Biolog. J. Armenia, *Special issue: Cyclodextrins*, 2001

COMPLEXATION OF DITOPIC GUESTS BY CYCLODEXTRINS AND DERIVATIVES

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The complexation of ditopic guests by cyclodextrins and their higher degree derivatives is reviewed. Special attention is paid to the complexation of ditopic guests by cyclodextrin dimers, that can lead either to the formation of 1:1 stoichiometry complexes, in which a cooperative effect over the equilibrium constant is observed, or to the generation of supramolecular polymers with n:n stoichiometries.

Рассмотриваются вопросы комплексообразования дитопических "гостей" циклодекстринами и их высокомолекулярными производными. Особое внимание уделяется комплексам дитопических "гостей" димерами циклодекстринов, что может вести либо к образованию 1:1 стехиометрических комплексов, в которых наблюдается совместный эффект над константой равновесия, либо к появлению надмолекулярных полимеров с n:n стехиометрией.

Քննարկվում են ցիկլոդեքստրինների և նրանց բարձրամոլեկուլային ածանցյալների հետ դիտոպիկ «հյուրերի» համալիրագոյացման խնդիրները: Հատուկ ուշադրություն է դարձվում ցիկլոդեքստրինների դիմերների և դիտոպիկ «հյուրերի» միջև համալիրագոյացմանը, որը կարող է տանել կամ 1:1 ստեխիոմետրիկ համալիրների գոյացմանը, որտեղ դիտվում է միացյալ գործոնի վեր լինելը հավասարության հաստատունից, կամ n:n ստեխիոմետրիայով վերնամոլեկուլյար պոլիմերների առաջացմանը:

I. Complexation of ditopic guests by natural cyclodextrins.

Natural cyclodextrins (CD) are cyclic oligomers, with a truncated cone shape, built up from 6, 7 or 8 glucopyranose units, linked by α-(1-4)-glycosidic linkages, named α, β and γ–CD, respectively (Figure 1). They are known to form inclusion complexes in water with a variety of organic molecules, a property used to increase the bioavailability and stability of poorly soluble drugs[1-3] and flavors [4], as photochemical sensors [5-8], enzyme mimics [9-12] or as pollutants removers in environmental processes [1].

Figure 1. Structure and schematic representation of α- β- and γ-cyclodextrin

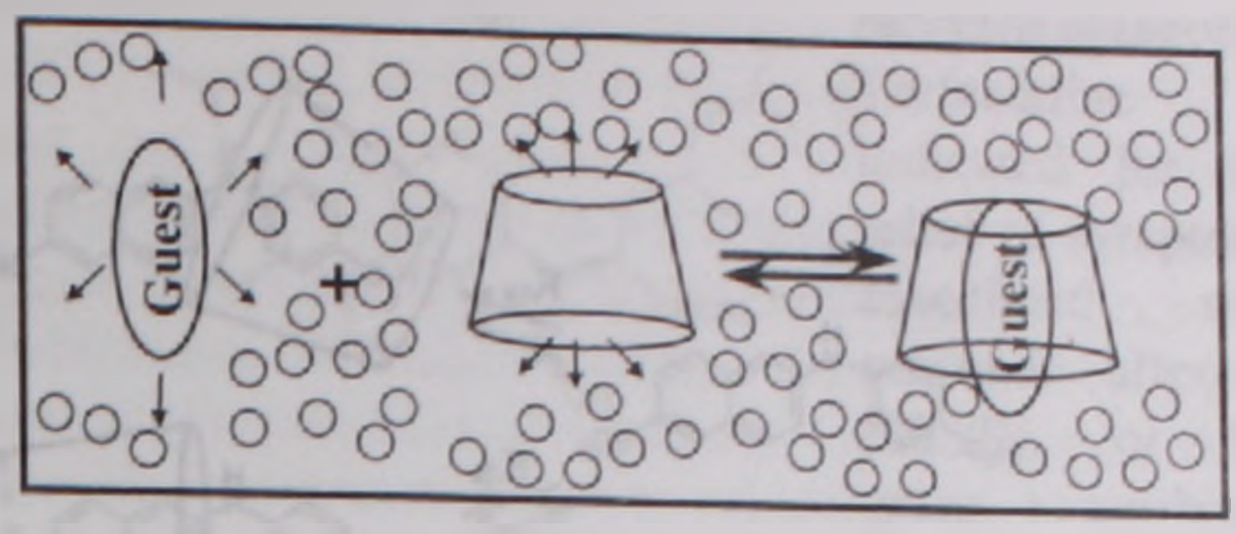
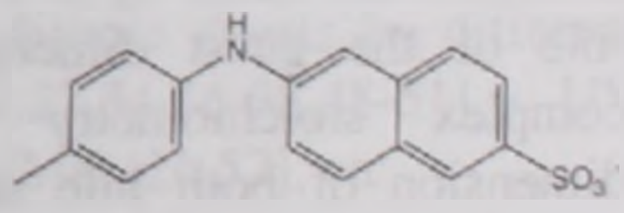


Figure 2. Schematic representation of a 1:1 stoichiometry cyclodextrin inclusion complex.

Due to their α-(1-4)-glycosidic linkages, all primary hydroxyl groups (C-6) are orientated toward one of the edges of the truncate cone, while the secondary hydroxyl groups (C-2 and C-3) are placed on the other edge. Since hydrogens of carbons 3, 5 and 6 and the non-bonding electron pairs of the glycosidic oxygen bridges are orientated toward the inside of the cavity, it has a hydrophobic environment with a high electron density [1,13]. These double characteristic of CDs, in one hand the existence of a hydrophobic cavity and on the other the existence of both hydrophilic hydroxyl rims give them the property to form inclusion complexes in water with a variety of organic molecules. During this process, the less polar guest molecule substitutes the energetically unfavored water molecules that occupy the CD cavity, as shown in figure 2. This process is regulated by non covalent interactions between host and guest: van der Waals forces, hydrogen bonding, electrostatic interactions [1,11].

During formation of the inclusion complex, the guest molecule enters, totally or partially, inside of the slightly apolar cavity of the CD. The simplest, and most frequent complex formed has a 1:1 stoichiometry (CD: guest), in which the guest is totally or partially included inside of a single CD. However, depending on the size of the CD cavity, or the dimensions and apolar sites of the guest molecule, other stoichiometries such as 2:1, 1:2, 2:2 or higher degree complexes do exist [14]. An example of the effect of the dimension of the cavity over the complex stoichiometry is the complexation of sodium deoxycholate (NaDC) by natural CDs. With α-CD, no complex is formed, while with β-CD and γ-CD 2:1 and 1:1 complexes are obtained. [15] In this review we will focus our attention on the complexation of ditopic guests by CDs and their higher degree derivatives (dimers, trimers, tetramers).

The 6-(p-toluidino)naphthalene-2-sulfonate (TNS) **1** has been one of the ditopic guests more wildly used as a model guest in order to compare the binding ability of different β-CD derivatives [16-23] or to determine the stability constant of guests molecules through competitive complexation processes [24,25].



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Recently, from steady-state and time-resolved fluorescence data, ^{13}C NMR titration, ROESY experiments and PCGA analysis, we have proposed that TNS forms two distinct 1:1 inclusion complexes, resulting from the complexation of both toluidin and naphthalensulfonate moieties (with two different microscopic equilibrium constants, K_{1a} and K_{1b}) and one 2:1 complex (with the microscopic equilibrium constants K_{2a} and K_{2b}) with β-CD and its monoamino derivative (β-$CDNH_2$), as shown in Figure 2 [23]. This is in agreement with Schneider *et al* [20]. The TNS molecule is first complexed by one CD (through the secondary face) by either of its two apolar sites (toluidino or naphthalensulfonate) and when the CD concentration increases the 2:1 complex if formed.

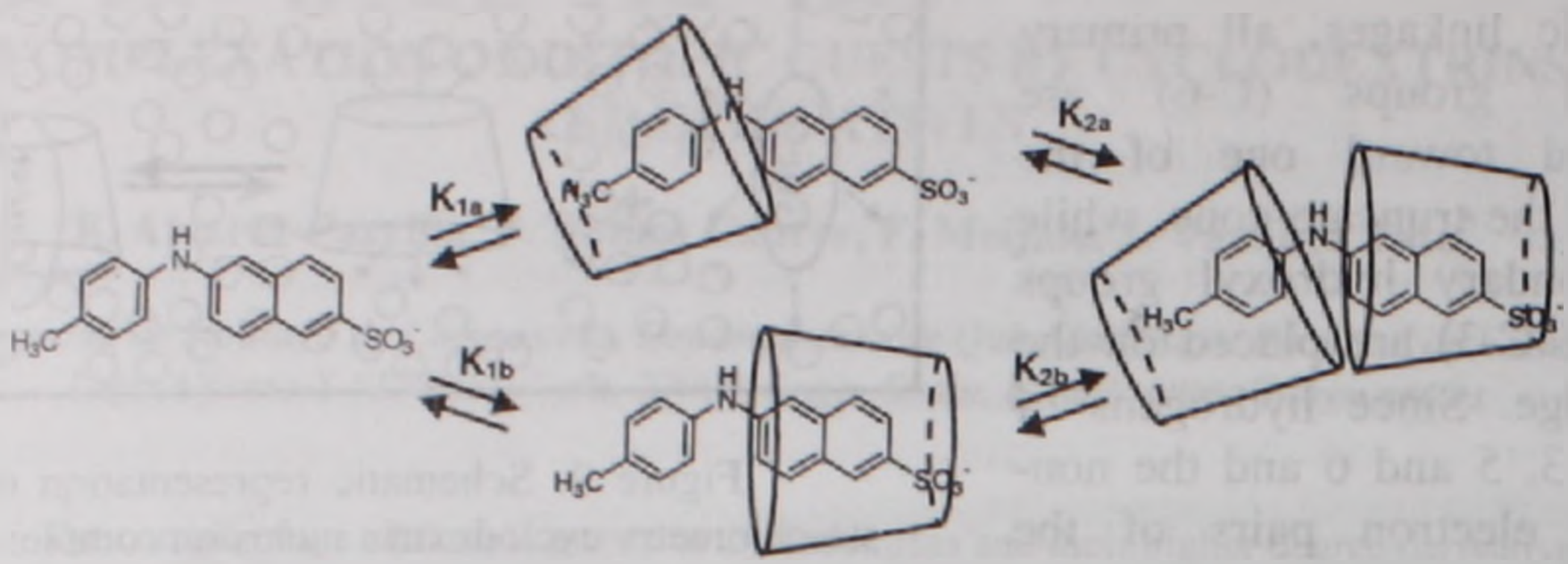
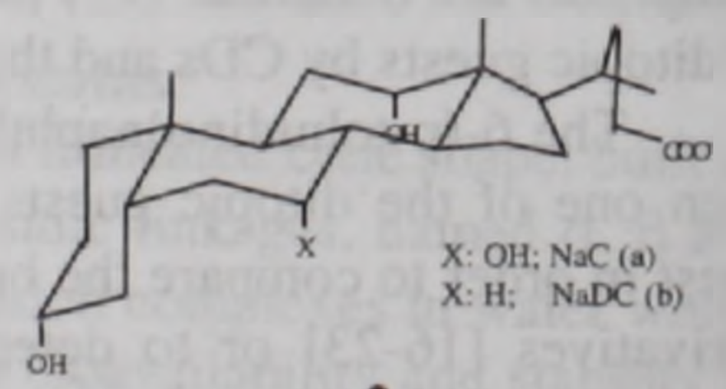


Figure 2. Schematic representation of the complexation of the ditopic guest TNS by β-CD, in which two 1:1 complexes and one 2:1 complex are obtained.

From the microscopic stability constants values (β-CD showed a higher K_{1a} value, while β-$CDNH_2$ showed a higher K_{1b} value) it was possible to conclude that the complexation behavior of TNS with β-CD was regulated by polarity factors, while that for β-$CDNH_2$ was regulated by both polarity and electrostatic interactions between the positively amino group and the negatively charged sulfonate moiety of TNS.

The complexation of the aminonaphthalene sulfonate derivative 6-(p-anilino)naphthalen-2-sulfonate (2,6-ANS) is another example in which electrostatic interactions play an important role on the complexation behavior of a ditopic guest. The structural difference with TNS is that the methyl group in position 6 of the benzene ring is substituted by a hydrogen atom. When ANS is complexed by β-CD it forms only two 1:1 complexes (similar to those of TNS). However, when it is complexed by protonated β-$CDNH_2$, it forms two 1:1 complexes and a 2:1 complex. This different behavior is due to the electrostatic interaction between the protonated amino group and the sulfonate ion [23].

The complexation of the bile salts, sodium cholate **(2a)** and its deoxyderivative sodium deoxycholate **(2b)**, by β-CD helps to understand the role of the guest dimension and polarity on the complex stoichiometry [26]. The longitudinal dimension of both bile salts is identical and large enough (between 12 and 15 Å) to allow the complexation by two β-CDs. From NMR experiments has been demonstrated that NaC forms a stable 1:1 complex, while NaDC forms a 2:1 complex. The only structural difference between both salts is located at C-7 position of the steroid body, NaC having a hydroxyl group and NaDC a hydrogen atom†. This confers a larger hydrophobic region to the NaDC than that of NaC, and consequently it can be complexed by two CDs. The conclusion is that the stoichiometry of the complex formed is regulated by their polarity.



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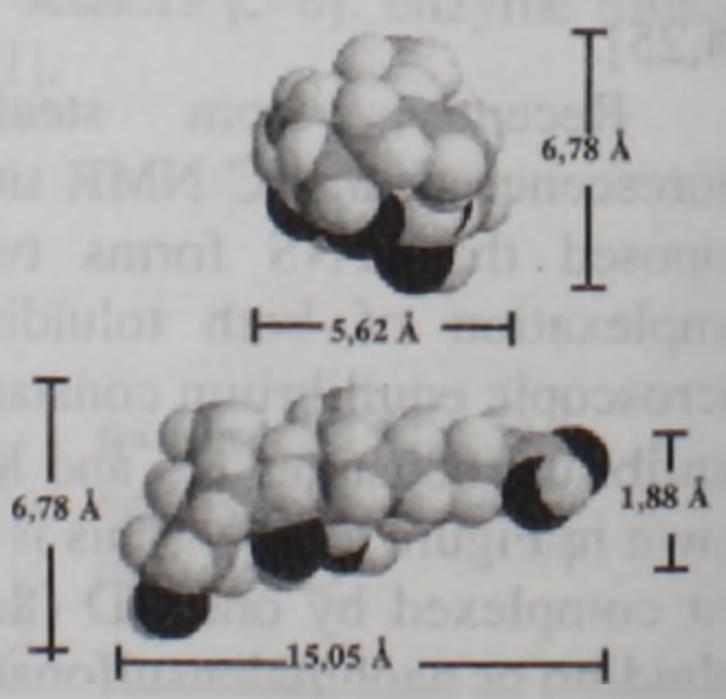
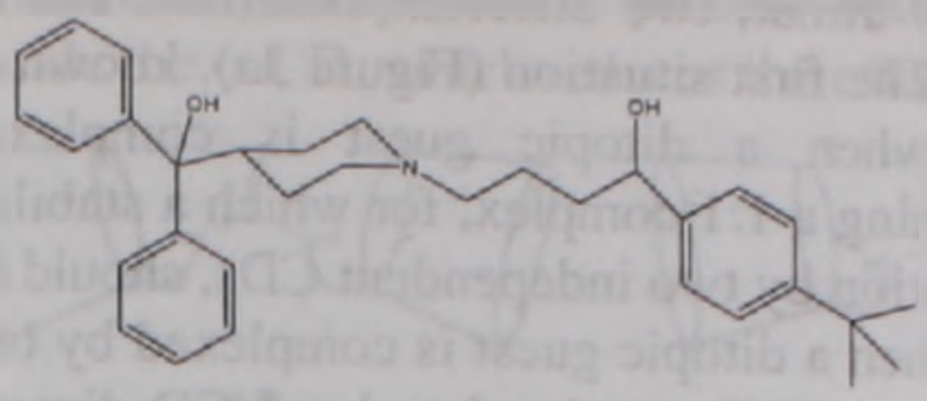


Other ditopic guests such as the histamine H_1-

†This difference has also a strong influence on the aggregation behaviour of both biosurfactants in water as it has been widely demonstrated [27].



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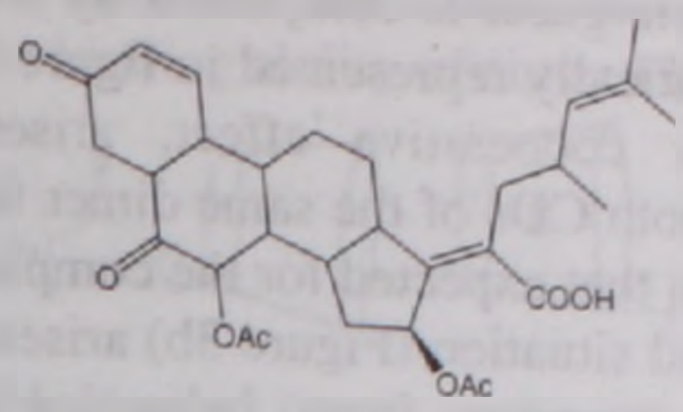

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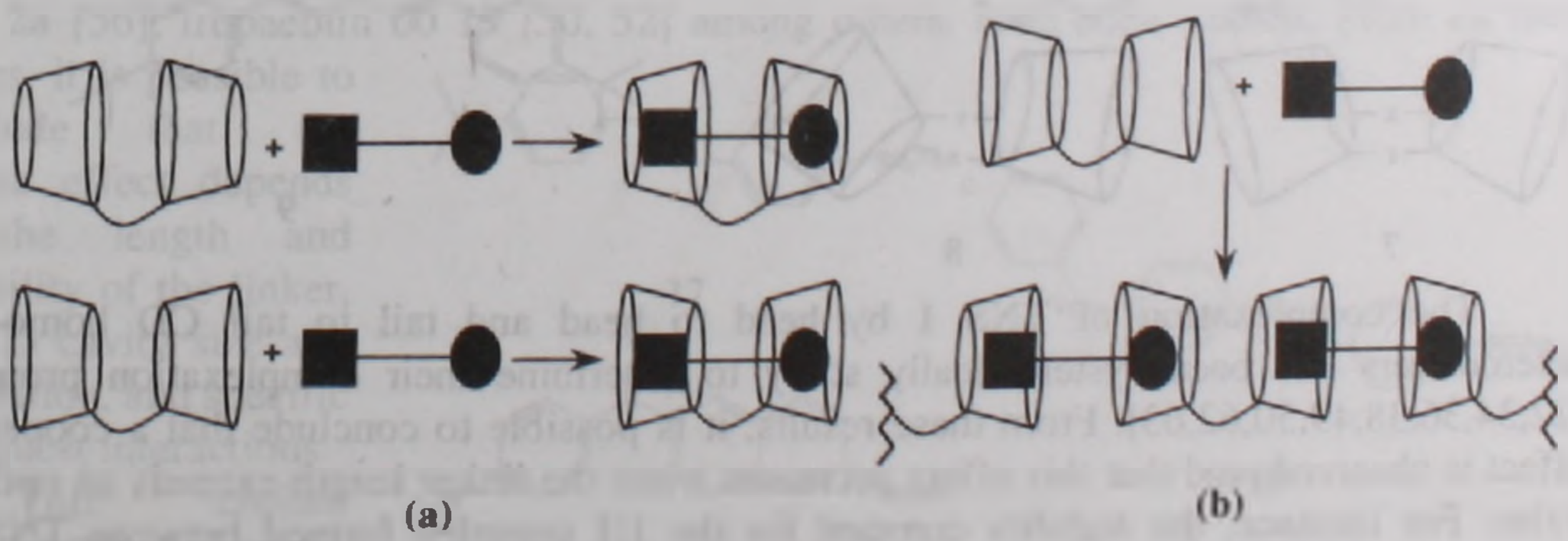
receptor antagonist Terfenadine 3, indicated for the relief of symptoms associated with seasonal allergies [28,29], or the gram + antibiotic helvolic acid 4 (unpublished results) used in dermatological diseases have been complexed by β-CD. Both drugs form 2:1 complexes. It was also evident an increase on their solubilization on water as a result of the complex formation. A study carried out by Wimmer *et al* [30] showed that retinol forms a 2:1 complex with γ-CD, which increases its stability toward UV light and oxygen oxidation and polymerization. Lawrence *et al* [31] observed high stability constants when a tetraaminoporphyrin was complexed by twσ-ĐMβ-CD (heptakis(2,6-di-O-methyl)-β-CD).

II. Complexation of ditopic guests by cyclodextrin dimers.

CD dimers are molecules in which two CD units are linked together through covalent unions. They can be classified in four groups depending on: a) the type of CD present in the structure: homo- [26,32-35] and heterodimer [33,34], when both CDs are or not of the same type; b) the side of the CD were the linking is located: head to head [26,36-39], tail to tail [34,35,38-40] and head to tail [41], where head and tail are the primary and secondary hydroxyl rims of CD; c) the linking bridge: diamine [42], diether [43], diester [44], disulfide [45], imidazolium [33] and diamide [42] are the most common ones; and d) the number of linking groups present in the structure: single and doubly bridged CD dimers [46,47]. Among all CD dimers, the most common ones are the head to head and tail to tail β-CD homodimers.

Over the last 10 years numerous CD dimers have been synthesized in order to study the influence of two adjacent CDs over the complexation of ditopic guests by different instrumental techniques: fluorescence spectroscopy [17,22,34,36-38,48-51], UV spectroscopy [39,52-54], differential calorimetry [35,44,55,56], NMR [26,57], etc.



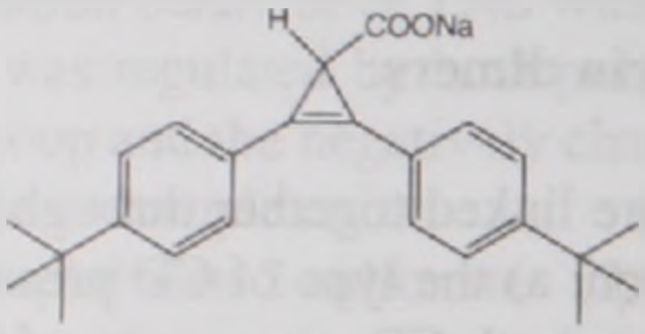
(a) (b)

Figure 3. Schematic representation of the structures that can be formed by the complexation of a ditopic guest by a CD dimer: (a) Chelate binding or cooperative effect; (b) Supramolecular polymer with a n:n stoichiometry.

When a ditopic guest is complexed by a CD dimer, two different situations can be achieved, as schematically represented in figure 3. The first situation (Figure 3a), known as chelate binding or cooperative effect, arises when a ditopic guest is complexed simultaneously by both CDs of the same dimer forming a 1:1 complex, for which a stability constant, higher than that expected for the complexation by two independent CDs, should be expected. The second situation (Figure 3b) arises when a ditopic guest is complexed by two CDs (through their secondary faces) belonging to two different head to head CD dimers, resulting in the formation of a supramolecular polymer with a n:n stoichiometry.

a) Chelate binding.

The chelate binding hypothesis was first suggested by Breslow *et al* [35,37,44, 47,55, 58-61] when proposing CD dimers as mimics for antibodies and enzymes. According to this hypothesis when a ditopic guest is complexed simultaneously by two CDs from the same dimer, the global stability constant should be larger than the square of that for the complexing of each binding site, since the free energy is doubled. As an example, the complexation of the ditopic host **5**, with two tert-butylphenyl groups, by dimer **6** showed a binding constant K_{11} 7 x 10^8 M^{-1}, which is similar to those of medium-affinity antibodies.



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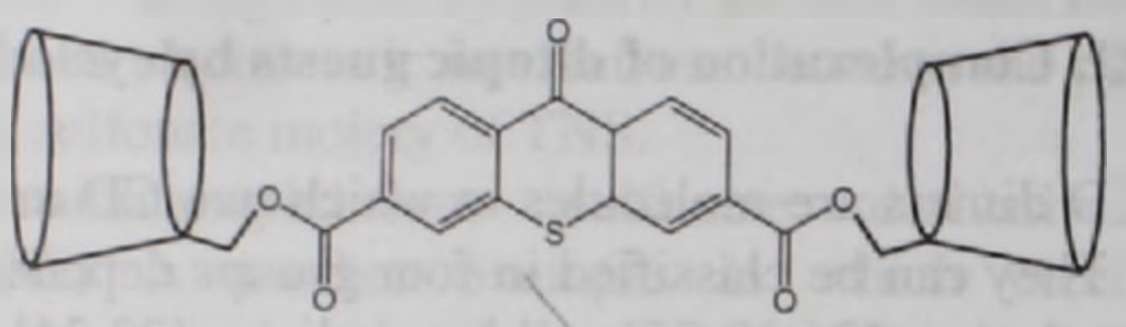

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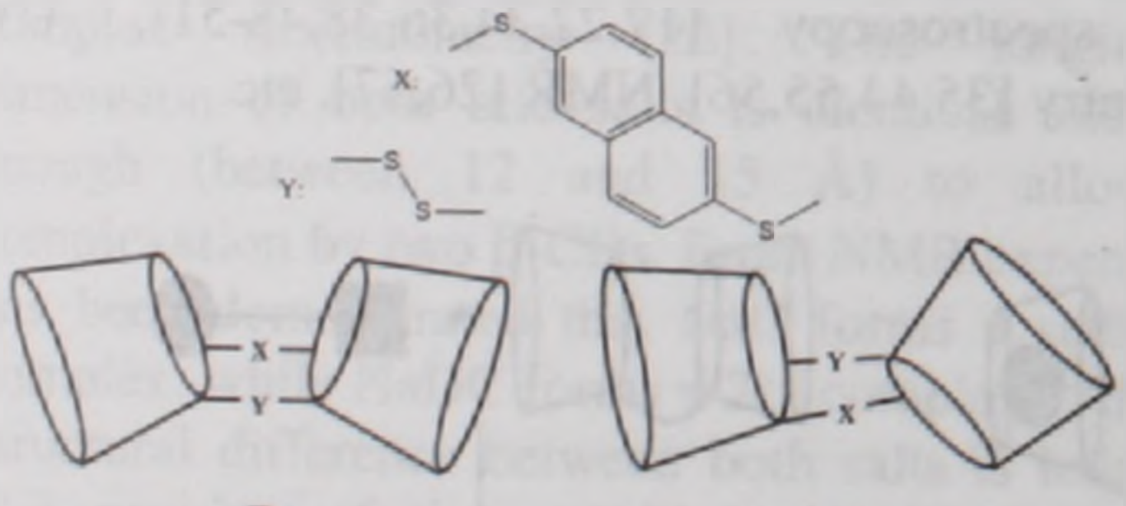
In order to study the stereochemical aspects of the complexation process, Breslow *et al* synthesized double linked dimers **7** and **8**, and studied their complexation behavior with the ditopic guest **9**, observing that with the occlusive or clamshell dimer **7** the ditopic guest is cooperatively complexed by both CDs ($K_{11} > 4 \times 10^{11}$ M^{-1}), while with the aversive or loveseat dimer **8**, no cooperative complexation was observed. In further studies these authors found that the binding of ditopic guests by CD dimers in water solution is regulated by enthalpic advantages, instead of the initially considered translational entropy process, that in fact was unfavorable [37,44,61].



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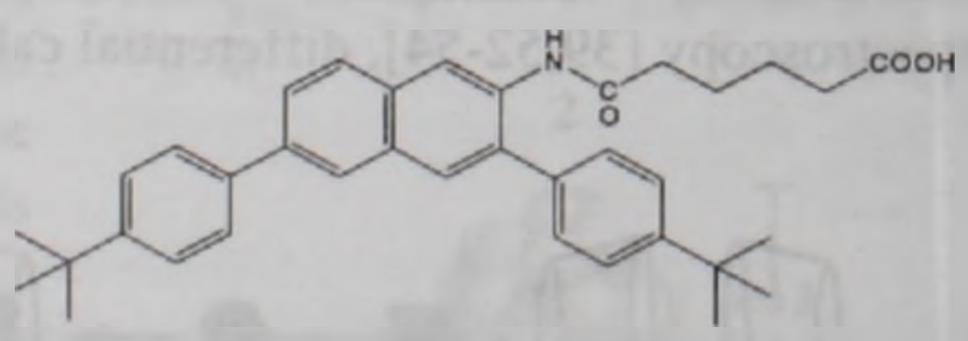

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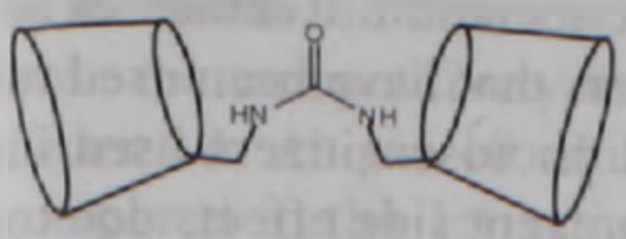
The complexation of TNS **1** by head to head and tail to tail CD homo- and heterodimers has been systematically study to determine their complexation properties [22,34,36,38,49,50,62,63]. From these results, it is possible to conclude that a cooperative effect is observed, and that this effect decreases when the linker length exceeds an optimum value. For instance, the stability constant for the 1:1 complex formed between TNS and dimers **10** and **11** reduces from 45700 to 9300 as the number of methylene groups increases, being in all cases higher than that for β-CD (K_{11} 3140 M^{-1} and K_{21} 86 M^{-1}) [22]. When TNS was complexed by the heterodimer **12**, a negative effect was observed, since there is a

competitive complexation process between TNS and the linker that is partially included inside the α-CD, which reduces the effective binding ability of dimer **12** [34].



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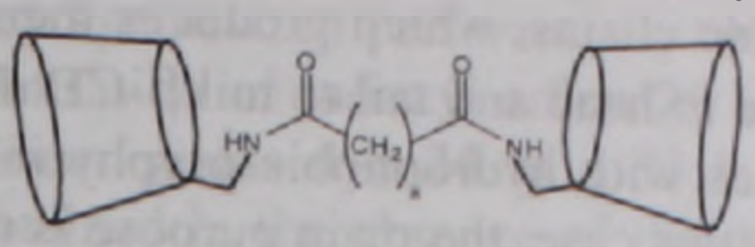

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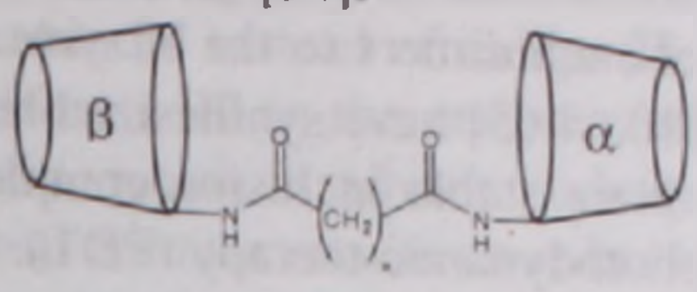

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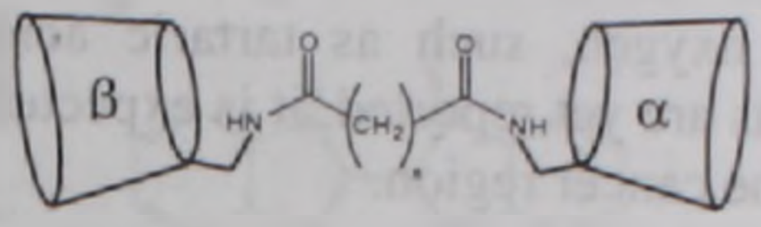

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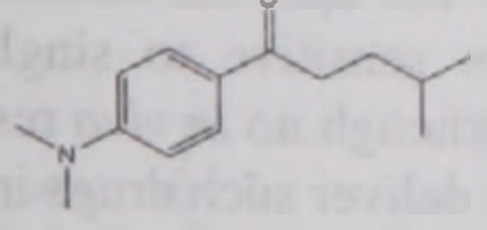

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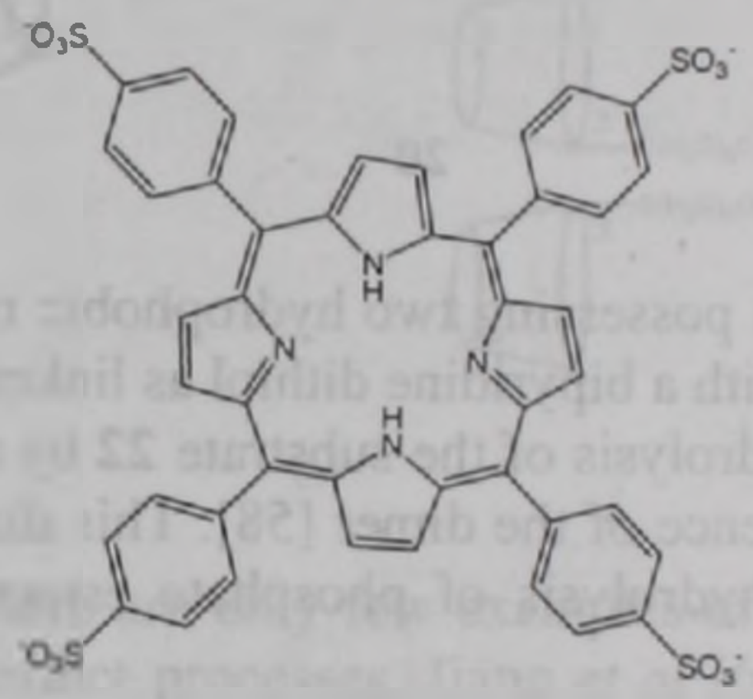
The effect of the cavity size of both CDs was studied by Toda *et al* [48]. They observed that the heterodimer **13** showed a cooperative and site-specific binding to DMBA **14**, in which the aromatic moiety is partially included inside of the α-CD cavity, while the alkyl group is included into the β-CD cavity.



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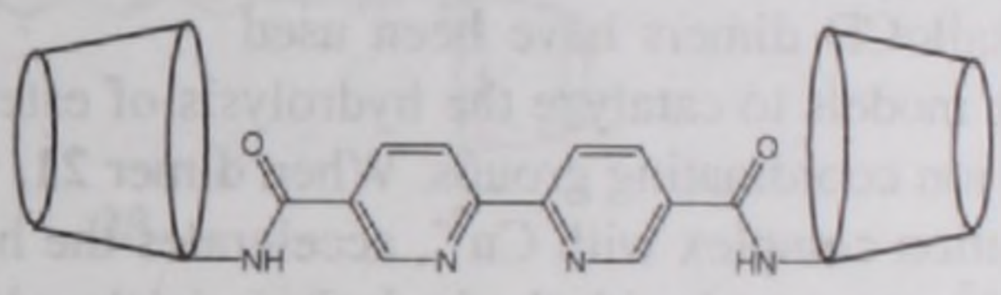

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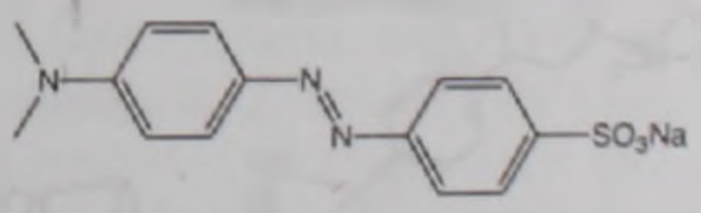
When the porphyrin derivative **15** was complexed by dimer **16** a final 2:2 complex was formed, i.e. two porphyrins are complexed by two CD dimers. The process is facilitated by the presence of 0.5 equivalents of Zn^{2+} due to the formation of a tetrahedral metal ion complex with the bipyridine units of both dimers [34].

Other ditopic guests such as methyl orange **17** [36, 49, 50, 52, 53], BNS **18** [35, 50], NaC **2a** [56], tropaeolin (0) **19** [50, 52] among others, have been studied. From all these results, it is possible to conclude that the chelate effect depends on the length and flexibility of the linker, the CD cavity size and orientation, and specific host-guest interactions.



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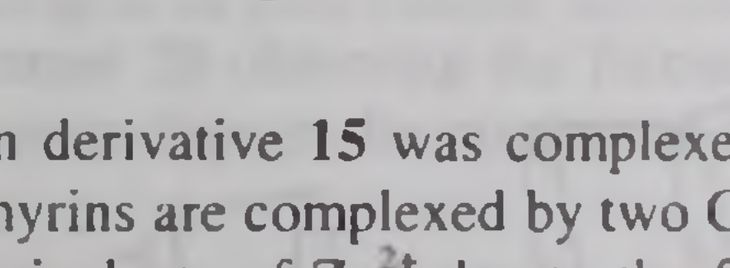

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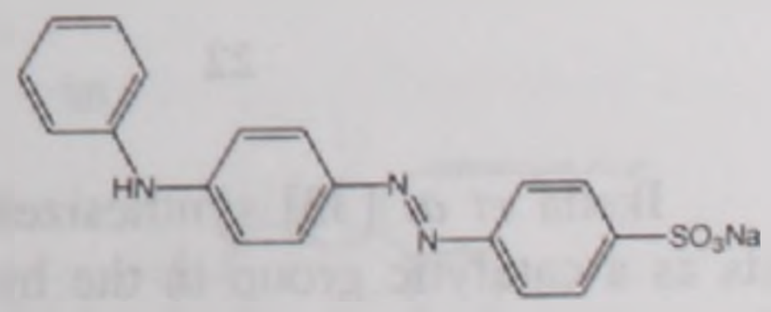

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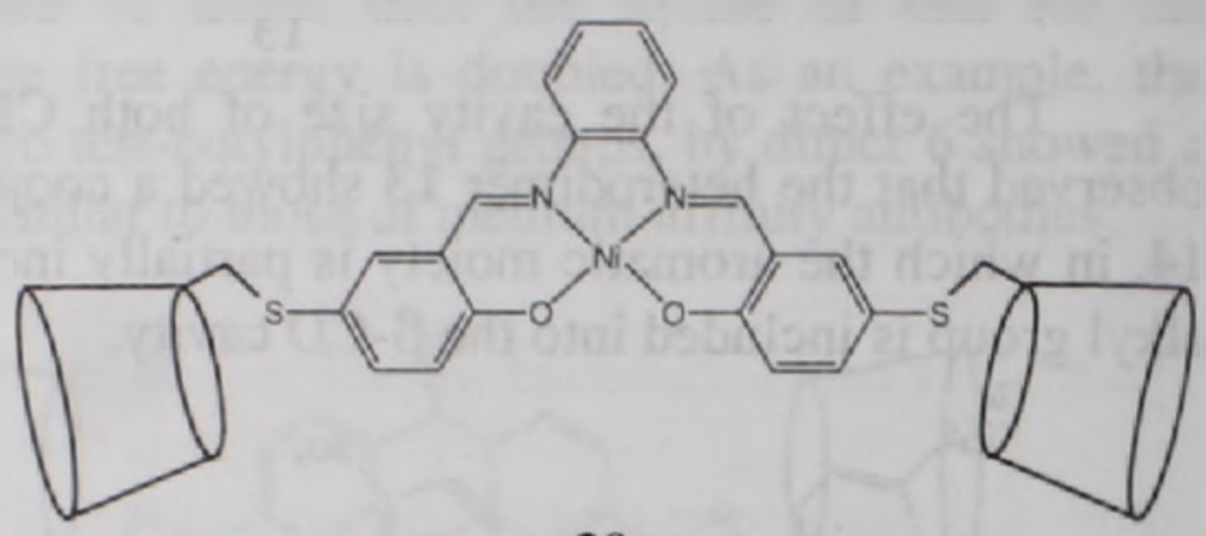
This chelate effect of CD dimers can be exploited in order to use them in different chemical and biological

applications. Breslow *et al* [61] found that some CD dimers can selectively inhibit dimeric and tetrameric enzymes as citrate synthase and lactic dehydrogenase, because of the binding of such dimers to the enzyme side chains, which produces their dissociation. Ruebner *et al* [40,64,65] have synthesized head to head and tail to tail β-CD dimers that have been used to obtain stable inclusion complexes with hydrophobic porphyrinoid photosensitizers used in photodynamic therapy (PDT). In this case, the main purpose is to prevent side effects due to unwanted targeting to organs others from the tumor. The optimal spacer length for each porphyrinoid derivative was established, the stability constants values being in the range 10^4 - 10^6 M^{-1}. For the specific release of the included drug at the tumor site, dimers with breaking points sensitive to singlet oxygen, such as tartaric acid moiety, were also synthesized. Although no *in vivo* results are yet reported, it is expected that these CD dimers will selectively deliver such drugs in the cancer region.

Maletic *et al* [66] reported the use of the orange-colored Nickel dimer **20** to selectively binding tripeptids containing either L-Phe-D-Pro or D-Phe-LPro, from a maximum of 24389 different tripeptides. These authors proposed that this selectivity could be exploited for the design of novel sequence-specific peptide-cleaving catalysts.



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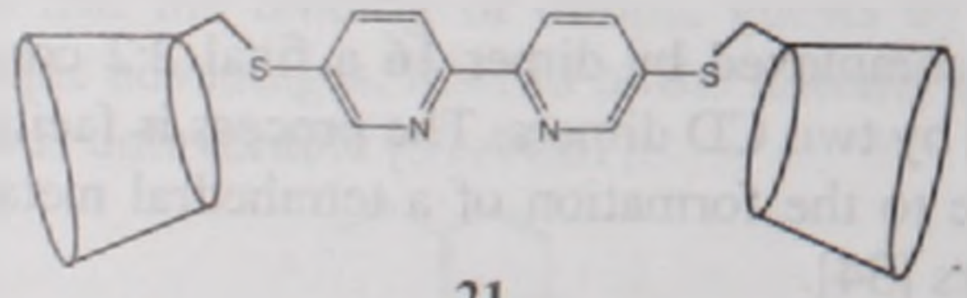
MetalloCD dimers have been used as enzyme models to catalyze the hydrolysis of esters possessing two hydrophobic moieties and metal ion coordinating groups. When dimer **21**, with a bipyridine dithiol as linker, forms a coordination complex with Cu^{2+}, accelerates the hydrolysis of the substrate **22** by a factor of 2.25×10^3, compared with the hydrolysis in the absence of the dimer [58]. This dimer has also shown a really good catalyst effect over the hydrolysis of phosphate esters in the presence of La^{3+} and H_2O_2.



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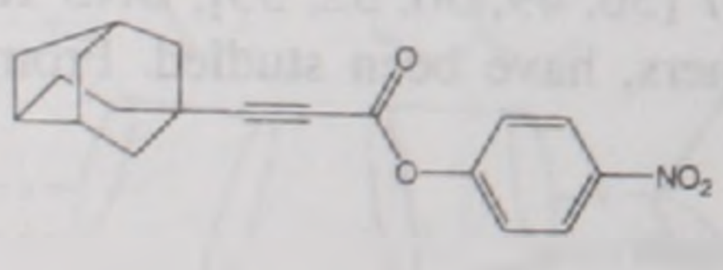

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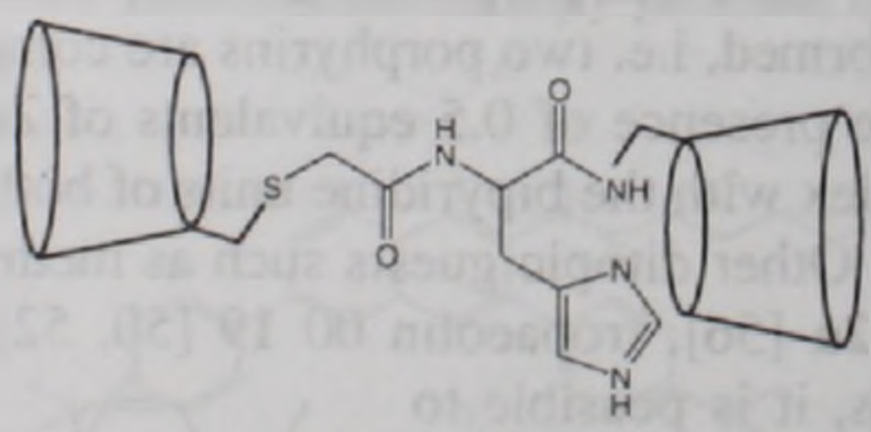
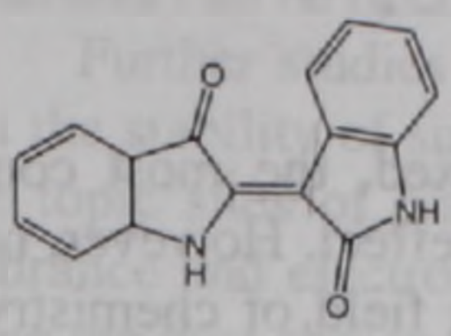


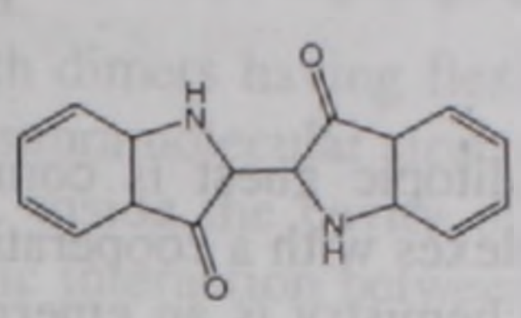
23

Ikeda *et al* [33] synthesized dimer **23** possessing a imidazole-appended group, that acts as a catalytic group in the hydrolysis of nitrophenyl alkanoates, obeying a Michaelis-Menten mechanism. No catalytic effect was observed when one β-CD in the dimer was substituted by α-CD.

An interesting use of CD dimers has been proposed by Easton *et al* [39] for the selectively synthesis of non-linear ditopic molecules from reagents complexed in both CD's of the dimer. In this way, they synthesized preferentially indirubin **24** instead of indigo **25**, from the competitively condensation of indoxyl anion **26** and isatin **27** in the presence of dimer **10**. At pH 10, this dimer yields dye **24** in a 33:1 ratio, which is advantageously compared to the 1:1 ratio obtained in the absence of the dimer. Similar results have been published by Ikeda *et al* [67] for the benzoin condensation reaction from two molecules of benzaldehyde.



24



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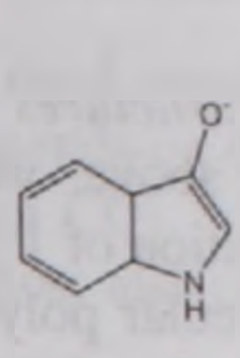

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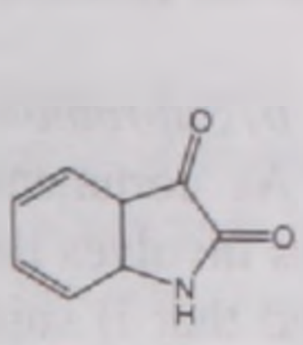

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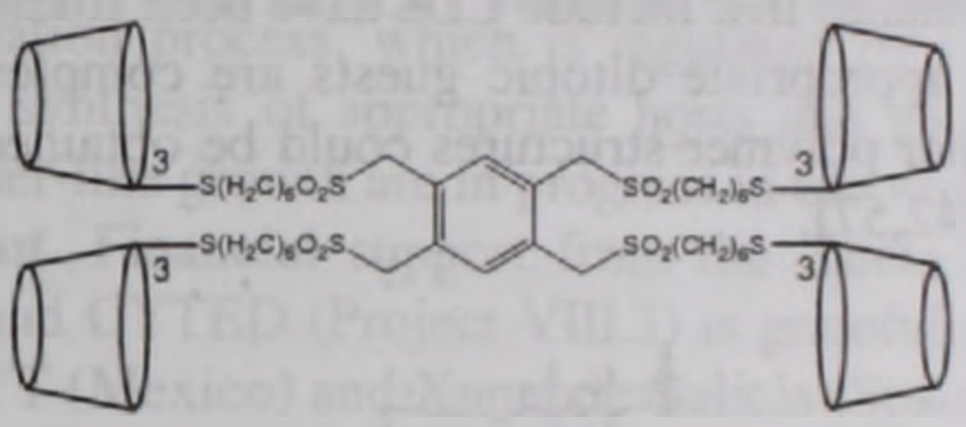
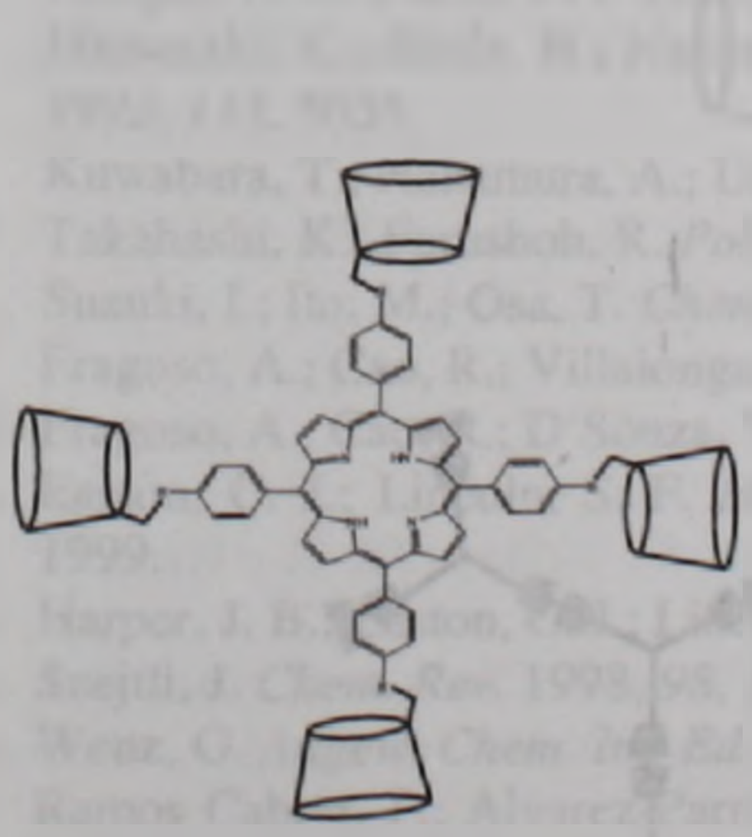


28

There are only few examples of the use of higher degree CD derivatives as hosts in chelate effect processes. Jiang *et al* [68] studied the complexation of tetraporphyrines and metalloporphyrines by tetramer **28** observing the formation of a 1:1 complex, with a K_{11} value as high as 10^8 M^{-1}, even though the number of aryl derivatives complexed is still unknown.



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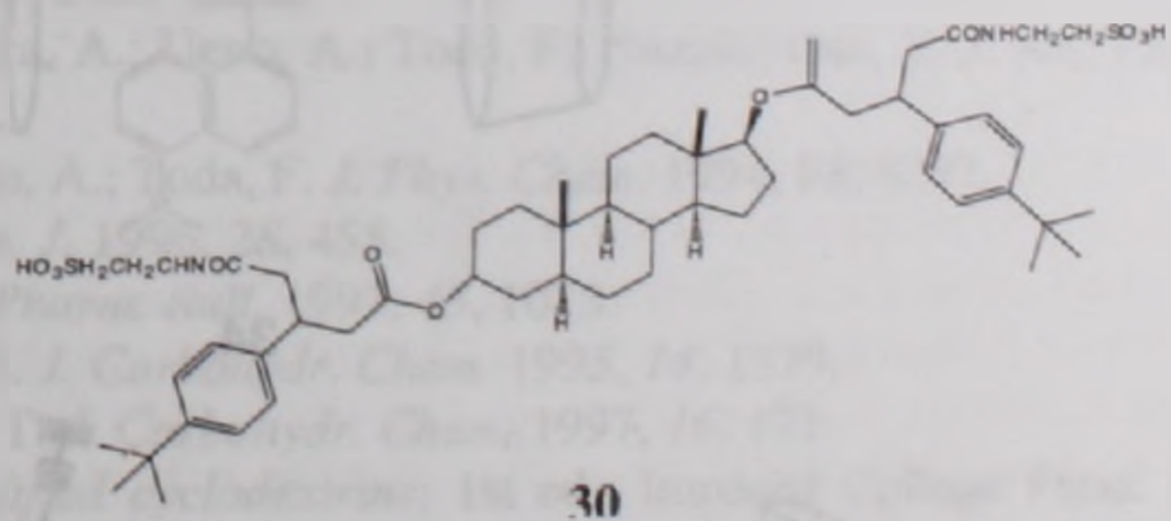
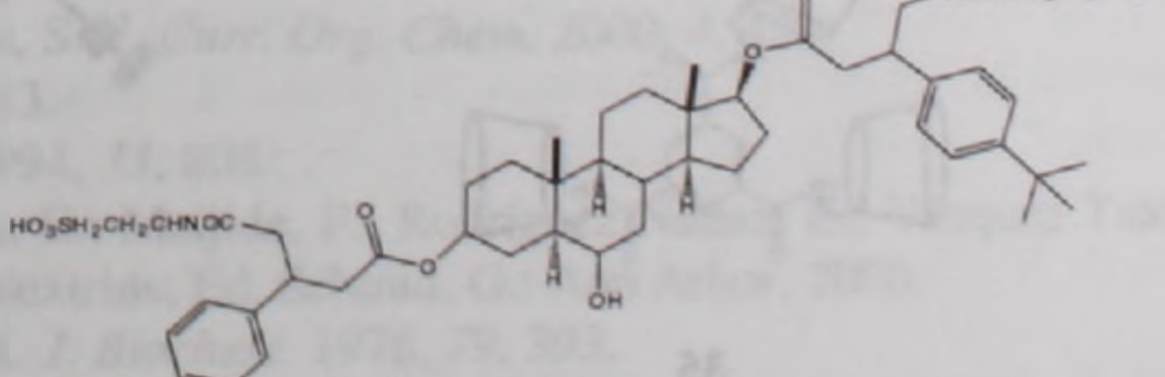


30

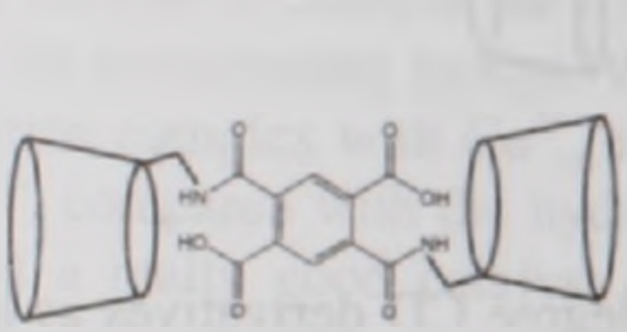


31

Quite interesting was the study of the regioselectivity of artificial enzymes, through chelate binding by CD derivatives carried out by Breslow *et al* [60,61]. The tetraphenylporphyrin tetramer **29** was synthesized, and its Mn(III) complex was used as a mimetic catalyst of cytocrom P-450 for the hydroxylation of saturated carbons. This tetramer complexed steroid **30** by two opposite CDs, placing the steroid body above the Mn(III) complex. When treated with iodosobenzene the hydroxylation of C-6 saturated carbon results in quantitative yield, with stereoselectivity toward the 6α-hydroxysteroid **31**. Further studies confirmed that this regioselectivity permitted to hydroxylate unactivated carbons even in the presence of olefinic and hydroxyl groups, which are more easily oxidized.

b) Supramolecular structures.

As commented on above, when a ditopic guest is complexed, the most common process involves the formation of 1:1 complexes with a cooperative effect. However, having in mind that i) supramolecular polymeric chemistry is an emerging field of chemistry that combines the polymeric chemistry with supramolecular chemistry to design "living" polymers by the self-assembly of complementary monomeric components through molecular interactions and recognition processes [69]; and ii) that no examples others than polyrotaxanes and polycatenanes that include CDs have been studied [70], we have proposed the hypothesis that when appropriate ditopic guests are complexed by head to head CD dimers linear supramolecular polymer structures could be obtained by the way of inclusion complex formation [23,26,42,57].



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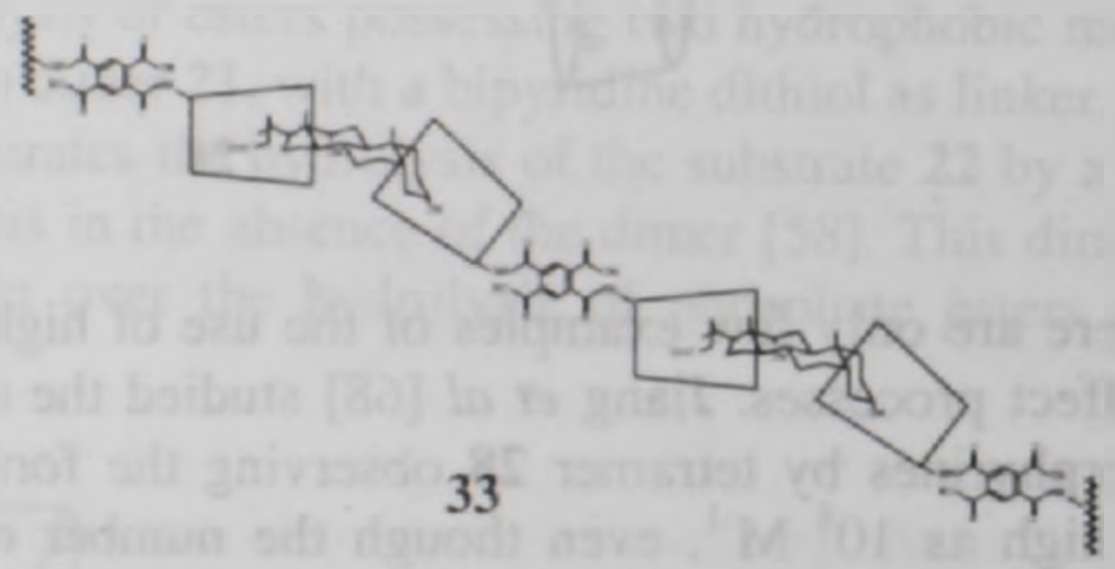

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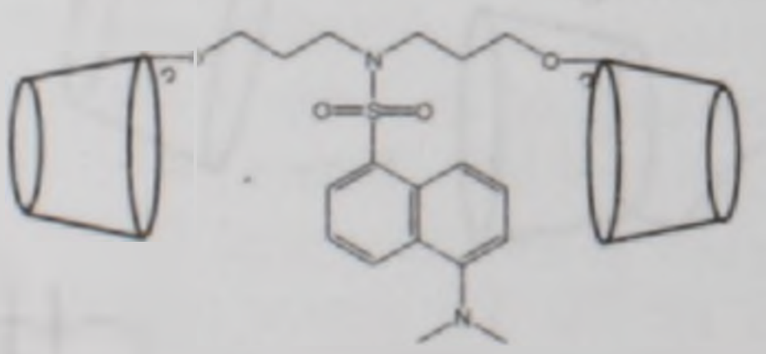

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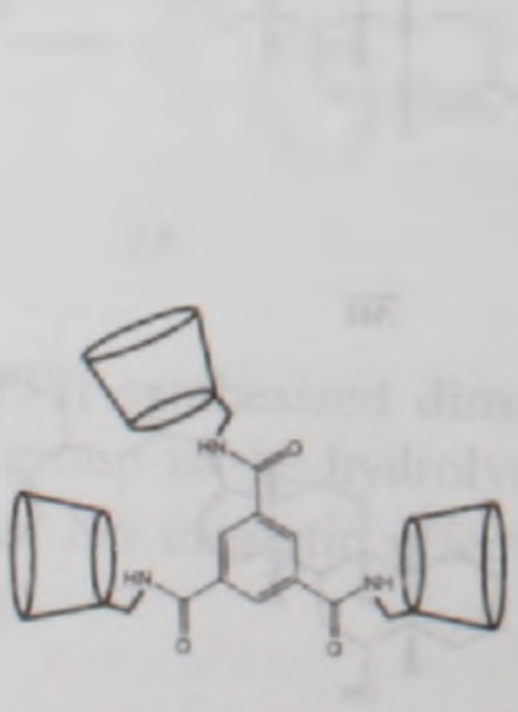
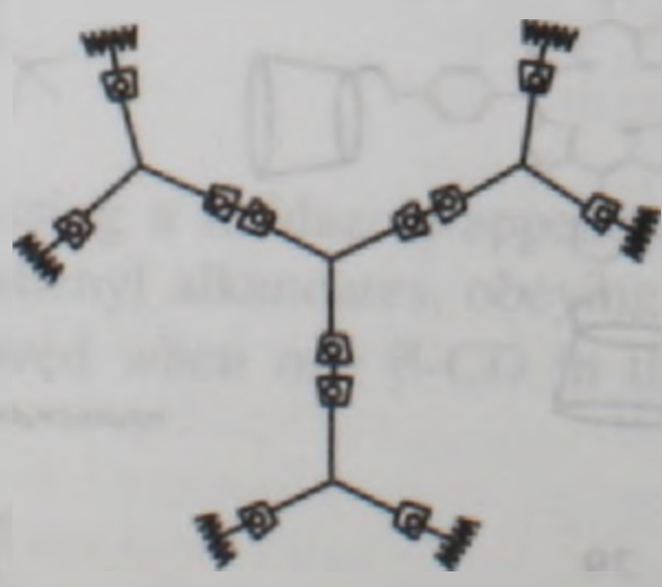


35



36

In order to prove such a hypothesis, sodium deoxycholate NaDC **2b** was used as ditopic guest, since previous studies showed that this molecule forms 2:1 complexes with β-CD and two amino derivatives through their secondary side [23,26,42,57,71]. As expected, when NaDC was complexed by head to head dimer **32** a linear supramolecular polymer **33** with a n:n stoichiometry was obtained [26]. On the other hand, Huskens, Reinhouldt *et al* [56] observed the formation of a 1:1 complex with chelate effect when NaDC was complexed by tail to tail dimer **34**. From these results, it is possible to conclude that depending on the geometry of both host and guest, either chelate effect or supramolecular structures can be obtained.

Further studies with dimers having flexible or rigid amine or amide linkers, showed that the stability of such supramolecular structures depends on the penetration degree of the two topic sites of NaDC inside the cavity of the two CDs, which is controlled by steric hindrance and electrostatic interaction between both host and guest, a flexible amide linker being the best choice [23,42].

When NaDC was complexed by trimer **35** a dendrimer-like supramolecular polymer **36** was obtained by the way of self-assembly of both structural units. By electron microscopy it was possible to observe different fractal structures that depend on the number of CDs involve in the complexation process, which is regulated by steric hindrance [72]. At the moment studies on the synthesis of appropriate hosts and guests in order to improve the supramolecular dendrimer-like growth are in progress in our research group.

Acknowledgement. Financial support from the Xunta de Galicia (Project XUGA PGIDT99PXI26201B) and CYTED (Project VIII.3) is gratefully acknowledged. E.A.P. and P.R.C. thanks CONACYT (Mexico) and Xunta de Galicia (Spain) for a research scholarship.

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