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Inclusion Complexes of β-Cyclodextrin with Dihydroxyphenols of Various Nature

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Abstract—The ways for the practical preparation of stable inclusion complexes of β-cyclodextrin with dihydroxyphenols of various nature are developed. Mutual orientation of hydroxy groups and the nature of the bridge in the bisphenols are shown to affect considerably their ability to the complex formation.

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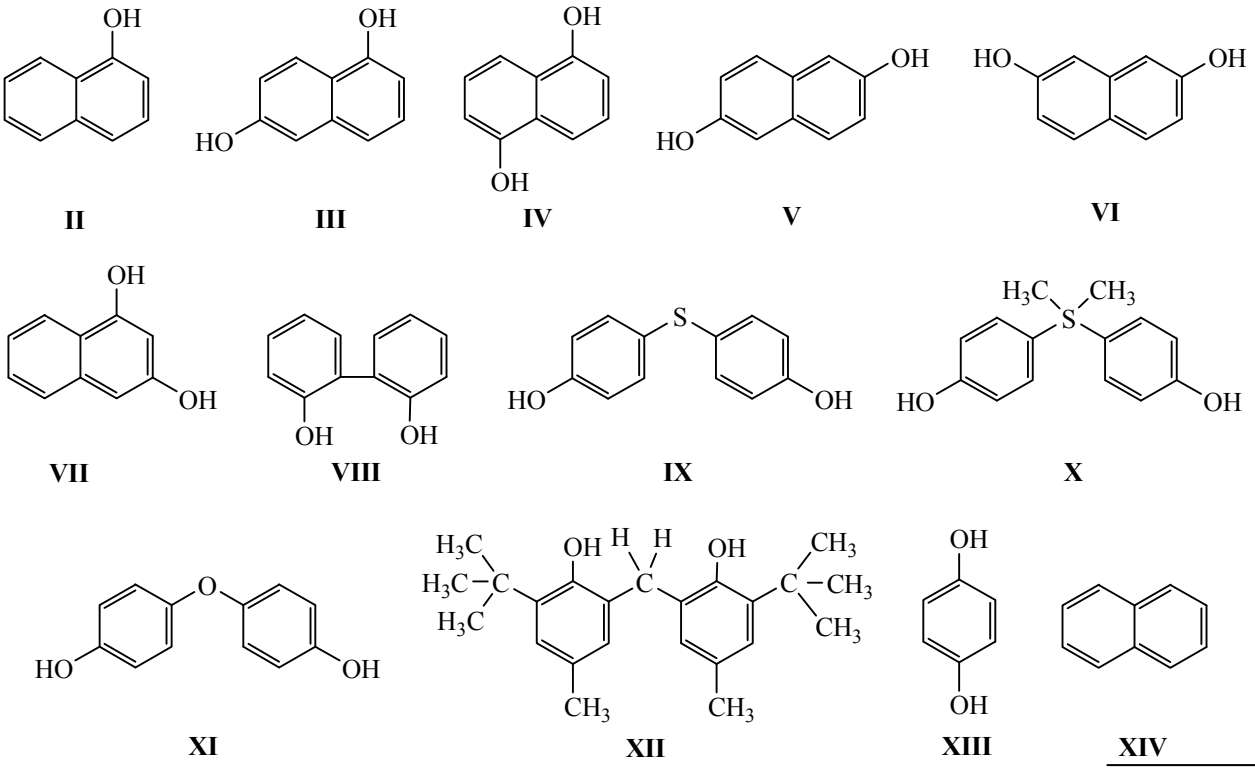
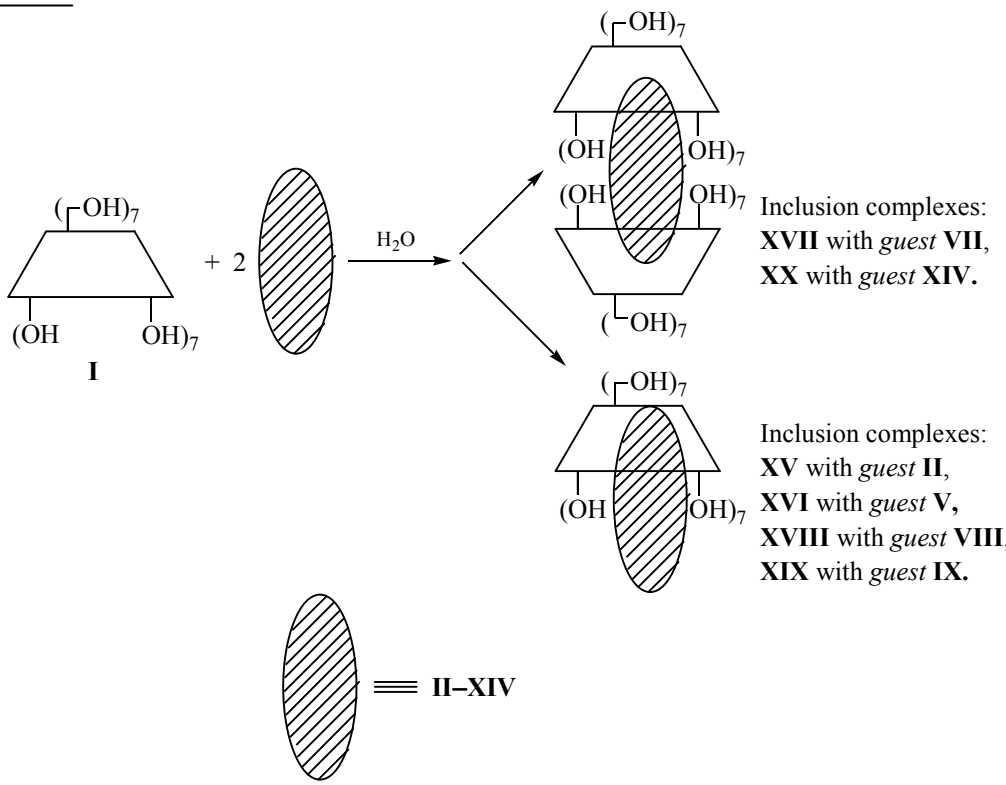
The cyclodextrins that possess internal cavity are known to form compounds of *guest – host* type with many compounds of aromatic nature. Such complexes find practical application for solving the interbranch science and technology problems (e.g., see [1]). Meanwhile, the inclusion complexes themselves often are unstable compounds and their synthesis can be based on different experimental approaches [2]. Earlier by an example of 1-(4-isobutylphenyl)propanoic acid (the substance of Ibuprofen drug) [3,4] and some other pharmacologically important aromatic monocarboxylic acids we developed practical ways for the synthesis of their stable inclusion compounds with cyclodextrin. We revealed that the nature of solvent and the procedure for the synthesis and isolation affect considerably the possibility of obtaining stable inclusion complexes and their stoichiometry, and therefore in each definite case the synthesis conditions and procedure for isolation should be selected specifically.

In this work we studied a possibility of formation of stable β-cyclodextrin (**I**) complexes with dihydroxyphenols **II–XIII** differing in the structure: either the phenols containing fused aromatic rings and hydroxy groups in various positions (naphthols **II–VII**), or bisphenols **VIII–XII** with bridges of different length and nature. Additionally, we studied a possibility of formation of the complexes with rather simple aromatic compounds: hydroquinone (**XIII**) and naphthalene (**XIV**). A feature of the selected compounds **II–XIII** is the existence of hydrophobic (aromatic) central nucleus that contains hydrophilic hydroxy groups on the periphery. The cyclodextrins are known to be of hydrophobic nature inside and hydrophilic at the outside [5], and this should promote formation of strong complexes with the above mentioned *guests*. Here we have to note that in solution labile inclusion complexes can form in equilibrium with parent components, but in this work we consider a possibility of isolation of stable inclusion compounds individually.

Like earlier [4], we studied formation of inclusion compounds of β-cyclodextrin with dihydroxyphenols **II–XIII** and naphthalene **XIV** by precipitation of the expected complex from hot (70ºC) aqueous solution or suspension of cyclodextrin with a respective *guest* taken in two-fold excess at slow cooling to 20ºC. The procedures of isolation were different depending on behavior of the *guest* and the expected complex in the reaction mixture. In the case of water-soluble *guest*s **II–VII, XIII** the initial reaction mixture was homogenous, and the sedimentated precipitates with the *guest*s **II, V** and **VII** were washed with acetone (all the *guests* **II–XIV** were well soluble in acetone while β-cyclodextrin insoluble) and dried in a vacuum. Individuality of the isolated complexes was confirmed by TLC and their compositions were revealed using ^{1}H NMR spectroscopy by comparison of intensity of the proton signals of β-cyclodextrin in the region 3.30–3.64 ppm and of the included *guest* in the region of 6.17–8.09 ppm (see Experimental). By this procedure complexes **XV–XVII** were prepared with *guests* **II, V** and **VII** with stoiciometric *guest–host* compositions



1:1, 1:1 and 1:2, respectively. With the water-soluble *guests* **III** and **IV** the precipitates formed on cooling turned to be the parent *guests* only, and they dissolved completely at the treatment with acetone. Taking into account that at the complex formation with cyclodextrin the complex might be well soluble in water at 20°C, we tested the filtrates of reaction mixtures in the experiments with *guests* **III** and **IV**: They were treated



with an excess of acetone and the precipitates were separated and dried in a vacuum. According to investigations using TLC and ^{1}H NMR spectroscopy, they contained β-cyclodextrin only without inclusion of a *guest*.

With *guests* **VI** and **XIII** the formation of a precipitate after cooling of the solution was not registered, therefore the reaction mixture was treated with acetone excess and the precipitates formed after treatment were separated, washed with acetone, dried, and analyzed like above. These precipitates also contained only β-cyclodextrin, without the included *guest*.

Guests **VIII–XII**, and **XIV** are insoluble in water under these experimental conditions, therefore for the interaction with cyclodextrin they were taken as suspensions. The reaction mixture then was filtered, but the precipitate filtered off was shown by means of above investigation to be free *guest*. Therefore then the filtrate was treated with acetone excess and the formed precipitate was treated and analyzed as above. In the cases of the *guests* **VIII, IX,** and **XIV** these precipitates consisted of the inclusion complexes **XVIII, XIX**, and **XX** with stoichiometry 1:1, 1:1 and 1:2, respectively. With gests **X, XI,** and **XII** all the precipitates formed at the treatment of filtrate with acetone consisted of the parent β-cyclodextrin and did not contain included guests.

Earlier we have shown a possibility of formation of stable complexes with cyclodextrin derivatives at the use as a solvent of dimethylformamide and with some other organic solvents [4]. Now we examined a possibility of formation of stable complexes in DMF and DMSO that well dissolve both β-cyclodextrin and *guests* **II–XIV**. We used the same general procedure of synthesis and isolation of expected complexes like in the case of *guests* **VI** and **XIII**. However, after treatment of reaction mixture with acetone we obtained the precipitate consisting only of parent β-cyclodextrin.

Thus, by the example of dihydroxynaphthalenes **II–VII** we can conclude that mutual orientation of hydroxy groups affects considerably the formation of stable inclusion complexes. In the case of bisphenols **VIII–XII** containing bridges differing in the length and nature, the inclusion complex formation is affected considerably by the nature of the connecting atom [carbon (**X, XII**), oxygen (**XI**), sulfur (**IX**)] or its absence (**VIII**), by the angle between the bonds connecting aromatic rings [in compounds **IX–XII** the angle is varied from 109° (**IX**) to 120°–124° (**XI**)], and by steric hindrances in the bisphenol (compounds **X** and **XII**).

This study opens the opportunity for practical preparation of stable inclusion complexes of β-cyclodextrin with dihydroxyphenols of different nature.

EXPERIMENTAL

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

For thin layer chromatography were used aluminum plates with fixed silica gel layer (Silufol UV-254), as eluents were applied systems MeCN–H_2O–25% aqueous NH_3, 6 : 3 : 2.

β-Cyclodextrin from "Sigma" was additionally dried.

Inclusion compound of β-cyclodextrin with 1,7-dihydroxynaphthalene (XV). To a solution of 0.20 g of β-cyclodextrin (**I**) in 4 ml of water at 70°C was added at stirring 0.06 g of naphthalene derivative **II**. The reaction mixture was left for cooling to room temperature, and 20 h later the precipitate formed was filtered off, washed with acetone (2 × 5 ml) and dried in a vacuum (1 mm Hg) at 50°C for 4 h. Yield 0.10 g (43%), mp 254–256°C (decomp.), R_f 0.83. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): β-cyclodextrin (**I**): 3.30–3.64 m (42H; C^2H–C^5H, C^6H_2), 4.31–4.62 br.s (7 H, C^6OH), 4.73–4.96 m (7H, C^1H), 5.58–5.88 br.s. (14H; C^2OH, C^3OH); naphthalene derivative **II**: 6.75 d (1H; C^2H_{ar}, $^3J_{HCCH}$ 7.3), 6.98–7.07 m (2H; C^3H_{ar}, C^6H_{ar}), 7.20 d (1H; C^4H_{ar}, $^3J_{HCCH}$ 8.1), 7.35 s (1H, C^8H_{ar}), 7.64 d (1H; C^5H_{ar}, $^3J_{HCCH}$ 8.8), 9.56 s (1H, C^7OH), 9.77 s (1H, C^1OH). Found, %: C 48.94; H 5.98. $C_{52}H_{78}O_{37}$. Calculated, %: C 48.22; H 6.07.

Inclusion compound of β-cyclodextrin with 2,6-dihydroxynaphthalene (XVI). Prepared by the same procedure as complex **XV** from 0.20 g of β-cyclodextrin (**I**) in 4 ml of water at 70°C and 0.06 g of naphthalene derivative **V**. Yield 0.10 g (43%), mp 255–257°C (decomp.), R_f 0.86. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): β-cyclodextrin (**I**): 3.30–3.63 m (42H; C^2H–C^5H, C^6H_2), 4.34–4.61 br.s (7 H, C^6OH), 4.67–5.00 m (7H, C^1H), 5.51–5.88 br.s (14H; C^2OH, C^3OH); naphthalene derivative **V**: 6.96 d (4H; C^1H_{ar}, C^3H_{ar}, C^5H_{ar}, C^7H_{ar}, $^3J_{HCCH}$ 9.0), 7.50 d (2H; C^4H_{ar}, C^8H_{ar}, $^3J_{HCCH}$ 8.4), 9.29 s (2H; C^2OH, C^6OH). Found, %: C 49.14; H 5.95. $C_{52}H_{78}O_{37}$. Calculated, %: C 48.22; H 6.07.

Inclusion compound of β-cyclodextrin with 1,3-dihydroxynaphthalene (XVII). Prepared by the same procedure as complex **XV** from 0.20 g of β-cyclodextrin (**I**) in 4 ml of water at 70°C and 0.06 g of naphthalene derivative **VII**. Yield 0.19 g (88%), mp 252–254°C (decomp.), R_f 0.87. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): β-cyclodextrin (**I**): 3.35–3.64 m (84H; C^2H–C^5H, C^6H_2), 4.30–4.67 br.s. (14 H, C^6OH), 4.75–4.94 m (14H, C^1H), 5.55–5.93 br.s (28H; C^2OH, C^3OH); naphthalene derivative **VII**: 6.49 d (1H; C^2H_{ar}, $^4J_{HCCCH}$ 2.1), 6.57 d (1H; C^4H_{ar}, $^4J_{HCCCH}$ 2.0), 7.80–8.02 m (4H; C^5H_{ar}, C^6H_{ar}, C^7H_{ar}, C^8H_{ar}), 9.45 s (1H, C^3OH), 10.04 s (1H, C^1OH). Found, %: C 47.53; H 6.06. $C_{94}H_{148}O_{72}$. Calculated, %: C 46.46; H 6.14.

Inclusion compound of β-cyclodextrin with 2,2'-binaphthol (XVIII). To a solution of 0.20 g of β-cyclodextrin (**I**) in 4 ml of water at 70°C was added at stirring 0.07 g of binaphthol **VIII**. The reaction mixture was left for cooling to room temperature and 20 h later it was poured to 7 ml of acetone and stirred. The precipitate formed was filtered off, washed with acetone (2 × 5 ml) and dried in a vacuum (1 mm Hg) for 4 h at 50°C. Yield 0.21 g (89%), mp 253–254°C (decomp.), R_f 0.32. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: β-cyclodextrin (**I**): 3.30–3.63 m (42H; C^2–C^5H, C^6H_2), 4.35–4.58 br.s (7H, C^6OH), 4.73–4.95 m (7H, C^1H), 5.68–5.75 br.s (14H; C^2OH, C^3OH); binaphthol **VIII**: 6.76–6.89 m (4H; $C^{3,3'}H_{ar}$, $C^{5,5'}H_{ar}$), 7.10–7.12 m (4H; $C^{4,4'}H_{ar}$, $C^{6,6'}H_{ar}$), 9.1–9.35 br.s (2H, $C^{2,2'}OH_{ar}$). Found, %: C 48.29; H 6.21. $C_{54}H_{80}O_{37}$. Calculated, %: C 49.09; H 6.10.

Inclusion compound of β-cyclodextrin with 4,4'-dihydroxydiphenyl sulfide (XIX). Prepared by the same procedure as complex **XVIII** from 0.20 g of β-cyclodextrin (**I**) in 4 ml of water and 0.08 g of bisphenol (**IX**). Yield 0.12 g (50%), mp 292–294°C (decomp.), R_f 0.80. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): β-cyclodextrin (**I**): 3.31–3.64 m (42H; C^2H–C^5H, C^6H_2), 4.38–4.60 br.s (7H, C^6OH), 4.73–4.97 m (7H, C^1H), 5.70–5.77 br.s (14H; C^2OH, C^3OH); bisphenol **IX**: 6.73 d (4H; $OCCH_{ar}$, $^3J_{HCCH}$ 8.4), 7.13 d (4H; $SCCH_{ar}$, $^3J_{HCCH}$ 8.4), 9.63 s (2H, $C^{4,4'}OH$). Found, %: C 48.66; H 5.78. $C_{54}H_{80}O_{37}S$. Calculated, %: C 47.93; H 5.96.

Inclusion compound of β-cyclodextrin with naphthalene (XX). Prepared by the same procedure as complex **XVIII** from 0.20 g of β-cyclodextrin (**I**) in 4 ml of water and 0.05 g of naphthalene **XIV**. Yield 0.08 g (38%), mp 262–264°C (decomp.), R_f 0.29. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: β-cyclodextrin (**I**): 3.35–3.64 m (84H; C^2H–C^5H, C^6H_2), 4.35–4.65 br.s (14 H, C^6OH), 4.75–4.99 m (14H, C^1H), 5.57–6.08 br.s (28H; C^2OH, C^3OH); naphthalene **XIV**: 7.45–7.78 m (4H; C^1H_{ar}, C^4H_{ar}, C^5H_{ar}, C^8H_{ar}), 7.85–8.09 m (4H; C^2H_{ar}, C^3H_{ar}, C^6H_{ar}, C^7H_{ar}). Found, %: C 47.50; H 6.07. $C_{94}H_{148}O_{70}$. Calculated, %: C 47.08; H 6.22.

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