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Improved preparation of perallylated cyclodextrins: facile synthesis of cyclodextrin-based polycationic and polyanionic compounds

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Abstract

An improved procedure for the perallylation of cyclodextrins allowed the preparation of O-perallylated α-, β-, and γ-cyclodextrins in 89, 91, and 88% yields, respectively. These were converted into two cyclodextrin-based functionalized compounds, the polycationic heptakis[2,3,6-tri-*O*-(6-amino-3-thiahexyl)]-β-cyclodextrin hydrochloride (**3**), and the polyanionic heptakis[2,3,6-tri-*O*-(sodium 5-carboxyl-3-thiapentyl)]-β-cyclodextrin (**4**), a potential inhibitor of HIV-1 replication.

Keywords: Cyclodextrins; Perallylated cyclodextrins; Photoaddition; Polycationic compound; Polyanionic compound

1. Introduction

Cyclodextrins are a family of cyclic oligosaccharides consisting of six, seven, or eight α-(1→4)-linked D-glucopyranose units, which are called cyclomaltohexa-, hepta,- and octa-oses (α-, β-, and γ-cyclodextrins), respectively. The most significant characteristic of cyclodextrins is their ability to form host–guest or inclusion complexes in aqueous solutions with various organic molecules.[1,2] As a result, cyclodextrins have found wide applications in food and pharmaceutical industries for micro-encapsulation of sensitive fine chemicals and for drug delivery.[3] Cyclodextrins were also used as model compounds for constructing artificial enzymes.[4] More recently, cyclodextrins have been exploited as scaffolds for presenting amino acids/peptides,[5,6] multivalent sugar ligands,[7–12] and for synthesizing polyanion-based HIV-1 inhibitors.[13]

We are interested in using cyclodextrins as scaffolds for constructing novel multivalent ligands, employing O-perallylated cyclodextrins as key synthetic intermediates. Allyl ethers can be readily derivatized to various functionalities and have been widely used in carbohydrate chemistry.[11,13–20] However, the preparation of homogeneous, perallylated cyclodextrins is a difficult task because of the inherently divergent nature of cyclodextrins.[11,13,20] Any degree of non-uniform derivatization would lead to a complex mixture, from which the desired product would be extremely difficult to isolate. Several groups have reported the synthesis of O-perallylated cyclodextrins, but the yields were usually unsatisfactory. The O-perallylated α-, β-, and γ-cyclodextrins were first synthesized in 24, 32, and 20% yields, respectively.[13] Recently Kraus et al. reported an improved synthesis, which gave the O-perallylated β-cyclodextrin in 49% yield.[20] We report here a modified procedure that gave excellent yields for all three O-perallylated cyclodextrins, together with a simple conversion of the O-perallylated β-cyclodextrin into cyclodextrin-based polycationic and polyanionic compounds.

2. Results and discussion

For the O-perallylation of β-cyclodextrin, we first repeated the reported procedure[13] by adding dried β-cyclodextrin powder to a suspension of sodium hydride

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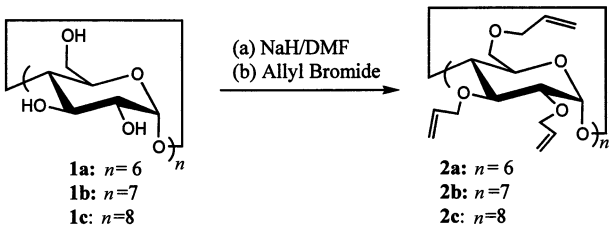
(NaH) in *N*,*N*′-dimethylformamide (DMF), followed by the addition of allyl iodide or allyl bromide to the suspension at 0 °C: the best yield obtained was 45% for the O-perallylated β-cyclodextrin. Performing the allylation with allyl bromide–NaH at 35 °C, according to the procedure of Kraus et al.,[20] gave a slightly improved yield (51%) of the O-perallylated β-cyclodextrin. We reasoned that two factors might contribute to the relatively low yield in the perallylation of cyclodextrins: the relatively low solubility of cyclodextrin in DMF at low temperature and the exothermic nature of the alkylation reaction, which could result in either incomplete allylation or decomposition of the product. Accordingly, we modified the procedure by (1) pre-dissolving the cyclodextrin in DMF (by heating and stirring) to form a clear solution before adding it to the NaH suspension in DMF and (2) conducting the allylation reaction with allyl bromide at low temperature (0 °C). Interestingly, this modification led to a reproducible, highly efficient allylation of the three cyclodextrins. Thus, the desired O-perallylated α-, β-, and γ-cyclodextrins were obtained in 89, 91, and 88% yields, respectively, by the modified procedure (Scheme 1). Each of the allylated cyclodextrins gave a single spot on TLC in several different solvent systems and the ^{1}H and ^{13}C NMR spectra were in good agreement with their structures. To confirm that there are no free hydroxyl groups left in the allylated products, we also performed acetylation (Ac_2O–pyridine) with the products. After work-up, the ^{1}H NMR of the treated sample did not show trace of *O*-acetyl signals that would otherwise appear at ~2.2 ppm (data not shown), suggesting that all hydroxyl groups in the products had been allylated. Although sonication was suggested in the literature for the allylation of cyclodextrins,[13,20] we observed that magnetic stirring alone was sufficient for the allylation, giving the respective O-perallylated cyclodextrins in excellent yields. It becomes clear that pre-dissolution of cyclodextrins in DMF and the control of reaction temperature are crucial for efficient alkylation.

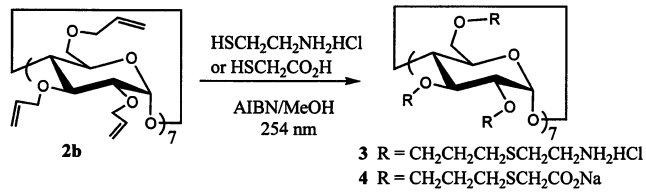
We next evaluated the synthesis of cyclodextrin-based polycationic and polyanionic compounds, taking advantage of the well-known photoaddition of thiols to allyl ethers as the key step.[21] A cyclodextrin-based polycationic compound, the cyclodextrin-based polyamine **3**, was synthesized by photoaddition of cysteamine to the O-perallylated β-cyclodextrin **2b** (Scheme 2). To achieve uniform derivatization, three molar equivalents (per allyl ether) of cysteamine were used and the reaction was monitored by recording ^{1}H NMR spectra of aliquot samples. As the reaction proceeds, the signal for the allyl protons (–*CH*=*CH*$_2$, 5.0–6.1 ppm) decreases and the signal for the S–C*H*$_2$ (2.7 ppm) in the product increases. After disappearance of the allyl proton signals, the desired polyamine **3** was isolated in 68% yield as its HCl salt by Sephadex G-15 gel filtration. Similarly, a polyanionic compound (**4**) isolated as its sodium salts was synthesized in 62% yield by photoaddition of mercaptoacetic acid to the O-perallylated β-cyclodextrin **2b**. Compound **4** may have the potential for suppressing HIV-1 replication, because similar polyanionic compounds have been shown to inhibit HIV-1 replication in certain host cells at an IC_{50} of 0.1–3 μM while not being toxic to the host cells at up to 60 μM.[13]



1a: n= 6
1b: n=7
1c: n=8

2a: n= 6
2b: n=7
2c: n=8

Scheme 1.



2b

3 R = $CH_2CH_2CH_2SCH_2CH_2NH_2HCl$
4 R = $CH_2CH_2CH_2SCH_2CO_2Na$

Scheme 2.

This modified procedure for the high-yield preparation of the O-perallylated α-, β-, and γ-cyclodextrins allows synthesis of the cyclodextrin-based polyamine **3**, under evaluation for constructing novel HIV epitope vaccines, and a cyclodextrin-based polyanionic compound (**4**) that is a potential inhibitor for HIV-1 infection.

3. Experimental

General methods.—α-, β-, and γ-Cyclodextrins (Aldrich) were dried by coevaporation with toluene before use. *N*,*N*-Dimethylformamide (Aldrich) was dried over 4 Å molecular sieves. All other chemicals were purchased from Aldrich and used as received. ^{1}H NMR spectra were recorded at 600 MHz on a Bruker Avance DMX 600 MHz spectrometer with Me_4Si (δ 0) as the internal standard. ^{13}C NMR spectra were recorded at 150.9 MHz on a Bruker Avance DMX 600 MHz spectrometer with Me_4Si (δ 0) as the internal standard. The ES-MS spectra were recorded on a Waters ZMD mass spectrometer. TLC was performed on Silica Gel FG_{254} (E. Merck). Carbohydrates were detected by charring with 10% ethanolic H_2SO_4. Amines were detected by ninhydrin spraying. The photoaddition reaction was carried out under nitrogen and monitored by taking ^{1}H NMR spectra of aliquots at

intervals until the disappearance of the allyl protons (δ 5.0–6.2, m, –$OCH_2CH{=}CH_2$). Flash column chromatography was performed on Silica Gel 60 (200–400 mesh, EM Science). Gel filtration was carried out on Sephadex G-15 (Pharmacia) using deionized water as the eluant.

Typical procedures for the allylation of cyclodextrins.—Each of the cyclodextrins (2 mmol) was dissolved in DMF (15 mL) by heating and stirring. The clear solution was then added dropwise to a cooled (0 °C) suspension of NaH (60% dispersion in mineral oil, 3 equiv per OH group in cyclodextrin) that was washed with dry hexane (2 × 10 mL) before being suspended in DMF (50 mL). After the suspension had been stirred for 1 h at 0–5 °C, a solution of allyl bromide (3 equiv per OH function) in DMF (10 mL) was added dropwise. The resulting mixture was first stirred for 1 h at 0–5 °C, and then for 2–4 h at 25 °C. At this point, TLC showed the formation of a single product. The reaction was quenched by addition of MeOH (5 mL). DMF and excess allyl bromide were removed by evaporation under diminished pressure. The residue was partitioned between EtOAc (200 mL) and water (30 mL). The organic layer was washed with brine (2 × 50 mL), dried over Na_2SO_4, and evaporated. Flash column chromatography of the residue on silica gel using 3:1 (v/v) hexane–EtOAc as the eluant gave the respective O-perallylated cyclodextrins.

Per-O-*allyl*-α-*cyclodextrin* (**2a**).—Yield 89%; R_f 0.39 (25:1 toluene–EtOH), and 0.32 (3:1 hexane–EtOAc); $[\alpha]_D^{23}$ +34° (*c* 0.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$–Me_4Si): δ 6.26–6.14 (m, 6 H, $OCH_2CH{=}CH_2$), 6.08–5.94 (m, 12 H, $OCH_2CH{=}CH_2$), 5.42–5.28 (m, 18 H, $OCH_2CH{=}CHH$), 5.28–5.16 (m, 18 H, $OCH_2CH{=}CHH$), 5.09 (d, 6 H, *J* 3.2 Hz, H-1), 4.63 (dd, 6 H, *J* 12.2, 6.1 Hz, $OCHHCH{=}CH_2$), 4.36 (dd, 6 H, *J* 12.2, 5.4 Hz, $OCHHCH{=}CH_2$), 4.30 (dd, 6 H, *J* 13.0, 6.0 Hz, $OCHHCH{=}CH_2$), 4.20 (dd, 6 H, *J* 13.0, 5.2 Hz, $OCHHCH{=}CH_2$), 4.14 (dd, 6 H, *J* 12.8, 5.2 Hz, $OCHHCH{=}CH_2$), 4.08 (dd, 6 H, *J* 12.8, 5.8 Hz, $OCHHCH{=}CH_2$), 3.96 (dd, 6 H, *J* 10.6, 3.6 Hz, H-6), 3.90 (dd, 6 H, *J* 10.6, 2.9 Hz, H-6′). 3.87 (dd =t, 6 H, *J* 9.5 Hz, H-4), 3.79–3.75 (m, 12 H, H-3, 5), 3.42 (dd, 6 H, *J* 9.8, 3.2 Hz, H-2); ^{13}C NMR (150.9 MHz, $CDCl_3$): 139.44 ($OCH_2CH{=}CH_2$), 138.18 ($OCH_2CH{=}CH_2$), 137.72 ($OCH_2CH{=}CH_2$), 119.45 ($OCH_2CH{=}CH_2$), 119.33 ($OCH_2CH{=}CH_2$), 118.44 ($OCH_2CH{=}CH_2$), 103.26 (C-1), 84.62 (C-3), 82.35 (C-2), 81.20 (C-4), 77.27 ($OCH_2CH{=}CH_2$), 74.84 ($OCH_2CH{=}CH_2$), 74.57 ($OCH_2CH{=}CH_2$), 73.91 (C-5), 71.72 (C-6); ES-MS: 1711.1 $[M-3H_2+Na]^+$, 1694.1 $[M+H]^+$, 866.6 $[M-3H_2+2Na]^{2+}$.

Per-O-*allyl*-β-*cyclodextrin* (**2b**).—Yield 91%; R_f 0.41 (25:1 toluene–EtOH), and 0.31 (3:1 hexane–EtOAc); $[\alpha]_D^{23}$ +53° (*c* 0.5, $CHCl_3$), lit.[20] $[\alpha]_D^{25}$ +92° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$–Me_4Si): δ 6.16–6.05 (m, 7 H, $OCH_2CH{=}CH_2$), 6.05–5.92 (m, 14 H, $OCH_2CH{=}CH_2$), 5.44–5.29 (m, 21 H, $OCH_2CH{=}CHH$), 5.25 (d, 7 H, *J* 3.4 Hz, H-1), 5.24–5.14 (m, 21 H, $OCH_2CH{=}CHH$), 4.57 (dd, 7 H, *J* 12.1, 5.3 Hz, $OCHHCH{=}CH_2$), 4.35 (dd, 7 H, *J* 12.1, 5.6 Hz, $OCHHCH{=}CH_2$), 4.30–4.17 (m, 14 H, $OCHHCH{=}CH_2$), 4.17–4.04 (m, 14 H, $OCHHCH{=}CH_2$), 3.99 (dd, 7 H, *J* 10.5, 2.4 Hz, H-6), 3.92–3.64 (m, 21 H, H-3, H-4 and H-5), 3.67 (d, 7 H *J* 10.5 Hz, H-6′), 3.43 (dd, 7 H, *J* 9.4, 3.4 Hz, H-2); ^{13}C NMR ($CDCl_3$): 138.84 ($OCH_2CH{=}CH_2$), 138.00 ($OCH_2CH{=}CH_2$), 137.52 ($OCH_2CH{=}CH_2$), 119.36 ($OCH_2CH{=}CH_2$), 119.30 ($OCH_2CH{=}CH_2$), 118.19 ($OCH_2CH{=}CH_2$), 101.33 (C-1), 82.64 (C-3), 81.86 (C-2), 81.68 (C-4), 77.07 ($OCH_2CH{=}CH_2$), 74.79 ($OCH_2CH{=}CH_2$), 74.75 ($OCH_2CH{=}CH_2$), 73.63 (C-5), 71.70 (C-6); ES-MS: 1994.4 $[M-3H_2+Na]^+$, 1977.4 $[M+H]^+$, 1008.4 $[M-3H_2+2Na]^{2+}$, 989.4 $[M+2H]^{2+}$.

Per-O-*allyl*-γ-*cyclodextrin* (**2c**).—Yield 88%; R_f 0.44 (25:1 toluene–EtOH), and 0.27 (3:1 hexane–EtOAc); $[\alpha]_D^{23}$ +56° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$–Me_4Si): δ 6.16–6.05 (m, 8 H, $OCH_2CH{=}CH_2$), 6.05–5.92 (m, 16 H, $OCH_2CH{=}CH_2$), 5.40–5.30 (m, 24 H, $OCH_2CH{=}CHH$), 5.30 (d, 8 H, *J* 3.7 Hz, H-1), 5.25–5.16 (m, 24 H, $OCH_2CH{=}CHH$), 4.60 (dd, 8 H, *J* 12.1, 5.3 Hz, $OCHHCH{=}CH_2$), 4.34 (dd, 8 H, *J* 12.1, 5.7 Hz, $OCHHCH{=}CH_2$), 4.30–4.16 (m, 16 H, $OCHHCH{=}CH_2$), 4.11 (dd, 8 H, *J* 13.0, 5.2 Hz, $OCHHCH{=}CH_2$), 4.05 (dd, 8 H, *J* 13.0, 5.8 Hz, $OCHHCH{=}CH_2$), 3.97 (dd, 8 H, *J* 10.5, 1.0 Hz, H-6), 3.90–3.74 (m, 24 H, H-3, H-4 and H-5), 3.62 (d, 8 H, *J* 10.5 Hz, H-6′), 3.45 (dd, 8 H, *J* 9.6, 3.6 Hz, H-2); ^{13}C NMR ($CDCl_3$): 138.77 ($OCH_2CH{=}CH_2$), 138.04 ($OCH_2CH{=}CH_2$), 137.48 ($OCH_2CH{=}CH_2$), 119.62 ($OCH_2CH{=}CH_2$), 119.46 ($OCH_2CH{=}CH_2$), 118.19 ($OCH_2CH{=}CH_2$), 101.36 (C-1), 82.88 (C-3), 81.95 (C-2), 81.27 (C-4), 77.24 ($OCH_2CH{=}CH_2$), 75.04 ($OCH_2CH{=}CH_2$), 74.72 ($OCH_2CH{=}CH_2$), 73.64 (C-5), 71.49 (C-6); ES-MS: 2276.3 $[M-3H_2+Na]^+$, 2259.3 $[M+H]^+$, 1149.4 $[M-3H_2+2Na]^{2+}$, 1130.4 $[M+2H]^{2+}$.

Per-O-*(6-amino-3-thiahexyl)-*β-*cyclodextrin hydrochloride* (**3**).—To a solution of **2b** (213.0 mg, 0.11 mmol) and AIBN (20.0 mg) in MeOH (10 mL) in a quartz flask was added cysteamine hydrochloride (771.4 mg, 6.79 mmol). After being degassed by bubbling N_2 into the solution for 30 min, the resulting mixture was stirred and irradiated (UV, 254 nm) under N_2. The progress of the reaction was monitored by ^{1}H NMR. After 5 days, ^{1}H NMR showed the disappearance of allyl proton signals. The volatiles were evaporated under diminished pressure, and the residue was purified by gel filtration on Sephadex G-15 using water as the eluent. Fractions containing the product were pooled and lyophilized to give the polyamine hydrochloride **3** (317.0 mg, 68%) as a colorless glass-like solid: $[\alpha]_D^{23}$ +22° (*c* 0.5, water); ^{1}H NMR (D_2O): δ 5.35–5.10 (m,

7 H, H-1), 4.20–3.50 (m, 70 H, OCH_2CH$_2$CH$_2$S–, H-3, H-5, H-6′ and H-6), 3.48–3.32 (m, 14 H, H-2 and H-4), 3.30–3.14 (m, 42 H, –CH_2NH$_2$HCl), 3.00–2.84 (m, 42 H, –SCH_2CH$_2$NH$_2$HCl), 2.84–2.60 (m, 42 H, –CH_2-SCH$_2$CH$_2$NH$_2$HCl), 2.10–1.85 (m, 42 H, –CH$_2$CH_2-CH$_2$S); ^{13}C NMR (D$_2$O): 101.00–99.00 (C-1), 84.00–80.00 (C-2, C-3, and C-4), 77–73.00 (C-5, and C-6), 73.00–70.00 (–OCH$_2$CH$_2$CH$_2$S), 41.22 (SCH$_2$CH$_2$-NH$_2$HCl), 31.92 (–OCH$_2$CH$_2$CH$_2$S), 31.23 (SCH$_2$-CH$_2$NH$_2$HCl), 30.15 (OCH$_2$CH$_2$CH$_2$S). We tried to record ES-MS, MALDI-MS, and FAB-MS of the polyamine hydrochloride **3** but failed to obtain useful information. For further characterization of the product, compound **3** was converted into its monosaccharide subunit through hydrolysis with 1 M HCl (70 °C for 3 h), and the product was analyzed by ES-MS. The ES-MS spectrum gave a strong signal at 532.45 $[M + H]^+$ for the fully substituted monosaccharide subunit, indicating that the monosaccharide subunits in polyamine **3** are uniformly substituted.

Per-O-*(sodium 5-carboxy-3-thiapentyl)-β-cyclodextrin* (**4**).—A solution of **2b** (229.2 mg, 0.12 mmol), mercaptoacetic acid (673.2 mg, 7.31 mmol), and AIBN (10.0 mg) in MeOH (10.0 mL) was stirred and irradiated (254 nm) under N_2. After ^{1}H NMR has shown the disappearance of allyl signals, MeOH was evaporated off and the residue was dissolved in 0.5 M aq NaOH (15 mL). The pH of solution was adjusted to 8–9 with Dowex 50W X2 (H^+ form) resin. The mixture was filtered and the resin washed with water (2 × 2 mL). The combined filtrate was lyophilized. The residue was subjected to gel-filtration on Sephadex G-15 with deionized water as eluent. The fractions containing the product were pooled and lyophilized to give **4** (321.3 mg, yield 62%): $[\alpha]_D^{23}$ +29° (*c* 0.5, water); ^{1}H NMR (D$_2$O): δ 5.30–5.05 (m, 7 H, H-1), 4.20–3.50 (m, 84 H, OCH_2CH$_2$CH$_2$S–, H-2, H-3, H-4, H-5, H-6′ and H-6), 3.30–3.20 (m, 42 H, –SCH_2CO$_2$Na), 2.88–2.55 (m, 42 H, –CH_2SCH$_2$CO$_2$Na), 2.10–1.85 (m, 42 H, –CH_2-CH$_2$SCH$_2$CO$_2$Na); ^{13}C NMR (D$_2$O): 182.00–180.00 (–SCH$_2$CO$_2$Na), 101.00–100.00 (C-1), 84.00–80.00 (C-2, C-3, and C-4), 75.00–70.00 (C-5, C-6, and –OCH$_2$-CH$_2$CH$_2$–), 39.18 (–SCH$_2$CO$_2$Na), 31.74 (–OCH$_2$CH$_2$-CH$_2$S–), 31.28 (–OCH$_2$CH$_2$CH$_2$S–). As with the polyamine **3**, the polyanionic compound **4** failed to give interpretable ES-MS, MALTI-TOF MS, and FAB-MS. Further characterization of **4** was attempted by hydrolysis of **4** with 2 M trifluoroacetic acid (100 °C, 4 h), followed by ES-MS analysis. ES-MS of the hydrolyzate product gave a strong signal at 599.42 $[M + Na]^+$ for the monosaccharide subunit of **4**, and no under-substituted intermediates (such as di- or mono-substituted monosaccharides) were observed in the ES-MS.

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