DOI: 10.1002/ejoc.200700933

Amphiphilic Cyclodextrins – Advances in Synthesis and Supramolecular Chemistry

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Dedicated to the memory of Lawrence J. Penkler, and to his inspiration

Keywords: Amphiphilic cyclodextrin / Self-assembly / Supramolecular chemistry / Drug delivery / Gene delivery

Amphiphilic cyclodextrins represent a new generation of these oligosaccharides, which are well known previously as host molecules in water. Cyclodextrins are now being modified with polar groups, lipophilic groups and conjugates which elaborate further their amphiphilicity and molecular recognition. The resulting amphiphiles are host molecules capable of forming all the assemblies expected of amphiphiles, but showing additional supramolecular properties. Examples of these macrocyclic amphiphiles are by now known that form thermotropic liquid crystals, while lyotropic assemblies include micelles, unimolecular micelles, nanoparticles, monolayers and bilayer vesicles. The assembly properties are modulated by both the lipidic and hydrophilic additions to the original cyclodextrin, however due to the mesomolecular size range substantial changes such as multiple glycosylation can be carried out without disrupting self-assembly. The assemblies in certain cases show molecular recognition both by the cyclodextrin cavities and by the conjugated groups such as glycosyls. Multiple noncovalent interactions, delivery to biological cells and DNA delivery are among the capabilities of those amphiphilic cyclodextrins that form bilayer vesicles.

1. Cyclodextrin Amphiphiles: A New Generation of Cyclodextrins

Cyclodextrins (CDs) are macrocyclic oligosaccharides composed of D-(+)-glucopyranosyl units linked α(1→4). The three main members of the cyclodextrin family, composed of six, seven and eight glucose units, are known as α-, β- (Figure 1), and γ-CD. These CDs have a truncated conical shape, a hydrophilic exterior and a hydrophobic cavity created by the inward-directed H3 and H5 atoms of the glucose units (Figure 1). This cavity enables them to act as hosts to lipophilic molecules.[1]

Cyclodextrins still dominate supramolecular chemistry in water, having prefigured supramolecular chemistry since their discovery by Villiers and demonstration of their in-

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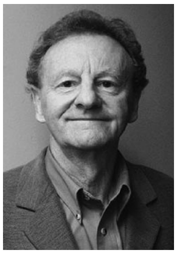

Raphael Darcy was born in Magh Ealla, Ireland, and studied at University College Dublin, a college of the National University of Ireland (Ollscoil na hEireann), and at the University of Basel. He obtained his doctorate from the former university in 1965 for work under the direction of James B. Thomson on steroids and triterpenoids. His interest in developing research at the chemistry-biology interface led to postdoctoral work at the Institute of Molecular Biophysics at Florida State University, Tallahassee, and at the Synvar (Syntex-Varian) research institute in Palo Alto, California. Work there on stable free radicals and spin-labelling of biomolecules with Edwin F. Ullman was continued during a lectureship at UCD, Dublin. Free-radical labelling of polysaccharides and oligosaccharides ultimately evolved into the subject of this review.

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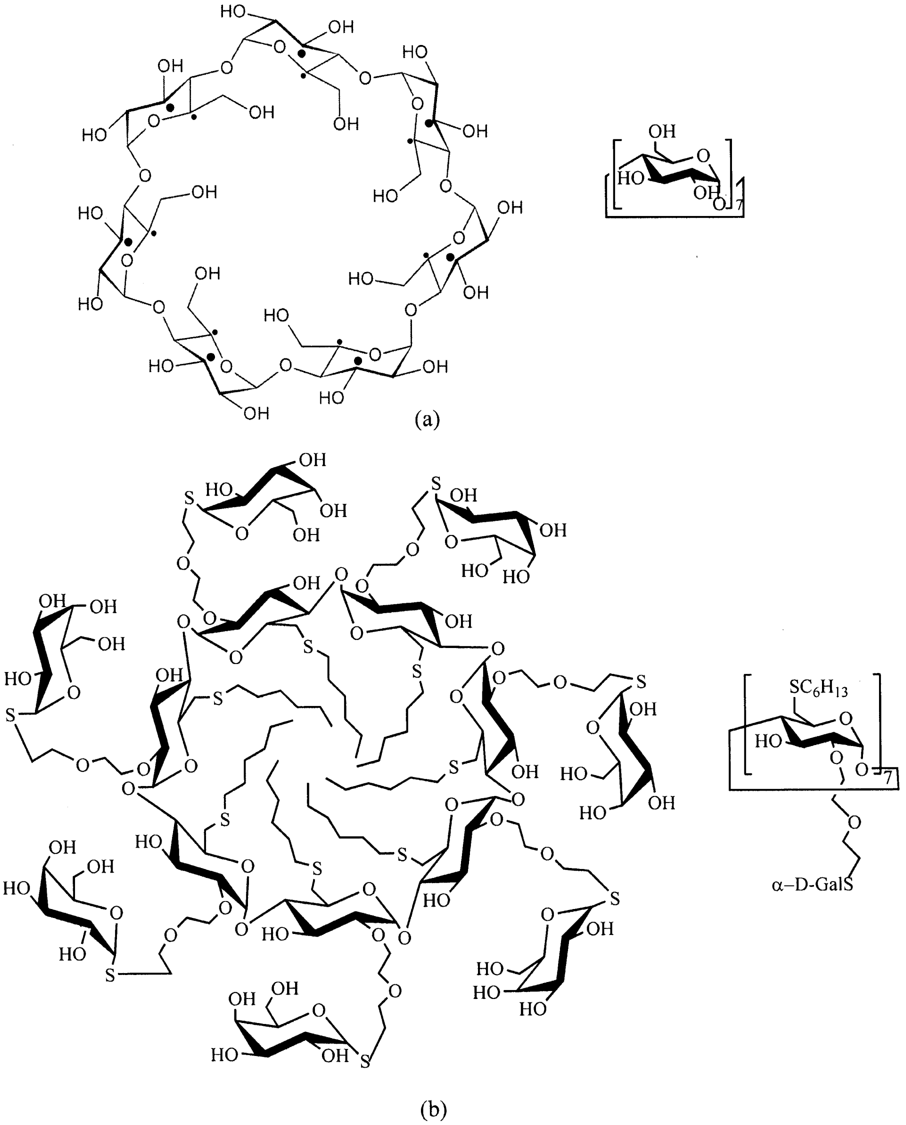


Figure 1. (a) Two representations of β-cyclodextrin, showing the H3 and H5 atoms (● and •) which create the hydrophobic cavity interior, (b) two representations of a member of a series of amphiphilic cyclodextrins forming nanoparticles and bilayer vesicles.

clusion properties by Schardinger and Pringsheim.[2] They are in effect off-the-shelf water-soluble hydrophobic cavities. Their wonder is that nature has constructed them from the most hydrophilic monomers available. Yet, in spite of being left the option of choosing from many other apparently more suitable materials, chemists have failed to invent host molecules which excel these oligomers of glucose in water, although a few rivals such as amphiphilic calixarenes[3] have been synthesised. Amylose also, the biosynthetic parent of cyclodextrins, is found in nature complexed with fatty acids, and it and some amphiphilic derivatives have been used in supramolecular complexes[4]

Apart from cyclodextrins as artificial enzymes,[5] the concept of cyclodextrins as drug carriers and targeting agents has been the main incentive for research into CDs as molecular encapsulators. Disappointingly however, this role has progressed not much further than their use as solubilisers, as mere excipients from the point of view of pharmacists.[6] Complexation with drugs can have advantages such as improvement of the drug's solubility and reduction in its side-effects. Yet a simple complex with a CD, where typically the binding constant is 10^2–10^4 molar,[7] is not effective for drug transport, since dissociation takes place too readily on dilution. This explains why, over the past three decades, research has been focusing on ways of chemically modifying the native CDs so that there can be cooperativity between their host cavities. The simplest effective cooperativity has been achieved by covalent linking to form dimers.[5] Incorporation into polymers has not been particularly successful in creating significant cooperativity. In assemblies such as polyrotaxanes,[8] cooperativity is dictated by the particular nature of the guest molecule, in this case a long linear guest such as a polyether, which causes a number of cyclodextrin molecules to thread onto it in a way which recalls the induced helix of amylose complexed with fatty acids. There remains the option of cooperativity by self-assembled cyclodextrins, and here amphiphilic cyclodextrins have so far yielded the most promising results. Amphiphilic CDs can self-organise in water to form monolayers, micelles, bilayer vesicles, or liquid-crystalline nanoparticles. The non-covalent interactions leading to self-assembly are generally those expected of amphiphiles; novel and unexpected interactions however will result from the fact that these are assemblies of host molecules.

The first amphiphilic cyclodextrins were made by Kawabata et al.[9] in 1986. The primary faces of β-CDs were made hydrophobic with alkylsulfinyl groups of various lengths. Monolayers were formed at the air-water interface with the hydrophilic secondary-OH face oriented towards the water, and inclusion of cholesterol by the layers was studied. Subsequent work by Ling et al.[10] showed that these water-insoluble amphiphiles could also form thermotropic liquid crystals. Since then, amphiphilic CDs have been designed which form the full range of lyotropic supramolecular assemblies. As assemblies formed by molecules which are already capable themselves of host-guest association, they offer potential for new dimensions in supramolecular chemistry.

2. Synthesis of Amphiphilic Cyclodextrins

2.1 General Approaches to Synthesis of CD Amphiphiles

Beta-cyclodextrin has been the starting molecule for most amphiphilic CDs made to date, and it may be assumed in this review to be the relevant CD unless otherwise stated. Modification of one or both faces of the β-cyclodextrin macrocycle can create CDs with amphiphilic character. Modification of one face can be most conveniently either mono- or per-substitution, that is, modification of one or all of the 6-hydroxyls, or of the 2,3-hydroxyls (Figure 2). Introduction of one or more lipophilic groups in this way has been found however to create CDs which have limited solubility in water, examples being those of Kawabata, and the many examples of CDs where there is full esterification of the secondary-hydroxyl side.[11] This is because the remaining unmodified hydroxyl groups on the opposite side do not provide the hydrophilic balance necessary for a variety of assemblies in water. This limitation and the improved results obtained by introducing hydrophilic modifications in addition are illustrated by the examples given in the following sections.

Selective mono-functionalisation of β-CD is normally via a 6-*O*-tosyl derivative[12] from which the azide and amine are accessible. Per-substitution of the primary-OH face can be via the per-halo derivatives,[13] which are amenable to nucleophilic reactions; while per-6-*O*-*tert*-butyldimethylsilylation can be used for protection during modifications to the secondary-OH face. The hydroxyls at the 2-position are the most acidic ($pK_a = 12.2$) and those at the 3-position are the most inaccessible, allowing a high degree of selecltivity for the 2-hydroxyl of this pair.[14]

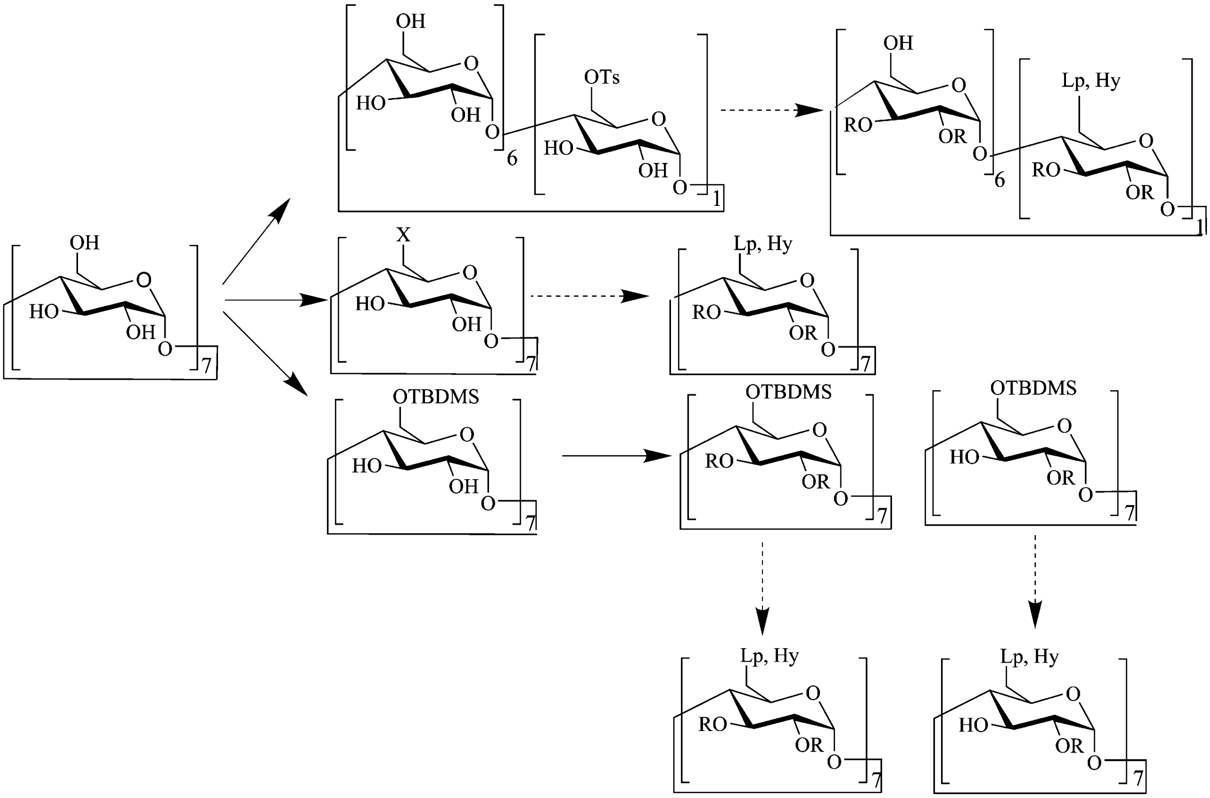


Figure 2. Common synthetic paths to amphiphilic cyclodextrins; Lp = lipophile, Hy = hydrophile; for Lp, R is hydrophilic; for Hy, R is lipophilic.

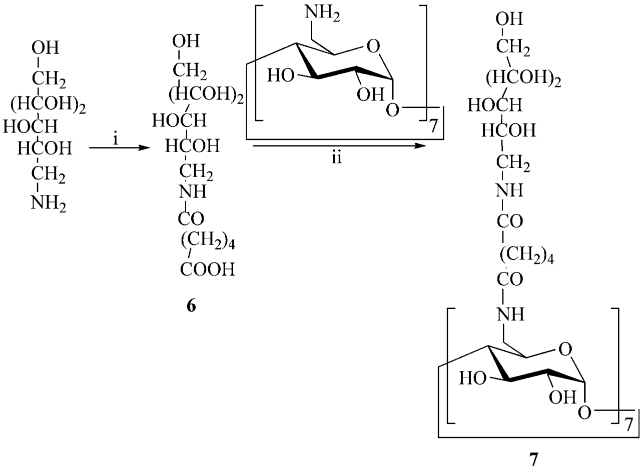
2.2 Alkylated, Arylated and Lipid-Conjugated CDs

Synthesis of alkylated α- and β-CD (Scheme 1) and their behaviour at an air-water interface, have been described by Jurczak et al.[15] Silyl-protected α- or β-CD was alkylated, then desilylated to give amphiphilic per-(2,3-di-*O*-alkyl)-CDs (**3**). The per-(6-thio)-α-cyclodextrin (**5a**) was also prepared for chemisorption on metal surfaces. A similar synthesis of per-(2,3-di-*O*-heptyl)-β- and -γ-CD has been described.[16]

CDs fully substituted with lipophilic chains (6-deoxy-6-*N*-myristoyl, 6-deoxy-6-*N*-caproyl, 6-deoxy-6-*O*-caproyl, 6-hydroxy-2,3-C6 ester β-CD) only on the primary side have also been described and used as nanoparticles for encapsulation.[17]

Hamelin and co-authors[18] synthesised silylated and benzylated CDs and studied their supramolecular assembly in water or organic solvents. These "Janus CDs" proved able to form dimers, exposing different molecular surfaces according to whether the environment was hydrophobic or hydrophilic. Introduction of *p*-alkoxy-phenylsulfinyl groups on the primary face had previously been described.[19] Phenylsulfinyl groups were enough to enable organisation into a monolayer at an air-water interface, though not as stably as the *n*-pentoxy-phenyl derivative. A comparison of α-, β- and γ-CD derivatives showed that the β-series gave highest collapse values on compression whatever the substituent. This was ascribed to the sevenfold symmetry of β-CD, as compared to the six- and eightfold symmetries of the α- and γ-CD, which better fit the symmetry of water. As a consequence, there is no water to lubricate collapse of the β-assembly.

Compound **7** (Scheme 2), having amphiphilic chains, was prepared from per-amino-β-CD using peptide chemistry.[20]

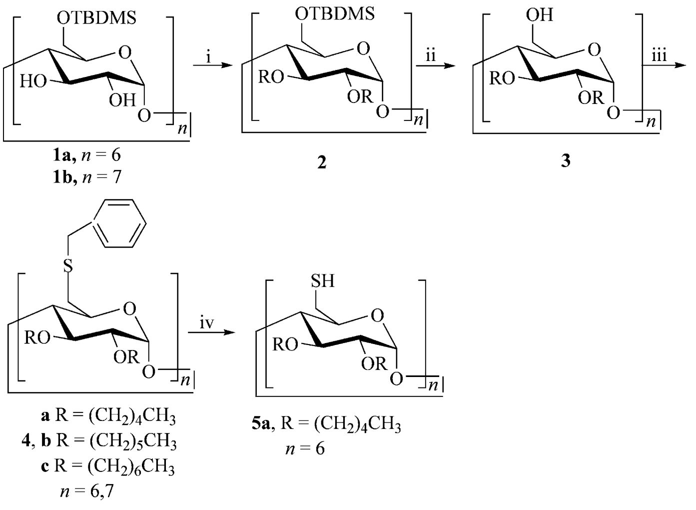


Reagents and conditions: i, HOOC-$(CH_2)_4$-COOMe, DCC, HOBt, DMF, r.t., 24 h, then 1N $NaOH_{aq}$; ii, EDC, r.t., 2 h, pH 4.5–6.

Scheme 2. Synthesis of a CD with amphiphilic chains.

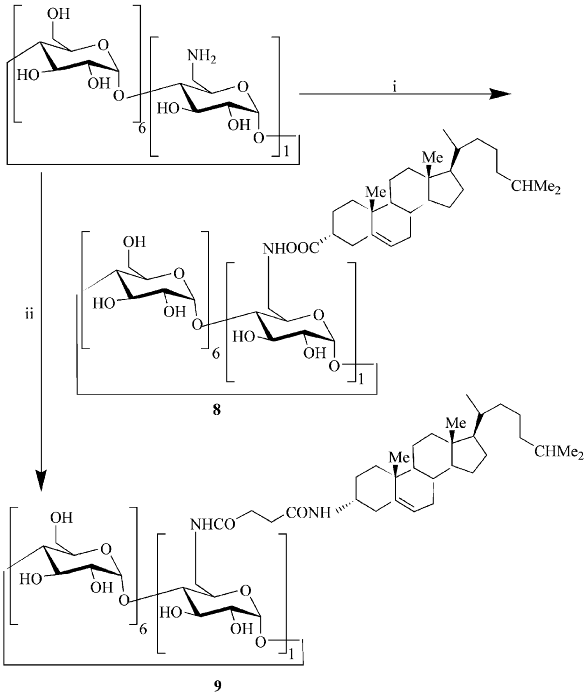
Binding behaviour was studied using anilinonaphthalene sulfonic acid as well as a variety of other guest molecules. The adipic-glucamine chains enhanced binding as these chains acted as an extension of the cavity. A similar result had been observed for 6-*S*-hydroxyethylated 6-thiocyclodextrins, where the amphiphilic chains in the γ-CD derivative confer the ability to include two molecules of anthraquinone-2-sulfonate.[21]

Cholesteryl-conjugated amphiphilic CDs have been mostly investigated by the groups of Djedaïni-Pilard and Perly,[22] the aim being to combine inclusion properties of the CD with the membrane properties of lipids. Mono-amino-β-CD was treated with cholesteryl chloroformate (Scheme 3) to give the cholesteryl-β-CD (**8**); or with succinic anhydride, then 3-α-amino cholesterol, to give a similar compound with a short spacer link (**9**). A methylated version (**16**) was also prepared[23] (Scheme 3). Methylation greatly increases the water solubility of β-CD by disrupting the intramolecular H-bond network, and Auzély-Velty and

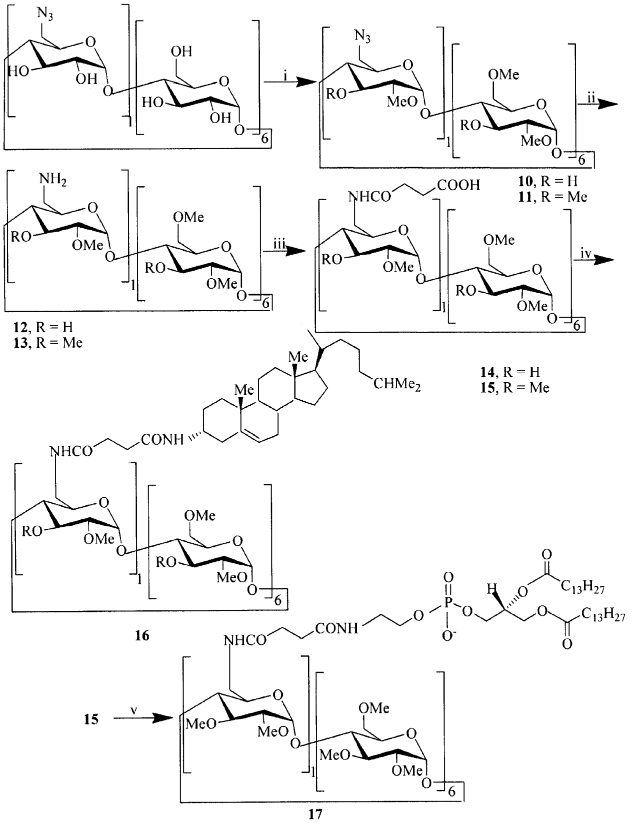


Reagents and conditions: i, NaH, R-I, DMF, r.t., 3 d; ii, TBAF, THF, reflux; iii, PPh_3, I_2, imidazole, toluene then benzyl mercaptan, NaOMe, DMF, 60 °C, 24 h; iv, Na/NH_3, NH_4Cl, THF.

Scheme 1. Synthesis of alkylated CDs.



Reagents and conditions: i, Cholesteryl chloroformate, Et_3N, DMF, r.t., 17 h; ii, Succinic anhydride, DMF, r.t., 3 h; 3-α-aminocholesterol, DIC/HOBt, DMF/THF, r.t., 48 h.



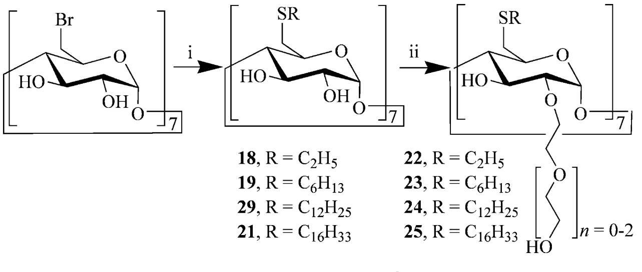
Reagents and conditions: i, **10**: ICH_3, NaH, DMF, r.t.; **11**: BaO, $Ba(OH)_2{,}8H_2O$, Me_2SO_4, DMSO/DMF, 8-9 °C; ii, PPh_3, NH_4OH 20%, DMF, r.t.; iii, Succinic anhydride, DMF, r.t.; iv, 3-α-aminocholesterol, DIC/HOBt,THF, r.t., 48 h; v, DIC, NHS, DMF, r.t., DMPE, Et_3N, $CHCl_3$, r.t.

Scheme 3. Preparation of lipid-conjugated CDs.

co-workers exploited this feature. The mono-azido-CD was first regioselectively methylated at positions 2 and 6, then the azido group was reduced to the mono-amino per-methylated CD (**12**), to which was attached the cholesteryl group on a spacer. A similar synthesis started from per-methylated CD (**15**). In the last step, the carboxy terminal of the spacer arm was activated with NHS and reacted with DMPE in presence of diisopropylethylamine under controlled conditions to avoid the loss of the aliphatic chains, to give the expected CD bearing a dimyristoyl-*glycero*-phosphoethanolamine group (**17**).[23] These cholesteryl-CD conjugates could form monodisperse micelles and incorporate into phospholipid membranes while retaining their inclusion capabilities.[24]

2.3 Oligo(ethylene oxide) Amphiphilic CDs

The first amphiphilic cyclodextrins to form bilayer vesicles were designed by Ravoo and Darcy.[25] Their synthesis started from the 6-per-bromo-CD which, upon nucleophilic substitution with the sodium or potassium salt of alkylthiols, led to the known per-alkylthio CDs **18**–**21** (Scheme 4). These then reacted with an excess of ethylene carbonate only at positions 2 of the CD, resulting in an average of two units of ethylene glycol per grafted oligomers **22**–**25**.[25a,25b] This concept was later extended to α- and γ-CD.[25c] With the resultant increase in the size and hydrophilicity of the cyclodextrin headgroup, the amphiphiles acquired a range of self-assembly properties previously not seen with CDs, forming bilayer vesicles, micelles or nanoparticles. Oligo(ethylene oxide) amphiphiles have been further elaborated in many ways, as described in the following sections.

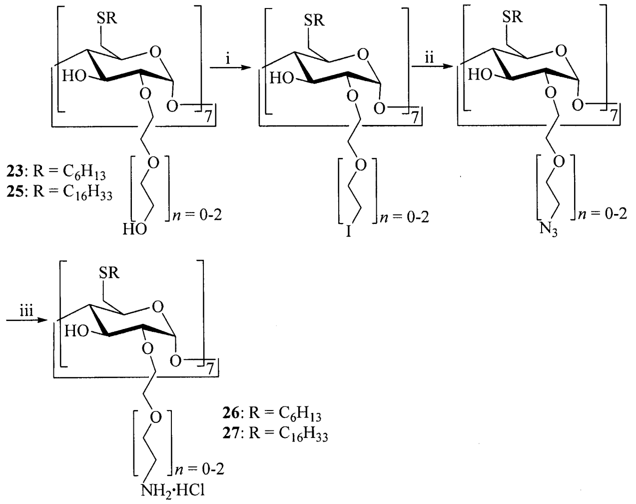


Reagents and conditions: i, RSH, *t*BuOK, DMF, 80 °C, 4 d; ii, K_2CO_3, ethylene carbonate, TMU, 150 °C, 4 h.

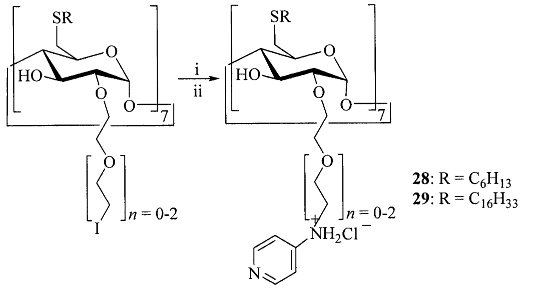
Scheme 4. Synthesis of oligo(ethylene oxide) β-CD amphiphiles.

2.4 Cationic CD Amphiphiles

Donohue et al.[26] described the synthesis of CDs in which oligo (ethylene oxide) amphiphiles **23** and **25**[25] were modified with amino groups on the oligomer chains (Scheme 5). Iodination of the chain extremities required a significantly higher temperature (100 °C) than 6-iodination (65 °C), subsequent azidation also being extremely slow. The per-azido compounds were reduced to the per-amino amphiphiles, used as their hydrochloride salts (**26**–**27**) in gene delivery studies (see later).[27] Pyridylamino amphiphiles **28**–**29** were obtained directly from the iodo derivatives.[28]



Reagents and conditions: i, DMF, PPh_3, NIS, 100 °C, 4 -5 h, 45-70%; ii, DMF, NaN_3, 100 °C, 4-5 d, ~70%; iii, DMF, PPh_3, 2 h, NH_3aq, then 1M HCl, 50-65%.



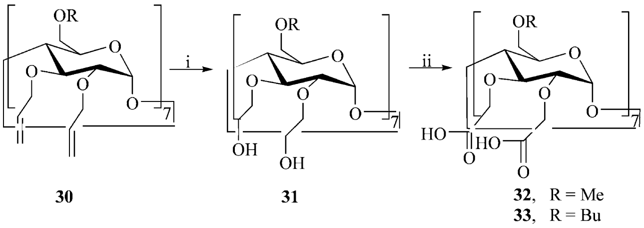
Reagents and conditions: i, 4-aminopyridine, DMF, 100 °C, 4 d; ii, MeOH/H_2O or acetone, AgCl, r.t.

Scheme 5. Synthesis of cationic amphiphilic CDs.

2.5 Anionic CD Amphiphiles

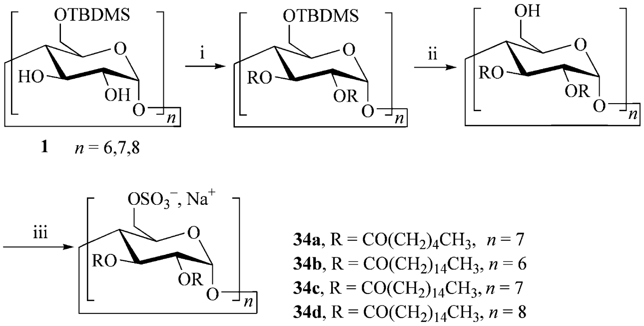
The allylation of CDs, as by De Clercq et al.,[29] made possible the attachment of various groups by subsequent oxidation or photochemical thiol addition. As an example of the former, Kraus et al.[30] (Scheme 6) used osmium tetroxide-catalysed oxidation of **30**[31] with 4-methyl morpholine as the auxiliary oxidant. They oxidised the resulting diastereoisomeric diols (**31**) to an aldehyde, then directly reduced this to the alcohol; this was oxidised to obtain carboxylated CDs **32**–**33** (Scheme 6).

The first sulfated amphiphilic CD was prepared by Dubes et al.[32] They obtained compound (**34a**) (Scheme 7) via esterification of the silyl-protected CD at positions 2 and 3 with hexanoic anhydride, using conditions similar to those described earlier by Lesieur et al.[33] After removal of the silyl groups the 6-hydroxyls were sulfated with SO_3·pyridine complex.



Reagents and conditions: i, OsO_4, 4-methylmorpholine *N*-oxide, acetone/H_2O then $NaIO_4$, H_2O and $NaBH_4$, H_2O; ii, TEMPO, NaClO, KBr, H_2O, pH 10.

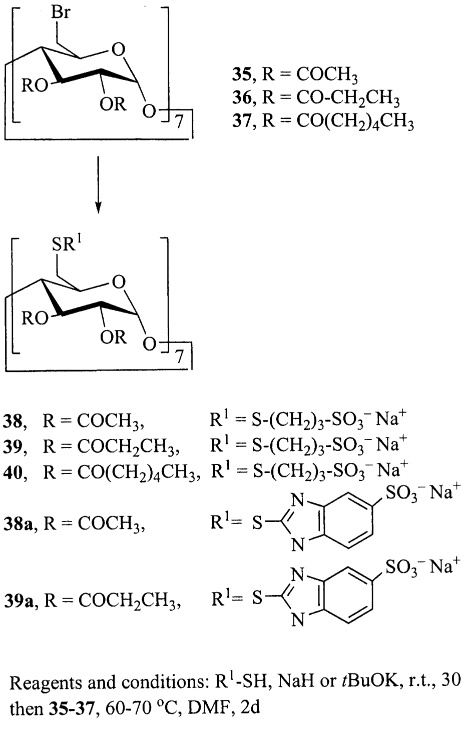
Scheme 6. Synthesis of carboxylated amphiphilic CDs.



Reagents and conditions: i, hexanoic anhydride, DMAP, pyridine; ii, BF_3·Et_2O, $CHCl_3$; iii, SO_3·Pyr, pyridine.

Scheme 7. Synthesis of sulfated amphiphilic CDs.

Sukegawa et al.[34] prepared sulfonated amphiphiles **34b**–**34d** by using a similar procedure. They showed that both sulfated and non-sulfated sets of compounds could form stable monolayers. However the sulfated CDs showed higher monolayer collapse-pressure values.



Reagents and conditions: R^1-SH, NaH or *t*BuOK, r.t., 30 min then **35-37**, 60-70 °C, DMF, 2d

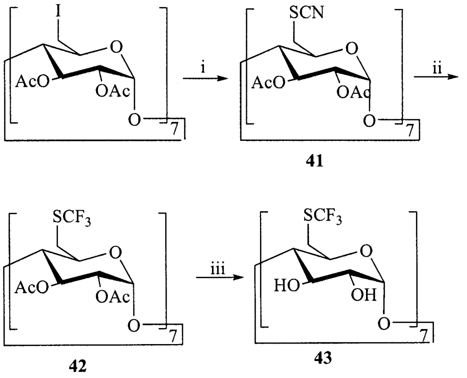
Scheme 8. Synthesis of sulfonated amphiphilic CDs.

Compound **34c** formed vesicles, and admixture to liposomes of cholesterol and dipalmitoyl phosphatidylcholine increased their diameter.

The complexation of clofazimine, an *anti*-leprosy drug, by sulfonated amphiphilic CDs was investigated by Schwinté et al.[35] These derivatives **38**–**40** (Scheme 8) were obtained from the acylated 6-per-bromo-β-CD through reaction with salts of sulfonated thiols such as 1-sulfonato-3-propanethiol.[36] These sulfonated amphiphiles, in contrast to compounds **34a**–**d**, were water-soluble. They could form micellar aggregates in water that solubilised clofazimine better than did unmodified β-CD.

2.6 Fluorinated CD Amphiphiles

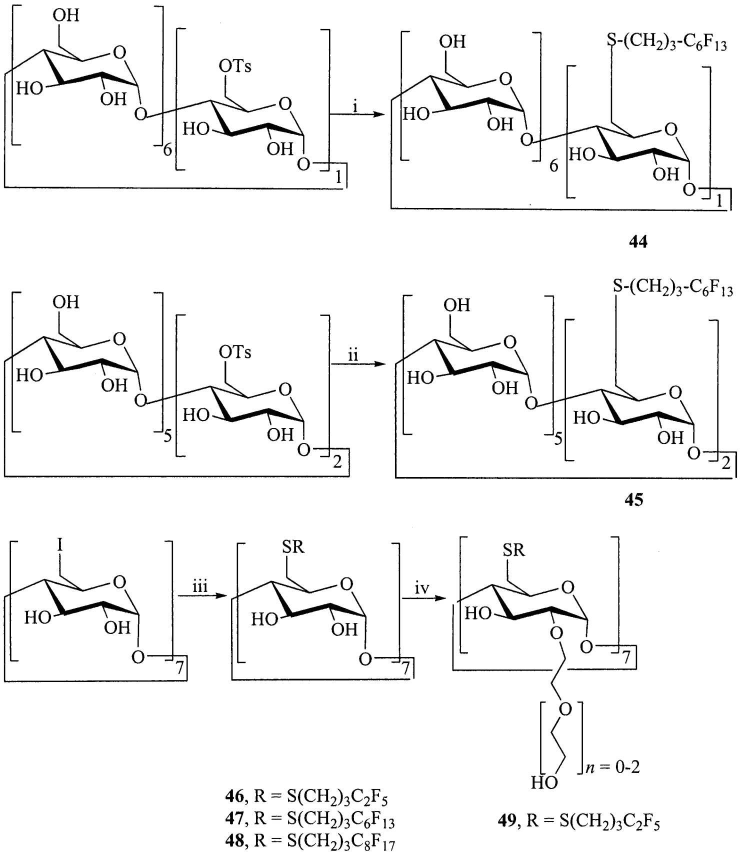
Highly fluorous regions of amphiphiles are not only hydrophobic, but lipophobic, and result in special self-assembly properties.[37] Granger et al.[38] prepared the 6-per-trifluoromethylthio-β-CD derivative **43** (Scheme 9), which formed monolayers at the air-water interface despite the short hydrophobic chains.



Reagents and conditions: i, KSCN, DMF, 100 °C, 1 h;
ii, CF_3SiMe_3, TBAF, THF, r.t., 3.5 h; iii, NaOH, MeOH, r.t., 12 h.

Scheme 9. Preparation of fluorous cyclodextrins according to Granger et al.[38]

Mono-, di- and per-fluoroalkylthio-CDs[39] were later made (Scheme 10) and shown to self-organise into nanospheres in aqueous media, unlike their analogous alkylated



Reagents and conditions: i, 3-(perfluorohexyl)propanethiol, MeONa/MeOH, DMF, 70 °C, 24 h;
ii, (a) benzyl chloride, DMSO, 20° C, 7 h; (b) DIBAL, toluene, 30 °C, 2 h; (c) *p*-toluenesulfonyl chloride, pyridine, 20 °C, 36 h; (d) Pd/C 10%, Pd black, MeOH/formic acid, 20 °C, 2 d;
(e) 3-(perfluorohexyl)propanethiol, MeONa/MeOH, DMF, 70 °C, 24 h;
iii, **46**–**47**, 3-(perfluoroethyl)propanethiol or 3-(perfluorohexyl)propanethiol, MeONa/MeOH, DMF, 70 °C, 24 h, **48**, [3-(perfluorooctyl)propyl]guanidinium salt, Cs_2CO_3, DMF, 60 °C, 72 h;
iv, ethylene carbonate, K_2CO_3, TMU, 150 °C, 4 h.

Scheme 10. Preparation of fluorous cyclodextrin amphiphiles according to Péroche et al. and Nolan.[39,40]

derivatives that formed apparently flat particles under conditions of cryo-TEM.[39b] Nolan[40] converted the perfluoroethylpropanethio-CD (**46**) to an amphiphile with oligo(ethylene oxide) chains on the secondary side (**49**) (Scheme 10), which was soluble in water and in most organic solvents. This formed nanospheres, though not bilayer vesicles. The same attempted conversion of compound (**47**) (C_9 chains) failed to give the oligo(ethylene oxide) derivative, in contrast to the reaction on the CD having C_8 hydrocarbon chains.

The synthesis of a γ-CD 6-per-fluoroalkyl ester has been described by Lim et al.[41] The cyclodextrin was simply reacted with an excess of heptafluorobutanoic acid, and the water-insoluble but methanol-soluble product was used in complexation experiments with surfactants.

2.7 Glycosylated CD Amphiphiles

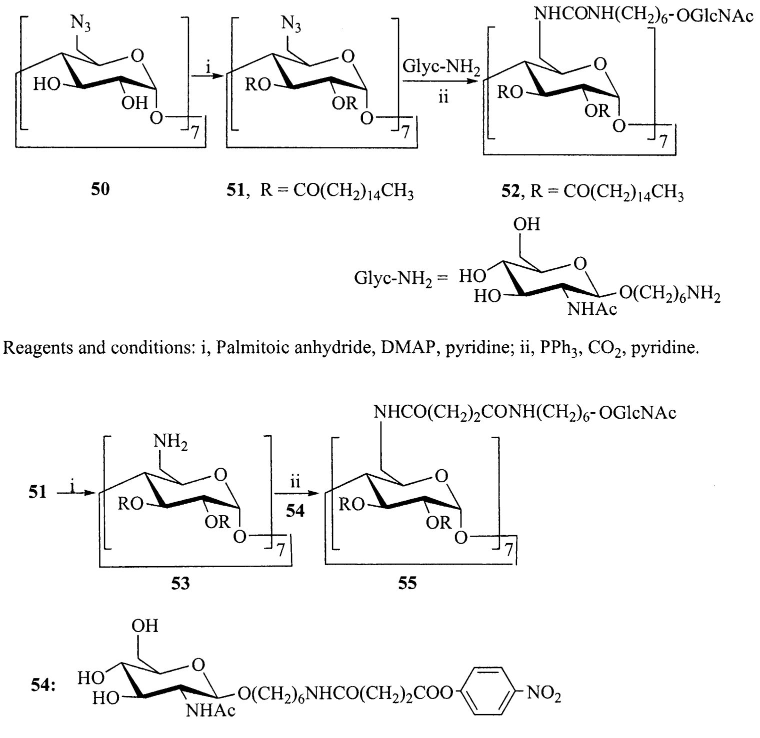
Giving accentuated amphiphilic character to cyclodextrins makes possible their self-assembly. However for interactions external to the assemblies, polar groups – those facing outwards in water – can cause noncovalent interactions additional to those of the cyclodextrin cavity. Molecular recognition in biological chemistry, and particularly in drug targeting, provides a challenging arena for such adaptations. Targeting of amphiphilic CDs has so far been confined to the use of glycosyl conjugates, and to study of their binding to carbohydrate-specific lectin proteins.

Sallas et al.[42] prepared CDs esterified on the secondary side and glycosylated on the primary side (**52**, **55**). Glycosylation involved reaction with a glucosamine having either a terminal amino group or an active ester group (Scheme 11).

A Staudinger reaction in pyridine and in presence of carbon dioxide led to the glycosylated CD **52** containing a urea function, and a peptide-like coupling involving a large excess of the active ester **54** led to the glycosylated CD **55**. It was shown using SPR that these compounds could be recognised by a GlcNAc-specific lectin (wheat germ agglutinin).

They further attempted to elongate the sugar moiety enzymatically with α-(1,4) galactosyl transferase through the use of liposomes (as these CD derivatives were not water-soluble). This gave mono-galactosylation only when starting from **52** and a mixture of variously substituted derivatives starting from **55**. Progress of the enzymatic reaction, which lasted three to six days, could be followed by MALDI-TOF spectroscopy.

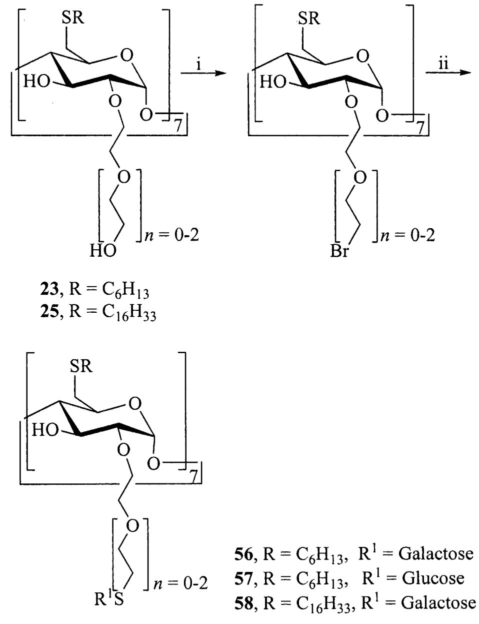
Other glycosylated amphiphilic CDs **56**–**58** have been prepared from oligo(ethylene oxide) CD amphiphiles by Mazzaglia et al.[43] (Scheme 12). Despite the introduction of seven glycosyl groups, these CDs still aggregated in water into vesicles. Their physicochemical properties and ability to bind to lectins are reviewed below.



Reagents and conditions: i, Palmitoic anhydride, DMAP, pyridine; ii, PPh_3, CO_2, pyridine.

Reagents and conditions: i, PPh_3, H_2O, THF, r.t., 7 d; ii, pyridine, r.t., 7 d

Scheme 11. Synthesis of glycosylated amphiphilic CDs according to Sallas et al.[42]



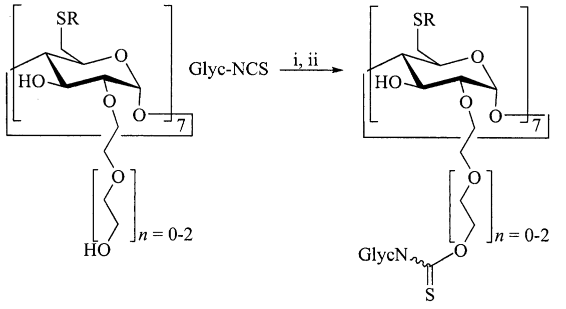
23, R = C_6H_{13}
25, R = $C_{16}H_{33}$

56, R = C_6H_{13}, R^1 = Galactose
57, R = C_6H_{13}, R^1 = Glucose
58, R = $C_{16}H_{33}$, R^1 = Galactose

Reagents and conditions: i, DMF, PPh_3, NBS, 65–80 °C, 3-4 h, 32–70 %; ii, DMF, R^1SNa, 80 °C, 7 d, 40 %.

Scheme 12. Synthesis of glycosylated amphiphilic CDs according to Mazzaglia et al.[43]

Other glycosylated amphiphilic CDs have been prepared by the same group (**62**–**64**) (Scheme 13). In this case, glycosylation was carried out on the oligo(ethylene oxide) chains directly using monosaccharide thiocyanates.[44]



59, Glyc = acetylated α-ManNCS
60, Glyc = acetylated β-FucNCS
61, Glyc = acetylated α-FucNCS

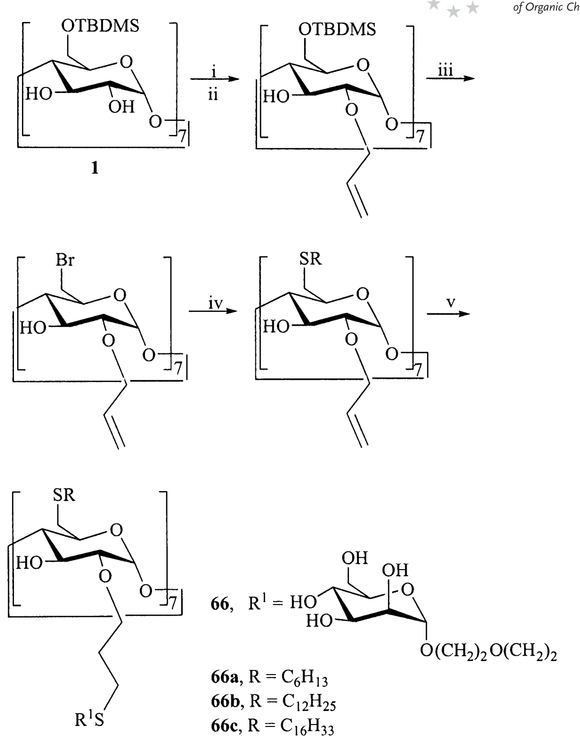
62, Glyc = α-Man
63, Glyc = β-Fuc
64, Glyc = α-Fuc

a, R = C_6H_{13}
b, R = $C_{12}H_{25}$
c, R = $C_{16}H_{33}$

Reagents and conditions : i, DABCO, toluene, r.t.; ii, NaOMe/ MeOH, (for **62b**–**c**, **63b**–**c**: MeOH/DMF); iii, MeOH/Et_3N/H_2O (8:1:1) (for **64b**–**c** MeOH/DMF).

Scheme 13. Synthesis of glycosylated amphiphilic CDs according to McNicholas.[44]

Photochemical addition of sugar thiol to allylic groups on a cyclodextrin[45] has provided another route to glycosyl conjugates. The substrate can be protected at its 6-positions by silyl groups and *O*-allylated at positions 2 (Scheme 14) or 2,3. This pathway has been further developed to create a variety of glycosylated amphiphilic CDs such as **66**[46] (Scheme 14).



66a, R = C_6H_{13}
66b, R = $C_{12}H_{25}$
66c, R = $C_{16}H_{33}$

Reagents and conditions: i, NaH, DMF, 0 °C, 90 min then r.t. overnight; ii, allyl bromide, DMF, 0 °C, 60 min then r.t. overnight; iii, PPh_3/Br_2, CH_2Cl_2, 0 °C then r.t. overnight; iv, R-SH, NaH, DMF, r.t., 90 min then 80 °C, 20 min, r.t.; v, acetylated R^1SH, MeOH/toluene, N_2, UV (λ= 254 nm), r.t., 3 d then NaOMe, MeOH/DMF, r.t., 5 h (**66a**), 18 h (**66b**–**c**).

Scheme 14. Synthesis of glycosylated amphiphilic CDs according to McNicholas.[46]

Salameh et al.[47] have described the preparation of a mono-galactosylated amphiphilic CD **68** (Scheme 15). In studies of interfacial properties, the galactosylated CD displayed a large collapse region and a high collapse pressure due to stabilisation of the film by the sugar.

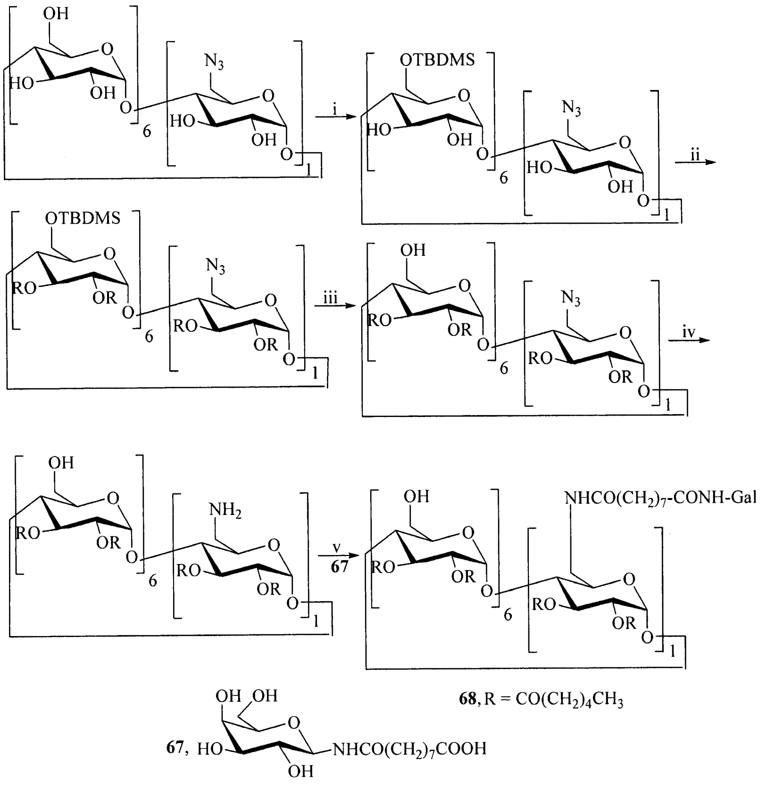
3. Amphiphilic Cyclodextrins and Supramolecular Chemistry

3.1 Self-Assembly

Early development of cyclodextrins capable of self-assembly led to many examples of amphiphiles capable of monolayer and multilayer formation at the air-water interface.[48] Admixture to phospholipid monolayers and liposomes was possible for the otherwise insoluble compounds, which could also be dispersed as nanoparticles. These developments have already been reviewed in summary.[11]

Micellar complexation of drugs was also demonstrated[35] as well as unimolecular micellar and inverted micellar behaviour in non-hydroxylic solvents.[49]

Hydrophilic-hydrophobic balance, molecular shape and solvation have all been enunciated as important criteria for formation of distinct lyotropic assemblies.[50] The grafting of short oligo(ethylene oxide) (n_{av} = 2) (PEG) chains onto



Reagents and conditions : i, TBDMSCl, pyridine; ii, hexanoic anhydride, DMAP, pyridine; iii, $BF_3 \cdot Et_2O$, $CHCl_3$; iv, Pd/C, H_2, MeOH; v, **67**, DCC, HOBT, DMF.

Scheme 15. Synthesis of a monoglycosylated amphiphilic CD.

the secondary side of the CDs eventually provided amphiphiles having the required balance and molecular shape for vesicle formation (Figure 3).[25a,25b,51]

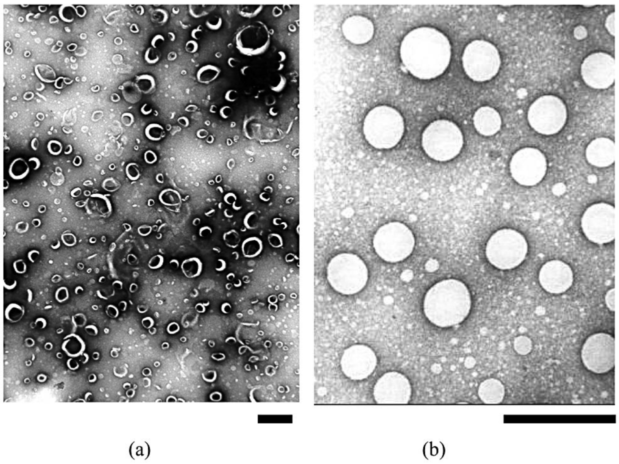


Figure 3.(a) Vesicles formed by amphiphilic cyclodextrin **25**,[25a] (b) Nanoparticles formed by amphiphilic cyclodextrin **64a**[46] (scale bars = 200 nm).

Such water-soluble amphiphilic cyclodextrins capable of assembly into micelles and bilayer vesicles have provided unique minimalist imitations of some biological systems, and promise a significant advance for cyclodextrins as water-competent host molecules. The three domains of cyclodextrin vesicles, namely water core, lipophilic membrane and external surface have capabilities such as improved transport of lipophilic molecules, transport also of hydrophilic molecules, enhanced molecular recognition and multivalent binding.

Vesicles of **25** showed the endothermic phase transition L beta to L alpha typical of lamellar lyotropic phases at 48 °C. The enthalpy of transition (59 kJ mol^{-1}), though high compared with phospholipids (30–40 kJ mol^{-1}), is much lower per lipid chain, indicating the greater rigidity of the CD amphiphile in an L alpha bilayer. For the CDs **22**, **23** with short alkylthio chains, the ratio of pegylation to lipophilic chain length decided whether polydisperse nanoparticles or micelles were formed.[11] The critical micelle concentrations (cmc) are about one hundred times smaller than those of traditional surfactants, and similar to those of CDs substituted with a single lipophilic chain [such as mono-6-(dodecylamino)-β-cyclodextrin].[52]

As shown by small-angle X-ray and light scattering, the shape and dimensions of the aggregates, despite their complex molecular geometry, can be described according to the thermodynamics of a core-shell model generally used for amphiphiles.[53]

Examples of these non-ionic CD amphiphiles have also been synthesised where the lipophilic chains contain disulfide links; reduction of these links with dithiothreitol results in collapse of the vesicles, showing their potential for controlled release of a drug, for example in the reducing environment of an endosome.[54]

The balance between hydrophobic and hydrophilic components in glycosylated amphiphilic cyclodextrins influences their self-assembly. The unglycosylated hexadecylthio oligo(ethylene oxide) cyclodextrin **25** forms nanoparticles, whereas the *N*-glycosyl-thiocarbamoyl derivative forms vesicles.[44]

Sulfated, and cationic oligo(ethylene oxide), amphiphilic CDs are others which form vesicles. As with the neutral amphiphiles, the lipophilic chain length decides whether nanoparticles or vesicles are formed.[26,34]

3.2 Inclusion by Assemblies

Inclusion by the three domains of cyclodextrin vesicles has been demonstrated. The hydrophilic fluorescent dye Rhodamine B is included in the water core of **27** as shown by addition of Triton X-100 surfactant, which releases the dye and reduces self-quenching.[26] Inclusion of fluorescein-labelled dextran has demonstrated the potential for inclusion of macromolecules such as proteins. Vesicles of **25** encapsulating diphenylhexatriene showed the endothermic phase transition typical of a lipid bilayer, coinciding with decrease in fluorescence polarisation for the dye, and showing its encapsulation within the lipid chains of the bilayer. The third domain, the surface cyclodextrin cavities of the vesicles, can act as receptors with multivalent recognition properties, as described in the next section.

A series of studies has been carried out by researchers at the University of Messina on the inclusion of porphyrins by CD vesicles, its effects on their photochemistry, and potential in phototherapy.[55] The interaction between the anionic 5,10,15,20-tetrakis(4-sulfonatophenyl)-21*H*,23*H*-porphyrin (TPPS) and cationic vesicles formed by **26** has been investigated by time-resolved fluorescence anisotropy. At porphyrin/CD molar ratios from 1:10 to 1:50, the porphyrin is solubilised in monomeric form (t_1 = 11.5 ns). At the lower porphyrin/CD molar ratios, the anisotropic decay exhibits a double-exponential behaviour showing a predominant component with a slow rotational correlation time. This component was assigned to vesicles with porphyrin molecules that are embedded in the oligo(ethylene oxide) surface. At high porphyrin loads, the smaller correlation time fits the siting of amounts of TPPS in a hydrophobic environment.[56] For the TPPS·**26** nanoparticles quantum yield is comparable to that of free TPPS. In vitro studies on tumor Hela cells treated with TPPS·**26** at different molar ratios showed significant cell death upon illumination with visible light.[56b,57]

The cationic amphiphilic cyclodextrin **26** affects the photochemical modification of the included drug diflunisal.[58] Langmuir–Schäfer multilayer films formed of cationic amphiphilic cyclodextrins and anionic porphyrins at the air-water interface sensitise the production of singlet oxygen.[59] These results for an electrostatically multilayered assembly bring CD amphiphiles into the research on polyionic CD layering,[60] as well as research on the incorporation of such CDs into heterolayers to enhance the bioactivity of guest molecules.[61]

3.3 Recognition by Assemblies

The surface of CD vesicles displays the hydrophobic cavities in a liquid crystalline array, which may be expected to have properties that imitate recognition by biological cells. Both recognitions, by individual cavities and by arrays of the surface cavities, have been demonstrated. The former had been predicted for guest molecules traditionally known to complex with natural cyclodextrins, while the multivalent interactions were predicted for guests capable of binding within more than one CD cavity. As measured by decreased electrophoretic mobility of complexed adamantane carboxylate, the β-cyclodextrin cavities, in spite of the presence of oligo(ethylene oxide) substituents on their peripheries, retain greater affinity than the α- or γ-CD amphiphile for this guest.[25c] Polyionic polymers having hydrophobic groups attached can coat the vesicles by multiple inclusions of these groups.[62]

In binding of galactosylated cyclodextrin vesicles to galactose-specific lectin, it was expected that in the liquid-crystalline surface the targeted molecules might adopt assembly patterns statistically optimised for "cluster" binding to the lectin sites. This multivalent binding was detected for the galactosylated amphiphile (**58**) admixed to non-galactosylated vesicles, in the first clear demonstration of the cluster effect in an artificial assembly.[43] The cluster effect has also been shown for vesicle binding to multiple sites on a synthetic guest.[63]

For assessment of their targeting to proteins, measurements based on the natural fluorescence of the protein in solution can be more accurate than perturbing methods such as surface plasmon resonance.[64] The galactosylated hexylthiocyclodextrin binds specifically to lectin from *Pseudomonas aeruginosa* better than the hexadecylthio-CD. The recognition properties of this particular cyclodextrin **56** may be partly due to the presence of micelles which interact more efficiently with the lectin binding sites.

4. DNA Delivery by CD Amphiphiles

Cationic CDs and their supramolecular assemblies have been developed as a new class of synthetic DNA vectors for transfection.[65] Viral vectors show high transfection efficiencies but with risk of immune reaction. As alternatives, non-viral vectors such as cationic liposomes, polymers and dendrimers have been extensively researched.[66] In common with these, cationic CD amphiphiles neutralise the charges on the phosphate DNA backbone and promote its condensation into a compact nanoparticulate complex for cell delivery.

CDs have well researched pharmaceutical and toxicological profiles as excipients in pharmaceutical formulations, and as oligosaccharides they are expected to have low immunogenicity. While the attachment of multiple cationic groups on the CD macrocycle confers the ability to act as synthetic vectors, it has been found that polycationic CD *amphiphiles* are at least five times more efficient again, that is 20000 times more efficient than uncomplexed DNA, and comparable to commercial cationic vectors.[27,67] The amphiphilicity may result in more efficient packing of the DNA within liquid crystalline complexes, probably lamellar, as are those of conventional cationic lipids.[68] The amphiphilic content of the nanoparticulate CD·DNA "lipoplexes" may also aid transmembrane cell delivery.

Conclusions

While much of the early research on cyclodextrins was concerned with converting them into imitators of proteins (enzymes), it now appears that their advancement as imitators of complex oligosaccharides and lipopolysaccharides has finally emerged. Cyclodextrins started as performing molecules, as totally saccharidic macrocyclocyclic[69] amphiphiles capable of molecular inclusion in water. This has tended to leave less limelight for other special characteristics: among oligosaccharides they are unique for their accessibility, monodispersity, and multiplicity of equivalent reactive sites. With exploitation of these characteristics, further elaboration of cyclodextrins by their conjugation to the fundamental moieties of hydrophiles and lipophiles has led to accentuation of their amphiphilicity, and to further interesting developments in the supramolecular chemistry of these wonderful molecules. These developments are already prefiguring significant new performances and applications.

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Received: October 1, 2007
Published Online: January 2, 2008