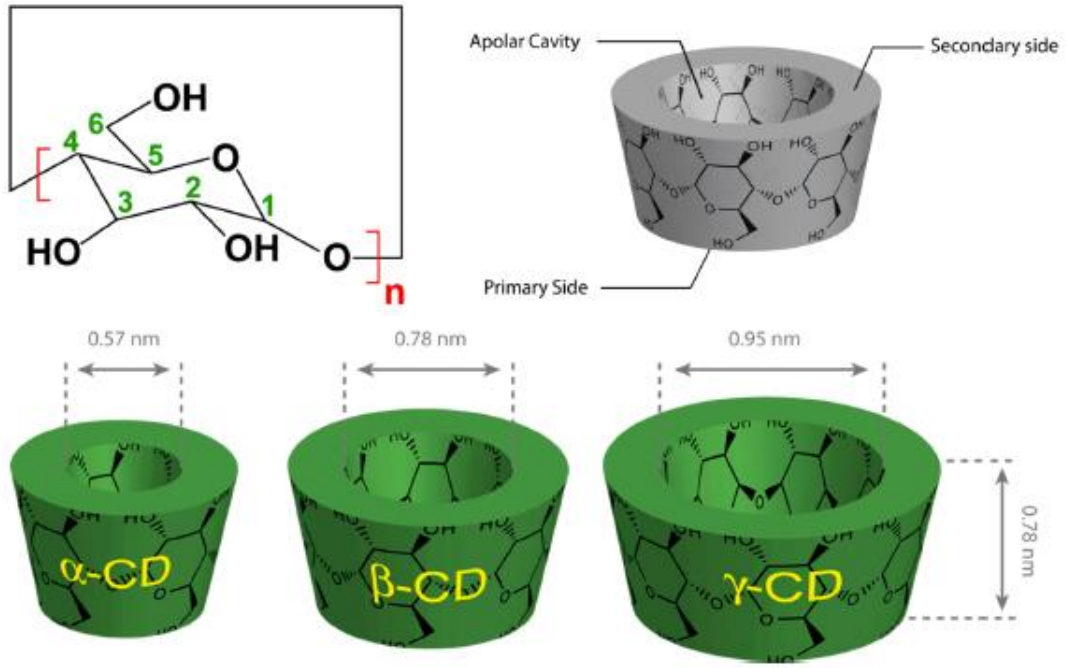
Cyclodextrins



Top: Functional structural scheme of α-CD ($n = 6$), β-CD ($n = 7$), and γ-CD ($n = 8$). Bottom: Geometric dimensi

TABLE 1

Dimensions of three natural cyclodextrins.

Type of cyclodextrin	Number of glucose units	Cavity diameter (Å)	Cavity height (Å)	Cavity volume (Å)
α	6	4.7–5.3	7.9	174
β	7	6.0–6.5	7.9	262
γ	8	7.–8.3	7.9	427

Cyclodextrins in drug formulations

Cyclodextrins in pharmaceutical formulations I: structure and physicochemical properties, formation of complexes, and types of complex

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Cyclodextrins are cyclic oligosaccharides that have been recognized as pharmaceutical adjuvants for the past 20 years. The molecular structure of these glucose derivatives, which approximates a truncated cone, bucket, or torus, generates a hydrophilic exterior surface and a nonpolar interior cavity. Cyclodextrins can interact with appropriately sized drug molecules to yield an inclusion complex. These noncovalent inclusion complexes offer a variety of advantages over the noncomplexed form of a drug. Cyclodextrins are primarily used to enhance the aqueous solubility, physical chemical stability, and bioavailability of drugs. Their other applications include preventing drug–drug interactions, converting liquid drugs into microcrystalline powders, minimizing gastrointestinal and ocular irritation, and reducing or eliminating unpleasant taste and smell. Here, we discuss the physical chemical properties of

Shape and polarity

- Given the chair conformation of the glucopyranose units, cyclodextrins are shaped like a truncated cone rather than as perfect cylinders.
- The hydroxyl functions are oriented to the cone exterior, with the primary hydroxyl groups of the sugar residues at the narrow edge of the cone and the secondary hydroxyl groups at the wider edge.
- The central cavity is lined with the skeletal carbons and ethereal oxygen of the glucose residues, which impart a lipophilic character. The polarity of the cavity has been estimated to be similar to that of an aqueous ethanolic solution.

- The inclusion complexes formed have several applications in pharmaceutical formulations. For example, cyclodextrins enhance the water solubility of poorly soluble drugs and improve their bioavailability, mask the bitter taste of the active ingredient, enable the development of chewable and orally disintegrating tablet formulations, and stabilize drugs from light, thermal, and oxidative degradation.
- Cyclodextrins are both large (molecule weight from almost 1000 to over 2000 Da) and hydrophilic, with a significant number of hydrogen donors and acceptors; therefore, they cannot be absorbed from the gastrointestinal tract in their intact form.
- Hydrophilic cyclodextrins are considered nontoxic at low to moderate oral dosages.

Biodistribution (pharmacokinetic) and toxicity

- The natural α- and β-cyclodextrins, unlike γ-cyclodextrin, cannot be hydrolyzed by human saliva and pancreatic amylase.
- However, both α- and β-cyclodextrins can be fermented by the intestinal microflora.
- α-Cyclodextrin is well tolerated when administered orally and is not associated with significant adverse effects. Only a small fraction of a-cyclodextrin is absorbed intact from the gastrointestinal tract and is mainly excreted unchanged in the urine following intravenous administration.
- By contrast, β-cyclodextrin cannot be administered parenterally because of its **low aqueous solubility and nephrotoxicity**. However, it is **nontoxic when administered orally**. The renal toxicity of α- and β-cyclodextrins, following parenteral administration, as well as problems with several modified cyclodextrins, have been well documented

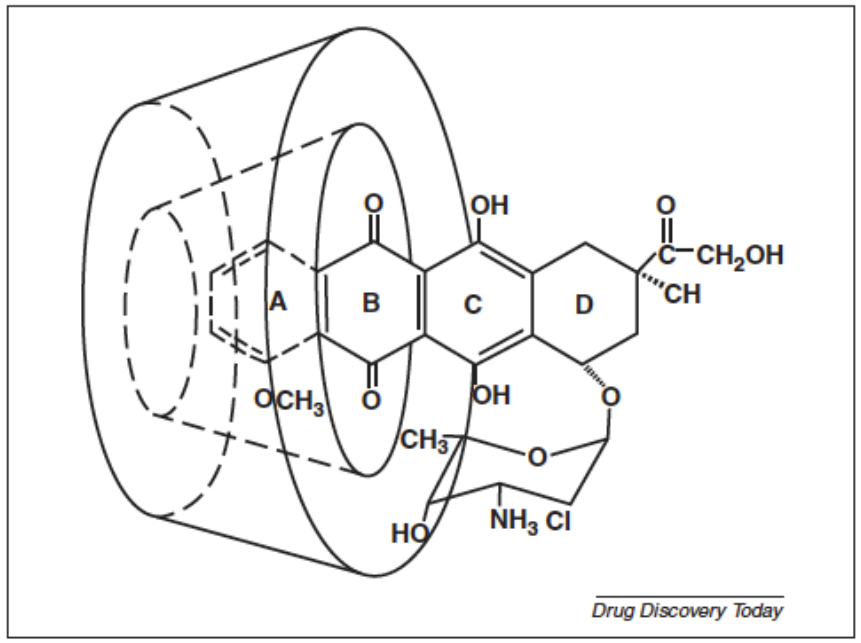


FIGURE 2

Proposed structure of the doxorubicin–γ-cyclodextrin complex.

- Cyclodextrins in aqueous solution are capable of forming inclusion complexes with many drugs by accepting into their central cavity (Fig. 2) a drug molecule or, more frequently, only the lipophilic portion of the therapeutics moiety.
- The driving forces behind complex formation are reported to be release of enthalpy rich water molecules from the cavity, electrostatic interactions, van der Waals interactions, hydrophobic interactions, hydrogen bonding, and release of conformational strain and charge-transfer interactions

Complex formation: interactions

- There are four energetically favorable interactions that help shift the equilibrium towards complex formation:
- (i) the displacement of polar water molecules from the apolar cyclodextrin cavity;
- (ii) the increased number of hydrogen bonds formed as the displaced water returns to the larger pool;
- (iii) a reduction in the repulsive interactions between the hydrophobic guest and the aqueous environment; and
- (iv) an increase in hydrophobic interactions as the guest molecule inserts itself into the apolar cyclodextrin cavity.

Cyclodextrins cavity size and inclusion complexes

- Based on dimensions, α-cyclodextrin can typically form a complex with compounds of lower molecular weight or compounds with an aliphatic side chain. β-Cyclodextrin will complex with aromatic and heterocyclic molecules, and γ-cyclodextrin will accommodate larger molecules, such as macrocycles and steroids.

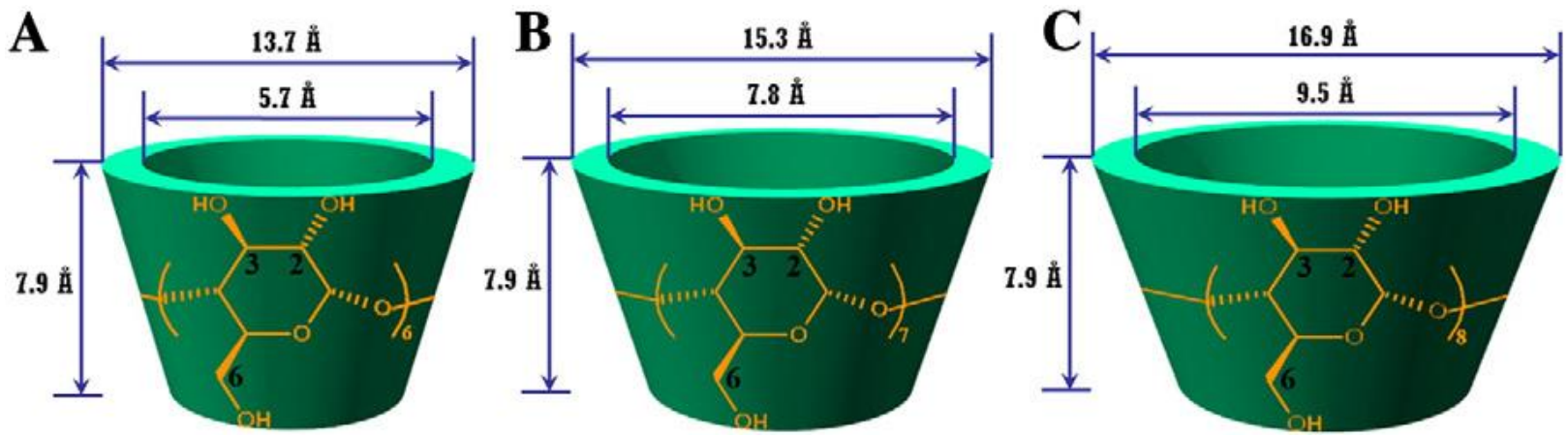


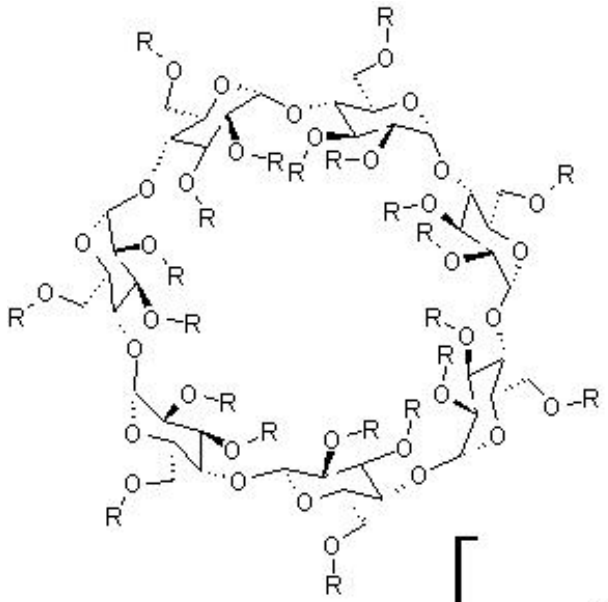
TABLE 3

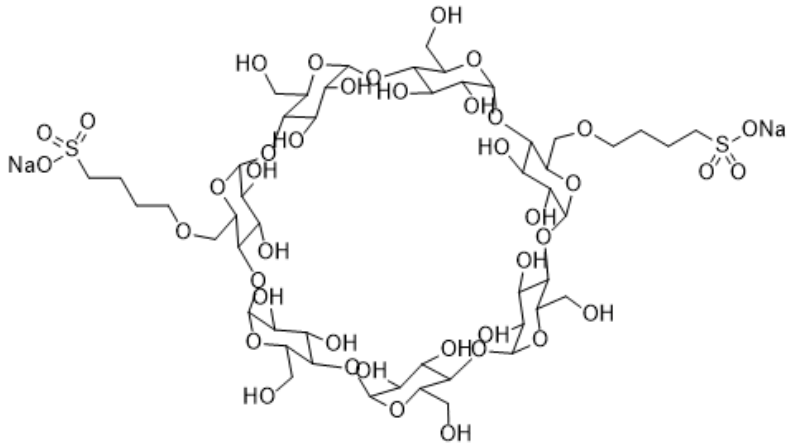
Examples of marketed products containing cyclodextrins[a].

Type of cyclodextrin	Drug name	Route of administration	Trade name	Market
α-Cyclodextrin	Cefotiam hexetil hydrochloride	Oral	Pansporin T	Japan
β-Cyclodextrin	Benexate hydrochloride	Oral	Ulgut, Lonmiel	Japan
	Omeprazole	Oral	Omebeta	Europe
	Piroxicam	Oral	Brexin	Europe
HP-β-cyclodextrin	Cisapride	Rectal	Propulsid	Europe
	Itraconazole	Oral, Intravenous	Sporanox	Europe, USA
	Mitomycin	Intravenous	Mitozytrex	USA
Randomly methylated β-cyclodextrin	17β-Estradiol	Nasal drops	Aerodiol	Europe
SBE-β-cyclodextrin	Voriconazole	Intravenous	Vfend	Europe, USA
	Ziprasidone maleate	Intramuscular	Geodon, Zeldox	Europe, USA
HP-γ-cyclodextrin	Diclofenac sodium	Eye drops	Voltaren	Europe

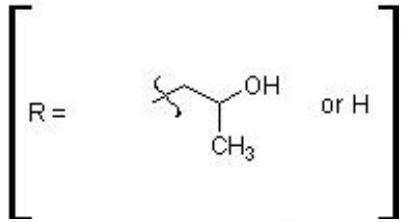
- Given the poor aqueous solubility of natural cyclodextrins as well as their toxicity when administered parenterally, several researchers have attempted to identify, prepare, and evaluate other cyclodextrin derivatives of pharmaceutical interest.
- These include the hydroxypropyl derivatives (HP) of β- and γ-cyclodextrins, the randomly methylated β-cyclodextrin, sulfobutylether β-cyclodextrin (SBE-β-cyclodextrin).

CD derivatives, HP and SBE β-cyclodextrins





a mixture of beta CD with different numaber of Sulfobutyl side chains.



Hydrophilic and hydrophobic derivatives

Hydrophilic cyclodextrins, namely HP-β-cyclodextrin and SBE-β-cyclodextrin, are considered nontoxic when administered in low to moderate doses by oral or intravenous routes.

HP-β-cyclodextrin has been shown to be well tolerated in humans

Lipophilic cyclodextrin derivatives, such as methylated cyclodextrin, are absorbed to a greater extent from the gastrointestinal tract into the systemic circulation and have been shown to be toxic after parenteral administration

Currently, there are over 30 marketed pharmaceutical products based on CD complexes

- A-type phase-solubility profiles are obtained when the solubility of the substrate (drug) increases with an increase in ligand (cyclodextrin) concentration. The A-type profile is further subdivided into three profiles. The A_L profile indicates that there is a linear increase in solubility as a function of ligand or solubilizer concentration; the A_P profile indicates an isotherm, wherein the curve deviates from linearity in a positive manner, suggesting that ligand or solubilizer is proportionately more effective at higher concentrations.
- Conversely, the A_N type relation indicates a negative deviation from linearity, which means that the ligand or solubilizer is proportionately less effective at higher concentration

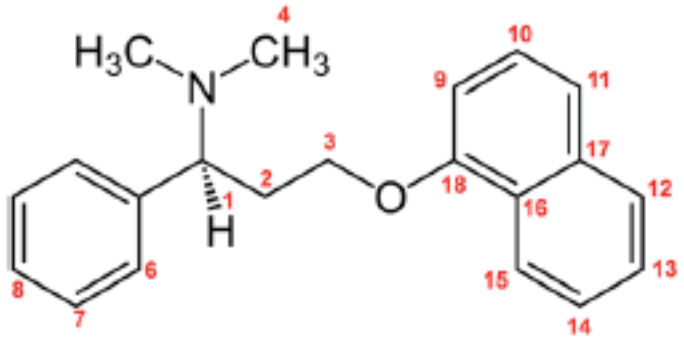
Inclusion complexes or aggregates?

- cyclodextrins are also known to form non-inclusion complexes and complex aggregates capable of dissolving drug through micelle-like structures.
- Phase-solubility profiles are incapable of verifying formation of inclusion complexes, and describe only how the increasing concentration of cyclodextrin influences drug solubility

NMR, CD and UV spectroscopic studies reveal uncommon binding modes of dapoxetine to native cyclodextrins†

András Darcsi,[a] Zoltán Szakács,*[b] Ferenc Zsila,[c] Gergő Tóth,[d] Ákos Rácz[d] and Szabolcs Béni*[a]

Dapoxetine, (S)-N,N-dimethyl[3-(naphthalen-1-yloxy)-1-phenylpropyl]-amine hydrochloride, (Priligy¨) is a novel, short acting selective serotonin reuptake inhibitor that has been developed specifically as an on-demand oral treatment of premature ejaculation.

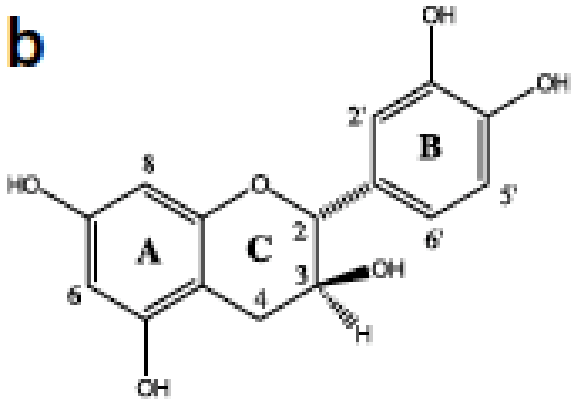


Cyclodextrin forms a more stable 1 : 1 complex with Dpx. The naphthyl ring is preferentially inserted, its sterically restricted fitting in the smaller cavity is supported by NOEs and the CD/UV titration results and confirmed by molecular modeling.

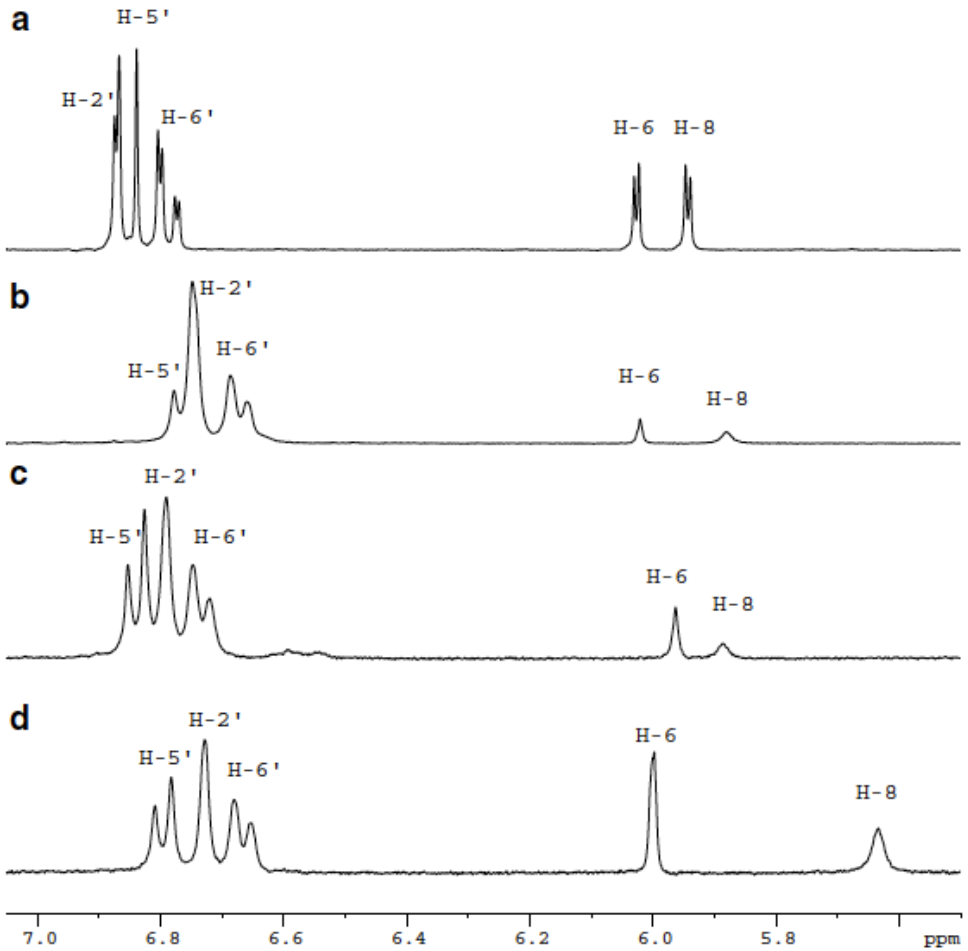
Surprisingly, 1H NMR-based Job's plots and titrations curves undoubtedly prove the simultaneous formation of a 2Dpx.CD complex, albeit its impact on NOEs and CD/UV data is less significant than in the g-CyD case. Here again, the superposition of several geometries can be suspected, with the dominant inclusion of the naphthyl ring of Dpx.

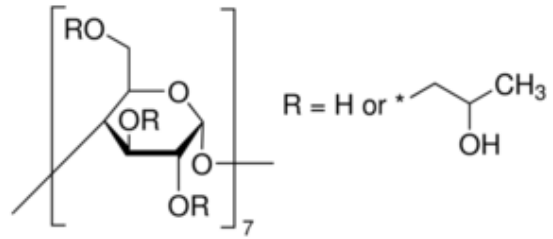
Studies of inclusion complexes of natural and modified cyclodextrin with (+)catechin by NMR and molecular modeling

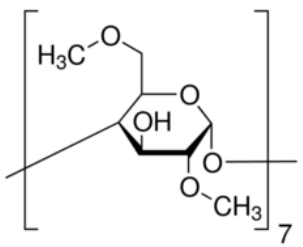
Carolina Jullian,[a,*] Sebastián Miranda,[b] Gerald Zapata-Torres,[b] Fernando Mendizábal[c] and Claudio Olea-Azar[b]



Catechins are scavengers of reactive oxygen species, and their resulting anti-oxidant properties are of great interest in dietetics and cosmetology. Furthermore, their antiviral and cancer inhibiting properties could have pharmaceutical applications.







3. ^{1}H NMR spectra: (a) CA without CDs; (b–d) inclusion complexes with β-CD, HP-β-CD, and DM-β-CD.

Designed positively charged cyclodextrin hosts with enhanced binding of penicillins as carriers for the delivery of antibiotics: The case of oxacillin

Marco Agnes[a], Angelos Thanassoulas[b], Polychronis Stavropoulos[b], George Nounesis[b], Georgios Miliotis[c], Vivi Miriagou[c], Evita Athanasiou[d], Gabor Benkovics[e], Milo Malanga[e], Konstantina Yannakopoulou[a,*]

CD in chromatography

Cyclodextrins (CDs), which possess a hydrophobic cavity, have a remarkable capacity to form inclusion complexes with various molecules through host-guest interactions. It is well known that the usefulness of CDs is due to the combination of the inclusion properties and structural features of these molecules. CDs are used extensively in separation science because CD-complexation phenomena offer a procedure of choice for separation of compounds and extraction processes, and provide a useful and versatile tool for protecting the environment. The present review shows the advantages accruing from the use of adsorbents containing cyclodextrins, in particular in chromatographic separations and in waste water treatment.

The main goal of this review is to provide a summary of the information concerning the synthesis of materials containing CDs and to give a general overview of the different possible applications of CDs as sorbents in the field of separation techniques. Recent and continuing interest in these adsorbents is evident from the number of papers that appear each year in the literature.

CDs in mobile phase for chiral separations

The first chromatographic separations (thin-layer chromatography and column liquid chromatography) with CDs used them as mobile phase additives in solution.

Several papers were published by Sybilska et al. on this subject. However, the use of CDs as mobile phase components requires large amounts of these substances which is an economic drawback (alpha- and gamma-CD can be costly).

Another problem is that beta- CD has a low solubility in water. For these reasons, several workers have attempted to immobilize CDs on appropriate supports including organic, polymeric, and mineral materials.

CD as stationary phase: CD polymers

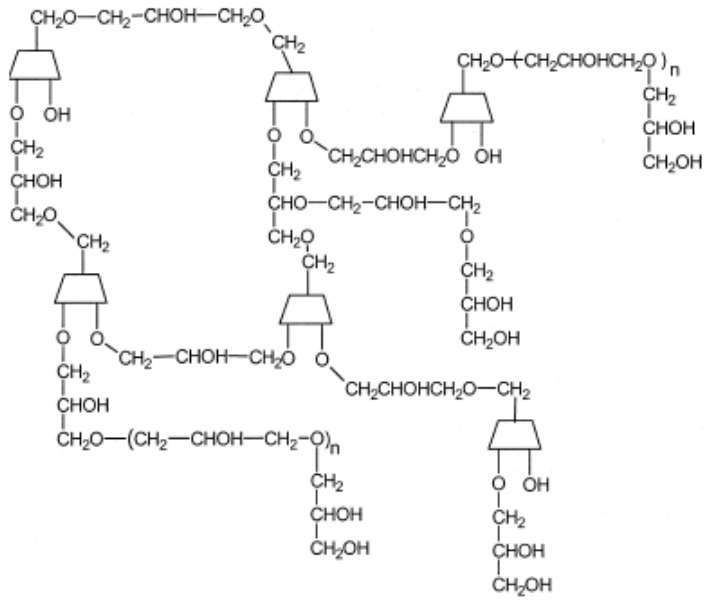


Figure 6. A possible structure of an ECP polymer [203].

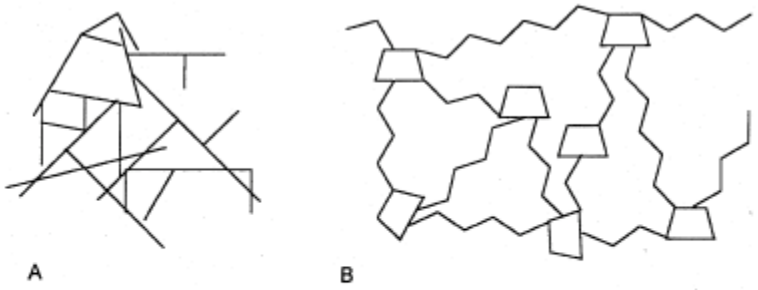
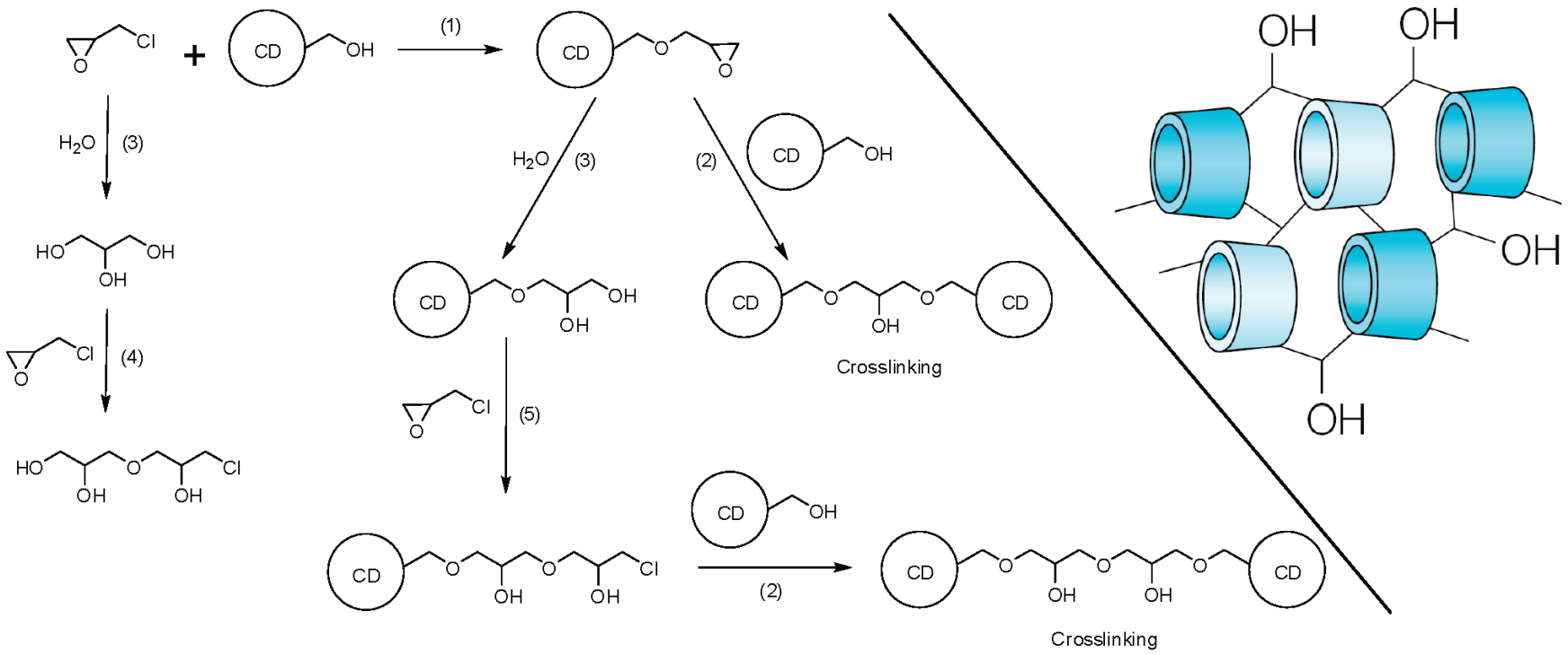


Figure 7. Comparison of the structure of A) a crosslinked epichlorohydrin dextran resin (Sephadex) and B) an ECP cyclodextrin polymer.

Among the CD polymers, the most popular is an O-alkylated polymeric resin (abbreviated ECP or ECH in the literature) produced by reaction of CDs with epichlorohydrin (abbreviated EPI)

CD crosslinking



chemical crosslinking of CD (α, β or γ) with epichlorohydrin (EPI) as a bifunctional cross-linking agent in alkaline media resulting in the formation of polymeric hydrogels.

CD linked to silica beads

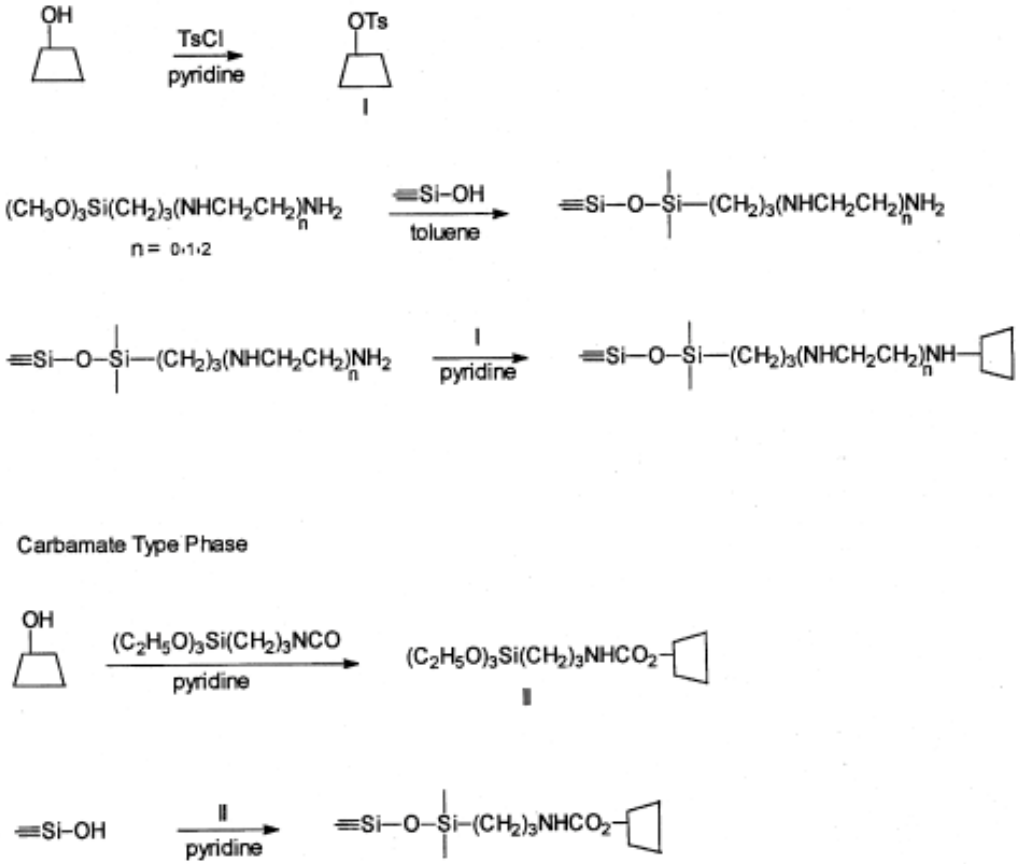


Figure11. Preparation of a cyclodextrin stationary phase according to Fujimura et al. [230–234].

CD material library

Liposomes

CD-based Polymers

CD conjugates to polymers

CDs and their derivatives have been successfully employed to construct supramolecular systems across length scales and to engineer novel functional materials, taking full advantage of host–guest interactions between the CD units and guest molecules. Besides, CDs can be utilized as molecular valves to switch the ON/OFF release of payload from hybrid nanosystems . Recently, a broad spectrum of CD-containing polymers with versatile architectures have been synthesized to assemble functional platforms .

These assemblies have found wide applications in drug delivery, gene Therapy, and medical imaging.

Supramole

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Cyclodextrin-based supramolecular systems for drug delivery: Recent progress and future perspective ☆

Jianxiang Zhang [a], Peter X. Ma [b,c,d,e,*]

This review will focus on the current progress in the construction of CD-based supramolecular systems and their applications for drug and gene delivery.

CD materials used for supramolecular self-assembly, their synthesis, and particulate delivery systems such as nanomicelles and nanoparticles will be summarized.

Amphiphilic CD for the formation of aggregates: liposomes

Cationic amphiphiles for gene delivery

Cationic CD amphiphiles were initially synthesized for supramolecular assembly of soft materials with special surface chemistry and charge. Recent attention has been focused on their potential for gene delivery.

An easy way to synthesize cationic β-CD amphiphiles is to introduce amino groups on the primary face of CDs with alkyl chains at positions 2 and 3, thereby per-6-amino- β-CD 2,3-di-O-alkyl ethers were prepared.

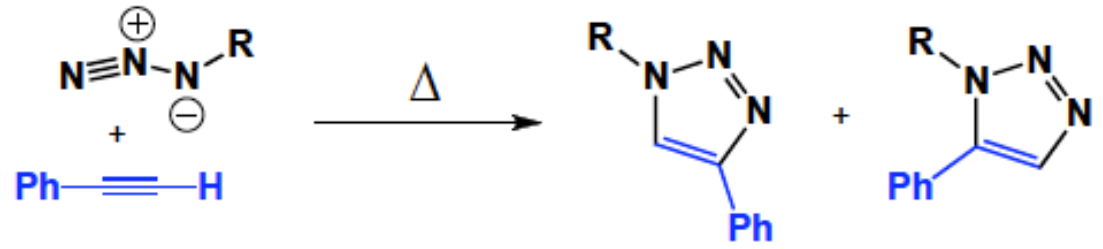
How to introduce an amino group?

Formation of vesicle aggregates

The 1H NMR spectra of 6a and 6b in tetrahydrofuran are broad at 25 °C but considerably sharpened at 50 °C, behavior consistent with aggregation. This is confirmed by light-scattering Experiment, showing the presence for 6b of relatively monodisperse vesicles of 350-nm apparent diameter.

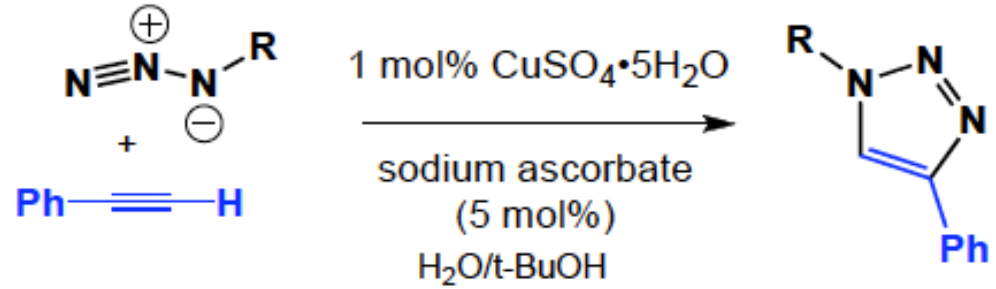
Azide-alkyne dipolar cycloadditions (aka “click” reaction)

Thermal reaction:



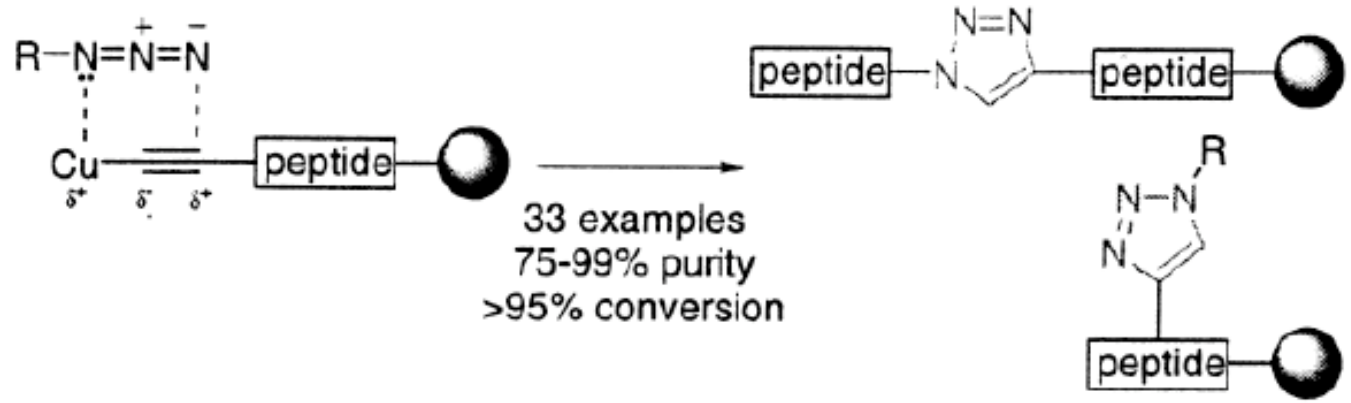
1:1 ratio

Cu-catalyzed reaction:



Only 1,4-product

Angew. Chem. Int. Ed. **2002,** *41,* 2596.



J. Org. Chem., **2002**, 67 (9), 3057-3064

Supramolecular systems based on CDs for gene delivery

Positive charge-modified CDs have been explored as novel vectors for gene delivery. In addition, CD units have also been covalently linked to various polycations to increase their transfection efficiency and decrease their toxicity.

Gene therapy holds promises for curing the effects of acquired and inherited diseases in a straightforward manner by adding, correcting, silencing, or replacing genes.

Nonviral polymeric vectors are expected to offer safe delivery of therapeutic genes to target sites. Polyplexes for gene delivery have been formed through charge interactions between the phosphate anions of DNA and cations of polymeric carriers such as polylysine, chitosan, polyamidoamine dendrimers, and polyethylenimine

(PEI).

In particular, linear PEI (LPEI) and fractured polyamidoamine dendrimers showed high transfections in various animal and cultured cells.

the secondary amines of these polymers are protonated under weakly acidic conditions in endosome/lysosome, and the buffering effects are thought to induce osmotic swelling of the endosomal and lysosomal interior, which results in the rupture of the endosome/lysosome and subsequent DNA release into cytoplasm.

Pseudorotaxanes CD/LPEI

Although these polycations have been used as transfection agents, most of these cationic materials have relatively high cytotoxicity and there are difficulties in their formulation.

LPEI-derived cytotoxicity is regarded as consisting of two steps: cell-surface membrane damage and activation of a mitochondrially mediated apoptotic program.

Preparation and characterization of various types of polypseudorotaxanes consisting of many CDs and various linear polymer chains, such as poly(e-lysine) (PL/CD) and LPEI (LPEI/CD).

In the LPEI/CD system, CD threading is likely to decrease the charge density of LPEIs without any covalent bonds, and unthreaded parts of LPEI can act as effective gene carriers.

Supramolecular “pseudorotaxane” polications for gene delivery

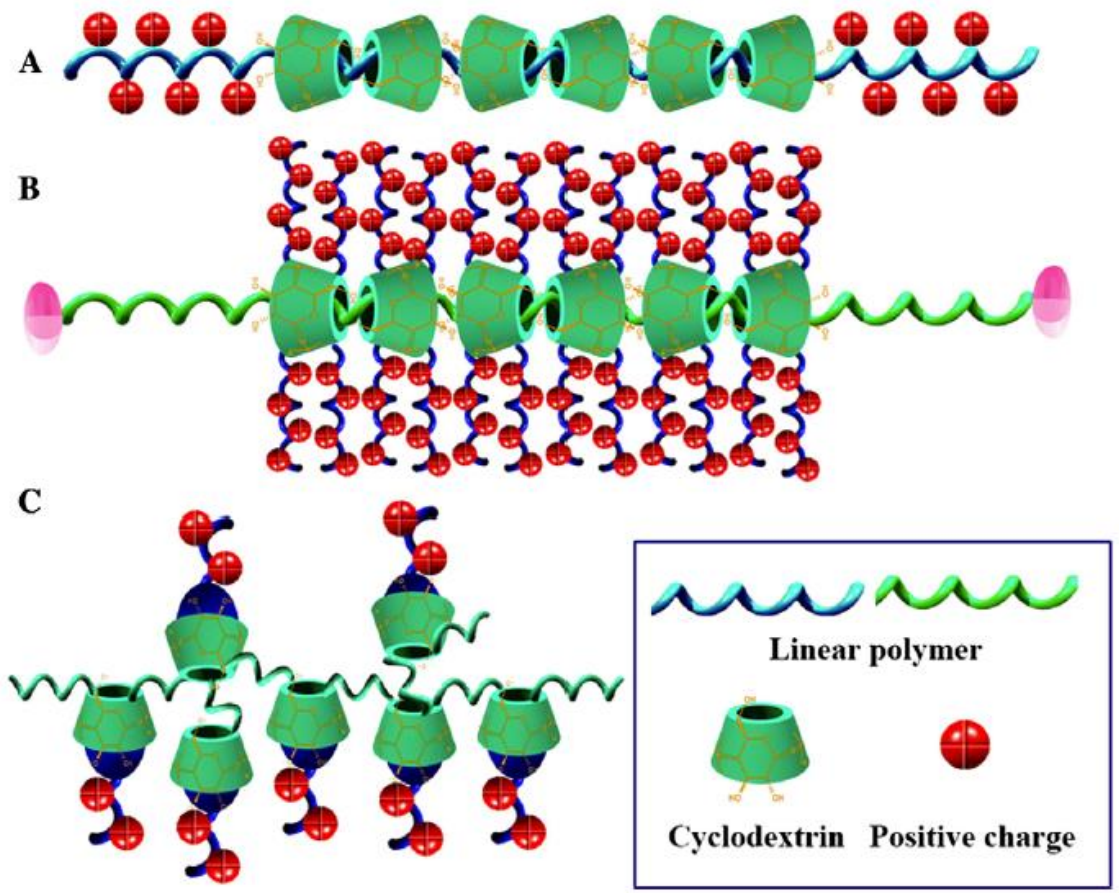
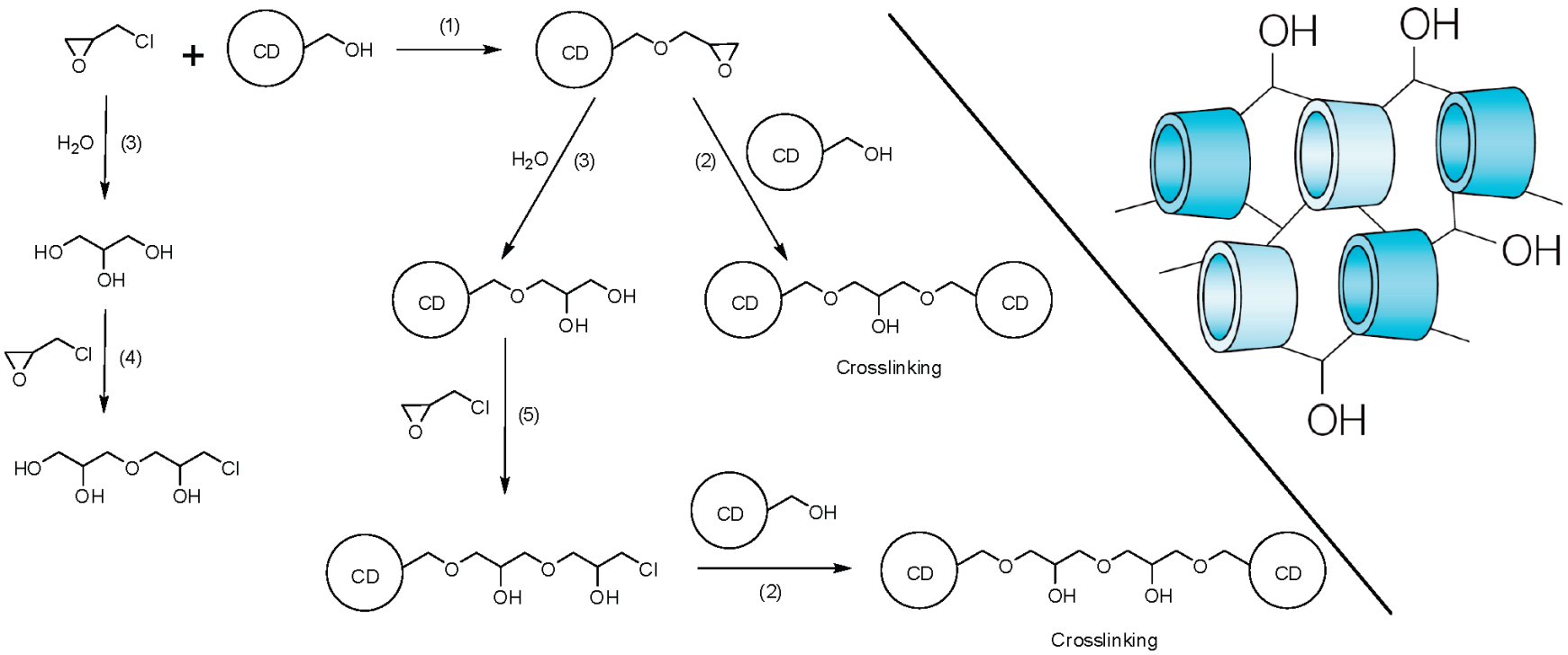


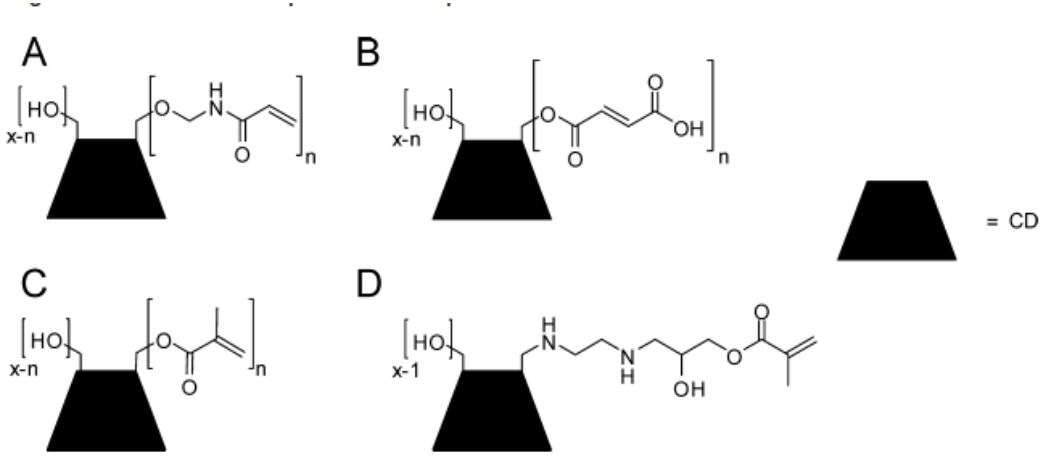
Fig. 9. CD-based supramolecular polycations for gene delivery. A. Threading of CD units onto positively charged polymers. B. CD-based polyrotaxane modified with positively charged moieties. C. Supramolecular polycations formed by the complexation of CD-polymer and positively charged molecules.

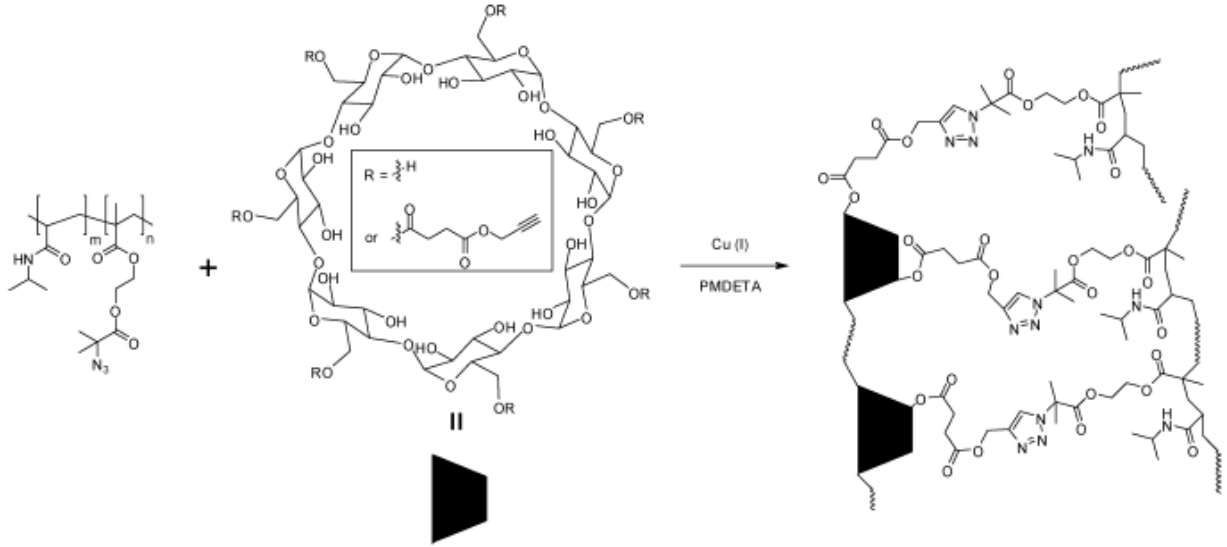
CD crosslinking



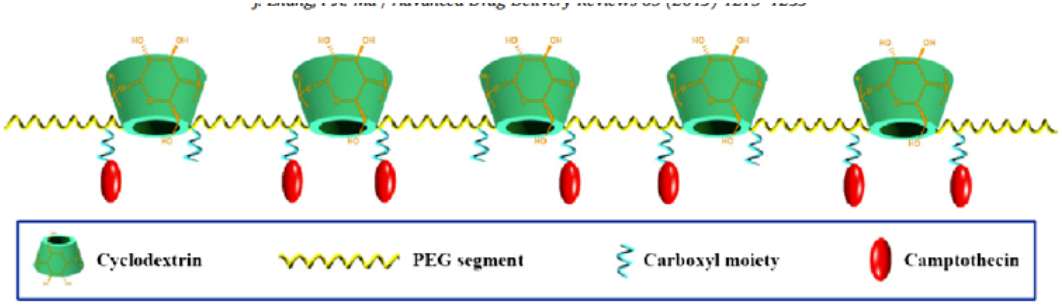
Mura et al. demonstrated that EPH-cross-linked CD gels could be loaded with large quantities of the nonsteroidal antiinflammatory drug naproxen, thereby exceeding ~30x its maximum aqueous solubility.

Direct CD polymerization and co-polymerization

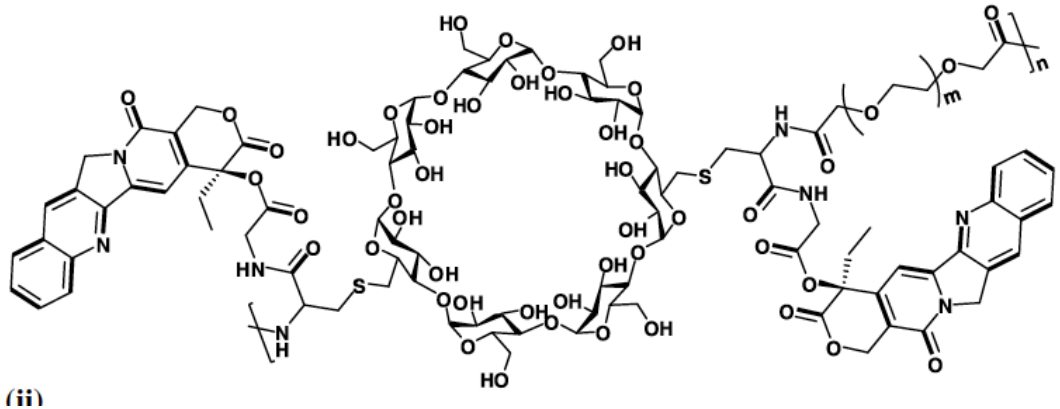




CD polymers and drug delivery



(i)



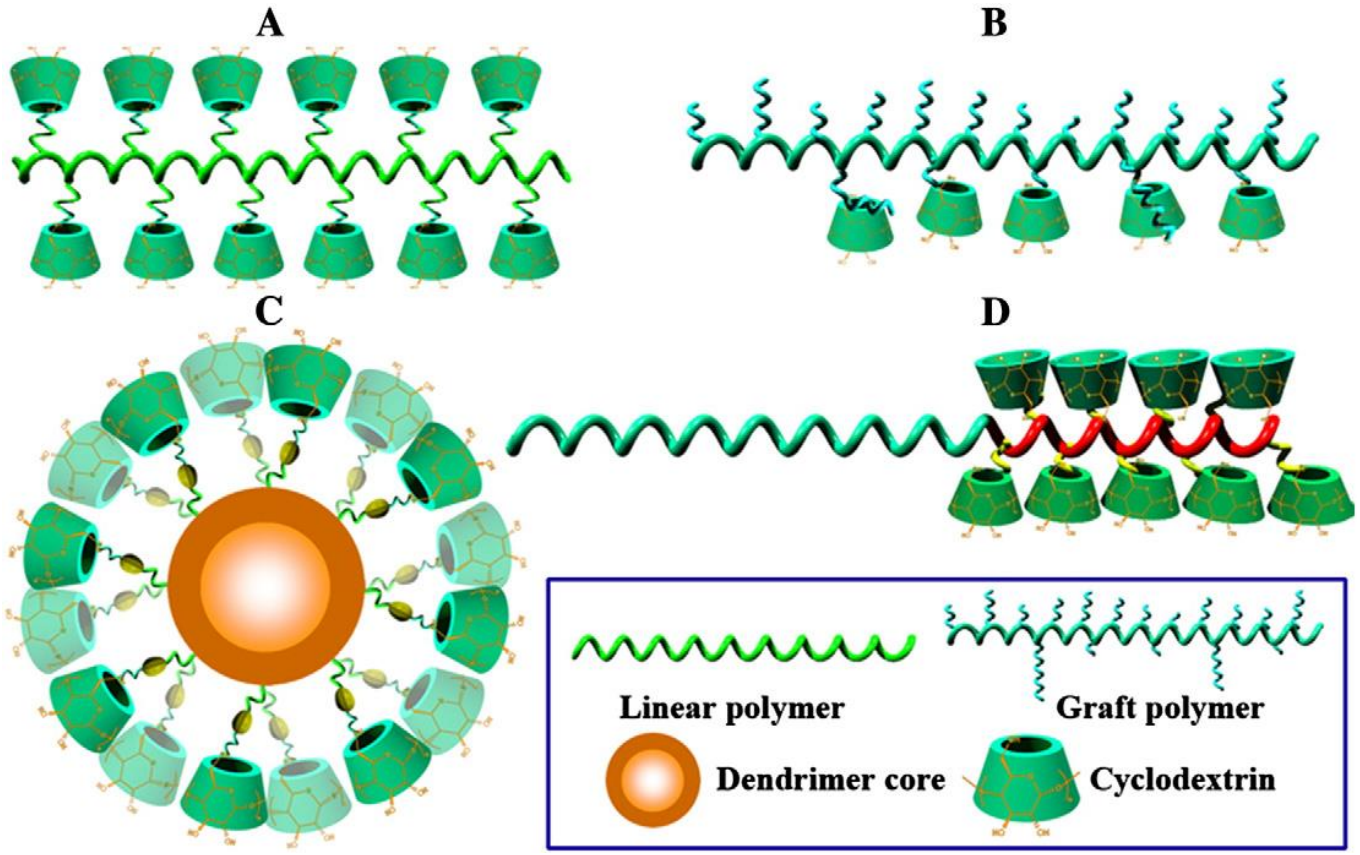
(ii)

Camptothecin (CPT), a highly potent antineoplastic agent, can be covalently conjugated onto CDPs via its 20-OH functionalized derivative (Fig. 4A). By copolymerization of diaminofunctionalized β-CD monomers with other difunctionalized comonomers such as dimethyl suberimidate or dithiobis(succinimidyl propionate), a series of linear, cationic, β-CD-containing polymers (βCDPs) were also synthesized as non-viral vectors.

Cyclodextrins-conjugated polymers

CDs have been covalently conjugated onto various polymers to modify physicochemical properties, to improve biocompatibility, to enhance drug/gene delivery capabilities, or to impart macromolecular hosts with multiple binding sites.

Linear, branched, hyperbranched, block, and dendritic polymers have been modified with CD units (Fig. 5). These CD-containing polymers were utilized to fabricate supramolecular assemblies across nano, micro, and macro-scales.



Schematic illustration of the typical structures of CD-pendent polymers studied for biomedical applications: A, CD-grafted linear polymer; B, CD-pendant graft copolymer; C, CD-conjugated dendrimer; and D, CD-flanking block copolymer

CD polypseudorotaxanes (CDPRs)

For drug delivery applications, biodegradable CDPRs have been developed that can be dissociated by hydrolyzing the terminal moieties (Fig. 6). These CDPRs generally consist of α-CD, PEG, and a biodegradable moiety [103]. The biodegradable moiety exists at both terminals of the PEG chain. As a conceptual proof study, Yui and coworkers synthesized biodegradable CDPRs based on α-CD and PEG, which are capped with L-phenylalanine (L-Phe) via a peptide spacer. The water solubility of these CDPRs can be improved by hydroxypropylation of CDs [104]. Enzymatic cleavage of the peptide linkage by papain or α-chymotrypsin may lead to dissociation of supramolecular structure and complete release of threaded CD units

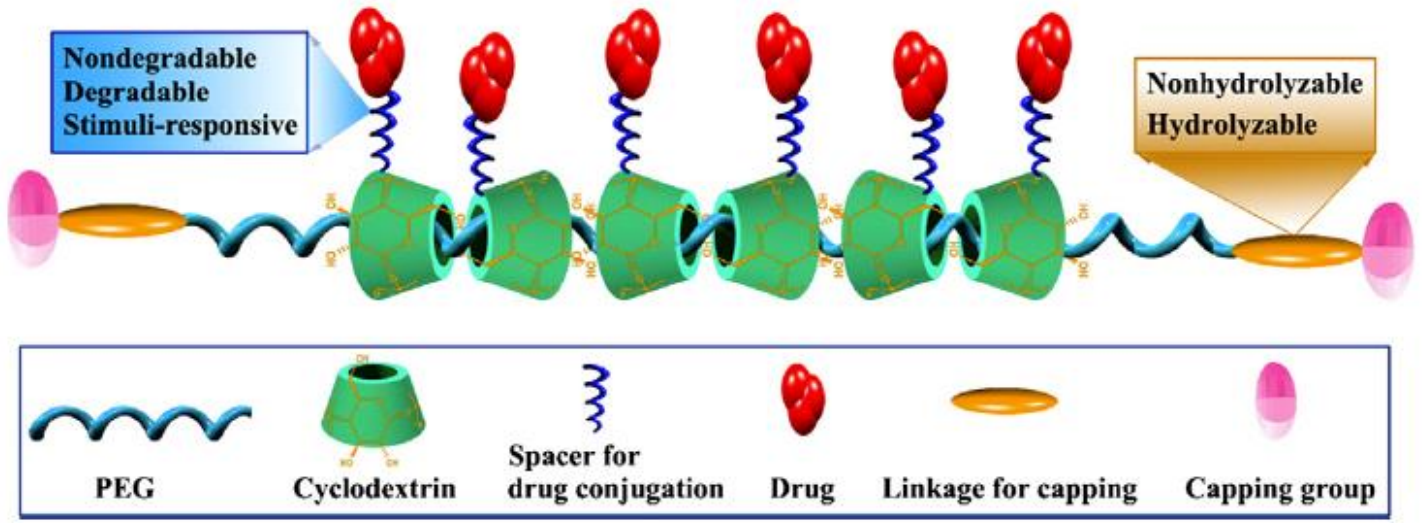


Fig. 6. Schematic illustration of supramolecular therapeutics based on CD-based polypseudorotaxane.

Polyrotax

Cyclodextrin-based supramolecular polymers

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In 1990, we reported for the first time that CDs formed inclusion complexes with some polymers to give poly-pseudorotaxanes.

For example, α-CD formed complexes with Poly (ethylene glycol) (PEG) and β-CD gave complexes with poly(propylene glycol) (PPG).

Later we found that γ-CD formed complexes with poly(methyl vinyl ether).

There is a good correlation between the sizes of the CD cavities and the cross-sectional areas of the polymers. CDs are arranged linearly along a polymer chain mainly in head-to-head and

tail-to-tail arrangements, as proved by STM images.