyclodextrin **99** via the hexa - 6 - azide, hexakis (6 - azido - 6 - deoxy) - β - cyclodextrin (**129**). IR spectral data are reported[92] for **128** and **129**. Tsujihara *et al.*[92] have also prepared a β - cyclodextrin 6 - amino derivative in which all, except one, primary hydroxyl groups have been replaced by amino groups with a secondary hydroxyl group having been mesitylsulfonated. Thus, reaction of a mixture of hepta - 6 - mesitylsulfonates of β - cyclodextrin **94** and **99** with sodium azide in DMF gave, as one of the products, hexakis (6 - azido - 6 - deoxy) - mono[2 - *O* - (2, 4, 6 - trimethylbenzenesulfonyl)] - β - cyclodextrin (**100**). Reduction of **100** (PtO_2 in acidic methanol) yielded a mixture of positional isomers of hexakis (6 - amino - 6 - deoxy) - mono [2 - *O* - (2, 4, 6 - trimethylbenzenesulfonyl)] - β - cyclodextrin (**101**), as the hexahydrochlorides. IR data are published[92] for **100** and **101**.

Another amino cyclodextrin derivative which also possesses other functional groups is known. Boger *et al.*[73] report the preparation of a permethylated monoamino α-cyclodextrin. Thus, mono (6 - amino - 6 - deoxy - 2, 3 - di - *O* - methyl) - pentakis (2, 3, 6 - tri - *O* - methyl) - α - cyclodextrin (**79**) was the product in a multistep synthesis from the mono - 6 - trityl derivative **80**.

Hepta - 6 - amino cyclodextrin derivatives with three to five secondary amino groups have also been reported:[86,87] bis (6 - amino - 6 - deoxy) - pentakis [2 (3), 6 - diamino - 2 (3), 6 - dideoxy] - β - cyclodextrin (**130**);[86] tetrakis [2 (3), 6 - diamino - 2 (3), 6 - dideoxy] - tris (6 - amino - 6 - deoxy) - β - cyclodextrin (**131**);[87] and tetrakis (6 - amino - 6 - deoxy) - tris [2 (3), 6 - diamino - 2(3), 6 - dideoxy] - β - cyclodextrin (**132**).[87] Compounds **130–132** were obtained from the tetradecamesylate **91** via a series of reactions. Thus, **91** (obtained from the parent cyclodextrin **2**) was treated[87] with sodium azide in DMF to form the hepta - 6 - azido heptamesylate **90**. Further treatment[87] of **90** with sodium ethoxide in DMF–ethanol gave a mixture of hepta - 6 - azido epoxides, from which the following compounds were isolated: bis (6 - azido -

Table 15. Asymmetric amino and azido cyclodextrin derivatives



Compound No.	U	V	W	X	Y	Z	n	m	Reference
126	-OH	-OH	-OH	-OH	-OH	$-NH_2$	6	1	79
127	-OH	-OH	-OH	-OH	-OH	$-NH_2$	7	2	29
128	-OH	-OH	-OH	-OH	-OH	$-NH_2$	7	1	92
129	-OH	-OH	-OH	-OH	-OH	$-N_3$	7	1	92
100		-OH	-OH	-OH	-OH	$-N_3$	7	1	92
101		-OH	-OH	-OH	-OH	$-NH_3^+Cl^-$	7	1	92
79	-OMe	-OMe	$-NH_2$	-OMe	-OMe	-OMe	6	1	73
130	-OH	-OH	$-NH_2$	-OH or $-NH_2$	$-NH_2$ or -OH	$-NH_2$	7	2	86
131	-OH	-OH	$-NH_2$	-OH or $-NH_2$	$-NH_2$ or -OH	$-NH_2$	7	3	87
132	-OH	-OH	$-NH_2$	-OH or $-NH_2$	$-NH_2$ or -OH	$-NH_2$	7	4	87
133*	-OH	-OH	$-N_3$	- O -		$-N_3$	7	2	87
134*	-OH	-OH	$-N_3$	- O -		$-N_3$	7	3	87
135*	-OH	-OH	$-N_3$	- O -		$-N_3$	7	4	87
136	-OH	-OH	$-N_3$	-OH or $-N_3$	$-N_3$ or -OH	$-N_3$	7	2	86
137	-OH	-OH	$-N_3$	-OH or $-N_3$	$-N_3$ or -OH	$-N_3$	7	3	87
138	-OH	-OH	$-N_3$	-OH or $-N_3$	$-N_3$ or -OH	$-N_3$	7	4	87

*The configuration at C-3 may have been inverted (relative to the configuration for C-3 indicated in the above structure) to provide for a cis epoxide.

6 - deoxy) - pentakis [6 - azido - 2 (3), 6 - dideoxy - 2, 3 - epoxy] - β - cyclodextrin (**133**);[86] tetrakis [6 - azido - 2 (3), 6 - dideoxy - 2, 3 - epoxy] - tris (6 - azido - 6 - deoxy) - β - cyclodextrin (**134**);[87] tetrakis (6 - azido - 6 - deoxy) - tris [6 - azido - 2 (3), 6 - dideoxy - 2, 3 - epoxy] - β - cyclodextrin (**135**).[87] Reaction of compounds **133–135** with sodium azide and ammonium chloride in DMF at 90–95° gave, respectively, the dodeca-, undeca- and decaazido derivatives: bis (6 - azido - 6 - deoxy) - pentakis [2 (3), 6 - diazido - 2 (3), 6 - dideoxy] - β - cyclodextrin (**136**);[86] tetrakis [2 (3), 6 - diazido - 2 (3), 6 - dideoxy] - tris (6 - azido - 6 - deoxy) - β - cyclodextrin (**137**);[87] and tetrakis (6 - diazido - 6 - deoxy) - tris [2 (3), 6 - diazido - 2 (3), 6 - dideoxy] - β - cyclodextrin (**138**).[87] Catalytic hydrogenation (PtO_2 in acidic methanol) of compounds **136–138** yielded the hydrochlorides of derivatives **130–132**. These hydrochlorides have been found to possess strong antimicrobial activity.[87] IR spectral data for compounds **131**, **132**, **134**, **135**, **137** and **138**

are available.[87] The structures given for **130–138** in Table 15 represent only nine of several possible isomeric forms of these compounds.

Less highly characterized amino cyclodextrin mixtures, often useful in industrial applications, have been reported. β-Cyclodextrin (**2**) was treated[171] with ethylenimine in toluene to form aminoethyl β-cyclodextrin derivatives which were reported to be useful as clathrating compounds or as paper sizes. Takeo *et al.*[75] prepared 2-aminated β-cyclodextrin (with a 0.39 degree of substitution) via the oxidation, oximation, reduction ($LiAlH_4$) and detritylation of the tetra - 6 - trityl derivative **77**. Treatment[143] of **2** with isatoic anhydride in water yielded a mixture of *O* - aminobenzoyl - β - cyclodextrin derivatives (0.77 degree of substitution). Parmerter *et al.*[169] have also prepared cyclodextrin derivative mixtures from the parent cyclodextrin **2** and a quaternary ammonium-substituted epoxide reagent (CH_2–CH–CH_2–$\overset{+}{N}Me_3Cl^-$) to give quaternary ammonium ether cyclodextrins useful as paper sizes, binders and fluocculants.

4. *Monosubstituted amino and azido derivatives of cyclodextrins.* Several monoamino or monoazido cyclodextrin derivatives, and related compounds are known (Table 16). The simplest 6-amino cyclodextrin, mono (6 - amino - 6 - deoxy) - α - cyclodextrin (**139**), was prepared by Melton and Slessor[77] from the mono - 6 - tosylate **102** via the mono - 6 - azide, mono (6 - azido - 6 - deoxy) - α - cyclodextrin (**140**). Reaction of freeze-dried **102** and sodium azide in water gave the mono - 6 - azide **140**. Hydrogenation of **140** over palladium black yield the mono - 6 - amine **139**. The azide **140** was utilized by Melton and Slessor[78] as a substrate in the preparation of the analogous 6′ - substituted maltose. Gibson, Melton and Slessor[108] studied the ninhydrin-promoted oxidative deamination of **139** (obtained via **140**) to form a cyclodextrin monoaldehyde. The mono - 6 - azide **140** was photolyzed by these authors[108] to give the same monoaldehyde as had been obtained from **139**.

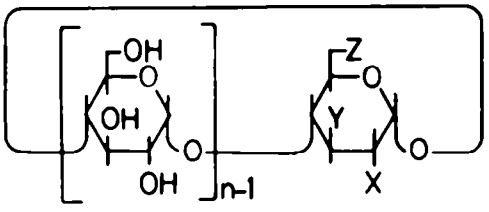
A number of polyamine cyclodextrin derivatives are known. The mono - ω - aminoethylamino compound, mono [6 - *N* - (2 - aminoethyl) amino - 6 - deoxy] - β - cyclodextrin (**141**), was prepared by Matsui *et al.*[97] from the mono - 6 - tosylate **103** and ethylenediamine. A 1 : 2 complex of **141** and Cu(II) was shown[97] to significantly accelerate the oxidation of furion at pH 10.5. Compound **141** also reacts[109,110] with retinal to give the Schiff base **145** which was used as a model compound for native visual pigments in UV absorption studies.[110] Higher polyamine analogs of **141** have been prepared by Tabushi *et al.*[96,98,99] who synthesized mono [6 - *N* - (7 - amino - 3 - azapentyl) amino - 6 - deoxy] - β - cyclodextrin (**142**) and mono [6 - *N* - (9 - amino - 3, 6 - diazaoctyl) - amino - 6 - deoxy] - β - cyclodextrin (**143**) from the primary monotosylate **103** and either diethylenetriamine or triethylenetetraamine. Compounds **142** and **143** complexed with Cu^{2+}, Zn^{2+} or Mg^{2+} (flexible metal ion "capping") were found to possess enhanced binding characteristics, when compared to the parent cyclodextrin **2**. Tabushi *et al.* also report the synthesis[96] of a cyclic polyamine derivative, mono [6 (1 - cyclo - 1, 4, 8, 11 - tetraazatetradecyl) - deoxy] - β - cyclodextrin (**144**) by a method analogous to those reported for the linear polyamine cyclodextrins **142** and **143**. Compound **143** was used[102] in the preparation of a cyclodextrin-polystyrene polymer.

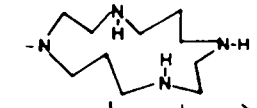
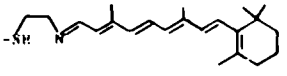
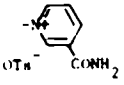
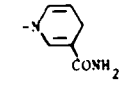
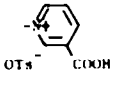
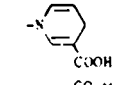
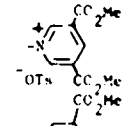
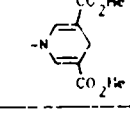
A quaternary trimethylammonio substituted cyclodextrin is also known. Matsui and Okimoto[100] report the preparation of the positively-charged cyclodextrin derivative, mono (6 - trimethylammonio - 6 - deoxy) - β - cyclodextrin hydrogen carbonate (**146**). Compound **146** was synthesized from the mono-tosylate **103** and trimethylamine in DMF. The ^1H NMR spectrum of **146** is reported, and the complexation characteristics and catalytic ability of this enzyme model have been studied.[100]

Monoamino cyclodextrin derivatives, substituted at a secondary, rather than a primary hydroxyl group, are also found in the literature. Mono (3 - amino - 3 - deoxy) - α - cyclodextrin (**147**) was produced[106] from the mono - 3 - tosylate **104** via a monoiodo intermediate. The ^{13}C NMR spectrum for **147** is reported.[106]

Cyclodextrin nicotinamide derivatives and related compounds are known.[111,112] The mono - 3 - tosylate **105** was treated[112] with a large excess of nicotinamide in DMF to form the cyclodextrin nicotinamide derivative, mono [3 - (3 - carbamoyl - 1 - pyridinio) - 3 - deoxy] - β - cyclodextrin tosylate (**148**). Reduction of **148** (aqueous Na_2CO_3–$Na_2S_2O_4$) gave the dihydronicotinamide cyclodextrin, mono [3 - (3 - carbamoyl - 4, 4 - dihydro - 1 - pyridyl) - 3 - deoxy] - β - cyclodextrin (**149**). Oxidation-reduction studies[112] were conducted in which **148** and **149** were used as models for naturally occurring NAD^+–NADH (oxidized and reduced forms of nicotinamide adenine dinucleotide). Similarly synthesized[111] were the nicotinic acid analogs of **148** and **149**, mono [3 - (3 - carboxy - 1 - pyridinio) - 3 - deoxy] - β -

Table 16. Monosubstituted amino and azido cyclodextrin derivatives

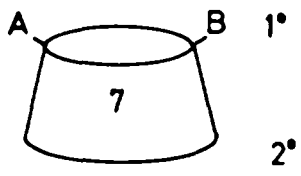


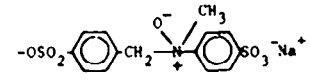
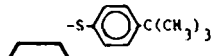
Compound No.	X	Y	Z	n	Reference
139	-OH	-OH	$-NH_2$	6	77
140	-OH	-OH	$-N_3$	6	77
141	-OH	-OH	$-NHCH_2CH_2NH_2$	7	97
142	-OH	-OH	$-NH(CH_2CH_2NH)_2H$	7	98
143	-OH	-OH	$-NH(CH_2CH_2NH)_3H$	7	98
144	-OH	-OH		7	96
145	-OH	-OH		7	110
146	-OH	-OH	$-\overset{+}{N}(CH_3)_3\ HCO_3^-$	7	100
147	-OH	$-NH_2$	-OH	6	106
148	-OH		-OH	7	112
149	-OH		-OH	7	112
150	-OH		-OH	7	111
151	-OH		-OH	7	111
152	-OH		-OH	7	111
153	-OH		-OH	7	111

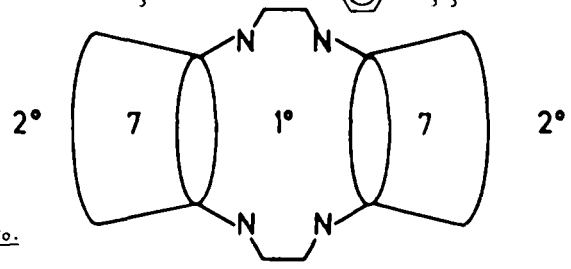
cyclodextrin tosylate (**150**) and mono [3 - (3 - carboxy - 4, 4 - dihydro - 1 - pyridyl) - 3 - deoxy] - β - cyclodextrin (**151**). Also prepared[111] were the 3, 5 - dicarbmethoxy analogs, mono [3 - (3, 5 - dicarbmethoxy - 1 - pyridinio) - 3 - deoxyl] - β - cyclodextrin tosylate (**152**) and mono [3 - (3, 5 - dicarbmethoxy - 4, 4 - dihydro - 1 - pyridyl) - 3 - deoxy] - β - cyclodextrin (**153**).

5. *Bifunctionalized amine and azide derivatives of cyclodextrins.* Several specifically disubstituted (at primary sites) cyclodextrin amine and azide derivatives have been reported (Table 17). Tabushi *et al.*[113] prepared bis (6 - azido - 6 - deoxy) - β - cyclodextrin (**154**) by the double nucleophilic displacement with azide ion of a diphenylmethane - *p, p'* - disulfonate "cap" of a rigidly "capped" cyclodextrin. Reduction (H_2–PtO_2) of **154** gave bis (6 - amino - 6 - deoxy) - β - cyclodextrin (**155**). An analogous double nucleophillic displacement by diethylamine gave bis [6 - (*N, N* - diethylamino) - 6 - deoxy] - β - cyclodextrin

Table 17. Bifunctionalized amino and azido cyclodextrin derivatives



Compound No.	A	B	Reference
154	$-N_3$	$-N_3$	113
155	$-NH_2$	$-NH_2$	113
156	$-NEt_2$	$-NEt_2$	113
157	$-SC(NH_2^+)NH_2$	$-SC(NH_2^+)NH_2$	113
158	$-SCH_2CH_2NH_2$	$-SCH_2CH_2NH_2$	113
159	$-NHCH_2CH_2NH_2$	$-NHCH_2CH_2NH_2$	114
160	$-N_3$		115
161	$-N_3$		115



Compound No.	Reference
162	114

(**156**). Treatment of the same capped β-cyclodextrin with thiourea gave **157**. Similarly prepared from 2-mercaptoethylamine was bis [6 - (2 - aminoethylthio) - 6 - deoxy] - β - cyclodextrin (**158**). IR and ^1H NMR data are reported for compounds **154–158**.[113] Tabushi *et al.*[114,116] also synthesized bis [6 - (*N* - 2 - aminoethylamino) - 6 - deoxy] - β - cyclodextrin (**159**) by heating the capped cyclodextrin[114] (or a diiodo analog prepared from the capped cyclodextrin)[116] with a large excess of ethylene–diamine. The ^1H and ^{13}C NMR spectra for **159** are reported.[114] Compound **159** was used to form a duplex cyclodextrin.[114] Recently, Tabushi *et al.*[115] reported mixed bifunctionalized cyclodextrins. Using a "flamingo cap" (an asymmetrical diaryl disulfonyl "capped" cyclodextrin), unsymmetrical introduction of two functional groups at two primary sites of cyclodextrins was accomplished. Two mixed derivatives containing azide groups were produced. The mixed arylsulfonyl azide **160** and the mercapto azide, mono (6 - azido - 6 - deoxy) - mono[6 - (4 - *t* - butylbenzenethio) - 6 - deoxy] - β - cyclodextrin (**161**) were both prepared by an initial attack on the "flamingo capped" compound using sodium azide in water to give **160**, followed by treatment with sodium *p*-(*tert*-butyl)thiophenolate to yield **161**. The ^1H NMR spectrum of **161** is reported.[115]

A special bifunctionalized cyclodextrin amine derivative has been reported by Tabushi *et al.*[114] who synthesized the tetraaza duplex cyclodextrin (**162**). Thus, **159** was treated with the appropriate capped cyclodextrin in DMF–pyridine to form **162**. The ^1H and ^{13}C NMR spectra of **162** are reported.[114] The complexation characteristics of **159** and **162** have been investigated.

E. *Halogen derivatives of cyclodextrins*

1. *Introduction.* Halo cyclodextrins have usually been synthesized as intermediates to other chemically modified cyclodextrins. Often the initial goal of synthetic schemes has been to produce cyclodextrins in which all primary hydroxyl groups are replaced by halides. Early attempts to achieve this goal

resulted in cyclodextrin derivatives in which the primary hydroxyl groups of the cyclodextrins were only partially replaced by halogen atoms. These asymmetrically substituted halide derivatives will be discussed first in this subsection. Subsequently, cyclodextrin derivatives which all primary sites are occupied by halogens (obtained as synthetic methods improved) will be discussed. Then, a very versatile bifunctionalized cyclodextrin halide derivative will be examined, followed by the discussion of monohalo cyclodextrin derivatives.

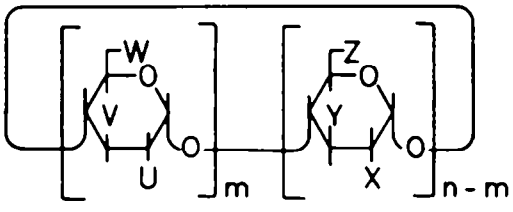
2. *Asymmetrical halo cyclodextrin derivatives.* In an attempt to produce the hepta - 6 - iodo derivative of **2**, Cramer *et al.*[29] treated the hepta - 6 - tosyl derivative **86** with sodium iodide in methylglycol. The resulting material **97** (Table 18) was found to be a mixture of cyclodextrin derivatives with a majority of the tosylate functions being replaced by iodo groups (5.5 iodo and 1.5 tosylate residues per β-cyclodextrin). Mixture **97** was employed[83] in the synthesis of cyclodextrin derivatives containing pendant imidazole moieties. Analogous attempts to prepare[29] hexa - 6 - iodo and hepta - 6 - iodo peracetates by the reaction of the peracetylated hexa - 6 - tosyl or hepta - 6 - tosyl derivatives **15** or **16** resulted in the synthesis of the peracetylated penta - 6 - iodo and hexa - 6 - iodo mono - 6 - tosylates, mono (2, 3 - di - *O* - acetyl - 6 - *O* - tosyl) - pentakis (2, 3 - di - *O* - acetyl - 6 - deoxy - 6 - iodo) - α - cyclodextrin (**37**) and hexakis (2, 3 - di - *O* - acetyl - 6 - deoxy - 6 - iodo) - mono (2, 3 - di - *O* - acetyl - 6 - *O* - tosyl) - β - cyclodextrin (**38**). Compound **38** was employed[29] in the preparation of the hexa - 6 - ethylxanthate **39**.

3. *Symmetrical halo cyclodextrin derivatives.* Takeo *et al.*[40] prepared primary bromo derivatives of the parent cyclodextrins **1**, **2** and **3**: hexakis (6 - bromo - 6 - deoxy) - α - cyclodextrin (**163**); heptakis (6 - bromo - 6 - deoxy) - β - cyclodextrin (**164**); and octakis (6 - bromo - 6 - deoxy) - γ - cyclodextrin (**165**) (Table 19). Compounds **163–165** were produced by the reaction of the parent cyclodextrins with 5 equivalents (based on the number of glucopyranose units) of methanesulfonyl bromide in DMF to give brominated, formylated products, which were then deformylated with sodium methoxide in methanol. Compounds **163–165** were subsequently acetylated[40] (acetic anhydride-pyridine) to give hexakis (2, 3 - di - *O* - acetyl - 6 - bromo - 6 - deoxy) - α - cyclodextrin (**23**), heptakis (2, 3 - di - *O* - acetyl - 6 - bromo - 6 - deoxy) - β - cyclodextrin (**24**), and octakis (2, 3 - di - *O* - acetyl - 6 - bromo - 6 - deoxy) - γ - cyclodextrin (**25**), respectively. The ^{1}H NMR (100 MHz) spectra of **23–25** are reported.[40] The hepta - 6 - bromo derivative **164** was utilized[44] in the preparation of the hepta - 2 - methyl compound **65**. Also, **164** was employed in the preparation of the corresponding hepta - 6 - deoxy compound.[33,40]

The peracetylated hepta - 6 - iodo derivative, heptakis (2, 3 - di - *O* - acetyl - 6 - deoxy - 6 - iodo - β - cyclodextrin (**18**), was synthesized by Cramer *et al.*[29] from the peracetylated hepta - 6 - mesyl derivative **14** by reaction with sodium iodide in acetic anhydride. When compound **18** was treated with potassium ethylxanthate the ethylxanthate derivative **19** resulted.

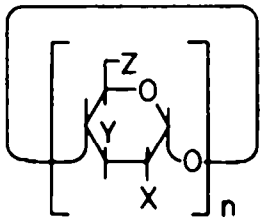
A hepta - 2 - methyl - hepta - 6 - bromo derivative, heptakis (6 - bromo - 6 - deoxy - 2 - *O* - methyl) - β - cyclodextrin (**66**), was prepared by Takeo and Kuge[44] as an intermediate in the synthesis of the hepta - 2 - methyl analog **65**. Derivative **66** was produced from the hepta - 6 - bromo compound **164** by treatment with dimethylsulfate, barium oxide, and barium hydroxide octahydrate in DMF.

Table 18. Asymmetrical halo cyclodextrin derivatives

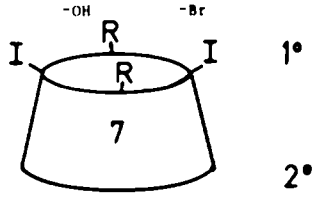


Compound No.	U	V	W	X	Y	Z	n	m	Reference
97	-OH	-OH	-OTs	-OH	-OH	-I	7	1.5	29
37	-OAc	-OAc	-OTs	-OAc	-OAc	-I	6	1	29
38	-OAc	-OAc	-OTs	-OAc	-OAc	-I	7	1	29

Table 19. Symmetrical halo cyclodextrin derivatives



Compound No.	X	Y	Z	n	Reference
163	-OH	-OH	-Br	6	40
164	-OH	-OH	-Br	7	40
165	-OH	-OH	-Br	8	40
23	-OAc	-OAc	-Br	6	40
24	-OAc	-OAc	-Br	7	40
25	-OAc	-OAc	-Br	8	40
18	-OAc	-OAc	-I	7	29
66	-OMe	-OH	-Br	7	44



Compound No.	R	Reference
166	-OH	116
221	-I	118

A very versatile di - 6 - iodo derivative, bis (6 - deoxy - 6 - iodo) - β - cyclodextrin (**166**) has been reported by Tabushi *et al.*[116] An arylsulfonyl "capped" cyclodextrin was treated with potassium iodide in DMF to form **166**. The diiodide, which is reactive toward even weak nucleophiles, can be further functionalized to give other bifunctionalized cyclodextrins. For example, reaction of **166** with ethylenediamine gave[116] the di - ω - aminoethylamino - β - cyclodextrin **159**. Derivatives containing imidazole moieties were also produced.[116]Derivative **166** has been utilized in structure proofs of four rigidly capped cyclodextrins.[115,117,118] The corresponding tetra - 6 - iodide, tetra (6 - deoxy - 6 - iodo) - β - cyclodextrin (**221**) has been similarly prepared from a "di-capped" cyclodextrin.[117,118] Derivative **221** was also employed in structure proofs of capped cyclodextrins.[117,118]

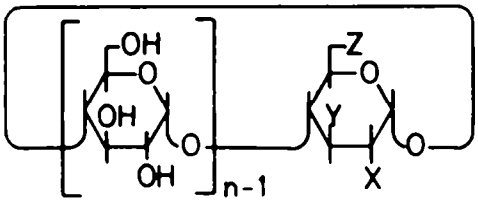
4. *Monohalo cyclodextrin derivatives.*Three mono - 6 - halo cyclodextrin derivatives are listed in Table 20: mono (6 - chloro - 6 - deoxy) - α - cyclodextrin (**167**), mono (6 - bromo - 6 - deoxy) - α - cyclodextrin (**168**), and mono (6 - deoxy - 6 - iodo) - α - cyclodextrin (**169**). Melton and Slessor[77] prepared **167–169** from the mono - 6 - tosylate **102**. Thus, reaction of freeze-dried **102** and tetramethylammonium chloride in DMF gave **167**. Similarly prepared (using lithium bromide) was the mono - 6 - bromide **168**. The mono - 6 - iodide was synthesized by the reaction of **102** and sodium iodide in water. Compounds **167–169** were subjected[78] to enzymatic hydrolysis by *Aspergillus oryzae* amylase (Taka amylase) to form the corresponding 6' - halo maltoses. Omichi and Matsushima[101] also utilized compounds **167–169** in the preparation of 6-halo maltotrioses, which were subsequently hydrolysed by Taka amylase A.

A single mono - 3 - halo cyclodextrin derivative, mono (3 - deoxy - 3 - iodo) - α - cyclodextrin (**170**) has appeared in the literature. Compound **170** was prepared[106] by the reaction of the mono - 3 - tosylate **104** and sodium iodide in water. A histamine-functionalized cyclodextrin derivative was obtained[106] from **170**.

F. *Nitrate derivatives of cyclodextrins*

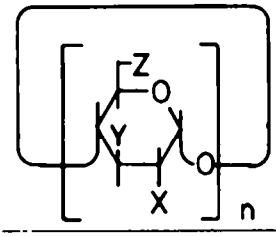
A few examples of cyclodextrin nitrate compounds appear in the literature (Table 21). In 1925 (prior to the resolution of the conflict concerning the number of glucopyranose residues contained in the parent cyclodextrins), Leibowitz and Silmann[122] reported what appears to be the preparation of cyclodextrin nitrate esters. Two partially nitrated derivatives, hexakis [2 (3) (6), 6 (2) (3) - di - *O* - nitro] - α - cyclodextrin (**171**) and heptakis [2 (3) (6), 6 (2) (3) - di - *O* - nitro] - β - cyclodextrin (**172**) were synthesized.[122] Compounds **171** and **172**, cyclodextrin derivatives in which two-thirds of the hydroxyl

Table 20. Monohalo cyclodextrin derivatives



Compound No.	X	Y	Z	n	Reference
167	-OH	-OH	-Cl	6	77
168	-OH	-OH	-Br	6	77
169	-OH	-OH	-I	6	77
170	-OH	-I	-OH	6	106

Table 21. Cyclodextrin nitrate derivatives



Compound No.	X	Y	Z	n	Reference
171	-OH	$-ONO_2$	$-ONO_2$	6	122
		or			
	$-ONO_2$	-OH	$-ONO_2$		
		or			
	$-ONO_2$	$-ONO_2$	-OH		
172	-OH	$-ONO_2$	$-ONO_2$	7	122
		or			
	$-ONO_2$	-OH	$-ONO_2$		
		or			
	$-ONO_2$	$-ONO_2$	-OH		
173	$-ONO_2$	$-ONO_2$	$-ONO_2$	6	122
174	$-ONO_2$	$-ONO_2$	$-ONO_2$	7	122
175	$-ONO_2$	$-ONO_2$	$-ONO_2$	8	60

groups are nitrated, were prepared by reactions of the parent cyclodextrins **1** and **2** with excess nitric and sulfuric acids. While substitution positions for the nitrate groups in these derivatives are not known, presumably a higher degree of substitution would occur at the more reactive primary hydroxyl groups. Elemental analysis of **171** and **172** gave[122] 11.4–11.7% nitrogen [11.1% is the theoretical value for $(C_6H_8O_9N_2)_X$] which is consistent with the proposed structures. The completely nitrated cyclodextrins, hexakis (2, 3, 6 - tri - *O* - nitro) - α - cyclodextrin (**173**) and heptakis(2, 3, 6 - tri - *O* - nitro) - β - cyclodextrin (**174**) were also formed[122] as byproducts of the reactions used to produce **171** and **172**. Elemental analysis results of 14.2–14.5% nitrogen [the theoretical value is 14.1% for $(C_6H_7O_{11}N_3)_X$] are consistent with the proposed structures.

Attempts by others to prepare polynitrated cyclodextrins have resulted in compounds in which not all of the hydroxyl groups have been nitrated. In order to obtain molecular weights of the parent cyclodextrins by the Barger method, Gruenhut *et al.*[123] obtained cyclodextrin nitrates from the reaction of the parent cyclodextrins **1** and **2** with dinitrogen pentoxide and sodium fluoride in chloroform. However, the elemental analysis results obtained for nitrogen (13.61% nitrogen for the nitrated α-cyclodextrin, 13.52% nitrogen for the nitrated β-cyclodextrin) are too low for these cyclodextrin derivatives to be completely nitrated compounds **173** and **174**. Another attempted polynitration by Freudenberg and Cramer[60] using dinitrogen pentoxide and acetonitrile at −20° resulted in the preparation of nitrated derivatives of the parent cyclodextrins **1–3**. While the nitrated α-cyclodextrin's elemental analysis[60] for nitrogen (14.2%) seemed to identify it as the polynitrate **173**, the elemental analysis for the β-cyclodextrin nitrate (13.2%) was too low for it to be compound **174**. Nitration[60] of γ-cyclodextrin (**3**) led to a material which gave a lower nitrogen analysis (12.7%) than would have been required for the polynitrated derivative, octakis (2, 3, 6 - tri - *O* - nitro) - γ - cyclodextrin (**175**).

More recently, Dawoud and Marawan,[124] in connection with their study of the IR spectra of various nitrated polysaccharides, prepared nitrated derivatives of **1** and **2**. However, the presence of OH stretching bands in the IR spectra for these derivatives,[124] and low values for the nitrogen elemental analyses (13.2–13.9%) argue against their having obtained either **173** or **174**. Apparently, a small number of the hydroxyl groups in these cyclodestrin derivatives had not been nitrated.

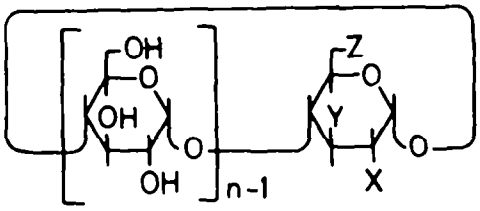
G. *Phosphorus-containing derivatives of cyclodextrins.*

Several cyclodextrin derivatives with phosphorus-containing functional groups are known (Table 22). A number of monosubstituted phosphate esters have been reported. Hennrich and Cramer[125] record the isolation of a monophosphoryl β-cyclodextrin from the reaction of diaryl pyrophosphates and the parent cyclodextrin **2**. Covalent catalysis in the hydrolysis of diaryl pyrophosphates by cyclodextrins is believed[7,125] to involve an initial complexation of the substrate by cyclodextrin, followed by the attack of a secondary cyclodextrin hydroxyl group on phosphorus, and the subsequent transfer of the phosphate group to a secondary site on the cyclodextrin. Thus, the material obtained by Hennrich and Cramer[125] is presumed to be a mixture of the salts of mono (2 - *O* - phosphoryl) - β - cyclodextrin (**176**) and mono (3 - *O* - phosphoryl) - β - cyclodextrin (**177**). Compounds **176** and **177** were subsequently prepared as their diammonium salts by Siegel *et al.*[126] from the reaction of bis (*m* - nitrophenyl) phosphate and β-cyclodextrin (**2**). Careful chromatography of the resulting product mixture yielded **176** and **177**. Compounds **176** and **177** were studied[126] to determine their effectiveness as general acid or general base catalysts with bound substrates. A mixture of diammonium salts of **176** and **177**, prepared in a manner similar to Breslow's method,[126] was employed by Eiki and Tagaki[127] as a catalyst for the oxidation of benzyl methyl sulfide to the sulfoxide by iodine.

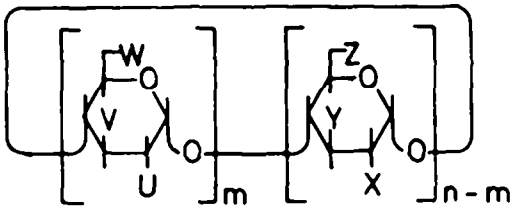
In addition to the secondary monophosphates, mono - 6 - phosphorous - containing derivatives of cyclodextrins have been reported. Siegel *et al.*[126] prepared the mono - 6 - analog of **176** or **177**, mono (6 - *O* - phosphoryl) - β - cyclodextrin (**178**), and a related compound, mono (6 - *O* - diphenylphosphoryl) - β - cyclodextrin (**179**). Compound **179** was synthesized[126] from the parent cyclodextrin **2** and diphenylphosphorochloridate in pyridine. Following workup and characterization[126] by NMR, **179** was hydrogenated (Pt in ethanol) for one week. Workup yielded compound **178** as its diammonium salt. The catalytic ability of **178** as a general acid and a general base catalyst was assessed by these researchers.[126]

Another cyclodextrin derivative with a single phosphorus-containing moiety is attributable to Brass and Bender[128] who report the isolation of a neutral mono-modified derivative, presumed to be a cyclic β - cyclodextrin methylphosphonate, **180**. Compound **180** was isolated from the products of the reactions of diaryl methylphosphonates with β - cyclodextrin (**2**). The presence of such a derivative was used to

Table 22. Modified cyclodextrins with phosphorus-containing groups



Compound No.	X	Y	Z	n	Reference
176	$-OPO_3H_2$	-OH	-OH	7	126
177	-OH	$-OPO_3H_2$	-OH	7	126
178	-OH	-OH	$-OPO_3H_2$	7	126
179	-OH	-OH	$-OPO_3Ph_2$	7	126
180			-OH	7	128



Compound No.	U	V	W	X	Y	Z	n	m	Reference
181	-	-	-	-OH	-OH	$-OPO_3Ph_2$	7	0	126
182	-OH	-OH	-OH	-OH or $-OPO_3H_2$	$-OPO_3H_2$ or -OH	-OH	6	3	129

support[128] a proposed mechanism for this hydrolysis; one which is similar to the mechanism described above for the hydrolysis of diaryl pyrophosphates by cyclodextrins.

Additional cyclodextrin derivatives with multiple phosphate moieties are known. Siegel *et al.*[126] report the preparation of heptakis (6 - O - diphenylphosphoryl) - β - cyclodextrin (**181**) by a method analogous to that employed in the synthesis of **179**, but using a large excess of the diphenylphosphorochloridate. In addition, Van Hooidonk *et al.*[129-131] describe the isolation of an α-cyclodextrin derivative which contained three secondary phosphoryl groups. Thus, tris [2 (3) - O - phosphoryl] - α - cyclodextrin (**182**) was prepared[129,130] by reactions analogous to those used for the synthesis of the mono - 2 - and mono - 3 - phosphorylated derivatives **176** and **177**, but having excess substrate present which allowed trisubstitution of the cyclodextrin. In Table 22, the structure for **182** represents one of several isomeric possibilities.

Cyclodextrin derivatives made from various phosphorus-containing acids, which might be useful in industrial applications, such as sewage flocculation or paper finishing, have also been reported.[132]

H. *Cyclodextrin derivatives containing imidazole moieties*

1. *Introduction.* Desire on the part of researchers for more complex enzyme models led to the synthesis of cyclodextrin derivatives with pendant imidazole groups. The catalytic activity of the enzyme chymotrypsin, with its histidine imidazole group, is believed to be due to acid-base catalysis by the pendant imidazole function on a bound substrate. Since cyclodextrins are able to bind a variety of substrates, the introduction of one or more pendant imidazole groups into a cyclodextrin molecule might provide an enzyme model for chymotrypsin. Attempts to prepare such enzyme models have led to

several cyclodextrin derivatives which possess imidazole groups either directly bound to the cyclodextrin, or connected via oxygen-, nitrogen- or sulfur-linked "arms" to the cyclodextrin framework.

In this summary, early work in this area which produced cyclodextrin imidazole derivative mixtures will be examined first. Subsequently, other cyclodextrins which contain one or more imidazole groups will be discussed.

2. *Cyclodextrin derivative mixtures with multiple pendant imidazole moieties.* Research by Cramer and Mackensen[83,119] led to the preparation of a number of mixtures of cyclodextrin derivatives with imidazole groups attached (Table 23). Reaction of the parent cyclodextrins **1** and **2** with 4 (5) - chloromethylimidazole and base (potassium *t*-butoxide or potassium hydroxide) gave[83,119] mixtures of the corresponding *O*-methylimidazole substituted cyclodextrins. Elemental analysis indicated an *average* substitution of three (for **1**) or two (for **2**) imidazole units for hydroxyl groups, presumably at the primary sites. Thus, mixtures of cyclodextrin derivatives designated by the "average" compounds tris [6 - *O* - (4 (5) - imidazolylmethyl)] - α - cyclodextrin (**183**) and bis [6 - *O* - (4 (5) - imidazolylmethyl)] - β - cyclodextrin (**184**) were obtained. Although **183** and **184** are named as single compounds, it must be remembered that the mixtures probably contain[3,77] derivatives with greater or fewer imidazole groups per molecule. Also substitution may have occurred at sites other than the primary hydroxyl groups.[77] Therefore the structures given for mixtures **183–192** in Table 23 represent only a few of many possible compounds which are presumably present in these mixtures.

An analogous mixture to that of **183**, but with linkage through nitrogen, was prepared[83] by the reaction of the hexa - 6 - benzenesulfonyl derivative **92** and 4 (5) - aminomethylimidazole in methanol in a steel bomb to give the mixture, bis [6 - deoxy - 6 - *N* - (4 (5) - imidazolylmethyl) amino] - α - cyclodextrin (**185**). Similarly obtained from the hepta - 6 - tosylate **86** was the derivative mixture, tris [6 - deoxy - 6 - *N* - (4 (5) - imidazolylmethyl) amino] - β - cyclodextrin (**186**). Treatment[83,119] of the hexa - 6 - tosylate **85** with histamine in a steel bomb gave the three - histamine - containing tris [6 - deoxy - 6 - *N* - (2 - imidazol - 4 (5) - ylethyl) amino] - α - cyclodextrin (**187**). Using **86**, histamine, and slightly different reaction conditions, the β-cyclodextrin derivative mixtures tris [6 - deoxy - 6 - *N* - (2 - imidazol - 4 (5) - ylethyl) amino] - β - cyclodextrin (**188**) and the tetrakis [6 - deoxy - 6 - *N* - (2 - imidazol - 4 (5) ylethyl) amino] - β - cyclodextrin (**189**) were produced.

Additional derivative mixtures were prepared in which the imidazole group was attached directly to the cyclodextrin via a ring nitrogen. The hepta - 6 - tosylate **86** was treated[119] with imidazole to give the mixture bis [6 - deoxy - 6 - (1 - imidazolyl)] - β - cyclodextrin (**190**). A mixture analogous to **190**, but with four imidazole groups per cyclodextrin molecule, was prepared[83] from the hepta - 6 - mesylate **88** or the iodo compound **97** and imidazole in a steel bomb reaction to give tetrakis [6 - deoxy - 6 - (1 - imidazolyl)] - β - cyclodextrin (**191**). Hexakis [6 - deoxy - 6 - (1 - imidazolyl)] - β - cyclodextrin (**192**) was synthesized[83] from the pertrifluoroacetate **10** and imidazole.

Compounds **183–192** have been examined[83,119] as catalysts for the hydrolysis of aryl acetates.

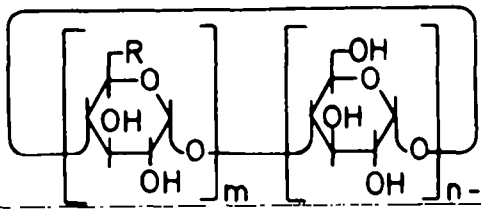
3. *Other cyclodextrin derivatives which contain imidazole moieties.* In addition to the cyclodextrin derivative mixtures discussed above, other cyclodextrin derivatives are known which have attached imidazole groups (Table 24). Kitaura and Bender[133] report the preparation of a monosubstituted α-cyclodextrin derivative which has a pendant imidazole group. Mono [(2 (3) - *O* - (*N* - [4 (5) - imidazolymethyl] hydroxamoylmethyl)] - α - cyclodextrin (**193**) resulted from reaction of the corresponding carboxymethyl cyclodextrin and 4 (5) - imidazolemethylhydroxylamine in the presence of base.[133] IR and UV data used to characterize **193** are given.[133] Compound **193** was examined as a catalyst in the hydrolysis of various aryl acetates and an aryl thioacetate.

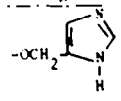
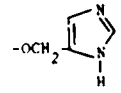
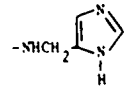
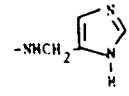
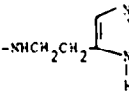
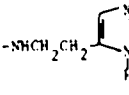
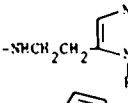
Another monosubstituted (at a secondary position) cyclodextrin derivative with a pendant imidazole group has been prepared.[106] The cyclodextrin–histamine derivative, mono [3 - deoxy - 3 - *N* - (2 - imidazol - 4 (5) - ylethyl) amino] - α - cyclodextrin (**194**) was obtained from the reaction of histamine and the mono - 3 - iodine **170** in water at 80°. Rate data for ester hydrolysis reactions involving **194** as a catalyst are provided[106] for this chymotrypsin enzyme model.

Mono primary-substituted, imidazole-containing cyclodextrin derivatives also appear in the literature. Mono [6 - deoxy - 6 - (1 - imidazolyl)] - β - cyclodextrin (**195**) was reported by Breslow *et al.*[121] who used the compound to catalytically cleave a cyclic phosphate ester of 4 - *tert* - butylcatechol. Also these researchers prepared[121] mono [6 - deoxy - 6 - (4 (5) - imidazolylmethyl) thio] - β - cyclodextrin (**196**) from 4 (5)-mercaptomethylimidazole and the mono - 6 - tosylate **103**.

A series of symmetrically disubstituted cyclodextrin derivatives with attached imidazole groups has been reported. The disubstituted analog of **196**, bis [6 - deoxy - 6 - (4 (5) - imidazolylmethyl) thio] - β -

Table 23. Mixtures of cyclodextrin derivatives with pendant imidazole moieties*

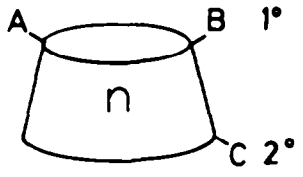


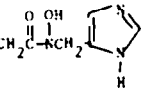
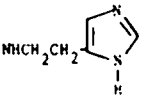
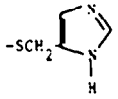
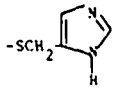
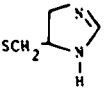
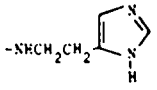
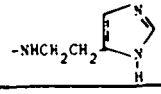
Compound No.	R	n	m	Reference
183		6	3	83
184		7	2	83
185		6	2	83
186		7	3	83
187		6	3	83
188		7	1	83
189		7	4	83
190		7	2	119
191		7	4	83
192		7	6	83

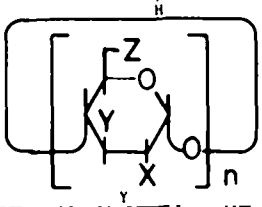
*Each table entry represents an imidazole cyclodextrin derivative which is representative of a particular mixture of imidazole-containing cyclodextrins. For each mixture, compounds with greater or fewer imidazole moieties than those for the representative compound are also presumed to be present. Also, isomeric forms for each multisubstituted derivative are presumed to be present in the mixture (see text).

cyclodextrin (**197**) was prepared[121] by the reaction of 4 (5) - mercaptomethylimidazole and a capped cyclodextrin in analogy to the preparation of **196**. Both compounds **196** and **197** were employed as ribonuclease mimics. A symmetrically bifunctionalized derivative, bis [6 - (1 - imidazolyl) - 6 - deoxy] - β - cyclodextrin (**198**) - a derivative with two nearly symmetrically attached (via ring nitrogen) imidazole groups has been prepared by Breslow *et al.*[134] from a capped cyclodextrin disulfonate derivative. The capped cyclodextrin was a mixture of two isomers, the 6^A, 6^C capped derivative and the 6^A, 6^D capped derivative (letters refer to the glucopyranose residues in the β-cyclodextrin). Compound **198**, which was synthesized from this capped derivative mixture and imidazole, may also be a mixture of the two isomers. Derivative **198** was employed[134] as a ribonuclease mimic in the hydrolysis of a cyclic phosphate-containing substrate. Kinetic results obtained for the mixed 6^A, 6^D and 6^A, 6^C isomers of **198** were later confirmed[120] using **198** which was the pure 6^A, 6^D isomer. Tabushi *et al.*[116] have studied **198**

Table 24. Cyclodextrin derivatives with pendant imidazole moieties



Compound No.	A	B	C	n	Reference
193	-OH	-OH		6	133
194	-OH	-OH		6	106
195		-OH	-OH	7	121
196		-OH	-OH	7	121
197			-OH	7	121
196			-OH	7	134
199			-OH	7	116



Compound No.	X	Y	Z	n	Reference
200	-OH	-OH		7	120

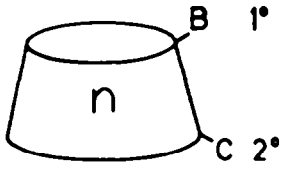
and another bis derivative, bis [6 - deoxy - 6 - *N* - (2 - imidazol - 4 (5) ylethyl) amino] - β - cyclodextrin (**199**), as carbonic anhydrase models. Derivative **199** was prepared[116] from the diiodide **166** and histamine in DMF.

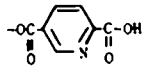
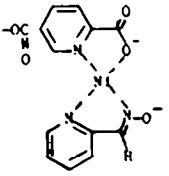
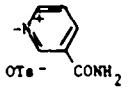
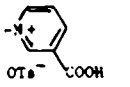
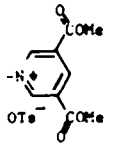
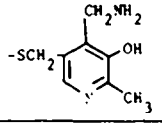
One hepta - 6 - imidazoylyl cyclodextrin is known.[120] Heptakis [6 - deoxy - 6 - (1 - imidazolyl)] - β - cyclodextrin (**200**) was obtained[120] from the hepta - 6 - tosylate **86** and imidazole. Breslow[120] has demonstrated that **200** is also an effective enzyme model for ribonuclease.

I. *Cyclodextrin derivatives containing pyridine moieties*

A few cyclodextrin derivatives with pendant pyridyl groups have been reported (Table 25). Breslow and Overman[135] prepared mono [2 (3) - *O* - (2 - carboxypyrid - 5 - yloxo)] - α - cyclodextrin (**201**) by treatment of the parent cyclodextrin cyclodextrin **1** with an equimolar quantity of the 5 - *m* - nitrophenyl ester of pyridine - 2, 5 - dicarboxylic acid in water. Workup and careful chromatography gave **201** in 55–65% yield. Nickel(II) and copper(II) complexes of **201** were investigated[135] as catalysts for the hydrolyses of *p*-nitrophenyl acetate and the *p*-nitrophenyl ester of glycine. Compound **201** was transformed[135] into a related metalloenzyme model **202** by treatment of **201** with a nickel(II) salt and one equivalent of pyridinecarboxaldoxime. Compound **202** was also examined[135] as a catalyst for ester hydrolysis. Derivatives **201** (complexed with various metal ions) and **202** were also employed in other "artificial" enzyme studies involving hydrolysis reactions.[136]

Table 25. Cyclodextrin with pendant substituted-pyridine moieties



Compound No.	B	C	n	Reference
201	-OH		6	135
202	-OH		6	135
148	-OH		7	112
150	-OH		7	111
152	-OH		7	111
203		-OH	7	105

A β - cyclodextrin nicotinamide derivative and two related compounds have been prepared.[111,112] Kojima *et al.*[112] synthesized mono [3 - (3 - carbamoyl - 1 - pyridinio) - 3 - deoxy] - β - cyclodextrin tosylate (**148**) as a model for NAD^+ (nicotinamide adenine dinucleotide, oxidized form). Derivative **148** was formed[111,112] from the mono - 3 - tosylate **105** and excess nicotinamide in DMF. Similarly prepared[111] were mono [3 - (3 - carboxy - 1 - pyridinio) - 3 - deoxy] - β - cyclodextrin tosylate (**150**) and mono [3 - (3, 5 - dicarbmethoxy - 1 - pyridinio) - 3 - deoxy] - β - cyclodextrin tosylate (**152**). The ^1H NMR spectra and half-wave potential of **148** are reported.[112]

Breslow *et al.*[105] published a synthesis of a β-cyclodextrin – pyridoxamine artificial enzyme, mono [6 - (4 - aminomethyl - 3 - hydroxy - 2 - methylpyrid - 5 - yl) methylthio - 6 - deoxy] - β - cyclodextrin (**203**). This compound was prepared[105] from the corresponding substituted pyridylmethyl thiol and the mono - 6 - tosylate **103** and was examined as an enzyme model for enzymatic reactions in which pyridoxamine phosphate participates.

J. *Cyclodextrin derivatives with sulfur-containing functional groups*

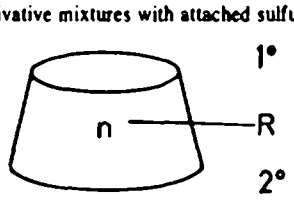
1. *Introduction.* A multitude of chemically modified cyclodextrin derivatives with sulfur-containing functional groups are known. In addition to the aryl sulfonates and mesylates (subsection C) and the capped cyclodextrins which involve sulfonate linkages (subsection R), many other sulfur-containing cyclodextrin derivatives have been reported. In this subsection, cyclodextrin sulfoalkylethers and cyclodextrin sulfates, which have been prepared as mixtures of derivatives, will be discussed first. Subsequently, somewhat better defined cyclodextrin derivatives with one or more sulfur-containing functional group(s) will be examined.

2. *Cyclodextrin derivative mixtures with sulfur-containing functional groups.* From the reaction of β-cyclodextrin (**2**) with sodium 2-chloroethanesulfonate and pyridine in toluene, Parmerter *et al.*[132] obtained a mixture of cyclodextrin derivatives in which some of the cyclodextrin hydroxyl groups had been converted to sulfoethyl ether functions (**204**) (Table 26). Mixture **204** was found[132] to have a degree of substitution of 0.35. Similarly prepared[132] (from propane sultone and 50% sodium hydroxide) were the corresponding mixtures of sulfopropyl ethers **205** and **206** from α-cyclodextrin and β-cyclodextrin, respectively. Depending on the proportions of the reactants,[132] the degree of substitution ranged from 0.27–1.6 for **206**. The degree of substitution for **205** was 0.80.[132] Employing closely-related synthetic methods, Lammers *et al.*[137] prepared **205** and **206** with reported average molecular weights of 1358 ± 76 and 2214 ± 152, respectively. Compounds **205** and **206** were designed[137] to increase the water solubility of cyclodextrin derivative complexes with apolar "guest" molecules. Although complexes of apolar "guest" molecules and the parent cyclodextrins have only limited solubilities in water,[137] complexes with **205** and **206** possess enhanced water solubilities.[137] The mixtures of cyclodextrin derivatives **205** and **206** which were prepared by the Lammers group[137] were found to increase the solubilities of certain hydrocarbons in aqueous solutions compared with the solubilities of these hydrocarbons in water.[138,139] From the solubility data, complex association constants were calculated.[138] Specifically, **205** forms 1 : 1 complexes with hexane and 2, 3 - dimethylbutane in aqueous solutions, while **206** forms 1 : 1 complexes with 2, 3-dimethylbutane and mainly 1 : 1 complexes with hexane (some 2 : 1 hexane: substituted cyclodextrin complexes were also observed).[139]

Other mixtures of cyclodextrin derivatives which possess sulfur-containing functional groups are known. Hamuro and Akiyama[140] prepared three cyclodextrin sulfate mixtures. The parent cyclodextrins **1–3** were esterified with sulfuric acid or HSO_3Cl in pyridine and the product polysulfates were isolated as the sodium salts **207–209**. The extent of esterification depended on the ester-forming reagent. When sulfuric acid was employed, elemental analyses of **207–209** showed a sulfur content of 6.39% for each compound. Esterification with HSO_3Cl gave **207–209** with 16.21–16.78% sulfur. The latter mixtures of **207–209** exhibited antiarterioschlerosis and antiinflammatory activities.[140]

3. *Cyclodextrin derivatives with multiple sulfur-containing functional groups.* Better defined cyclodextrin derivatives which possess several sulfur-containing functional groups also appear in the literature (Table 27). Cramer *et al.*[29] treated the peracetylated hepta - 6 - iodide **18** with potassium ethylxanthate in acetone to form heptakis (2, 3 - di - *O* - acetyl - 6 - deoxy - 6 - ethoxythiocarbonylmercapto) β - cyclodextrin (**19**). Similarly prepared from the hexa - 6 - iodo - mono - 6 - tosylperacetate

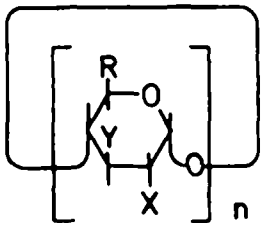
Table 26. Cyclodextrin derivative mixtures with attached sulfur-containing functional groups*



Compound No.	R	n	Reference
204	$-OCH_2CH_2SO_3^-Na^+$	7	132
205	$-OCH_2CH_2CH_2SO_3^-Na^+$	6	132
206	$-OCH_2CH_2CH_2SO_3^-Na^+$	7	132
207	$-OSO_3^-Na^+$	6	140
208	$-OSO_3^-Na^+$	7	140
209	$-OSO_3^-Na^+$	8	140

*The number of R groups attached to the cyclodextrin may range from 0 to 21 within a mixture. See text for details.

Table 27. Cyclodextrin derivatives with multiple sulfur-containing functional groups



Compound No.	X	Y	R	n	Reference
19	-OAc	-OAc	$-CH_2S\overset{\overset{S}{\|\|}}{C}OEt$	7	29
39	-OAc	-OAc	6/7 $-CH_2S\overset{\overset{S}{\|\|}}{C}OEt$ 1/7 $-CH_2OAc$	7	29
210	$-OSO_3^-$ Et_3NH^+	$-OSO_3^-$ Et_3NH^+	$-CH_2OSO_3^-$ Et_3NH^+	6	141
211	$-OSO_3^-Na^+$	$-OSO_3^-Na^+$	$-\overset{\overset{O}{\|\|}}{C}-O^-Na^+$	7	142

38 was hexakis (2, 3 - di - *O* - acetyl - 6 - deoxy - 6 - ethoxythiocarbonylmercapto) - mono (2, 3, 6 - tri - *O* - acetyl) - β - cyclodextrin (**39**). ORD and UV spectra for **19** are recorded.[29]

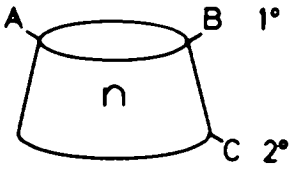
Bernstein *et al.*[141] prepared the polytriethylammonium salt of α-cyclodextrin polysulfate, hexakis (2, 3, 6 - tri - *O* - sulfo) - α - cyclodextrin (**210**). Treatment of the parent cyclodextrin **1** with Et_3N–SO_3 in DMF gave **210**, which showed complement-inhibiting activity *in vivo* and *in vitro*.[141] Lewis and Bernstein[142] also synthesized a related compound, heptakis (5 - carboxy - 5 - demethyl - 6 - deoxy - 2, 3 - di - *O* - sulfo) - β - cyclodextrin (**211**), which was isolated as the polysodium salt and exhibited complement-inhibiting activity.[142]

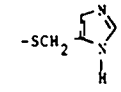
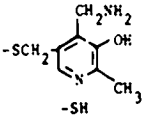
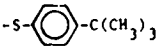
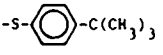
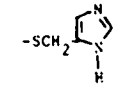
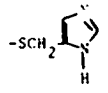
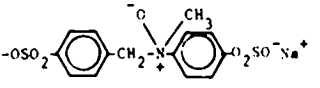
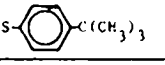
4. *Mono- and disubstituted cyclodextrin derivatives with sulfur-containing functional groups.* A number of mono- and difunctionalized sulfur-containing cyclo-dextrins are listed in Table 28. Both α-cyclodextrins resulting from replacement of a primary and a secondary hydroxy group with a thiol function are known: mono [2 (3) - deoxy - 2 (3) - mercapto] - α - cyclodextrin (**212**) and mono (6 - deoxy - 6 - mercapto) - α - cyclodextrin (**213**). Bender *et al.*[3] prepared **212** and **213** in an attempt to improve the catalytic properties of the parent cyclodextrin **1**. However, neither **212** nor **213** exhibited significant rate enhancement (over that of **1**) in the rate of the hydrolysis of *m*-nitrophenyl acetate.[3] Siegel[104] synthesized the β-cyclodextrin analog of **213**, mono (6 - deoxy - 6 - mercapto) - β - cyclodextrin (**214**) from the mono - 6 - tosylate **103** by displacement of the tosyl group with thiourea, followed by the base-catalysed hydrolysis of the resulting thiouronium salt (the mono-substituted analog of **157**). Compound **214** functioned as a ligand in iron–sulfur complexes **219** and **220** (Table 29) which have been utilized as ferrodoxin models.[104]

Monosubstituted cyclodextrins with groups linked to the cyclodextrin framework via sulfide linkages have been reported. Fujita *et al.*[79] prepared mono (6 - deoxy - 6 - methylthio) - β - cyclodextrin (**81**) and mono (6 - *t* - butylthio - 6 - deoxy) - β - cyclodextrin (**83**) from the approprite mercaptans and the mono - 6 - tosylate **103**. ^1H NMR and IR characterization data are supplied.[79] Compounds **81** and **83** were investigated as catalysts in the hydrolyses of *m*- and *p*-substitued phenyl acetates. An X-ray structural analysis of **83** was published recently.[81] Fujita, Shinoda and Imoto[80] have also synthesized closely-related alkylthio-substituted cyclodextrins by the same synthetic method. Thus, mono (6 - deoxy - 6 - propylthio- - β - cyclodextrin (**82**), mono (6 - *t* - butylthio - 6 - deoxy) - β - cyclodextrin (**83**) and mono [6 - deoxy - 6 - (2 - hydroxyethylthio] - β - cyclodextrin (**215**) were prepared and studied as catalysts for the hydrolysis of *m*- and *p*-substituted phenyl acetates. ^1H NMR and IR spectra for **82**, **84** and **215** are reported.[80]

Two mono substituted cyclodextrin derivatives in which heterocyclic moieties are connected to the

Table 28. Mono and disubstituted cyclodextrin derivatives with sulfur-containing functional groups

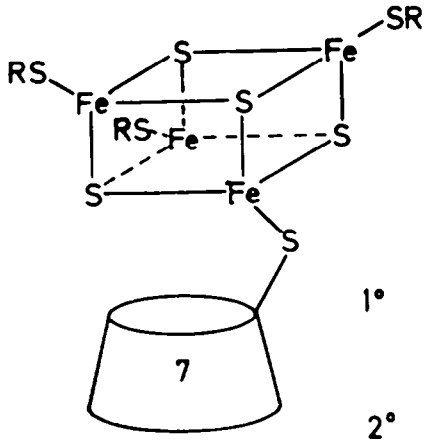


Compound No.	A	B	C	n	Reference
212	-OH	-OH	-SH	6	3
213	-SH	-OH	-OH	6	3
214	-SH	-OH	-OH	7	104
81	-SMe	-OH	-OH	7	79
82	-SPr	-OH	-OH	7	80
83	$-SC(CH_3)_3$	-OH	-OH	7	79
84	$-SCH_2C(CH_3)_3$	-OH	-OH	7	80
215	$-SCH_2CH_2OH$	-OH	-OH	7	80
196		-OH	-OH	7	121
203		-OH	-OH	7	105
216	-SH	-SH	-OH	7	113
217	-SPh	-SPh	-OH	7	113
218			-OH	7	115
157	$-SC(NH_2^+)NH_2$	$-SC(NH_2^+)NH_2$	-OH	7	113
158	$-SCH_2CH_2NH_2$	$-SCH_2CH_2NH_2$	-OH	7	113
197			-OH	7	121
160	$-N_3$		-OH	7	115
161	$-N_3$		-OH	7	115

cyclodextrin via sulfide linkages have appeared. The imidazole-linked derivative, mono [6 - deoxy - 6 - (4 (5) - imidazolylmethyl) thio] - β - cyclodextrin (**196**) was prepared by Breslow *et al.*[121] from 4 (5) - mercaptomethylimidazole and the mono - 6 - tosylate **103** for use as a ribonuclease mimick. The substituted pyridyl-linked derivative, mono [6 - (4 - aminomethyl - 3 - hydroxy - 2 - methylpyrid - 5 - yl) methylthio - 6 - deoxy] - β - cyclodextrin (**203**) was synthesized by Breslow *et al.*[105] as a β-cyclodextrin-pyridoxamine artificial enzyme. Compound **203** resulted from reaction of the mono - 6 - tosylate **103** with the corresponding substituted pyridine thiol.

Several symmetrically disubstituted cyclodextrins which possess sulfur-containing functional groups are known. The di - 6 - thiol analog of **214**, bis (6 - deoxy - 6 - mercapto) - β - cyclodextrin (**216**), was formed by Tabushi *et al.*[113] from the decomposition of the thiourea - β - cyclodextrin adduct **157** with base, followed by workup and chromatography. Reaction of diphenylmethane - *p* - *p'* - disulfonyl - capped cyclodextrin with thiourea produced compound **157**. Similarly prepared were the di - 6 - phenylthio derivative, bis (6 - deoxy - 6 - phenylthio) - β - cyclodextrin (**217**), and a sulfur-linked

Table 29. β-Cyclodextrin-containing tetrameric iron–sulfur complexes



Compound No.	R	Reference
219		104
220	$-C(CH_3)_3$	104

alkylamino derivative, bis [6 - (2 - aminoethylthio) - 6 - deoxy] - β - cyclodextrin (**158**). IR and ^1H NMR data are reported[113] for compounds **157**, **158**, **216** and **217**. A cyclodextrin derivative related to **217**, bis [6 - (4 - *t* - butylbenzenethio) - 6 - deoxy] - β - cyclodextrin (**218**), was synthesized by Tabushi *et al.*[115] via a similar reaction of a capped cyclodextrin and sodium *p-tert*-butylthiophenolate. The ^1H NMR spectrum of **218** is given.[115] The disubstituted analog of **196**, bis [6 - deoxy - 6 - (4 (5) - imidazolylmethyl) thio] - β - cyclodextrin (**197**) was prepared[121] from reaction of a capped cyclodextrin with 4 (5)-mercaptomethylimidazole.

Mixed symmetrically-disubstituted cyclodextrin derivatives have been reported. Reaction of a "flamingo capped" cyclodextrin[115] (an *N* - benzyl - *N* - methylaniline *N*-oxide capped cyclodextrin) with azide ion in water gave the arylsulfonyl azide **160**. Further treatment of **160** with sodium *p-tert* - butylthiophenolate gave mono (6 - azido - 6 - deoxy) - mono [6 - (4 - *t* - butylbenzenethio) - 6 - deoxy] - β - cyclodextrin (**161**). Spectral characterization data for **161** are reported.[115]

K. *Cyclodextrin derivatives with alcohol, aldehyde, ketone or oxime functionality*

Several functionalized cyclodextrins with pendant alchohol, aldehyde or ketone groups are listed in Table 30. In some cases, oxime derivatives of the keto or aldehydo cyclodextrins were also reported.

Carter and Lee[144] prepared the α - 1, 6 - glucosyl substituted cyclodextrins, mono [6 - *O* - (α - 1 - glucosyl)] - α - cyclodextrin (**222**) and mono [6 - *O* - (α - 1 - glucosyl)] -β - cyclodextrin (**223**), as specific substrates for the assay of an enzyme component of the glycogen debranching system in yeast. The adsorption chromatographic behavior or **222** and **223** was also investigated.[144]

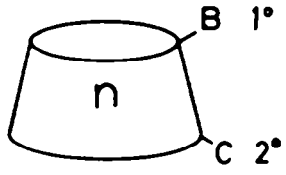
Several examples of cyclodextrins with pendant hydroxyl-containing groups are known. Hydroxypropyl - β - cyclodextrin isomers (with one or more hydroxyl-containing groups) of mono [2 (3) (6) - *O* - (3 - hydroxypropyl)] - β - cyclodextrin (**224**) have been utilized in a liquid crystal temperature-indicating device.[145] Fujita *et al.*[80] prepared the mono - 6 - substituted derivative, mono [6 - deoxy - 6 - (2 - hydroxyethyl) thio] - β - cyclodextrin (**215**), by reaction of the appropriate thiol with the mono - 6 - tosylate **103**. Compound **215** was used as a catalyst in studies of the kinetics and selectivities of hydrolysis of several *meta*- and *para*-substituted phenyl acetates.[80] ^1H NMR and IR spectral data are reported for **215**.[80]

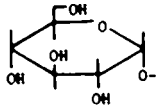
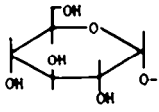
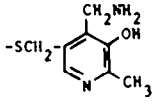
Treatment[146] of α-cyclodextrin (**1**) with 2, 3 - epoxy - 1 - propanol in the presence of sodium hydroxide in water gave mono [2 (3) - *O* - (2, 3 - dihydroxypropyl)] - α - cyclodextrin (**225**). Compound **225** was subsequently transformed into an oxime-modified cyclodextrin which was examined as an enzyme model.[146] A β-cyclodextrin derivative, analogous to **225** but having only a 0.15 degree of

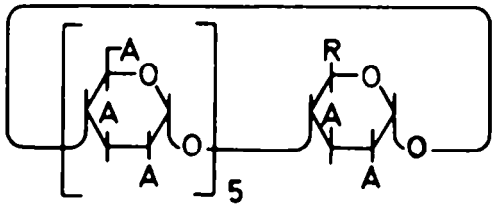
substitution, was prepared[147] by the same methods. This glycerol ether of β-cyclodextrin, and the related trihydroxybutyl ether (0.27 degree of substitution) obtained[147] from 2 and 2, 3 - epoxy - 1, 4-butanediol in the presence of base, form inclusion complexes with flavoring agents and H_3BO_3, and also find applications as emulsifiers, paper sizes, and crosslinking agents.

Another cyclodextrin with a multifunctional sidechain which contains a hydroxyl group was prepared by Breslow *et al.*[105] These authors synthesized mono [6 - (4 - aminomethyl - 3 - hydroxy - 2 - methypyrid

Table 30. Cyclodextrin derivatives with alcohol, ketone, aldehyde or oxime functionality



Compound No.	B	C	n	Reference
222		-OH	6	144
223		-OH	7	144
224	-OH or $-OCH_2CH_2CH_2OH$	$-OCH_2CH_2CH_2OH$ or -OH	7	145
215	$-SCH_2CH_2OH$	-OH	7	80
225	-OH	$-OCH_2\underset{\underset{OH}{|}}{C}HCH_2OH$	6	146
203		-OH	7	105
226	$-OCH_2CH_2\overset{\overset{O}{\|}}{C}CH_3$ or -OH	-OH or $-OCH_2CH_2\overset{\overset{O}{\|}}{C}CH_3$	7	148
227	$-OCH_2CH_2\overset{\overset{N-OH}{\|}}{C}CH_3$ or -OH	-OH or $-OCH_2CH_2\overset{\overset{N-OH}{\|}}{C}CH_3$	7	148
228	-OH	$-OCH_2CHO$	6	146
229	-OH	$-OCH_2CH{=}N{-}OH$	6	146



Compound No.	A	R	Reference
230	-OH	-CHO	108
231	$-OSi(CH_3)_2$ (H)	$-CH{=}N{-}OCH_3$	108

- 5 - yl) methylthio - 6 - deoxy] - β - cyclodextrin (**203**) for use as an enzyme mimic in typical pyridoxamine reactions. Compound **203** was prepared by treating the corresponding thiol with the mono - 6 - tosylate **103**.

A keto cyclodextrin derivative was formed from the parent cyclodextrin **2** and methyl vinyl ketone in the presence of aqueous sodium hydroxide.[148] A mixture of isomers (some may have more than one cyclodextrin hydroxyl group functionalized) of mono [2 (3) (6) - *O* - (2 - (methyloxo) ethyl)] - β - cyclodextrin (**226**) with a 0.46 degree of substitution resulted. The corresponding oxime isomers **227** were also reported.[148]

Cyclodextrin derivatives which contain aldehyde groups are also known. Mono [2 (3) - *O* - (formylmethyl)] - α - cyclodextrin (**228**) was prepared[146] by the periodate oxidation of the glycerol ether **225**. In similar fashion, other workers[147] formed a β-cyclodextrin aldehyde derivative mixture analogous to **228**. The corresponding oxime **229** was prepared by Van Hooidonk *et al.*[146] from **228** and hydroxylammonium chloride in water at pH 5. A 300 MHz ^{1}H NMR spectrum of **229** is reported.[146]

The oxidative deamination of the mono - 6 - amine **139** yielded[108] mono (5 - demethyl - 6 - deoxy - 5 - formyl) - α - cyclodextrin (**230**). Derivative **230** was prepared[108] by treatment of **139** with ninhydrin and sodium bicarbonate in water, followed by chromatographic purification. Compound **230** was also formed[108] by photolysis of the mono - 6 - azide **140**. The perdimethylsilyl *O*-methyl oxime **231** was prepared[108] from **230** by stepwise treatment with methoxylamine hydrochloride in pyridine and then with tetramethyldisilazane and dimethylchlorosilane.

L. *Carboxylic acid and related derivatives of cyclodextrins*

1. *Introduction.* Several cyclodextrin derivatives with attached carboxyl, carbamoyl or related functional groups appear in the literature. Many of these derivatives are mixtures in which varying numbers of the hydroxyl groups of the parent cyclodextrin have been functionalized. In this subsection, such derivative mixtures will be examined first. Subsequently, other cyclodextrin derivatives which were isolated as single compounds will be discussed.

2. *Mixtures of cyclodextrin derivatives with carboxyl or related groups.* Carboxymethyl ether mixtures **232** and **233** (Table 31) have been obtained from the parent cyclodextrins **1** and **2**, respectively, by several researchers. The β-cyclodextrin derivative mixture was first formed by Parmerter *et al.*[132] from the reaction of the parent cyclodextrin **2** and sodium chloroacetate in 2 - propanol - water to give **233** with a 0.066 degree of substitution. The sodium salts of both **232** and **233** were prepared by Lammers *et al.*[137] by an analogous method to give the sodium salts of **232** and **233** with *average* molecular weights of 1160 ± 54 and 1541 ± 169, respectively. These authors prepared the sodium salts **232** and **233** in order to increase the water solubilities of inclusion compounds formed from **232** and **233** as sodium salts relative to the corresponding inclusion compounds obtained with the parent cyclodextrins **1** and **2**. Mixtures **232** and **233** were utilized as their sodium salts by Lammers *et al.*[138,139] in determining the complexation constants and composition of the complexes with hexane and 2, 3-dimethylbutane. The sodium salt of **233** (degree of substitution ≅ 1) was used by Foldi and Szinnyei[149] in sustained release pharmaceutical preparations. Andresz *et al.*[150] synthesized **233** from the parent cyclodextrin **2** and chloroacetic acid in the presence of base. Further treatment[150] of **233** with diazomethane followed by reaction of the resulting ester **234** with hydrazine hydrate gave the carboxymethylhydrazid of β-cyclodextrin **235**. Derivative **235** (with 11.69% N) was utilized in the preparation of a cyclodextrin-containing polymer.[150]

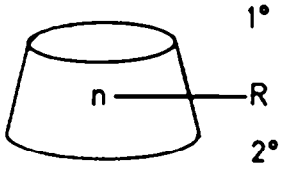
A mixture of the carboxyethyl ethers of β-cyclodextrin (**236** with a degree of substitution = 0.045) was prepared[132] from **2** and propiolactone, or by basic hydrolysis of the propionamide **239**, and is reported to be useful in sewage flocculation applications,[132] paper finishing,[132] as a binder,[132] and as a drug substituent.[149]

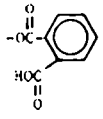
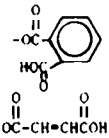
Mixtures of the cyanoethyl ethers of **1** and **2** (**237** and **238**, respectively) have also been reported.[148] Mixture **237** (degree of substitution = 0.6) was prepared from the parent cyclodextrin **1** and acrylonitrile. Similarly **238** (degree of substitution 0.75–2.8) was formed. An analogous mixture of carbamoylethyl ethers of **2** (**239** with a degree of substitution = 0.25) was obtained[132,148] from acrylamide and the parent cyclodextrin **2**.

Mixture **240** was prepared for use as a microencapsulation agent in timed-release pharmaceuticals.[149]

Treatment[143] of the parent cyclodextrins **1** and **2** with various cyclic anhydrides yielded cyclodextrin derivative mixtures with pendant carboxylic acid groups. Thus, reaction[143] of **1** with phthalic anhydride and pyridine in toluene gave **241** (degree of substitution = 1.1). Similarly prepared[143] from β-cyclodextrin

Table 31. Mixtures of cyclodextrin derivatives with pendant carboxylic acid or other related functional groups*



Compound No.	R	n	Reference
232	$-OCH_2\overset{O}{\overset{\|}{C}}OH$	6	137
233	$-OCH_2\overset{O}{\overset{\|}{C}}OH$	7	137
234	$-OCH_2\overset{O}{\overset{\|}{C}}OMe$	7	150
235	$-OCH_2\overset{O}{\overset{\|}{C}}N(H)-NH_2$	6	150
236	$-OCH_2CH_2\overset{O}{\overset{\|}{C}}OH$	7	132
237	$-OCH_2CH_2CN$	6	148
238	$-OCH_2CH_2CN$	7	148
239	$-OCH_2CH_2\overset{O}{\overset{\|}{C}}NH_2$	7	148
240	$-OCH_2CH_2CH_2\overset{O}{\overset{\|}{C}}OH$	7	149
241		6	143
242		7	143
243	$-\overset{O}{\overset{\|}{C}}-CH=CH-\overset{O}{\overset{\|}{C}}OH$	7	143

*The number of R groups attached to the cyclodextrin may range from 0 to 21 within a mixture. See text for details.

was **242** (21.5% CO_2H). Treatment[143] of **2** with maleic anhydride in DMF yielded **243** (3.5% CO_2H). Mixture **241–243** have reported[143] applications as clathrating agents, lubricants, and placticizers.

3. *Cyclodextrin derivatives with pendant carboxyl or related functional groups.* In contrast to the cyclodextrin derivative mixtures just described, a number of well-characterized, chemically-modified cyclodextrins with pendant carboxylic acid, amide and ester functional groups are listed in Table 32. Mono [2 (3) - *O* - (carboxymethyl)] - α - cyclodextrin (**244**) and its methyl ester mono [2 (3) - *O* - (carbomethoxy) methyl] - α - cyclodextrin (**245**) were prepared by Bender *et al.*[3,133,151] Compound **244** was obtained from the parent cyclodextrin **1** and sodium iodoacetate in DMSO. Treatment[133,151] of **244** with diazomethane gave the methyl ester **245**. The ^1H NMR spectrum of **244** and IR spectra of **244** and **245** are reported.[133,151]

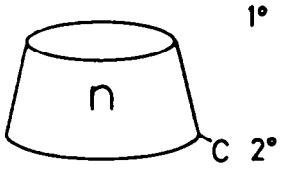
Three substituted hydroxamic acids were derived from the methyl ester **245**. Mono [2 (3) - *O* - (*N* - hydroxy - *N* - methylcarbamoylmethyl)] - α - cyclodextrin (**246**) was prepared[3,151] from **245** and *N*-methylhydroxylamine in DMSO. IR spectral data for **246** are reported.[151] Similarly synthesized[133] from **245** and the appropriate *N*-substituted hydroxyl amine was mono [2 (3) - *O* - (*N* - hydroxy - *N*,*N* - dimethylamino) ethyl] carbamoylmethyl)] - α - cyclodextrin (**247**). An imidazole moiety-containing analog **193** (Table 24) was also prepared.[133] Compounds **193**, **246** and **247** were found[3,133,151] to exhibit enhanced catalytic power in ester hydrolyses relative to the parent cyclodextrin **1**.

Breslow *et al.*[135,136] report the synthesis of mono [2 (3) - *O* - (2 - carboxypyrid - 5 - yloxo)] - α - cyclodextrin (**201**), which when complexed with various metal ions, or with metal ions and another ligand

(**202**), produced metalloenzyme mimics. Several other biomimetic cyclodextrin derivatives with pendant carboxyic acid, amide or ester groups have appeared in the literature. Compounds **148–153** (which are discussed in detail in subsection I) have been employed as models for biological oxidation-reduction reactions.[111,112]

Oxidation of all of the primary hydroxyl groups in the parent cyclodextrins **1** and **2** yielded[152] hexakis(5 - carboxy - 6 - deoxy - 5 - demethyl) - α - cyclodextrin (**248**) and heptakis (5 - carboxy - 6 -

Table 32. Cyclodextrin derivatives with pendant carboxylic acid functional groups and related compounds



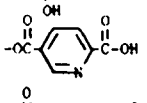
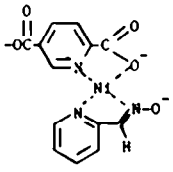
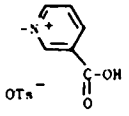
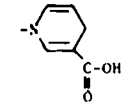
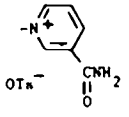
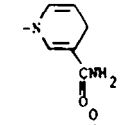
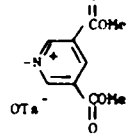
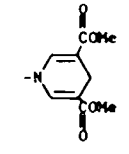
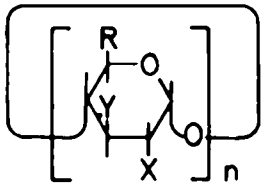
Compound No.	C	n	Reference
244	$-OCH_2COH$	6	3
245	$-OCH_2COCH_3$	6	151
246	$-OCH_2CNCH_3$ (O, OH)	6	151
247	$-OCH_2CNCH_2CH_2N(CH_3)_2$ (O, OH)	6	133
201		6	135
202		6	135
150		7	111
151		7	111
148		7	112
149		7	112
152		7	111
153		7	111

Table 32 (*Contd*)



Compound No.	X	Y	R	n	Reference
248	-OH	-OH	-CONH	6	152
249	-OH	-OH	-CONH	7	152
211	$-OSO_3Na$	$-OSO_3Na$	-CONa	7	142

deoxy - 5 - demethyl) - β - cyclodextrin (**249**), respectively. Derivatives **248** and **249**, prepared by either the catalytic oxidation (Pt/O_2) or the N_2O_4 oxidation of the parent cyclodextrins, were utilized in IR spectral studies.[152]

A similar compound, the persodium salt of heptakis(5 - carboxy - 5 - demethyl - 6 - deoxy - 2, 3 - di - *O* - sulfo) - β - cyclodextrin (**211**), is reported[142] to possess complement inhibiting activity. Derivative **211** was obtained[142] from **2** and NO_2 in carbon tetrachloride in the presence of molecular sieves, followed by treatment with a trimethylamine–sulfur trioxide complex.

M. *Carbonate and carbamate derivatives of cyclodextrins*

O O
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1. *Introduction.* Several carbonate (ROCOR') and carbamate (ROC–NR'R") derivatives of cyclodextrins are known. Most often, these derivatives were obtained as mixtures which were not subsequently separated into their individual components. Often the positions of substitution in these modified cyclodextrins are either unknown or not reported. The initial discussion in this subsection will deal with these derivative mixtures (Table 33). Subsequently, a well-characterized β-cyclodextrin percarbanilate will be mentioned.

2. *Mixtures of carbonate and carbamate derivatives of cyclodextrins.* Carbonates of α- and β-cyclodextrins were prepared by Kennedy and Cho Tun.[153] Mixtures of the cyclic carbonates of the parent cyclodextrins (**250** or **251**) and the ethyl carbonates (**252** or **253**) resulted from treatment[153] of **1** or **2** with ethyl chloroformate in DMSO–dioxane. The relative ratios of **250** : **252** and **251** : **253** depended on the mode of workup and were determined by IR spectroscopy.[153] The cyclic carbonate mixtures **250** and **251** were presumed to involve the substitution of adjacent secondary hydroxyl groups.[153]

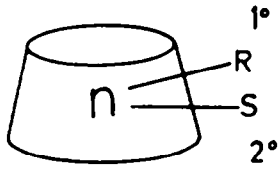
Hull *et al.*[154] report three carbamate derivatives of β-cyclodextrin (**2**). Treatment of **2** with an acidic, aqueous solution of potassium isocyanate (or an aqueous solution of urea) gave the β-cyclodextrin carbamate mixture **254** (degree of substitution = 0.012–0.095). Similarly synthesized from the corresponding alkyl isocyanates and **2** were the β-cyclodextrin cyclohexylcarbamate mixture **255** (degree of substitution = 2.8) and the β-cyclodextrin octadecylcarbamate mixture **256** (degree of substitution = 0.65).

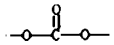
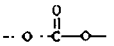
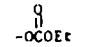
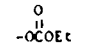
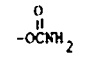
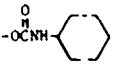
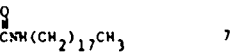
3. *β-Cyclodextrin percarbanilate derivative.* In addition to the cyclodextrin derivative mixtures just discussed, a better-characterized β-cyclodextrin percarbanilate has been reported (Table 34). Wolff and Rist[155] obtained heptakis [2, 3, 6 - tri - *O* - (*N* - phenylcarbamoyl)] - β - cyclodextrin (**257**) from the parent cyclodextrin **2** and phenyl isocyanate. Repeated reprecipitations gave pure (elemental analysis) **257**.

N. *Cyclodextrin derivatives with silicon-, boron- or tin-containing functional groups*

Cyclodextrin derivatives with functional groups containing silicon, boron, or tin atoms are listed in Table 35. Cramer *et al.*[29] report the synthesis of the pertrimethylsilyl β-cyclodextrin, heptakis (2, 3, 6 - tri - *O* - trimethylsilyl) - β - cyclodextrin (**258**), and the analogous compound in which only the secondary

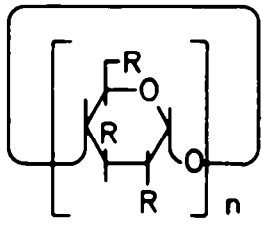
Table 33. Cyclodextrin carbonate and carbamate derivative mixtures*



Compound No.	R	S	n	Reference
250			6	153
251			7	153
252	-OH		6	153
253	-OH		7	153
254	-OH		7	154
255	-OH		7	154
256	-OH		7	154

*The derivative mixtures are composed of cyclodextrins containing from 0 to 21 R and/or S groups per cyclodextrin. See text for details.

Table 34. β-Cyclodextrin percarbanilate



Compound No.	R	n	Reference
257		7	155

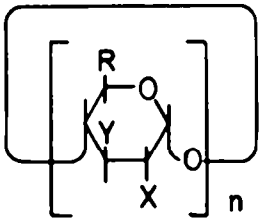
hydroxyl groups have been silylated, heptakis (2, 3 - di - *O* - trimethylsilyl) - β - cyclodextrin (**259**). Compound **258** was prepared from the parent cyclodextrin **2** and trimethylsilyl chloride in pyridine. Derivative **259** was obtained using *N*-trimethylsilylacetamide in pyridine.

Gibson *et al.*[108] synthesized the perdimethylsilyl analog of **1**, hexakis (2, 3, 6 - tri - *O* - dimethylsilyl) - α - cyclodextrin (**260**), by treating the parent cyclodextrin **1** with tetramethyldisilazane and dimethylchlorosilane in pyridine. Similarly, a perdimethylsilyl *O* - methyl oxime **231** was prepared. The mass spectra of both **231** and **260** are reported.[108]

The perdiethylborylated analogs of the parent cyclodextrins **1** and **2** were obtained by Koester *et al.*[156] from the parent cyclodextrins and triethylborane (activated by a catalytic amount of pivalic acid or diethylboryl pivalate). Thus, hexakis (2, 3, 6 - tri - *O* - diethylboryl) - α - cyclodextrin (**261**) and heptakis (2, 3, 6 - tri - *O* - diethylboryl) - β - cyclodextrin (**262**) were produced.

A tributylstannyl cyclodextrin derivative is also known. Smith *et al.*[157] synthesized heptakis (6 - *O* - tributylstannyl) - β - cyclodextrin (**263**) as a model compound for a Mössbauer spectral study of various cellulosic materials which had been treated with a bis (tri - *n* - butyltin) oxide-containing fungicide.

Table 35. Cyclodextrin derivatives with silicon-, boron- or tin-containing functional groups



Compound No.	X	Y	R	n	Reference
258	$-OSiMe_3$	$-OSiMe_3$	$-CH_2OSiMe_3$	7	29
259	$-OSiMe_3$	$-OSiMe_3$	$-CH_2OH$	7	29
260	$-OSiMe_2H$	$-OSiMe_2H$	$-CH_2OSiMe_2H$	6	108
231	$-OSiMe_2H$	$-OSiMe_2H$	1/6 $-CH=NOMe$ 5/6 $-CH_2OSiMe_2H$	6	108
261	$-OBEt_2$	$-OBEt_2$	$-CH_2OBEt_2$	6	156
262	$-OBEt_2$	$-OBEt_2$	$-CH_2OBEt_2$	7	156
263	$-OH$	$-OH$	$-CH_2OSnBu_3$	7	157

Similar trialkylstannyl alkoxide derivatives of cyclodextrins have been prepared *in situ* by other workers.[41,76]

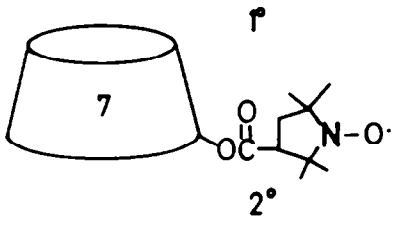
O. *Spin-labeled cyclodextrin derivative*

Paton and Kaiser[158] obtained the *N*-oxide radical of mono [2 (3) - *O* - (2, 2, 5, 5 - tetramethyl - 3 - pyrrolidinyl) oxo] - β - cyclodextrin (**264**) (Table 36) using Bender's synthetic method.[46] Thus **264** was prepared[158] from the corresponding *m*-nitrophenyl substituted pyrrolidine *N*-oxide and the parent cyclodextrin **2**. These authors report[158] the detection of a "Michaelis" complex for this model enzyme system.

P. *Deuterated derivatives of cyclodextrins*

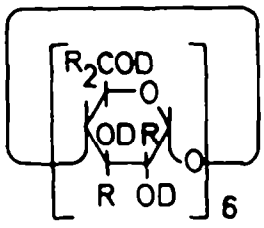
Two deuterated derivatives of cyclodextrins are presented in Table 37. Hamer *et al.*[159] obtained the α-cyclodextrin derivative in which all the hydroxyl protons have been exchanged for deuterons, hexakis (2, 3, 6 - tri - *O* - deuterio) - α - cyclodextrin (**265**), by treating the parent cyclodextrin **1** with deuterium oxide. Further reaction of **265** with deuterium oxide in the presence of Raney nickel gave a derivative in

Table 36. A spin-labeled cyclodextrin derivative



Compound No.	Reference
264	158

Table 37. Deuterated cyclodextrin derivatives



Compound No.	R	Reference
265	-H	159
266	-D	159

which the hydrogens attached to carbons 2, 3 and 6 had also been replaced by deuterium, hexakis (2, 3, 6 - tri - *O* - deuterio - 2, 3, 6, 6 - tetradehydro - 2, 3, 6, 6 - tetradeuterio) - α - cyclodextrin (**266**). The ^1H coupled ^{13}C NMR spectrum of **266** was a subject of study.[159]

Casu *et al.*[160] investigated the isotopic hydrogen–deuterium exchange equilibria for the parent cyclodextrins **1** and **2**. Equilibrium constants for the exchange reactions

$$2ROH + D_2O \rightleftarrows 2ROD + H_2O \quad (1)$$

and

$$ROH + CH_3OD \rightleftarrows ROD + CH_3OH \quad (2)$$

(where ROH = **1** or **2**) were determined.[160] In addition, ^1H NMR spectra of partially deuterated **2** are recorded.[160]

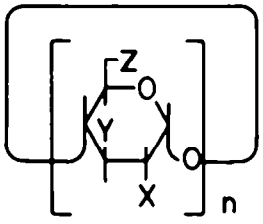
Q. *Deoxy derivatives of cyclodextrins*

A few deoxy derivatives of cyclodextrins—cyclodextrins in which one or more hydroxyl groups have been replaced by hydrogens—are known (Table 38). Takeo *et al.*[40] prepared the poly - 6 - deoxy compounds, hexakis (6 - deoxy) - α - cyclodextrin (**267**), heptakis (6 - deoxy) - β - cyclodextrin (**268**), and octakis (6 - deoxy) - γ - cyclodextrin (**269**) from the corresponding poly - 6 - deoxy peracetates, hexakis (2, 3 - di - *O* - acetyl - 6 - deoxy) - α - cyclodextrin (**20**), heptakis (2, 3 - di - *O* - acetyl - 6 - deoxy) - β - cyclodextrin (**21**), and octakis (2, 3 - di - *O* - acetyl - 6 - deoxy) - γ - cyclodextrin (**22**). Thus, treatment of **20–22** (obtained from the corresponding poly - 6 - bromo peracetates **23–25** by reaction with sodium borohydride in DMSO) with sodium methoxide in methanol gave **267–269**. The 100 MHz ^1H NMR spectra of **20–22** and **267–269** are reported.[40] The preparation of **21** and **268** (by methods analogous to those just cited[40]) were also reported by Takeo *et al.*[33] in a ^{13}C NMR-based study of the parent cyclodextrins **1–3** and their peracetates **4–6**.

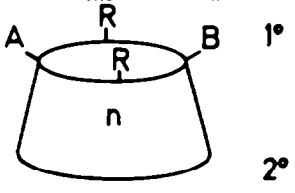
The mono - 6 - deoxy analogs of the parent cyclodextrins **1** and **2** are also known. Mono(6 - deoxy) - α - cyclodextrin (**270**) was obtained by Melton and Slessor[77] by reduction of the mono - 6 - iodide **169** with H_2(Raney nickel) in 1 : 9 pyridine–water followed by chromatography. Compound **270** was utilized[78] for the preparation of the corresponding 6'-deoxy maltose. Thus, treatment of **270** with *Aspergillus oryzae* amylase (Taka amylase) yielded the desired 6'-deoxy maltose. Tabushi *et al.*[117] prepared the corresponding β-cyclodextrin mono - 6 - deoxy derivative, mono (6 - deoxy) - β - cyclodextrin (**271**), for use as a ^1H NMR standard.

In addition, symmetrically disposed di - 6 - deoxy and tetra - 6 - deoxy - β - cyclodextrins have been reported.[117,118] Sodium borohydride reduction in DMSO of the di- and tetra-iodides **166** and **221** gave[117,118] the corresponding deoxy compounds: bis (6 - deoxy) - β - cyclodextrin (**272**) and tetrakis (6 - deoxy) - β - cyclodextrin (**273**). Depending on the diiodide used, **272** may be the 6^A, 6^C- or the 6^A, 6^D-dideoxy compound.[117,118] Similarly, depending on which isomeric tetraiodide is employed, isomers of **273** might be obtained. The 6^A, 6^C, 6^D, 6^F-tetradeoxy isomer of **273** was reported.[117]

Table 38. Deoxy derivatives of cyclodextrins



Compound No.	X	Y	Z	n	Reference
267	-OH	-OH	-H	6	40
268	-OH	-OH	-H	7	40
269	-OH	-OH	-H	8	40
20	-OAc	-OAc	-H	6	40
21	-OAc	-OAc	-H	7	40
22	-OAc	-OAc	-H	8	40



Compound No.	A	B	R	n	Reference
270	-H	-OH	-OH	6	77
271	-H	-OH	-OH	7	117
272	-H	-H	-OH	7	117
273	-H	-H	-H	7	117

Compounds **272** and **273** were used in structure determinations of the corresponding iodides. ^{1}H and ^{13}C NMR and mass spectral data are available[117,118] for **272** and **273**.

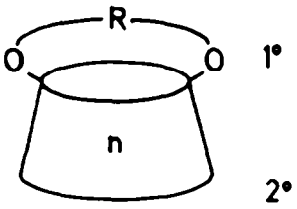
R. *Rigidly capped cyclodextrins*

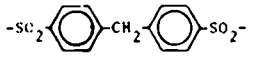
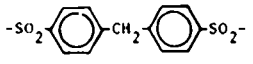
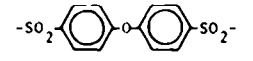
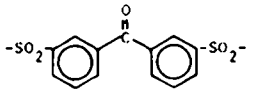
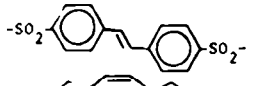
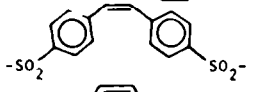
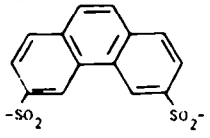
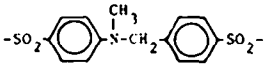
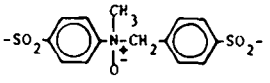
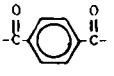
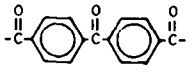
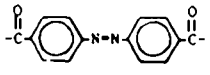
1. *Introduction.* Modifications of cyclodextrins for use as enzyme models and for other applications have led to the preparation of a number of "capped" cyclodextrins. Emert and Breslow[84] initially used the term "capped" to describe cyclodextrins which had been modified with bulky substituents at all primary hydroxyl groups in a cyclodextrin to form a floor on the primary side of the cyclodextrin torus. Tabushi *et al.*[98] have referred to cyclodextrin polyamines coordinated with divalent metal ions as "capped" cyclodextrins. However, the introduction of disulfonyl and dicarbonyl "capped" cyclodextrins[13] (Table 39) necessitated the differentiation of these two types of capped cyclodextrin derivatives. Thus, cyclodextrin derivatives of the type listed in Table 39 are designated as *rigidly capped cyclodextrins*, while the capped cyclodextrin derivatives initially cited[84,98] are known as *flexibly capped cyclodextrins.*

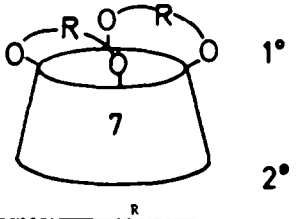
In this subsection, only the rigidly capped cyclodextrins will be examined. Initially, disulfonyl capped cyclodextrins will be discussed. Thereafter, the carbonyl-linked capped cyclodextrins will be examined. Finally, a doubly-capped β-cyclodextrin will be mentioned.

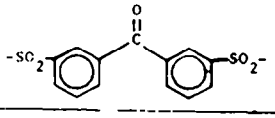
2. *Disulfonate-capped cyclodextrins.* Rigidly capped cyclodextrin analogs of the parent cyclodextrins **1** and **2** resulted from the reaction[113,161] of **1** and **2** with diphenylmethane-p, p'-disulfonyl chloride in pyridine which formed 6^{A}, 6^{C} - *O, O'* - (4, 4' - diphenylmethanesulfonyl) - α - cyclodextrin (**274**) and 6^{A}, $6^{C(D)}$ - *O, O'* - (4, 4' - diphenylmethanesulfonyl) - β - cyclodextrin (**275**), respectively. Compound **275** was shown to be a mixture of isomers[134] (6^{A} - 6^{C} - capped and 6^{A} - 6^{D} - capped). Tabushi *et al.*[161] studied the interactions of **275** with sodium 1 - anilino - 8 - naphthalenesulfonate and determined the binding constant for the complexation by fluoresence measurements.

Table 39. Rigidly capped cyclodextrins



Compound No.	R	n	Reference
274		6	113
275		7	161
276		7	121
277		7	121
278		7	118
279		7	118
280		7	162
281		7	162
282		7	115
283		7	115
284		7	161
285		7	163
286		7	164



Compound No.	R	Reference
287		117

Derivatives **274** and **275** were also utilized as starting materials in the preparation of a number of symmetrically bifunctionalized cyclodextrin derivatives. Thus, Tabushi *et al.*[113] synthesized the diazido and diamino derivatives **154–158** and two sulfur-containing derivatives **216** and **217** by reaction of **275** with the appropriate nucleophile, followed by workup and purification. Similar reactions with **274** were proposed.[113] Breslow *et al.*[134] obtained a bisimidazole derivative **198** from **275** by treatment with imidazole in DMF. Tabushi *et al.*[114] utilized **275** in the preparation of a duplex cyclodextrin **162** (Table 17) via the bis(aminoethylamino) cyclodextrin **159**. Tabushi *et al.*[116] also converted **275** into the symmetrical diiodide **166** for use as an intermediate in the preparation of a carbonic anhydrase model. Fujita *et al.*[79] examined **275** as a catalyst in the hydrolysis of phenyl acetates.

Bifuctionalized cyclodextrins obtained from **275** were shown[134] to be mixtures of the 6^A, 6^C and 6^A, 6^D isomers. Although such mixtures were employed in the synthetic applications just mentioned, the desirability of preparing corresponding cyclodextrin derivatives which would not be contaminated by isomers led to the search for procedures which would give single capped compounds. Breslow *et al.*[120,121] prepared the diphenyl ether analog of **275**, 6^A, $6^{C(D)}$ - *O, O'* - (4, 4' - diphenyloxamethanedisulfonyl - β - cyclodextrin (**276**) and the biphenyl analog of **275**, 6^A, $6^{C(D)}$ - *O, O'* - (4, 4' - biphenyldisulfonyl) - β - cyclodextrin (**277**). Since the sulfonyl groups in the capping reagents utilized for the synthesis of **276** and **277** were thought to be further apart than those in the reagent utilized in preparing **275**,[121] enrichment of 6^A, 6^D substitution in **276** and **277** was postulated.[121] Comparison of the catalytic activities of bis-imidazole derivatives obtained from **276** and **277** with that of the bis-imidazole derivative prepared from **275** indicates[121] progressive enrichment of 6^A, 6^D substitution. Characterization data for **276** and **277** are reported.[121] Tabushi *et al.*[118] have identified capping reagents which produce regiospecific 6^A, 6^C- or 6^A, 6^D-capped β-cyclodextrin. Treatment[118] of β-cyclodextrin (**2**) with benzophenone - 3, 3' - disulfonyl chloride in pyridine gave the 6^A, 6^C, capped derivative, 6^A, 6^C - *O, O'* - 3, 3' - diphenyloxodisulfonyl) - β - cyclodextrin (**278**). Similar treatment of **2** with *trans* - stilbene - 4, 4' - disulfonyl chloride yielded 6^A, 6^D - *O, O'* - (*trans* - stilbene - 4, 4' - disulfonyl) - β - cyclodextrin (**279**). ^1H and ^{13}C NMR data for **278** and **279** are available.[118] Detailed structural studies of **278** and **279** were undertaken[117,162] which resulted in the preparation of 6^A, 6^D - *O, O'* - (*cis* - stilbene - 4, 4' - disulfonyl) - β - cyclodextrin (**280**),[162] the *cis* analog of **279** and **287**,[117] a doubly-capped analog of **278**. Compound **280** was produced[118,161] by the photoisomerization of **279** or by treatment of the parent cyclodextrin **2** with *cis* - stilbene - 4, 4' - disulfonyl chloride in pyridine. A related capped derivative, 6^A, 6^D - *O, O'* - (3, 6 - phenanthrenedisulfonyl) - β - cyclodextrin (**281**) can be obtained[162] from **280** by a photochemical method, or alternatively by treatment of the parent cyclodextrin **2** with phenanthrene - 3, 6 - disulfonyl chloride. Spectral characterization data for **280** and **281** are given.[162]

Asymmetrical introduction of two different functional groups into two symmetrically disposed primary sites in a cyclodextrin has been facilitated by the efforts of Tabushi *et al.*[115] These researchers have prepared[115] the asymmetrically capped cyclodextrin, 6^A, $6^{C(D)}$ - *O, O'* - [1, 2 - bis(4 - diphenylsulfonyl) - 2 - azapropane] - β - cyclodextrin (**282**). Compound **282** resulted from treatment of the parent cyclodextrin **2** with *N* - benzyl - *N* - methylaniline - *p, p'* - disulfonyl chloride in pyridine. Subsequent reaction of **282** with *m*-chloroperbenzoic acid in ethylene glycol yielded the corresponding *N*-oxide **283**. Extensive characterization studies of **282** and **283** are reported.[115] Stepwise reactions of **283** with two different nucleophiles (via an intermediate such as **160**) yield functionalized cyclodextrins of type illustrated by the azido sulfide **161** (Table 17).

3. *Dicarboxylate-capped cyclodextrins.* In addition to the disulfonate-capped cyclodextrins discussed above, dicarboxylate-capped derivatives are known. Tabushi *et al.*[161] prepared 6^A, $6^{C(D)}$ - *O, O'* - (*p* - benzenedicarbonyl) - β - cyclodextrin (**284**) from the parent cyclodextrin **2** and terephthaloyl chloride in pyridine. Binding of sodium 1 - anilino - 8 - naphthalenesulfonate by derivative **284** was investigated[161] and the binding constant was determined by fluorescence measurements. Specific host–guest energy transfers were also studied[163] employing 6^A, $6^{C(D)}$ - *O, O'* - (4, 4' - diphenyloxodicarbonyl) - β - cyclodextrin (**285**). Derivative **285** was synthesized[163] from the parent cyclodextrin **2** and 4, 4'-bis-chlorocarbonyl) benzophenone. IR and ^1H NMR spectra for **285** are given.[163]

An azobenzene-capped cyclodextrin, 6^A, $C^{(D)}$ - *O, O'* - (4, 4' - azobenzenedicarbonyl) - β - cyclodextrin (**286**), was reported by Ueno *et al.*[164–167] Derivative **286** was synthesized from 4, 4' - bis(chlorocarbonyl)azobenzene and **2** in pyridine. Photocontrol of the binding ability of **286** was observed[164] due to the ability of the azo group to photoisomerize (*trans* ⇆ *cis*). The complexing ability of **286** with a number of substrates including amino acids,[165,166] aryl molecules,[166] and common organic solvents[167] has been probed.

4. *A doubly-capped cyclodextrin.* Tabushi *et al.*[117,118] prepared 6^A, 6^C - *O*, *O'* - (3, 3' - diphenyloxodisulfonyl) - 6^D, 6^F - *O''*, *O'''* - (3, 3' - diphenyloxodisulfonyl) - β - cyclodextrin (**287**), the dicapped analog of **278**. Derivative **287** was obtained[117] by treatment of the parent cyclodextrin **2** with an excess of benzophenone - 3, 3' - disulfonyl chloride. Detailed characterization of **287** was conducted[117] and this compound was utilized in the structure proof of **278**.

III. SELECTIVE MODIFICATION TECHNIQUES

The organization of this work (grouping cyclodextrin derivatives with similar functionalities together) has necessitated fragmentation of reported synthetic sequences. This was done to facilitate the retrieval of information regarding specific compounds. However, there are a few reported synthetic strategies which have shown (or have a great potential for showing) general applicability in the synthesis of certain types of cyclodextrin derivatives. Since these strategies are not often apparent from the fragmented presentation of their component parts, a brief discussion of these strategies follows.

Monosubstituted cyclodextrins have found great utility in a wide range of applications. Generally, the mono - 6 - substituted cyclodextrins may be obtained via the mono - 6 - substituted tosylates **102** or **103** using the method of Melton and Slessor.[77] Treatment of **102** or **103** with an appropriate nucleophile yields the desired mono - 6 - substituted cyclodextrin. Monosubstitution at a secondary hydroxyl group to obtain the mono - 2 (3) - substituted derivatives is most generally accomplished using Bender's method[7,46] (Fig. 3). An acyl-linked cyclodextrin derivative can be prepared by treating the parent cyclodextrin with an appropriate aryl ester in which the desired group is contained in the carboxylate portion of the ester. Complexation of the substrate by the parent cyclodextrin, followed by covalent catalysis by one of the secondary hydroxyl groups (attack at the carbonyl carbon of the ester) yields a covalent acyl cyclodextrin intermediate, which can be isolated in many cases. This strategy has been exploited in preparing many cyclodextrin derivatives.

Substitution of two symmetrically disposed primary hydroxyl groups to give symmetrically or asymmetrically disubstituted cyclodextrin derivatives is best accomplished via displacement of a rigidly capped cyclodextrin (or by attack on an intermediate diiodide which was derived from the rigidly capped cyclodextrin) by Tabushi's[113,115] or Breslow's[120,134] methods. This strategy has been utilized extensively to prepare symmetrically disposed di - 6 - substituted cyclodextrins. α-Cyclodextrin derivatives with three symmetrically disposed (primary) functional groups may be prepared by the method of Boger *et al.*[73] via the 6^A, 6^C, 6^E-tritrityl derivative **72** and the trimesyl derivative **75**.

Poly - 6 - substituted cyclodextrin derivatives can be obtained employing the method of Boger *et al.*[37] Two efficient strategies are described which facilitate the selective modification of all the primary hydroxyl groups in the parent cyclodextrin.

IV. CONCLUSION

While many chemically-modified cyclodextrins have been reported in the literature, the need for more and better characterized cyclodextrin derivatives for present and future applications is recognised. Recent and continuing interest in these versatile compounds is demonstrated by the increasing number of papers dealing with modified cyclodextrins which appear each year in the chemical literature. Preparation of pure, well-characterized, chemically-modified cyclodextrin derivatives will continue to provide a challenge to those who desire to utilize these compounds. Hopefully, this review will stimulate even more rapid development in the synthesis of chemically-modified cyclodextrins and their applications.

V. REFERENCES

[1]D. French, *Adv. Carbohyd. Chem.* **12**, 189 (1957).
[2]F. Cramer and H. Hettler, *Naturwissenschaften* **54**, 625 (1967).
[3]D. W. Griffiths and M. L. Bender, *Adv. Cat.* **23**, 209 (1973).
[4]A. Mifune and A. Shima, *Yuki Gosei Kagaku Kyokai Shi* **35**, 116 (1977); [*Chem. Abstr.* **87**, 136158m (1977)].
[5]R. J. Bergeron, *J. Chem. Ed.* **54**, 204 (1977).
[6]W. Saenger, *Angew. Chem. Int. Ed., Engl.* **19**, 344 (1980).
[7]M. L. Bender and M. Komiyama, *Cyclodextrin Chemistry*. Springer-Verlag, Berlin (1978).
[8]M. Kojima and F. Toda, *Kagaku to Seibutsu* **18**, 702 (1980); [*Chem. Abstr.* **94**, 140051h (1981)].
[9]T. Kuge and K. Takeo, *Depun Kagaku* **21**, 151 (1974).
[10]I. Tabushi and T. Nisitani, *Kaguku (Kyoto)* **32**, 768 (1977); [*Chem Abstr.* **89**, 2092t (1978)].
[11]I. Tabushi, *Koen Yoshi-Shinpojumu "Kagaku no Mirai"* **18** (1979); [*Chem. Abstr.* **92**, 89673s (1980)].
[12]I. Tabushi and T. Nishitani, *Kagaku no Ryoiki* **34**, 385 (1980); [*Chem. Abstr.* **93**, 90690x (1980)].
[13]I. Tabushi, *Acc. Chem. Res.* **15**, 66 (1982).
[14]M. Hatano, *Petrotech (Tokyo)* **2**, 634 (1979); [*Chem. Abstr.* **92**, 44141a (1980)].

[15]S. Kobayashi and K. Kainuma, *Shokuhin Kogyo* **24**, 34 (1981); [*Chem. Abstr.* **94**, 190361e (1981)].
[16]A. Villiers, *C. R. Acad. Sci.* **112**, 536 (1891).
[17]J. Szejtli, E. Fenyvesi and B. Zsadon, *Staerke* **30**, 127 (1978).
[18]F. Schardinger, *Zentralbl. Bakteriol. Parensitenk., Abt. II* **29**, 188 (1911).
[19]H. Pringsheim and A. Steingroever, *Chem. Ber.* **57**, 1579 (1924).
[20]K. Freudenberg and R. Jacobi, *Justus Liebigs Ann. Chem.* **518**, 102 (1935).
[21]W. S. McClenahan, E. B. Tilden and C. S. Hudson, *J. Am. Chem. Soc.* **64**, 2139 (1942).
[22]K. Freudenberg, E. Plankenhorn and H. Knauber, *Chem. Ind.* 731 (1947).
[23]K. Freudenberg, E. Plankenhorn and H. Knauber, *Justus Liebigs Ann. Chem.* **558**, 1 (1947).
[24]D. French, M. L. Levine, J. H. Pazur and E. Norberg, *J. Am. Chem. Soc.* **71**, 353 (1949).
[25]D. French, M. L. Levine and J. H. Pazur, *J. Am. Chem. Soc.* **71**, 356 (1949).
[26]D. M. Sand and H. Schlenk, *Anal. Chem.* **33**, 1624 (1961).
[27]H. Schlenk, J. L. Gellerman and D. M. Sand, *Ibid.* **34**, 1529 (1962).
[28]H. Schlenk and D. M. Sand, *Ibid.* **34**, 1676 (1962).
[29]F. Cramer, G. Mackensen and K. Sensse, *Chem. Ber.* **102**, 494 (1969).
[30]B. Casu, M. Reggiani, G. G. Gallo and A. Vigevani, *Carbohyd. Res.* **12**, 157 (1970).
[31]K. Takeo and T. Kuge, *Arg. Biol. Chem.* **34**, 1416 (1970).
[32]S. Hirano, *Org. Magn. Resonance* **3**, 353 (1971).
[33]K. Takeo, K. Hirose and T. Kuge, *Chem. Lett.* 1233 (1973).
[34]K. Takeo, Y. Kondo and T. Kuge, *Kyoto Furitsu Daigaku Gakujutsu* **22**, 106 (1970).
[35]D. Gagnaire, D. Mancier and M. Vincendon, *Org. Magn. Resonance* **11**, 344 (1978).
[36]B. Pfannemueller, G. Richter and E. Husemann, *Carbohyd. Res.* **47**, 63 (1976).
[37]J. Boger, R. J. Corcoran and J. M. Lehn, *Helv. Chim. Acta* **61**, 2190 (1978).
[38]W. Lautsch, R. Wiechert and H. Lehmann, *Kolloid-Z.* **135**, 134 (1954).
[39]W. Lautsch and R. Wiechert, *Ibid.* **153**, 103 (1957).
[40]K. Takeo, T. Suimimoto and T. Kuge, *Staerke* **26**, 111 (1974).
[41]T. Ogawa and M. Matsui *Carbohydr. Res.* **56**, C1-C6 (1977).
[42]Y. Kongo and K. Takeo, *Carbohydr. Res.* **52**, 232 (1976).
[43]R. Bergeron, Y. Machida and K. Bloch, *J. Biol. Chem.* **250**, 1223 (1975).
[44]K. Takeo and T. Kuge, *Staerke* **28**, 226 (1976).
[45]Y. Kurono, V. Stamoudis and M. L. Bender, *Bioorg. Chem.* **5**, 393 (1976).
[46]R. L. Van Etten, G. A. Cower, J. F. Sebastian and M. L. Bender, *J. Am. Chem. Soc.* **89**, 3253 (1967).
[47]M. Furue, A. Harada and S. Nozakura, *J. Polym. Sci., Polym. Lett. Ed.* **13**, 357 (1975).
[48]A. Harada, M. Furue and S. Nozakura, *Macromolecules* **9**, 701 (1976).
[49]A. Harada, M. Furue and S. Nozakura, *Macromolecules* **10**, 676 (1977).
[50]M. Komiyama and M. L. Bender, *Proc. Nat. Acad. Sci.* (USA) **73**, 2969 (1976).
[51]M. Komiyama and M. L. Bender, *Bioorg. Chem.* **8**, 249 (1979).
[52]M. F. Czarniecki and R. Breslow, *J. Am. Chem. Soc.* **100**, 7771 (1978).
[53]G. L. Trainor and R. Breslow, *J. Am. Chem. Soc.* **103**, 154 (1981).
[54]A. Harada, M. Furue and S. Nozakura, *Polym. J.* **12**, 29 (1980).
[55]S. M. Parmerter and E. E. Allen, *U.S. Pat.* 3,565,887 (23 Feb. 1971); [*Chem. Abstr.* **75**, 6242a (1971)].
[56]J. C. Irvine, H. Pringsheim and J. MacDonald, *J. Chem. Soc.* **125**, 942 (1924).
[57]K. Freudenberg and W. Rapp, *Chem. Ber.* **69**, 2041 (1936).
[58]K. Freudenberg and M. Meyer-Delius, *Chem. Ber.* **71**, 1596 (1938).
[59]K. Freudenberg and F. Cramer, *Ztschr. Naturforsch.* **3b**, 464 (1948).
[60]K. Freudenberg and F. Cramer, *Chem. Ber.* **83**, 296 (1950).
[61]B. Casu, M. Reggiani, G. G. Gallo and A. Vigevani, *Tetrahedron* **24**, 803 (1968).
[62]F. Shahidi, P. G. Farrell and J. T. Edward, *J. Soln. Chem.* **5**, 807 (1976).
[63]T. Hayakawa, T. Yamada, S. Hidaka, M. Yamagishi, K. Takeda and F. Toda, *Polym. Prep., Am. Chem. Soc., Div. Polym. Chem.* **20**, 530 (1979).
[64]B. Casu, M. Reggiani and G. R. Sanderson, *Carbohydr. Res.* **76**, 59 (1979).
[65]R. I. Gelb, L. M. Schwartz, J. E. Markinac and D. A. Laufer, *J. Am. Chem. Soc.* **101**, 1864 (1979).
[66]Y. Nakai, S. Nakajima, K. Yamamoto, K. Terada and T. Konno, *Chem. Pharm. Bull.* **28**, 1552 (1980).
[67]J. Szejti, A. Lipták, I. Jodál, P. Fügedi, P. Nánási and A. Neszmélyi, *Staerke* **32**, 165 (1980).
[68]J. Staerk and H. Schlenk, *149th Am. Chem. Soc. Mtg.* 1965, Abstract 11c.
[69]Y. Machida, R. Bergeron, P. Flick and K. Bloch, *J. Biol. Chem.* **248**, 6246 (1973).
[70]R. Breslow, H. Kohn and B. Siegel, *Tetrahedron Letters* 1645 (1976).
[71]R. J. Bergeron, M. P. Meeley and Y. Machida, *Bioorg. Chem.* **5**, 121 (1976).
[72]J. Boger and J. R. Knowles, *Ciba Found. Symp.* **60**, 225 (1978); [*Chem. Abstr.* **92**, 36766t (1980)].
[73]J. Boger, D. G. Brenner and J. R. Knowles, *J. Am. Chem. Soc.* **101**, 7630 (1979).
[74]J. Boger and J. R. Knowles, *J. Am. Chem. Soc.* **101**, 7631 (1979).
[75]K. Takeo, F. Yagi and T. Kuge, *Kyoto Furitsu Daigaku Gakujutsu Hokoku, Nogaku* 159 (1972); [*Chem. Abstr.* **79**, 18987t (1973)].
[76]T. Ogawa and M. Matsui, *Jpn. Kokai Tokkyo Koho* 78,149,913 (27 Dec. 1978); [*Chem. Abstr.* **90**, 152547e (1979)].
[77]L. D. Melton and K. N. Slessor, *Carbohydr. Res.* **18**, 29 (1971).
[78]L. D. Melton and K. N. Slessor, *Can. J. Chem.* **51**, 327 (1973).
[79]K. Fujita, A. Shinoda and T. Imoto, *J. Am. Chem. Soc.* **102**, 1161 (1980).
[80]K. Fujita, A. Shinoda and T. Imoto, *Tetrahedron Lett.* **21**, 1541 (1980).
[81]K. Hirotsu, T. Higuchi, K. Fugita, T. Ueda, A. Shinoda, T. Imoto and I. Tabushi, *J. Org. Chem.* **47**, 1143 (1982).
[82]S. Umezawa and K. Tatsuta, *Bull. Chem. Soc. Jpn.* **41**, 464 (1968).
[83]F. Cramer and G. Mackensen, *Chem. Ber.* **103**, 2138 (1970).
[84]J. Emert and R. Breslow, *J. Am. Chem. Soc.* **97**, 670 (1975).
[85]R. Breslow, M. F. Czarniecki, J. Emert and H. Hamaguchi, *J. Am. Chem. Soc.* **102**, 762 (1980).
[86]Tanabe Seiyaku Co., Ltd., *Jpn. Kokai* 76, 142,088 (7 Dec. 1976); [*Chem. Abstr.* **89**, 75435a (1978)].
[87]K. Tsujihara and H. Kurita, *Chem. Lett.* 1333 (1978).

[88]H. Kurita, M. Kawazu and K. Takashima, *Jpn. Kokai* 74 85, 014 (15 *Aug.* 1974); [*Chem. Abstr.* **81**, 169767p (1974)].
[89]H. Kurita, M. Kawazu and K. Takashima, *Jpn. Kokai* 74 85, 015 (15 Aug. 1974); [*Chem. Abstr.* **82**, 4533s (1975)].
[90]H. Kurita, M. Kawazu and K. Takashima, *Ger. Offen.* 2,425,663 (4 Dec. 1975); [*Chem. Abstr.* **84**, 166583b (1976)].
[91]H. Kurita, M. Kawazu and K. Takashima, *Jpn. Kokai* 75,140,475 (11 Nov. 1975); [*Chem. Abstr.* **84**, 136002u (1976)].
[92]K. Tsujihara, H. Kurita and M. Kawazu, *Bull. Chem. Soc. Jpn.* **50**, 1567 (1977).
[93]H. Kurita, M. Kawazu and K. Takashima, *Jpn. Kokai* 75,140,476 (11 Nov. 1975); [*Chem. Abstr.* **84**, 136003v (1976)].
[94]K. Tsujihara and H. Kurita, *Jpn. Kokai* 77,138,580 (18 Nov. 1977); [*Chem. Abstr.* **88**, 158469m (1978)].
[95]K. Tsujihara and H. Kurita, *Jpn. Kokai* 77,138,581 (18 Nov. 1977); [*Chem. Abstr.* **88**, 141692f (1978)].
[96]I. Tabushi and N. Shimizu, *Jpn. Kokai Tokkyo Koho* 78,102,985 (7 Sept. 1978); [*Chem. Abstr.* **90**, 39196b (1979)].
[97]Y. Matsui, T. Yokoi and K. Mochida, *Chem. Lett.* 1037 (1976).
[98]I. Tabushi, N. Shimizu, T. Sugimoto, M. Shiozuka and K. Yamamura, *J. Am. Chem. Soc.* **99**, 7100 (1977).
[99]I. Tabushi and N. Shimizu, *Jpn. Kokai Tokkyo Koho* 78,102,986 (7 Sept. 1978); [*Chem. Abstr.* **90**, 39197c (1979)].
[100]Y. Matsui and A. Okimota, *Bull. Chem. Soc. Jpn.* **51**, 3030 (1978).
[101]K. Omichi and Y. Matsushima, *J. Biochem.* (Tokyo) **84**, 835 (1978).
[102]I. Tabushi, N. Shimizu and K. Yamamura, *Jpn. Kokai Tokkyo Koho* 79 61,291 (17 May 1979); [*Chem. Abstr.* **91**, 124391b (1979)].
[103]I. Tabushi, N. Shimizu and K. Yamamura, *Jpn. Kokai Tokkyo Koho* 79 61,289 (17 May 1979); [*Chem. Abstr.* **91**, 108650e (1979)].
[104]B. Siegel, *J. Inorg. Nucl. Chem.* **41**, 609 (1979).
[105]R. Breslow, M. Hammond and M. Lauer, *J. Am. Chem. Soc.* **102**, 421 (1980).
[106]Y. Iwakura, K. Uno, F. Toda, S. Onozuka, K. Hattori and M. L. Bender, *J. Am. Chem. Soc.* **97**, 4432 (1975).
[107]S. Onozuka, M. Kojima, K. Hattori and F. Toda, *Bull. Chem. Soc. Jpn.* **53**, 3221 (1980).
[108]A. R. Gibson, L. D. Melton and K. N. Slessor, *Can. J. Chem.* **52**, 3905 (1974).
[109]I. Tabushi, K. Shimokawa and Y. Kuroda, *Kokagaku Toronkai Koen Yoshishu* 62 (1979); [*Chem. Abstr.* **92**, 215674h (1980)].
[110]I. Tabushi, Y. Kuroda and K. Shimokawa, *J. Am. Chem. Soc.* **101**, 4759 (1979).
[111]K. Hattori, M. Kojima and F. Toda, *Jpn. Kokai Tokkyo Koho* 80 36,209 (13 Mar. 1980); [*Chem. Abstr.* **93**, 186750t (1980)].
[112]M. Kojima, F. Toda and K. Hattori, *Tetrahedron Letters* **21**, 2721 (1980).
[113]I. Tabushi, K. Shimokawa and K. Fujita, *Tetrahedron Letters* 1527 (1977).
[114]I. Tabushi, Y. Kuroda and K. Shimokawa, *J. Am. Chem. Soc.* **101**, 1614 (1979).
[115]I. Tabushi, T. Nabeshima, H. Kitaguchi and K. Yamamura, *J. Am. Chem. Soc.* **104**, 2017 (1982).
[116]I. Tabushi, Y. Kuroda and A. Mochizuki, *J. Am. Chem. Soc.* **102**, 1152 (1980).
[117]I. Tabushi, L. C. Yuan, K. Shimokawa, K. Yokota, T. Mizutani and Y. Kuroda, *Tetrahedron Letters* **22**, 2273 (1981).
[118]I. Tabushi, Y. Kuroda, K. Yokota and L. C. Yuan, *J. Am. Chem. Soc.* **103**, 711 (1981).
[119]F. Cramer and G. Mackensen, *Angew. Chem. Int. Ed., Engl.* **5**, 601 (1966).
[120]R. Breslow, *Isr. J. Chem.* **18**, 187 (1979).
[121]R. Breslow, P. Bovy and C. L. Hersch, *J. Am. Chem. Soc.* **102**, 2115 (1980).
[122]J. Leibowitz and S. H. Silmann, *Chem. Ber.* **58**, 1889 (1925).
[123]N. S. Gruenhut, M. L. Cushing and G. V. Caesar, *J. Am. Chem. Soc.* **70**, 424 (1948).
[124]A. F. Dawoud and A. Marawan, *Carbohydr. Res.* **26**, 65 (1973).
[125]N. Hennrich and F. Cramer, *J. Am. Chem. Soc.* **87**, 1121 (1965).
[126]B. Siegel, A. Pinter and R. Breslow, *J. Am. Chem. Soc.* **99**, 2309 (1977).
[127]T. Eiki and W. Tagaki, *Chem. Lett.* 1063 (1980).
[128]H. J. Brass and M. L. Bender, *J. Am. Chem. Soc.* **95**, 5391 (1973).
[129]C. Van Hooidonk and J. C. A. E. Breebaart-Hansen, *Recl. Trav. Chim. Pays-Bas* **89**, 289 (1970).
[130]C. Van Hooidonk and C. G. Groos, *Recl. Trav. Chim. Pay-Bas* **89**, 845, (1970).
[131]C. Van Hooidonk and J. C. A. E. Breebaart-Hansen, *Recl. Trav. Chim. Pays-Bas* **90**, 680 (1971).
[132]S. M. Parmerter, E. E. Allen, Jr. and G. A. Hull, *U.S. Pat.* 3,426,011 (4 Feb. 1969); [*Chem. Abstr.* 71, 13331z (1969)].
[133]Y. Kitaura and M. L. Bender, *Bioorg. Chem.* **4**, 237 (1975).
[134]R. Breslow, J. B. Doherty, G. Guillot and C. Lipsey, *J. Am. Chem. Soc.* **100**, 3227 (1978).
[135]R. Breslow and L. E. Overman, *J. Am. Chem. Soc.* **92**, 1075 (1970).
[136]R. Breslow, *Adv. Chem.* **100**, 21 (1971).
[137]J. N. J. J. Lammers, J. L. Koole and J. Hurkmans, *Staerke* **23**, 167 (1971).
[138]N. N. J. J. Lammers, J. L. Koole and A. J. G. Van Diemen, *Recl. Trav. Chem. Pays-Bas* **91**, 483 (1972).
[139]J. N. J. J. Lammers and A. J. G. Van Diemen, *Recl. Trav. Chim. Pays-Bas* **91**, 733 (1972).
[140]J. Hamuro and M. Akiyama, *Jpn. Kokai* 75 36,422 (5 Apr. 1975); [*Chem. Abstr.* **83**, 79544a (1975)].
[141]S. Bernstein, J. P. Joseph and V. Nair, *U.S. Pat.* 4,020,160 (26 Apr. 1977); [*Chem. Abstr.* **87**, 29026v (1977)].
[142]A. J. Lewis and S. Bernstein, *U.S. Pat.* 4,247,535 (27 Jan. 1981); [*Chem. Abst.* **94**, 214614t (1981)].
[143]S. M. Parmerter and E. E. Allen, Jr., *U.S. Pat.* 3,453,260 (1 Jul. 1969); [*Chem. Abstr.* 71, 82872p (1969)].
[144]J. H. Carter and E. Y. Lee, *Anal. Biochem.* **39**, 521 (1971).
[145]T. Yamada and U. Maeno, *Jpn. Kokai Tokkyo Koho* 79 06,883 (19 Jan. 1979); [*Chem. Abstr.* **92**, 13703f (1980)].
[146]C. Van Hooidonk, D. C. De Korte and M. A. C. Reuland-Meereboer, *Recl. Trav. Chim. Pays-Bas* **96**, 25 (1977).
[147]S. M. Parmerter, E. E. Allen, Jr. and D. H. Le Roy, *U.S. Pat.* 3,453,259 (1 Jul. 1969); [*Chem. Abstr.* 71, 82875s (1969)].
[148]S. M. Parmerter, E. E. Allen, Jr. and G. A. Hull, *U.S. Pat.* 3,453,258 (1 Jul. 1969); [*Chem. Abstr.* 71, 92872c (1969)].
[149]Z. Foldi and E. Szinnyei, *Hung. Teljes* 16,601 (28 May 1979); [*Chem. Abstr.* **92**, 22773f (1980)].
[150]H. Andresz, G. C. Richter and B. Pfannemueller, *Makromol. Chem.* **179**, 301 (1978).
[151]W. B. Gruhn and M. L. Bender, *Bioorg. Chem.* **3**, 324 (1974).
[152]B. Casu, G. Scovenna, A. J. Cifonelli and A. S. Perlin, *Carbohydr. Res* **63**, 13 (1968).
[153]J. F. Kennedy and H. Cho Tun, *Carbohydr. Res.* **26**, 401 (1973).
[154]G. A. Hull and E. E. Allen, Jr., *U.S. Pat.* 3,459,732 (5 Aug. 1969); [*Chem. Abstr.* 71, 113224k (1969)].
[155]I. A. Wolff and C. E. Rist, *J. Am. Chem. Soc.* **70**, 2779 (1948).
[156]R. Koester, K. L. Amen and W. V. Dahlhoff, *Justus Liebigs Ann. Chem.* 752 (1975).
[157]P. J. Smith, A. J. Crowe, D. W. Allen, J. S. Brooks and R. Formstone, *Chem. Ind.* (London) 874 (1977).
[158]R. M. Paton and E. T. Kaiser, *J. Am. Chem. Soc.* **92**, 4723 (1970)
[159]G. K. Hamer, F. Balza, N. Cyr and A. S. Perlin, *Can. J. Chem.* **56**, 3109 (1978).
[160]B. Casu, M. Reggiani, G. G. Gallo and A. Vigevani, *Chem. Soc.*, (London), *Spec. Publ.* 217 (1968).
[161]I. Tabushi, K. Shimokawa, N. Shimizu, H. Shirakata and K. Fujita, *J. Am. Chem. Soc.* **98**, 7855 (1976).

[162]I. Tabushi and L. C. Yuan, *J. Am. Chem Soc.* **103**, 3574 (1981).
[163]I. Tabushi, K. Fujita and L. C. Yuan, *Tetrahedron Letters* 2503 (1977).
[164]A. Ueno, H. Yoshimura, R. Saka and T. Osa, *J. Am. Chem. Soc.* **101**, 2779 (1979).
[165]A. Ueno, R. Saka and T. Osa, *Chem. Lett.* 841 (1979).
[166]A. Ueno, R. Saka and T. Osa, *Chem. Lett.* 1007 (1979).
[167]A. Ueno, R. Saka and T. Osa, *Chem. Lett.* 29 (1980).
[168]A. Parfoudry, N. Cyr and A. S. Perlin, *Carbohydr. Res.* **59**, 299 (1977).
[169]S. M. Parmerter, E. E. Allen, Jr. and G. A. Hull, *U.S. Pat.* 3,453,257 (1 Jul. 1969); [*Chem. Abstr.* **71**, 91821y (1969)].
[170]I. Tabushi, N. Shimizu and K. Yamamura, *Jpn. Kokai Tokkyo Koho* 79 61,290 (17 May 1979); [*Chem. Abstr.* **91**, 124390a (1979)].
[171]S. M. Parmerter and E. E. Allen, Jr., *U.S. Pat.* 3,553,191 (5 Jan. 1971); [*Chem. Abstr.* **74**, 88879e (1971)].
[172]J. Szejtli, *Cyclodextrins and Their Inclusion Complexes*. Akadémiai Kiadó, Budapest (1982).