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Investigation of Acylation of β-Cyclodextrin and Its Silyl Derivative with Benzoyl and Acetylsalicyloyl Chlorides

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Abstract — Acylation of β-cyclodextrin and its silyl derivative with benzoic and acetylsalicylic acid chlorides results in formation of the conjugates containing rests of benzoic and acetylsalicylic acids interesting in pharmacological aspect. It is found that heating slightly increases conversion at this reaction but effect of the solvent nature on the conversion is complicated. Thus, acylation of free β-cyclodextrin in pyridine and DMF proceeds at the primary hydroxyl groups, but after its treatment with sodium hydride in DMF this process carries out with formation of the products due to substitution at the secondary hydroxyls in not high yield. The inclusion complex of "guest–host" type of acetylsalicylic acid with β-cyclodextrin which composition is determined as 1 : 1 is prepared. On the whole, the conjugation and formation of the inclusion compound lead to increase in its solubility in water compared to acetylsalicylic acid.
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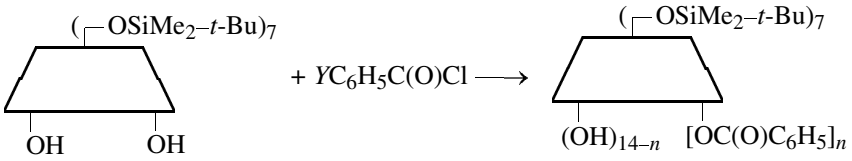
It is known that easily accessible β-cyclodextrin and numerous of its derivatives are widely employed in pharmacology, mainly as "containers" for some medicines owing to their unique property of encapsulating different hydrophobic compounds (by formation of the inclusion compounds of "guest–host" type) [1]. Such "encapsulating" protects the included medicine from bio-decomposition, and contributes to increase in its solubility and, that is of significant importance, to effective and selective delivery of the medicine to the essential place for required time. However, since recently much attention is paid to the investigation of covalent binding, or conjugation, of a medicine to cyclodextrin that allows preparing new medicines with more prolonged and goaldirected action [2].

In this connection, in the present work we investigated binding of β-cyclodextrin **I** with the "Aspirin" medicine by means of the conjugation. Acetylsalicylic acid itself is known possessing anti-inflammatory, febrifuge, and sedative effects and anti-aggregate activity (inhibits the thrombocite aggregation in blood) but it poorly soluble in water (2.5 g l^{-1}), that complicates its use because of irritation of stomach mucous membrane.

At the first stage of our work we investigated covalent binding of the β-cyclodextrin derivative with a model compound, namely benzoyl chloride, accounting for the antiinflammatory and antiaggregation activity of benzoic acid. First of all, we began to investigate acylation of the secondary hydroxyl groups of accessible per[6-*O*-(*tert*-butyl)(dimethyl)silyl]-β-cyclodextrin **II**. This choice is explained by both its relatively good solubility in common solvents unlike the nonsubstituted β-cyclodextrin, and simplicity in interpretation of the obtained results. Benzoyl chloride was entered to the reaction with cyclodextrin derivative **II** at 20°C in pyridine which served both as a solvent and an acceptor of liberated hydrochloric acid. The presence of fourteen free hydroxyl groups in the molecule of compound **II** allows preparing a number of substituted products. At benzoylation we used the molar ratio of cyclodextrin derivative **II** to benzoyl chloride equal to either 1 : 3, 1 : 7 or 1 : 14. The products of acylation **III**–**V** were isolated as individual substances and were characterized by ^{1}H NMR spectroscopy. Therewith, in all the cases we observed a high extent of substitution (Table 1) which was determined from integral intensity ratio of methyl protons of *tert*-butyl group to the protons of benzene ring. Here and further in the text we imply average extent of substitution n. Note that similar benzoylation

of β-cyclodextrin has been described but mainly as per-benzoylation of free β-cyclodextrin under more rigid conditions and with great (eight-fold) molar excess of benzoyl chloride [3].

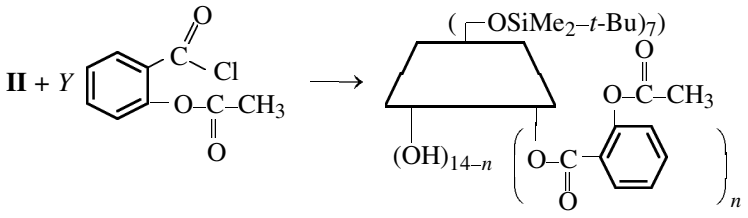


II **III–VII**

To account for our data on significant influence of solvent nature and reaction conditions on the extent and regioselectivity of β-cyclodextrin and its derivatives functionality [4, 5] the elucidation of solvent and temperature effects on the extent of substitution of hydroxyl groups in β-cyclodextrin derivative **II** by benzoic acid rest was of our interest. For this goal we performed a reaction in dioxane with triethylamine as an acceptor of hydrochloric acid, at 20 and 60°C.

Products **VI** and **VII** were isolated as individual substances, and analysis of their ^{1}H NMR spectra showed that the extent of substitution in compound **XI** is equal to 9.8, and in compound **VII** 10.6. Hence, heating slightly increases the extent of substitution in the acylation reaction, and replacement the solvent, namely pyridine, by dioxane leads to the lower extent of substitution: in pyridine with fourteen equivalents of benzoyl chloride the extent of substitution is equal to 12, but in dioxane medium it is 9.8 (at 15 equivalents of the acylating reagents) (Table 1).

Taking into account these data, at the next stage of our work we started direct synthesis of the conjugates of cyclodextrin with medicine "Aspirin" by the reaction of compound **II** with acetylsalicyloyl chloride **VIII**. The reaction was carried out in three different solvents (dioxane, DMF, pyridine) with different molar ratio of the starting reagents **II** and **VIII**. We showed that conducting the reaction with seven molar equivalents of acetylsalicyloyl chloride in DMF led to higher extent of substitution than in pyridine (Table 2).



VIII **IX–XIII**

Table 1. Acylation of per-6-*O*-(*tert*-butyl)(dimethyl)silyl-β-cyclodextrin derivative with benzoyl chloride

Product	Solvent	Quantity of molar equivalents of benzoyl chloride, (*Y*)	Extent of substitution, (*n*)	Yield, %	R_f	mp, °C
III	Pyridine	3	1	64	0.72	226–229 (decomp.)
IX	(20°C)	7	6.4	40	0.79	168–170
X		14	12	67	0.87	118–120
XI	Dioxane	15 (20°C)	9.8	54	0.81	132–135
XII		15 (60°C)	10.6	58	0.89	122–125

Table 2. Acylation of per-6-*O*-(*tert*-butyl)(dimethyl)silyl-β-cyclodextrin with acetylsalicyloyl chloride

Product	Solvent	Quantity of molar equivalents of benzoyl chloride, (*Y*)	Extent of substitution, (*n*)	Yield, %	R_f	mp, °C
IX	Pyridine	7	3	61	0.63	180–183
XI		14	6	68	0.71	133–135
XIX		4	2	38	0.60	190–192
X	DMF	7	4.6	45	0.65	160–162
XIII		20	11	42	0.62	85–87
XII	Dioxane	14	8	43	0.74	118–120

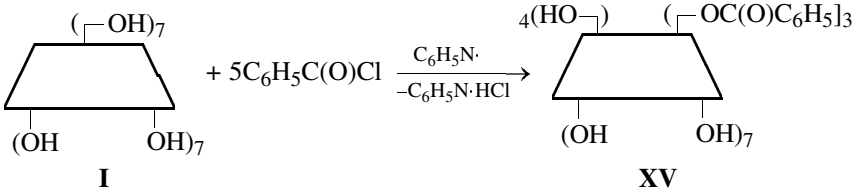
Analysis of spectroscopic data for the reactions in pyridine and dioxane at the reagents molar ratio 1 : 14 showed that the highest extent of substitution is achieved with dioxane (Table 2).

The prepared products **IX**–**XII** were isolated in 61, 45, 68, and 43% yields respectively and were characterized by ^{1}H NMR spectroscopy. Thus, in their ^{1}H NMR spectra were registered the signals of benzene ring protons near δ 7.0–8.4 ppm and of the acyl group methyl protons at δ 2.22–2.24 ppm. The extent of substitution in the products was determined from the ratio of integral intensities of the protons of *tert*-butyl group and aromatic rings.

To prepare the product of complete substitution of secondary hydroxyl groups by the rest of acetylsalicylic acid, we performed the reaction with 20 equivalents of acetylsalicyloyl chloride in DMF with triethylamine as an acceptor of liberated hydrochloric acid. However, according to the ^{1}H NMR spectroscopy data, prepared product **XIII** has extent of substitution 11 only, so probably preparation of peracylated compound at secondary hydroxyl groups under the mentioned conditions is impossible due to the steric factors accumulating upon the reaction progress.

To obtain the products with low extent of substitution, some experiments were performed with pyridine as a solvent at the ratio of compound **II** and acyl reagent 1 : 1 and 1 : 4. We found that at equimolecular ratio of the reagents acylation did not occur, but with four molar equivalents of acid chloride **XIII** the reaction led to the formation of product **XIV** with the extent of substitution equal to 2. It can be assumed that this is a result of inclusion of the acyl reagent into cyclodextrin cavity.

Further we investigated more complicated object for acylation, namely β-cyclodextrin possessing differ by activity primary and secondary hydroxyl groups. At the reaction of β-cyclodextrin with five molar equivalents of benzoyl chloride in pyridine medium product **XV** was prepared, isolated in 64% yield, and characterized by ^{1}H and ^{13}C NMR spectroscopic data. As is known, the acylation proceeds initially at the more active primary hydroxyl groups in C^6 position [4, 6].



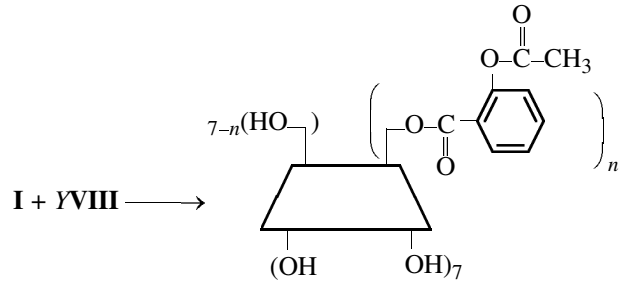
I **XV**

Analysis of the ^{1}H and ^{13}C NMR spectra demonstrated that acylation proceeds at primary hydroxyl groups and the extent of substitution in product **XV** is equal to 3. Thus, in its ^{13}C NMR spectrum the signal of the atom C^{6A} [1] appeared at δ_C 64.4 ppm, downfield compared to the corresponding signal of the starting β-cyclodextrin, δ_C 60.5 ppm, and the signal of C^{5A} at δ_C 69.9 ppm is shifted upfield compared to C^5 in compound **I** which chemical shift was fixed near δ_C 72.5 ppm (the letter A is added for designation of the corresponding carbon atom C^6 bearing acyloxy group). The similar shift of the of carbon atom signals in the glucose fragment has been observed earlier in

[1] Product of acylation at the secondary hydroxyl groups is denoned with additional A letter.

the products of β-cyclodextrin acylation at primary hydroxyl groups [4].

Accounting for all these facts the investigation of β-cyclodextrin acylation was performed in pyridine medium with entering to the reaction a varied quantity of chloride **VIII**: 2, 5 and 7 molar equivalents. Products **XVI**–**XVIII** were isolated by precipitation from preliminary concentrated reaction mixture with ethanol and characterized by means of ^{1}H and ^{13}C NMR spectroscopy.



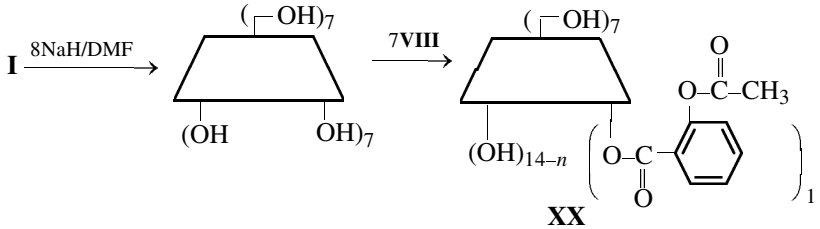
XVI–**XIX**

Thus, in the ^{1}H NMR spectrum the characteristic signals near δ 7.05–8.30 ppm corresponding to the benzene ring protons were observed together with the signals of methyl protons of acyl group at δ 2.15–2.28 ppm. From the integral intensities ratio of the protons signals of cyclodextrin frame (C^2H–C^5H, C^6H_2) and the protons of acetylsalicylic acid rests, quantity of the entered acyl fragments was determined. In all the cases the direct acylation of β-cyclodextrin with acid chloride **VIII** proceeded at the primary hydroxyl groups as is evidenced by downfield shift of the signals of C^{6A} nuclei in the ^{13}C NMR spectra of products **XVI**–**XVIII** (δ_C 63.9 ppm) compared to the corresponding signals in starting β-cyclodextrin (δ_C 60.5 ppm). Acylation of the primary hydroxyl groups is confirmed additionally by characteristic upfield shift of the signal of C^5 nucleus from δ_C 72.5 ppm in compound **I** to δ_C 69 ppm in compounds **XVI**–**XVIII**. It is important to note that in the ^{13}C NMR spectra of products **XVI**–**XVIII** we did not observe any shifts of the carbon atoms signals at C^2 and C^3 positions of cyclodextrin frame, i.e. these positions are involved in acylation.

To study the effect of a solvent on the reaction proceeding, acylation with 7 equivalents of acid chloride **VIII** was performed in DMF in the presense of triethylamine. The solvent choice first of all was determined by good solubility of the starting β-cyclodextrin. On the basis of analysis of the ^{1}H and ^{13}C NMR spectra of prepared product **XIX** we concluded that acylation proceeded at the primary hydroxyl groups and led to the formation of the product with less extent of substitution (n = 2) than at acylation in pyridine at the same molar ratio of acyl reagent and β-cyclodextrin.

We also conducted direct acylation of nonsubstituted β-cyclodextrin at the secondary hydroxyl groups by acetylsalicyloyl chloride. For this purpose we used the method based on deprotonation of secondary hydroxyl groups at C^2 position by sodium hydride causing formation of 2-oxy anion which then attacks the electrophilic reagent, acetylsalicyloyl chloride. Hydroxyl groups at C^2 positions of cyclodextrin frame are known to be more acidic both due to the formation of hydrogen bonds between the protons of hydroxyl groups at C^3 atoms and oxygen atoms of hydroxyl groups at C^2 positions which stabilize the oxianion formed, and owing to the electron-acceptor influence of acetal fragment [7].

The acylation of secondary hydroxyl groups of β-cyclodextrin leads to formation of product **XX** with low extent of substitution (n = 1). The structure and individuality of product **XX** was confirmed by ^{1}H NMR spectroscopy and TLC. In its ^{1}H NMR spectrum the signals of the benzene ring protons are observed near δ 7.1–8.3 ppm, and of the acyl group protons at 2.30 ppm. Despite the low extent of substitution, note that solubility of compound **XX** in water is found higher than acetylsalicylic acid and it approximately 10 times exceeds solubility of β-cyclodextrin, therewith solubility of β-cyclodextrin derivative **XVI** with one acyl fragment at primary hydroxyl group is close to solubility of acetylsalicylic acid itself, and moreover, with increase in the extent of substitution of the acylated products **XVII**–**XIX** their solubility in water falls down. So, for preparing water soluble compounds it is reasonable to synthesize the derivatives with the extent of substitution about one and preferably at the secondary hydroxyl groups.



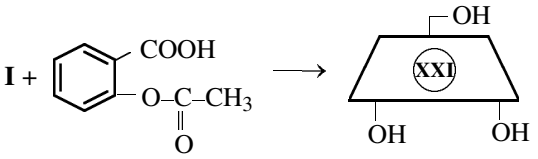
XX

Table 3. Acylation of β-cyclodextrin with acetylsalicyloyl chloride

Product	Solvent	Quantity of molar equivalents of benzoyl chloride, (*Y*)	Extent of substitution, (*n*)	Yield, %	mp, °C
XXI	Pyridine	2	1	86	198–202
XXII		5	3.5	63	203–205
XXIII		7	7	40	182–185
XIX	DMF	7	2	46	223–226 (decomp.)
XX[a]		7	1	60	204–206

[a] Product of acylation at the secondary hydroxyl groups.

Finally, we studied a possibility of formation an inclusion complex of acetylsalicylic acid itself **XXI** with β-cyclodextrin **I** in water. For this goal, equimolar quantities of acid **XXI** and βcyclodextrin were dissolved in minimum volume of water at heating (60–70°C). The solution was allowed to slowly cooling to room temperature, and then precipitated complex was filtered off and washed with acetone.



The individuality and structure of the inclusion complex **XXII** were proven by the data of ^{1}H NMR spectroscopy. Comparison of the integral intensities of methyl and aromatic protons for acetylsalicylic acid with those of cyclodextrin frame evidenced 1 : 1 guest : host ratio. Note also, that in the ^{1}H NMR spectrum, downfield shift of the signals of protons at 2 and 5 positions of cyclodextrin frame by 0.04 and 0.03 ppm respectively was observed which is typical of the inclusion compounds with cyclodextrin [8]. Additionally, as ^{1}H NMR spectroscopic data showed, the signals of aromatic protons of the inclusion compound **XXII** were registered 0.01 ppm upfield. Noteworthy that solubility of the prepared complex (19.7 g l^{-1}) is found to be higher that the solubility of acetylsalicylic acid and is close to solubility of pure β-cyclodextrin (18.5 g l^{-1}).

Thus, our investigation opens a possibility for goal-directed preparation of the pharmacologically significant conjugates and inclusion compounds consisting of cyclodextrin and benzoic acid derivatives.

EXPERIMENTAL

All the experiments were performed in absolute solvents purified by typical methods.

^{1}H NMR spectra were recorded on a Bruker WP-250 (250 MHz) spectrometer, external reference TMS. For TLC the aluminum plates with fixed layer of silica gel were applied, eluent benzene–ethanol 3 : 1 (A), acetonitrile–water 5 : 2 (B), and acetonitrile–water–ammonia 6 : 3 : 1 (C).

Acylation of per-6-*O*-(*tert*-butyldimethylsilyl)-β-cyclodextrin II with benzoyl chloride *(general procedure).* (1). To a solution of 0.50 g of cyclodextrin derivative **II** in 5 ml of pyridine, a solution of 0.11 g of benzoyl chloride in 2 ml of benzene was added dropwise at stirring and then the solution was kept for 24 h at 20°C. Precipitated pyridine hydrochloride was filtered off, and filtrate was concentrated in a vacuum to obtain syrup-like liquid which was poured by small portions into 25 ml of water with ice at stirring. The precipitate formed was filtered off, washed with water (5 ml twice) then water was removed by azeotropic distillation with benzene. The product was purified by column chromatography, eluting with the A system. Solvents were removed, and the residue was kept for 3 h at 60°C in a vacuum (1 mm Hg). Yield of compound **III** is 0.34 g (64%), mp 226–229°C (decomp.), R_f 0.72 (A). ^{1}H NMR spectrum, d, ppm, (acetone-d_6): 0.10 s [42H, $Si(CH_3)_2$], 0.92 s [63H, $C(CH_3)_3$], 3.21–5.25 m (42H; C^2H–C^5H, C^6H_2), 5.35–5.50 br.s (7H, C^1H), 5.92–6.10 m (13H; C^2OH, C^3OH), 7.41–8.23 m (5H, C H_{arom}). Found, %: C 53.22; H 8.62. $C_{91}H_{172}O_{36}Si_7$. Calculated, %: C 53.61; H 8.50.

(2). Synthesis of compound **IV** was carried out similarly from 0.50 g of compound **II** and 0.25 g of benzoyl chloride. Yield 0.27 g (40%), mp 168–170°C, R_f 0.79 (A). ^{1}H NMR spectrum, d, ppm, (acetone-d_6): 0.13 s [42H, $Si(CH_3)_2$], 0.91 s [63H, $C(CH_3)_3$], 3.73–5.21 m (42H; C^2H–C^5H, C^6H_2), 5.50 d (7H, C^1H), 5.85–6.11 m (7.6H; C^2OH, C^3OH), 7.31–8.20 m (32H, CH_{arom}). Found, %: C 60.72; H 7.11. $C_{128.8}H_{193.6}\cdot O_{41.4}Si_7$. Calculated, %: C 59.47; H 7.50.

(3) Synthesis of compound **V** was carried out similarly from 0.50 g of compound **II** and 0.51 g of benzoyl chloride. Yield 0.55 g (67%), mp 118–120°C, R_f 0.87 (A). ^{1}H NMR spectrum, d, ppm, (acetone-d_6): 0.18 s [42H, Si$(CH_3)_2$], 0.93 s [63H, C$(CH_3)_3$], 3.71–5.22 m (42H; C^2H–C^5H, C^6H_2), 5.50 br.s (7H, C^1H), 5.62–5.79 m (2H, C^3OH), 7.14–8.02 m (60H, CH_{arom}). Found, %: C 64.47; H 6.70. $C_{168}H_{216}O_{47}Si_7$. Calculated, %: C 63.37; H 6.84.

(4) Synthesis of compound **VI** was carried out similarly from 0.50 g of compound **II** dissolved in 7 ml of dioxane, 0.43 g of triethylamine, and 0.54 g of benzoyl chloride. Yield 0.41 g (54%), mp 132–135°C, R_f 0.81 (A). ^{1}H NMR spectrum, d, ppm, (acetone-d_6): 0.14 s [42H, Si$(CH_3)_2$], 0.97 s [63H, C$(CH_3)_3$], 3.76–5.01 m (42H; C^2H–C^5H, C^6H_2), 5.53 d (7H, C^1H), 5.92–6.11 m (4.2H, C^3OH), 7.05–8.25 m (49 H, CH_{arom}). Found, %: C 61.45; H 7.32. $C_{152.6}H_{207.2}O_{44.8}Si_7$. Calculated, %: C 62.02; H 7.07.

(5) Synthesis of compound **VII** was carried out similarly from 0.50 g of compound **II** dissolved in 7 ml of dioxane, 0.43 g of triethylamine, and 0.54 g of benzoyl chloride. The reaction mixture was kept at 60–70°C for 11 h. Yield 0.46 g (58%), mp 122–125°C, R_f 0.89 (A). ^{1}H NMR spectrum, d, ppm, (acetone-d_6): 0.14 s [42H, Si$(CH_3)_2$], 0.95 s [63H, C$(CH_3)_3$], 3.76–5.05 m (42H; C^2H–C^5H, C^6H_2), 5.52 d (7H, C^1H), 5.91–6.09 m (3.4H, C^3OH), 7.09–8.25 m (53H, CH_{arom}). Found, %: C 61.03; H 7.12. $C_{158.2}H_{210.4}O_{45.6}Si_7$. Calculated, %: C 62.54; H 6.98.

Acylation of per-6-*O*-(*tert*-butyldimethylsilyl)-β-cyclodextrin II with acetylsalicyloyl chloride VIII *(general procedure).* (1) To a solution of 0.50 g of compound **II** in 5 ml of pyridine, 0.36 g of acid chloride **VIII** in 2 ml of benzene was added dropwise at stirring and then the reaction mixture was kept at 20°C for 24 h. The reaction mixture was filtered off to remive formed pyridine hydrochloride, concentrated in a vacuum to syrup-state, and then the liquid was poured by small portions into 25 ml of glacial water at stirring. The precipitate formed was filtered off, washed with water (twice per 5 ml) after that water was removed by azeotropic distillation with benzene. The product was purified by the method of column chromatography, eluting by the system A. Solvents were removed, and the residue was kept for 3 h at 60°C in a vacuum. Yield of compound **IX** is 0.38 g (61%), mp 180–183°C, R_f 0.63 (A). ^{1}H NMR spectrum, d, ppm, (acetone-d_6): 0.11 s [42H, Si$(CH_3)_2$], 0.92 s [63H, C$(CH_3)_3$], 2.24 s [9H, C(O)CH_3], 3.15–4.82 m (42H; C^2H–C^5H, C^6H_2), 4.92–5.15 d (7H, C^1H), 5.23–5.57 m (11H; C^2OH, C^3OH), 7.05–8.41 m (12H, CH_{arom}). Found, %: C 54.21; H 7.98. $C_{111}H_{186}O_{44}Si_7$. Calculated, %: C 55.06; H 7.74.

(2) Synthesis of compound **X** was performed similarly from 0.50 g of compound **II** dissolved in 5 ml of DMF, 0.20 g of triethylamine, and 0.36 g of acid chloride **VIII**. Yield of compound **X** is 0.31 g (45%), mp 160–162°C, R_f 0.65 (A). ^{1}H NMR spectrum, d, ppm, (acetone-d_6): 0.14 s [42H, Si$(CH_3)_2$], 0.95 s [63H, C$(CH_3)_3$], 2.22 s [13.8H, C(O)CH_3], 3.63–4.91 m (42H; C^2H–C^5H, C^6H_2), 5.35–5.60 d (7H, C^1H), 5.70–5.91 m (9.4H; C^2OH, C^3OH), 7.04–8.30 m (18.4H, CH_{arom}). Found, %: C 56.95; H 7.14. $C_{125.4}H_{195.6}O_{48.8}Si_7$. Calculated, %: C 56.19; H 7.35.

(3) Synthesis of compound **XI** was performed similarly from 0.50 g of compound **II** dissolved in 5 ml of pyridine, and 0.72 g of acid chloride **VIII** dissolved in 2 ml of benzene. Yield of compound **XI** is 0.51 g (68%), mp 133–135°C, R_f 0.71 (A). ^{1}H NMR spectrum, d, ppm, (acetone-d_6): 0.13 s [42H, Si$(CH_3)_2$], 0.94 s [63H, C$(CH_3)_3$], 2.23 s [18H, C(O)CH_3], 3.52–4.81 m (42H; C^2H–C^5H, C^6H_2), 5.52 d (7H, C^1H), 5.56–5.98 m (8H; C^2OH, C^3OH), 7.06–8.41 m (24H, CH_{arom}). Found, %: C 58.14; H 6.88. $C_{138}H_{204}O_{53}Si_7$. Calculated, %: C 57.00; H 7.07.

(4) Synthesis of compound **XII** was performed similarly from 0.50 g of compound **II**, 0.43 g of triethylamine in 5 ml of dioxane, and 0.72 g of acid chloride **VIII** in 2 ml of dioxane. Yield 0.36 g (43%), mp 118–120°C, R_f 0.74 (A). ^{1}H NMR spectrum, d, ppm, (acetone-d_6): 0.15 s [42H, Si$(CH_3)_2$], 0.95 s [63H, C$(CH_3)_3$], 2.24 s [24H, C(O)CH_3], 3.53–5.02 m (42H; C^2H–C^5H, C^6H_2), 5.43–5.61 d (7H, C^1H), 5.68–5.91 m (6H, C^3OH), 7.06–8.25 m (32H, CH_{arom}). Found, %: C 56.89; H 6.93. $C_{156}H_{216}O_{59}Si_7$. Calculated, %: C 57.97; H 6.74.

(5) Synthesis of compound **XIII** was performed similarly from 0.50 g of compound **II**, 0.58 g of triethylamine in 5 ml of DMF, and 1.03 g of acid chloride **VIII** dissolved in 2 ml of DMF. Yield of compound **XIII** is 0.40 g (42%), mp 85–87°C, R_f 0.62 (A). ^{1}H NMR spectrum, d, ppm, (acetone-d_6): 0.16 s [42H, Si$(CH_3)_2$], 0.97 s [63H, C$(CH_3)_3$], 2.25 s [33H, $^{-1}$C(O)CH_3], 3.17–4.74 m (42H; C^2H–C^5H, C^6H_2), 5.48–5.50 d (7H, C^1H), 5.56–5.82 m (3H, C^3OH), 6.66–8.41 m (44H, CH_{arom}). Found, %: C 57.93; H 6.92. $C_{183}H_{234}O_{68}Si_7$. Calculated, %: C 59.11; H 6.34.

(6) Synthesis of compound **XIX** was performed similarly from 0.50 g of compound **II** dissolved in 5 ml of pyridine, and 0.21 g of acid chloride **VIII** dissolved in 2 ml of benzene. Yield of compound **XIV** is 0.22 g (38%), mp 190–192°C, R_f 0.60 (A). ^{1}H NMR

spectrum, d, ppm, (acetone-d_6): 0.12 s [42H, $Si(CH_3)_2$], 0.93 s [63H, $C(CH_3)_3$], 2.30 s [6H, $C(O)CH_3$], 3.34–4.13 m (42H; C^2H–C^5H, C^6H_2), 4.98–5.01 d (7H, C^1H), 5.32–5.51 m (12H; C^2OH, C^3OH), 7.09–8.31 m (8H, CH_{arom}). Found, %: C 53.60; H 8.27. $C_{102}H_{180}O_{41}Si_7$. Calculated, %: C 54.23; H 8.03.

Acylation of β-cyclodextrin with benzoyl chloride. To a solution of 0.50 g of β-cyclodextrin in 8 ml of pyridine, 0.31 g of benzoyl chloride in 2 ml of benzene was added dropwise at stirring, and the reaction mixture was kept at 20°C for 24 h. Then it was concentrated in a vacuum to syrup-state, and 30 ml of chloroform was added. The precipitate formed was filtered off, washed with chloroform (2 × 10 ml), and dried in a vacuum to obtain 0.41 g (64%) of compound **XV**, mp 176–179°C, R_f 0.93 (B). ^1H NMR spectrum, d, ppm, (DMSO-d_6): 3.10–4.72 m (42H; C^2H–C^5H, C^6H_2), 4.19–4.48 br.s (4H, C^6OH), 4.82–5.11 br.s (7H, C^1H), 5.35–5.76 m (14H; C^2OH, C^3OH), 7.23–9.04 m (15H, CH_{arom}). ^{13}C NMR spectrum, δ_C, ppm, (DMSO-d_6): 60.5 (C^6OH), 64.4 [$C^6OC(O)$], 69.9 [$C^5C^6OC(O)$], 72.1–74.7 (C^2, C^3, C^5), 79.0–84.2 (C^4), 101.5–104.2 (C^1), 127.5–134.9 (C_{arom}), 166.3 [C(O)]. Found, %: C 53.01; H 5.59. $C_{63}H_{82}O_{38}$. Calculated, %: C 52.28; H 5.71.

Acylation of β-cyclodextrin with acetylsalicyloyl chloride (XIII). *(general procedure).* (1) To a solution of 0.50 g of β-cyclodextrin in 8 ml of pyridine, 0.18 g of acid chloride **VIII** in 2 ml of benzene was added dropwise at stirring, and the reaction mixture was kept at 20°C for 24 h. Pyridine hydrochloride was filtered off, filtrate was concentrated, and the residue was rubbed in ethanol (10 ml), and formed precipitate was filtered off, washed with ethanol (2 × 5 ml), and dried in a vacuum. Yield of compound **XVI** is 0.49 g (86%), mp 198–202°C, R_f 0.76 (B). ^1H NMR spectrum, d, ppm, (DMSO-d_6): 2.26 s [3H, $C(O)CH_3$], 3.09–3.91 m (42H; C^2H–C^5H, C^6H_2), 4.18–4.43 br.s (6H, C^6OH), 4.84 br.s (7H, C^1H), 5.58–5.89 br.s (14H; C^2OH, C^3OH), 7.15–8.15 m (4H, CH_{arom}). ^{13}C NMR spectrum, δ_C, ppm, (DMSO-d_6): 20.8 ($C(O)CH_3$), 59.6 (C^6OH), 63.5 [$C^6OC(O)$], 69.0 [$C^5C^6OC(O)$], 70.9–75.0 (C^2, C^3, C^5), 81.8 (C^4), 102.0 (C^1), 122.0–134.8 (C_{arom}), 155.6 [$COC(O)$], 169.2 [C(O)]. Found, %: C 46.74; H 6.10. $C_{51}H_{76}O_{38}$. Calculated, %: C 47.22; H 5.91.

(2) Synthesis of compound **XVII** was performed similarly from 0.50 g of β-cyclodextrin and 0.44 g of acid chloride **VIII**. Yield of compound **XVII** is 0.47 g (63%), mp 203-205°C, R_f 0.78 (B). ^1H NMR spectrum, d, ppm, (DMSO-d_6): 2.05–2.35 m [10.5H, $C(O)CH_3$], 3.13–4.08 m (42H; C^2H–C^5H, C^6H_2), 4.23–4.59 br.s (3.5H, C^6OH), 4.72–4.89 br.s (7H, C^1H), 5.60–6.04 br.s (14H; C^2OH, C^3OH), 7.05–8.11 m (14H, CH_{arom}). ^{13}C NMR spectrum, δ_C, ppm, (DMSO-d_6): 20.8 ($C(O)CH_3$), 59.4 (C^6OH), 63.9 [$C^6OC(O)$], 68.9 [$C^5C^6OC(O)$], 71.5–74.0 (C^2, C^3, C^5), 80.1–83.0 (C^4), 101.0–103.1 (C^1), 122.1–135.0 (C_{arom}), 150.1 [$COC(O)$], 169.2 [C(O)]. Found, %: C 51.11; H 5.45. $C_{73.5}H_{91}O_{45.5}$. Calculated, %: C 51.85; H 5.39.

(3) Synthesis of compound **XVIII** was performed similarly from 0.50 g of β-cyclodextrin and 0.61 g of acid chloride **VIII**. Yield of compound **XVIII** is 0.40 g (40%), mp 182–185°C, R_f 0.72 (C). ^1H NMR spectrum, d, ppm, (DMSO-d_6): 2.03–2.40 m [21H, $C(O)CH_3$], 3.25–4.15 m (42H; C^2H–C^5H, C^6H_2), 4.72–4.91 br.s (7H, C^1H), 5.65–6.05 br.s (14H; C^2OH, C^3OH), 7.05–8.15 m (28H, CH_{arom}). ^{13}C NMR spectrum, δ_C, ppm, (DMSO-d_6): 20.6 ($C(O)CH_3$), 63.8 [$C^6OC(O)$], 69.0 [$C^5C^6OC(O)$], 71.5–73.8 (C^2, C^3), 81.8 (C^4), 102.5 (C^1), 122.1–135.0 (C_{arom}), 150.1 [$COC(O)$], 169.2 [C(O)]. Found, %: C 57.23; H 5.02. $C_{105}H_{112}O_{56}$. Calculated, %: C 55.56; H 4.97.

(4) To a solution of 0.50 g of β-cyclodextrin, 0.34 g of triethylamine in 8 ml of DMF, 0.61 g of acid chloride **VIII** in 2 ml of DMF was added dropwise at stirring, and the reaction mixture was kept at 20°C for 24 h. Formed triethylamine hydrochloride was filtered off, and filtrate was concentrated in a vacuum to syrup-state, and then was poured into 20 ml of acetone by small portions at stirring. The precipitate was filtered off and washed with acetone (2 × 5 ml), and with chloroform (2 × 5 ml), and dried in a vacuum to obtain 0.30 g (46%) of compound **XIX**, mp 223–226°C (decomp.), R_f 0.67 (C). ^1H NMR spectrum, d, ppm, (DMSO-d_6): 2.15–2.30 m [6H, $C(O)CH_3$], 3.03–3.91 m (42H; C^2H–C^5H, C^6H_2), 4.51–4.87 br.s (5H, C^6OH), 4.80–4.96 br.s (7H, C^1H), 5.65–5.91 br.s (14H; C^2OH, C^3OH), 7.08–8.29 m (8H, CH_{arom}). ^{13}C NMR spectrum, δ_C, ppm, (DMSO-d_6): 20.9 ($C(O)CH_3$), 59.9 (C^6OH), 63.2 [$C^6OC(O)$], 69.3 [$C^5C^6OC(O)$], 71.3–75.1 (C^2, C^3, C^5), 82.1 (C^4), 102.1 (C^1), 122.2–135.1 (C_{arom}), 156.2 [$COC(O)$], 169.3 [C(O)]. Found, %: C 48.99; H 5.73. $C_{60}H_{82}O_{41}$. Calculated, %: C 49.38; H 5.66.

Acylation of β-cyclodextrin with acetylsalicyloyl chloride VIII at the secondary hydroxyl groups. To a solution of 0.50 g of β-cyclodextrin in 10 ml of DMF, 0.085 g of sodium hydride was added, the reaction mixture was stirred for 1 h, and then 0.61 g of acid chloride **VIII** in 2 ml of DMF was added dropwise at stirring. After 24 h the reaction was stopped

by addition of 3 ml of methanol. The reaction mixture was filtered off, filtrate was concentrated in a vacuum to syrup-state, and was poured into 50 ml of acetone by small portions at stirring. The precipitate was filtered off and washed with acetone (3 × 10 ml), and dried in a vacuum to obtain 0.34 g (60%) of compound **XX**, mp 204–206°C, R_f 0.74 (C). ^{1}H NMR spectrum, d, ppm, (DMSO-d_6): 2.30 s [3H, C(O)CH_3], 3.05–4.22 m (42H; C^2H–C^5H, C^6H_2), 4.43–4.61 br.s (7H, C^6OH), 4.72–5.10 br.s (7H, C^1H), 5.63–5.88 br.s (13H; C^2OH, C^3OH), 7.11–8.30 m (4H, CH_{arom}). Found, %: C 46.28; H 6.02. $C_{51}H_{76}O_{38}$. Calculated, %: C 47.22; H 5.91.

The inclision compound of β-cyclodextrin with acetylsalicylic acid. Equimolar quantities of β-cyclodextrin (0.500 g) and acetylsalicylic acid (0.08 g) was dissolved in 12 ml of water at heating (60–70°C). The reaction mixture was left to cooling to room temperature, and precipitate formed was filtered off, washed with acetone (2 × 5 ml), and dried in a vacuum to obtain 0.25 g (43%) of compound **XXII**, mp 225–228°C (decomp.), R_f 0.1 (C). ^{1}H NMR spectrum, d, ppm, (DMSO-d_6): cyclodextrin: 3.05–4.02 m (42H; C^2H–C^5H, C^6H_2), 4.48 br.s (7H, C^6OH), 4.83 d (7H, C^1H), 5.70 m (14H; C^2OH, C^3OH); acetylsalicylic acid: 2.25 s (3H, CH_3), 7.18–7.22 d (1H, C^3H_{arom}), 7.38–7.42 t (1H, C^5H_{arom}), 7.60–7.65 t (1H, C^4H_{arom}), 7.91–7.95 d (1H, C^6H_{arom}), 12.3 s (1H, COOH). Found, %: C 47.39; H 5.06. $C_{51}H_{78}O_{39}$. Calculated, %: C 46.58; H 5.98.

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