Methods for Selective Modifications of Cyclodextrins

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Received November 25, 1997 (Revised Manuscript Received February 23, 1998)

Contents

1. Introduction

The modification of cyclodextrins offers both enormous opportunities and challenges for chemists. Opportunities are provided by the fact that, through modifications, cyclodextrins can provide exquisite molecules that can be invaluable in investigations at the frontiers of chemistry ranging from enzyme-like catalytic activity[1] and antibody-like binding[2] to aesthetically pleasing molecules. Challenges are provided by the presence of the hydrophobic cavity and a large number of hydroxyl groups.[3] Hydroxyl groups present at the 2-, 3-, and 6-positions compete for the reagent and make selective modification extremely difficult. The hydrophobic cavity often has a tendency to interfere with the well laid out plan of a chemist by complexing with the reagent to direct its activity to an unexpected place.[4]

Cyclodextrins, in their native state, are rigid molecules and offer limited utility in terms of size, shape, and availability of chemically useful functional groups. Cyclodextrins have thus been called structural and functional straightjackets.[5] It is a credit to those who have catapulted these unusual molecules to such prominence despite their limitations. It is mind boggling to think of the progress that could be made if cyclodextrins of any size, shape, and most importantly containing any functional groups were available. The best method to provide such a facility is to selectively convert the hydroxyl groups to other desired functionalities. The three types of hydroxyl groups available on two different sides of cyclodextrin make the challenge of selective conversion a daunting task. Several chemists who have not been satisfied with what nature has provided with cyclodextrins and who have wanted more from them have chipped away at this monumental task. It is to the credit of these people that a variety of new cyclodextrins are now available.[6−8]

Cyclodextrins are modified for a variety of reasons ranging from achieving solubility in a desired solvent to investigating the mechanisms of enzyme-catalyzed reactions. The strategy for modification depends on the purpose of the final product. For example, if a highly water soluble cyclodextrin is desired for application in a drug formulation, then a random conversion of hydroxyl groups to sulfate groups can be easily achieved and the product will have the desired solubility in water.[9,10] Similarly, if a cyclodextrin with a high solubility in organic solvents is desired, one can easily convert the hydroxyl groups to silyl ethers in a random fashion.[11] This product will be highly soluble in organic solvents and can be used to disperse indicator dyes which would otherwise tend to aggregate. However, in both these cases, the final product is not homogeneous and cannot be subjected to rigorous characterization like elemental analysis. On the other hand, if an enzyme mechanism is to be investigated using cyclodextrin derivatives, then this compound needs to be homogeneous with a structure that is well characterized. The number of substituents, the exact position that they are attached to, and all the stereochemical changes

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S0009-2665(97)00012-5 CCC: $30.00
Published on Web 06/16/1998

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that have taken place during its synthesis have to be established before the mechanistic information about the artificial enzyme can be reliably derived.

1.1. Scope of This Review

In this review, we present a systematic analysis of methods that are available for modification of cyclodextrins. The focus is on methods for transformation where the number and the exact positions of modifications are ascertained and pure compounds with unambiguous structures are obtained. In cases where the products have unusual and interesting properties, these attributes are mentioned. We have not attempted to cite every cyclodextrin derivative that has been made. This has already been achieved in an excellent and recent review.[12] We have also not included modified cyclodextrins obtained by purely synthetic routes, i.e., strategies to obtain these molecules from appropriately derivatized monosaccharides rather than cyclodextrins. A recent review describes strategies for the preparation of synthetic cyclic oligosacharides.[7]

Keith Stine was born on August 6, 1962 in Jersey City, NJ. He received his undergraduate degree in Chemistry from Fairleigh Dickinson University in Madison, NJ, in 1984. He earned his Ph.D. at MIT in 1988, having studied phase transitions in liquid crystals under the direction of Professor Carl W. Garland. He then spent two years as a postdoctoral scholar in the Department of Chemistry and Biochemistry at UCLA where he studied the phase behavior and microstructural properties of Langmuir monolayers working with Professor Charles M. Knobler. In 1990, he joined the Chemistry Department at the University of Missouri—St. Louis, where he is now Associate Professor of Chemistry. His research interests include the study of surfactant films, self-assembled monolayers, and aggregates, especially the role that supramolecular chemistry can serve in the design and utilization of these systems.

Valerian T. D'Souza was born in Pangla, India. He did his undergraduate studies at St. Xavier's College, Bombay. His Master's research was carried out under the direction of Professor V. V. Nadkarny at the Nadkarny-Sacasa Research Laboratory at St. Xavier's College, Bombay. He earned his Ph.D. in Physical Organic Chemistry studying the mechanism of thiol–olefin cooxidation reactions under the direction of Professor H. Harry Szmant at the University of Detroit. He did his postdoctoral research at Northwestern University with Professor Myron L. Bender, one of the founding fathers of the field of bioorganic chemistry. As a postdoctoral fellow, he worked on the mechanism of action of chymotrypsin and the study of its miniature organic models. He joined the Chemistry faculty at the University of Missouri—St. Louis in 1987 and was promoted to a Associate Professor in 1993. His research interests are uses of organic models to study enzyme mechanisms and synthesis and catalytic properties of modified cyclodextrins.

1.2. An Overview of Methods for Modification of Cyclodextrins

Methods for selective modification of cyclodextrin can be divided into three categories: (1) the "clever"

method, where the chemistry of cyclodextrin is exploited to get the desired product by the shortest route; (2) the "long" method, where a series of protection and deprotection steps have taken place in order to selectively reach the positions which would otherwise not be selectively accessible; (3) the "sledgehammer" method, where cyclodextrin is indiscriminately reacted to give a mixture of products and then the desired product is painstakingly separated out from other isomers and homologues by chromatographic methods.

An example from the first category is the synthesis of 2-tosyl-β-cyclodextrin by reacting cyclodextrin with *m*-nitrophenyl tosylate.[4] In this synthesis, the complexation property of cyclodextrin is taken advantage of to direct the tosyl group to the secondary side. This avoids the natural tendency of cyclodextrin to react on its primary side and predominantly gives cyclodextrins substituted at the 2-position. An example of the second category is the alkylation of the primary side, which is outlined in Figure 5 (steps **I**−**III**, **VII**, and **VI**).[13] This involves in sequence (1) protection of the primary side with silyl groups, (2) protection of the secondary side with acetyl groups, (3) desilylation of the primary side, (4) reaction of the primary hydroxyl group with an appropriate alkyl halide, and finally (5) deprotection of the secondary side to give the desired product. In this strategy, each reaction is carefully chosen to give a high yield and the product should be easily separable and purifiable; however, the overall yield of the final product is often very small. An example of the third category is ditosylation of the secondary side of cyclodextrin.[14] In this case, tosyl chloride is reacted with cyclodextrin to give a mixture of products. This mixture is separated using reverse phase HPLC. Given the choice between three categories, one would always choose the first strategy because it is most productive and least painful; however, a method in the first category is not always available when a modified cyclodextrin of a specific structure is needed.

1.3. Chemistry Involved in Methods for Modification of Cyclodextrins

It is important to understand the various chemical factors that are involved in these methods for modification of cyclodextrins to fully appreciate and be able to apply them for syntheses that have not yet been attempted. The glucopyranose ring contains secondary hydroxyl groups at the 2- and 3-positions and primary hydroxyl groups at the 6-positions. The whole molecule assumes a rigid structure because of the formation of a belt of intramolecular hydrogen bonds between hydroxyl groups at the 2- and 3-positions of adjacent glucose units. The rotation of the secondary hydroxyl groups is thus restricted, whereas rotation of the primary hydroxyl groups is free, thus reducing the effective diameter of the cavity on the primary side of the molecule.[1] The presence of the hydroxyl groups makes the upper and lower end of the molecule hydrophilic. The cavity of cyclodextrins is rendered hydrophobic because of the presence of glycosidic oxygens and C−H units. The inner diameter of the cavity on the secondary side varies from 5.7 to 9.5 Å as the number of glucose units increases from 6 (in α-CD) to 8 (in γ-CD).[3]

Two primary factors need to be considered in the chemistry of cyclodextrins for their modification, the nucleophilicity of the hydroxyl groups and the ability of cyclodextrins to form complexes with the reagents used. All modifications of cyclodextrins take place at the hydroxyl groups. Since hydroxyl groups are nucleophilic in nature, the initial reaction, which directs the regioselectivity and the extent of modification (mono, di, tri, etc.) of all subsequent reactions, is an electrophilic attack on these positions.

Of the three types of hydroxyl groups present in cyclodextrins, those at the 6-position are the most basic (and often most nucleophilic), those at the 2-position are the most acidic, and those at the 3-position are the most inaccessible.[15,16] Thus, under normal circumstances, an electrophilic reagent attacks the 6-position (**I** in Figure 1). It is important to recognize that more reactive reagents will attack the hydroxyl groups less selectively. Thus, more reactive reagents will not only react with hydroxyl groups at the 6-positions but also with those on the secondary side; whereas, less reactive reagents will react more selectively with the 6-position hydroxyl groups. An example of this is that the less reactive reagent *tert*-butyldimethylsilyl chloride (TBDMSCl) will react selectively with hydroxyl groups at the 6-positions,[17] while the more reactive reagent trimethylsilyl chloride (TMSCl) will react with all the hydroxyl groups indiscriminately.[18]

Since the hydroxyl groups at the 2-position are the most acidic, they will be the first to get deproto-

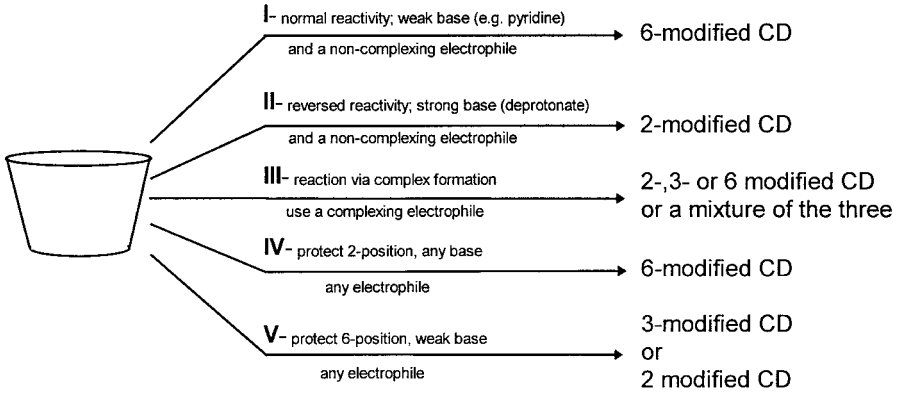

Figure 1. Overview of the methods for modification of cyclodextrins.

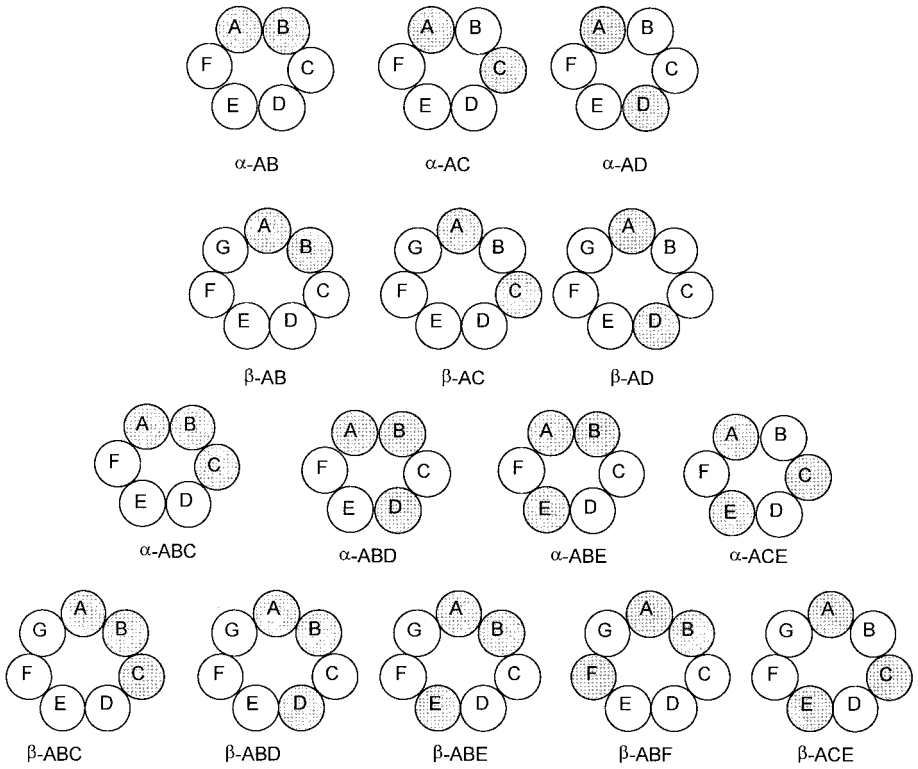

Figure 2. Possible positional isomers of di- and trimodified α- and *β*-cyclodextrins.

nated.[19] The oxyanion thus formed is more nucleophilic than the nondeprotonated hydroxyl groups at the 6-position (**II** in Figure 1). However, this situation is complicated by proton transfers between these two positions which can lead to a product mixture consisting of modifications at the 2- as well as the 6-positions. The effect of solvents or the strength of the electrophiles in these proton transfers has not been investigated. In practice, we have observed that addition of the electrophilic reagent as a solid in one portion reduces the amount of the latter product.

An interesting factor affecting the chemistry of the hydroxyl groups is provided by the ability of cyclodextrins to form complexes (**III** in Figure 1). If the electrophilic reagent forms a complex with cyclodextrin, then the orientation of the reagent within the complex introduces an additional factor in determining the nature of the product.[4] If the complex formed is very strong, then the predominant product formed will be dictated by the orientation of the reagent within the complex. On the other hand, if the complex is weak, then the product formation will be directed by the relative nucleophilicities of the hydroxyl groups. It is also important to note that solvents play an important role in determining the strength and the orientation of the complex between the reagent and cyclodextrin. Thus, tosyl chloride reacts with α-cyclodextrin in pyridine to give the 6-tosylated product, whereas, in aqueous base, it gives the 2-tosylated product.[20] The size of the cyclodextrin cavity also has a pronounced effect on the strength and the orientation of the complex and affects the product of the reaction. For example, in aqueous solutions, tosyl chloride reacts with α-cyclodextrin to give the 2-substituted product; whereas with *β*-cyclodextrin, it gives the 6-substituted product.[21] Even the most inaccessible hydroxyl groups at the 3-position can be modified using this property of cyclodextrin. For example, naphthalenesulfonyl chloride reacts with *β*-cyclodextrin to give the 3-substituted product.[22] However, methods to design reagents which can bind cyclodextrins with a specific orientation to give substitution at a specific hydroxyl group have not yet been well developed. With advances in computational chemistry, one hopes that a day will come when we will be able to direct reagents to specific parts of cyclodextrin by using its ability to bind these reagents.

A strategy used to avoid complications due to binding of the reagent into the cavity of cyclodextrin, and thus give products which are not expected by their normal nucleophilicity, is to protect the hydroxyl groups and direct the incoming reagent exclusively to the other open hydroxyl groups. For example, if one protects the 2-position of cyclodextrin, one can direct the incoming electrophile to the 6-position (**IV** in Figure 1). A specific example of this is peralkylation of the primary side of cyclodextrin in which the secondary side is first protected by esterification and then the primary side is reacted with alkyl halides.[17] Similarly, protection of the primary side enables one to direct the incoming electrophile exclusively to hydroxyl group at the 2-positions (**V** in Figure 1). Pertosylation of this side has been achieved using this strategy,[23] and TBDMS is the most popular protecting group since it is easy to attach and easy to remove.[17,24] However, cyclodextrins have shown a propensity to circumvent even this apparently foolproof strategy. This has been demonstrated in the reaction of the electrophile *N*-methyl-4-(chloromethyl)-2-nitroaniline with 6-protected *β*-cyclodextrin which directed the electrophile to the 3-position instead of the expected 2-position.[25] This could probably form a strategy to access the

usually inaccessible hydroxyl groups at the 3-position. Thus, if a cyclodextrin modified at the 3-position is needed and if it cannot be obtained by the reaction of the electrophile with cyclodextrin, then one could add suitable protecting groups at the 6-position to see if the electrophile can be directed toward the 3-position. Since a coherent strategy for directing incoming electrophiles by taking advantage of the complex forming ability of cyclodextrins has not been developed, such generalizations cannot yet be made.

In this review, mono-, di-, tri-, and permodifications refers to modification at respectively one, two, three, and all hydroxyl groups at one site (either the 2-, 3-, or 6-positions) of cyclodextrins. Higher modifications of cyclodextrins are not well documented in the literature. It is important to note that of the four types of modifications mentioned above, only di- and trimodifications give positional isomers. As shown in Figure 2, both α- and β-cyclodextrins give three (AB, AC, and AD) disubstituted isomers. On the other hand, α- and β-cyclodextrins have respectively four (ABC, ABD, ABE, and ACE) and five (ABC, ABD ABE, ABF, and ACE) trisubstituted positional isomers. We now analyze the literature in of terms methods of modifications of cyclodextrins at *specific* sites resulting in a *known* degree of modification.

2. Primary Face Modification

Since primary hydroxyl groups are more nucleophilic than their secondary counterparts, they are easily modified into other functional groups. Selective permodification of all the primary hydroxyl groups is relatively easier than mono-, di-, or trisubstitution because symmetrical substitution is achieved when the reaction is allowed to run for a longer time with appropriate amounts of reagents. Regioisomerism further complicates this situation when selective di- or trisubstituted cyclodextrins are to be prepared. Usually these products require chromatographic purifications.

Strong electrophiles such as alkyl,[26] phosphoryl,[27] silyl,[17] sulfonyl,[4,20] or carboxylic acid chlorides[18] react with hydroxyl groups of cyclodextrin to produce an alkylated, silylated, sulfonated, or acetylated product along with an acid which is neutralized by using a basic solvent or a weak base. The reason for the use of a base or basic solvent is that cyclodextrins are stable under basic conditions whereas they decompose in the presence of a strong acid.[28,29] All these reagents are very reactive and attack the hydroxyl groups of cyclodextrins indiscriminately producing mono-, di-, or trisubstituted products. Increasing the size of these reagents is not helpful in controlling the selectivity; even a bulky group like trityl is not selective and gives a mixture of products which requires chromatographic treatment.[30−32] The most popular reagent for producing primary side modified cyclodextrins, TBDMSCl, under optimal conditions gives 90% of the major product which can be easily separated out by flash column chromatography or by recrystallization.[33] There are several reports where investigators have used the "long" method to obtain pure samples of 6-substituted cyclodextrin. This is achieved in one case by first blocking the 6-position using the *tert*-butyldimethylsilyl (TBDMS) group and then acetylating the remaining hydroxyl groups.[13] The product is desilylated and glycosylated on the primary side and then deacetylated to obtain mono-6-glycosylcyclodextrin.[13]

Among all the substituents, the sulfonyl group acts as a good leaving group and can be displaced by nucleophiles to synthesize useful derivatives. 6-Sulfonates serve as precursors for the preparation of the 6-deoxycyclodextrin compounds. A large number of nucleophiles attack the carbon atom at the 6-position in these sulfonates to give the corresponding modified cyclodextrins. However, alkaline bases cannot be used as nucleophiles due to the elimination reaction which result in a 3,6-anhydro product as shown in Figure 4.[34]

2.1. Monosubstitution at the 6-Position of Cyclodextrins

The most popular method for monomodifications at the 6-position of cyclodextrins is by a nucleophilic attack of a reagent containing the appropriate group on mono-6-sulfonylcyclodextrin (**II** in Figure 3). These monosulfonates are prepared by reacting 1 equiv of benzene or *p*-toluenesulfonyl chloride with cyclodextrin in pyridine or DMF containing a base (**I** in Figure 3). Monotosylation of cyclodextrin is often a nonselective process and produces a mixture of primary as well as secondary side tosylated products along with di- or tritosylated derivatives. Thus, depending on the desired purity of the final product, it requires extensive purification. The yield of the final product is often reduced because the tosylate can undergo an exchange by chloride ions or an elimination process to give either the 3,6-anhydro compound or an alkene. Pyridine, a non-user-friendly solvent of choice for this reaction, forms a pyridinium complex with the cavity and complicates the workup process. However, the major advantage of this solvent is its ability to direct the reaction to the 6-position as compared to DMF where sulfonation occurs on both faces of cyclodextrin. Despite all these problems and drawbacks, monotosylates have been extensively investigated[6,30,35] and improvements in their preparation have been reported.[36] The method of choice[37] for the synthesis of monotosylcyclodextrin is to react cyclodextrin with tosyl chloride in 1:1 equivalent ratio in aqueous alkaline medium for a short time to give the mono-6-tosylate in fairly good yield. The product is obtained in a reasonable purity either by repeated crystallization from water or by chromatography on a charcoal column.[37] In some cases, the complex-formation property of cyclodextrin has been used to direct the reagent to the primary side. For example, reaction of tosyl chloride with β-cyclodextrin in basic aqueous medium to give monosulfonation on the primary side has been attributed to the formation of a complex prior to the reaction.[21]

6-Tosylcyclodextrins are important precursors for a variety of modified cyclodextrins because a nucleophile can attack the electrophilic carbon atom at the 6-position to produce a corresponding functionality (**II** in Figure 3). A nucleophilic displacement of the

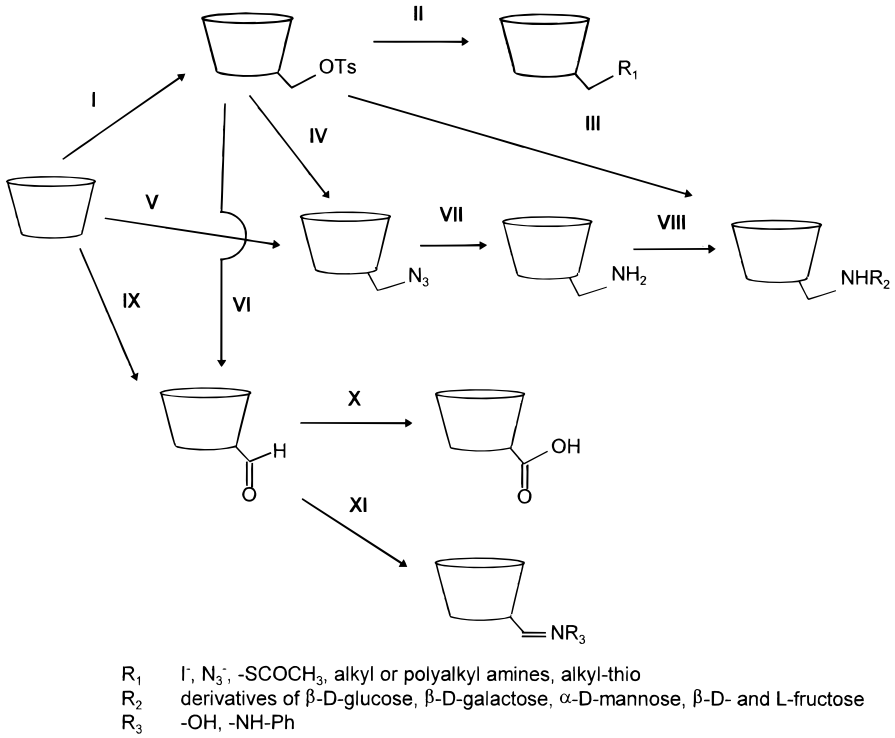

Figure 3. Overview of methods for monosubstitution at the 6-position of cyclodextrins.

tosyl group by suitable nucleophiles such as iodide, azide, thioacetate, hydroxylamine, alkyl, or poly(alkylamines) affords[38] monoiodo-,[39] azido-,[30,40] thio-,[41,42] (hydroxylamino)-,[43] or (alkylamino)cyclodextrins.[35,44] This strategy is also used in the synthesis of artificial enzymes where only one functional group which act as a catalyst is attached to the 6-position of cyclodextrins.[45,46] This is achieved by reacting a nucleophile containing the catalytic group with the 6-tosylated cyclodextrin to give the artificial enzyme. Artificial enzymes based on cyclodextrin are discussed in another paper in this issue.[47]

A variety of other derivatives have been prepared by displacing the tosyl group from the 6-position of cyclodextrin. A bulky group like 4-*N*-(*tert*-butoxycarbonyl)-2-ethylimidazolyl has been connected to cyclodextrin and characterized by X-ray diffraction.[48] Various derivatives such as seleno-, *p*-picolinyl-, (chloroanilino)-, and ((aminoethyl)amino)cyclodextrins[49] have been synthesized to assess their complexation and thermodynamic behavior. Monotoluidinyl or (alkylamino)cyclodextrins can recognize the size, shape, and chirality of amino acids with good enantioselectivity.[50] (Alkylbipyridino)cyclodextrins enhance the dimerization of viologen radicals as compared to methylalkyl viologens.[51] The mono(hydroxylamine) derivative of cyclodextrin obtained from the monotosylate shows a 1900-fold increase in trans-acylating behavior as compared to unmodified cyclodextrin.[52]

Monothio derivatives are synthesized from monotosylates or monoiodocyclodextrins and the respective alkanethiolate ion (**II** in Figure 3). A variety of mercaptocyclodextrin derivatives have been obtained from monotosylated cyclodextrins and have been used to study immobilized films on a gold surface.[53] The direct synthesis of monothiocyclodextrins with aromatic thiol and unprotected cyclodextrin in DMF or pyridine is performed by a thio-Mitsunobu reaction. This reaction gives a mixture mono-, di-, and trisubstituted products which are purified by chromatography.[54]

Monoamino derivatives of cyclodextrin have made important contributions in this area. These are conveniently obtained from monoazides of cyclodextrin by reduction with triphenylphosphine in the presence of aqueous ammonia (**VII** in Figure 3).[55] Monoazides of cyclodextrin are indirectly obtained by heating the monotosylate with sodium or lithium azide salt in DMF (**IV** in Figure 3).[30] A direct approach to make mono-azides is through Vilsmeier−Haack type reactions in which cyclodextrins are heated with sodium azide containing triphenylphosphine in DMF (**V** in Figure 3).[55] Monoamines show greater solubility and react with isocyanate without a need to protect the primary hydroxyl groups to produce isothiocyanatocyclodextrins.[56] The amide formed by reaction with acrylolyl chloride undergoes 1,3-cycloadditions with nitrile oxides with reversed regioselectivity relative to other terminal alkenes.[57] Monoamines are invaluable in attaching desired groups to the primary side of cyclodextrins via carbodiimide (DCC) coupling technology (**VIII** in Figure 3). This strategy has been used to connect various sugar units such as *β*-D-glucose, *β*-D-galactose, α-D-mannose, and *β*-D- and L-fructose to cyclodextrins through alkyl chains. These compounds have been used to investigate their antennae effects.[58] Monoamines condense with D- or D-*N*-dansylleucine in DMF containing DCC and 1-hydroxybenzotriazole at room temperature to form D- or L-mono-6-(*N*-dansylleucylamino)-6-deoxy-*β*-cyclodextrin in 50% yield.[59]

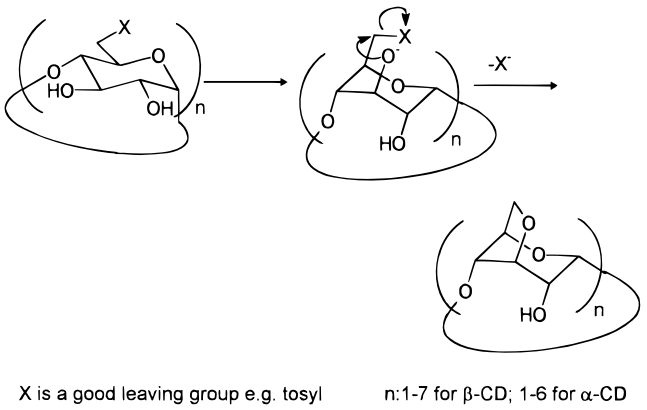

Figure 4. Conversion of a 6-substituted cyclodextrin to a 3,6-anhydrocyclodextrin.

Monoaldehydic cyclodextrins are an important class of derivatives because they provide a route for further modifications. The monoaldehyde has been synthesized by oxidizing 6-tosyl-β-cyclodextrin using DMSO (**VI** in Figure 3).[37,60,61] However, the monoaldehyde can be synthesized directly by reacting cyclodextrins with Dess−Martin periodinane (DMP) in 85−100% yield (**IX** in Figure 3).[62−64] This process avoids complications in the synthesis of monotosylcyclodextrin mentioned earlier. Oxidation of the monoaldehyde leads to the corresponding carboxylic acid (**X** in Figure 3).[61] Hydroxylamine or hydrazine reacts with the monoaldehyde to produce a monooxime or a monohydrazone derivatives (**XI** in Figure 3).[61]

Alkyl ethers of cyclodextrins cannot be synthesized from tosylates because nucleophiles in this case (alkoxide ions) act as strong bases which pick up protons from hydroxyl groups at the 3-position and produce the 3,6-anhydro compound by ring inversion as shown in Figure 4.[34] Alkyl ethers of β-CD are obtained by the "long" method in which the primary side is first protected by TBDMS (**I** in Figure 5). This is followed by permethylation of the secondary face (both 2- and 3-positions) (**II** in Figure 5, $R_2 = CH_3$), desilylation of the primary side, and then monotosylation of the primary side (**III** and **IV** in Figure 5). The reaction of an alkoxide ion with this protected tosylate gives the desired alkyl ether on the primary side without the formation of the 3,6-anhydro derivative (**V** in Figure 5).[34] The main problem with this approach is that methyl groups on the secondary side cannot be easily removed. This limitation can be overcome by using acetyl groups to protect the secondary side which can be subsequently hydrolyzed (**II** in Figure 5, R_2 = Ac). An example of this is the synthesis of mono-6-*O*-α-D-glycopyranosyl-α-cyclodextrin which is obtained from 2,3-acetylated cyclodextrin and tetra-*O*-benzyl-α-D-glycopyranosyl bromide in methylene chloride containing tetraethylammonium bromide.[17] The ester groups on the secondary side are hydrolyzed under aqueous alkaline conditions to afford the final product. This "long" method has been made shorter by directly protecting the secondary side using TBDMSCl without first protecting the primary side (**VIII** in Figure 4). This protection strategy takes advantage of the acidity of the hydroxyl groups at the 2-position to selectively deprotonate them. This increases their nucleophilicity and reactivity toward TBDMSCl as compared to that of the hydroxyl groups on the primary side. The secondary side protected cyclodextrin can now be exploited for selective alkylation on the primary face (**IX** in Figure 4, R_3 = benzyl).[65] The advantage of this approach is that the protecting group TBDMS is easily removed under mild conditions once the desired modifications on the primary side are completed (**X** in Figure 4).

A direct approach for alkylation involves treating aqueous alkaline solutions of cyclodextrins with alkyl halides to afford a mixture of products which are separated by chromatographic means.[26,66,67] Hydroxypropylation is an example of a random reaction which results in a mixture of O-2, O-3, and O-6 derivatives. This substitution can be controlled by the concentration of alkali used during the reaction.[68] Other examples of direct alkylation are mono(dicyanoanthracene) derivatives which have been synthesized to improve the binding properties of cyclodextrins.[69] Another direct approach for monoalkylation is the pyrolysis of solid complexes of cyclodextrins−aromatic diazo compounds via insertion of carbene into hydroxyl groups. The mixture of 2-, 3-, and 6-*O*-isomers formed are separated by HPLC to give the

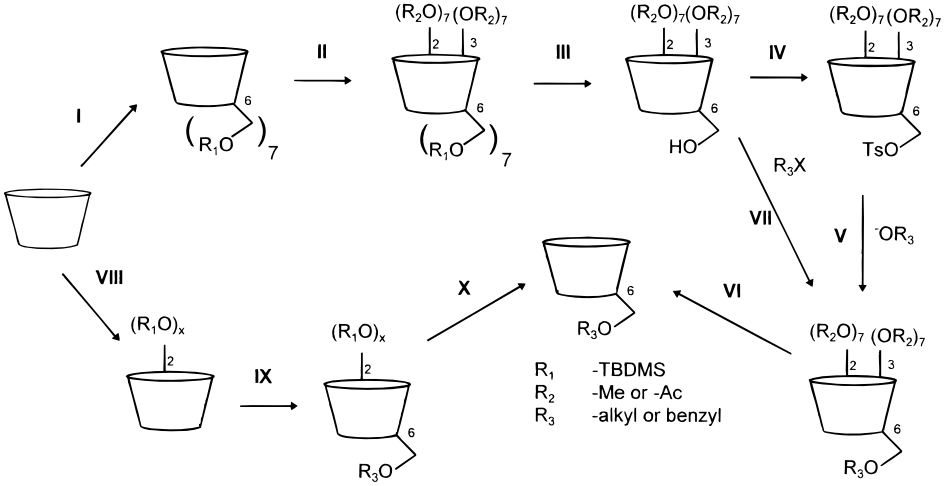

Figure 5. Strategies for monoalkylation of the primary side of cyclodextrins.

desired monoalkylcyclodextrin derivative.[70]

Recently, some cyclodextrins dimers using the primary sides have shown extraordinary binding properties as strong as those of antibodies.[71−73] Other dimeric cyclodextrins show interesting properties such as preferential binding of nonlinear substrates.[74] The simplest of these are synthesized[75] by air oxidation of 6-deoxy-6-mercaptocyclodextrins to corresponding disulfide dimers. Other dimers are prepared by reduction of this mono(disulfide) and condensation with isomeric monothiocyclodextrins.[2] The ethylenediamine−cyclodextrin dimer is synthesized reacting ethylenediamine with monotosylcyclodextrin stepwise to attach a cyclodextrin moiety to each end of a ethylenediamine molecule.[76] Similar dimers are also made by heating capped (disulfonated) cyclodextrins with ethylenediamine in two steps.[77] Dimerization of monoazidocyclodextrins can be achieved (up to 91% yield) by linking two units through urea in DMF.[78,79] Symmetrically and unsymmetrically dimerized α- and β-cyclodextrins are synthesized by reacting 3- and 6-aminocyclodextrins with dicarboxy acid esters.[80] In an interesting example, aminocyclodextrin is connected to histidine in the presence of dicyclohexylcarbodiimide (DCC) in DMF. This is further coupled to 6-((carboxymethyl)-thio)-6-cyclodextrin (obtained from the reaction of cyclodextrin iodide with sodium sulfidoacetate) in the presence of DCC to give a cyclodextrin dimer in which an imidazole is appended to the linker. This compound shows a greater rate of hydrolysis and substrate specificity for certain types of phenyl esters as compared to cyclodextrins.[81] Cyclodextrin dimers and their properties are discussed in another article in this issue.[47]

2.2. Disubstitution at the 6-Position of Cyclodextrins

Disubstituted cyclodextrins are obtained by using more than 1 equiv of reagent with cyclodextrin under suitable conditions to give a mixture of products. It is a cumbersome process due to the formation of positional and regioisomers which requires extensive purification by HPLC. Statistical calculations suggest that disubstitution can produce 33 regioisomers in the case of β-cyclodextrins,[82] which indicates the enormous complexity of this process. Use of an oversized reagent like mesitylenesulfonyl chloride is not effective in limiting the number of substitutions on the primary face to two or three.[83,84] As in sulfonation reactions in general,[85] these can also be plagued by substitutions on the secondary side and exchange (of the sulfonates) with chloride ions present in the medium to further lower the yield of a final product. Toluenesulfonyl[84,86−89] or mesitylenesulfonyl[83,90,91] chlorides react with α-, β-, or γ-cyclodextrin in pyridine and generate a mixture of bis(sulfonates) in a low yield which are separated by HPLC. Reaction of tosyl chloride with cyclodextrins is reported to give a mixture of di-O-6,[86] di-O-2,[14,22] or di-O-3[92] derivatives along with other products. These are separated by reverse-phase column chromatography to give the desired disubstituted products. Despite all these difficulties, a variety of disulfonates are reported in the literature.[6]

A particularly efficient method to obtain disubstituted sulfonates of cyclodextrins is by reaction of arenedisulfonyl chlorides with cyclodextrins to give AB, AC, and AD isomers.[93−95] Although these disulfonyl chlorides give a mixture of regioisomers, they show distinct regiospecificity based on their structures. An elegant method to control the regiospecificity to produce AB, AC, or AD isomers by the use of the geometry of the reagents has been described.[96] For example, as shown in Figure 6, *trans*-stilbene- and biphenyl-based capping reagents preferentially give AD isomers,[96,97] benzophenone-based reagents give AC isomers, and 1,3-benzenedisulfonyl chlorides[87] (especially the electron-rich 4,6-dimethoxybenzene-1,3-disulfonyl chloride[98]) gives the AB isomer. Anthraquinone-2,6-disulfonyl chloride gives AC and AD isomers in low yield after purification by HPLC.[99] Bis(9,10-dicyanoanthracenesulfonyl chloride) produces two isomers (AD and AC) in a ratio of 3:1, showing some degree of selectivity.[100]

γ-Cyclodextrin produces 4 regioisomers (AB, AC, AD, and AE) when treated with 2-naphthylsulfonyl chloride in pyridine which are then separated by HPLC. These are converted to bis(2-anthracenyl-9-carbonyl)-γ-cyclodextrins by reacting with anthracene carboxylate in DMSO.[101]

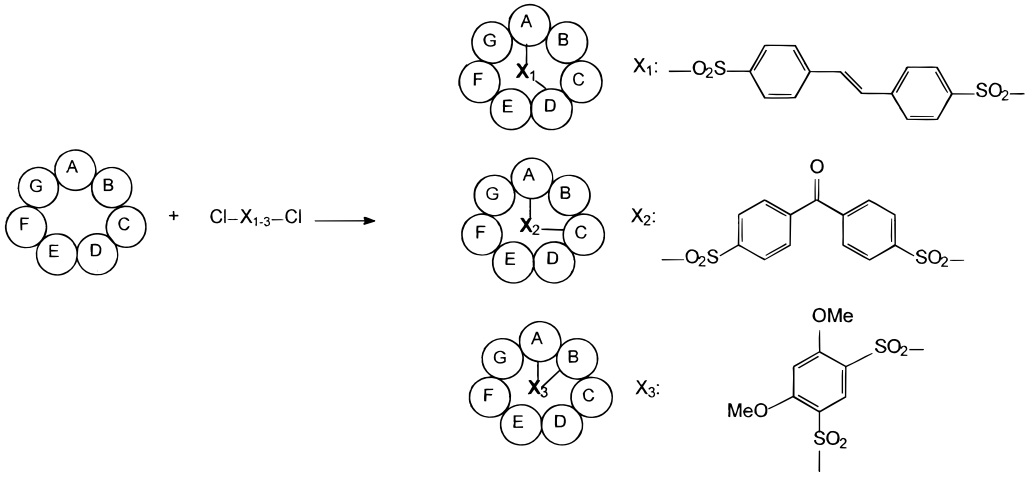

Figure 6. Use of the geometry of reagents to direct the regiospecificity in disubstitution of cyclodextrins.

Disulfonated cyclodextrins are important intermediates in the synthesis of disubstituted cyclodextrins. The strategy is to displace the ditosylates with nucleophiles in a manner similar to reactions of monotosylates (**II** in Figure 3). It is important to note that the positional isomerism (AB, AC, and AD) of the ditosylate is retained in these disubstituted derivatives. A variety of bifunctional cyclodextrins such as thio, amino, alkylamino, azido, etc.,[93,102] are obtained from disulfonated derivatives and respective reagents. Several other disubstituted cyclodextrins synthesized using this strategy have demonstrated very interesting properties. Disulfonates have been transformed to bis(alloxyphenyl)-α- or β-cyclodextrin derivatives and converted to cyclodextrin-containing copolymers in a multistep process. These copolymers are used in enatiomeric separation in supercritical fluid chromatography.[97] Dianthracenylcyclodextrins form intramolecular complexes and give regioselective photodimerization.[103,104] The bis(naphthalenesulfonate) of γ-cyclodextrin[105] behaves as a flexible host and can be used as a fluorescent sensor for a variety of organic compounds.[106] Bis[2-(1-naphthylpropyl)propanoyl]-γ-cyclodextrin synthesized from its ditosylate and (*R*)- or (*S*)-2-(1-naphthyl)propanoic acid sodium salt in DMSO discriminates between deoxycholic acid epimers.[107]

Another strategy for synthesis of substituted cyclodextrins is to convert the ditosylates to dideoxy−diiodo derivatives by a reaction with KI and then react these diiodides with appropriate nucleophiles. For example, these disulfonates are converted into diiodo derivatives which on treatment with histamine in DMF produce dideoxy−dihistamine compounds.[108] Regioisomers of diiodo and permethylated diiodo derivatives of α-, β-, and γ-cyclodextrins are obtained from suitable disulfonates.[108−110] The trehalose group has been connected to β-cyclodextrin by the reaction of diiodocyclodextrin with a cysteamine derivative of the sugar and found to have analytical and kinetic applications.[111] A large number of isomeric diamino compounds containing alkyl, imidazole, or thiophene groups have been synthesized via diiodides from the respective disulfonyl esters of cyclodextrins.[108,112−118]

Disulfonated or dihalogenated cyclodextrins react with alkanethiolates in aqueous or DMF medium to give thioethers of cyclodextrins. Thiolate ions act as good nucleophiles rather than strong bases and do not produce elimination products or 3,6-anhydro compounds. Bis(methylthio), Bis((pyridinoalkyl)-thio),[109] and bis(phenylthio)-β-cyclodextrins are prepared from ditosylates using the appropriate thiolate reagent.[86,119] Although the preparation of derivatives with two different types of alkylthio groups on a cyclodextrin molecule increases the number of regioisomers formed, these have been prepared and separated in the case of β-cyclodextrins.[120]

2.3. Trisubstitution at the 6-Position of Cyclodextrins

Esters of cyclodextrin containing three acyl or sulfonyl groups at the 6-positions are generally prepared by treating their respective acid chlorides in the presence of a base or basic solvent.[88] These reagents are highly electrophilic and attack primary or secondary hydroxyl groups of the molecule indiscriminately producing a mixture of products with variable degrees of substitution. This situation along with the complication created by regioisomers makes the separation and the purification of these products a very tedious process. Despite these problems, the literature contains well-characterized examples as triacetylated α-cyclodextrin[121] and trisulfonated β-cyclodextrin.[88,122] Trisulfonates are obtained by reacting 1 equiv of cyclodextrin with 3 equiv of sulfonyl chloride in pyridine which results in a mixture of over- and undersubstituted derivatives. These compounds are separated and purified by a lengthy process of chromatography. Trimesylates of α-[90] and γ-cyclodextrins[114] are obtained from mesyl chloride and the respective cyclodextrin in dry pyridine. In another investigation, the three regioisomers of ditosylated cyclodextrins were individually reacted with 1 equiv of *p*-toluenesulfonyl chloride. Five regioisomers of tri-6-tosyl-β-cyclodextrin thus prepared were separated and characterized.[122]

Trialkyl ethers are not obtained by displacing sulfonate groups by strong bases such as alkoxide ions due to the elimination reaction (an example of elimination is shown in Figure 4). These are directly prepared by reacting alkyl halides with cyclodextrin alkoxide ion in aqueous or DMF media resulting in a mixture of products. For example, tritritylated α-cyclodextrin is synthesized by a reaction of trityl chloride with cyclodextrin in pyridine to give a mixture of di-, tri-, and tetrasubstituted products.[123−125] This mixture of products is separated by chromatography. These examples suggest that selectivity is difficult to achieve on the basis of size because even the trityl group is not big enough to produce exclusively one derivative.[126] These tritylated cyclodextrins are used for chromatographic purposes.[127] Tritritylated α-cyclodextrin is permethylated (at all remaining hydroxyl groups) under anhydrous conditions in DMF and detritylated under mild acidic conditions. This compound is treated with sulfonyl chloride in pyridine at room temperature to make the trisulfonated derivative.[125,128] Trisubstituted cyclodextrins are more conveniently prepared by de novo synthesis from linear starting material. For example, 6-trimethylated and triacetylated α- and β cyclodextrins have been synthesized from 6′-O-methylmaltosyl fluoride and 6′-O-acetylmaltosyl fluoride respectively in phosphate buffer containing the enzyme cyclodextrin glycosyl transferase (CGTase) of *Bacillus macerans* with yield up to 42% after HPLC purification.[121,126] These de novo strategies are discussed in a previous review.[7] Selective trisilyl ethers at the 6-positions are rarely reported, although such ethers with variable degree of substitution are mentioned in the literature.[11]

Sulfonates are good leaving groups and can be replaced by nucleophiles such as substituted amines to make tris(alkylamino) or aromatic alkylamino derivatives.[128] Imidazolylalkylamines also serve as nucleophilic reagents to replace the sulfonate groups to produce triamino derivatives of cyclodextrins.[118,129] These transformations are similar to reactions of

monotosylates (**II** in Figure 3).

On treatment with aqueous sodium hydroxide, tritosylates of α- and β-cyclodextrins produce 3,6-anhydro derivatives.[88,90,122] Tris(thiobenzyl)-, tris(thiochlorobenzyl)-, and tris(thiomethoxybenzyl)-cyclodextrins are prepared from tosylates and the respective thiolates.[114] There is no example in the literature for trihalogenocyclodextrin, although the tetraiodo compound is synthesized from the doubly capped bis(sulfonate) of β-cyclodextrin and potassium iodide in DMF at high temperature.[95]

Reaction of sodium azide on permethylated-6-trimesylated cyclodextrins in DMF gives permethylated-6-triazidocyclodextrins.[125] These are also directly prepared from cyclodextrin as a mixture of mono-, di-, and triazido derivatives and Ph_3P in DMF containing sodium azide. This mixture is then separated and purified by HPLC. The triazides are reduced to triamines of cyclodextrins with triphenylphosphine in ammonia solution.[55] The amino functionalities behave as better nucleophiles than the hydroxyl groups in these bifunctional cyclodextrins. Triaminocyclodextrin derivatives are selectively converted to the corresponding amides by stearoyl or *n*-octanoyl chloride.[114]

2.4. Persubstitution at the 6-Position of Cyclodextrins

According to statistical calculations, permodification of the primary face should give 57% yield (assuming 91% yield per reaction; $0.91^6 = 0.57$) in the case of α-cyclodextrin. However, the actual yield of hexa-6-substituted cyclodextrin is often found to be much lower. Steric crowding, the geometry of the molecule, the type of inclusion complex formed, and positional isomerism decrease the yield of the product as the degree of substitution increases.[130]

Persulfonates are generally prepared directly from cyclodextrins and a large amount of sulfonyl chloride in pyridine. The good leaving group behavior of the sulfonate ion poses a major limitation in this reaction because as the reaction proceeds, the tosylated groups at the 6-position tend to change to the 3,6-anhydro form (Figure 4) even in the absence of a base at room temperature. Usually, freshly prepared sulfonated derivatives need to be used for further modification to get homogeneous products and reproducible results. During this reaction, in the presence of a base or basic solvent, the secondary face is sulfonated to some degree and leads to formation of partial 2,3-epoxy derivatives (mono, di, etc). Therefore, it is has been stated[8] that many reports of so-called pure persulfonated cyclodextrins are in reality a mixture of compounds. Despite all these complications and difficulties, many workers have reported pertosylation or -mesylation of the primary side of cyclodextrins.[18,112,131−135] Highly pure per-6-tosylated cyclodextrin derivatives for further synthetic manipulations can be obtained by a "long" method. This strategy is similar to the one described in Figure 5 (steps **I**−**IV**) except that a large excess of tosyl chloride is used in the tosylation reaction. In this procedure, the primary side of cyclodextrins is silylated and the secondary face is esterified. This product is further desilylated and tosylated on the primary side. Peracetylated-6-tosylated cyclodextrins thus obtained are used for the synthesis of other derivatives without the fear of formation of 3,6-anydro compounds.[24]

Per-6-deoxy-6-substituted cyclodextrins are easily obtained by displacing the 6-sulfonate groups with suitable nucleophiles such as halides, azides, or thiolate ions in reactions similar to **II** in Figure 3. Pertosylated cyclodextrins are treated with sodium halides in DMF to obtain perhalogenated compounds.[24] Perhalogeno-6-deoxycyclodextrins are also directly prepared by reacting cyclodextrins with triphenylphosphine and bromine or iodine in DMF.[112,136] Isolation and purification of the of the Vilsmeier−Haack reagent $[(CH_3)_2NCHBr]^+Br^-$ prior to reaction with cyclodextrin avoids severe problems of removal of triphenylphosphine oxide in this reaction.[137]

Perbromocyclodextrins were originally obtained from the reaction of methanesulfonyl bromide and cyclodextrin in DMF at elevated temperature.[138] A more soluble version of this compound is prepared by reacting per-6-silylated cyclodextrin with methyl iodide under anhydrous basic conditions to give per-(2,3-methyl-6-silyl)cyclodextrin. This compound is desilylated and then brominated by a reaction with triphenylphosphine dibromide in DMF to give per-(2,3-dimethyl-6-bromo-6-deoxy)cyclodextrin.[139] Methanesulfonyl chloride has been used for the synthesis of perchlorocyclodextrin[140] by exploiting Vilsmeier−Haack type reactions.[141,142] This is a very simple method and gives a very high yield (>90%) of the pure product. This method has been exploited in the synthesis of other derivatives of cyclodextrin.[143] Recently, perchloro- and perbromocyclodextrins have also been prepared directly by heating cyclodextrins with the Vilsmeier−Haack type reagent halomethylenemorpholinium halide in DMF. This reagent gives similar products in other aprotic solvents such as *N*-methyl-2-pyrolidinone, *N*-dimethylacetamide, *N*,*N*′-dimethylpropyleneurea, and pyridine in low yield suggesting that DMF is not involved in this reaction and halodimethyleneammonium halide is not the reactive intermediate.[144]

Per-6-deoxy-6-halogenocyclodextrins are an important class of compounds which can be used for the selective functionalization of the primary face because of their greater stability as compared to per-6-sulfonates. However, their use is limited because of their insolubility in less polar solvents. They are soluble in polar solvents such as pyridine, DMF, DMSO, or HMPA. Their solubility in nonpolar solvents can be increased by esterification of the secondary hydroxyl groups. The secondary side of halogenated cyclodextrins can be acetylated with acetic anhydride in pyridine in a very high yield for further selective functionalization (**I** in Figure 7).[143,145] A large number of cyclodextrin derivatives including percyanocyclodextrins have been obtained by displacing the bromo groups from the 6-positions as shown in Figure 7.[146]

Alkylamines react with periodocyclodextrins at a high temperature to produce secondary amines in a

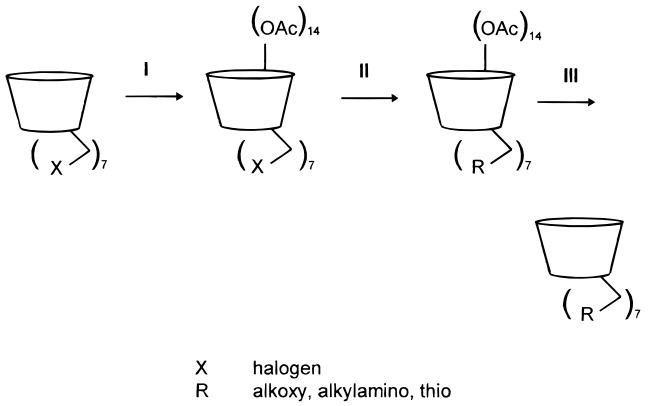

Figure 7. Strategy for the synthesis of per-6-substituted cyclodextrins by Displacement of halogens at the 6-position.

very good yield.[147] This approach is not applicable to perbromo- or perchlorocyclodextrins. Amino acid derivatives have been obtained from periodocyclodextrin in DMF by using suitable reagents in a very good yield.[148] Per-6-halogenated cyclodextrins are converted to the respective per-6-deoxycyclodextrins in a very high yield when treated $NaBH_4$ in DMSO.[149] Alkyane-[150] or aromatic[151,152] thiolate ions displace the halogen groups from the 6-positions to produce thio derivatives which have been used to study their amphiphilic and surface behavior. Sulfur-containing amino acid derivatives of cyclodextrins are similarly prepared as alkylthio compounds.[153]

In an interesting example, per-*N*-(aminoethyl)-aminocyclodextrin reacts with (2-carboxyethyl)thymine containing 1-ethyl-3-(dimethylamino)propylcarbodiimide hydrochloride in water at pH 5 to give cyclodextrins modified with 1-(2-carboxyethyl)thymine on the primary side. These appended thymine groups undergo photodimerization when exposed to UV light, and this process is reversed upon exposure of a different wavelength.[154]

Peralkylation of the primary face is a difficult process but can be achieved indirectly after many steps. The reaction scheme is similar to the one outlined for monosubstitution in Figure 5 (steps **I**−**III**, **VII**, and **VI**). The primary face of cyclodextrins is first protected by silyl groups and the secondary side is esterified. The primary face is then desilylated and reacted with an alkyl halide under strongly basic conditions to produce an alkyl ether.[17,24,130] Similarly, per-2,3-acetyl-6-iodocyclodextrin reacts with naphthyl alkoxide under anhydrous conditions in DMF to produce per-6-naphthoylcyclodextrin after hydrolysis.[155] This water-soluble compound forms a stable complex with a merocyanine dye and shows 100% transfer of energy from the naphthalene chromophore to the complexed dye.[156] It is not possible to control the selectivity by simply increasing the size of the alkyl groups, as up to *n*-nonyl functionality has been completely incorporated into all three positions.[157] Peralkylation of the primary side directly after protection of the secondary side (as in **VIII**−**X** in Figure 5) with silyl ether has not yet been reported.

A common synthetic approach for the synthesis of silyl ethers on the primary side is the treatment of *tert*-butyldimethylsilyl chloride (TBDMSCl) in pyridine with cyclodextrins at room temperature.[17,158] The major product in this reaction is the 6-substituted derivative along with minor amounts of over- and undersubstituted derivatives. An improved method of silylation in which the final product was purified by flash column chromatography has been published.[159] Silyl ethers of cyclodextrins are widely investigated because silyl groups are good protecting groups due to their ease of removal.[17,24,159] TBDMS is relatively more selective in pyridine or DMF at room temperature and proceeds to mostly the 6-positions whereas at higher temperature it starts reacting with the secondary side of cyclodextrins.[158] Trimethylsilyl chloride (TMSCl) is less discriminatory than TBDMSCl and attacks all three positions of cyclodextrins in pyridine at room temperature.[18,160]

Perazidocyclodextrins are obtained from per-6-mesitylated cyclodextrins and sodium azide in DMF in 92% yield.[161] In early reports, they are synthesized by reacting the per-6-sulfonate with the azide salt in DMF.[40,130,162] These are also synthesized from 6-chloro-6-deoxy [143] or 6-bromo-6-deoxy[163] derivatives by reacting with sodium azide in DMF at high temperature in a very high yield. Perazidocyclodextrins can be selectively alkylated, benzylated, and acylated on the secondary side.[143,163] Per(2,3-acetylated-6-azido-6-deoxy)cyclodextrin which is prepared by acetylation of the perazido compound gives a 1,3 dipolar cycloaddition product with 2-butyne dicarboxylic acid ester at high temperature in aqueous alkaline medium. This 1,2,3-triazole heterocyclic compound is obtained in 91% yield and is highly water soluble.[164]

Reduction of the azido group by Ph_3P in aqueous ammonia solution followed by treatment with dilute hydrochloric acid yields the corresponding amine salt.[143] This is a rather straightforward method for making aminocyclodextrins and other substituted amino derivatives.[143] A major drawback with this approach is the difficulty of removing Ph_3P/Ph_3PO from the final product. This is due to formation of a complex between Ph_3P/Ph_3PO with aminocyclodextrin which is not broken down immediately after acidification. A complete removal of triphenylphosphine from acidic solution of aminocyclodextrins cannot be achieved even after stirring in this medium for a long time, but its amount can be reduced to a negligible level.

Pertosylate or perhalogen derivatives are converted to 3,6-anhydrocyclodextrins when treated with strong base (Figure 4).[85,133,135,138,164] The base picks up a proton from the C-3 hydroxyl group to form an anion which on ring inversion attacks the C-6 electrophilic carbon. Tosylate and halide ions are good leaving groups, and the resulting 3,6-anhydro compound has a $^1C_4$ conformation. 3,6-Anhydrocyclodextrins contain oxygen atoms in their cavities and act as hosts for metal cations or ammonium ions according to FAB-MS investigations.[164]

Selective esterification of the primary face has not been achieved until recently when pivaloylation or diphenylacetylation was accomplished directly on this side.[165] Cyclodextrins react with diphenylacetyl or pivolyl chloride in pyridine at low temperature to

produce a mixture of esters. After purification by column chromatography, these esters were obtained in very good yields. These are also indirectly synthesized by following a sequence of silylation of the primary face, acetylation of the secondary side, and desilylation and esterification of the primary side with appropriate reagents (similar to the scheme in Figure 5, steps **I**−**III** and **VII**; R_3 = acyl group). Selective deacetylation of the final product under milder conditions gives the desired per-6-ester of cyclodextrins.[165]

3. Secondary Face Modification

The secondary side is more crowded than the primary side due to the presence of twice the number of hydroxyl groups. Hydrogen bonding between hydroxyl groups at the 2- and 3-positions makes them rigid and less flexible as compared to C-6 hydroxyl groups. All these factors make the secondary side less reactive and harder to selectively functionalize than the primary face. During the course of a reaction, as the degree of substitution increases, the secondary side becomes even more crowded. This results in steric hindrance of the incoming nucleophile which forces the attacking group toward the other face and decreases the selectivity. Positional isomerism on the secondary side further complicates the situation. This side is stated to be catalytically very important,[166,167] and therefore, modifications of this face are believed to produce valuable derivatives for catalysis, enzyme mimics, etc.

3.1. Monosubstitution at the 2-Position of Cyclodextrins

An authentic sample of mono-2-tosyl-β-cyclodextrins was first prepared using a group transfer strategy.[4] *m*-Nitrophenyl tosylate was reacted with cyclodextrin DMF/aqueous buffer at pH 10 in a low yield. This reaction proceeds via complex formation to transfer the tosyl group to the 2-position (**I** and **II** in Figure 8).[4] The tosyl group gets transferred preferentially to the 2-position due to the orientation of the reagent within the host molecule. Several

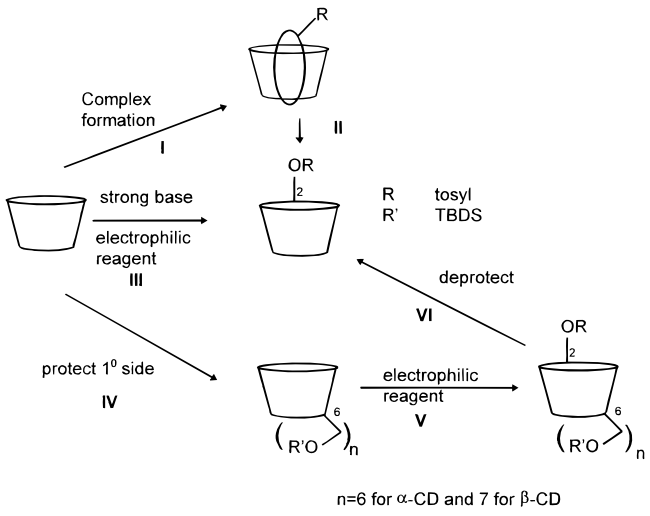

Figure 8. Strategies for modification at the 2-position of cyclodextrins.

workers have prepared mono-2-tosylate of cyclodextrins as a mixture with other isomers by using an aqueous alkaline medium or DMF and *p*-toluenesulfonyl chloride. These have been well characterized after chromatographic purification of the mixture.[20,21,168,169] Dibutyltin oxide has been used to facilitate this reaction in DMF.[170] The mono-2-mesylate of β-cyclodextrin with a mesyl group at the 6-position has also been reported.[171] Other examples of mono-2-sulfonates such as nitrobenzenesulfonyl or naphthalenesulfonyl groups, also obtained as mixtures and later purified, are mentioned in the literature.[22,26,172] The hydroxyl groups at the 2-positions are more acidic than those at the 6-position, and this feature has been exploited by using NaH as a strong base under anhydrous conditions for selective tosylation at the 2-position (**III** in Figure 8).[19] Yields in all these cases are affected by the elimination of the sulfonate group due to its good leaving behavior.[4] The elimination of the tosyl group at the 2-position by the hydroxyl groups affords the *manno*-2,3-epoxycyclodextrin (**I** in Figure 9).

Formation of an inclusion complex by the cavity of cyclodextrins also plays a very prominent role in determining the reaction site for the incoming group. An included reagent may react with the hydroxyl groups at the 2-, 3-, or 6-positions depending on the nature of the complex.[4] Some of these problems can be overcome by protection of the primary side before tosylation of the secondary side (**IV** in Figure 8). For example, per-6-silyl-mono-2-tosylcyclodextrin is synthesized by the reaction of 6-silylated cyclodextrin with tosyl chloride in THF with NaH as a base in 32% yield after purification (**V** in Figure 8).[173] An advantage of this strategy is that the reaction as well as the purification steps can be carried out in organic solvents and the desilylation can be carried out easily (**VI** in Figure 8) to yield the desired tosylate.

Exclusive esterification of the 2-position is an extremely difficult process, but some examples such as a mono-2-ester of cyclodextrin containing the ferrocene[174] or pyrrolidine oxide[175] group have been reported. These are prepared by a group transfer strategy (steps **I** and **II** in Figure 8) in which an ester is hydrolyzed (via complex formation) in the presence of the cyclodextrin. Thus, hydrolyses of (*p*-nitrophenyl)ferrocinnamic or pyrolidine acid ester with cyclodextrin in aqueous or DMSO medium at basic pH affords the corresponding cyclodextrin ester. These reactions were performed to study the rate of hydrolysis of esters in the presence of cyclodextrins, which suggested a large enhancement in the rate,[174] and the synthetic utility of these reactions is limited.

Although symmetrical alkyl ethers with substitutions at all three positions have been synthesized, very few examples of monoderivatives at the 2-position are known. It is not easy to make such derivatives due to the indiscriminate reaction of alkyl halides with the cyclodextrin alkoxide at the 2-, 3-, or 6-positions which results in a mixture of compounds. Mono-2-methyl, -ethyl, and -allyl, derivatives are prepared directly from cyclodextrins and the respective dialkyl sulfates in aqueous alkali solution, giving a low yield after purification.[176] Mono-2-propyl

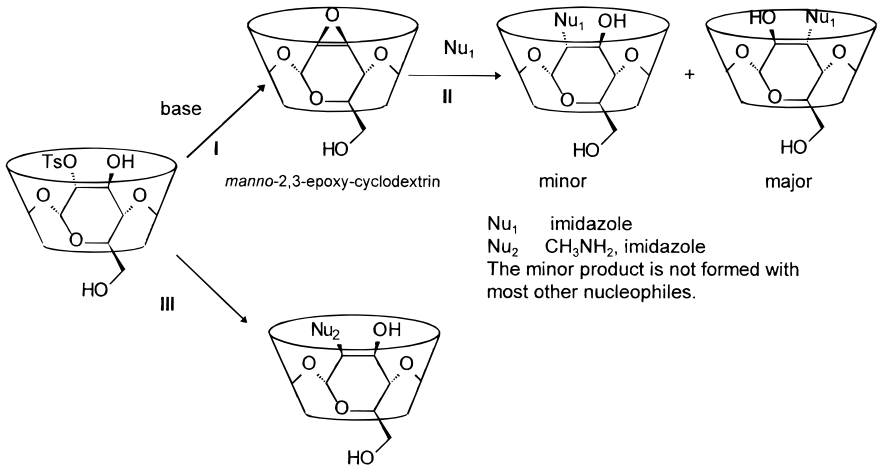

Figure 9. Reactions of mono-2-tosylcyclodextrin.

derivatives are obtained upon hydrogenation of the mono-2-allylcyclodextrins.[176] Monoalkyl ethers with terminal aromatic esters appended through amide linkage show intramolecular inclusion complex formation.[177] Mono(isoalloxazinomethyl)cyclodextrin is another example of a mono-2-ether which is obtained by exploiting the acidity of a 2-hydroxyl group by reacting with a strong base and subsequent conversion of the product to a flavin moiety after several steps.[178−180] Dicyanoanthracenylmethyl bromide attacks the 2- and 6-alkoxide ion of cyclodextrin in alkaline medium to give a mixture of products which is purified by chromatography. Comparative study of their binding properties suggests that the 2-derivative binds better than the 6-linked cyclodextrin compound.[181] Pyrolysis of solid complexes of aromatic diazo compounds with cyclodextrins and subsequent HPLC separation of the regioisomers also provide monoether derivatives at the 2-position.[70]

As mentioned earlier, the tosyl group at the 2-position is generally eliminated in the presence of bases by the hydroxyl group at the 3-position to afford the *manno*-2,3-epoxycyclodextrin (**I** in Figure 9). However, in some cases, certain bases seem to act as nucleophiles instead and bring about S_N2 type reactions (**III** in Figure 9). Mono-2-tosyl-β-cyclodextrin reacts with imidazole at 60 °C in DMF to give mono-2-imidazolyl-β-cyclodextrin in low yield. Kinetic studies suggest that 2-imidazolylcyclodextrin works as a better enzyme mimic than its 6-substituted derivative.[182] Similarly, methylamine reacts with the 2-tosyl derivative at room temperature to produce mono(2-methylamino)cyclodextrin in a very high yield (**III** in Figure 9). However, the elimination reaction takes place if this reaction is performed at high temperature to give the 2,3-epoxy derivatives (**I** in Figure 9).[183] These compounds react with CS_2 in aqueous triethylamine to give dithiocarbamate derivatives which are used as models for superoxide dismutase (SOD).[184] The reason for this change in the behavior of the base to a nucleophile in these reactions is not clear. It is important to note that the stereochemistry at the 2-position is inverted in S_N2 type reactions.[183]

Mono-2,3-epoxycyclodextrins are prepared from the respective monotosylate on the secondary side in a basic medium.[122] Two types of epoxides are produced during the reaction depending on the position of the sulfonate group on the pyranose unit. Mono-2-sulfonate is converted to *manno*-2,3-epoxycyclodextrin (**I** in Figure 9) whereas the mono-3-sulfonate gives the *allo*-2,3-epoxy derivative (**III** in Figure 10).[20,122,168,172,185] The per-6-silylated *manno*-mono-2,3-epoxy derivative is obtained from the per-6-silyl-mono-2-tosyl derivative.[173]

Mono-2-aminocyclodextrins have been synthesized from peracetylated α-, β-, or γ-cyclodextrin by cleaving the cyclodextrin ring in a concentrated acidic medium and coupling with D-glucosamine derivatives which gives final products after series of cyclization and deprotection reactions.[186] The mono-2-amino derivative was also prepared recently from perbenzoylated β-cyclodextrin by a series of reactions including selective de-O-benzoylation at one of the 2-positions, oxidation, oxime formation, and reduction of the oxime at that position to give mono-2-amino-β-cyclodextrin.[187] There is one example of mono-2-iodo-2-deoxycyclodextrin which has been obtained from permethylated cyclodextrin. In this reaction, glycosidic bond is cleaved thiolytically and the resulting product is converted to a glycal. Finally, cycloglycosidation is achieved to afford mono-2-iodo derivative in a good yield after treating a glycal with iodinium reagent.[188] Synthesis of cyclodextrin derivatives via ring cleavage and insertion of a sugar unit are treated in a previous review.[7]

3.2. Disubstitution at the 2-Position of Cyclodextrins

p-Toluenesulfonyl chloride reacts with β-cyclodextrin in DMF in the presence of dibutyltin oxide to give a mixture of regioisomers at the 2-position. This mixture is then separated and purified by chromatography.[14] 3-Nitrobenzenesulfonyl chloride reacts with α-cyclodextrins to give selectively three isomers of disulfonates at the 2-position.[22] This selectivity is attributed to formation of an inclusion complex with the reagent. Since the chlorosulfonyl group of included 3-nitrobenzenesulfonyl chloride faces toward the secondary side, it forms 2-substituted derivatives.[22] Whereas *p*-nitrobenzenesulfonyl chloride gives a mixture of 2- and 3-sulfonated products,

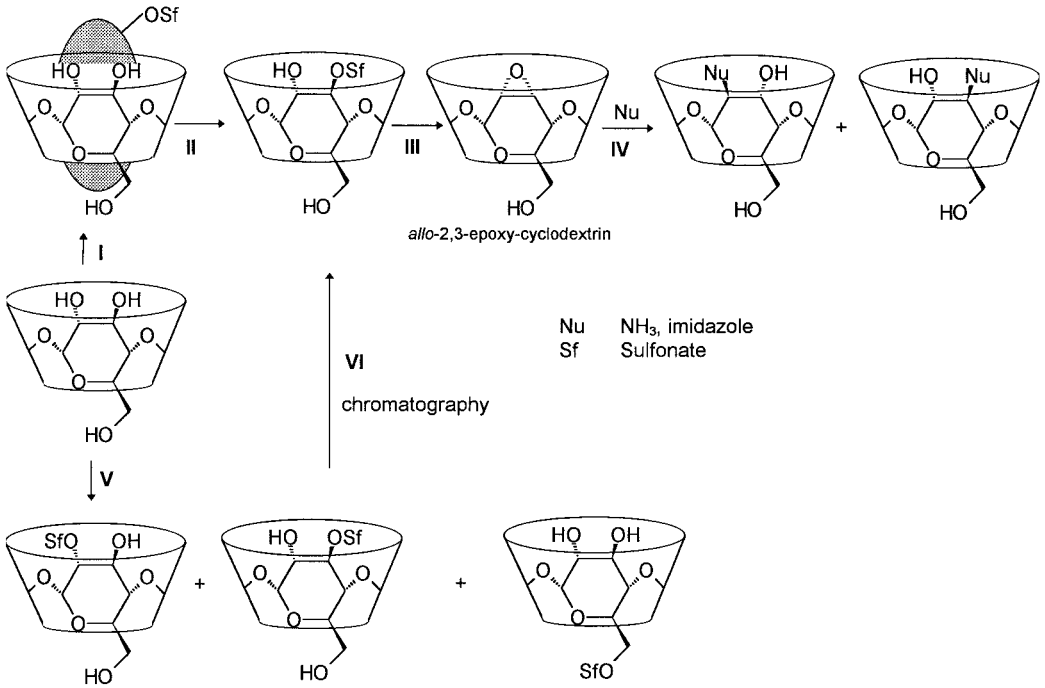

Figure 10. Strategies to access the 3-position of cyclodextrins.

α-naphthalenesulfonyl chlorides are known to give almost exclusively 2-sulfonate with very little of the 3-substituted product. *β*-Naphthalenesulfonyl chloride is used to selectively give the di-3-sulfonated product in aqueous acetonitrile solvent. When these disulfonates are treated with a base, the base picks us protons from 3-hydroxyl groups which attack C-2 electrophilic carbons to give *manno*-di-2,3-epoxy-cyclodextrins.[14,22,92] The nucleophilic ring opening of this epoxide to give substitutions at the 3-position is discussed in a later section.

Selective dialkylation is a very difficult process, and the degree of substitution varies depending upon the nature of the reagent.[189] The dibenzyl derivative of *β*-cyclodextrin has been made by protecting the primary face by TBDMS.[190]

3.3. Persubstitution at the 2-Position of Cyclodextrins

Selective perfunctionalization of the secondary side is a difficult process due to the greater reactivity of the primary hydroxyl groups. A strong base selectively produces an 2-alkoxide ion which reacts with alkyl or sulfonyl chloride.[19] This discriminatory behavior becomes less significant with increasing degree of substitution due to steric crowding, and the incoming electrophile finds the attack at the open primary hydroxyl groups more attractive as the reaction proceeds. This problem can be overcome by protecting the primary face of cyclodextrins with suitable group such as TBDMS.

Per-2-tosylation of cyclodextrin is achieved by protecting the 6-positions by silyl groups and then tosylating cyclodextrin in pyridine with tosyl chloride at elevated temperature.[23,191] Desilylation of this product provides the desired pertosylated cyclodextrin. This reaction scheme is similar to the one shown in Figure 8 (steps **IV**−**VI**) except that a large excess of tosyl chloride is used. Overall yields of the tosylated derivatives are low because of their tendency to form 2,3-epoxy derivatives in the basic medium. Per-2-sulfonates have been used as precursors for the synthesis of *manno*-per-2,3-epoxy-cyclodextrins.[191] *manno*-epoxycyclodextrins have also been synthesized from 6-silylated cyclodextrins without isolating the 2-sulfonate.[192,193] This reaction is very sensitive to moisture and should be performed carefully to get reproducible results.

The protected *manno*-per-2,3-epoxycyclodextrins undergoes a ring-opening reaction on heating with water. Deprotection of this product generates cycloaltrin which has alternating $^4C_1/^1C_4$ pyranose chairs in the ring.[194] Ring opening of the per-2,3-epoxycyclodextrin by nucleophiles gives 3-substituted cycloaltrin which is discussed in a later section.

Peralkylation is generally carried out by protecting the primary side and then reacting the hydroxyl groups with appropriate alkyl halides under basic conditions. Per-2-alkylated or benzylated cyclodextrins are made by reacting 6-silylated cyclodextrins with the respective halides under basic conditions.[24,195,196] Very few reactions of direct alkylation of unprotected cyclodextrins are known. An exception to this is the per-2-methylated cyclodextrin which is obtained by reacting methyl iodide with cyclodextrin under anhydrous condition in DMF containing NaH.[19] 2-Naphthoyloxy groups have been connected to the 2-positions of per-3-*O*-methyl-6-deoxy-*β*-cyclodextrin by reacting it with naphthoyl chloride in pyridine with the goal of investigating the fluorescence behavior.[197]

An interesting procedure to access the hydroxyl groups at the 2-position has been reported recently. This process takes advantage of the migratory property of silyl groups. Per(2,6-di-*O*-*tert*-butyldimethylsilyl)cyclodextrins react with alkyl or benzyl halides under strongly basic conditions to produce per-2-

alkylated-3,6-silylated derivatives which after desilylation afford per-2-alkylated derivatives.[198] This is a two-step reaction in which silyl groups migrate from the 2- to the 3-positions generating the 2-alkoxide ions of cyclodextrin in the first step. Alkylation of the 2-positions takes place in the second step, which gives the final product after desilylation.[198]

3.4. Monosubstitution at the 3-Position of Cyclodextrins

Direct reaction selectively at the 3-position is a very complicated and difficult process because of higher reactivity of 2- or 6-hydroxyl groups. Most modifications at the 3-position are obtained by a reaction of a nucleophile with *manno*-mono-2,3-epoxycyclodextrin (**II** in Figure 9). Tosyl chloride has been reacted indiscriminately with cyclodextrin to give the mono-3-tosylate of α- and *β*-cyclodextrins along with 2- or 6-tosylates as previously mentioned (**V** in Figure 10).[20,199−201] The products are then separated and purified by chromatographic techniques (**VI** in Figure 10). However, two reagents 2-naphthalenesulfonyl and 3-nitrobenzenesulfonyl chlorides have been shown to give a higher yield of the 3-substituted cyclodextrin.[22,202,203] Cyclodextrins are reported to form complexes with the reagent to direct the electrophile toward the hydroxyl group at either the 3-position (**I** and **II** in Figure 10) or the 2-position. In aqueous acetonitrile solution, the former reagent gives 29% yield of the 3-sulfonate and only 3.9% and 0.4% of 2- and 6-sulfonates, respectively. Dansyl chloride has been reported to be the reagent of choice for reaction with *γ*-CD to give a mixture 2- and 3-substituted products which are then chromatographically separated.[204]

Mono-3-sulfonates react with alkali thiolates in DMF to produce corresponding thio derivatives of cyclodextrins in a S_N2 type reaction.[205] These sulfonates are also converted to *allo*-mono-2,3-epoxy cyclodextrins under basic conditions (**III** in Figure 10).[22,92,203] Ring opening of the *allo*-epoxide with a nucleophile like imidazole is shown to produce a mixture of mono-2- and mono-3-imidazolyl cyclodextrin products in a ratio of 1:3 (**IV** in Figure 10).[213]

In general, nucleophiles react with *manno*-mono-2,3-epoxycyclodextrins (obtained from 2-tosylates) to give a substitution at the 3-position (**II** in Figure 9). It is important to note that the sugar unit produced by this reaction is a derivative of altrose and has $^1C_4$ conformation. Alkylamino derivatives at the 3-position are prepared by ring opening of the *manno*-2,3-epoxide.[206−208] Mono-3-aminocyclodextrins are synthesized by treating *manno*-2,3-epoxycyclodextrins with aqueous ammonia solution at room temperature.[168,209,210,220] Similarly, hydroxylamine reacts with this epoxide to give 3-hydroxylaminocyclodextrin.[211] The hydroxylamino derivative is converted to the corresponding oxime by air oxidation. The oxime is further hydrolyzed by $NaHSO_3$ to a cyclodextrin ketone.[212] However, it has been reported that imidazole attacks both the 2- and 3-positions of the *manno*-epoxide to give mono-2- and mono-3-imidazolyl derivatives, which is an exception to exclusive C-3 opening in these reactions.[213]

Thiolate ions are often reacted with the *manno*-2,3-epoxide to attach desired functional groups to the 3-position of cyclodextrins. A pyridoxamine derivative of cyclodextrins has been obtained by opening the epoxy ring using this strategy.[169,214,215] Mono-3-thiocyclodextrin is obtained by treating the epoxide with sodium thioacetate and subsequently hydrolyzing this thioester with aqueous alkaline solution.[216] These thio derivatives react with alkyl di- or tetrahalides under basic conditions to form dimers[217,218] or tetramers of cyclodextrins.[219] Cyclodextrin tetramer has a very high binding constant for arylporphyrins and metalloporphyrins,[219] whereas dimers show relatively moderate values.[217]

Various nucleophiles such as ethylenediamine, lithium azide, or anhydrous ammonia are used to open the epoxy ring of per-6-silyl-mono-2,3-epoxycyclodextrin in DMF to produce exclusively 3-substituted derivatives.[173,220] The azido group is reduced to produce the amine derivative of the protected cyclodextrin. This compound is also directly obtained by a reaction of anhydrous ammonia and the protected epoxide.[220] 6-Protected amino-α- and *β*-cyclodextrins are coupled with the phenyl ester of a dicarboxylic acid to form a protected homo or heterodimers. The products are desilylated with tetrabutylammonium flouride (TBAF) in refluxing THF to give the corresponding cyclodextrin derivatives.[220,221] The aminocyclodextrins from this reaction have been coupled with formylcalix[4]arene to cap their secondary face.[173]

A mono-3-alkylcyclodextrin is obtained by protecting the primary face with TBDMS and reacting cyclodextrin with a specific alkyl halide (*N*-methyl-4-(chloromethyl)-2-nitroaniline) in lutidine at high temperature.[25] The protected cyclodextrin is believed to complex with this reagent to direct its reactive site toward the hydroxyl group at the 3-position to give this product. This strategy cannot be generalized to access the 3-position with other electrophilic reagents because the orientation of the reagent bound to protected cyclodextrins cannot yet be predicted. A more general strategy to access mono-3-alkylcyclodextrin is the pyrolysis of solid complexes of aromatic diazo compounds followed by HPLC purification of the regioisomers formed in this reaction.[70,222] A disadvantage of this strategy is that it can be used with only those compounds whose diazo derivative is accessible.

3.5. Disubstitution at the 3-Position of Cyclodextrins

Sulfonating reagents such as 3- or 4-nitrobenzenesulfonyl and 1- or 2-naphthalenesulfonyl chloride can react with cyclodextrins to produce a mixture of sulfonated products at the 2-, 3-, or 6-positions. These products can be further separated and purified into respective isomers.[22] However, 2-naphthalenesulfonyl chloride has been reported to be the ideal reagent for synthesis of 3-substituted disulfonates.[22,92] It is believed that naphthalenesulfonyl chloride forms a complex with cyclodextrins in which sulfonyl group is directed toward 3-hydroxyl groups to give the 3-substituted product as a mixture of AC and AD

isomers. 3-Disulfonates are transformed into *allo*-di-2,3-epoxides in the presence of a base by an attack of the 2-alkoxide ion on the sulfonyl groups at the 3-position (similar to **III** in 10).[22,92]

In general, di-3-substituted cyclodextrins are prepared by a ring-opening reaction of *manno*-di-2,3-epoxide (formed from di-2-tosylates) with nucleophiles (similar to **II** in 9). The regiospecificity (AB, AC, or AD) of these products is determined by the ditosylate that is employed. *altro*-Di-3-aminocyclodextrins are formed when *manno*-di-2,3-epoxide is treated with ammonia solution at high temperature.[223,224] *manno*-Diepoxide reacts with imidazole in an imidazole−HCl buffer at pH 7.0 at high temperature to produce a mixture of di-3- and di-2-imidazolylcyclodextrins.[225] Similarly, *allo*-2,3-diepoxide has been reported to react with imidazole to yield a mixture of products. However, chromatographic techniques allow isolation and purification of the product in which the disubstitution has taken place at the 3-position.[226]

Examples of selective dialkylation at the 3-positions are not available in the literature. Reports of di-3-substituted derivatives of sulfur or other alkylamines are also very rare.

3.6. Persubstitution at the 3-Position of Cyclodextrins

The hydroxyl groups at the 3-positions are the least reactive probably due to their involvement in hydrogen bonding with 2-hydroxyl groups. The 3-position is more hindered and not easily available for further modification. Selective persulfonation at the 3-positions is still a challenge and cannot yet be achieved. If the primary side is protected, sulfonation proceeds to the 2-position hydroxyl groups.[189,191] Sulfonyl chlorides fail to react with 3-position hydroxyls with 2- and 6-positions protected by *tert*-butyldimethylsilyl groups[193] probably due to steric hindrance by the bulky silyl functionality. TBDMS has a tendency to migrate from the 2- to 3-hydroxyl groups under strongly basic conditions,[198] which also limits the attack of sulfonyl groups at 3-positions. Although the use of trimethylsilyl groups for protection at the 2- and 6-positions decreases the bulk of silyl groups in this reaction; these groups are easily hydrolyzed under neutral or acidic conditions, and the 3-tosylated cyclodextrin is not obtained.[193]

Per-2-sulfonated cyclodextrins give per-2,3-epoxycyclodextrins under basic conditions which serve as intermediates in the synthesis of *altro*-cyclodextrins (cycloaltrins). Nucleophiles attack the 3-position of these epoxides to give cycloaltrins in which each sugar unit is a derivative of altrose (similar to **II** in Figure 9). These cycloaltrins can be synthesized with the desired functional group at the 3-position of all the sugar units. β-Cycloaltramine has been obtained by reacting the *manno*-per-2,3-epoxide of cyclodextrin with ammonia solution at room temperature.[227] *manno*-Per-2,3-epoxide reacts with water when refluxed for 5 days to produce cycloaltrin as a mixture of rapidly interconverting $^1C_4/^4C_1$ conformations.[228]

4. Permodification at the 2- and 6-Positions of Cyclodextrins

Cyclodextrins are readily modified at 2- and 6-positions under rigorous conditions due to the greater reactivity of these hydroxyl groups, and this property has been used to selectively functionalize these positions without affecting the 3-positions.

In general dialkyl sulfates react with cyclodextrin in DMSO−DMF in the presence of $BaO/Ba(OH)_2$ to give 2,6-dialkylcyclodextrins.[229] The size of the alkyl group has little effect on the selectivity, and alkyl chain lengths up to 12 carbon atoms are easily incorporated at both the 2- and 6-positions. A large number of alkyl-2,6-cyclodextrin ethers ranging from methyl to *n*-dodecyl have been reported.[230−235]

Silylation of cyclodextrins proceeds to both the 2- and 6-positions in pyridine, if the reaction mixture is kept at elevated temperature.[158,236,237] Alkylsilyl reagent serves as an excellent protecting group which can easily be removed after selective modification.[17,24]

Selective per-di-2,6-sulfonic esters of cyclodextrins continue to be inaccessible, although other esters have been prepared. Electron-withdrawing groups (e.g. the tosyl group) on the primary side seem to decrease the reactivity of the hydroxyl groups at the 2-position, and pertosylation of this position becomes very difficult. The ease with which 6-sulfonates form 3,6-anhydro derivatives also complicates this reaction. Although generally organic acid chlorides react indiscriminately with cyclodextrins in pyridine and esterify all the positions of cyclodextrins,[130] per-2,6-diacyl derivatives have been synthesized by reaction with acyl chloride in pyridine.[165]

5. Permodification at All Three Positions of Cyclodextrins

All of the hydroxyl groups can be converted to ester functionalities by using suitable reagents under appropriate conditions. Organic acid chlorides attack all three positions indiscriminately in pyridine or any other solvent containing a tertiary amine as a base and produce esters of cyclodextrins. The size of the alkyl or aromatic group has little effect on the substitution pattern, and homogeneous persubstituted products are produced. Acetylation[13,18,32,131,238−240] and benzoylation[18,130,241] are achieved with acetic anhydride and benzoyl chloride, respectively, in pyridine when reactions are allowed to run for a long time. Cinnamoyl chloride also react with cyclodextrins in pyridine to give peracylated derivatives after chromatographic purification. These cinnamoylated molecules form intramolecular cyclobutane rings on irradiation to trap *N*-methylpyrrolidin-2-one (NMP) molecules and release them upon irradiation of different wavelength.[242] In some cases, esters on the primary face of the peracylated cyclodextrin thus obtained is hydrolyzed to give selectively per-2,3-diesterified product.[130]

Another strategy to produce a persubstituted cyclodextrin is to react a partially modified cyclodextrin with an appropriate reagent to attach desired groups on the remaining free hydroxyl groups. For example, selective esterification of 3-hydroxyl groups can be

accomplished by first alkylating the 2- and 6-positions of cyclodextrins.[243,244] However, this approach does not have a synthetic significance. Naphthalenecarboxylic acid ester reacts with per-2,6-methylated cyclodextrin under basic conditions to give per-3-naphthoyloxy-2,6-methylated cyclodextrin. This molecule is used to investigate energy-hopping dynamics.[245] Per-2,3-methylated cyclodextrin is reacted with a bromoacetate in DMF/NaH to attach a carboxymethyl groups at the 6-positions. These are used to attach a specific number of peptides, lipids, or other molecules to serve as supramolecular assemblies.[246] Another example is the introduction of 14 naphthoyloxy groups on the primary and secondary side of per-3-alkylated-β-cyclodextrin. This molecule shows excimer formation and energy-hopping properties.[247] Per-6-azidocyclodextrins are alkylated at the 2- and 3-positions with alkyl halides containing up to 12 carbon atoms under basic conditions. These azido groups have been reduced to amines and used in monolayer studies.[130,163,248,249]

Alkyl halides react with cyclodextrin alkoxide ions to produce the corresponding cyclodextrin ethers in very good yields.[18,131,229] Once again, increasing the size of the alkyl group has no effect on the selectivity.[243,250−252] Peralkylation of these molecules improves their solubility in organic solvent. Permethylated cyclodextrins are more water soluble than unmodified cyclodextrins[229] and widen their potential for further exploitation.

Complete silylation at all three positions is possible with trimethylsilyl chloride, although this reaction has little synthetic utility.[18,160,253] Silylation of cyclodextrins greatly enhances their solubility in various organic solvents. Cyclodextrins which have been selectively persilylated at either the primary or the secondary face are extensively used to attach desired groups at the free hydroxyl groups. These permodified cyclodextrins are easily desilylated under mild conditions to give selectively modified cyclodextrins.[17,24,201] Secondary side esterified-6-silylated cyclodextrins have been used for enantioselective separation of biologically active compounds by capillary gas chromatography.[254]

6. Conclusion

Cyclodextrins have been catapulted into prominence in the last few decades because of their catalytic,[255] enzyme mimic,[46] complexation,[256,257] drug encapsulation,[258] asymmetric,[259] and molecular recognition[260] behavior. They are also used in purification, stabilization of products, polymerization, food preservation, chemical treatment, and other industrial processes.[3] Since structural and available functional group limitations have stymied their utility, these molecules have been subjected to exhaustive synthetic manipulations and a large number of good methods have been developed for their modifications. In this review, we have presented a systematic analysis of available methods by which cyclodextrins with a desired functional group at a specific position can be synthesized. It is hoped that chemists who require a specific structure and functional groups in a cyclodextrin type molecule can decipher the chemistry underlying the method for necessary modification, study similar examples in the literature, and be able to design and execute their own synthetic methodology.

Although, as mentioned in an earlier paper in this issue,[261] it is indeed true that very few modified cyclodextrins hold a promise for industrial use, they will be found invaluable in areas where cost of the material is not an issue. Being chiral entities, selectively modified molecules[260] have potential for asymmetric synthesis, molecular recognition, molecular switches, and chiral separations.[262] Since they are expected to be nontoxic and form complexes with various flavors, perfumes, vitamins, and essential oils,[263] they have a promising future in biodegradable materials[264] and health-related products. Synthesis of artificial receptors which recognize and bind with transition metals is an important field[265] which could find application in waste treatment. Modified cyclodextrins show better complexing behavior than unmodified cyclodextrins and hold greater potential in the formulation of slow-releasing drugs.[266] Cyclodextrins are spectroscopically inert and can be converted to photosensitive molecules by attaching chromophores to them which function as chemosensors.[260] Theoretical studies of cyclodextrins[267,268] and their derivatives[269] with help of computer-generated 3D models provided information about their lipophilic,[270] hydrophobic, and complexation[271] behavior. This insight will lead to a better understanding of these molecules and help in devising new synthetic approaches and applications for these novel molecules.

7. References

(1) Szejtli, J. *Cyclodextrins and Their Inclusion Complexes*; Akadémiai Kiadó: Budapest, 1982.
(2) .Okabe, Y.; Yamamura, H.; Obe, K.-I.; Ohta, K.; Kawai, M.; Fujita, K. *J. Chem. Soc., Chem. Commun.* **1995**, 581.
(3) Szejtli, J. *Cyclodextrin Technology*, Kluwer Academic Publisher: Dordrecht, The Netherlands, 1988.
(4) Ueno, A.; Breslow, R. *Tetrahedron Lett.* **1982**, *23*, 3451.
(5) Ashton, P. R.; Ellwood, P.; Staton, I.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 80.
(6) *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Lehn, J.-M., Eds.; Vol. 3, Cyclodextrins; Szejtli, J., Osa, T., Eds.; Pergamon: Oxford, U.K., 1996.
(7) Gattuso, G.; Nepogodiev, S. A.; Stoddart, J. F. *Chem. Rev.* **1998**, *98*, 1959 (this issue).
(8) Croft, A. P.; Bartsch, R. A. *Tetrahedron* **1983**, *39*, 1417.
(9) Weisz, P. B.; Joullie, M. M.; Hunter, C. M.; Kumor, K. M.; Zhang, Z.; Levine, E.; Macarak, E.; Weiner, D.; Barnathan, E. S. *Biochem. Pharm.* **1997**, *54*, 149.
(10) Folk, J.; Weisz, P. B.; Joullie, M. M.; Li, W. W.; Ewing, W. R. *Science* **1989**, *243*, 1490.
(11) Armstrong, D. W. *U.S. Pat.* 4539399, 1985 (*Chem. Abstr.* **1985**, *103*, 226754).
(12) Jicsinszky, L.; Fenyvesi, E. Cyclodextrin Derivatives. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Lehn, J.-M., Eds.; Vol. 3, Cyclodextrins; Szejtli, J., Osa, T., Eds.; Pergamon: Oxford, U.K., 1996; p 57.
(13) Fügedi, P.; Nanasi, P. *Carbohydr. Res.* **1988**, *175*, 173.
(14) Fujita, K.; Ishizu, T.; Oshiro, K.; Obe, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2960.
(15) Hybl, A.; Rundle, R. E.; William, D. E. *J. Am. Chem. Soc.* **1965**, *87*, 2779.
(16) Saenger, W.; Noltemeyer, M.; Manor, P. C.; Himgerty, B.; Klar, B. *Bioorg. Chem.* **1976**, *5*, 187.
(17) Takeo, K.; Uemura, K.; Mitoh, H. *J. Carbohydr. Chem.* **1988**, *7*, 293.
(18) Cramer, F.; Mackensen, G.; Kensse, K. *Chem. Ber.* **1969**, *102*, 494.
(19) Rong, D.; D'Souza, V. T. *Tetrahedron Lett.* **1990**, *31*, 4275.
(20) Fujita, K.; Nagamura, S.; Imoto, T. *Tetrahedron Lett.* **1984**, *25*, 5673.

(21) Takahashi, K.; Hattori, K.; Toda, F. *Tetrahedron Lett*. **1984**, *25*, 3331.
(22) Fujita, K.; Nagamura, S.; Imoto, T.; Tahara, T. Koga, T. *J. Am. Chem. Soc.* **1985**, *107*, 3233.
(23) Coleman, A. W.; Zhang, P.; Parrot-Lopez, H.; Ling, C. C.; Miocque, M.; Mascrier, L. *Tetrahedron Lett*. **1991**, *32*, 3997.
(24) Takeo, K.; Mitoh, H.; Uemura, K. *Carbohydr. Res.* **1989**, *187*, 203.
(25) Tian, S.; Forgo, P.; D'Souza, V. T. *Tetrahedron Lett*. **1996**, *37*, 8309.
(26) Coates, J. H.; Easton, C. J.; Lincoln, S. F.; Van Eyk, S. J.; May, B. L.; William, M. L.; Brown, S. E.; Lepore, A.; Liao, M. L.; Luo, Y.; Macolino, V. Schiesser, D. S.; Whalland, C. B.; McKenzie, I. S. C. PCT Int. Apl., WO 9113100, 1991 (*Chem. Abstr*. **1992**, *117*, 29142).
(27) Siegel, B.; Pintér, A.; Breslow, R. *J. Am. Chem. Soc.* **1977**, *99*, 2309.
(28) Alm, R. S. *Acta Chem. Scand*. **1952**, *6*, 1186.
(29) French, D.; Knapp, D. W.; Pazur, J. H. *J. Am. Chem. Soc*. **1950**, *72*, 5150.
(30) Melton, L. D.; Slessor, K. N. *Carbohydr. Res.* **1971**, *18*, 29.
(31) Tanaka, M.; Kawaguchi, Y.; Niinae, T.; Shozo, T. *J. Chromatogr*. **1984**, *314*, 193.
(32) Cottaz, S.; Driguez, H. *Synthesis* **1989**, 755.
(33) Zhang, P.; Ling, C. C.; Coleman, A. W.; Parrot-Lopez, H.; Galons, H. *Tetrahedron Lett.* **1991**, *32*, 2769.
(34) Yi, G.; Bradshaw, J. S.; Rossiter, B. E.; Malik, A.; Li, W.; Lee, M. L. *J. Org. Chem*. **1993**, *58*, 4844.
(35) Petter, R. C.; Salek, J. S.; Sikorsky, C. T.; Kumaravel, G.; Lin, F.-T. *J. Am. Chem. Soc.* **1990**, *112*, 3860.
(36) Gao, X.-M.; Tong, L.-H.; Inoue, Y.; Tai, A. *Synth. Commun*. **1995**, *25*, 703.
(37) Martin, K. A.; Czarnik, A. W. *Tetrahedron Lett*. **1994**, *35*, 6781.
(38) Murakami, Y.; Kikuchi, J.; Hisaeda, Y.; Yayashida, O. *Chem. Rev*. **1996**, *96*, 721.
(39) Ueno, A.; Moriwaki, F.; Osa, T.; Hamada, F.; Murai, K. *Tetrahedron* **1987**, *43*, 1571.
(40) Tsujihara, K.; Kurita, H.; Kawazu, M. *Bull. Chem. Soc. Jpn*. **1977**, *50*, 1567.
(41) Griffiths, D. W.; Bender, M. L. *Adv. Catal.* **1973**, *54*, 625.
(42) Siegel, B. *J. Inorg. Nucl. Chem*. **1979**, *41*, 609.
(43) Fikes, L. E.; Winn, D. T.; Sweger, R. W.; Johnson, M. P.; Czarnik, A. W. *J. Am. Chem. Soc.* **1992**, *114*, 1493.
(44) Tabushi, I.; Shimizu, N. Jpn. Kokai Tokkyo Koho 78,102,985, Sept 7, 1978 (*Chem Abstr*. **1979**, *90*, 39196b).
(45) Breslow, R. *Pure Appl. Chem*. **1994**, *66*, 1573.
(46) Breslow, R. *Acc. Chem. Res*. **1995**, *28*, 146.
(47) Breslow, R., Dong, S. *Chem Rev.* **1998**, *98*, 1997 (this issue).
(48) Diblasio, B.; Galdiero, S.; Saviano, M.; Desimone, G.; Benedetti, E.; Pedone, C.; Gibbons, W. A.; Deshenaux, R.; Rizzarelli, E.; Vecchio, G. *Supramol. Chem*. **1996**, *7*, 47.
(49) Inoue, Y.; Liu, Y.; Tong, L.-H.; Shen, B.-J.; Jin, D.-S. *J. Am. Chem. Soc.* **1993**, *115*, 10637.
(50) Liu, Y.; Zhang, Y.-M.; Qi, A.-D.; Chen, R.-T.; Yamamoto, K.; Wada, T.; Inoue, Y. *J. Org. Chem*. **1997**, *62*, 1826.
(51) Park, J. W.; Choi, N. H.; Kim, J. H. *J. Phys. Chem*. **1996**, *100*, 769.
(52) Martin, K. A.; Mortello, M. A.; Sweger, R. W.; Lewis, E.; Winn, D. T.; Clary, S.; Johnson, M. P.; Czarnik, A. W. *J. Am. Chem. Soc.* **1995**, *117*, 10443.
(53) Nelles, G.; Weisser, M.; Back, R.; Wohlfart, P.; Wenz, G. Mittler-Neher, S. *J. Am. Chem. Soc.* **1996**, *118*, 5039.
(54) Sallas, F.; Leroy, P.; Marsura, A.; Nicholas, A. *Tetrahedron Lett.* **1994**, *35*, 6079.
(55) Hanessian, S.; Benalil, A.; Laferriere, C. *J. Org. Chem*. **1995**, *60*, 4786.
(56) Garciá Fernández, J. M.; Mellet, C. O.; Maciejewski, S.; Defaye, J. *J. Chem. Soc., Chem. Commun.* **1996**, 2741.
(57) Meyer, A. G.; Easton, C. J.; Lincoln, S. F.; Simpson, G. W. *Chem. Commun*. **1997**, 1517.
(58) Parrot-Lopaz, H.; Leray, E.; Coleman, A. W. *Supramol. Chem*. **1993**, *3*, 37.
(59) Ikeda, H.; Nakamura, M.; Ise, N.; Toda, F.; Ueno, A. *J. Org. Chem*. **1997**, *62*, 1411.
(60) Huff, J. B.; Bieniarz, C. *J. Org. Chem*. **1994**, *59*, 7511.
(61) Yoon, J.; Hong, S.; Martin, K. A.; Czarnik, A. W. *J. Org. Chem*. **1995**, *60*, 2792.
(62) Cornwell, M. J.; Huff, J. B.; Bieniarz, C. *Tetrahedron Lett*. **1995**, *36*, 8371.
(63) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155.
(64) Dess, D. B.; Martin, J. C. *J. Am. Chem*. **1991**, *113*, 7277.
(65) Tian, S.; D'Souza, V. T. *Tetrahedron Lett*. **1994**, *35*, 9339.
(66) Coates, J. H.; Easton, C. J.; Lincoln, S. F.; Van Eyk, S. J.; May, B. L.; Singh, P.; Stile, M. A.; William, M. L. PCT Int. Apl., WO 9113100, 1990 (*Chem. Abstr*. **1991**, *114*, 88647).
(67) Coates, J. H.; Easton, C. J.; Van Eyk, S. J.; Lincoln, S. F.; May, R. L.; Whalland, C. B.; William, M. L. *J. Chem. Soc., Chem. Commun*. **1991**, 759.
(68) Pitha, J.; Rao, C. T.; Lindberg, B.; Seffers, P. *Carbohydr. Res.* **1990**, *200*, 429.
(69) Hubbard, B. K.; Beilstein, L. A.; Heath, C. E.; Abelt, C. J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1005.
(70) Smith, S. H.; Forrest, S. M.; Williams, D. C.; Cabell, M. F.; Acquavella, M. F.; Abelt, C. J. *Carbohydr. Res.* **1992**, *230*, 289.
(71) Fujita, K.; Ejima, S.; Imoto, T. *J. Chem. Soc., Chem. Commun*. **1984**, 1277.
(72) Breslow, R.; Chung, S. *J. Am. Chem. Soc*. **1990**, *112*, 9659.
(73) Sikorski, C. T.; Petter, R. C. *Tetrahedron Lett*. **1994**, *35*, 4275.
(74) Breslow, R. *Isr. J. Chem*. **1992**, *32*, 23.
(75) Fujita, K.; Ejima, S.; Imoto, T. *J. Chem. Soc., Chem. Commun*. **1984**, 1277.
(76) Beeson, J.; Czarnik, A. W. *Bioorg. Med. Chem*. **1994**, *2* (4), 297.
(77) Tabushi, I.; Kuroda, Y.; Shimokawa, K. *J. Am. Chem. Soc.* **1979**, *101*, 1614.
(78) Kovacs, J.; Sallas, F.; Pinter, I.; Marsura, A. Jicsinszky, L. *J. Inclusion Phenom. Mol. Recognit. Chem*. **1996**, *25*, 53.
(79) Sallas, F.; Kovac, J.; Pinter, I.; Jicsinsky, L.; Marsura, A. *Tetrahedron Lett*. **1996**, *37*, 4011.
(80) Easton, C. J.; Van Eyk, S. J.; Lincoln, S. F.; May, B. L.; Papageorgiou, J.; William, M. L. *Aust. J. Chem*. **1997**, *50* (1), 9.
(81) Akiike, T.; Nagano, Y.; Yamamoto, Y.; Nakamura, A.; Ikeda, H.; Ueno, A.; Toda, F. *Chem. Lett*. **1994**, *1089*.
(82) Tian, S. Ph.D. Dissertation, University of Missouri—St. Louis, 1997; p 26.
(83) Fujita, K.; Mantsunaga, A.; Imoto, T. *J. Am. Chem. Soc.* **1984**, *106*, 5740.
(84) Fujita, K.; Yamamura, H.; Imoto, T. *J. Org. Chem*. **1985**, *50*, 4393.
(85) Ashton, P. R.; Ellwood, P.; Staton, I.; Stoddart, J. F. *J. Org. Chem*. **1991**, *56*, 7274.
(86) Fujita, K.; Matsunaga, A.; Imoto, T. *Tetrahedron Lett*. **1984**, *25*, 5533.
(87) Tabushi, I.; Nabeshima, T.; Fujita, K.; Matsunaga, A.; Imoto, T. *J. Org. Chem*. **1985**, *50*, 2638.
(88) Fujita, K.; Tahara, T.; Yamamura, H.; Imoto, T.; Koga, T.; Fujioka, T.; Mihashi, K. *J. Org. Chem*. **1990**, *55*, 877.
(89) Fujita, K.; Yamamura, H.; Imoto, T.; Fujioka, T.; Mihashi, K. *J. Org. Chem*. **1988**, *53*, 1943.
(90) Fujita, K. *NATO ASI Ser. C* **1986**, *165 (Chem. React. Org. Inorg. Constrained Syst.)*, 11 (*Chem. Abstr*. **1986**, *105*, 186600).
(91) Fujita, K.; Yamamura, H.; Mantsunaga, A.; Imoto, T.; Mihashi, K.; Fujioka, T. *J. Am. Chem. Soc.* **1986**, *108*, 4509.
(92) Fujita, K.; Tahara, T.; Imoto, T.; Koga, T. *J. Am. Chem. Soc.* **1986**, *108*, 2030.
(93) Tabushi, I.; Shimkawa, K.; Fujita, K. *Tetrahedron Lett*. **1977**, *18*, 1527.
(94) Tabushi, I.; Kuroda, Y.; Yokota, K.; Yuan, L. C. *J. Am. Chem. Soc*. **1981**, *103*, 711.
(95) Tabushi, I.; Shimokawa, K.; Shimizu, N.; shirakata, H.; Fujita, K. *J. Am. Chem. Soc.* **1976**, *98*, 7855.
(96) Tabushi, I.; Yamamura, K.; Nabeshima, T. *J. Am. Chem. Soc.* **1984**, *106*, 5267.
(97) Yi, G.; Bradshaw, J. S.; Rossiter, B. E.; Rees, S. L.; Petersson, P.; Markides, K. E.; Lee, M. L. *J. Org. Chem*. **1993**, *58*, 2561.
(98) Breslow, R.; Canary, J. W.; Varney, M.; Waddell, S. T.; Yang, D. *J. Am. Chem. Soc.*, **1990**, *112*, 5212.
(99) Aquino, A. M.; Abelt, C. J.; Berger, K, L.; Darragh, C. M.; Kelley, S. E.; Cossette, M. V. *J. Am. Chem. Soc.* **1990**, *112*, 5819.
(100) Acquavella, M. F.; Evans, M. F.; Farrah, S. W.; Nevoret, L. J.; Abelt, C. J. *J. Org. Chem*. **1994**, *59*, 2894.
(101) Ueno, A.; Moriwaki, F.; Azuma, A.; Osa, T. *J. Org. Chem*. **1989**, *54*, 295.
(102) Tabushi, I.; Yuan, L. C.; Fujita, K. *Tetrahedron Lett.* **1977**, *18*, 2503.
(103) Ueno, A.; Moriwaki, F.; Osa, T.; Hamada, F.; Murai, K. *J. Am. Chem. Soc*. **1988**, *110*, 4323.
(104) Ueno, A.; Moriwaki, F.; Azuma, A.; Osa, T. *Carbohydr. Res*. **1989**, *192*, 173.
(105) Ueno, A.; Moriwaki, F.; Azuma, A.; Osa, T. *J. Org. Chem*. **1989**, *54*, 295.
(106) Hamada, F.; Minato, S.; Osa, T.; Ueno, A. *Bull. Chem. Jpn*. **1997**, *70*, 1339.
(107) Suzuki, I.; Kato, Y.; Osa, T. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1061.
(108) Cucinotta, V.; D'Alessandro, F.; Impellizzeri, G.; Vecchio, G. *Carbohydr. Res.* **1992**, *224*, 95.
(109) Breslow, R.; Canary, J. W.; Varney, M.; Waddell, S. T.; Yang, D. *J. Am. Chem. Soc.* **1990**, *112*, 5212.
(110) Tanimoto, T.; Tanaka, M.; Yuno, T.; Koizumi, K. *Carbohydr. Res.* **1992**, *223*, 1.
(111) Cucinotta, V.; Grasso, G.; Pedotti, S.; Rizzarelli, E.; Vecchio, G. *J. Inclusion Phenom. Mol. Recognit. Chem*. **1996**, *25*, 39.
(112) Breslow, R.; Czarniecki, M. F.; Emert, J.; Hamaguchi, H. *J. Am. Chem. Soc*. **1980**, *102*, 762.
(113) Eliseev, A. V.; Yatsimirskii, J. *J. Org. Chem*. **1994**, *59*, 264.
(114) Kurita, H.; Moriya, T.; Otake, T.; Mori, H.; Morimoto, M. Eur. Pat. 447141, 1991 (*Chem. Abstr*. **1991**, *116*, 174676).

(115) Pikramenou, Z.; Johnson, K. M.; Nocera, D. G. *Tetrahedron Lett.* **1993**, *34*, 3531.
(116) Breslow, R.; Bovy, P.; Hersh, C. L. *J. Am. Chem. Soc.* **1980**, *102*, 2115.
(117) Tabushi, I.; Kuroda, Y.; Mochizuki, A. *J. Am. Chem. Soc.* **1980**, *102*, 1152.
(118) Cramer, F.; Mackensen G. *Angew. Chem.* **1966**, *78*, 641.
(119) Ueno, A.; Minato, S.; Osa, T. *Anal. Chem.* **1992**, *64*, 1154.
(120) Fujita, K.; Matsunaga, A.; Yamamura, H.; Imoto, T. *J. Org. Chem.* **1988**, *53*, 4520.
(121) Cottaz, S.; Apparu, C.; Driguez, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2235.
(122) Fujita, K.; Tahara, T.; Koga, T. *Chem. Lett.* **1989**, 821.
(123) Ling, C. C.; Coleman, A. W.; Miocque, M. *Carbohydr. Res.* **1992**, *223*, 287.
(124) Eshima, K.; Mantsushita, Y.; Hasegawa, E.; Nishide, H.; Tsuchida, E. *Chem. Lett.* **1989**, 381.
(125) Boger, J.; Brenner, D. G.; Knowles, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7630.
(126) Ueno, A.; Tomita, Y.; Osa, T. *Chem. Lett.* **1983**, 1635.
(127) Tanaka, M.; Okazaki, J.; Ikeda, H.; Shono, T. *J. Chromatogr.* **1989**, *370*, 293.
(128) Coleman, A. W.; Ling, C. C.; Miocque, M. *Angew. Chem.* **1992**, *104*, 1402; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1381.
(129) Cramer, F.; Mackensen, G. *Chem. Ber.* **1970**, *103*, 2138.
(130) Boger, R. J.; Corcoran, R. J.; Lehn, J. M. *Helv. Chim. Acta* **1978**, *61*, 2190.
(131) French, D. *Adv. Carbohydr. Chem.* **1957**, *12*, 189.
(132) Fujita, K.; Ohta, K.; Masunari, K.; Obe, K.; Yamamura, H. *Tetrahedron Lett.* **1992**, *33*, 5519.
(133) Yamamura, H.; Ezuka, T.; Kawase, Y.; Kawai, M.; Butsugan, Y.; Fujita, K. *J. Chem. Soc., Chem. Commun.* **1993**, 636.
(134) Yamamura, H.; Kawase, Y.; Kawai, M.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 585.
(135) Yamamura, H.; Fujita, K. *Chem. Pharm. Bull.* **1991**, *39*, 2505.
(136) Gadelle, A.; Defaye, J. *Angew. Chem.* **1991**, *103*, 94; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 79.
(137) Vizitiu, D.; Walkinshaw, C. S.; Gorin, B. I.; Thatcher, R. J. G. *J. Org. Chem.* **1997**, *62*, 8760.
(138) Takeo, K.; Kuge, T. *Staerke* **1974**, *26*, 11.
(139) Alker, D.; Ashton, P. R.; Harding, V. D.; Koeniger, R.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Tetrahedron Lett.* **1994**, *35*, 9091.
(140) Khan, A. R.; D'Souza, V. T. *J. Org. Chem.* **1994**, *59*, 7492.
(141) Khan, A. R. Ph.D. Dissertation, University of Missouri—St. Louis, 1994; p 104.
(142) Bohme, H.; Viehe, H. G. *Imiminium Salts in Organic Chemistry*; John Wiley & Sons: New York, 1976; Vol. 9, Parts I and II.
(143) Guillo, F.; Hamelin, B.; Jullien, L.; Canceill, J.; Lehn, J.-M.; De Robertis, L.; Driguez, H. *Bull. Soc. Chim. Fr.* **1995**, *132*, 857.
(144) Chmurski, K.; Defaye, J. *Tetrahedron Lett.* **1997**, *38*, 7365.
(145) Baer, H. H.; Shen, Y.; Gonzalez, F. S.; Berenguel, A. V.; Garcia, J. I. *Carbohydr. Res.* **1992**, *235*, 129.
(146) Gorin, B. I.; Riopelle, R. J.; Thatcher, G. R. J. *Tetrahedron Lett.* **1996**, *37*, 4647.
(147) Parazak, D. P.; Khan, A. R.; D'Souza, V. T.; Stine, K. J. *Langmuir* **1996**, *12*, 4046.
(148) Ashton, P. R.; Königer, R.; Stoddart, J. F.; Alker, D.; Harding, V. D. *J. Org. Chem.* **1996**, *61*, 903.
(149) Baer, H. H.; Berenguel, A. V. *Carbohydr. Res.* **1992**, *228*, 307.
(150) Ling, C. C.; Darcy, R.; Risse, W. *J. Chem. Soc., Chem. Commun.* **1993**, 438.
(151) Chmurski, K.; Jurczak, J.; Kasselouri, A.; Coleman, A. W. *Supramol. Chem.* **1994**, *3*, 171.
(152) Chmurski, K.; Coleman, A. W.; Jurczak, J. *J. Carbohydr. Chem.* **1996**, *15*, 787.
(153) Robertis, L. de.; Lancelon-Pin, C.; Driguez, H.; Attioui, F.; Bonaly, R.; Marsura, A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1127.
(154) Nozaki, T.; Maeda, M.; Maeda, Y.; Kitano, H. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1217.
(155) Jullien, L.; Canceill, J.; Valeur, B.; Bardez, E.; Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2438.
(156) Jullien, L.; Canceill, J.; Valeur, B.; Bardez, E.; Lefevre, J.-P.; Leh, J.-M.; Marchi-Artzner, V.; Pansu, R. *J. Am. Chem. Soc.* **1996**, *118*, 5432.
(157) Bates, P. S.; Kataky, R.; Parker, D. *J. Chem. Soc., Chem, Commun.* **1993**, 691.
(158) Fügedi, P. *Carbohydr. Res.* **1989**, *192*, 366.
(159) Pregel, M. J.; Buncel, E. *Can. J. Chem.* **1991**, *69*, 130.
(160) Beadle, J. B. *J. Chromatogr.* **1969**, *42*, 201.
(161) Tabushi, I.; Shimizu, N.; Sugimoto, T.; Shiozuka, M.; Yamamura, K. *J. Am. Chem. Soc.* **1977**, *99*, 7100.
(162) Umezawa, S.; Tatsuta, K. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 464.
(163) Parrot-Lopez, H.; Ling, C.-C.; Zhang, P.; Baszkin, A.; Abrecht, G.; Rango, C. D.; Coleman, A. W. *J. Am. Chem. Soc.* **1992**, *114*, 5479.
(164) Roehri-Stoeckel, C.; Dangles, O.; Brouillard, R. *Tetrahedron Lett.* **1997**, *38*, 1551.
(165) Santojo-Gonalez, F.; Isac-Garcia, J.; Vargas-Berenguel, A.; Robles-Diaz, R.; Calvo-Flores, F. G. *Carbohydr. Res.* **1994**, *262*, 271.
(166) D'Souza, V. T.; Bender, M. L. *Acc. Chem. Res.* **1987**, *20*, 146.
(167) VanEtten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242.
(168) Ikeda, H.; Nagano, Y.; Du, Y.; Ikeda, T.; Toda, F. *Tetrahedron Lett.* **1990**, *31*, 5045.
(169) Breslow, R.; Czarnik, A. W.; Lauer, M.; Leppkes, R.; Winkler, J.; Zimmerman, S. *J. Am. Chem. Soc.* **1986**, *108*, 1969.
(170) Murakami, T.; Harata, K.; Morimoto, S. *Tetrahedron Lett.* **1987**, *28*, 321.
(171) Fujita, K.; Ishizu, T.; Minamiura, N.; Yamamoto, T. *Chem. Lett.* **1991**, 1889.
(172) Fujita, K.; Tahara, T.; Nagamura, S.; Imoto, T.; Koga, T. *J. Org. Chem.* **1987**, *52*, 636.
(173) van Dienst, E. V.; Snellink, B. H. M.; von Piekartz, I.; Gansey, M. H. B. G.; Venema, F.; Feiters, M. C.; Nolte, R. J. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Org. Chem.* **1995**, *60*, 6537.
(174) Czarniecki, M. F.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 7771.
(175) Paton, R. M.; Kaiser, E. T. *J. Am. Chem. Soc.* **1970**, *92*, 4723.
(176) Jindrich, J.; Pitha, J.; Lindberg, B.; Seffers, P.; Harata, K. *Carbohydr. Res.* **1995**, *266*, 75.
(177) Hanessian, S.; Benalil, A.; Viet, M. T. P. *Tetrahedron* **1995**, *51*, 10131.
(178) Kitaura, Y.; Bender, M. L. *Bioorg. Chem.* **1975**, *4*, 237.
(179) D'Souza, V. T.; Rong, D. WO9217508, 1992.
(180) Rong, D.; Ye, H.; Boehlow, T. R.; D'Souza, V. T. *J. Org. Chem.* **1992**, *57*, 163.
(181) Hubbard, B. K.; Beilstein, L. A.; Heath, C. E.; Abelt, C. J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1005.
(182) Rao, K. R.; Srinivasan, T. N.; Bhanumathi, N.; Sattur, P. B. *J. Chem. Soc., Chem. Commun.* **1990**, 10.
(183) Fragoso, A.; Cao, R.; Villalonga, R. *J. Carbohydr. Res.* **1995**, *14*, 1379.
(184) Fragoso, A.; Cao, R.; D'Souza, V. T. *J. Carbohydr. Res.* **1997**, *16*, 171.
(185) Zhang, B.; Breslow, R. *J. Am. Chem. Soc.* **1993**, *115*, 9353.
(186) Sakairi, N.; Wang, L X.; Kuzuhara, H. *J. Chem. Soc., Perkin Trans.* **1995**, *4*, 437.
(187) Sakairi, N.; Kuzuhara, H.; Okamoto, T.; Yajima, M. *Bioorg. Med. Chem.* **1996**, *4*, 2187.
(188) Sakairi, N.; Kuzuhara, H. *Chem. Lett.* **1993**, 1093.
(189) Irie, T.; Fukunaga, K.; Yoshida, A.; Uekama, K.; Fales, H. M. *Pharm. Res.* **1988**, *5*, 713.
(190) Moriya, T.; Kurita, H.; Otake, T.; Mori, H.; Morimoto, M. Eur. Pat. 532026, 1993 (*Chem. Abstr.* **1993**, *119*, 30337).
(191) Coleman, A. W.; Zhang, P.; Ling, C. C.; Mahuteau, J.; Parrot-Lopez, H.; Miocque, M. *Supramol. Chem.* **1992**, 1.
(192) Khan, A. R.; Barton, L.; D'Souza, V. T. *J. Chem. Soc., Chem. Commun.* **1992**, 1112.
(193) Khan, A. R.; Barton, L.; D'Souza, V. T. *J. Org. Chem.* **1996**, *61*, 8301.
(194) Nogami, Y.; Nasu, K.; Koga, T.; Ohta, K.; Fujita, K.; Immel, S.; Lindner, H. J.; Schmitt, G. E.; Lichtenthaler, F. W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1899.
(195) Moriya, T.; Saiko, K.; Kurita, H.; Matsumoto, K.; Otake, T.; Mori, H. Mori, M.; Ueba, N.; Kunita, N. *J. Med. Chem.* **1993**, *36*, 164.
(196) König, W. A.; Icheln, D.; Runge, T.; Pfaffenberger, B.; Ludwig, P.; Hühnerfuss, H. *J. High Res. Chromatogr.* **1991**, *14*, 530.
(197) Berberan-Santos, M. N.; Canceill, J.; Brochon, J. C.; Jullien, L.; Lehn, J. M.; Pouget, J.; Tauc, P.; Valeur, B. *J. Am. Chem. Soc.* **1992**, *114*, 6427.
(198) Ashton, P. R.; Boyd, S. E.; Gattuso, G.; Hartwell, E. Y.; Koenig, R.; Spencer, N.; Stoddart, J. F. *J. Org. Chem.* **1995**, *60*, 3898.
(199) Onozuka, S.; Kojima, M.; Hattori, K.; Toda, F. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3221.
(200) Iwakura, Y.; Uno, K.; Toda, F.; Onozuka, S.; Hattori, K.; Bender, M. L. *J. Am. Chem. Soc.* **1975**, *97*, 4432.
(201) Kojima, M.; Toda, F.; Hattori, K. *Tetrahedron Lett.* **1980**, *21*, 2721.
(202) Fujita, K.; Tahara, T.; Egashira, Y.; Imoto, T.; Koga, T. *Tetrahedron Lett.* **1992**, *33*, 5385.
(203) Tahara, T.; Fujita, K.; Koga, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1409.
(204) Wang, Y.; Ikeda, T.; Ueno, A.; Toda, F. *Chem. Lett.* **1992**, 863.
(205) Seltzman, H. H. *Gov. Rep. Announce Index (U.S.)* **1988**, *89*, 935761 (*Chem. Abstr.* **1988**, *111*, 226859).
(206) Akkaya, E. V.; Czarnik, A. W. *J. Am. Chem. Soc.* **1988**, *110*, 8553.
(207) Kojima, M.; Toda, F.; Hattori, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1647.
(208) Ikeda, T.; Kojin, R.; Yoon, C. J.; Ikeda, H.; Iijima, M.; Toda, F. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1987**, *5*, 93.
(209) Fujita, K.; Egashira, Y.; Imoto, T.; Fujoka, T.; Mihashi, K.; Tahara, K.; Koga, T. *Chem. Lett.* **1989**, 429.
(210) Murakami, T.; Harata, K.; Morimoto, S. *Chem. Lett.* **1988**, 553.
(211) Mortellaro, A. M.; Czarnik, A. W. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1635.

(212) Mortellaro, M. A.; Hong, S.; Winn, D. T.; Czarnik, A. W. *Bioorg. Med. Chem. Lett.* **1994**, *4* (16), 2035.
(213) Yuan, D.-Q.; Ohta, K.; Fujita, K. *J. Chem. Soc., Chem. Commun.* **1996**, 821.
(214) Breslow, R.; Chung, S. *Tetrahedron Lett.* **1989**, *30*, 1390.
(215) Breslow, R.; Czarnik, A. W. *J. Am. Chem. Soc.* **1983**, *83*, 1390.
(216) Breslow, R.; Greenspoon, N.; Guo, T. Zarzycki, R. *J. Am. Chem. Soc.* **1989**, *111*, 8296.
(217) Jiang, T.; Sukumaran, D. K.; Soni, S.-D.; Lawrence, D. S. *J. Org. Chem.* **1994**, *59*, 5149.
(218) Jiang, T.; Lawrence, D. S. *J. Am. Chem. Soc.* **1995**, *117*, 1857.
(219) Jiang, T.; Li, M.; Lawrence, D. S. *J. Org. Chem.* **1995**, *60*, 7293.
(220) Venema, F.; Baselier, C. M.; van Dienst, E.; Ruël, B. H. M.; Feiters, M. C.; Engbersen, J. F. J.; Reinhoudt, D. N.; Nolte, R. J. M. *Tetrahedron Lett.* **1994**, *35*, 1773.
(221) Venema, F.; Baselier, C. M.; Feiters, M. C.; Nolte, R. J. M. *Tetrahedron Lett.* **1994**, *35*, 8661.
(222) McAlpine, S. R.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 2750.
(223) Fujita, K.; Egashira, Y.; Imoto, T.; Fujioka, T.; Mihashi, K.; Tahara, K.; Koga, T. *Chem. Lett.* **1989**, 429.
(224) Fujita, K.; Egashira, Y.; Imoto, T.; Fujioka, T.; Mihashi, K.; Tahara, T.; Koga, T. *Chem. Lett.* **1989**, 129.
(225) Chen, W.-H.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **1996**, *37*, 7561.
(226) Chen, W.-H.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **1997**, *38*, 4599.
(227) Khan, A. R.; Tong, W.; D'Souza, V. T. *Supramol. Chem.* **1995**, *4*, 243.
(228) Fujita, K.; Shimada, H.; Otha, K.; Nogami, Y.; Nasu, K.; Koga, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1621.
(229) Szejtli, J.; Lipták, A.; Jodál, I.; Fügedi, P.; Nánási, P.; Neszmélyi, A. *Starch/Staerke* **1980**, *32*, 165.
(230) Irie, T.; Fukunaga, K.; Pitha, J.; Uekama, K.; Fales, H. M.; Sokolowski, E. A. *Carbohydr. Res.* **1989**, *192*, 167.
(231) Bergeron, R.; Melley, M. P.; Machida, Y. *Bioorg. Chem.* **1976**, *5*, 121.
(232) Hirayama, F.; Kurihara, M. Horiuchi, Y.; Utuski, T.; Uekama, K.; Yamasaki, M. *Pharm. Res.* **1993**, *10*, 208.
(233) Armstrong, D. W.; Chang, C. *J. Agric. Food Chem.* **1990**, *38*, 1674.
(234) Armstrong, D. W.; Li, W. *Anal. Chim. Acta* **1990**, *234*, 365.
(235) Bates, P. S.; Parker, D.; Patti, A. F. *J. Chem. Soc., Perkin Trans 2* **1994**, 657.
(236) Lai, C. S. I.; Moody, G. J.; Thomas, J. D. R.; Mulligan, D. C., Stoddart, J. F.; Zarzycki, R. *J. Chem. Soc., Perkin Trans 2* **1988**, 319.
(237) Coleman, A. W.; Zhang, P.; Ling, C. C.; Parrot-Lopez, H.; Galon, H. *Carbohydr. Res.* **1992**, *224*, 307.
(238) Freudenberg, K.; Jacobi, R. *Liebigs Ann. Chem.* **1935**, *518*, 102.
(239) Freudenberg, K.; Plankenhorn, E.; Knauber, H. *Liebigs Ann. Chem.* **1947**, *558*, 1.
(240) Bernabé, M.; Martin-Lomas, M.; Penadés, S.; Köster, R.; Dahlhoff, W. V. *J. Chem. Soc., Chem. Commun.* **1985**, 1001.
(241) Ellwood, P.; Spencer. C. M.; Spencer, N.; Stoddart, J. F.; Zarzycki, R. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, *12*, 121.
(242) Arad-Yellin, R.; Green, B. S. *Nature* **1994**, *371*, 320.
(243) Keim, W.; Koehns, A.; Meltzow, W.; Roemer, H. *J. High Res. Chromatogr.* **1991**, *14*, 507.
(244) Wenz, G.; von der Bey, E.; Schmidt, L. *Angew. Chem.* **1992**, *104*, 758.
(245) Berberan-Santos, M. N.; Canceill, J.; Gratton, E.; Jullien, L.; Lehn, J.-M.; So, P.; Sutin, J.; Valeur, B. *J. Phys. Chem.* **1996**, *100*, 15.
(246) Akerfeldt, K. S.; DeGardo, W. F. *Tetrahedron Lett.* **1994**, *35*, 4489.
(247) Berberan-Santos, M. N.; Canceill, J.; Brochon, J. C.; Jullien, L.; Lehn, J.-M.; Pouget, J.; Tauc, P.; Valeur, B. *J. Am. Chem. Soc.* **1992**, *114*, 6427.
(248) Szurmai, Z.; Lipták, A.; Szejtli, J. *Staerke* **1990**, *42*, 447.
(249) Parrot-Lopez, H.; Djedaini, F.; Perly, B.; Coleman, A. W.; Galons, H.; Miocque, M. *Tetrahedron Lett.* **1990**, *31*, 1999.
(250) Bates, P. S. *Chem. Ber.* **1992**, 211.
(251) Bates, P. S.; Kataky, R.; Parker, D. *J. Chem. Soc., Chem. Commun.* **1993**, 691.
(252) Bates, P. S. *J. Chem. Soc., Chem. Commun.* **1992**, 153.
(253) Gibson, A. R.; Melton, L. D.; Slessor, K. N. *Can. J. Chem.* **1974**, *52*, 3905.
(254) Jacques, K.; Buda, W. M.; Venema, A.; Sandra, P. *J. Chromatogr. A* **1994**, *666* (1−2), 131.
(255) Breslow, R. *J. Mol. Catal.* **1994**, *91*, 161.
(256) Essalim, A.; Saint-Aman, E.; Serve, D. *Bull. Soc. Chim. Fr.* **1994**, *131*, 407.
(257) Szejtli, J. *Supramol. Chem.* **1995**, *6*, 217.
(258) Albers, E.; Mueller, B. W. *Crit. Rev. Ther. Drug Carrier Syst.* **1995**, *12*, 311.
(259) Takahashi, K.; Hattori, K. *J. Inclusion. Phenom. Mol. Recognit. Chem.* **1994**, *17*, 1.
(260) Ueno, A. *Supramol. Sci.* **1996**, *3*, 31.
(261) Szejtli, J. *Chem Rev.* **1998**, *98*, 1743 (this issue).
(262) Easton, C. J.; Lincoln, S. F. *Chem. Soc. Rev.* **1996**, *25*, 163.
(263) Allegre, M.; Deratani, A. *Agro-Food-Ind. Hi-Tech.* **1994**, *5*, 9.
(264) Sreenivasan, K. *Polym. Degrad., Stability* **1996**, *53*, 73.
(265) Raymo, F. M.; Stoddart, J. F. *Chem. Ber.* **1996**, *129*, 981.
(266) Loftsson, T.; Brewster, M. E. *J. Pharm. Sci.* **1996**, *85*, 1017.
(267) Immel, S.; Brickmann, J.; Lichtenthaler, F. W. *Liebigs Ann.* **1995**, 929.
(268) Lichtenthaler, F. W.; Immel, S. *Liebigs Ann.* **1996**, 27.
(269) Immel, S.; Lichtenthaler, F. W. *Starch/Staerke* **1996**, *48*, 225.
(270) Lichtenthaler, F. W.; Immel, S. *J. Incl. Phenom. Mol. Recognit. Chem.* **1996**, *25*, 3.
(271) Lichtenthaler, F. W.; Immel, S. *Starch/Staerke* **1996**, *48*, 145.

CR970012B