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α-Cyclodextrin Compounds Containing Benzoic, Acetylsalicylic, and 2-(4-Isobutylphenyl)propionic Acid Residues

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Abstract—Selectively substituted derivatives of α-cyclodextrin and hexa-*O*-*tert*-butyldimethylsilyl-α-cyclodextrin containing a definite number of acylated primary or secondary hydroxy groups were synthesized using benzoic, acetylsalicylic, and 2-(4-isobutylphenyl)propionic acid chlorides in various solvents in the presence of different bases. The acyl residues were assigned to the C^2, C^3, or C^6 atoms in the carbohydrate fragments on the basis of ^{13}C NMR data. Desilylation of the silyl derivatives with ammonium fluoride in methanol gave the corresponding *O*-acyl derivatives having free primary hydroxy groups in the α-cyclodextrin skeleton.

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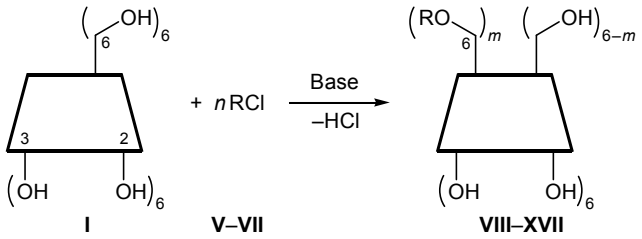
Regioselective functionalization of cyclodextrins is an experimentally difficult problem due to the presence of a large number of chemically different hydroxy groups. In most cases, this problem is solved by protection of hydroxy groups in the cyclodextrin skeleton by various protecting groups [1]. We previously developed procedures for selective acylation of free (unprotected) hydroxy groups in α- [2] and β-cyclodextrins [2, 3]. These procedures allowed us to synthesize β-cyclodextrin derivatives containing covalently bonded (conjugated) residues of some pharmacologically important acids [4]. In some cases such "coupling" makes it possible to create on the basis of known pharmacologically active compounds new medicines with prolonged and more selective action [5]. Attention was mainly given to derivatives of β-cyclodextrin as least expensive and most accessible substrate.

In continuation of these studies in the present work we made an attempt to synthesize derivatives of α-cyclodextrin (**I**) having benzoic (**II**), acetylsalicylic (**III**), and 2-(4-isobutylphenyl)propionic acid (**IV**) residues. Drugs containing fragments of acids **III** and **IV** exhibit anti-inflammatory, antipyretic, analgesic, and antithrombotic (inhibit platelet aggregation) activity, but they are poorly soluble in water [for example, the solubilities of acetylsalicylic and 2-(4-isobutylphenyl)-propionic acids are as low as 2.5 and 0.021 g/l, respectively], which complicates their administration because of local irritation of mucous membrane in stomach. The choice of α-cyclodextrin as a drug-carrier matrix was determined by its considerably better solubility in water (145 g/l) as compared to β-cyclodextrin (18.5 g/l), which was expected to improve pharmacological properties of the resulting compounds upon biological testing.

Taking into account our data on selective acylation of α- and β-cyclodextrins [2–4], as acylating agents we used the corresponding acid chlorides, namely benzoyl chloride (**V**), 2-acetoxybenzoyl chloride (**VI**), and 2-(4-isobutylphenyl)propionyl chloride (**VII**). The reactions were carried out in DMF in the presence of different amines (triethylamine, pyridine), as well as in pyridine. Though α-cyclodextrin is sparingly soluble in pyridine, the reaction mixture rapidly became homogeneous as the reaction progressed. For the sake of comparison all experiments were performed under similar conditions (see Experimental). The acylation with 2, 5, and 7 equiv of acid chloride **V**–**VII** gave α-cyclodextrin derivatives with a degree of primary hydroxy group substitution *m* of 1, 4, and 6, respectively (Scheme 1). The average degree of acylation (*m*) was estimated by ^1H NMR spectroscopy, from the intensity ratio of signals from protons in the benzoic

Scheme 1.

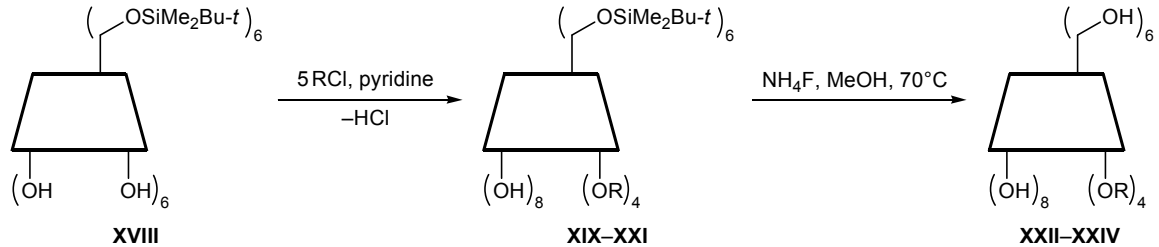


V, **VIII**–**X**, R = PhC(O), **VI**, **XI**–**XIII**, R = 2-$AcOC_6H_4C(O)$; **VII**, **XIV**–**XVII**, R = $Me_2CHCH_2C_6H_4CH(Me)C(O)$; **VIII**, **XI**, *n* = 2, *m* = 1; **XIV**, *n* = *m* = 2; **IX**, **XII**, **XV**, *n* = 5, *m* = 4; **XVI**, *n* = *m* = 5; **X**, **XIII**, **XVII**, *n* = *m* = 6.

(**VIII**–**X**), acetylsalicylic (**XI**–**XIII**), or 2-(4-isobutylphenyl)propionic acid residues (**XIV**–**XVII**) and those in the cyclodextrin skeleton in the region δ 3.20–4.45 ppm. The degree of acylation of compounds **VIII**–**XIII**, **XV**, **XVII** was relatively high; for compounds **IX**, **X**, **XII**, **XIII**, **XV**, and **XVII**, it was only slightly smaller than the number of equivalents (*n*) of acid chloride **V**–**VII** involved in the reaction. The degree of acylation of **XIV** and **XVI** was the maximum possible (*m* = 2 and 5, respectively), presumably due to higher reactivity of propionyl chloride **VII** compared to benzoyl chlorides **V** and **VI**. When the acylation was incomplete (compounds **VIII**–**XIII**, **XV**, **XVII**), prolonged reaction did not result in higher degree of acylation, but the yield of by-products increased. It was difficult to determine the predominant acylation direction (i.e., whether it occurred at primary hydroxy groups on C^6 or at secondary hydroxy groups on C^2 and C^3) because of problems in signal assignment, whereas ^{13}C NMR spectra turned out to be more informative. In the ^{13}C NMR spectra of all compounds **VIII**–**XVII**, signals from the $C^{6'}$ atoms linked to acyloxy substituent were displaced downfield (δ_C 63.5–64.0 ppm) relative to those from C^6 linked to free hydroxy groups (δ_C 60.1–60.6 ppm). Signals from $C^{5'}$ in the carbohydrate fragment containing an acyloxy residue on $C^{6'}$ appeared in a stronger field (δ_C 69.0–69.9 ppm) relative to the corresponding signal from non-acylated carbohydrate fragment. These findings were consistent with published data [3, 4, 6]. In addition, we previously found that signals from carbonyl carbon atoms in partly and completely acetylated α- and β-cyclodextrins can also be used to determine the site of acylation. The carbonyl carbon atoms in the acetoxy groups on C^2, C^3, and C^6 gave three separate signals in the ^{13}C NMR spectra [2, 7]. The carbonyl carbon atoms in compounds **VIII**–**XVII** gave only one signal, which may be regarded as an additional proof for substitution at hydroxy groups on C^6 only.

While developing studies in this line, we synthesized analogous acylated α-cyclodextrin derivatives containing residues of acids **II**–**IV** on C^2 and C^3 (at broad part of the cyclodextrin skeleton). As substrate we used accessible 6-hexa-*O*-*tert*-butyl(dimethyl)silyl-α-cyclodextrin (**XVIII**) in which primary hydroxy groups on C^6 were protected with silyl groups. Taking into account specificity of the synthesis of compounds **VIII**–**XVII**, the acylation was carried out in pyridine with 5 equiv of acid chloride **V**–**VII** (Scheme 2; see Experimental). The average degree of substitution was determined by ^1H NMR spectroscopy from the intensity ratio of signals from protons in the corresponding acid residue and signals from protons in the *tert*-butyl groups on the silicon atom (δ 0.60–1.00 ppm). In all cases we isolated silyl derivatives **XIX**–**XXI** which contained four acyl residues at the broad part of the cyclodextrin skeleton. The site of acylation (at C^2 or C^3) was determined by ^{13}C NMR spectroscopy. Compound **XIX** displayed in the ^{13}C NMR spectrum a downfield shift of the C^2 signal from δ_C 72.3 (in the spectrum of initial compound **XVIII**) to 73.9 ppm and an upfield shift of the C^1 signal from δ_C 101.6 to 98.9 ppm, while the C^4 signal (δ_C 81.1 ppm) did not change its position. These data indicated that acylation involved only the hydroxy group on C^2. The above assignment of ^1H and ^{13}C signals was additionally con-

Scheme 2.



XIX, **XXII**, R = PhC(O), **XX**, **XXIII**, R = 2-$AcOC_6H_4C(O)$; **XXI**, **XXIV**, R = $Me_2CHCH_2C_6H_4CH(Me)C(O)$.

firmed by the two-dimensional {^{1}H–^{13}C} HETCOR spectrum (see figure).

A more complicated pattern was observed in the ^{13}C NMR spectrum of acyl derivative **XX** which displayed signals from C^1 at δ_C 98.8 ppm and C^4 at δ_C 80.9 ppm; this means that the hydroxy groups on C^2 and C^3 were acylated. Compound **XXI** showed a similar pattern. In the ^{1}H NMR spectrum of **XX** signals from methyl protons in the acetyl groups appeared as two singlets with equal intensities at δ 2.25 and 2.38 ppm, and the ^{13}C NMR spectrum of **XX** contained two signals with equal intensities* corresponding to carbonyl carbon atoms in the acyloxy groups on C^2 and C^3. We can conclude that two acyloxy groups are linked to C^2, and the other two, to C^3.

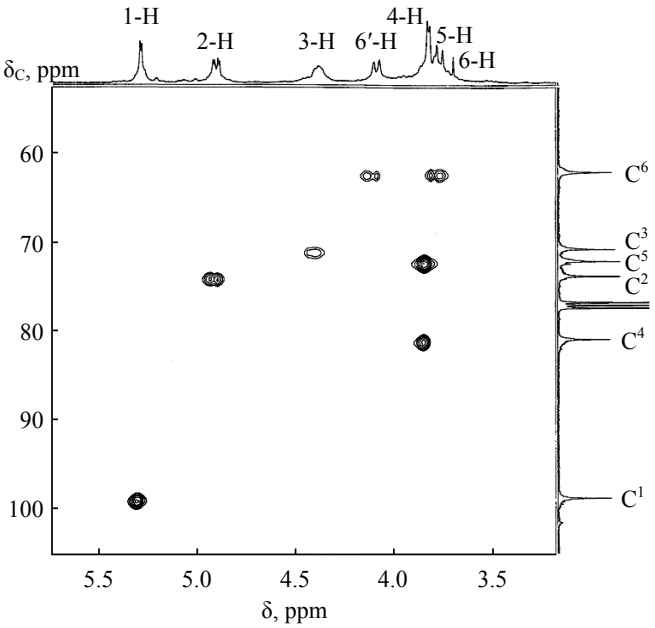
Compounds **XIX**–**XXI** were deprotected by treatment with a solution of ammonium fluoride in methanol [8]. As a result, compounds **XXII**–**XXIV** were formed in high yields (Scheme 2), and the acyl groups were conserved, which was confirmed by ^{1}H NMR data (see Experimental).

Thus we have proposed procedures for the synthesis of α-cyclodextrin derivatives containing a required number of pharmacologically important acid residues at both primary hydroxy groups on C^6 (narrow part of the cyclodextrin skeleton) and secondary hydroxy groups on C^2 and C^3 (broad part). Such compounds attract interest as nanosized structures for pharmacological studies, which may ensure highly efficient selective and specific drug delivery.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Jeol ECX400 spectrometer at 400 and 100.53 MHz, respectively, using tetramethylsilane as internal reference. Thin-layer chromatography was performed on Silufol UV-254 plates using acetonitrile–water (5 : 1, A), acetonitrile–water–25% aqueous ammonia (6 : 3 : 1, B), benzene–ethanol (5 : 1, C), and benzene–ethanol (7 : 1, D) as eluents; the chromatograms were developed by treatment with iodine vapor. α-Cyclodextrin (Merck, Germany) was subjected to additional thorough dehydration.

6^I-*O*-Benzoyl-α-cyclodextrin (VIII). *a*. A solution of 0.29 g (2.06 mmol) of benzoyl chloride (**V**) in 5 ml of DMF was added over a period of 20 min under



Two-dimensional HETCOR {^{1}H–^{13}C} NMR spectrum of compound **XIX** in $CDCl_3$.

stirring at 0°C to a solution of 1.00 g (1.03 mmol) of α-cyclodextrin and 0.23 g (2.26 mmol) of triethylamine in 25 ml of DMF. The mixture was stirred for 24 h at 20°C and filtered, the filtrate was evaporated to a volume of 2 ml, and the residue was ground with 40 ml of diethyl ether, washed with chloroform (3× 10 ml), and dried under reduced pressure (1 mm) for 4 h at 90°C. Yield 0.94 g (85%), mp 277–279°C (decomp.), R_f 0.53 (A). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.25–4.25 m (36H, 2-H, 3-H, 4-H, 5-H, 6-H), 4.75–4.79 m (6H, 1-H), 5.10–5.40 br.s (17H, 6-OH, 2-OH, 3-OH), 7.35–8.10 m (5H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 60.6 (C^6), 63.9 ($C^{6'}$), 69.9 ($C^{5'}$); 73.7, 73.9, 74.5 (C^2, C^3, C^5); 82.6 (C^4), 102.5 (C^1), 128.0–134.2 (C_{arom}), 166.5 (C=O). Found, %: C 48.08; H 5.93. $C_{43}H_{64}O_{31}$. Calculated, %: C 47.96; H 5.99.

b. As described above in *a*, from 1.00 g (1.03 mmol) of α-cyclodextrin and 0.18 g (2.26 mmol) of pyridine in 25 ml of DMF and 0.29 g (2.06 mmol) of benzoyl chloride (**V**) in 5 ml of DMF we obtained 1.02 g (92%) of compound **VIII**, mp 277–279°C (decomp.), R_f 0.53 (A). The ^{1}H and ^{13}C NMR spectra of the product coincided with those given above.

Tetrakis(6-*O*-benzoyl)-α-cyclodextrin (IX). *a*. As described above for compound **VIII**, the reaction of 1.00 g (1.03 mmol) of α-cyclodextrin and 0.57 g (5.65 mmol) of triethylamine in 25 ml DMF with 0.72 g (5.14 mmol) of benzoyl chloride (**V**) in 5 ml of

* In order to compare signal intensity, the ^{13}C NMR spectrum of compound **XX** (Fourier transform) was recorded with a long pulse delay (8 s).

DMF gave 0.63 g (44%) of compound **IX**, mp 269–271°C (decomp.), R_f 0.76 (A). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.25–4.25 m (36H, 2-H, 3-H, 4-H, 5-H, 6-H), 4.74–4.80 m (6H, 1-H), 5.09–5.39 br.s (14H, 6-OH, 2-OH, 3-OH), 7.25–8.15 m (20H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 60.6 (C^6), 63.9 ($C^{6'}$), 69.9 ($C^{5'}$); 73.7, 73.9, 74.5 (C^2, C^3, C^5), 82.6 (C^4), 102.6 (C^1), 127.9–134.3 (C_{arom}), 166.5 (C=O). Found, %: C 55.80; H 5.43. $C_{64}H_{76}O_{34}$. Calculated, %: C 55.33; H 5.51.

b. As described above for compound **VIII**, by reaction of 1.00 g (1.03 mmol) of α-cyclodextrin and 0.48 g (5.65 mmol) of pyridine in 25 ml of DMF with 0.72 g (5.14 mmol) of benzoyl chloride (**V**) in 5 ml of DMF we obtained 0.86 g (60%) of compound **IX**, mp 269–271°C (decomp.), R_f 0.76 (A). The ^{1}H and ^{13}C NMR spectra of the product coincided with those given above.

Hexakis(6-*O*-benzoyl)-α-cyclodextrin (X). *a*. As described above for compound **VIII**, the reaction of 1.00 g (1.03 mmol) of α-cyclodextrin and 0.80 g (7.91 mmol) of triethylamine in 25 ml of DMF with 1.01 g (7.20 mmol) of benzoyl chloride (**V**) in 5 ml of DMF gave 1.38 g (84%) of compound **X**, mp 234–236°C, R_f 0.79 (A). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.25–4.25 m (36H, 2-H, 3-H, 4-H, 5-H, 6-H), 4.77 d (6H, 1-H, $^3J_{HH}$ = 3.5 Hz), 5.06–5.37 br.s (12H, 2-OH, 3-OH), 7.20–8.20 m (30H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 64.0 ($C^{6'}$), 69.9 ($C^{5'}$), 73.9, 74.5 (C^2, C^3), 82.6 (C^4), 102.6 (C^1), 127.7–134.5 (C_{arom}), 166.5 (C=O). Found, %: C 58.75; H 5.27. $C_{78}H_{84}O_{36}$. Calculated, %: C 58.64; H 5.30.

b. As described above for compound **VIII**, the reaction of 1.00 g (1.03 mmol) of α-cyclodextrin and 0.63 g (7.91 mmol) of pyridine in 25 ml of DMF with 1.01 g (7.20 mmol) of benzoyl chloride (**V**) in 5 ml of DMF gave 1.41 g (86%) of compound **X**, mp 234–236°C, R_f 0.79 (A). The ^{1}H and ^{13}C NMR spectra of the product coincided with those given above.

c. As described above for compound **VIII**, a suspension of 1.00 g (1.03 mmol) of α-cyclodextrin in 25 ml of pyridine was treated with 1.01 g (7.20 mmol) of benzoyl chloride (**V**) in 5 ml of pyridine. Yield 1.43 g (87%), mp 234–236°C, R_f 0.79 (A). The ^{1}H and ^{13}C NMR spectra of the product coincided with those given above.

6^I-[*O*-(2-Acetoxybenzoyl)]-α-cyclodextrin (XI). *a*. A solution of 0.41 g (2.06 mmol) of acid chloride **VI** in 5 ml of benzene was added over a period of 20 min under stirring at 0°C to a solution of 1.00 g (1.03 mmol) of α-cyclodextrin and 0.41 g (2.26 mmol) of triethylamine in 25 ml of DMF. The mixture was stirred, kept for 24 h at 20°C, and filtered, the filtrate was concentrated to a volume of 4 ml, the residue was poured into 40 ml of acetone, and the precipitate was filtered off, washed with acetone (3×5 ml), ground with 10 ml of chloroform, washed with chloroform (3×5 ml), and dried for 4 h at 90°C under reduced pressure (1 mm). Yield 1.10 g (94%), mp 268–270°C (decomp.), R_f 0.69 (B). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.20 s (3H, CH_3), 3.20–4.45 m (36H, 2-H, 3-H, 4-H, 5-H, 6-H), 4.50–4.75 br.s (5H, 6-OH), 4.78–4.92 m (6H, 1-H), 5.10–5.55 br.s (12H, 2-OH, 3-OH), 7.10–8.15 m (4H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.9 (CH_3), 60.4 (C^6), 63.5 ($C^{6'}$), 69.0 ($C^{5'}$), 70.9–75.5 (C^2, C^3, C^5), 82.6 (C^4), 102.5 (C^1), 122.5–134.8 (C_{arom}), 150.9 ($C^{2''}$), 164.2 (6-OC=O), 169.5 [**C**(O)CH_3]. Found, %: C 48.22; H 5.71. $C_{45}H_{66}O_{33}$. Calculated, %: C 47.62; H 5.86.

b. As described above in *a*, the reaction of 1.00 g (1.03 mmol) of α-cyclodextrin and 0.18 g (2.26 mmol) of pyridine in 25 ml of DMF with 0.41 g (2.06 mmol) of acid chloride **VI** in 5 ml of benzene gave 1.13 g (97%) of compound **XI**, mp 268–270°C (decomp.), R_f 0.69 (B). The ^{1}H and ^{13}C NMR spectra of the product coincided with those given above.

Tetrakis[6-*O*-(2-acetoxybenzoyl)]-α-cyclodextrin (XII). *a*. As described above for compound **XI**, the reaction of 1.00 g (1.03 mmol) of α-cyclodextrin and 0.57 g (5.65 mmol) of triethylamine in 25 ml of DMF with 1.02 g (5.14 mmol) of acid chloride **VI** in 5 ml of benzene. Yield 0.68 g (41%), mp 210–212°C, R_f 0.77 (B). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.05–2.25 m (12H, CH_3), 3.20–4.45 m (36H, 2-H, 3-H, 4-H, 5-H, 6-H), 4.48–4.73 br.s (2H, 6-OH) 4.79–4.91 m (6H, 1-H), 5.10–5.55 br.s (12H, 2-OH, 3-OH), 7.09–8.16 m (16H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.9 (CH_3), 60.4 (C^6), 63.5 ($C^{6'}$), 69.0 ($C^{5'}$), 70.9–75.4 (C^2, C^3, C^5), 82.6 (C^4), 102.5 (C^1), 122.5–134.8 (C_{arom}), 150.9 ($C^{2''}$), 164.2 (6-OC=O), 169.5 [**C**(O)CH_3]. Found, %: C 53.45; H 5.18. $C_{72}H_{84}O_{42}$. Calculated, %: C 53.33; H 5.22.

b. As described above in *a*, from 1.00 g (1.03 mmol) of α-cyclodextrin and 0.45 g (5.65 mmol) of pyridine in 25 ml of DMF and 1.02 g (5.14 mmol) of acid chloride **VI** in 5 ml of benzene we obtained 0.82 g (49%) of compound **XII**, mp 210–212°C, R_f 0.77 (B). The ^{1}H and ^{13}C NMR spectra of the product coincided with those given above.

Hexakis[6-*O*-(2-acetoxybenzoyl)]-α-cyclodextrin (XIII). *a*. A solution of 1.43 g (7.20 mmol) of acid chloride **VI** in 5 ml of benzene was added over a period of 20 min under stirring at 0°C to a solution of 1.00 g (1.03 mmol) of α-cyclodextrin and 0.80 g (7.91 mmol) of triethylamine in 25 ml of DMF. The mixture was stirred, kept for 24 h at 20°C, and filtered, the filtrate was concentrated to a volume of 4 ml and poured into 40 ml of diethyl ether, and the precipitate was filtered off, washed with diethyl ether (3×10 ml), dried, and ground with 10 ml of water. The precipitate was filtered off, dried, and dissolved in 2 ml of acetone, the solution was poured into 20 ml of diethyl ether, the mixture was stirred, and the precipitate was filtered off and dried for 4 h at 90°C under reduced pressure (1 mm). Yield 1.16 g (58%), mp 190–192°C, R_f 0.80 (B). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.02–2.40 m (18H, CH_3), 3.20–4.45 m (36H, 2-H, 3-H, 4-H, 5-H, 6-H), 4.86 d (6H, 1-H, $^3J_{HH}$ = 3.4 Hz), 5.10–5.55 br.s (12H, 2-OH, 3-OH), 7.05–8.19 m (24H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.9 (CH_3), 63.5 ($C^{6'}$), 69.0 ($C^{5'}$), 71.5–73.9 (C^2, C^3), 82.4 (C^4), 102.5 (C^1), 122.1–135.1 (C_{arom}), 150.8 ($C^{2''}$), 164.2 (C=O), 169.5 [**C**(O)CH_3]. Found, %: C 55.63; H 5.13. $C_{90}H_{96}O_{48}$. Calculated, %: C 55.56; H 4.97.

b. As described above in *a*, the reaction of 1.00 g (1.03 mmol) of α-cyclodextrin and 0.63 g (7.91 mmol) of pyridine in 25 ml of DMF with 1.43 g (7.20 mmol) of acid chloride **VI** in 5 ml of benzene gave 1.24 g (62%) of compound **XIII**, mp 190–193°C, R_f 0.80 (B). The ^{1}H and ^{13}C NMR spectra of the product coincided with those given above.

c. As described above in *a*, the reaction of a suspension of 1.00 g (1.03 mmol) of α-cyclodextrin in 25 ml of pyridine with 1.43 g (7.20 mmol) of acid chloride **VI** in 5 ml of benzene gave 1.28 g (64%) of compound **XIII**, mp 190–193°C, R_f 0.80 (B). The ^{1}H and ^{13}C NMR spectra of the product coincided with those given above.

Bis{6-*O*-[2-(4-isobutylphenyl)propionyl}-α-cyclodextrin (XIV). *a*. A solution of 0.46 g (2.06 mmol) of acid chloride **VII** in 5 ml of DMF was added over a period of 20 min under stirring at 0°C to a solution of 1.00 g (1.03 mmol) of α-cyclodextrin and 0.23 g (2.26 mmol) of triethylamine in 25 ml of DMF. The mixture was stirred, kept for 24 h at 20°C, concentrated to a volume of 4 ml, and poured into 40 ml of acetone, and the precipitate was filtered off, washed with acetone (3×5 ml), ground with 10 ml of chloroform, washed with chloroform (3×5 ml), and dried for 4 h at 90°C under reduced pressure (1 mm). Yield 0.62 g (45%), mp 222–224°C, R_f 0.66 (C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.84 d (12H, CH_3, $^3J_{HH}$ = 8.0 Hz), 1.26–1.42 m (6H, CH_3), 1.73–1.89 m [2H, C**H**$(CH_3)_2$], 2.40 d (4H, CH_2, $^3J_{HH}$ = 4.6 Hz), 3.15–3.90 m (38H, CH, 2-H, 3-H, 4-H, 5-H, 6-H), 4.20–4.40 m (4H, 6-OH), 4.79 d (6H, 1-H, $^3J_{HH}$ = 3.4 Hz), 4.95–5.55 br.s (12H, 2-OH, 3-OH), 6.98–7.22 m (8H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 18.3–18.7 (CH_3), 22.5 (CH_3), 30.0 [**C**H$(CH_3)_2$], 40.4 (**C**HCH_3), 44.5 (CH_2), 60.2 (C^6), 63.7 ($C^{6'}$), 69.2 ($C^{5'}$), 72.2–73.4 (C^2, C^3, C^5), 82.5 (C^4), 102.3 (C^1), 126.5–140.0 (C_{arom}), 174.4 (C=O). Found, %: C 55.34; H 7.01. $C_{62}H_{92}O_{32}$. Calculated, %: C 55.19; H 6.87.

b. Compound **XIV** was synthesized as described above in *a* by reaction of 1.00 g (1.03 mmol) of α-cyclodextrin and 0.18 g (2.26 mmol) of pyridine in 25 ml of DMF with 0.46 g (2.06 mmol) of acid chloride **VI** in 5 ml of DMF. Yield 0.68 g (49%), mp 222–224°C, R_f 0.66 (C). The ^{1}H and ^{13}C NMR spectra of the product coincided with those given above.

Tetrakis{6-*O*-[2-(4-isobutylphenyl)propionyl}-α-cyclodextrin (XV). A solution of 1.15 g (5.14 mmol) of acid chloride **VII** in 5 ml of DMF was added over a period of 20 min under stirring at 0°C to a solution of 1.00 g (1.03 mmol) of α-cyclodextrin and 0.57 g (5.65 mmol) of triethylamine in 25 ml of DMF. The mixture was stirred, kept for 24 h at 20°C, concentrated to a volume of 4 ml, and poured into 40 ml of water. The precipitate was filtered off, washed with water (3×5 ml), dried, and dissolved in 2 ml of chloroform, the solution was poured into 35 ml of hexane, the mixture was stirred, and the precipitate was filtered off, washed with hexane (3×5 ml), and dried for 4 h at 90°C under reduced pressure (1 mm). Yield 0.92 g (52%), mp 220–222°C, R_f 0.82 (C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.84 d (24H, CH_3, $^3J_{HH}$ = 7.9 Hz), 1.20–1.43 m (12H, CH_3), 1.71–1.89 m [4H, C**H**$(CH_3)_2$], 2.39 d (8H, CH_2, $^3J_{HH}$ = 4.7 Hz), 3.15–3.90 m (40H, 2-H, 3-H, 4-H, 5-H, 6-H), 4.20–4.40 m (2H, 6-OH), 4.81 d (6H, 1-H, $^3J_{HH}$ = 3.3 Hz), 5.05–5.73 br.s (12H, 2-OH, 3-OH), 6.95–7.24 m (16H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 18.2 (CH_3), 22.2 (CH_3), 29.7 [**C**H$(CH_3)_2$], 40.3 (**C**HCH_3), 44.4 (CH_2), 60.1 (C^6), 63.6 ($C^{6'}$), 69.3 ($C^{5'}$), 71.8–73.6 (C^2, C^3, C^5), 81.9 (C^4), 102.1 (C^1), 126.4–140.1 (C_{arom}), 174.0 (C=O). Found, %: C 61.42; H 7.18. $C_{88}H_{124}O_{34}$. Calculated, %: C 61.24; H 7.24.

Pentakis{6-*O*-[2-(4-isobutylphenyl)propionyl]}-α-cyclodextrin (XVI) was synthesized as described

above for compound **XIV** by reaction of 1.00 g (1.03 mmol) of α-cyclodextrin and 0.45 g (5.65 mmol) of pyridine in 25 ml of DMF with 1.15 g (5.14 mmol) of acid chloride **VII** in 5 ml of DMF. Yield 1.71 g (87%), mp 218–220°C, R_f 0.84 (C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.84 d (30H, CH_3, $^3J_{HH}$ = 8.0 Hz), 1.20–1.43 m (15H, CH_3), 1.71–1.89 m [5H, C**H**$(CH_3)_2$], 2.39 d (10H, CH_2, $^3J_{HH}$ = 4.6 Hz), 3.15–3.90 m (41H, CH, 2-H, 3-H, 4-H, 5-H, 6-H), 4.17–4.38 m (1H, 6-OH), 4.81 d (6H, 1-H, $^3J_{HH}$ = 3.4 Hz), 5.05–5.73 br.s (12H, 2-OH, 3-OH), 6.95–7.24 m (20H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 18.2 (CH_3), 22.2 (CH_3), 29.7 [**C**H$(CH_3)_2$], 40.3 (**C**HCH_3), 44.3 (CH_2), 60.2 (C^6), 63.6 ($C^{6'}$), 69.3 ($C^{5'}$), 71.8–73.6 (C^2, C^3, C^5), 81.9 (C^4), 102.1 (C^1), 126.3–140.2 (C_{arom}), 174.1 (C=O). Found, %: C 63.89; H 7.31. $C_{101}H_{140}O_{35}$. Calculated, %: C 63.37; H 7.37.

Hexakis{6-*O*-[2-(4-isobutylphenyl)propionyl]}-α-cyclodextrin (XVII). *a*. A solution of 1.62 g (7.20 mmol) of acid chloride **VII** in 5 ml of DMF was added over a period of 20 min under stirring at 0°C to a solution of 1.00 g (1.03 mmol) of α-cyclodextrin and 0.80 g (7.91 mmol) of triethylamine in 25 ml of DMF. The mixture was stirred, kept for 24 h at 20°C, and filtered, the filtrate was concentrated to a volume of 4 ml, 30 ml of diethyl ether was added, the mixture was filtered and concentrated, the precipitate was filtered off, washed with hexane (2×20 ml), dried, and ground with 10 ml of water, and the precipitate was filtered off, washed with water (3×5 ml), dried, and dissolved in 2 ml of acetone. The solution was poured into 35 ml of water, the mixture was stirred, the precipitate was filtered off and dissolved in 2 ml of acetone, the solution was poured into 35 ml of hexane, the mixture was stirred, and the precipitate was filtered off and dried for 4 h at 90°C under reduced pressure (1 mm). Yield 1.79 g (83%), mp 164–166°C, R_f 0.86 (C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.84 d (36H, CH_3, $^3J_{HH}$ = 8.0 Hz), 1.20–1.43 m (18H, CH_3), 1.71–1.89 m [6H, C**H**$(CH_3)_2$], 2.39 d (12H, CH_2, $^3J_{HH}$ = 4.6 Hz), 3.15–3.90 m (42H, CH, 2-H, 3-H, 4-H, 5-H, 6-H), 4.81 d (6H, 1-H, $^3J_{HH}$ = 3.4 Hz), 5.05–5.73 br.s (12H, 2-OH, 3-OH), 6.95–7.24 m (24H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 18.2 (CH_3), 22.2 (CH_3), 29.7 [**C**H$(CH_3)_2$], 40.3 (**C**HCH_3), 44.3 (CH_2), 63.6 ($C^{6'}$), 69.3 ($C^{5'}$), 72.1–73.5 (C^2, C^3), 81.9 (C^4), 102.1 (C^1), 126.3–140.2 (C_{arom}), 174.2 (C=O). Found, %: C 65.10; H 7.53. $C_{114}H_{156}O_{36}$. Calculated, %: C 65.13; H 7.48.

b. Compound **XVII** was synthesized as described above in *a* by reaction of 1.00 g (1.03 mmol) of α-cyclodextrin and 0.63 g (7.91 mmol) of pyridine in 25 ml of DMF with 1.62 g (7.20 mmol) of acid chloride **VII** in 5 ml of DMF. Yield 1.84 g (85%), mp 164–166°C, R_f 0.86 (C). The ^{1}H and ^{13}C NMR spectra of the product coincided with those given above.

c. Compound **XVII** was synthesized as described above in *a* by reaction of a suspension of 1.00 g (1.03 mmol) of α-cyclodextrin in 25 ml of pyridine with 1.62 g (7.20 mmol) of acid chloride **VII** in 5 ml of pyridine. Yield 1.92 g (89%), mp 164–166°C, R_f 0.86 (C). The ^{1}H and ^{13}C NMR spectra of the product coincided with those given above.

Hexakis{6-*O*-[*tert*-butyl(dimethyl)silyl]}tetrakis-(2-*O*-benzoyl)-α-cyclodextrin (XIX). A solution of 0.85 g (6.03 mmol) of benzoyl chloride (**V**) in 5 ml of pyridine was added over a period of 20 min under stirring at 0°C to a solution of 2.00 g (1.21 mmol) of compound **XVIII** in 20 ml of pyridine. The mixture was stirred, kept for 24 h at 20°C, and filtered, the filtrate was concentrated to a volume of 4 ml and poured into 75 ml of water, and the precipitate was filtered off, ground with 10 ml of a 0.5 M aqueous solution of $NaHCO_3$, washed with water (3×10 ml), and dried for 4 h at 90°C under reduced pressure (1 mm). Yield 2.38 g (95%), mp 179–181°C, R_f 0.82 (D). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.06 s [36H, $Si(CH_3)_2$], 0.89 s (54H, *t*-Bu), 2.25–2.80 br.s (8H, 2-OH, 3-OH), 3.78 m (6H, 6-H), 3.80 m (6H, 5-H), 3.86 d.d (6H, 4-H, $^3J_{3,4}$ - 4.0 Hz), 4.12 d.d (6H, 6′-H, ^2J = 11.7 Hz), 4.36–4.44 br.s (6H, 3-H), 4.89 d.d (6H, 2-H, $^3J_{2,3}$ = 10.3 Hz), 5.29 d (6H, 1-H, $^3J_{1,2}$ = 3.3 Hz), 7.25–8.15 m (20H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: –5.1 and –5.0 [$Si(CH_3)_2$], 18.4 [C(**C**$H_3)_3$], 26.0 [**C**$(CH_3)_3$], 62.2 (C^6), 70.9 (C^3), 72.2 (C^5), 73.9 ($C^{2'}$), 81.1 (C^4), 98.9 ($C^{1'}$), 101.6 (C^1), 128.0–134.1 (C_{arom}), 166.0 (C=O). Found, %: C 58.11; H 7.90. $C_{100}H_{160}O_{34}Si_6$. Calculated, %: C 57.89; H 7.77.

Hexakis{6-*O*-[*tert*-butyl(dimethyl)silyl]}bis-[2,3-di-*O*-(2-acetoxybenzoyl)]-α-cyclodextrin (XX) was synthesized in a similar way from 2.00 g (1.21 mmol) of compound **XVIII** in 20 ml of pyridine and 1.20 g (6.03 mmol) of acid chloride **VI** in 5 ml of benzene. Yield 2.48 g (89%), mp 157–159°C, R_f 0.58 (D). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.06 s [36H, $Si(CH_3)_2$], 0.89 s (54H, *t*-Bu), 2.25 s and 2.38 s [12H, $CH_3C(O)$], 3.25–4.40 m (36H, 2-H, 3-H, 4-H, 5-H, 6-H), 4.55–5.05 br.s (8H, 2-OH, 3-OH), 5.10–5.20 m (6H, 1-H), 6.95–8.12 m (16H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: –5.1 and –5.0 [$Si(CH_3)_2$], 18.4 [C(**C**$H_3)_3$], 21.0 and 21.1 [C(O)**C**H_3], 26.0 [**C**$(CH_3)_3$],

62.1 (C^6), 71.5–75.2 (C^2, C^3, C^5), 80.9 ($C^{4'}$), 81.9 (C^4), 98.8 ($C^{1'}$), 101.6 (C^1), 122.5–135.6 (C_{arom}), 150.2 ($C^{2''}$), 164.1 and 164.3 (C=O), 170.0 and 170.4 [**C**(O)CH_3]. Found, %: C 56.17; H 7.55. $C_{108}H_{168}O_{42}Si_6$. Calculated, %: C 56.23; H 7.34.

Hexakis{6-*O*-[*tert*-butyl(dimethyl)silyl]}bis{2,3-di-*O*-[2-(4-isobutylphenyl)propionyl]}-α-cyclodextrin (XXI). A solution of 1.35 g (6.03 mmol) of acid chloride **VII** in 5 ml of pyridine was added over a period of 20 min under stirring at 0°C to a solution of 2.00 g (1.21 mmol) of compound **XVIII** in 20 ml of pyridine. The mixture was stirred, kept for 24 h at 20°C, and filtered, the filtrate was concentrated to a volume of 4 ml and poured into 75 ml of water, and the precipitate was filtered off, ground with 10 ml of a 0.5 M solution of $NaHCO_3$ in aqueous acetone (1:1), washed with water (3×10 ml), and dried for 4 h at 90°C under reduced pressure (1 mm). Yield 2.47 g (85%), mp 110–112°C, R_f 0.85 (D). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.06 s [36H, $Si(CH_3)_2$], 0.70–1.00 m (78H, CH_3, *t*-Bu), 1.30–1.42 m (12H, CH_3), 1.75–1.92 m [4H, C**H**$(CH_3)_2$], 2.42 d (8H, CH_2, $^3J_{HH}$ = 4.7 Hz), 3.03–4.25 m (40H, CH, 2-H, 3-H, 4-H, 5-H, 6-H), 4.87 d (6H, 1-H, $^3J_{HH}$ = 3.3 Hz), 4.90–5.10 br.s (8H, 2-OH, 3-OH), 6.95–7.34 m (16H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: –5.1 and –5.0 [$Si(CH_3)_2$], 18.3 (CH_3), 18.4 [$C(\mathbf{C}H_3)_3$], 22.4 [$CH(\mathbf{C}H_3)_2$], 26.0 [$\mathbf{C}(CH_3)_3$], 30.3 [$\mathbf{C}H(CH_3)_2$], 40.6 ($\mathbf{C}HCH_3$), 45.1 (CH_2), 61.9 (C^6), 70.0–74.1 (C^2, C^3, C^5), 80.9 ($C^{4'}$), 82.0 (C^4), 99.0 ($C^{1'}$), 101.6 (C^1), 126.2–141.9 (C_{arom}), 173.4 and 174.9 (C=O). Found, %: C 62.00; H 8.50. $C_{124}H_{208}O_{34}Si_6$. Calculated, %: C 61.76; H 8.69.

Tetrakis(2-*O*-benzoyl)-α-cyclodextrin (XXII). A solution of 1.50 g (0.723 mmol) of silyl derivative **XIX** and 0.40 g (10.8 mmol) of ammonium fluoride in 40 ml of methanol was heated for 24 h under reflux (70°C). The mixture was evaporated to dryness, the residue was ground with 10 ml of water, and the precipitate was washed with water (3×10 ml) and dried for 4 h at 90°C under reduced pressure (1 mm). Yield 0.90 g (90%), mp 171–173°C, R_f 0.77 (A). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.45–4.30 m (36H, 2-H, 3-H, 4-H, 5-H, 6-H), 4.40–4.90 br.s (14H, 6-OH, 2-OH, 3-OH), 5.08 m (6H, 1-H), 7.35–8.12 m (20H, H_{arom}). Found, %: C 55.26; H 5.79. $C_{64}H_{76}O_{34}$. Calculated, %: C 55.33; H 5.51.

Compounds **XXIII** and **XXIV** were synthesized in a similar way.

Bis[2,3-di-*O*-(2-acetoxybenzoyl)]-α-cyclodextrin (XXIII) was synthesized from 1.50 g (0.650 mmol) of compound **XX** using 0.36 g (9.75 mmol) of ammonium fluoride in 40 ml of methanol. Yield 0.92 g (87%), mp 165–167°C, R_f 0.78 (B). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.17 s and 2.24 s (12H, CH_3), 3.46–4.32 m (36H, 2-H, 3-H, 4-H, 5-H, 6-H), 4.40–4.85 br.s (14H, 6-OH, 2-OH, 3-OH), 5.09 m (6H, 1-H), 7.35–8.12 m (16H, H_{arom}). Found, %: C 53.68; H 5.16. $C_{72}H_{84}O_{42}$. Calculated, %: C 53.33; H 5.22.

Bis{2,3-di-*O*-[2-(4-isobutylphenyl)propionyl]}-α-cyclodextrin (XXIV) was synthesized from 1.50 g (0.622 mmol) of compound **XXI** using 0.35 g (9.33 mmol) of ammonium fluoride in 40 ml of methanol. Yield 0.96 g (89%), mp 158–160°C, R_f 0.80 (C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.85 d (24H, CH_3, $^3J_{HH}$ = 7.9 Hz), 1.23–1.45 m (12H, CH_3), 1.65–1.88 m [4H, C**H**$(CH_3)_2$], 2.35 d (8H, CH_2, $^3J_{HH}$ = 4.7 Hz), 3.10–4.12 m (40H, CH, 2-H, 3-H, 4-H, 5-H, 6-H), 4.20–4.60 m (6H, 6-OH), 4.70–5.15 m (6H, 1-H), 5.15–5.85 br.s (8H, 2-OH, 3-OH), 6.95–7.30 m (16H, H_{arom}). Found, %: C 61.42; H 7.19. $C_{88}H_{124}O_{34}$. Calculated, %: C 61.24; H 7.24.

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