ISSN 1070-3632, Russian Journal of General Chemistry, 2009, Vol. 79, No. 6, pp. 1167–1170. © Pleiades Publishing, Ltd., 2009.
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Cyclodextrin and Some Its Derivatives Inclusion Compounds with "Ibuprofen" Remedy Substrate

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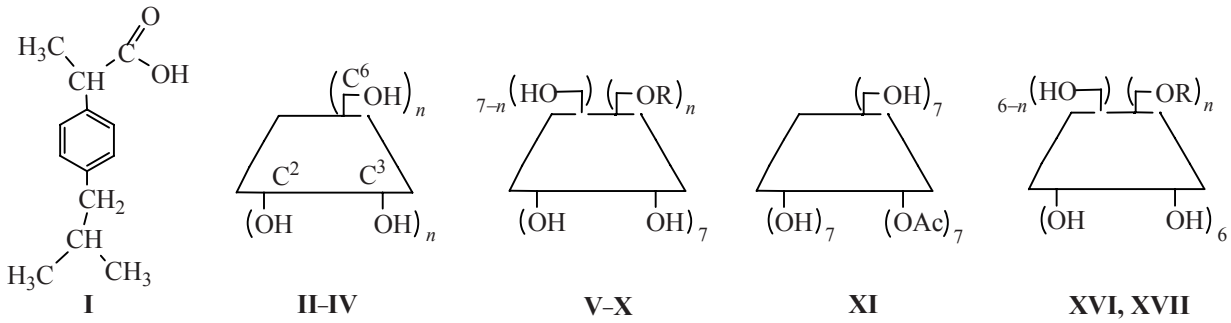
Received October 16, 2008

Abstract—The practical pathways are proposed for the synthesis of cyclodextrins and some of their derivatives inclusion compounds with the "Ibuprofen" remedy substrate. The effect of the cavity size, nature of the solvent and character and number of substituents at the cyclodextrin carcass on the possibility of isolation of the inclusion compounds that are of pharmacological significance, are elucidated.

DOI: 10.1134/S1070363209060231

The cyclodextrin complexes with various compounds (the inclusion compounds of *guest–host* type) are of great significance e.g., for the study of metabolism of some biologically important compounds and for targeted delivery of medicine means (e.g., see reviews [1]). However, preparation of the complexes in mach is tentative because it is based on the different experimental approaches [2] and in a great extent depends on the nature of the cyclodextrin (its internal cavity size, substituents, or absence of the latter), choice of the solvent, and particular procedure. Earlier we have proposed a method for the preparation of the β-cyclodextrin and its silyl and phosphorus-containing derivatives inclusion compounds with the "Ibuprofen" remedy substrate, 1-(4-isobutylphenyl)propanoic acid **I** and its synthetic precursors [3]. We have found that the solvent and the cyclodextrin nature affect considerably the stoichiometry of the formed complexes and the possibility of their isolation. Accounting for the pharmacological significance of such inclusion compounds, in this work we continued the study of the dependence of their preparation on the nature of free cyclodextrins α-(**II**, n = 6), β-(**III**, n = 7) and γ-(**IV**, n = 8) that differ considerably by the internal cavity size (0.176, 0.346 and 0.510 nm^3, respectively) and solubility in water (145, 18.5 and 232 g l^{-1}, respectively) [4]. In addition, we studied a possibility of formation of the inclusion compounds by the β-cyclodextrin derivatives bearing functional groups in the C^6 positions of the cyclodextrin carcass glycoside fragments at various degree of substitution (n): acetyl (**V**, n = 2; **VI**, n = 4), tosyl (**VII**, n = 2; **VIII**, n = 4) and silyl (**IX**, n = 4; **X**, n = 7). Besides, we studied the β-cyclodextrin derivative **XI** possessing 7 acetyl groups in C^2, C^3 positions of the glycoside fragments.

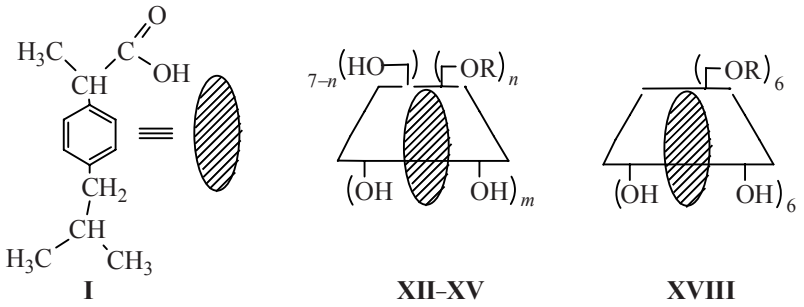
In the first step of the study, we explored formation of inclusion compounds of acid **I** with unsubstituted cyclodextrins **II**–**IV** by the method of join precipitation of the complex from a hot (70°C) water solution of cyclodextrin and the acid at slow cooling to 20°C. The precipitate formed was washed and dried in a vacuum. Individuality of the complex was confirmed by TLC and its composition was revealed on the basis of the data of ^{1}H NMR spectroscopy by the comparison of intensity of the signals of methyl protons of the *sec*-butyl fragment of the acid **I** and the protons of the cyclodextrin frame (see Experimental). We found that under these conditions α-cyclodextrin **II** does not form inclusion compounds while β-cyclodextrins **III** and γ-cyclodextrins **IV** do form inclusion complexes **XII** and **XIII** respectively, of 1:1



I **II–IV** **V–X** **XI** **XVI, XVII**

II: $n = 6$; **III**: $n = 7$; **IV**: $n = 8$; **V**: $n = 2$, R = Ac; **VI**: $n = 4$, R = Ac; **VII**: $n = 2$, R = n-$S(O)_2C_6H_4Me$; **VIII**: $n = 4$, R = n-$S(O)_2C_6H_4Me$; **IX**: $n = 4$, R = $SiMe_2$-t-Bu; **X**: $n = 7$, R = $SiMe_2$-t-Bu; **XVI**: $n = 3$, R = $SiMe_2$-t-Bu; **XVII**: $n = 6$, R = $SiMe_2$-t-Bu.

composition, in 67 and 57% yield. Tacking into account good solubility of α-cyclodextrin in water, we carried out similar experiments taking water in a half amount, but in this case also we did not register formation of the α-cyclodextrin compex with the acid **I**[1]. Cyclodextrins **II–IV** are well enough soluble in DMSO and DMFA, therefore we attempted to obtain individual complexes using these solvents. However, we failed to register formation of respective complexes under these conditions also.



I **XII–XV** **XVIII**

XII: $n = m = 7$, R = H; **XIII**: $n = m = 8$, R = H; **XIV**: $n = 4$, $m = 7$, R = $SiMe_2$-t-Bu; **XV**: $n = m = 7$, R = $SiMe_2$-t-Bu.

Among other cyclodextrin derivatives **V–X,** the acetyl derivatives **V**, **VI** and **XI** only turn to be soluble in water, but attempted interaction of compounds **V**, **VI** and **XI** with acid **I** by the same procedure did not lead to formation of inclusion compounds. Taking into account a high enough solubility of derivatives **V–X** in organic solvents (in distinct to the parent cyclodextrins **II–IV**), we attempted to obtain and isolate the inclusion compounds using as a solvent either DMFA, DMSO, dioxane, acetone, or hexane (see Experimental). We found that silyl derivatives **IX**, **X** form respective inclusion compounds **XIV**, **XV** with acid **I** in DMFA and dioxane (in water they are insoluble). By comparison of integral intensities in the ^{1}H NMR spectra of the signals of aromatic protons of the acid **I** with that of the signals of *tert*-butyltdimethylsilyl group protons and cyclodextrin frame of compounds **IX** and **X** we established that the complexes **XIV** and **XV** are of *guest–host* 1:1 composition.

Thus, indroduction of bulky *t*-butyl groups to the β-cyclodextrin molecule promotes formation of stable inclusion comppounds. Taking this into account, for the increase of "inclusing" power of α-cyclodextrin we prepared two its derivatives, **XVI** and **XVII**, that bear respectively 3 and 6 silyl residues in C^6 positions of glucoside fragments. These compounds were tested on the complex formation with acid **I**, with the same solvents and under the same conditions as were used for the synthesis and isolation of the complexes of β-cyclodextrin silyl derivatives **IX** and **X**. We found that

[1] Here and thereafter is noteworthy that it is possible that in solution exist labile inclusion complexes in equilibrium with the parent compounds, but in this work we consider a possibility of isolation of individual complexes.

the α-cyclodextrin derivative **XVI** with 3 silyl groups do not form inclusion compounds under these conditions while the derivative **XVII** bearing 6 silyl groups form inclusion compound **XVIII** of 1:1 composition that could be isolated, but only when either DMFA, or dioxane, or acetone were used as a solvent.

Thus, the cavity size, nature of solvent, character and number of substituents at the cyclodextrin carcass affect considerably the possibility of formation and isolation of the inclusion complexes with acid **I**. The carried out investigation opens practical pathways for preparation of important in pharmacological aspect inclusion compounds and new remedies forms based on the cyclodextrins and some their derivatives and remedy Ibuprofen.

EXPERIMENTAL

The ^{1}H NMR spectra were registered on a Bruker AC-200 instrument at the operating frequency 200.13 MHz, external reference TMS.

For thin layer chromatography were used aluminum plates with fixed silica gel layer (Silufol UV–254). Eluents: acetonitrile–water–25% aqueous ammonia 6 : 3 : 2 (A), benzene–ethanol 3 : 1 (B).

The α- and β-cyclodextrin acetyl derivatives **V**, **VI** and **XI** are prepared along the procedure in [5], the tosyl derivatives **VII**, **VIII** as in [6] and the silyl derivatives **IX**, **XVI** and **X**, **XVII** as in [7] and [8], respectively.

β-Cyclodextrin from "Sigma" was additionally carefully dried.

Inclusion compound of β-cyclodextrin with 1-(4-isobutylphenyl)propanoic acid (XII). To a solution of 0.20 g of β-cyclodextrin **III** in 4 ml of water at 70°C was added at stirring 0.07 g of acid **I**. The reaction mixture was left for cooling to room temperature, the precipitate dropped in 20 h was filtered off, washed with acetone (2×5 ml) and dried in a vacuum (1 mm Hg) for 4 h at 50°C. Yield 0.16 g (67%), mp 237–240°C (decomp.), R_f 0.80 (A). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): β-cyclodextrin: 3.29–3.63 m (42H; C^2H–C^5H, C^6H_2), 4.32–4.75 br.s (7H, C^6OH), 4.66–4.99 m (7H, C^1H), 5.56–5.89 br.s (14H; C^2OH, C^3OH); acid **I**: 0.84 d [6H; $(CH_3)_2$, $^3J_{HCCH}$ 6.4], 1.33 d (3H; CH_3, $^3J_{HCCH}$ 7.0), 1.70–1.95 m [1H, C*H*$(CH_3)_2$], 2.40 d (2H; CH_2, $^3J_{HCCH}$ 6.8), 3.58–3.72 m (1H, CH), 7.02–7.28 m (4H, CH_{arom}), 12.2 s [1H, C(O)OH]. Found, %: C 48.12; H 6.75. $C_{55}H_{88}O_{37}$. Calculated, %: C 49.25; H 6.61.

Inclusion compound of γ-cyclodextrin with 1-(4-isobutylphenyl)propanoic acid (XIII). To a solution of 0.20 g of γ-cyclodextrin **IV** in 4 ml of water at 70°C was added at stirring 0.06 g of acid **I**. The reaction mixture was left for cooling to room temperature, 20 h later the precipitate dropped was filtered off, washed with acetone (2×5 ml) and dried in a vacuum (1 mm Hg) for 4 h at 50°C. Yield 0.13 g (57%), mp 247–249°C (decomp.), R_f 0.83 (A). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, γ-cyclodextrin **IV**: 3.35–3.64 m (48H; C^2H–C^5H, C^6H_2), 4.39–4.69 br.s (8H, C^6OH), 4.81–5.09 m (8H, C^1H), 5.56–6.06 br.s (16H; C^2OH, C^3OH); acid **I**: 0.79–1.00 m [6H, $(CH_3)_2$], 1.30–1.48 m (3H, CH_3), 1.74–1.92 m [1H, C*H*$(CH_3)_2$], 2.36–2.46 m (2H, CH_2), 3.63–3.80 m (1H, CH), 7.05–7.29 m (4H, CH_{arom}), 12.40 s [1H, C(O)OH]. Found, %: C 47.91; H 6.68. $C_{61}H_{98}O_{42}$. Calculated, %: C 48.73; H 6.57.

Inclusion compound of tetra-[6-*O*-(*tert*-butyl)(dimethyl)silyl]-β-cyclodextrin with 1-(4-isobutylphenyl)propanoic acid (XIV). To a solution of 0.20 g of the β-cyclodextrin derivative **IX** in 4 ml of DMFA was added 0.05 g of acid **I** and the mixture was stirred for 24 h at 20°C. The reaction mixture was then poured to ice water (8 ml), the precipitate dropped was stirred and then filtered off, washed with water (2×5 ml) and dried in a vacuum (1 mm Hg) for 4 h at 50°C. Yield 0.19 g (83%), mp 218–220°C, R_f 0.72 (B). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz), β-cyclodextrin derivative **IX**: –0.14 to 0.30 br.s [24H, $Si(CH_3)_2$], 0.71–1.10 s [36H, $C(CH_3)_3$], 3.34–3.62 m (42H; C^2H–C^5H, C^6H_2), 3.85–4.06 br.s (3H, C^6OH), 4.70–4.92 m (7H, C^1H), 5.60–5.94 br.s (14H; C^2OH, C^3OH); acid **I**: –0.14–0.3 br.s [6H, $(CH_3)_2$], 1.33 d (3H; CH_3, $^3J_{HCCH}$ 7.0), 1.72–1.90 m [1H, C*H*$(CH_3)_2$], 2.45 d (2H; CH_2, $^3J_{HCCH}$ 7.0), 3.34–3.62 m (1H, CH), 7.07–7.20 m (4H, CH_{arom}), 12.3 s [1H, C(O)OH]. Found, %: C 53.66; H 7.98. $C_{79}H_{144}O_{37}Si_4$. Calculated, %: C 52.76; H 8.07.

Inclusion compound of per[6-*O*-(*tert*-butyl)(dimethyl)silyl]-β-cyclodextrin with 1-(4-isobutylphenyl)propanoic acid (XV). *a.* in DMFA. To a solution of 0.17 g of β-cyclodextrin derivative **X** in 4 ml of DMFA was added 0.04 g of acid **I** and the mixture was stirred for 24 h at 20°C. The reaction mixture was poured to ice water (8 ml) and stirred, and then the precipitate dropped was filtered off, washed with water (2×5 ml) and dried in a vacuum (1 mm Hg) for 4 h at 50°C.

b. In dioxane. The synthesis was carried out like in the method *a* from 0.17 g of β-cyclodextrin derivative **X** in 4 ml of dioxane and 0.04 g of acid **I**.

Yields: (method *a*) 0.17 g (89%), (method *b*) 0.14 g (74%), mp 209–211°C, R_f 0.72 (B). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): β-cyclodextrin derivative (**X**): –0.1 to 0.2 br.s [42H, $Si(CH_3)_2$], 0.71–1.10 s [63H, $C(CH_3)_3$], 3.32–3.92 m (42H; C^2H–C^5H, C^6H_2), 4.70–4.92 m (7H, C^1H), 5.62–6.00 br.s (14H; C^2OH, C^3OH); acid **I**: –0.10 to 0.20 br.s [6H, $(CH_3)_2$], 1.32 d (3H; CH_3, $^3J_{HCCH}$ 7.0), 1.70–1.90 m [1H, $CH(CH_3)_2$], 2.39 d (2H; CH_2, $^3J_{HCCH}$ 7.0), 3.32–3.93 m (1H, CH), 7.05–7.20 m (4H, CH_{arom}), 12.30 s [1H, C(O)OH]. Found, %: C 55.52; H 8.18. $C_{97}H_{186}O_{37}Si_7$. Calculated, %: C 54.41; H 8.26.

Inclusion compound of per[6-*O*-(*tert*-butyl)(dimethyl)silyl]-α-cyclodextrin with 1-(4-isobutylphenyl)propanoic acid (XVIII). *a.* in DMFA. To a solution of 0.20 g of α-cyclodextrin derivative **XVII** in 2 ml of DMFA was added 0.05 g of acid **I** and the mixture was stirred for 24 h at 20°C. The reaction mixture was then poured to ice water (4 ml), stirred and the precipitate dropped was filtered off, washed with water (2×3 ml) and dried in a vacuum (1 mm Hg) for 4 h at 50°C.

b. In dioxane. The synthesis was carried out like in the method *a*, from 0.15 g of α-cyclodextrin derivative **XVII** in 3 ml of dioxane and 0.04 g of acid **I**.

c. in acetone. The synthesis was carried out like in the method *a*, from 0.20 g of α-cyclodextrin derivative **XVII** in 15 ml of acetone and 0.05 g of acid **I**.

Yield: (method *a*) 0.15 g (75%), (method *b*) 0.11 g (65%), (method *c*). 0.07 g (41%), mp 242–244°C, R_f 0.65 (B). The ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz.): α-cyclodextrin derivative **XVII**: –0.02–0.25 br.s [36H, $Si(CH_3)_2$], 0.65–1.10 br.s [54H, $C(CH_3)_3$], 3.26–3.89 m (36H; C^2H–C^5H, C^6H_2), 4.68–4.90 m (6H, C^1H), 5.60–5.56 br.s (12H; C^2OH, C^3OH); acid **I**: –0.02 to 0.25 br.s [6H, $(CH_3)_2$], 1.30 d (3H; CH_3, $^3J_{HCCH}$ 6.0), 1.70–1.95 m [1H, $CH(CH_3)_2$], 2.38 d (2H; CH_2, $^3J_{HCCH}$ 7.1), 3.58–3.72 m (1H, CH), 7.05–7.19 m (4H, CH_{arom}), 12.30 s [1H, C(O)OH]. Found, % : C 56.32; H 8.58. $C_{85}H_{162}O_{32}Si_6$. Calculated, % : C 54.75; H 8.76.

ACKNOWLEDGMENTS

This work was supported financially by Russian Foundation for Basic Research (grant no. 08–03–00374a) and the Grant of the President of Russian Federation for supporting advanced scientific schools of Russian Federation (grant no. NSh-582.2008.3).

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