CHEMICAL REVIEWS

Volume 103, Number 11

Capped Cyclodextrins

Eric Engeldinger,* Dominique Armspach,* and Dominique Matt*

Laboratoire de Chimie Inorganique Moléculaire, Université Louis Pasteur, UMR 7513, 1 rue Blaise Pascal, 67008 Strasbourg CEDEX, France

Received May 22, 2003

Contents

1. Introduction

1.1. Toward CD-Capping

Cyclodextrins (CDs) are a family of naturally occurring, water-soluble oligosaccharides forming a bucket-shaped macrocycle and made up of α-(+)-glucopyranose units, which adopt a $^4C_1$ chair conformation. The most common members which are produced on an industrial scale contain 6, 7, or 8 units and are named α-, β-, or γ-CD, respectively (Figure 1). Macrocycles containing more than eight units have also been isolated, but because they do not form well-defined molecular cavities, their use is quite limited. As a result of their conical shape, they display a large and a narrow cavity entrance. The former, bearing the secondary hydroxyl groups, is called the secondary face, whereas the latter, bearing the primary hydroxyl groups, is referred to as the primary face. The cavity interior is lined up with the O-4 oxygen atoms, the H-3 hydrogen atoms at the secondary face, as well as the H-5 hydrogen atoms near the primary face, thus conferring it a hydrophobic character. CDs are therefore prone to form inclusion complexes with various organic compounds, which make them ideal candidates for many supramolecular applications. The utility of native CDs in these particular areas is however rather restricted. The alcohol functions are the only chemical functionalities available, and the intramolecular hydrogen network the latter form around each face provides native CDs with a rigid structure that is not easily subjected to topological changes. Thus, control over the binding strength toward organic guests having various shapes and chemical functions is far from being straightforward. Furthermore, native CDs are only soluble in water or very polar organic solvents, making their use in common organic solvents quite limited. Synthetic chemists have therefore been prompted to alter the physical and chemical properties of native CDs by either anchoring regiospecifically organic moieties onto the primary face, which leads to mono- or multiply functionalized CD-derivatives, or simply by modifying one, two, or all three types of alcohol functions present in the macrocycle in the same way (persubstitution).[1] The latter strategy (i.e., permethylation, peracylation,...) is often used to tune the solubilities of CDs in given organic solvents or to modify the binding abilities toward particular organic guests in aqueous solution. The former allows the introduction of entities providing the CD with, for instance, additional hydrophobic area or a guest-rigidifying character, in which case the grafted moiety inhibits or reduces the rotational freedom of the bound guest. It can also serve as a coordinating site for metals, which may act as

10.1021/cr030670y CCC: $44.00
Published on Web 10/17/2003

Eric Engeldinger was born in Luxembourg in 1975. He studied Chemistry at the Centre Universitaire de Luxembourg and at the Université Louis Pasteur in Strasbourg, where he obtained a Diplôme d'Etudes Approfondies in Transition Metal Chemistry and Molecular Engineering in 1999. He received his Ph.D. in 2003 under the supervision of Dr. D. Armspach and Dr. D. Matt. He currently holds a position as a research assistant in environmental medicine and analytical chemistry at the Laboratoire National de Santé in Luxembourg.

Dominique Armspach was born in Mulhouse (France) in 1965. As a former student of the Ecole Nationale Supérieure de Chimie de Mulhouse, he joined Professor J. F. Stoddart's group at the University of Birmingham in 1990, where he completed his Ph.D. degree on the synthesis of catenated cyclodextrins in 1994. He then spent two and a half years at the University of Basel as postdoctoral fellow in the Inorganic Chemistry Institute before taking up his current post as Lecturer in Organic Chemistry in Strasbourg in 1996. His present interests focus on synthetic methology, supramolecular chemistry, and organometallic chemistry associated with molecular receptors.

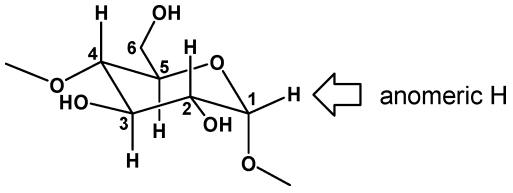
catalytic centers, either in metalloenzyme mimics or in catalysis involving phosphorus- or nitrogen-containing ligands (vide infra). Such entities, grafted onto one of the CD faces, have been termed "caps" by Breslow,[2] suggesting that the anchored moiety sits above the cavity entrance. The first "caps" were attached to only *one* glucose unit, leaving them rather flexible (flexible caps). Soon after, Tabushi introduced, for the first time, CD derivatives equipped with so-called "rigid caps".[3] In these systems, an organic fragment links two glucose units at one end of the CD, thus forming a bridge (Figure 2). Such caps, which may induce significant cavity distortions, have been believed to provide better complementarity between the receptor and bound guests than their flexible counterparts, and, in this respect, lead to higher binding constants or higher catalytic reaction rates. A useful application of these capped systems

Dominique Matt was born in Strasbourg (France) but grew up in Berlin (Germany). He studied chemistry at the Ecole Nationale Supérieure de Chimie de Strasbourg and obtained his Doctorat d'Etat in 1980 under the supervision of Dr. P. Braunstein (CNRS) at the Université Louis Pasteur. After a postdoctoral stay with Professor L. M. Venanzi at the ETH, Zurich, he spent one year at BASF–Ludwigshafen (Germany), where he developped a low-pressure process for the synthesis of acetic acid. Since 1983, he has held a position in the CNRS at the Université Louis Pasteur in Strasbourg, where he became Directeur de Recherche in 1991. His research interests are centered at the interface of coordination, organometallic, and supramolecular chemistry, with an emphasis on the study of metallo-cavitands and phosphine synthesis. He is a member of the Société Chimique de France.

concerns the selective difunctionalization of the primary and the secondary face, upon nucleophilic substitution of the cap.

1.2. Scope of This Review

In this review we will discuss all studies involving CD derivatives bearing *bridging* caps that have been described so far and which include guest complexation, catalytic reactivity, and photochemical studies. The review is composed of two main parts: the first one dealing with purely organic caps and the second one with caps comprising one or more metal centers. Where possible, comparisons in terms of guest binding strength or catalytic rates, with "flexibly capped" analogues will be made. It will be apparent that in many studies rigid capping of the CD indeed leads to a more promising outcome. Unless otherwise specified, the term "cap" designates herein a unit that bridges one of the CD entrances (type I cap).



2. Caps Bearing No Metal Centers

2.1. Enhancing the Binding Abilities by Formation of Inter-Glucose Bridges

Breslow found that introducing flexible *N*-methyl- or *N*-ethylformamido moieties onto the primary face of a β-CD (**1** and **2**) produced significant rate enhancements[2] (up to 18 times faster) for acetyl transfers from either *m*-nitrophenylacetate or *m-tert*-butylphenylacetate to one of the secondary hydroxyl

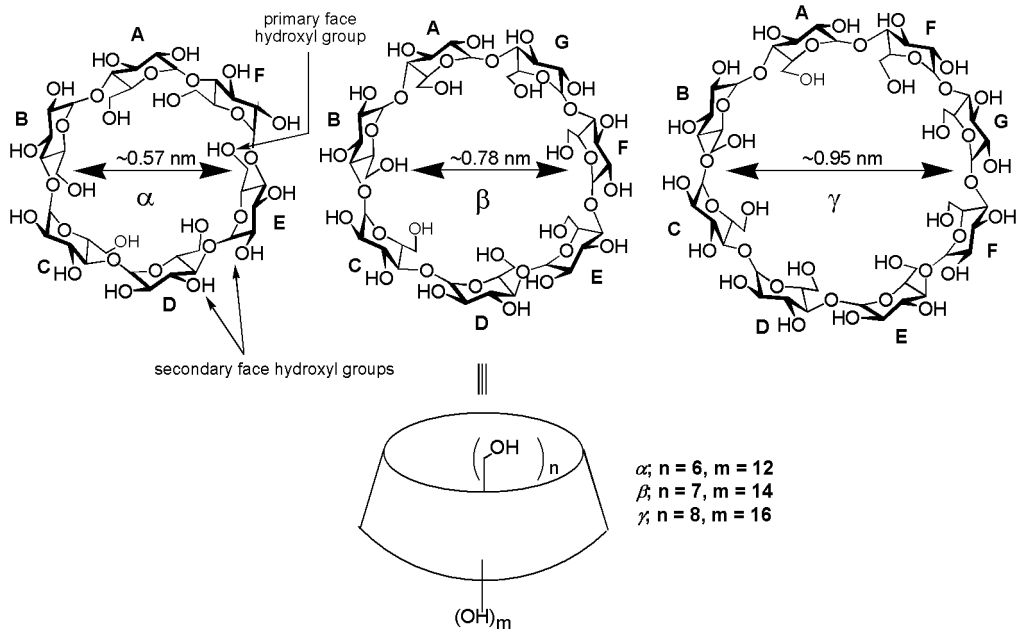


Figure 1. Schematic representations of the most commonly encountered CDs.

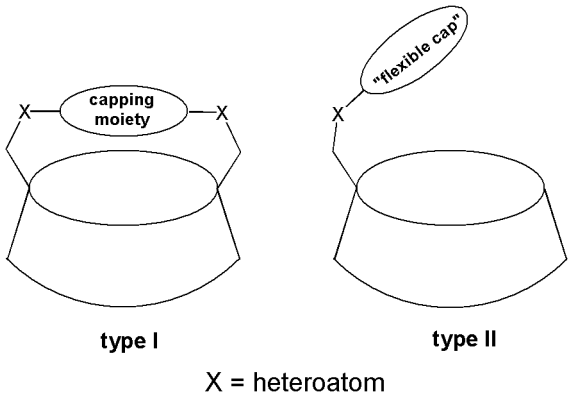
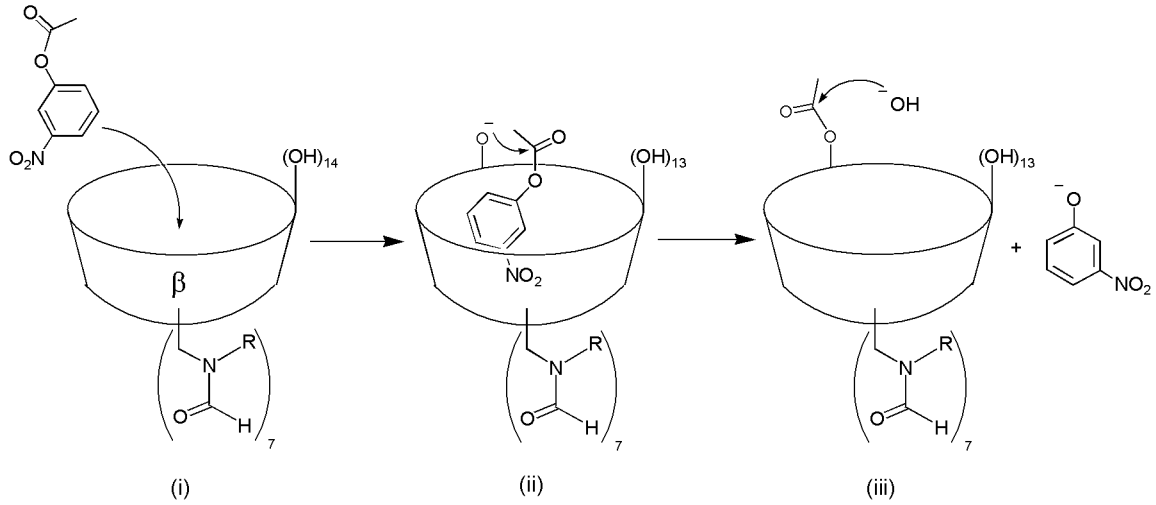


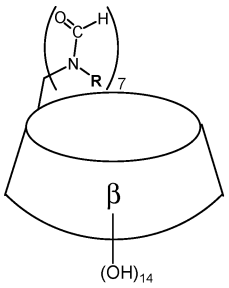
Figure 2. Schematic representations of a CD cavity equipped with a rigid (type I) or a flexible cap (type II).

groups (Scheme 1) with respect to nonmodified CDs.[4] Apparently the methyl and ethyl residues of the pendant groups provide a hydrophobic floor, which reduces rotational freedom of a bound substrate and allows better positioning of integrated functional groups than in an unmodified CD. Interestingly, the overall binding constants were not enhanced and even reduced in some cases due to a cavity that has become smaller through intrusion of the pendant group. On the other hand, competition experiments with adamantane-1-carboxylic acid (**3**), a compound known to fit well the reduced cavity size, established a more than 20 times stronger binding of the latter with **1** or **2** compared to native β-CD. In fact, both receptors, the modified and the unmodified CDs, operate in a similar fashion. The unmodified CDs were found to bind a first guest so as to provide a cavity floor before trapping a second one. The binding constant of the ternary complex turned out to be 100 times higher than the binary one, thus demonstrating the utility of a cap in **1** and **2**.

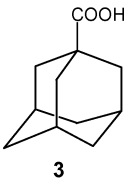
Scheme 1. Step-by-Step Representation of the CD-Catalyzed *m*-Nitophenylacetate Hydrolysis (carried out in buffered aqueous solution, pH 9−12 usually)[a]



[a] (*i*) Trapping of the substrate through the secondary face entrance, (*ii*) nucleophilic attack of a CD-alkoxide followed by the expulsion of the nitrophenolate fragment, (*iii*) regeneration of the CD-alkoxide after nucleophilic hydroxide attack on the CD-acetyl group.

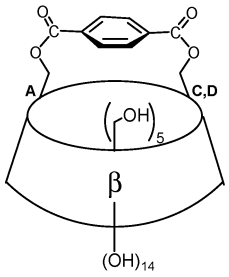


1, R = CH_3
2, R = CH_2CH_3

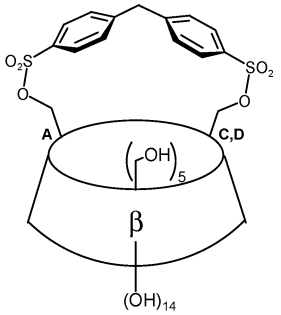


3

The concept of enhancing the hydrophobic area of the cavity, in other words, decreasing the internal surface exposed to water, was further investigated by Tabushi et al. A way to circumvent the problem of cavity intrusion by pending functional groups attached to the CD was to rigidly cap the macrocycle. This was achieved for the first time in 1976 with the synthesis of disulfonate-bridged β-CDs, **4** and **5**.[3] 1-Anilino-8-naphthalenesulfonate turned



4

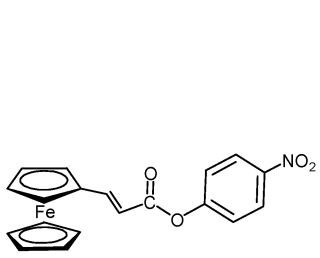


5

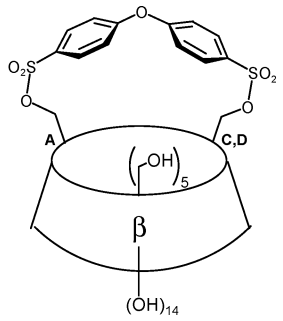
out to be bound 11 and 24 times stronger by these CDs, respectively, than by native β-CD. **4** binds adamantane-1-carboxylic acid over 3 times stronger than do Breslow's "flexibly capped" CDs **1** and **2** (although both compounds were claimed to be pure, Breslow later found[5] that they were actually mixtures of both A,C and A,D regioisomers). Soon afterward, a similarly capped α-CD was prepared by Tabushi.[6]

Fujita et al. observed a dramatic selectivity inversion in the ester hydrolysis of *m*- and *p*-nitrophenylacetate[7] when the regioisomer mixture **5**[3] was used instead of native β-CD,[8] flexibly capped **1**,[2] or various monofunctionalized β-CDs.[7] With the latter compounds, the *meta* isomer is converted ca. 5 times faster, while **5** displays a marked *para* selectivity ($k_c/K_d \cong 10$; k_c = hydrolysis rate, K_d = dissociation constant). In a detailed study, they found that **5** binds the *para* isomer much better than the *meta* isomer, but the nucleophilic attack of the alkoxide on the entrapped ester proceeds at comparable rates for both isomers. Thus, the observed *para* selectivity of **5** is essentially due to the higher binding constant of the *para* isomer. With β-CD, both isomers give rise to similar binding strengths. Hence, the observed *meta* selectivity of native β-CD and **1** arises from a shorter distance between the reacting hydroxyl group and the bound *meta* ester with respect to the bound *para* ester.

When ferrocenylacrylic ester **6** was hydrolyzed using capped **7**, the reaction rate was somewhat higher than with native β-CD[8] and over 4 times higher than with flexibly capped **1** (10^6 times the rate of the noncatalyzed reaction).[9] It is possible that



6

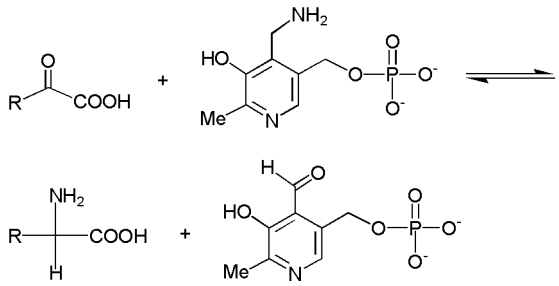


7

intrusion of the *N*-methyl residue of flexibly capped **1** into the cavity takes place during the catalytic process, lowering the energy level of the inclusion complex with respect to the unsubstituted β-CD complex. It is worth mentioning that, for the first time, these rates approached those obtained with some natural enzymes. The authors of this work also suggested that the intermediate immediately formed after nucleophilic attack on the ester carbonyl has the aryl fragment being partially lifted out of the cavity and thus less well bound than the substrate in the initial host−guest complex.

A quite interesting transaminase model was designed by Breslow et al. These enzymes transform α-ketoacids into amino acids while producing pyridoxal phosphate from pyridoxamine phosphate (Scheme 2). A pyridoxamino residue was either singly (**8**) or

Scheme 2. Enzymatic Transamination Reaction



doubly linked (**9**, **10**) to β-CD (Figure 3).[10] In the isomers **9a**, **9b**, the pyridoxamine group is *endo* oriented with respect to the cavity, while in **10a**, **10b** it points toward the exterior. A competition experiment with a mixture of phenylpyruvic acid/pyruvic acid (1:100 ratio) resulted in a 1:1 ratio of phenylalanine and alanine when using **8**, thus reflecting a 100-fold increase in reactivity for phenylpyruvic acid as a result of better binding of the aromatic guest by the CD cavity. An analogous experiment using the *endo* pair **9** produced only a 50-fold increase, while with the *exo* pair **10**, phenylpyruvic acid was only about 21 times more active. 4-*tert*-Butylphenylpyruvic (**11**) acid was found to be 150 times more reactive than phenylpyruvic acid with flexible **8**. The reactivity increase dropped to 30 in the presence of either the *endo* or the *exo* pair. This trend was

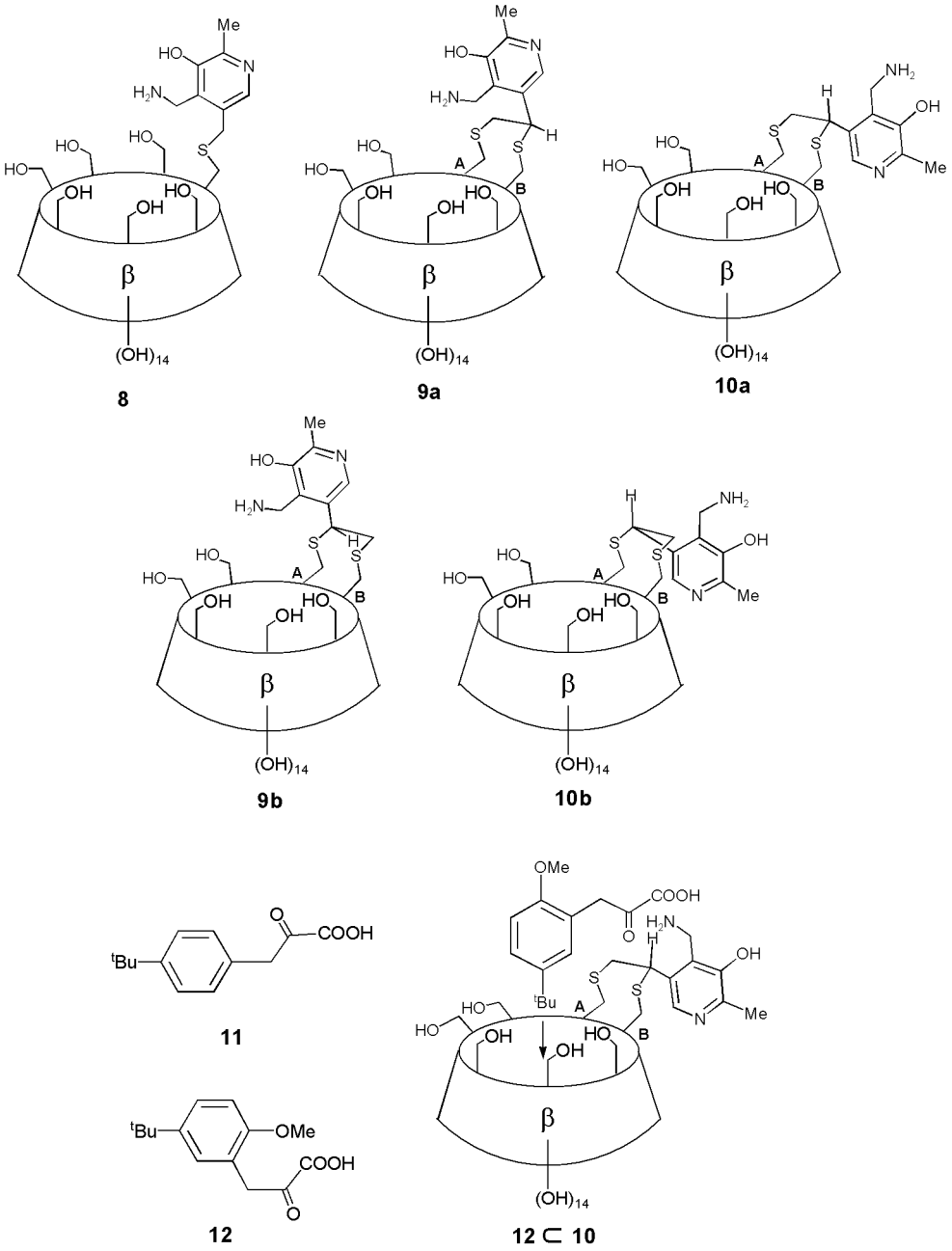
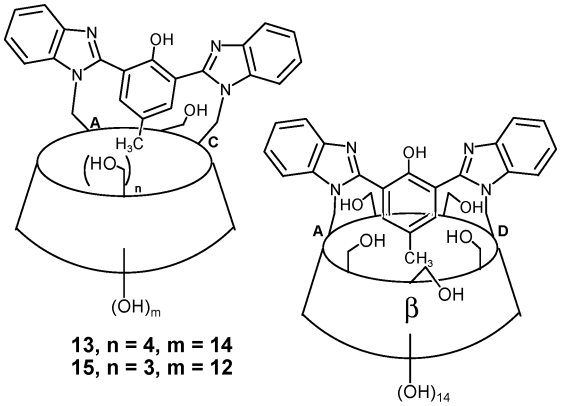


Figure 3. (Top) Flexibly linked pyridoxamine group (**8**) vs rigidly linked pyridoxamine groups, the latter of which can adopt *endo* (**9**) or *exo* (**10**) configurations. (Bottom) Favorable binding of **12** by **10** with the amino group of **10** closely positioned to the carboxylic group of **12**.

interestingly inverted when the *t*-Bu group was moved to the *meta* position and a methoxy function added. Thus, a 2-methoxy-5-*tert*-butylpyruvic acid (**12**)/pyruvic acid mixture (1:10 ratio) in the presence of the flexible transaminase revealed only a 2-fold selectivity in favor of **12**. The selectivity was only slightly enhanced when the *endo* pair was used (2.8-fold), but with the *exo* pair, it rose to 40. Apparently the high reactivity of the *exo* pair in the last experiment originates from the fact that a geometry in which the pyridoxamine group points away from the cavity and can parallel the cavity axis is required if the *t*-Bu group is in the *meta* position. Compounds **8** and **10** can of course both adopt such a configuration, but the *restricted* flexibility of **10** as a result of the double linkage strongly favors the required geometry. This study nicely illustrates how a rigidified functional group linked to a CD may efficiently induce selectivity.

In a recent study, Fujita et al. attempted to improve the resolution of NMR resonances of functionalized CDs by grafting a large aromatic moiety. The phenylenebisbenzimidazole-capped hosts **13** and **14** were prepared either from A,C or A,D-ditosylated β-CD derivatives.[11] The analogous A,C-capped α-CD derivative **15** has also been reported.[12] It turned out that all signals in the ^{1}H and ^{13}C NMR spectra, including those of the aromatic bridge, are well spread out for both compounds, thus producing a strong differentiation of all glucose units. Complete assignment was achieved by means of the COSY and NOESY spectra. The strong differentiation of the two protons in *ortho* position with respect to the methyl group in A,C-bridged **13** and **15** (>1 ppm) as



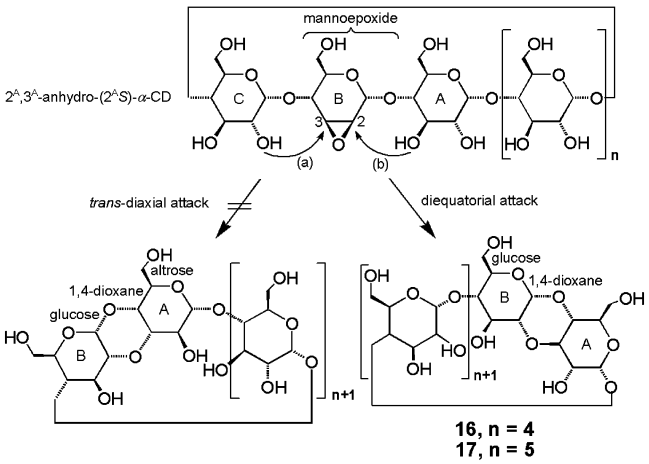
13, n = 4, m = 14
15, n = 3, m = 12

14

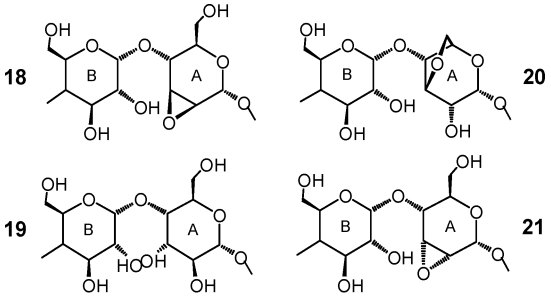
well as through-space correlations suggest that the methylphenyl residue is inclined toward the cavity interior. In **14** the methylphenyl unit is assumed to be located deeply inside the cavity, as deduced from an NMR study. Accordingly, while adamantane-1-carboxylate was moderately bound in **13** (5×10^4 M^{-1}), no inclusion complex could be detected with **14**.

Usually nucleophilic attack on 2,3-*manno*-epoxides of cyclodextrins, such as $2^A,3^A$-anhydro-(2^AS)-α-CD, occurs in the favorable *trans*-diaxial fashion on the C-3 atom, leading to the formation of an altropyranose ring. However, as found by Fujita et al., if the nucleophile is a hydroxyl from a neighboring glucose unit in α-CD, the attack takes place exclusively on the C-2 atom (diequatorial epoxide opening), giving $3^A,2^B$-anhydro-α-CD **16**,[13] which displays the *shortest* possible bridge between two adjacent glucose units. This effect was rationalized in terms of sterically hindered *trans*-diaxial ring opening. A detailed molecular dynamics simulation study[14] suggested that the product resulting from C-2 attack was indeed thermodynamically as well as kinetically favored as a result of its more rigid structure compared to that displayed by the hypothetical product resulting from the diaxial attack. An X-ray study confirmed the theoretical results[14] and gave evidence for the less pronounced conical shape of the macrocycle **16** (tilt angles for the $3^A,2^B$-anhydro ring system $\tau \approx 60°$ vs $>100°$ for nondistorted CDs[15]) (Scheme 3).

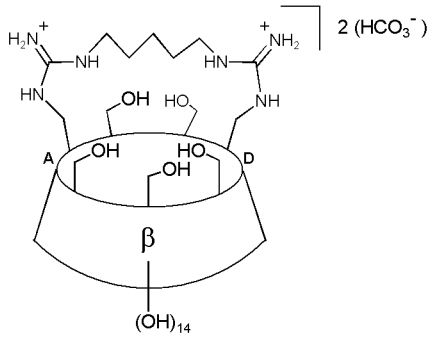
Scheme 3. Two Possible Epoxide Ring-Opening Pathways



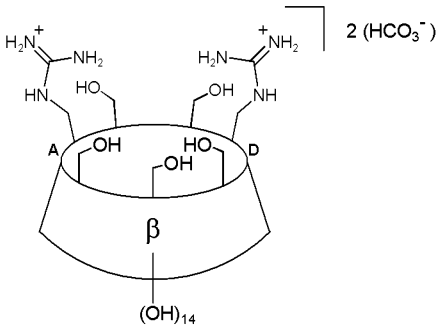
16, n = 4
17, n = 5



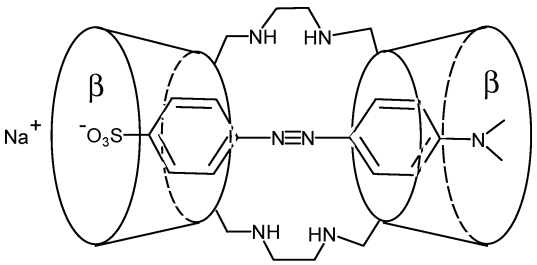
A and B units only



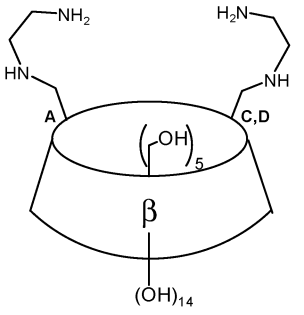
22a



22b



methylorange ⊂ 23



24

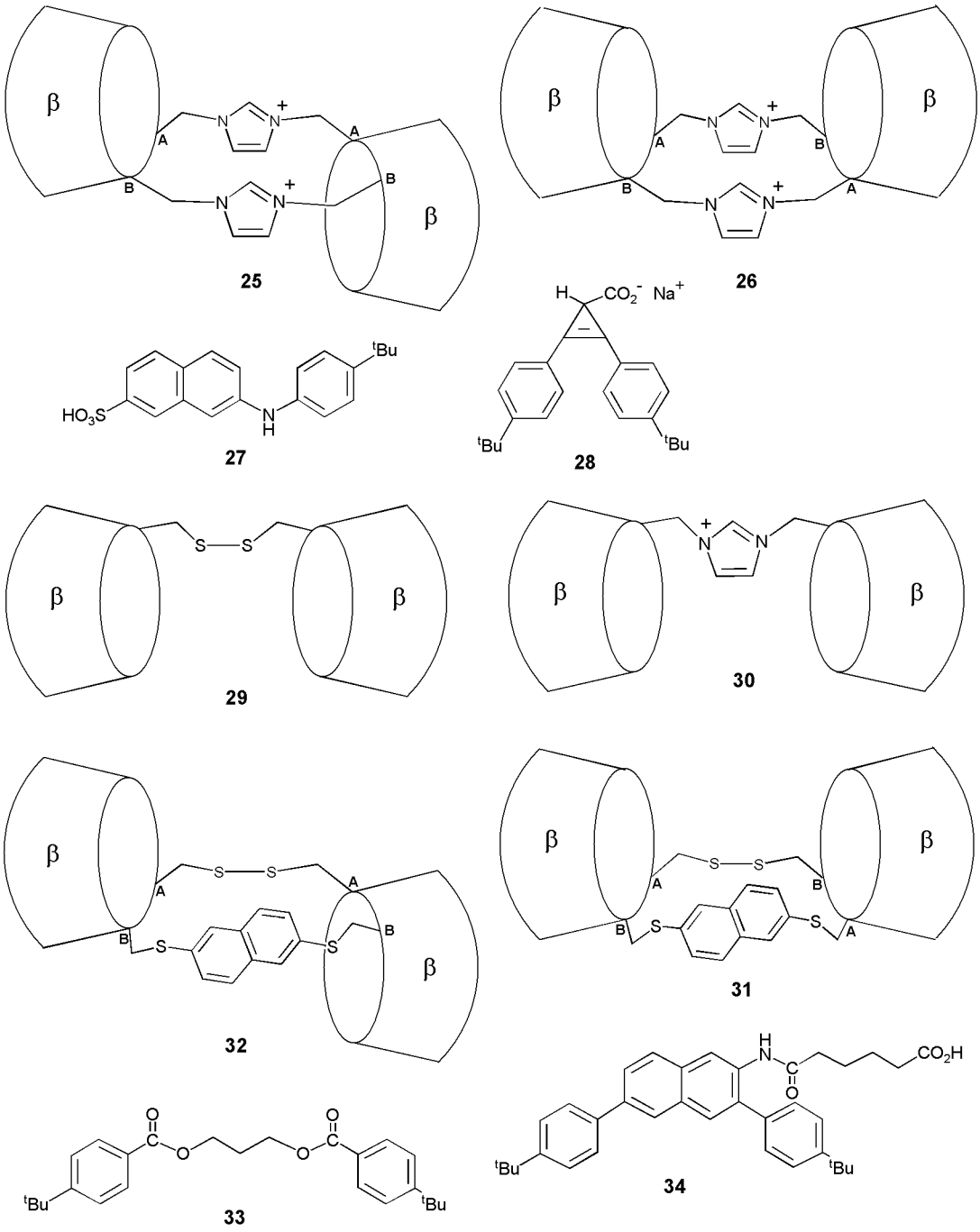


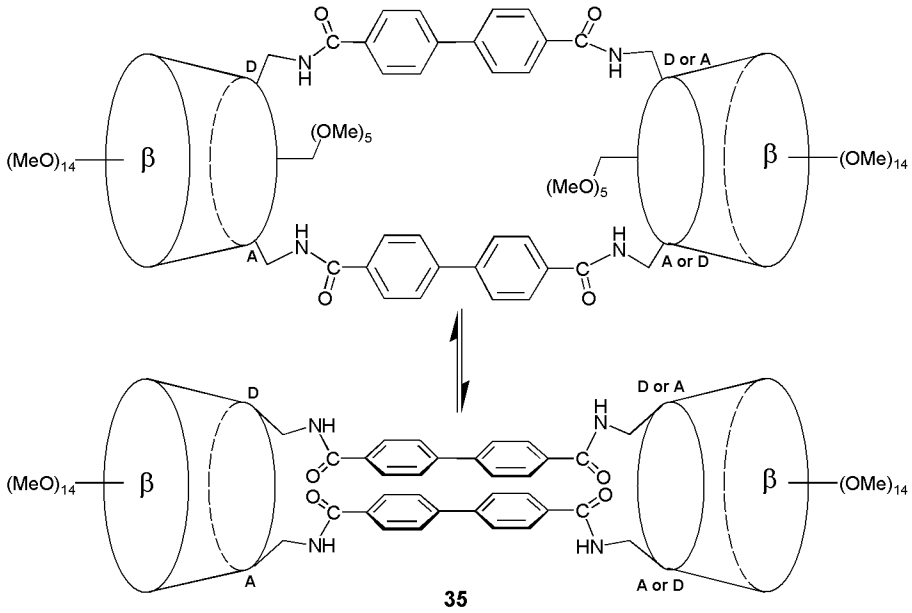
Figure 4. Singly linked and both aversive and occlusive doubly linked CD-dimers, together with some suitably shaped guest molecules.

Interestingly, a study on the binding strengths of methylorange by a series of β-CDs having a distorted cavity, **17**−**21**, revealed that the only host leading to a binding constant as well as binding free energy higher (up to 2.75 times higher at 10°C) than those of the parent β-CD is **17**, which contains an additional interglucosidic ether function.[16] It was assumed that the slightly smaller cavity size of **17** with respect to the other hosts leads to a significant gain in free enthalpy upon inclusion of methylorange.

Aiming at the encapsulation, and hence blocking of phosphotyrosine functionalities located on protein surfaces, Smith et al. synthesized a β-CD derivative, A,D-bridged with a doubly positively charged cap, **22a**.[17] It was anticipated that the rigid cap is able to bind phosphotyrosine more strongly than the "flexibly capped" analogue **22b**.[18]

Ligase-type enzyme models are suitable for either simultaneous binding of two functionalized substrates or binding of ditopic ones. "Double recognition" may be achieved with molecules having two receptor units. This feature has been successfully realized by Tabushi in the so-called *duplex cyclodextrin* **23**,[19] which comprises two β-CDs linked by ethylene diamino groups at A,D or A,C positions (note that starting from a mixture of A,D- and A,C-capped β-CDs **4**, six different regioisomers of the duplex cyclodextrin were obtained). Fluorescence studies showed that **23** binds methylorange 6 times more tightly than does the β-CD tetramine **24**, thus

Scheme 4. Equilibrium (occlusive and aversive isomer mixture) between the "Open" and "Stacked" Conformations of 35



demonstrating the simultaneous encapsulation of the guest by the double cavity system.

Doubly linked CD dimers have also been reported by Breslow et al. In an attempt to improve the binding of CDs toward certain guests, as well as to overcome flexibility problems associated with some inclusion complexes, they synthesized occlusive CD-dimers linked in A,B positions, along with their aversive counterparts (Figure 4).[20] It has been clearly established that **25**, because of its aversive character, cannot bind cooperatively ditopic guests such as **27**, unlike the occlusive dimer **26**, which leads to stronger overall binding. Nevertheless, the binding constants for guests **27** or **28** turned out to be significantly lower than those observed with singly linked dimers **29** and **30**. No explanation has been found yet for these lower affinities. However, when dimer **31**, which bears neutral linkers of different lengths, was used to entrap a substrate having an appropriate shape such as **33**, a binding constant of 10^{10} M^{-1} was found[21] using a competition fluorescence method. Even stronger binding was observed for **34**, to such an extent that the exact constant value could not be determined by the same competition method. A lower limit has been fixed at 4×10^{11} M^{-1}, a value that lies in the range of very strong antigen−antibody complexes. The aversive **32**, as expected, did not produce outstanding binding abilities. This study illustrates that recognition of a substrate with appropriate geometry can be dramatically improved if the host possesses a rigid structure, induced by double linkage.

The binding abilities of another doubly bridged CD-dimer (**35**, Scheme 4) as well as a CD-trimer (**36**, Figure 5) have been studied by Kuroda et al.[22] Their synthesis was achieved by connecting A- and D-substituted, permethylated β-CD derivatives in a head-to-head fashion with two biphenyl linkers. The isomers resulting from each coupling reaction, i.e., (A-bp-A)(D-bp-D) and (A-bp-D)$_2$ (**35**) and (A-bp-A)(D-bp-A)(D-bp-D) and (A-bp-D)$_3$ (**36**), could not be separated and were thus used as mixtures. Fluorescence studies carried out with **35** in water gave rise to excimer emission at room temperature. Upon heating to 348 K, the intensity of the latter dropped to 1/10 of the initial value, which suggests the presence in solution of the equilibrium drawn in Scheme 4. Support for this assumption came from the observation that in organic solution (i.e., MeOH or $CHCl_3$) the excimer emission is canceled and the fluorescence of **35** resembles that of the singly linked dimer **37**. Hence, the driving force for the stacking behavior of the biphenyl moieties seems to be mainly due to the hydrophilic character of the medium. In keeping with this feature, **35** binds the anthracene derivative **38** less strongly than its singly linked counterpart **37** ($K = 5200$ vs 8600 M^{-1}, respectively). The dislocation of the stacked biphenyl groups prior to guest-encapsulation takes up an extra amount of energy. The tightest binding, being also entropically favored over the one into **37** as a result of the double connection between CD receptors, occurred with the trimeric host **36** ($K = 27000$ M^{-1}). This property was also attributed to the presence of an additional binding site in this trimer.

A novel synthetic strategy has recently been reported by Sinaÿ et al. for the preparation of a doubly linked CD dimer, **39**.[23] Thus, the α-CD derivative **39a** (Scheme 5) was first converted into the double CD **39b** by olefin metathesis. Subsequent hydrogenation, followed by removal of the TBDMS groups and alkylation of the resulting alcohol groups, afforded diolefin **39c**. Ring-closing metathesis, followed by double-bond hydrogenation and cleavage of the benzyl groups, led to dimer **39** in a fairly good overall yield (49%).

An alternative to the generally used aromatic caps has been reported by Cucinotta et al., who prepared the trehalose-capped β-CD derivative, **40** (21% yield).[24,25] The use of the trehalose moiety provides an enhancement of the chiral and hydrophobic inner-cavity environment. ROESY and circular dichroism

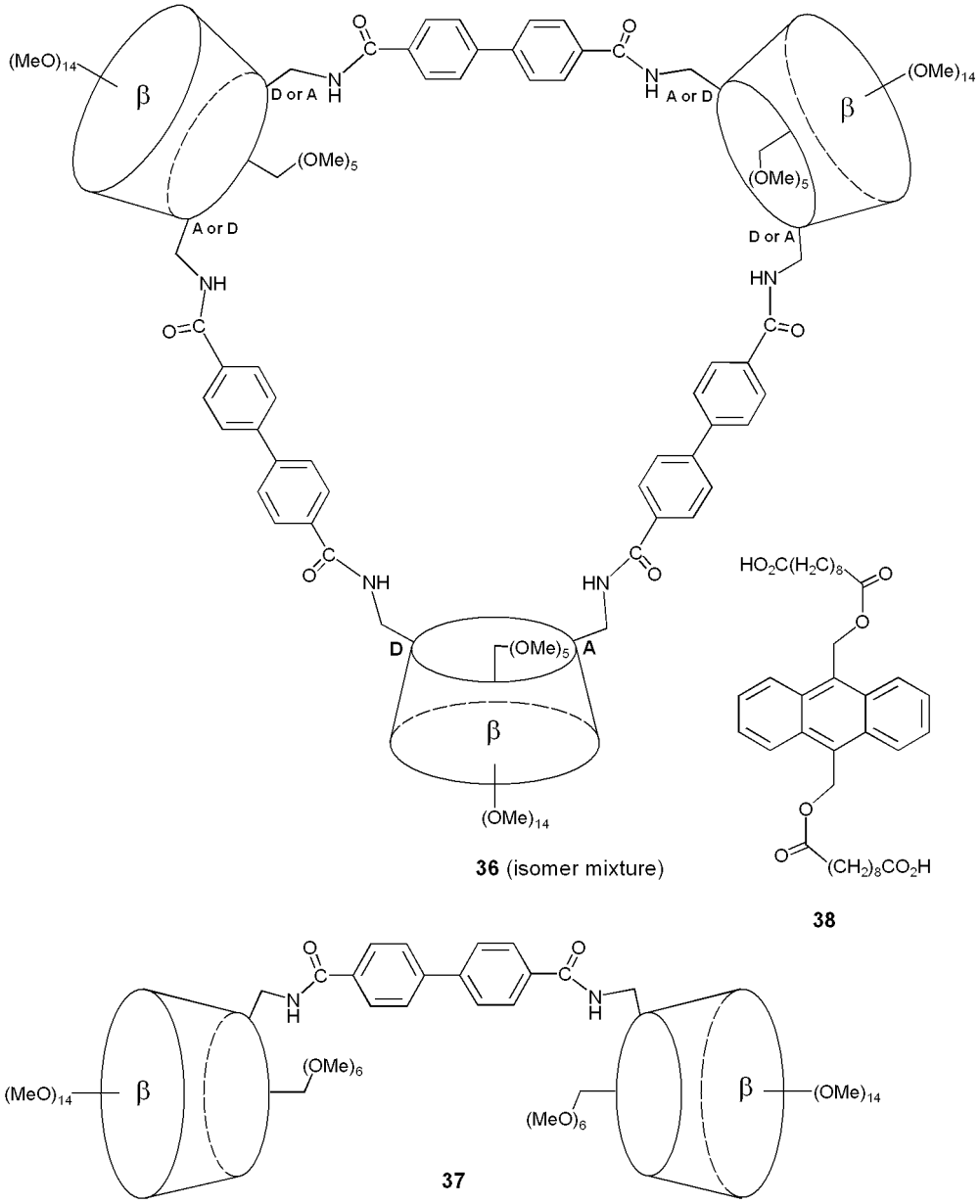


Figure 5. Circular CD-trimer (**36**) and singly linked CD-dimer (**37**), the former of which binds anthracene-derivative **38** over 3 times as strong as the latter.

experiments show that at basic pH (so as to maintain the amino groups unprotonated) the plane of an included anthraquino-2-sulfonate (**41**) anion parallels the CD axis, with the sulfonate group pointing outside the cavity. When the inclusion takes place at slightly acidic pH, the protonated amino groups give rise to electrostatic interactions with the negatively charged SO_3^- function, thus leading to an upside-down arrangement of the guest with respect to the previous one. Interestingly, this binding mode leads to an almost 4.5 times higher binding constant than the purely hydrophobic binding mode and a 6-fold binding enhancement with respect to unsubstituted β-CD. Fujita et al. also described the synthesis of a series of similarly designed, so-called molecular sugar bowls.[26] Thus, compounds **42**−**44** were obtained in moderate yields (13−16%) starting from A,C-, A,D-, and A,E-functionalized γ-CD's. **44** displays C_2-symmetry, while **42**, with the shortest N···N separation, shows the strongest asymmetry. No studies dealing with inclusion complexes have been reported to date.

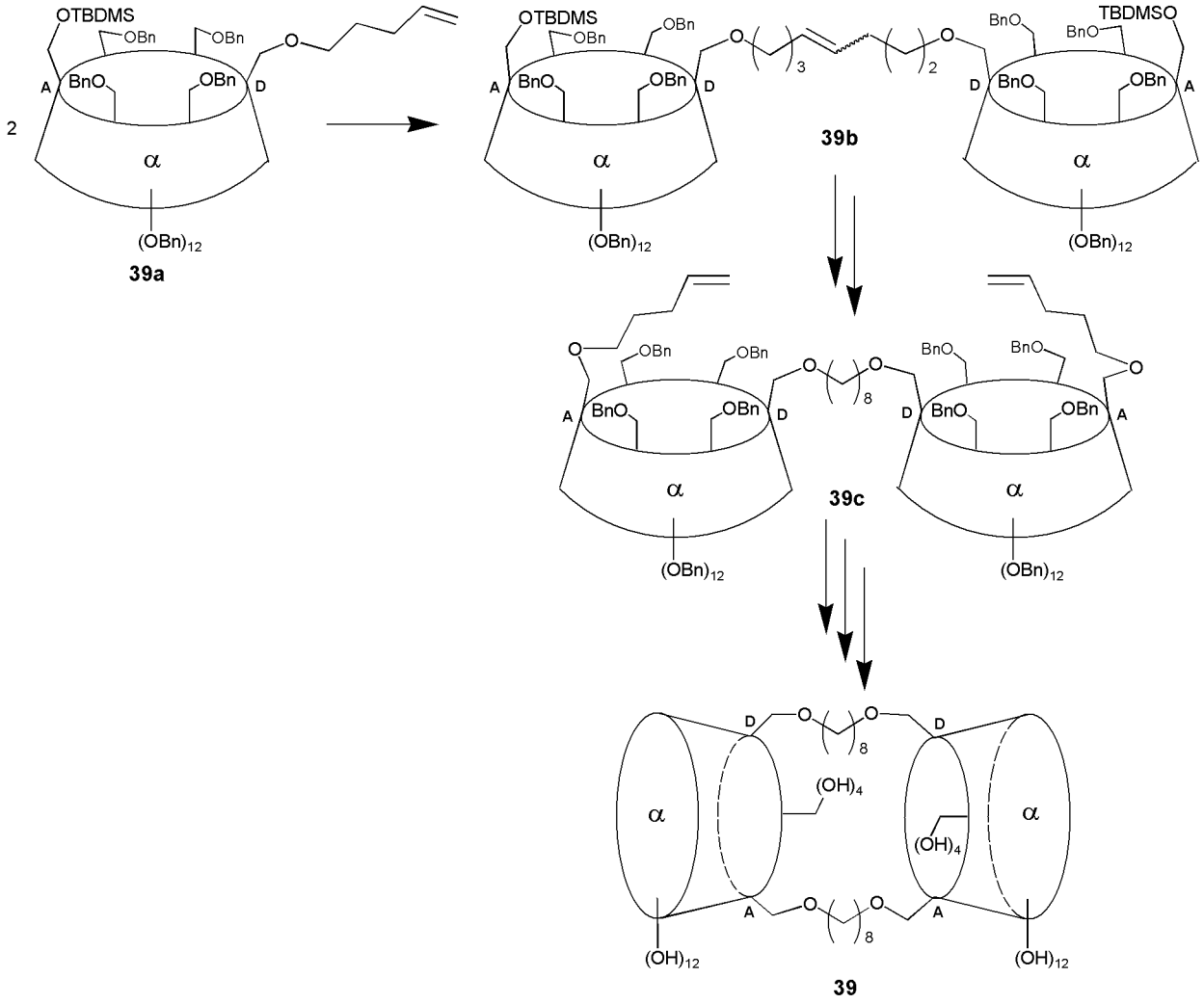
Chiral bridges derived from amino acids have also been used to cap CDs. Thus, Marchelli et al. reacted an A,D-diamino-β-CD derivative with *N*,*N*′-3,6,9-trioxaundecanoyl-(L,L)-bis-alanine to produce **45** in 17% yield.[27] The chiral recognition properties of **45** have been tested in capillary electrophoresis. Mixtures of D- and L-dansyl-glutamic as well as D- and L-dansyl-aspartic acid have been successfully separated.

2.2. CD-Difunctionalization through Regioselective Capping of the Primary and the Secondary Face

2.2.1. Primary Face Functionalization

As mentioned above, Tabushi's first "rigidly capped" β-CDs turned out to be a mixture of A,C and A,D derivatives. It became quickly apparent that pure regioisomers were necessary for catalytic applica-

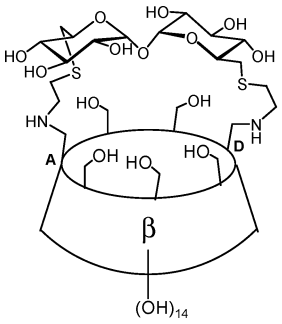
Scheme 5. Synthesis of a Doubly Linked CD-Dimer via Ring-Closing Metathesis



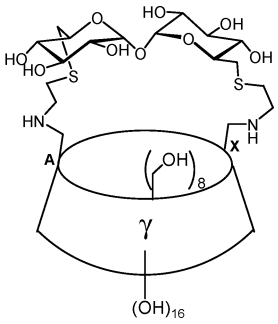
tions. Such compounds were first obtained using benzophenone-3,3′-disulfonyl and *trans*-stilbene-4,4′-disulfonyl fragments, the length and rigidity of which are optimal for A,C and A,D capping, respectively (**46**, 40% preparative yield; **47**, 20% preparative yield).[28,29] Reaction of a second capping reagent with **46** afforded the doubly capped species **48**, whereas **47** underwent no second capping, polymeric material being formed instead. These observations supported the structures proposed for **46** and **47**. Furthermore, the reaction with bis(phenylsulfonyl) dichloride also proved to be regioselective,[30] giving A,D-substituted **49** in a preparative yield of 17.5%. Interestingly, the regioselectivities were not affected by the concentration of reactants, except when *trans*-stilbene-4,4′-disulfonyl chloride was used (the A,C/A,D ratio approaches 1 at higher concentrations). A,B-Capped **50** was obtained from β-CD (in excess) in 40% preparative yield using *m*-benzenedisulfonyl chloride as capping reagent.[31] ^{13}C NMR spectroscopy proved to be a useful tool for the assignment of the A,B regiochemistry. Thus, the C-1, C-4, and C-6 signals of the A- and B-substituted glucose units undergo significant shifts with respect to the corresponding signals in the unsubstituted units. Such an effect, improperly called the remote substituent effect, was not observed in A,C- and A,D-capped CDs. It should be mentioned though that Breslow only managed to synthesize **50** in about 5% yield.[10] Apparently partial decomposition resulting from the lability of the sulfonate-ester groups occurred. Introduction of stabilizing methoxy groups on the capping reagent raised the yield to about 12%. Treatment of the same capping reagent with a β-CD in which the secondary face was permethylated gave only 3.5% of the corresponding A,B derivative **51**.[32]

Three modified versions of Tabushi's A,C-bridged **46** were obtained by Bradshaw et al. as intermediates during the synthesis of CD-oligosiloxane copolymers.[33] They synthesized the secondary face-permethylated (**52**) and perpentylated (**53**) β-CDs, in ca. 25% preparative yields. Pure **54**, a related α-CD derivative, was obtained in 16% yield.

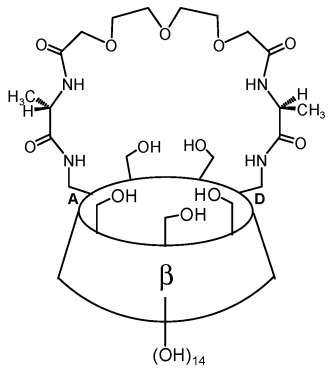
Tabushi et al. also reported the synthesis of the β-CD derivative **55** (20% yield) (Scheme 6), which is bridged with a dissymmetrical cap and was used for the subsequent introduction (vide infra) of two different functional groups.[34] No data as regards the regioselectivity of the capping reagent or the regioisomer obtained were given though. Upon oxidation of **55**, the nitroso compound **56** was formed. Treatment of the latter with an excess of NaN_3, followed by reaction with an excess of sodium *p-tert*-butylthiophenolate, afforded the unsymmetrically substi-



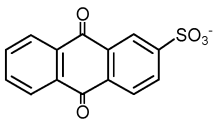
40



42, X = C
43, X = D
44, X = E



45



41

tuted compound **57** in 59% yield. It was shown that the sulfonate group *para* to the *N*-oxide moiety reacted much faster with N_3^- than the other sulfonate (Scheme 6).

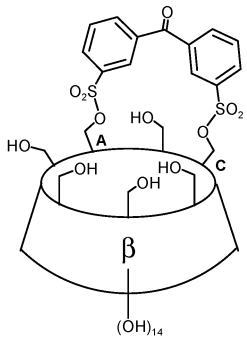
Applying the capping reaction to monosubstituted CDs may lead to regioselective trifunctionalization. Fujita et al. reacted dibenzofuran-2,8-di(sulfonyl chloride) with monotosylated β-CD,[35] yielding the mixture of products **58**−**62**, two of which display an A,C,E substitution pattern (23% combined yield). The three other regioisomers were produced in only 4.5% yield.

Transannular capping was extended to γ-CD by Ueno et al. It was not clear at first whether the reaction of γ-CD with azobenzene-4,4′-di(sulfonyl chloride) afforded an A,D- or A,E-capped species or even a mixture of both compounds (13% yield).[36,37] Eventually, the ratio was found to be 94:6 in favor of the C_2-symmetrical compound **63**.[38] A,B-Capped γ- and α-CD derivatives analogous to the previously reported compound **51**[10] were synthesized by Breslow et al.,[39] but only a small amount of the α-CD derivative was isolated (2.3% yield).

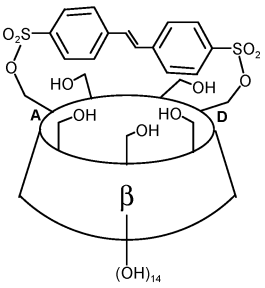
It was not until very recently that a regioselective A,C-difunctionalization method based on capping was found for α-CDs. Fujita et al. reported an 18% yield for product **64**, using dibenzofuran-2,8-disulfonyl chloride as capping reagent.[40] A,C-Substitution was inferred from the strong shielding effect the H-6 protons of the B glucose unit undergo.

2.2.2. Secondary Face Functionalization

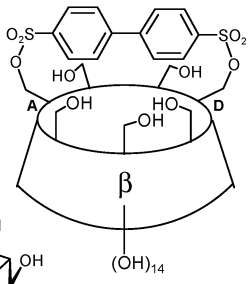
Regiospecific difunctionalization of the secondary face has turned out to be a much more difficult task than that of the primary one because of the less pronounced nucleopholic character of the secondary hydroxyl groups. Furthermore, distinction has to be made between the 2- and the 3-hydroxyl groups.



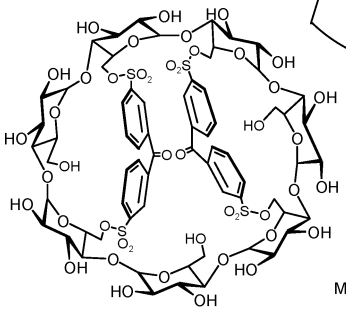
46



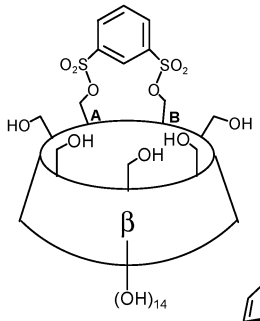
47



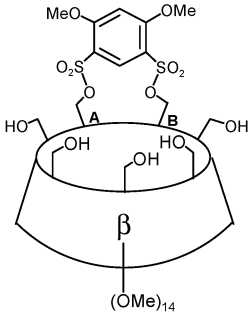
49



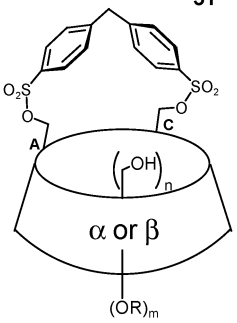
48



50



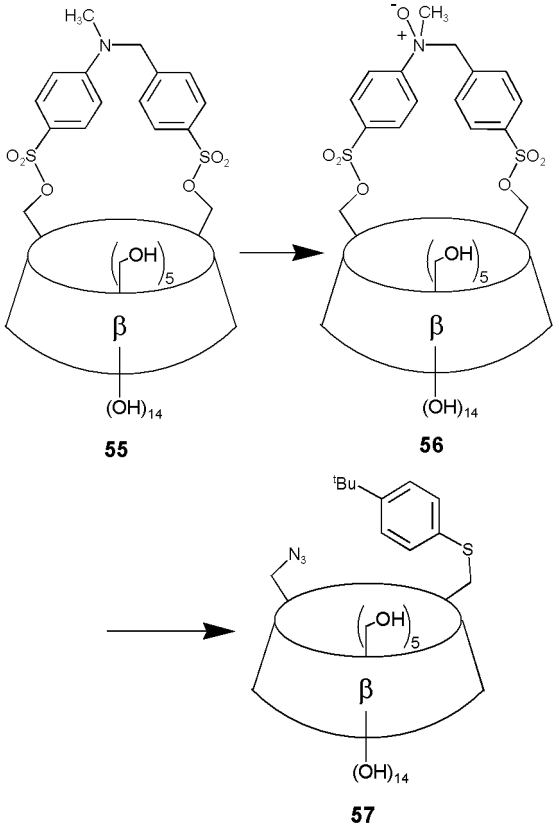
51



52, n = 5; R = CH_3; m = 14
53, n = 5; R = C_5H_{11}; m = 14
54, n = 4; R = CH_3; m = 12

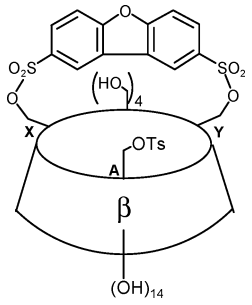
Teranishi et al. recently described synthetic methodologies for the regioselective secondary face difunctionalization of β- and γ-CD with reasonable yields. They are based on the use of imidazolyl leaving groups instead of chlorides. Reaction of benzophenone-3,3′-di(sulfonylimidazole) with γ-CD afforded $2^A,2^B$-capped **65** in 30% preparative yield.[41] Amaz-

Scheme 6. Functionalization of *β*-CD with a Dissymmetrical Cap and the Subsequent Introduction of Two Nonidentical Groups onto the Primary Face

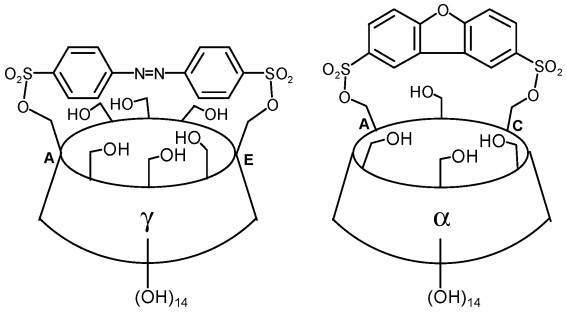


55 **56** **57**

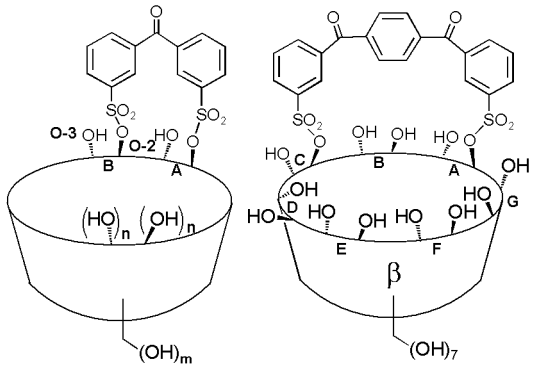
ingly, no 6-*O*-substituted products were detected. It should be mentioned that the 2-hydroxyl groups did not require any kind of activation beforehand. Likewise, treating α- and *β*-CD with benzophenone-3,3′-di(sulfonylimidazole) afforded the corresponding $2^A,2^B$-bridged species **66** and **67** in 30% and 33% yield, respectively.[42] Similarly, the $2^A,2^C$-capped compound **68** was obtained by reacting *β*-CD with 1,4-dibenzoylbenzene-3′,3″-di(sulfonylimidazole) (18% yield).[43] Synthesis of a $2^A,2^D$-capped *β*-CD derivative **70** was also achieved, using di(sulfonylimidazole) **69** as capping reagent (42% yield).[44] Characteristic ^{1}H and ^{13}C NMR downfield shifts of the H-1, H-2, and H-3 protons (the shifts are more pronounced for H-2 than for the other two protons) of the substituted glucose units as well



58, X = B; Y = D
59, X = C; Y = E
60, X = D; Y = F
61, X = E; Y = G
62, X = B; Y = G

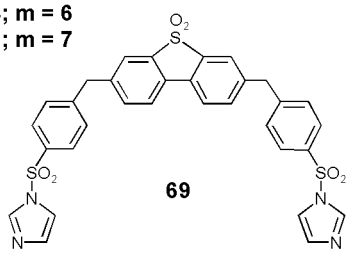


63 **64**

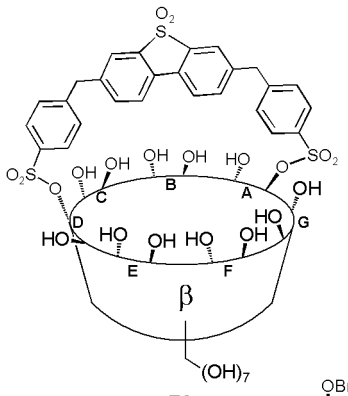


65, n = 6; m = 8
66, n = 4; m = 6
67, n = 5; m = 7

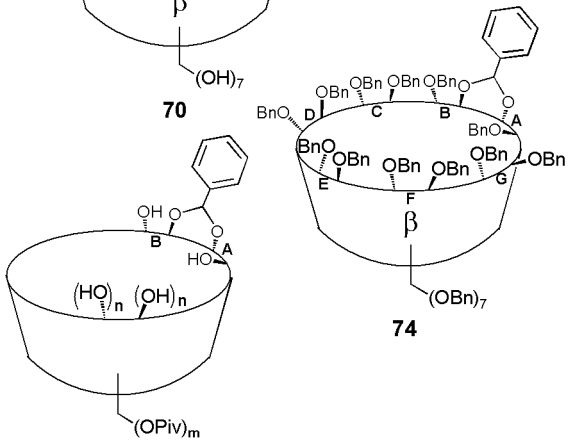
68



69



70



71, n = 4; m = 6
72, n = 5; m = 7
73, n = 6; m = 8

74

Piv =

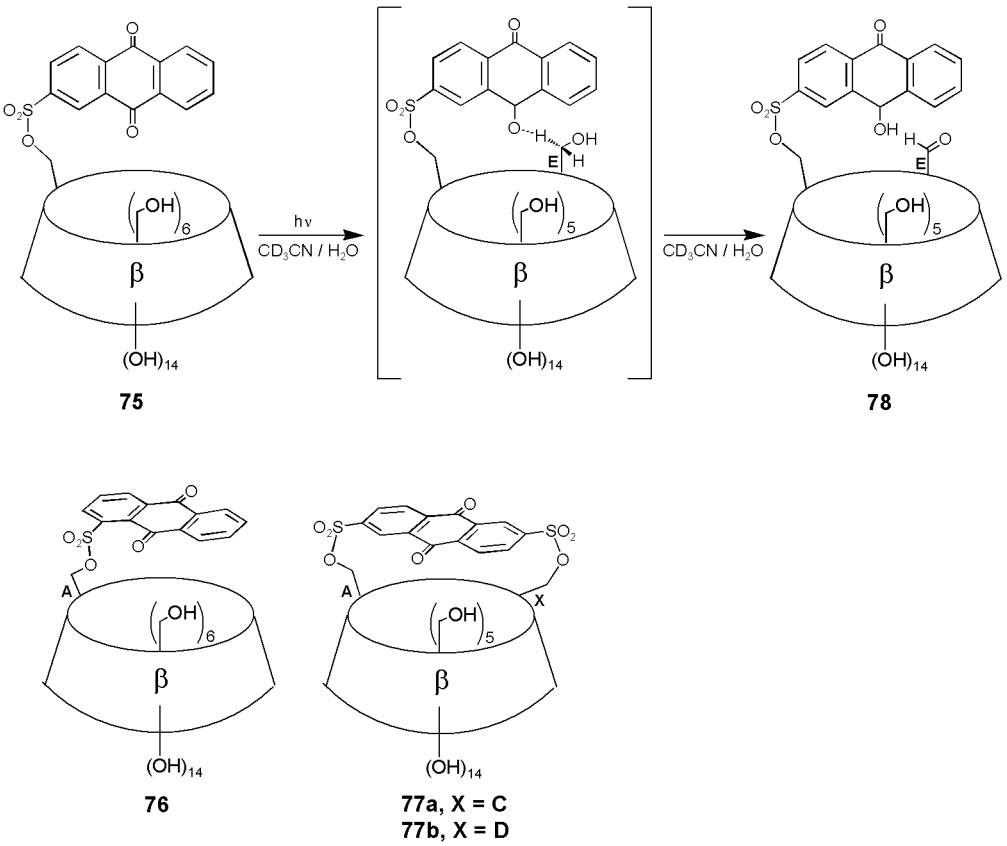


Figure 6. Photochemical reactions occurring with anthraquinone-capped CDs.

as of the corresponding C-2 atoms (the C-1 and C-3 atoms are upfield shifted) allowed the assignment of a 2-*O*-substitution pattern in the above-described compounds.

An example of mixed 2,3-*O*-bridging of contiguous glucose units has been reported by Sakairi et al.[45,46] 6-*O*-Pivaloyl-protected α-, *β*-, and *γ*-CDs were treated with benzaldehyde dimethylacetal using Evans' conditions[47] to obtain compounds **71**−**73** in 37%, 46%, and 54% yield, respectively. Removal of the pivaloyl groups and subsequent perbenzylation of **72** gave **74**, the interglycosidic benzylidene moiety of which underwent selective reductive cleavage at the 2-*O* position, the final product having a single HO-2 and twenty benzyl groups. This preference is possibly a result of the electron-withdrawing character of the anomeric center. The selective 2,3-*O*-substitution pattern was demonstrated using 2D HOHAHA, PFG-HMQC, and PFG-HMBC NMR techniques on the 2,3-*O*-diacetyl derivative of **74**. Alternatively, **72** could also be permethylated after de-*O*-pivaloylation and subjected to reductive cleavage at the 2-*O*-position.[48]

2.3. Photochemical Behavior of Capped CDs

Several reports have dealt with CDs transannularly bridged with moieties prone to undergo various photochemical reactions, such as photoinduced energy or electron transfer from or to encapsulated guests. Modified or improved catalytic activities as well as enhanced binding abilities have also been achieved through photoisomerization of the CD cap.

Abelt et al. studied the reactivity of *β*-CDs flexibly or rigidly capped with anthraquinone units (compounds **75**−**77**) upon irradiation (Figure 6).[49] The capping reaction between *β*-CD and anthraquinone-2-sulfonyl chloride results in an unseparable mixture of the A,D and A,C (80:20 ratio) derivatives **77** in a rather low yield (9%). Very similar photochemical behavior was observed for all four compounds. Irradiation of either one of them in a D_2O/*i*-Pr*O*D-d_7 solution under anaerobic conditions led to the formation of a hydroquinone cap (not drawn) as a result of proton transfer from a primary alcohol group to one of the quinone carbonyl functions, which could subsequently be reverted back to quinone by passing air through the solution. However, upon irradiation of any of the CD derivatives in aqueous CD_3CN, formation of a new product was detected. In the case of **75,** the presence of an aldehyde function was clearly detected (formation of **78**). Molecular modeling suggests that, in the absence of *i*-PrOH, aldehyde formation originates from intramolecular proton transfer from a C-6 hydroxyl, preferentially in the E position, to the quinone. This behavior makes such CD hosts unsuitable for photoinduced electron-transfer reactions.

Similar CD proton abstraction was also observed with Tabushi's *m*,*m*′-disulfonylbenzophenone-A,C-capped *β*-CD **46** (Figure 7).[50] In aqueous acetonitrile media, the regioisomeric aldehydes **79** and **80** were mainly formed, together with a mixture of pinacols, after irradiation and reaction with O_2. According to molecular modeling, deprotonation of the C-6 hydroxyls is promoted in positions E and F. In aqueous *i*-PrOH, which acts as proton donor, three dimeric pinacols, **81**−**83,** were detected as the major products,

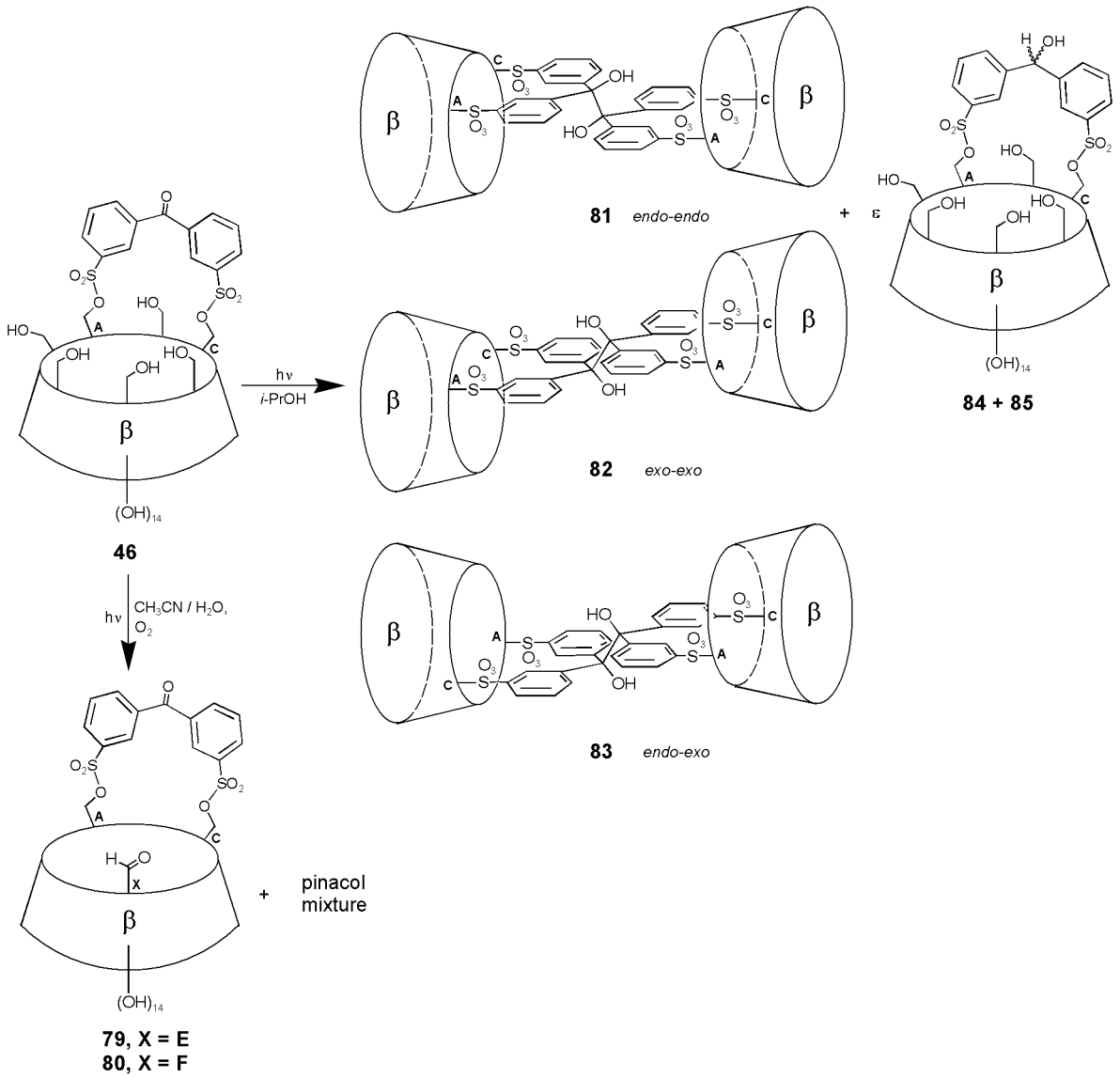


Figure 7. Photochemical reactions occurring with an A,C benzophenone-capped CD.

as in the case of benzophenone, together with little amounts of the two benzhydrol diastereoisomers **84** and **85**.

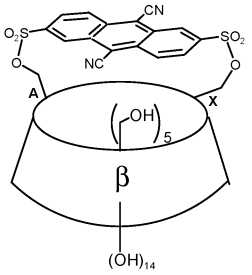
A much lower tendency for CD proton abstraction was anticipated for the dicyanoanthracene-capped compound **86**. Unfortunately, the reaction between β-CD and 9,10-dicyanoanthracene-2,6-di(sulfonyl chloride) afforded only a very small amount (1% yield!) of an inseparable mixture of the easily hydrolyzed A,D and A,C isomers (76:24 ratio) **86**.[51] Their instability is caused by the strongly electron-withdrawing character of the aromatic moiety. A static and dynamic fluorescence quenching study on **86** involving different amines as quenchers revealed that binding by the capped host was only more efficient than with native β-CD if the guest geometry is suited for more or less complete encapsulation, which is the case for amine **87**.[52] Because of better encapsulation of the somewhat long amines **88** and **89** in β-CD, the binding constants of these guests turned out to be lower with **86** than with β-CD. It was furthermore observed that the dynamic components represent at least 21% of the Stern−Volmer constants of the tested quenchers, which implies that potential photooxidation reactions would take place to some extent outside the cavity (Table 1).

The first evidence for energy transfer from a CD host to a bound guest was given by Tabushi et al. Phosphorescence measurements in aqueous DMF revealed the existence of triplet−triplet energy transfer from benzophenone-4,4′-dicarboxylate capped β-CD **90** (no regioselectivities were given) to bound bromonaphthalene or bromoethylnaphthalene in 60% and 50% quantum yields, respectively.[53] No significant transfer occurred when simple benzophenone-4,4′-di-(methylcarboxylate) was used instead as a sensitizer, an observation that corroborates the encapsulation of the photoactive guests. Moreover, as expected, no energy transfer was found to take place between the CD host and the very hydrophilic trisodium naphthalene-1,3,6-trisulfonate.

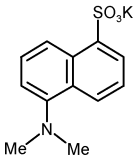
Kuroda et al. reported on controlled electron transfer from a β-CD-sandwiched porphyrin, **91**, onto a bound guest.[54] Its synthesis resulted from a coupling reaction between a thiolato-substituted porphyrin and 2 equiv of A,D-diiodo-β-CD. This reaction gave

Table 1. Stern−Volmer Constants ($dm^3 \cdot mol^{-1}$) for the Fluorescence Quenching of 86 with Some Amines as well as their Binding Constants with β-CD

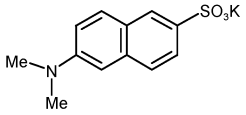
amine	**86**	β-CD
87	280 ± 10	110 ± 6
88	475 ± 3	1270 ± 30
89	254 ± 10	358 ± 22



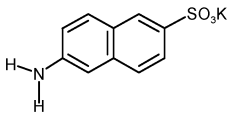
86a, X = C
86b, X = D



87



88

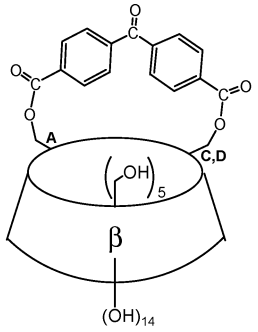


89

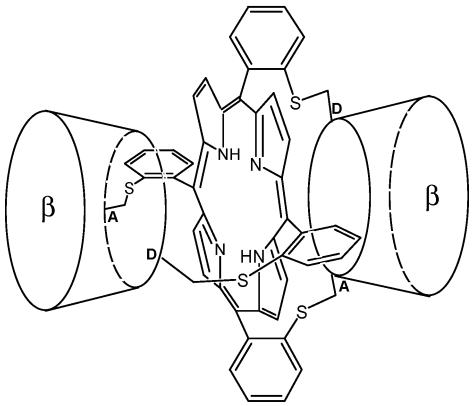
a mixture of five different isomers (Scheme 7),[55] three of which are so-called side-type isomers and originate from the $\alpha\alpha\beta\beta$ porphyrin atropisomer, whereas the two remaining diagonal-type ones comprise an $\alpha\beta\alpha\beta$ porphyrin atropisomer unit (a procedure for the exclusive synthesis of the side-type isomers has also been reported[56]). The fluorescence of **91** (which in fact is an equimolar mixture of two possible diagonal-type isomers) was readily quenched in the presence of either anthroquinone-2-sulfonate or naphthoquinone as shown by the nonlinear dependency between substrate concentration and fluorescence strength. Benzoquinone, on the other hand, gave only weak quenching, commensurate with its weak binding to the host, as opposed to the other quinones.

Complete *cis*-photoisomerization of the A,D-*trans*-4,4′-stilbene-disulfonate-capped β-CD **47**, yielding **92**, was achieved without reaching a photostationary state,[57] which is usually observed for noncyclic stilbene derivatives (Scheme 8). Upon further irradiation, the *cis i*somer **92** underwent a rarely encountered cyclization reaction, leading to the phenantrene-capped species **94** (probably via intermediate **93**).

Cis/trans photoisomerization leading to modified binding abilities of the CD cavity have been reported by Ueno et al. Reaction of β-CD with 4,4′-bis(chlorocarbonyl)-*trans*-azobenzene afforded capped **95** in 20% yield[58] (exclusive A,D-functionalization was demonstrated later[59]). Upon irradiation, **95** was converted into the *cis* isomer **96**, which displays a much larger cavity space. All aromatic and olefinic



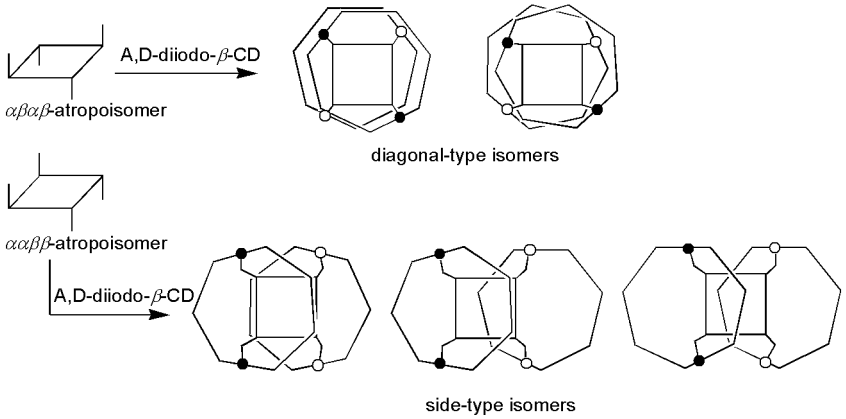
90



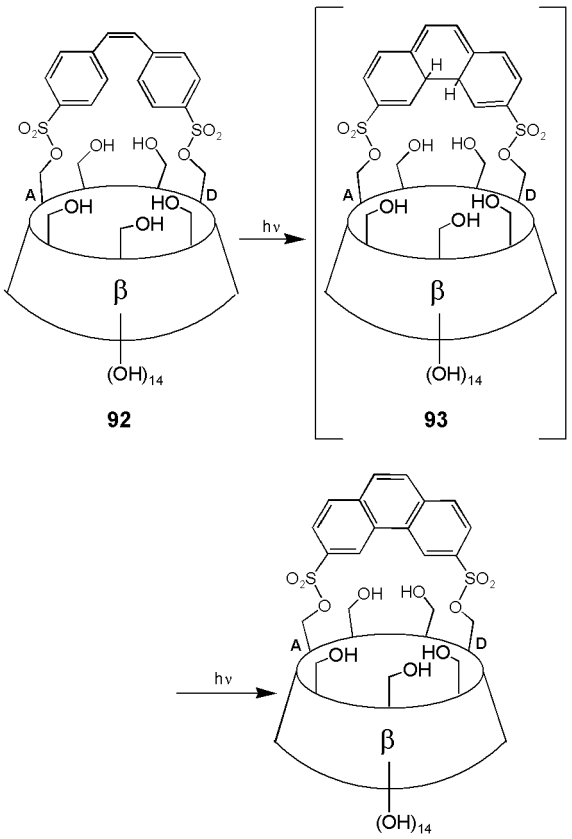
91

guest substances tested with **96** led to higher binding constants than with β-CD. Conversely, smaller association constants than with β-CD were found for **95** and the same guests, except for toluene, which was included more tightly into **95**. This feature confirms Breslow's earlier results showing that the cavity size may be significantly changed upon capping.[2] The most striking feature of **96** is its ability to bind 4,4′-bipyridine, whereas **95** did not at all. For each of the other substrates being tested, the cavity of **96** provided enough space to include even a second guest. This behavior was in particular observed for amino acids **97**−**99**,[60] the size of which decreases in the order L-Trp > L-Phe > L-Val. The second binding constants decrease in the same order, which is consistent with the assumption that the guest, which fills up the cavity space best, is bound the tightest. On the other hand, **95** forms no inclusion complex at all with neither L-Trp (too large) nor L-Val (too small), whereas two L-Phe can be included. Although all aforementioned guest inclusion reactions followed a stoichiometrical behavior (they form either (guest ⊂ host) or ($guest_2$ ⊂ host) complexes), as evidenced by circular dichroism experiments, nonstoichiometrical changes were sometimes observed between host **95** and certain guests. This effect was related to noncovalent interactions between the substrate and the CD cavity outer wall rather than the inside. Intramolecular hydrogen-bond disruption within the CD was also considered to be a possible cause for this phenomenon. Substances likely to give rise to nonstoichiometrical behavior during titration included those bearing amino and/or carboxylic acid functions[61] as well as some organic solvents.[62]

Scheme 7. Schematic Representation of the Possible Dimeric Isomers Formed (during the synthesis of 91) by Reacting the Two Porphyrin-Atropoisomers with A,D-Diiodo-β-CD



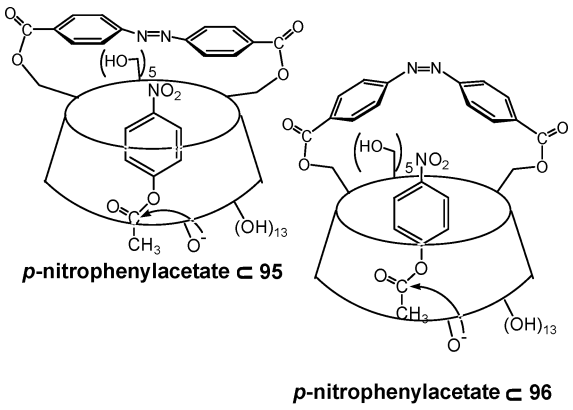
Scheme 8. Photoinduced Cyclization of a *cis*-4,4′-Stilbene Cap

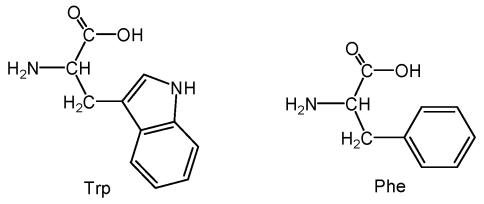


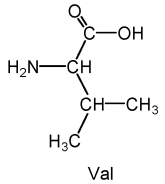
p-Nitrophenylacetate was found to be more favorably hydrolyzed by **96** than by **95**,[63] as could be deduced from the 5-fold increase in the apparent overall hydrolysis rate (k_c/K_m; these constants were evaluated from a Lineweaver−Burk plot[64]). This observation reflects in fact the tighter binding produced by **96**, even if the maximum rate constant (k_c) obtained with **96** is smaller than with **95**. It seems that the substrate undergoes deeper inclusion in **96**, which brings the ester group in a less favorable position to a secondary hydroxyl group than in **95**. Note that neither **95** nor **96** display any catalytic activity in the hydrolysis of *m*-nitrophenylacetate, while β-CD promotes the hydrolysis of the *meta* isomer (see above, "*meta* selectivity"[7]). This inversion is triggered by the larger cavity space provided by **96**, which allows binding of the *p*-isomer in **96**.

The possibility of linking two prefunctionalized glucose units using photochemical ring-closing reactions has also been reported. The anthracene moieties of γ-CDs **100**−**103** underwent (reversible) dimerization upon irradiation, thus affording capped compounds **104**−**107**.[65] Although the "*trans*-dimer" is usually the favored configuration in C-9-substituted, photoinduced anthracene dimers, **104** displays a *cis* geometry, in fact the sole configuration that may be obtained from the A,B-substituted CD **100**. Capped **104** turned out to be the least stable of the four synthesized compounds, owing to the strain within the short bridge (Scheme 9).

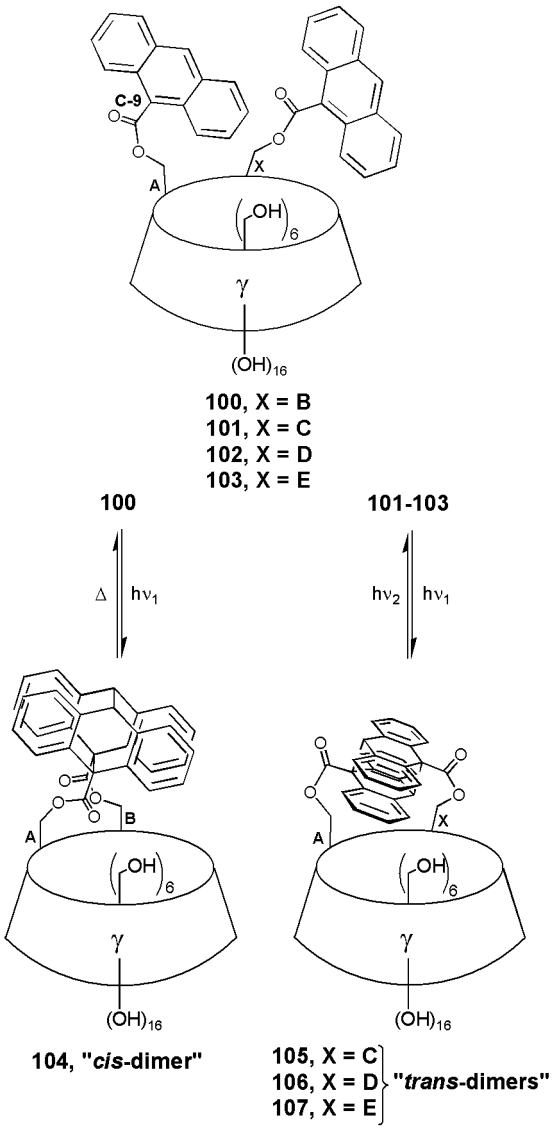
The first stereospecific photoinduced olefin oxidation triggered by a CD was achieved by Kuroda et







Scheme 9. Unusual *cis*-Dimerization of a C-9-Substituted Anthracene Moiety (104), which is only Possible in the Case of an AB Disubstitution Pattern on the CD



al.[66] Equimolar amounts of the sandwiched porphyrin **91** (diagonal-type isomers) and linoleic acid (octadeca-9,12-dienoic acid) in the presence of singlet oxygen afforded a 82:18 mixture of the hydroperoxidated products **108a**,**b**/**109a**,**b**, respectively (Figure 8). No regioselectivities were observed when a particular porphyrin derivative bearing no receptor sites (**110**) was used. Clearly the CD catalyst favors hydroperoxidation of the C12−C13 double bond. Moreover, significant ee's of 20% and 12% for **108a** and **108b**, respectively, were measured.

3. Caps Bearing Metal Centers

3.1. Bridging the Secondary Face

The binuclear nature of copper(II) complexes resulting from the reaction in $NaOH/H_2O$ solutions of copper(II) salts with either α- or β-CD has been investigated by Matsui et al.[67] Potentiometric and conductometric titrations as well as molecular models have led to the identification of structures **111** and **112**, where the 3^A and 2^B as well as 3^D and 2^E positions have been bridged by a Cu^{II} ion through covalent bonding (Figure 9).[68] Both metal ions are themselves linked to each other either through two μ-OH (**111**) or one μ-OH and one μ-O (**112**) bridges. Interestingly, both CDs, initially dextrorotatory, have become levorotatory upon complexation. This effect is likely to arise from the important distortion of the CD macrocycles upon bridging. A later study by Polavarapu et al. provided spectroscopic evidence for covalent linking of the Cu^{II} ions to the CD torus.[69] Major changes in the vibrational circular dichroism spectrum of α- and β-CD upon copper complexation in the exocyclic C−O−H bending vibrations region as well as an important decrease of the exocyclic C−O stretching bands demonstrate the involvement of secondary hydroxyl groups in copper bonding.

Dismukes et al. synthesized an analogous binuclear β-CD-manganese(III) complex, **113**, to provide a model for Mn^{III} and Mn^{IV} cluster-containing enzymes.[70] A reversible two-electron oxidation was observed by cyclic voltammetry, whereas reduction to the usually more stable Mn^{II} states was not possible.

A quite different outcome was observed by Klüfers et al. when reacting β-CD with Cu^{II} in the presence of LiOH instead of NaOH. In this case, the sandwich-type $Cu^{II}_4Li_7$-complex **114** precipitated.[71] An X-ray diffraction study revealed that both cavities are linked via metal centers coordinated to the partially deprotonated secondary face. Each of the four Cu^{II} ions acts as a double linker between two glucose units facing each other, and seven tricoordinated Li^+ ions are involved in bridging adjacent glucose units. The partial hydroxyl deprotonation was explained by the existence of an interglycosidic hydrogen-bond network, which prevents full deprotonation.

Complete deprotonation of the secondary hydroxyls together with a uniform metal coordination pattern linking two γ-CDs was achieved using lead(II) as the metal in the presence of NaOH.[72] In **115,** each secondary alkoxide anion is coordinated to two bridging Pb^{II} ions. The highly symmetrical CD dimer, which comprises 16 Pb^{II} ions altogether, is believed to be formed via a cooperative mechanism. Each Pb^{II} ion adopts a square pyramidal configuration, the Pb lone pairs being alternatively oriented inward and outward.

As will be seen in the next section, the introduction of a metal center into an organic cap provides the host with an additional recognition site, to which a bound guest bearing appropriate functionalities can coordinate and thus enhance the binding strength of the host and possibly accelerate a catalytic reaction.

3.2. Metals as Supplementary Recognition Sites

The first metalloenzyme model compound (**116**) was developed by Breslow et al.[73] The nickel atom of this compound actually does not act as a second recognition site. It was rather meant to connect the active pyridine-carboxaldoxime group to the CD cavity. *p*-Nitrophenylacetate hydrolysis proceeded 4 times faster than the uncatalyzed reaction. A com-

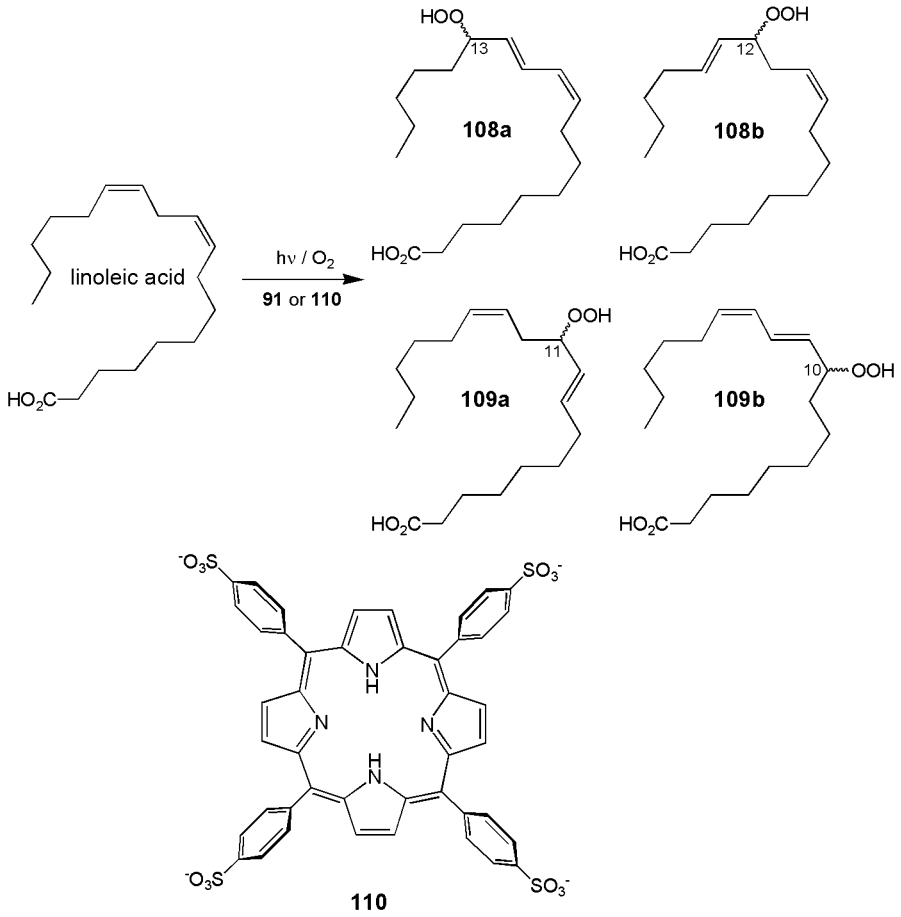
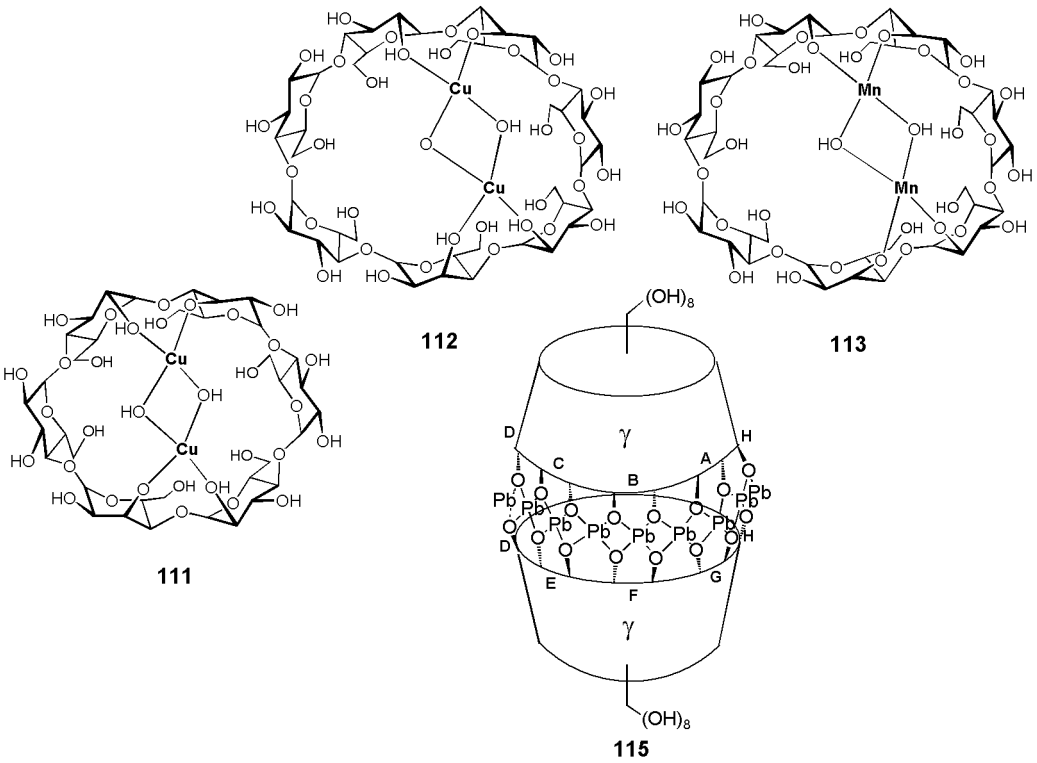


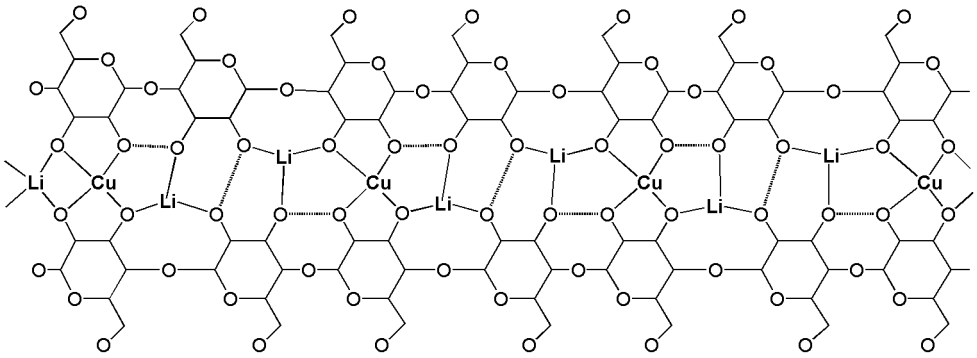
Figure 8. Photoinduced oxidation of linoleic acid using either **91** or **110**.

petitive inhibition experiment with cyclohexanol firmly established the substrate binding by the cavity prior to reaction. Tabushi et al. demonstrated the utility of a metal center covalently bound to the CD as a second recognition site for coordinating the anionic functionalities of encapsulated hydrophobic substrates, thus conferring it cooperative binding abilities.[74] For example, **117** binds 1-anilino-8-naphthalenesulfonate 4 times stronger than without a zinc center. Metal-capped **118** (A,C and A,D regioisomer mixture), for which the presence of a chelate was verified by electronic spectroscopy,[75] exhibited 6.6 times tighter binding of cyclohexyl-1,4-dicarboxylate than the metal-free derivative.[76] Interestingly, certain anionic guests, such as cyclohexylcarboxylate, produced slightly stronger hydrophobic interactions with **117** than with **118**, while coordinated to the metal center. This effect was attributed to the more flexible nature of the cap in **117**, which allows the coordinated guest to optimally fit the cavity.

Rizzarelli et al. successfully tethered a L-hystidyl-L-hystidyl entity to the positions A and C of a β-CD derivative.[77] The resulting diimidazolyl ligand **119** was reported to display chelating behavior toward Cu^{II}, thus making it a potential receptor for anionic organic guests.

The molecular recognition of amino acids by Cu^{II} chelate complexes obtained from **120**−**122** has been investigated by means of ligand-exchange chromatography (LEC−HPLC).[78] Enantiomer separation of racemic mixtures of Phe (**98**) or *p*-Tyr (**123**) could only be achieved with the A,B regioisomer **120**. The circular dichroism spectrum of a ternary complex of **120** displays specific shapes and intensities depending on the absolute configuration of the included amino acid. Such differences between L- and D-amino acids were neither observed with A,C-capped **121** nor with A,D-capped **122**, suggesting no significant interactions between the interior of the cavity and the guest. Support for this observation was provided by competition experiments with the noncoordinating adamant-1-ol. Progressive addition of this alcohol to a ternary complex of **120** led to a decrease of the absolute value of the molecular ellipticity $|\Delta\epsilon|$ in circular dichroism for both D- and L-amino acids owing to the competition reaction. For **121** and **122,** the spectra of the corresponding binary complexes remained unchanged, which is in keeping with a coordination of the amino acid outside the CD cavity. It was suggested that in the cases of **121** and **122** the metal caps partially closed the primary cavity entrance, thus preventing simultaneous coordination of the guest and intracavity interaction. The discrimination observed with **120** is quite different from the one believed to take place in monohistamino-functionalized β-CD cavities, such as **124**.[79−81] In the latter case, discrimination was assigned to the formation of an unsymmetrical *cis*-CuN_2 unit. Assuming that the imidazole-N atom favors *trans*-binding of the incoming amino group (and not of the carboxylate), it becomes obvious that only D-Trp can be trapped inside the cavity.





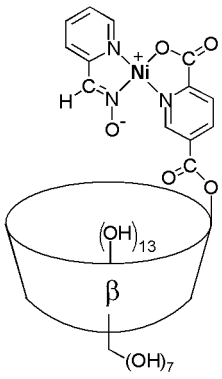
114 (the position of the remaining O*H* protons is not shown)

Figure 9. Native CDs capped at the secondary face with metal ions.

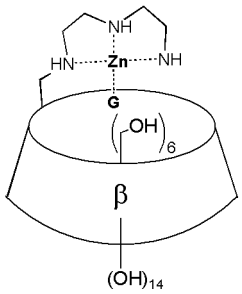
Aiming at the development of novel synthetic analogues of natural siderophiles (molecules produced by microorganisms under iron-deficient conditions to bind and solubilize iron), Boger et al. described the first examples of C_3-symmetrical metal-capped CDs (**125** and **126**).[82] These were obtained after regioselective functionalization of the A,C and E positions of an α-CD and subsequent methylation of the remaining hydroxyl groups. Introduction of three 2,3-dihydroxybenzoylamino groups afforded a hexadentate ligand able to bind a single metal center. Indeed, formation of complex **125** was shown to take place in aqueous medium at pH values higher than 4 by UV−vis spectroscopy. Moreover, at basic pH, coordination of an Al^{III} ion, leading to **126**, could be evidenced in the ^{1}H NMR spectrum by the upfield shifts of the aromatic protons and of the B,D,F-methyl signals upon complexation. Furthermore, the downfield shifts of certain proton signals of *p*-nitrophenolate upon addition of the latter to a solution containing **126** demonstrated the ability of the CD-receptor to bind this anion.

The $PtCl_2$ complex **127** of the aforementioned A,B-diamino-*β*-CD led to the third crystal structure determination of a metal-capped CD.[83] It is noteworthy that apart from the slight inward tilting of the substituted glucose units, the macrocyclic torus is not subjected to important distortion upon complexation. All glucose units have kept their initial $^4C_1$ chair conformation. Bearing in mind that the intramolecular HO-2−HO-3 hydrogen-bond network is still intact, any dramatic shape modifications of the cavity resulting from the bridging of two glucose units appears unfavorable as long as this rigidifying property remains. One way to induce shape modification, while still retaining hydrosolubilty, consists of using CDs where all nonsubstituted hydroxy groups have been methylated.[84]

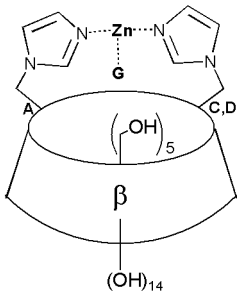
Evidence for the impressive flexibility acquired by a CD torus that has no hydroxy groups is given by the crystal structure of the $PtCl_2$-capped A,D-diamino-α-CD **128**.[85] Here the cavity has undergone an unprecedented narrowing upon transannular bridging with a very short connector. The B and F units



116



117



118

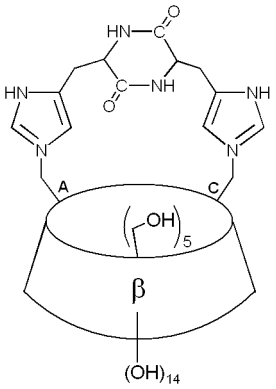
have furthermore adopted a $^0S_2$ skew−boat conformation, which was probably induced by hydrogen bonding to a single included (adventitious) water molecule. It can be easily anticipated that such important spatial modifications of the host cavity may lead to unexpected guest selectivities.

In another example, the potential multitopic coordinating character of the primary face methoxy groups (see chapter III) could be illustrated.[86] A VT NMR study established the fluxional behavior of the four primary face ether groups of the bipyridyl−silver complex **129**, which compete for metal coordination (Scheme 10).

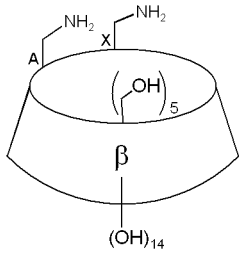
3.3. Metals as Catalytic Centers

An 8-fold reaction rate increase was found for the carbon dioxide hydration in the presence of the bisimidazole regioisomeric mixture **118**[5] when compared to the reaction carried out with complex **130**,[87] which lacks a cavity. In keeping with the base-dependent nature of the catalysis, two extra amino groups, as in the bis(*N*-histamino) derivative **131,** were introduced to improve the catalytic process. Indeed hydration proceeded 10 times faster than with **118** but only 3 times as fast as with the corresponding "cavity-free" complex **132**. When the catalytic reactions were carried out in imidazole buffer in the presence of **131**, an extra imidazole molecule was reported to coordinate the metal center.[75]

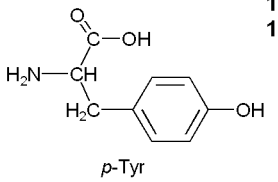
Czarnik et al. reported on a catalytic system (**133**) in which a Co^{III}-cyclen moiety is grafted onto the primary face of a β-CD. Noticeably, the metal center bridges an adjacent glucose unit via coordination of its hydroxyl group.[88] An 900-fold rate acceleration of *p*-nitrophenylacetate hydrolysis compared to the non-catalyzed reaction was achieved.[89] As for Breslow's Ni^{II}-CD catalyst **116**,[73] intracavity binding of the



119

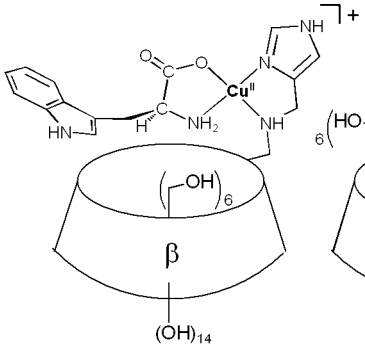


120, X = B
121, X = C
122, X = D

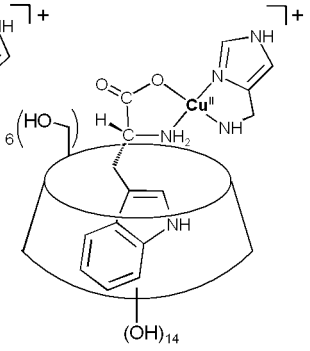


p-Tyr

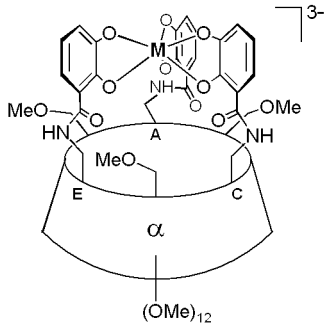
123



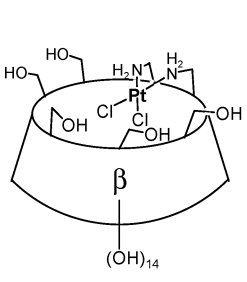
124•Cu^{II}•(L-Trp)



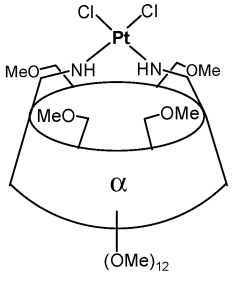
124•Cu^{II}•(D-Trp)



125; M = Fe^{III}
126; M = Al^{III}

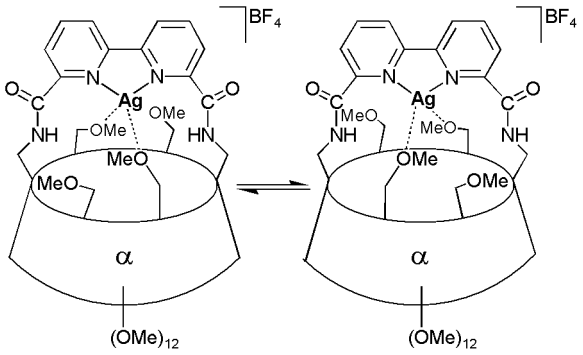


127



128

Scheme 10. Fluxional Behavior of the Primary Methoxy Groups within the Ag(bipy)-Capped CD 129

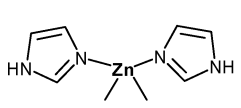


129

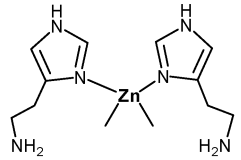
substrate was verified by performing the cyclohexanol inhibition experiment.

Well-improved epoxidation rates of cyclohexene in aqueous media were achieved in the presence of **134** (diagonal-type isomers) and iodosobenzene with respect to **135**, which bears no hydrophobic binding sites.[90] The enhanced reactivity of this otherwise almost unreactive olefin was attributed to the favorable binding of cyclohexene by the cavity. Conversely, an effective contact between the highly reactive oxene (Fe^{+}=O) species and the olefin in heterogeneous media is very difficult in the case of **135**. A possible better stabilization of the oxene in the presence of a hydrophobic environment has also been considered.

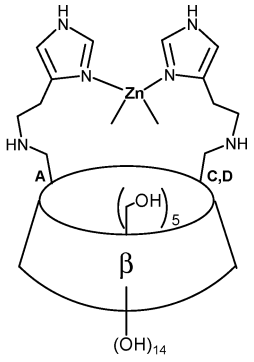
The stabilization of the naturally occurring Fe_4S_4 cluster in aqueous solution was achieved by grafting two A,D-dimercaptan-functionalized β-CDs onto the cluster, in a sandwich-type fashion, affording **136** (Figure 10).[91] Clusters such as **136** are used as model compounds for mimicking the active site core of ferredoxin. Indeed, **136** possesses a 21 times larger



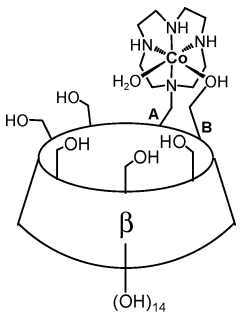
130



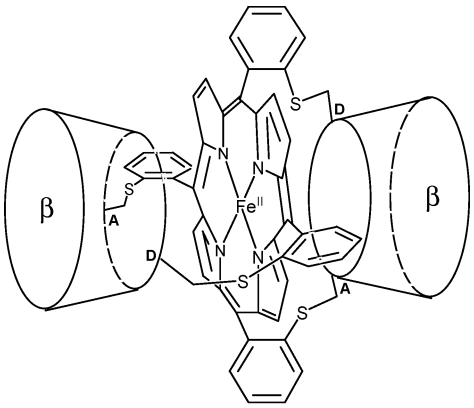
132



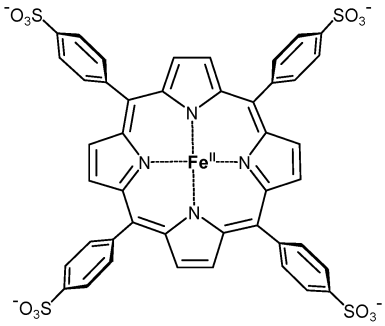
131



133



134



135

stability in water than the reference arylthiolate cluster **137** in 5% DMF−H_2O media. Interestingly, the stability increase was only 13-fold for the *flexibly*-capped species **138**.

A variant version of the 2,6-bis(iminoaryl)pyridine−$FeCl_2$ olefin polymerization catalysts, recently described by Brookhart and Gibson, has been found by Armspach and Matt. Replacement of the classical chain size-controlling iminoaryl residues with permethylated α- and β-CD derivatives afforded tridentate ligands **139** and **140**, respectively.[92] The MAO-activated (methylaluminoxane) complex **140**−$FeCl_2$ displays a similar behavior in the polymerization of ethylene as the known 2,6-bis[imino(2,6-dimethylphenyl)]pyridine-based Fe^{II} complex, in terms of molecular weight and cristallinity of the polymer, although the latter is more active. The significantly lower activity of the α-CD derivative **139** is thought to be the result of the smaller cavity size of the latter as well as difficulties in catalyst activation by MAO, partly arising from unfavorable interactions between the Lewis acid and the CD-ether oxygen atoms.

Catalytic systems relying on P(III) ligands are among the most studied for their numerous industrial applications and CD-based diphosphanes able to produce catalytically active chelate complexes have recently been prepared.[93−95] β-CD-derived ligand **141**, whose A and B glucose units bear two very short PPh_2 coordinating arms, was found to form 11-membered ring *cis*-chelate complexes **142** and **143** when reacted with [$PtCl_2$(COD)] and [$Rh(COD)_2$]BF_4, respectively.[96] Complex **143** produces ee's up to 92%, as in the hydrogenation of itaconic acid. A wealth of other prochiral olefins has also been hydrogenated, but the enantioselectivities are not as high. α-CD-based diphosphites **144** and **145** form even larger

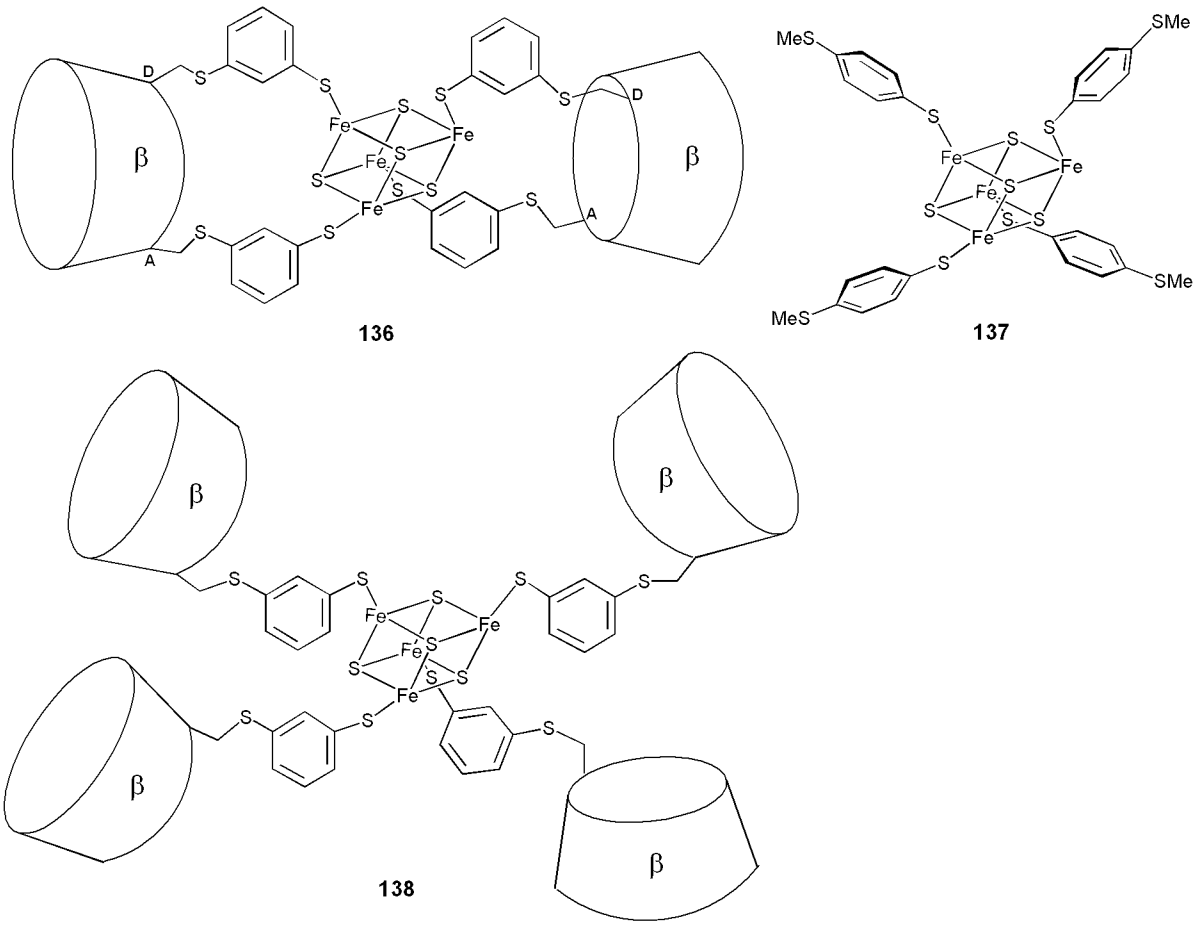
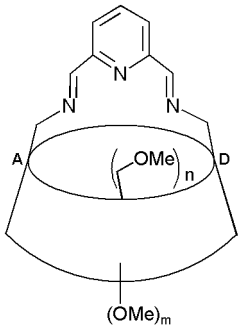


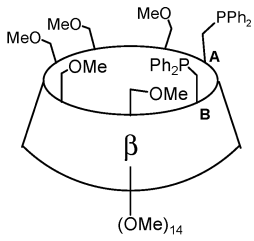
Figure 10. Sandwich-type CD-dimer **136** and their less water stable counterparts **137** and **138**.

chelate complexes but only with cationic starting complexes.[97] Thus, catalytically relevant Rh(I) complexes **146** and **147** as well as Ag(I) complexes **148** and **149** were all isolated in high yields. Only dissymmetric **146** is active in the hydrogenation of prochiral olefins, whereas its regioisomer **147**, in which substrate access to the catalytic center is more difficult, proved almost inactive. In addition, **146** produces an ee (84%, *R* isomer) higher than that obtained with **143** (62%, *S* isomer) for the hydrogenation of dimethylitaconate. The inversion of configuration on going from **143** to **146** seems to indicate that the mecanism of stereodifferentiation does not operate in the same way for both catalysts. Ligands **144** and **145** were also tested in the hydroformylation of 1-octene. No significant differences with other bulky diphosphites, both in terms of activity and selectivity, were observed. As the complexes were all formed "in situ", the presence of oligomeric species where the metal center is located further away from the cavity cannot be ruled out during the catalytic reaction.

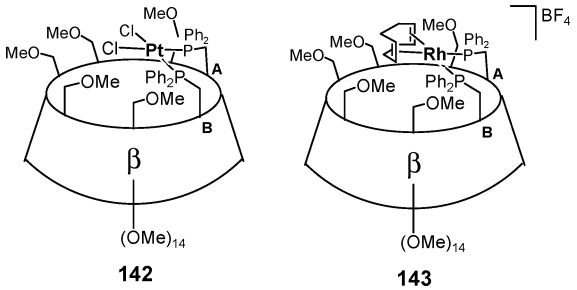
During the synthesis of both **144** and **145**, the introduction of catecholate spacers gave rise to the intriguing capped CD side products **150** and **151** respectively, upon partial cleavage of the benzyl protecting groups. The molecular structure of one of them, namely **150**, revealed that despite the short-



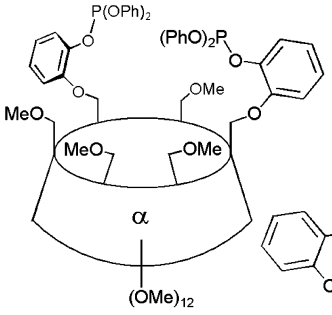
139; n = 4, m = 12
140; n = 5, m = 14



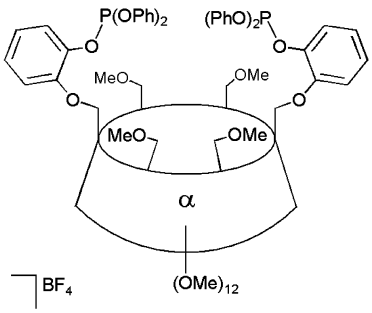
141

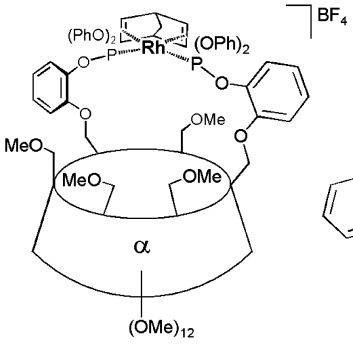


142 **143**



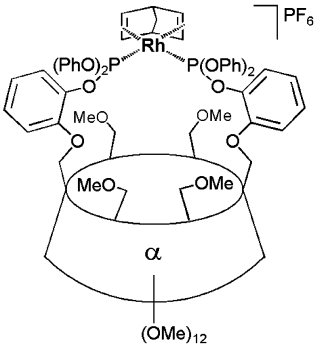
144



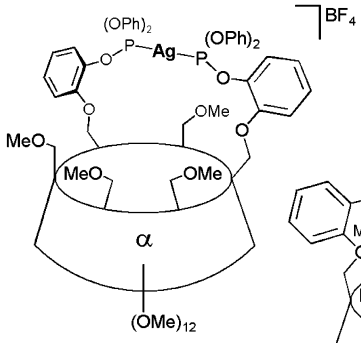


145

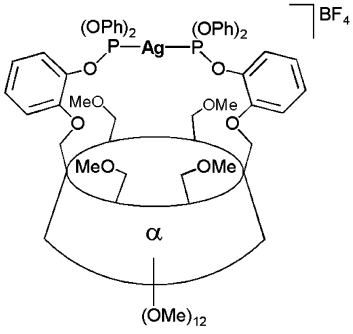
146



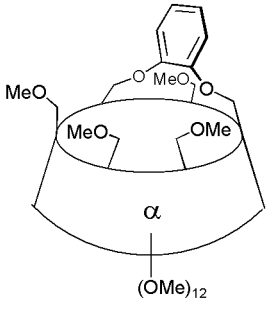
147



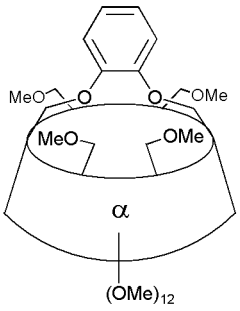
148



149



150

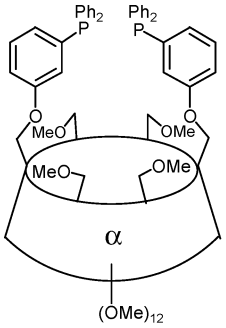


151

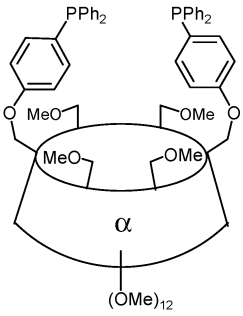
ness of the cap, the individual glucose units remain in the standard $^4C_1$ conformation, although some of them are markedly tilted toward the cavity interior.

3.4. CD-Based *trans*-Spanning Diphosphines

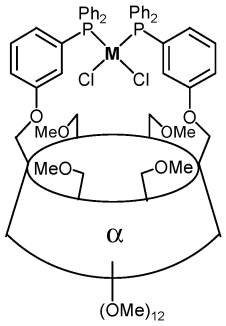
Flexible, but only to a certain extent, permethylated difunctionalized CDs have proved to constitute ideal platforms for making *trans*-spanning diphos-



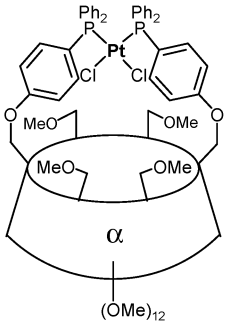
152



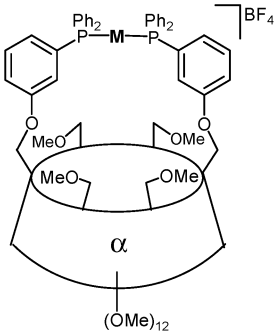
153



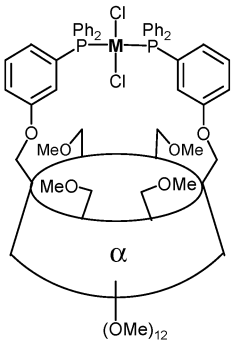
154, M = Pt
155, M = Pd



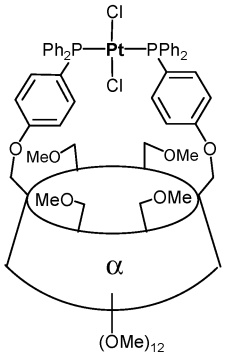
156



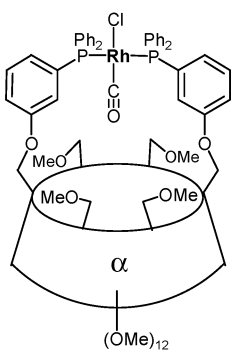
157, M = Ag
158, M = Au



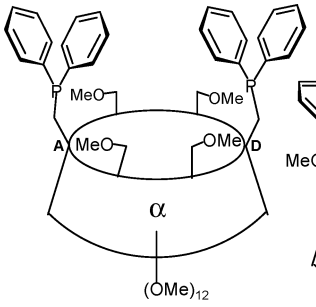
159, M = Pt
160, M = Pd



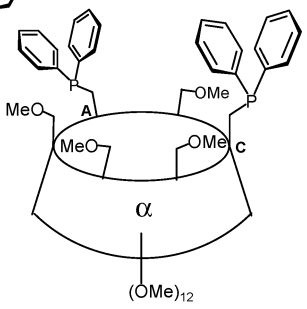
161



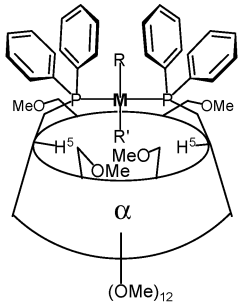
162



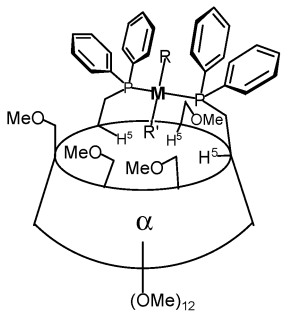
163



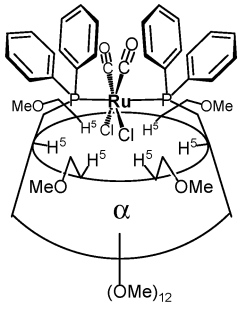
164



165; M=Pd, R=R'=Cl
167; M=Pt, R=R'=Cl
169; M=Pd, R=CH_3, R'=Cl



166; M=Pd, R=R'=Cl
168; M=Pt, R=R'=Cl
170; M=Pd, R=CH_3, R'=Cl

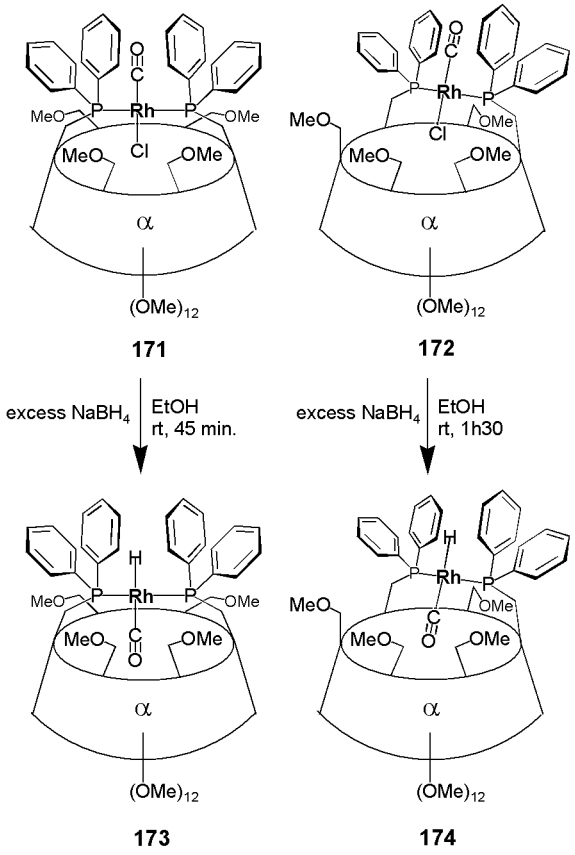


175

phines. The chelating C_2-symmetrical bidentates **152** and **153** were obtained from α-CD using a regioselective difunctionalization procedure, which allows the convenient tethering of two triarylphosphine fragments onto two diametrically opposed (A and D) glucose units.[84,98] Although the formation of *cis* chelate complexes **154**−**156** has been observed, both ligands clearly favor *trans* chelation, as exemplified by complexes **157**−**162**.[98] Note that **155** and **160** as well as **156** and **161** are rapidly interconverting so that isolation of the individual isomers was not possible.

Bidendates with very short diarylalkylphosphine arms, such as **163** and **164**, do not give rise to *cis* complexes, unlike the AB-difunctionalized **141**, but afford *trans* chelation only, when opposed to metals having either square planar or octahedral coordination spheres as in **165**−**172** and **175**. The ligands possess however a certain degree of flexibility and **163** is, for example, able to stabilize the trigonal silver(I) complex **176** where the bite angles drops to 143°.

Scheme 11. Chloride/Hydride Substitution Reaction, Leading to the Inclusion of the Carbonyl Ligand



171 172

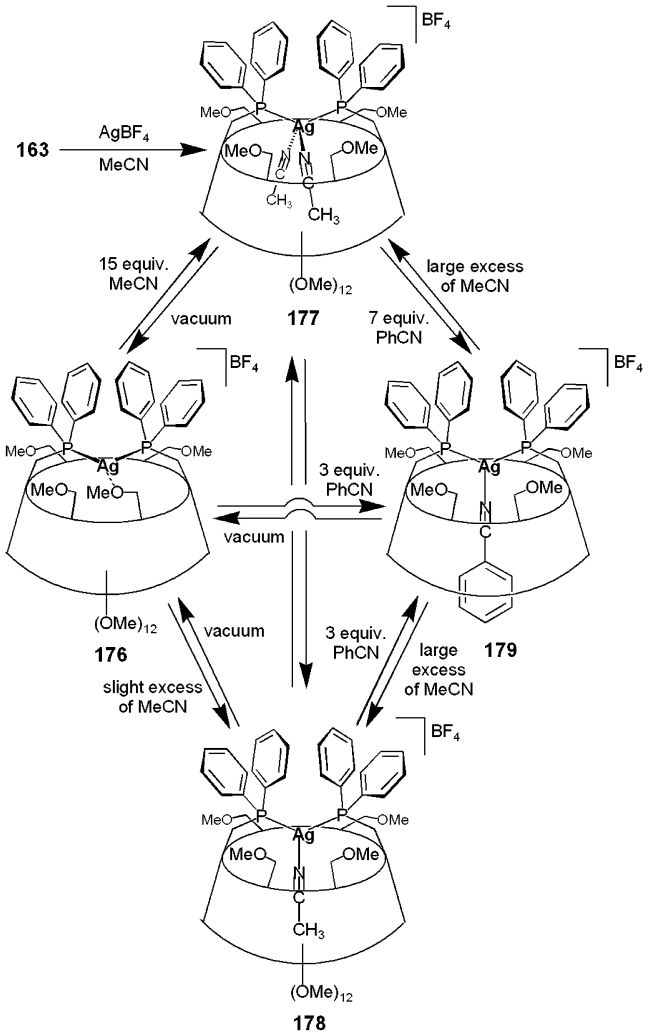
excess $NaBH_4$, EtOH, rt, 45 min. excess $NaBH_4$, EtOH, rt, 1h30

173 174

Another feature of **163** concerns its ability to function as a hemilabile ligand. Together with four methoxy groups belonging to the primary face, the two P(III) centers of **163** form a circularly arranged P_2O_4 12-electron-donor set able to complex an Ag^+ ion in a dynamic way, each of the four oxygen atoms coordinating successively the silver ion. Furthermore, the particular structure of **163** and of **164** as well, characterized by the presence of P(III) units lying close to the cavity entrance, leads upon complexation to complexes where the first coordination sphere is partly entrapped in the CD. Thus, when reacted with metal chlorides, both ligands systematically produce complexes in which the M−Cl unit is maintained inside the CD through weak Cl···H-5 interactions, as in **165**−**172**. Upon treatment of **171** and **172** with $NaBH_4$, the chloride ligand is replaced with a hydride one, which causes the CO ligand to be captured by the cavity (Scheme 11).

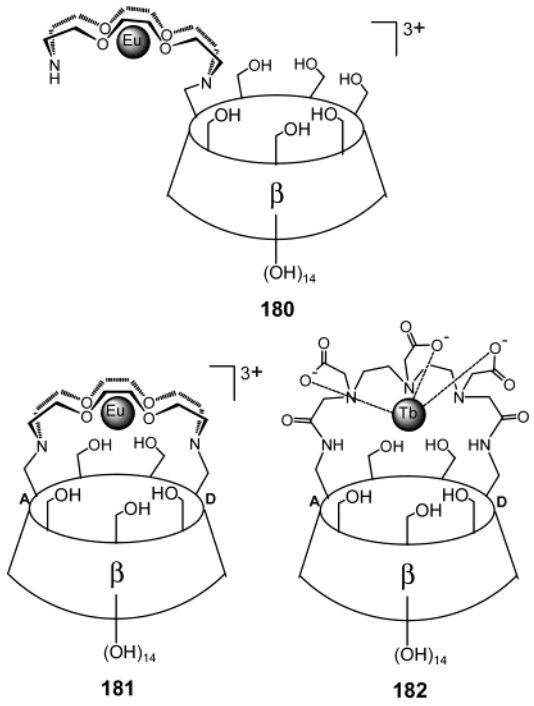
The chelate complex **176** reacts with acetonitrile in excess to afford a mixture of two equilibrating complexes **177** and **178**, whose coordinated nitriles lie inside the CD cavity (Scheme 12). The inner-cavity ligands can be substituted by a benzonitrile molecule to afford the complex **179**. This study provides the first identification of an $[Ag(phosphine)_2(acetonitrile)_2]^+$ cation. The unexpected stabilization of this species probably rests on a *cavity effect*, the CD walls favoring recombination of the complex after facile dissociation of the nitrile ligands.[99]

Scheme 12. Nitrile Ligand-Exchange Reactions Occurring inside a CD Cavity



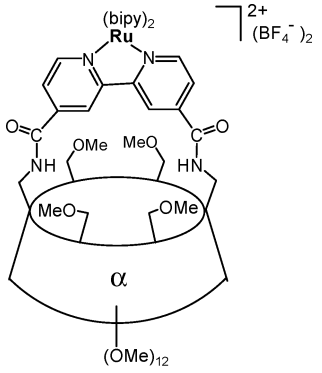
3.5. Photochemical Interactions between Included Guests and a Rigidly Positioned Metal Center

Attempts to develop chemosensors bearing photoactive centers able to emit light upon recognition of a guest by an adjacent binding site led Nocera et al. to the design of the β-CD derivative **180**, which is flexibly capped with a diaza crown-ether unit prone to coordinate a lanthanide center.[100] In a benzene-containing D_2O solution, the Eu^{III} luminescence, which is weak, was found to depend on the benzene concentration. This phenomenon was attributed to an absorption−energy transfer−emission (AETE) process; note, luminescence was not observed with a related Eu^{III}–aza complex that does not contain an appended CD. However, emission was easily quenched by H_2O (study carried out in D_2O), indicating that the metal-containing cap is not maintained in close proximity to the guest and therefore must be pointing away from the cavity. The rigidly A,D-capped version of the previous host, **181**, was expected to remedy the lack of energy transfer efficiency, because of the shorter distance separating the cap from the cavity.[101] Unfortunately, owing to the location of the highly positive metal charge close to the cavity, a drastic decrease of the binding strength of **181** toward benzene was observed.[102] Therefore, no emission



resulting from energy transfer from bound benzene could be brought to a fore. This problem was solved by introducing a cap bearing three carboxylate functions (**182**), which neutralize the lanthanide ion charge.[103] Due to the interference of ligand-to-metal charge transfer from the carboxylate groups to Eu^{III} with the AETE process, Tb^{III} was chosen as emission center instead. Thus, encapsulated mono- or bicyclic aromatic compounds were able to trigger highly sensitive luminescence responses. The fact that this property was found to be preserved in microfluidic media led recently to the design of a novel supramolecular microfluidic optical chemosensor, after incorporation of **182** into a sol−gel film.[104]

The first example of electron transfer through a CD cavity from a ruthenium(II) center to a bound guest molecule has been reported by Armspach and Matt. Benzoquinone was shown to form a 1:1 inclusion complex with the tris(bipyridyl)Ru^{II}-capped, permethylated α-CD derivative **183**.[105] Upon irradiation of the



exo-oriented metal center, the fluorescence quenching by benzoquinone at variable guest concentrations was studied. Static and diffusional quenching processes through electron transfer were found to take place

along with intracavity electron transfer, which accounts for ca. 10% of the overall quenching process.

4. Conclusion

As has become apparent from the studies discussed in this review, the capping of cyclodextrins has proven its usefulness in a number of applications. Not only does it constitute an efficient means to achieve di- or trifunctionalization of one of the cavity face, but it also allows the positioning of functional groups above the cavity entrance at a given location. Numerous studies have capitalized on this feature to tune for example the receptor binding properties in aqueous media. Thus, depending on the nature, the shape, and the size of the cap, substrate preferences can be dramatically altered with respect to those observed for native or flexibly functionalized CDs. With photoactive caps, it is possible to design systems displaying vectorial through-space photochemical processes as in the photosynthetic center of plants. Bringing functionalities close to the cavity entrance by means of a rigid cap also promotes coordinative as well as noncovalent bonds between the capping unit and the cavity chiral inner walls or an included guest. This has profound implications for the future development of CD-based systems displaying supramolecular and asymmetric catalysis, whether metal mediated or not.

5. Abbreviations

Bn	benzyl
bp	biphenyl
COD	cycloocta-1,5-diene
DMF	dimethylformamide
ee	enantiomeric excess
HPLC	high-pressure liquid chromatography
Piv	pivaloyl
Phe	phenylalanine
TBDMS	*tert*-butyldimethysilyl
Trp	tryptophan
Tyr	tyrosine
Val	valine
VT NMR	variable-temperature NMR

6. Acknowledgments

E.E. thanks the Ministère de la Culture, de l'Enseignement Supérieur et de la Recherche du Grand-Duché de Luxembourg for a grant.

7. References

(1) Khan, A. R.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977.
(2) Emert, J.; Breslow, R. *J. Am. Chem. Soc.* **1975**, *97*, 670.
(3) Tabushi, I.; Shimokawa, K.; Shimizu, N.; Shirakata, H.; Fujita, K. *J. Am. Chem. Soc.* **1976**, *98*, 7855.
(4) Cramer, F.; Kampe, W. *J. Am. Chem. Soc.* **1965**, *87*, 1115.
(5) Breslow, R.; Doherty, J. B.; Guillot, G.; Lipsey, C. *J. Am. Chem. Soc.* **1978**, *100*, 3227.
(6) Tabushi, I.; Shimokawa, K.; Fujita, K. *Tetrahedron Lett.* **1977**, *18*, 1527.
(7) Fujita, K.; Shinoda, A.; Imoto, T. *J. Am. Chem. Soc.* **1980**, *102*, 1161.
(8) VanEtten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242.
(9) Breslow, R.; Czarniecki, M. F.; Emert, J.; Hamaguchi, H. *J. Am. Chem. Soc.* **1980**, *102*, 762.
(10) Breslow, R.; Canary, J. W.; Varney, M.; Waddell, S. T.; Yang, D. *J. Am. Chem. Soc.* **1990**, *112*, 5212.
(11) Yuan, D.-Q.; Koga, K.; Fujita, K. *Tetrahedron Lett.* **1997**, *38*, 7593.
(12) Yuan, D.-Q.; Koga, K.; Yamaguchi, M.; Fujita, K. *Chem. Commun.* **1996**, 1943.
(13) Fujita, K.; Tahara, T.; Sasaki, H.; Egashira, Y.; Shingu, T.; Imoto, T.; Koga, T. *Chem. Lett.* **1989**, 917.
(14) Immel, S.; Fujita, K.; Fukudome, M.; Bolte, M. *Carbohydr. Res.* **2001**, *336*, 297.
(15) Lichtenthaler, F. W.; Immel, S. *Liebigs Ann.* **1996**, 27.
(16) Fujita, K.; Okabe, Y.; Ohta, K.; Yamamura, K.; Tahara, T.; Nogami, Y.; Koga, K. *Tetrahedron Lett.* **1996**, *37*, 1825.
(17) Hauser, S. L.; Cotner, E. S.; Smith, P. J. *Tetrahedron Lett.* **1999**, *40*, 2865.
(18) Cotner, E. S.; Smith, P. J. *J. Org. Chem.* **1998**, *63*, 1737.
(19) Tabushi, I.; Kuroda, Y.; Shimokawa, K. *J. Am. Chem. Soc.* **1979**, *101*, 1614.
(20) Breslow, R.; Halfon, S.; Zhang, B. *Tetrahedron* **1995**, *51*, 377.
(21) Breslow, R.; Chung, S. *J. Am. Chem. Soc.* **1990**, *112*, 9659.
(22) Sasaki, H.; Nagasaka, M.; Kuroda, Y. *Chem. Commun.* **2001**, 2630.
(23) Lecourt, T.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron Lett.* **2002**, *43*, 5533.
(24) Cucinotta, V.; Grasso, G.; Pedotti, S.; Rizzarelli, E.; Vecchio, G. *J. Incl. Phenom. Mol. Recog. Chem.* **1996**, *25*, 39.
(25) Cucinotta, V.; Grasso, G.; Vecchio, G. *J. Incl. Phenom. Mol. Recog. Chem.* **1998**, *31*, 43.
(26) Koga, K.; Ishida, K.; Yamada, T.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **1999**, *40*, 923.
(27) Corradini, R.; Buccella, G.; Galaverna, G.; Dossena, A.; Marchelli, R. *Tetrahedron Lett.* **1999**, *40*, 3025.
(28) Tabushi, I.; Yuan, L. C.; Shimokawa, K.; Yokota, K.; Mizutani, T.; Kuroda, Y. *Tetrahedron Lett.* **1981**, *22*, 2273.
(29) Tabushi, I.; Kuroda, Y.; Yokota, K.; Yuan, L. C. *J. Am. Chem. Soc.* **1981**, *103*, 1.
(30) Tabushi, I.; Yamamura, K.; Nabeshima, T. *J. Am. Chem. Soc.* **1984**, *106*, 5267.
(31) Tabushi, I.; Nabeshima, T.; Fujita, K.; Matsunaga, A.; Imoto, T. *J. Org. Chem.* **1985**, *50*, 2638.
(32) Chen, Z.; Bradshaw, J. S.; Yi, G.; Pyo, D.; Black, D. R.; Zimmerman, S. S.; Lee, M. L.; Tong, W.; D'Souza, V. T. *J. Org. Chem.* **1996**, *61*, 8949.
(33) Yi, G.; Bradshaw, J. S.; Rossiter, B. E.; Reese, S. L.; Petersson, P.; Markides, K. E.; Lee, M. L. *J. Org. Chem.* **1993**, *58*, 2561.
(34) Tabushi, I.; Nabeshima, T.; Kitaguchi, H.; Yamamura, K. *J. Am. Chem. Soc.* **1982**, *104*, 2017.
(35) Atsumi, M.; Izumida, M.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **2000**, *41*, 8117.
(36) Ueno, A.; Moriwaki, F.; Osa, T.; Hamada, F.; Murai, K. *Tetrahedron Lett.* **1985**, *26*, 3339.
(37) Ueno, A.; Moriwaki, F.; Osa, T.; Hamada, F.; Murai, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 465.
(38) Ueno, A.; Moriwaki, F.; Osa, T.; Hamada, F.; Murai, K. *J. Am. Chem. Soc.* **1988**, *110*, 4323.
(39) Breslow, R.; Schmuck, C. *J. Am. Chem. Soc.* **1996**, *118*, 6601.
(40) Koga, K.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **2000**, *41*, 6855.
(41) Teranishi, K.; Hisamatsu, M.; Yamada, T. *Tetrahedron Lett.* **2000**, *41*, 933.
(42) Teranishi, K. *Chem. Commun.* **2000**, 1255.
(43) Teranishi, K. *Tetrahedron Lett.* **2000**, *41*, 7085.
(44) Teranishi, K. *Tetrahedron Lett.* **2001**, *42*, 5477.
(45) Sakairi, N.; Kuzuhara, H. *Chem. Lett.* **1993**, 2077.
(46) Sakairi, N.; Nishi, N.; Tokura, S.; Kuzuhara, H. *Carbohydr. Res.* **1996**, *291*, 53.
(47) Sakairi, N.; Kuzuhara, H. *Chem. Lett.* **1993**, 2077.
(48) Matsuoka, K.; Shiraishi, Y.; Terunuma, D.; Kuzuhara, H. *Tetrahedron Lett.* **2001**, *42*, 1531.
(49) 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.
(50) Berger, K. L.; Nemecek, A. L.; Abelt, C. J. *J. Org. Chem.* **1991**, *56*, 3514.
(51) Acquavella, M. F.; Evans, M. E.; Farraher, S. W.; Névoret, C. J.; Abelt, C. J. *J. Org. Chem.* **1994**, *59*, 2894.
(52) Acquavella, M. F.; Evans, M. E.; Farraher, S. W.; Névoret, C. J.; Abelt, C. J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 385.
(53) Tabushi, I.; Fujita, K.; Yuan, L. C. *Tetrahedron Lett.* **1977**, *18*, 2503.
(54) Kuroda, Y.; Ito, M.; Sera, T.; Ogoshi, H. *J. Am. Chem. Soc.* **1993**, *115*, 7003.
(55) Kuroda, Y.; Hiroshige, T.; Sera, T.; Shiroiwa, Y.; Tanaka, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1989**, *111*, 1912.
(56) Kuroda, Y.; Hiroshige, T.; Sera, T.; Ogoshi, H. *Carbohydr. Res.* **1989**, *192*, 347.
(57) Tabushi, I.; Yuan, L. C. *J. Am. Chem. Soc.* **1981**, *103*, 3574.
(58) Ueno, A.; Yoshimura, H.; Saka, R.; Osa, T. *J. Am. Chem. Soc.* **1979**, *101*, 1, 2779.

(59) Moriwaki, F.; Kaneko, H.; Ueno, A.; Osa, T.; Hamada, F.; Murai, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3619.
(60) Ueno, A.; Saka, R.; Osa, T. *Chem. Lett.* **1979**, 841.
(61) Ueno, A.; Saka, R.; Osa, T. *Chem. Lett.* **1979**, 1007.
(62) Ueno, A.; Saka, R.; Osa, T. *Chem. Lett.* **1980**, 29.
(63) Ueno, A.; Takahashi, K.; Osa, T. *Chem. Commun.* **1981**, 94.
(64) Lineweaver, H.; Burk, D. *J. Am. Chem. Soc.* **1934**, *56*, 658.
(65) Ueno, A.; Moriwaki, F.; Azuma, A.; Osa, T. *J. Org. Chem.* **1989**, *54*, 295.
(66) Kuroda, Y.; Sera, T.; Ogoshi, H. *J. Am. Chem. Soc.* **1991**, *113*, 2793.
(67) Matsui, Y.; Kurita, T.; Date, Y. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3229.
(68) Matsui, Y.; Kurita, T.; Yagi, M.; Okayama, T.; Mochida, K.; Date, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2187.
(69) Bose, P. K.; Polavarapu, P. L. *Carbohydr. Res.* **2000**, *323*, 63.
(70) Nair, B. U.; Dismukes, G. C. *J. Am. Chem. Soc.* **1983**, *105*, 124.
(71) Fuchs, R.; Habermann, N.; Klüfers, P. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 852.
(72) Klüfers, P.; Schuhmacher, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1863.
(73) Breslow, R.; Overman, L. E. *J. Am. Chem. Soc.* **1970**, *92*, 1075.
(74) Tabushi, I.; Shimizu, N.; Sugimoto, T.; Shiozuka, M.; Yamamura, K. *J. Am. Chem. Soc.* **1977**, *99*, 7100.
(75) Tabushi, I.; Kuroda, Y. *J. Am. Chem. Soc.* **1984**, *106*, 4580.
(76) Tabushi, I.; Kuroda, Y.; Mizutani, T. *Tetrahedron* **1984**, *40*, 545.
(77) Bonomo, R.; Impellizzeri, G.; Pappalardo, G.; Rizzarelli, E.; Vecchio, G. *Gazz. Chim. Ital.* **1993**, *123*, 593.
(78) Bonomo, R.; Pedotti, S.; Vecchio, G.; Rizzarelli, E. *Inorg. Chem.* **1996**, *35*, 6873.
(79) Impellizzeri, G.; Maccarone, G.; Rizzarelli, E.; Vecchio, G.; Corradini, R.; Marchelli, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1348.
(80) Cucinotta, V.; D'Alessandro, F.; Impellizzeri, G.; Vecchio, G. *J. Chem. Soc., Chem. Commun.* **1992**, 1743.
(81) Corradini, R.; Dossena, A.; Impellizzeri, G.; Maccarone, G.; Marchelli, R.; Rizzarelli, E.; Sartor, G.; Vecchio, G. *J. Am. Chem. Soc.* **1994**, *116*, 10267.
(82) Coleman, A. W.; Ling, C.-C.; Miocque, M. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1381.
(83) Cucinotta, V.; Grasso, G.; Pedotti, S.; Rizzarelli, E.; Vecchio, G.; Di Blasio, B.; Saviano, M.; Pedone, C. *Inorg. Chem.* **1996**, *35*, 7535.
(84) Armspach, D.; Matt, D. *Carbohydr. Res.* **1998**, *310*, 129.
(85) Armspach, D.; Matt, D. *Inorg. Chem.* **2001**, *40*, 3505.
(86) Armspach, D.; Matt, D.; Kyritsakas, N. *Polyhedron* **2001**, *20*, 663.
(87) Tabushi, I.; Kuroda, Y.; Mochizuki, A. *J. Am. Chem. Soc.* **1980**, *102*, 1152.
(88) Akkaya, E. U.; Czarnik, A. W. *J. Am. Chem. Soc.* **1988**, *110*, 8553.
(89) Akkaya, E. U.; Czarnik, A. W. *J. Phys. Org. Chem.* **1992**, *5*, 540.
(90) Kuroda, Y.; Hiroshige, T.; Ogoshi, H. *Chem. Commun.* **1990**, 1594.
(91) Kuroda, Y.; Sasaki, Y.; Shiroiwa, Y.; Tabushi, I. *J. Am. Chem. Soc.* **1988**, *110*, 4049.
(92) Armspach, D.; Matt, D.; Perruch, F.; Lutz, P. *Eur. J. Inorg. Chem.* **2003**, 805.
(93) Reetz, M. T.; Rudolph, J. *Tetrahedron: Asymmetry* **1993**, *4*, 2405.
(94) Reetz, M. T.; Waldvogel, S. R.; Goddard, R. *Tetrahedron Lett.* **1997**, *38*, 5967.
(95) Reetz, M. T.; Frömbgen, C. *Synthesis* **1999**, 1555.
(96) Wong, Y. T.; Yang, C.; Ying, K.-C.; Jia, G. *Organometallics* **2002**, *21*, 1782.
(97) Engeldinger, E.; Armspach, D.; Matt, D.; Toupet, L.; Wesolek, M. *C.R. Chimie* **2002**, 359.
(98) Armspach, D.; Matt, D. *Chem. Commun.* **1999**, 1073.
(99) Engeldinger, E.; Armspach, D.; Matt, D.; Jones, P. G. *Chem. Eur. J.* **2003**, 3091.
(100) Pikramenou, Z.; Nocera, D. G. *Inorg. Chem.* **1992**, *31*, 532.
(101) Pikramenou, Z.; Johnson, K. M.; Nocera, D. G. *Tetrahedron Lett.* **1993**, *34*, 3531.
(102) Rudzinski, C. M.; Hartmann, W. K.; Nocera, D. G. *Coord. Chem. Rev.* **1998**, *171*, 115.
(103) Mortellaro, M. A.; Nocera, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 7414.
(104) Rudzinski, C. M.; Young, A. M.; Nocera, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 1723.
(105) Armspach, D.; Matt, D.; Harriman, A. *Eur. J. Inorg. Chem.* **2000**, 1147.

CR030670Y