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β-Cyclodextrin and Its Silyl Derivative Inclusion Complexes and Conjugates with Medicine Preparation "Ibuprofen" and Its Synthetic Precursors

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Abstract — A possibility of formation of various inclusion complexes and conjugates of β-cyclodextrin and its silyl derivatives with the medicine preparation "Ibuprofen" and its synthetic precursors in dependence of nature of solvent and size of cyclodextrin cavity is demonstrated.
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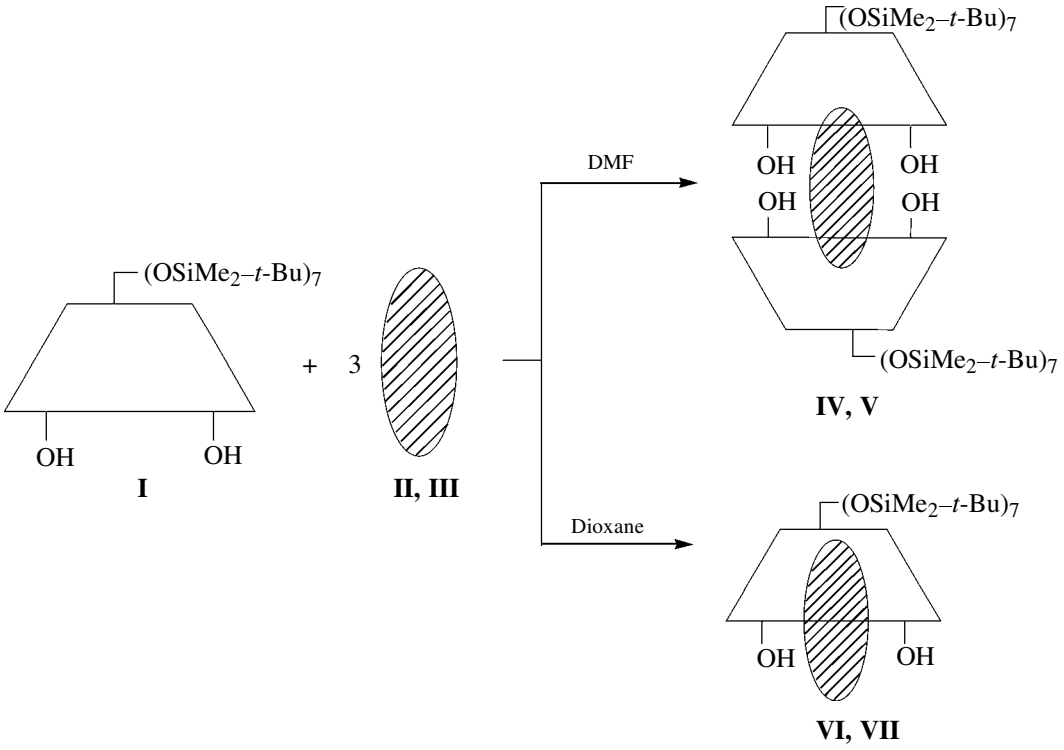
β-Cyclodextrin and some of its derivatives met wide application in pharmacology as "containers" for medicine preparations owing to their ability of incapsulation of various hydrophobic compounds to form inclusion compounds of "host–guest" mode [1]. Such an incapsulation protects the included medicine against biodegradation, promotes increase of its solubility and, that is very important, promotes effectively and selectively transport of the medicine to certain location in a certain time gap. Besides the inclusion, in the recent period attention was paid also to covalent "binding" (conjugation) of medicine preparations with cyclodextrin allowing in some cases to create new medicine preparation with prolonged and specific action [2]. Earlier we have studied preparation of the β-cyclodextrin and its silyl derivative conjugates with the pharmacologically significant benzoic acid chlorides [3].

In continuation of our studies in the area of creation new medicine forms on the basis of β-cyclodextrin and its derivatives we consider medicine preparation "Ibuprofen." The "Ibuprofen" is a nonsteroid antiplogistic preparation with anesthetic and antipyretic action. However, it shows side effect of promotion to ulcer erosion of gastrointestinal tract. Conjugation of "Ibuprofen" with β-cyclodextrin can probably allow avoiding of these unwanted effects. But often the inclusion complexes are unstable substances, and their preparation is based on different experimental approaches [4] and each specific case requires finding of appropriate conditions and developing certain procedure for preparation and isolation. In this connection we studied the ability of formation inclusion compounds by β-cyclodextrin silyl derivatives with some precursors of the medicine preparation "Ibuprofen" and with 1-(4-isobutylphenyl)propionic acid itself.

In the first step we studied preparation of inclusion complexes of per[6-*O*-(tbutyldimethylsilyl)]cyclodextrin (**I**) with synthetic precursors of "Ibuprofen" **II** and **III**. For the study we used solvents DMF and dioxane, accounting for satisfactorily solubility of initial reagents. To a weighted sample of (β-cyclodextrin derivative **I** dissolved in a solvent at stirring was slowly added triple excess of a "guest" compound. After 24-h stirring the solution was poured at stirring to water and formed complex was filtered off. The obtained products individuality as inclusion compounds was confirmed by the data of ^{1}H NMR spectroscopy and TLC. In the ^{1}H NMR spectra of inclusion compounds **IV** and **V** observed the proton of both β-cyclodextrin derivative **I** and, respectively, of methyl(4-isobutylphenyl)ketone **II** or 1-(4-isobutylphenyl)ethyl chloride **III** with integral intensity ratio 2 : 1. Obviously a complex was formed with one guest molecule **II** or **III** per two host molecules **I**. Thus, in DMF even with excess of guest compound the inclusion complex of 2 : 1 composition (**IV** or **V**) are formed.

It is noteworthy that similar reaction in dioxane led to formation of inclusion complexes of another, 1 : 1, composition: **VI** and **VII**. In ^{1}H NMR spectra of the complexes **IV** and **VI** in the aromatic region ob-

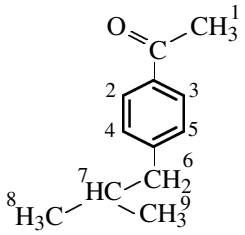
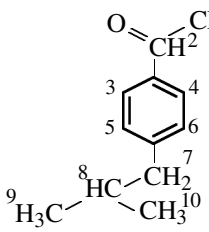


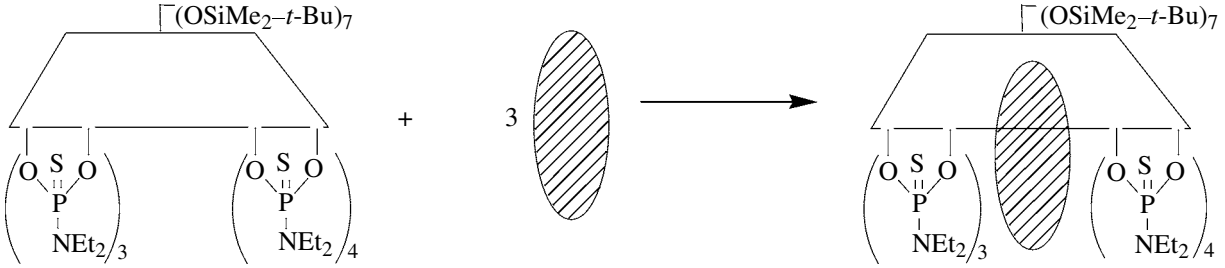
served upfield shift of benzene ring protons by 0.1 ppm.

Thus we found that solvent influences stoichiometry of the forming compklex: in DMF predominates the host–guest complex of 1 : 2 composition while in dioxane 1 : 1. Increase in amount of introduced guest compound (even to four molar equivalents of **III**) in dioxane eventually leads to 1 : 1 complex. It can also be assumed that inclusion of guest molecule to the complex occurs at the extended side of cyclodextrin torr because silyl protecting groups at promary hydroxyls are bulky enough to prevent access to molecular cavity through narrow side of the cyclodextrin torr. Probably methyl(4-isobutylphenyl)ketone **II** due to presence of carbonyl group in its molecule forms hydrogen bonds with secondary hydroxyls of (β-cyclodextrin derivative **I**, as seen from higher melting poins (with decomposition) of its complexes **IV** and **VI** in comparison with the inclusion complexes **V** and **VII** formed by 1-(4-isobutylphenyl)ethyl chloride **III**) (see the table). As the derivative **III** is a racemic mixture, ^{1}H NMR spectra of its inclusion complexes **V** and **VII** show magnetic nonequivalence(diastereomeric anisochromism): two doublets of approximately equal intensity at diastereomeric anisochromism 1.29 and 1.78 ppm of methyl protons at asymmetric carbon atom and multiplication of the signals of aromatic protons induced probably by chiral cyclodextrin environment around the guest **III**. In addition, ^{1}H NMR spectra of complexes **V** and **VII**, like those of complexes **IV** and **VI** show 0.1 ppm upfield shift of the proton signals in aromatic region of the included guest **III**. These data attest additionally in favor of formation of inclusion compounds.

In the next step we prepared inclusion complexes of methyl(4-isobutylphenyl)ketone **II** with silylated (β-cyclodextrin **I** modified at the secondary hydroxyl groups. For increasing in size of molecular cavity, to the **I** molecule we introduced second phoshorus-containing stratum which also confers additional rigidity to the cyclodextrin carcass. We used our earlier obtained cyclophosphorylated derivative **VIII** [5] as a host for the guest **II**. The inclusion complex **IX** was prepared in DMF as a solvent and isolated similarly to described above. In ^{1}H NMR spectrum of compound **IX** were registered both the signals of (β-cyclodextrin derivative **VIII** and methyl(4-isobutylphenyl)ketone **II** with integral ratio 1 : 1, indicating formation of a complex with one host molecule per one guest, in distinct with the abovementioned case of application compound **I** as a host, where under similar conditions is formed complex **IV** with two host molecules per one guest. Thus, increase cavity in size allows to obtain complex with another stoichiometry, namely, 1 : 1.

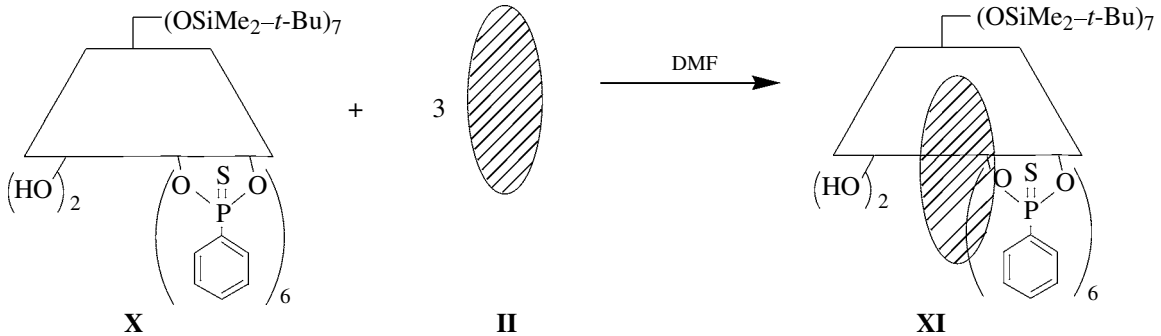
Characteristics of inclusion compounds **IV**–**VII**

Inclusion compound	Guest	Solvent	mp (decomp.), °C	Yield, %
IV	**II**	DMF	277–280	61
VI		Dioxane	272–275	67
V	**III**	DMF	244–246	55
VI		Dioxane	222–225	57



VIII **II** **IX**

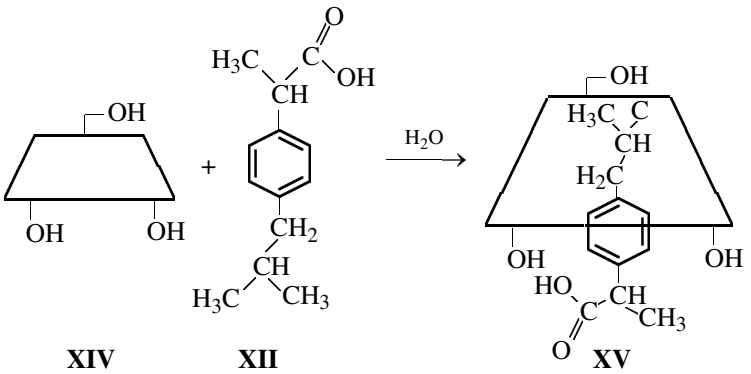
Complex of similar composition (1 : 1) is formed in the reaction of incompletely cyclophosphorylated (β-cyclodextrin **X** [6] which bears cyclophenylthiophosphonate fragments at the broad side of cyclodextrin frame, with methyl(4-isobutylphenyl)ketone **II**.



X **II** **XI**

registered at the formation of inclusion compounds by silylated (β-cyclodextrin **I** with 1-(4-isobutylphenyl)-propanoic acid **XII** (the medicine means "Ibuprofen") under similar conditions: in DMF (method *a*) and in dioxane (method *b*). Initila compounds were taken in proportion: one mole (β-cyclodextrin derivative **I** and three molar equivalents of the guest, both in DMF and dioxane. Consideration of ^{1}H NMR spectra of the complex **XIII** obtained in both the solvents showed that inclusion compound **XIII** consists of one host and two guest molecules. Probably one guest molecule is located completely in the cavity and another on the outside of the cyclodextrin torr.

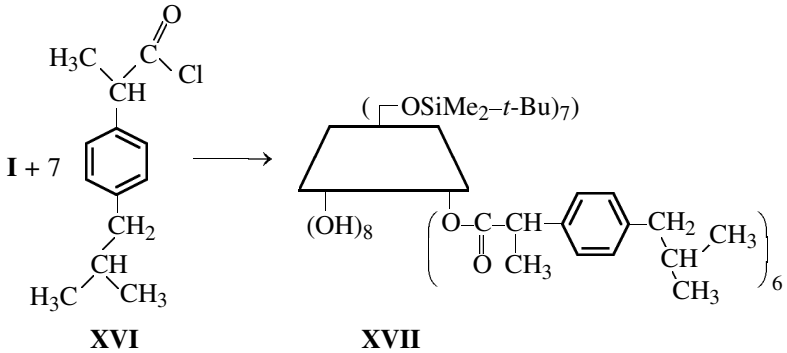
We also prepared inclusion complex from unsubstituted (β-cyclodextrin **XIV** and acid **XII** in water. For this purpose a mixture of one mole of (β-cyclodextrin and two moles of acid **XII** was dissolved in minimum amount of water at 80°C and the mixture was slowly cooled to room temperature. The dropped complex was filtered off and washed with acetone.



XIV **XII** **XV**

According to the data of ^{1}H NMR spectroscopy the host–guest complex **XV** formed has composition 1 : 1. In the spectrum the signals of H^3 and H^5 protons of the cyclodextrin frame were shifted downfield by 0.01 and 0.03 ppm respectively, that is typical of the inclusion complexes with unsubstituted cyclodextrin [7].

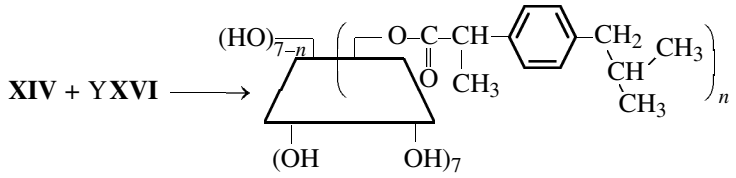
To finish this study, we performed chemical binding (conjugation) of (β-cyclodextrin and its silylated derivative with 1-(4-isobutylphenyl)propanoic acid chloride **XVI**. Acylation of free secondary hydroxyls of (β-cyclodextrin derivative **I** by 7 molar equivalents of acid chloride **XVI** led to compound **XVII** which according to ^{1}H NMR data has average degree of substitution 6. Compound **XVII** was isolated by column chromatography in 66% yield.



XVI **XVII**

In addition, we prepared similar (β-cyclodextrin derivatives acylated at primary hydroxyl groups. As a solvent was used pyridine, because earlier we showed that in this solvent the primary hydroxyl groups are acylated most completely [2, 8].

Compounds **XVIII**–**XX** were isolated in yields 58, 60, and 65%, respectively; their individuality and structure were confirmed by ^{1}H and ^{13}C NMR spectroscopy and TLC. The number of introduced acyl fragments was determined from the integral intensity



XIV + Y**XVI** → **XVIII–XX**

XVIII, Y = 2, n = 1.4; **XIX**, Y = 5, n = 5; **XX**, Y = 7, n = 7.

ratio of the proton signals of cyclodextrin carcass and acid **XII**. Consideration of ^{13}C NMR specra led to conclusion that in all the cases the direct acylation of (β-cyclodextrin occurred at primary hydroxyl groups. In ^{13}C NMR spectra we observed downfield shift of thesignals of C^{6A*} atoms of compounds **XVIII–XX** (δ_C 63 ppm) as compared with corresponding signals in the parent (β-cyclodextrin (δ_C 60 ppm), and upfield shift of C^5 signal from δ_C 72 ppm in the parent (β-cyclodextrin to δ_C 69 ppm (C^{5A} in **XVIII–XX**). The fact of acylation at primary hydroxyl groups is confirmed by the observation that signals of carbon atoms C^2 and C^3 of cyclodextrin carcass in ^{13}C NMR spectra of compounds **XVIII–XX** are not shifted.

Thus, we have proposed pathways for creation of (β-cyclodextrin and its silyl derivative inclusion complexes and conjugates with the medicine means "Ibuprofen" and its synthetic precursors of pharmacological importance.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were registered on Bruker AC-200 with operating frequencies 200.13 and 50.32 MHz, external reference TMS. For TLC were used aluminum plates with fixed silica gel layer, the eluents are: benzene–ethanol 3 : 1 (A), methanol–chloroform 1 : 3 (B), benzene–acetonitrile 1 : 1 (C), ethyl acetate–acetic acid–water 3 : 1 : 3 (D).

All experiments with 1-(4-isobutylphenyl)propanoic acid chloride were performed under inert atmosphere, anhydrous pyridine was used.

Inclusion compounds of per[6-*O*-(*tert*-butyldimethylsilyl)]-(β-cyclodextrin I with methyl(4-isobutylphenyl)ketone II *(general procedure). a*. In DMF. to a solution of 0.50 g of (β-cyclodextrin derivative **I** in 2.5 ml of DMF was added 0.14 g of ketone **II** and the mixture was stirred for 24 h at 20°C. The reaction mixture was poured to water by small portion (10 ml) with stirring, the precipitate dropped was filtered off, washed with water (2 × 2 ml), then with methanol (3 ml), and stored in a vacuum (1 mm Hg) for 4 h at 40–50°C. Yield of compound **IV** 0.32 g (61%), mp 277–280°C (decomp.), R_f 0.50 (A). ^1H NMR spectrum (DMSO-d_6), (δ, ppm: the (β-cyclodextrin derivative **I**: 0.01 s [84H, $Si(CH_3)_2$], 0.84 s [126H, $C(CH_3)_3$], 3.15–4.10 m (84H; C^2H–C^5H, C^6H_2), 4.80 br.s (14H, C^1H), 5.75 br.s (28H; C^2OH, C^3OH); methyl(4-isobutylphenyl)ketone: 0.87 s (6H; H^8, H^9), 1.80–1.95 m (1H, H^7), 2.48 d (1H, H^6), 2.56 s (3H, H^1), 7.31 d (2H; H^4, H^5), 7.89 d (2H; H^2, H^3). Found, %: C 54.04; H 8.51. $C_{180}H_{352}O_{71}Si_{14}$. Calculated, %: C 53.44; H 8.77.

b. In dioxane. Synthesis of compound **VI** was performed by similar procedure from 0.50 g of β-cyclodextrin derivative **I** in 2.5 ml of dioxane, and 0.14 g of ketone **II**. Yield 0.37 g (67%), mp 272–275°C (decomp.), R_f 0.53 (A). ^1H NMR spectrum (DMSO-d_6), δ, ppm: (β-cyclodextrin derivative **I**: 0.01 s [42H, $Si(CH_3)_2$], 0.84 s [63H, $C(CH_3)_3$], 3.16–4.09 m (42H; C^2H–C^5H, C^6H_2), 4.80 br.s (7H, C^1H), 5.75 br.s (14H; C^2OH, C^3OH); methyl(4-isobutylphenyl)ketone: 0.88 d (6H; H^8, H^9), 1.78–1.95 m (1H, H^7), 2.48 d (1H, H^6), 2.55 s (3H, H^1), 7.31 d (2H; H^4, H^5), 7.88 d (2H; H^2, H^3). Found, %: C 53.92; H 8.90. $C_{96}H_{184}\cdot O_{36}Si_7$. Calculated, %: C 54.62; H 8.79.

Inclusion compounds of per[6-*O*-(*tert*-butyldimethylsilylsilyl)]-(β-cyclodextrin I with 1-(4-isobutylphenyl)ethyl chloride III *(general procedure). a*. In DMF. To a solution of 0.50 g of (β-cyclodextrin derivative **I** in 2.5 ml of DMF was added 0.15 g of the ethyl chloride **III** and mixture was stirred for 24 h at 20°C. The reaction mixture was poured to water in small portions (10 ml) at stirring and precipitate formed was filtered off, washed with water (2 × 2 ml), then with methanol°· (3 ml) and stored in a vacuum (1 mm Hg) for 4 h at 40–50°C. Yield of compound **V** 0.29 g (55%), mp 244–246°C (decomp.), R_f 0.49 (A). ^1H NMR spectrum (DMSO-d_6), δ, ppm: (β-cyclodextrin derivative **I**: 0.01 s [84H, $Si(CH_3)_2$], 0.81 s [126H, $C(CH_3)_3$], 3.19–4.02 m (84H; C^2H–C^5H, C^6H_2), 4.81 br.s (14H, C^1H), 5.62–5.91 m (28H; C^2OH, C^3OH); 1-(4-isobutylphenyl)ethyl chloride 0.88 d (6H; H^9, H^{10}), 1.26 d (3H, H^1), 1.74–1.80 m (1H, H^8), 1.78 d (3H, H^1), 2.45 d (2H, H^7), 5.12–

5.25 m (1H, H^2), 7.08–7.20 m (2H; H^5, H^6), 7.32–7.40 m (2H; H^3, H^4). Found, %:C 54.22; H 8.64. $C_{180}H_{353}O_{70}Si_{14}Cl$. Calculated, %: C 53.17; H 8.75.

b. In dioxane. Synthesis of compound **VII** was conducted by similar procedure from 0.50 g of β-cyclodextrin derivative **I** in 2.5 ml of dioxane and 0.15 g of the ethyl chloride **III**. Yield of compound **VII** 0.35 g (64%) mp 222–225°C (decomp.), R_f 0.46 (A). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: (β-cyclodextrin derivative **I**: 0.01 s [42H, $Si(CH_3)_2$], 0.82 s [63H, $C(CH_3)_3$], 3.19–3.98 m (42H; C^2H–C^5H, C^6H_2), 4.79 d (7H, C^1H), 5.51–5.89 m (14H; C^2OH, C^3OH); 1-(4-isobutylphenyl)ethyl chloride: 0.86 d (6H; H^9, H^{10}), 1.29 d (3H, H^1), 1.70–1.75 m (1H, H^8), 1.78 d (3H, H^1), 2.38–2.48 m (2H, H^7), 5.25–5.38 m (1H, H^2), 7.08–7.40 m (4H; H^3, H^4, H^5, H^6). Found, %: C 54.63; H 8.64. $C_{96}H_{185}O_{35}Si_7Cl$. Calculated, %: C 54.09; H 8.75.

Inclusion compounds of derivative VIII with methyl(4-isobutylphenyl)ketone II. To a solution of 0.50 g of β-cyclodextrin derivative **VIII** in 2.5 ml of DMF was added 0.09 g of methyl(4-isobutylphenyl)-ketone **II** and the mixture was stirred for 24 h at 20°C. The reaction mixture was poured to water in small portions (10 ml) at stirring, the precipitate formed was filtered off, washed with water (2 × 2 ml), then with methanol (3 ml), and stored in a vacuum (1 mm Hg) for 4 h at 40–50°C. Yield of compound **IX** 0.33 g (62%), mp 145–148°C, R_f 0.90 (B). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: derivative **VIII**, 0.09 s [42H, $Si(CH_3)_2$], 0.93 s [63H, $C(CH_3)_3$], 1.15 br.s [42H, $N(CH_2CH_3)_2$], 3.01–3.35 m [28H, $N(CH_2CH_3)_2$], 3.43–4.02 m (42H; C^2H–C^5H, C^6H_2), 4.99 d (7H, C^1H); methyl(4-isobutylphenyl)ketone, 0.98 s (6H; H^8, H^9), 1.83–2.01 m (1H, H^7), 2.55 d (1H, H^6), 2.62 s (3H, H^1), 7.24 d (2H; H^4, H^5), 7.88 d (2H; H^2, H^3). Found, %: C 47.89; H 8.03; P 7.20. $C_{124}H_{240}N_7O_{36}P_7S_7Si_7$. Calculated, %: C 48.94; H 7.95; P 7.12.

Inclusion compound of derivative X with methyl(4-isobutylphenyl)ketone II. To a solution of 0.50 g of β-cyclodextrin derivative **X** in 2.5 ml of DMF was added 0.10 g of methyl(4-isobutylphenyl)-ketone **II**. The mixture was stirred for 24 h at 20°C. Then the reaction mixture was poured to water in small portions (10 ml) at stirring, the precipitate formed was filtered off, washed with water (2 × 2 ml) and methanol (3 ml) and kept in a vacuum (1 mm Hg) for 4 h at 40–50°C. Yield of compound **XI** 0.32 g (60%), mp 200–203°C (decomp.), R_f 0.92 (ß). The ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: derivative **X**: 0.09 s [42H, $Si(CH_3)_2$], 0.91 s [63H, $SiC(CH_3)_3$], 3.38–4.21 m (42H; C^2H–C^5H, C^6H_2), 4.97–5.21 m (7H, C^1H), 7.09–8.12 m (30H, CH_{arom}); methyl(4-isobutylphenyl)ketone: 0.98 s (6H; H^8, H^9), 1.82–1.99 m (1H, H^7), 2.55 d (1H, H^6), 2.62 s (3H, H^1), 7.09–8.12 m (4H, CH_{arom}). Found, %: C 54.48; H 6.73; P 6.27. $C_{132}H_{202}O_{36}P_6S_6Si_7$. Calculated, %: C 53.93; H 6.93; P 6.32.

Inclusion compounds of per[6-*O*-(*tert*-butyldimethylsilyl)]-β-cyclodextrin I with 1-(4-isobutylphenyl)propanoic acid XII *(general procedure). a*. In DMF. To a solution of 0.50 g of (β-cyclodextrin derivative **I** in 2.5 ml DMF was added 0.16 g of acid **XII** and the mixture was stirred for 24 h at 20°C. Reaction mixture was poured to water in small portions (10 ml) at stirring, the precipitate formed was filtered off, washed with methanol (3 ml) and kept in a vacuum (1 mm Hg) for 4 h at 40–50°C.

b. In dioxane. The sinthesis was conducted similarly using 0.50 g of β-cyclodextrin derivative **I** in 2.5 ml of dioxane and 0.16 g of acid **XII**. Yield of compound **XIII** 0.46 g (75%), mp 218–221°C, R_f 0.61 (A). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: β-cyclodextrin derivative **I**: 0.02 s [42H, $Si(CH_3)_2$], 0.86 s [63H, $C(CH_3)_3$], 3.20–4.02 m (42H; C^2H–C^5H, C^6H_2), 4.81 d (7H, C^1H), 5.58–5.63 m (14H; C^2OH, C^3OH); 1-(4-isobutylphenyl)propanoic acid **XII**: 0.87 s [12H, $(CH_3)_2$], 1.35 d (6H, CH_3), 1.79–1.85 m [2H, $CH(CH_3)_2$], 2.42 d (4H, CH_2), 3.52–3.60 m (2H, CH), 7.06–7.21 m (8H, CH_{arom}), 12.2 s (2H, COOH). Found, %: C 56.88; H 8.70. $C_{110}H_{204}O_{39}Si_7$. Calculated, %: C 56.28; H 8.76.

Inclusion compound of β-cyclodextrin with 1-(4-isobutylphenyl)propanoic acid XII. A mixture of 0.50 g of β-cyclodextrin and 0.18 g of acid **XII** was dissolved in 9 ml of water at heating (80°C). The reaction mixture was then left to cool to room temperature, the precipitate formed was filtered off, washed with acetone (2 × 5 ml) and dried in a vacuum (1 mm Hg) for 4 h at 40-50°C. Yield of compound **XV** 0.38 g (64%), mp 237–240°C (decomp.), R_f 0.46 (D). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: β-cyclodextrin: 3.30–3.72 m (42H; C^2H–C^5H, C^6H_2), 4.46 t (7H, C^6OH), 4.83 d (7H, C^1H), 5.67–5.75 m (14H; C^2OH, C^3OH); 1-(4-isobutylphenyl)propanoic acid **XII**: 0.85 d [6H, $(CH_3)_2$], 1.33 d (3H, CH_3), 1.73–1.84 m [1H, $CH(CH_3)_2$], 2.41 d (2H, CH_2), 3.58–3.72 m (1H, CH), 7.08–7.24 m (4H, CH_{arom}), 12.2 s (1H, COOH). Found, %: C 48.69; H 6.56. $C_{55}H_{88}O_{37}$. Calculated, %: C 49.25; H 6.61.

Acylating per[6-*O*-(*tert*-butyldimethylsilyl)]-(β-cyclodextrin I by 1-(4-isobutylphenyl)propanoic acid chloride XVI. To a solution of 0.50 g of (β-

cyclodextrin derivative **I** in 5 ml of pyridine was added dropwise at stirring a solution of 0.41 g of the acid chloride **XVI** in 2 ml of benzenea and the mixture was kept at 20°C for 24 h. Pyridine hydrochloride precipitate formed was filtered off, the filtrate was evaporated in a vacuum, the residue was dissolved in 5 ml of benzene, the solution was filtered to remove dropped pyridine hydrochloride, solvent was then evaporated in a vacuum. The product was purified by column chromatography, the eluent is A system. The solvent was removed and residue was kept in a vacuum (1 mm Hg) for 3 h at 60°C. Yield of compound **XVII** 0.52 g (66%), mp 95–98°C, R_f 0.93 (A). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 0.10 s [42H, Si(CH$_3$)$_2$], 0.83–0.89 m [36H, (CH$_3$)$_2$], 0.92 s [63H, C(CH$_3$)$_3$], 1.46–1.50 m (18H, CH$_3$), 1.82–1.86 m [6H, C*H*(CH$_3$)$_2$], 2.44 d (12H, CH$_2$), 3.58–3.64 m (6H, CH), 3.32–5.45 m (49H; C^{1}H–C^{5}H, C^{6}H$_2$), 5.82–6.10 m (8H; C^{2}OH, C^{3}OH), 7.02–7.43 m (24H, CH$_{arom}$). Found, %: C 64.22; H 8.59. $C_{162}H_{264}O_{41}Si_7$. Calculated, %: C 63.49; H 8.68.

Acylating β-cyclodextrin with (4-isobutylphenyl)propanoic acid chloride XVI. *a*. To a solution of 0.50 g of β-cyclodextrin in 8 ml of pyridine at stirring was added dropwise 0.20 g of acid chloride **XVII** in 2 ml of benzene and the mixture was kept at 20°C for 24 h. The reaction mixture was evaporated and residue was grinded in chloroforme (5 ml), the solid formed was filtered off, recrystallized from ethanol (10 ml) and dried in vacuum (1 mm Hg) 3 h at 60 C. Yield of compound **XIX** 0.36 g (58%), mp 232–235°C (decomp.), R_f 0.43 (D). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.84 d [8.4H, (CH$_3$)$_2$], 1.29–1.38 m (4.2H, CH$_3$), 1.71–1.87 m [1.4H, C*H*(CH$_3$)$_2$], 2.40 d (2.8H, CH$_2$), 3.28–3.68 m (42H; C^{1}H–C^{5}H, C^{6}H$_2$), 3.42–3.47 m (1.4H, CH), 4.28–4.37 m (5.6H, C^{6}OH), 4.83 d (7H, C^{1}H), 5.62–5.83 m (14H; C^{2}OH, C^{3}OH), 6.98–7.25 m (5.6H, CH$_{arom}$). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 18.2–18.6 (CH$_3$), 22.3 [(CH$_3$)$_2$], 29.8 [*C*H(CH$_3$)$_2$], 40.3 (*C*HCH$_3$), 44.3 (CH$_2$), 60.0 (C^{6}OH), 63.8 [*C*^{6}OC(O)], 69.3 [*C*^{5}C^{6}OC(O)], 72.1–73.2 (C^2, C^3, C^5), 81.7 (C^4), 102.1 (C^1), 127.0–139.8 (CH$_{arom}$), 174.2 [C(O)]. Found, %: C 51.12; H 6.74. $C_{60.2}H_{92.4}O_{36.4}$. Calculated, %: C 51.70; H 6.66.

b. To a solution of 0.50 g of β-cyclodextrin in 8 ml of pyridine at stirring was added dropwise 0.49 g of acid chloride **XVII** in 2 ml of benzene and the mixture was kept at 20°C for 24 h. The pyridine hydrochloride dropped was filtered off, the filtrate was evaporated, the residue was grinded with ether (5 ml), the solid formed was filtered off, recrystallized from benzene–ethanol 3 : 1 mixture (10 ml) and dried in a vacuum (1 mm Hg) 3 h at 60 C. Yield of compound **XX** 0.55 g (60%), mp 220–233°C (decomp.), R_f 0.51 (D). ^{1}H NMR spectrum (DMSO-d_6), (δ, ppm: 0.78–0.84 m [30H, (CH$_3$)$_2$], 1.21–1.32 m (15H, CH$_3$), 1.74–1.77 m [5H, CH(CH$_3$)$_2$], 2.38 d (10H, CH$_2$), 3.12–3.85 m (42H; C^{1}H–C^{5}H, C^{6}H$_2$), 3.45–3.50 m (5H, CH), 4.21–4.35 m (2H, C^{6}OH), 4.82 d (7H, C^{1}H), 5.52–5.79 m (14H; C^{2}OH, C^{3}OH), 6.95–7.11 m (20H, CH$_{arom}$). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 18.2 (CH$_3$), 22.2 [(CH$_3$)$_2$], 29.7 [*C*H(CH$_3$)$_2$], 40.2 (*C*HCH$_3$), 44.3 (CH$_2$), 59.9 (C^{6}OH), 63.5 [*C*^{6}OC(O)], 69.5 [*C*^{5}C^{6}OC(O)], 71.8–73.7 (C^2, C^3, C^5), 81.9 (C^4), 102.0 (C1), 127.1–139.7 (CH$_{arom}$), 173.9 [C(O)]. Found, %: C 61.51; H 7.36. $C_{107}H_{150}O_{40}$. Calculated, %: C 61.90; H 7.28.

c. To a solution of 0.50 g of β-cyclodextrin in 8 ml of pyridine at stirring was added dropwise 0.69 g of acid chloride **XVII** in 2 ml of benzene and the mixture was kept at 20°C for 24 h. The pyridine hydrochloride dropped was filtered off, the filtrate was evaporated, the residue was grinded with ¿¯«®e (5 ml), the solid formed was filtered off, washed with water (2 × 5 ml), residual water was removed by azeotropic distillation with benzene and solid was dried in a vacuum (1 mm Hg) 3 h at 60 C. Yield of compound **XXI** 0.70 g (65%), mp 157–160°C, R_f 0.59 (D). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.78–0.85 m [42H, (CH$_3$)$_2$], 1.24–1.30 m (21H, CH$_3$), 1.72–1.81 m [7H, C*H*(CH$_3$)$_2$], 2.37 br.s (14H, CH$_2$), 3.13–3.77 m [42H; C^{1}H–C^{5}H, C^{6}H$_2$), 3.47–3.51 m (5H, CH), 4.82 d (7H, C^{1}H), 5.66–5.82 m (14H; C^{2}OH, C^{3}OH), 6.96–7.22 m (28H, CH$_{arom}$). ^{13}C NMR spectrum (DMSO-d_6), δ$_C$, ppm: 18.2 (CH$_3$), $_{22\cdot2}$ [(CH3)2], 29.7 [*C*H(CH$_3$)$_2$], 40.3 (*C*HCH$_3$), 44.3 (CH$_2$), 63.2 [*C*^{6}·OC(O)], 69.3 [*C*^{5}C^{6}OC(O)], 72.0–73.0 (C^2, C^3, C^5), 81.8 (C^4), 102.1 (C^1), 127.1–139.6 (CH$_{arom}$), 174.2 [C(O)]. Found, %: C 64.64; H 7.55. $C_{133}H_{182}O_{42}$. Calculated, %: C 65.13; H 7.48.

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