ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 4, pp. 753–757. © Pleiades Publishing, Ltd., 2014.
Original Russian Text © G.I. Kurochkina, M.K. Grachev, T.A. Batalova, 2014, published in Zhurnal Obshchei Khimii, 2014, Vol. 84, No. 4, pp. 679–683.

Nanoscaled Inclusion Complexes of β-Cyclodextrin with Binuclear Compounds Based on Diols Containing Fragments of Selected Aromatic Monocarboxylic Acids

G. I. Kurochkina[a], M. K. Grachev[a], and T. A. Batalova[b]

[a] *Moscow Pedagogical State University, Nesvizhskii per. 3, Moscow, 119021 Russia*
e-mail: mkgrachev@yandex.ru

[b] *Amur State Medical Academy, Blagoveshchensk, Russia*
e-mail: Batalova_ta@mail.ru

Received July 22, 2013

Abstract—Stable nanoscaled mono- and dimeric inclusion complexes of β-cyclodextrin with hosts based on symmetric diols of various length containing fragments of benzoic, nicotinic, or isonicotinic acid were synthesized.

Keywords: β-cyclodextrin, inclusion complex, diol

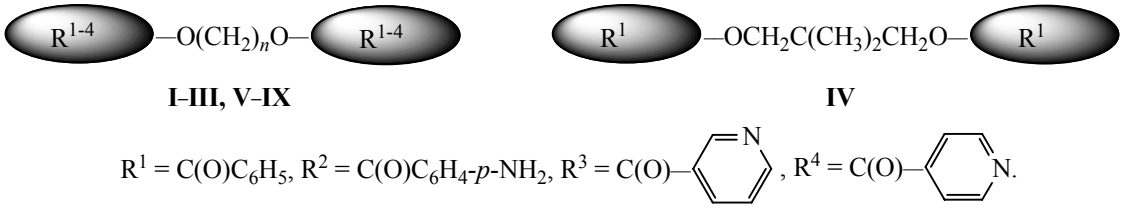
DOI: 10.1134/S1070363214040252

Recently we investigated practical ways to prepare inclusion compounds based on cyclodextrins with selected aromatic monocarboxylic acids interesting due to pharmaceutical possibilities [1]. In particular, we have determined the effect of the cavity size and solvent nature as well as the nature and number of substituents at cyclodextrin scaffold on the possibility to isolate individual complexes. Preliminary trials of some of the prepared complexes have shown their pharmaceutical potential [2]. In developing those studies, we investigated the preparation of stable (both against isolation and storage) inclusion compounds of β-cyclodextrin with *hosts*, consisting of two nuclei: two covalently bound fragments of either 2-(4-isobutylphenyl)propionic acid (Ibuprofen active component), acetylsalicylic acid (Aspirin active component), or benzoic acid. The length and the nature (diamide or diester) of the linkage between the nuclei were varied [3]. Such nanoscaled cyclodextrin derivatives showed good bioadhesion to gastrointestinal tract mucous; therefore, significant fraction of the introduced drug should be absorbed in the upper segment of gastrointestinal tract thus accelerating the desired pharmaceutical effect [4]. Moreover, using of the nanosized cyclodextrin complexes allows enhancement of bioavailability of lipophilic drugs at intravenous or oral administration along with increase in the solubility and absorption of the drug. Even at high dose the effect of such complexes on kidneys is reversible and similar to that of traditional drugs. Evidently, the efficiency enhancement due to better solubility and bioavailability should decrease the therapeutic dose and therefore reduce the total toxicity of the drug [5].

In view of the above, this work consisted of the study of the formation of inclusion complexes between β-cyclodextrin and symmetric binuclear *guests* based on diols of varied length (n = 2–4) containing fragments of benzoic (R^1OH), *p*-aminobenzoic (R^2OH), nicotinic (R^3OH), or isonicotinic (R^4OH) acid to be used in further pharmaceutical tests. The symmetric binuclear guests **I–IX** were prepared via one of the general methods: by interaction of the corresponding glycol with benzoic acid chloride (R^1Cl) in pyridine (procedure *a*, compounds **I, II**, and **IV**) or by interaction of the suitable 1,2- or 1,4-dihaloalkylene with sodium salt of the corresponding acid in DMF (procedure *b*, compounds **I, III**, and **V–IX**) (Scheme 1).

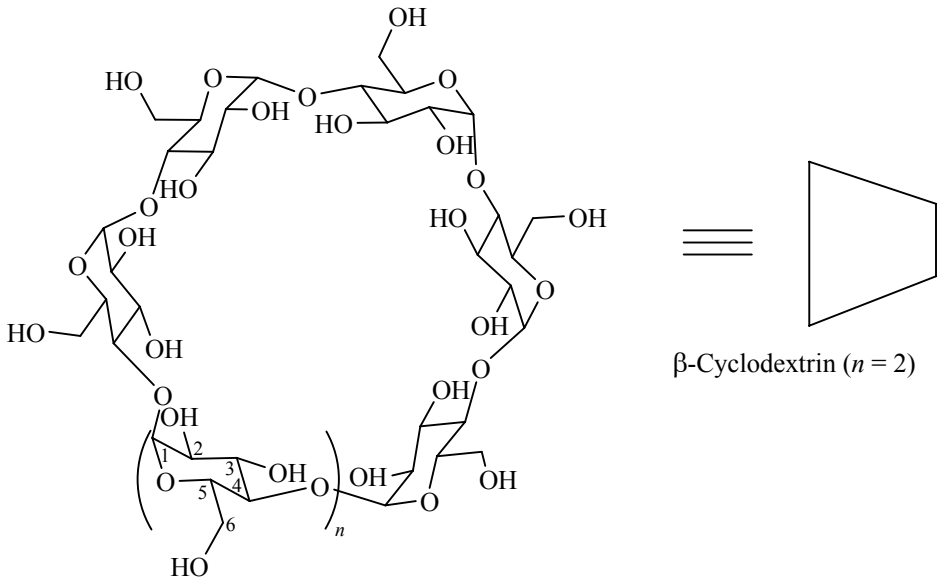
Similarly to the previous report [3], the formation of the inclusion compounds was studied by precipitation of the desired complex from hot (70°C) aqueous solution of two-fold molar excess of β-cyclodextrin with respect to the *guest* **I–IX** amount,

Scheme 1.

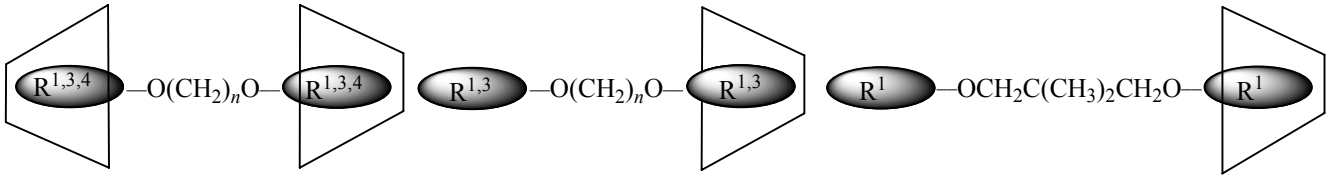


I: R^1, $n = 2$; **II**: R^1, $n = 3$; **III**: R^1, $n = 4$; **V**: R^2, $n = 2$; **VI**: R^3, $n = 2$; **VII**: R^3, $n = 4$; **VIII**: R^4, $n = 2$; **IX**: R^4, $n = 4$.

Scheme 2.



Scheme 3.



followed by slow cooling the reaction mixture to 20°C. All the guests were soluble in acetone (in contrast to β-cyclodextrin); therefore, the so formed precipitate was washed with acetone and dried in a vacuum. Individuality of the complexes was probed by TLC (**X, XI, XV**, and **XVI**); in the cases of complexes **XII–XIV** and **XVI**I the efficient eluents for TLC test were not found, and the product composition was determined from ^{1}H NMR spectra [comparison of integral intensity of β-cyclodextrin proton signals (see structure in the Scheme 2) at 3.21–5.80 ppm with that of the included *guest* protons].

It was shown that under the selected conditions of preparation and isolation, β-cyclodextrin formed stable dimeric complexes with *guests* **I, III**, and **VII–IX**; in the cases of *guests* **II, IV,VI** the stable monomeric complexes of B type were formed (**XV–XVII**, respectively). In the case of *guest* V no stable inclusion compound was formed. Complexes **X–XVII** were

isolated in 30–50% yields. The relatively severe conditions of the products drying in a vacuum (1 mmHg, 50°C, 4 h) confirmed the stability of the products. Similarly to the previous report [3], the structurally related *guests*, for example, compounds **I–IV** and **VI–IX** formed the stable complexes of varied stoichiometry. It was assumed [6] that the variation in the complex composition was due to intricate, hardly predictable parallel non-covalent interactions in the equilibrium system *guest–host*–solvent (Scheme 3).

This study opens the possibility towards practical use of preparation of the stable inclusion complexes of β-cyclodextrin with *guests* containing covalently bound fragments of pharmaceutically active components.

EXPERIMENTAL

^{1}H (400 MHz) and ^{13}C (100.53 MHz) NMR spectra of solutions in DMSO-d_6 were recorded using the Jeol ECX400 instrument, external reference TMS. Elemental analysis was performed using the FlashEA 1112HT instrument. Thin layer chromatography was carried out using aluminum plates with a fixed silica gel layer (Silufol-254); eluents were C_6H_6–dioxane, 3 : 1 (A), C_6H_6–$CHCl_3$, 1 : 1 (B), and aqueous 4 wt% solution of NH_3–EtOH–BuOH, 5 : 5 : 4 (C). β-Cyclodextrin (Merck) was dried prior to the experiments.

***O,O′*-Bisbenzoyl-1,2-ethylenediol (I).** *a*. 3.65 g of benzoyl chloride was added to the solution of 0.81 g of ethylene glycol in 4 mL of pyridine at stirring and cooling (20°C). The mixture was stirred during 1 h, the formed precipitate of pyridinium hydrochloride was filtered off. The filtrate was evaporated to oily state and triturated with 20 mL of water. The formed precipitate was washed with water (3 × 10 mL), dissolved in 3 mL of acetone, then 10 mL of water was added, and the precipitate was filtered off. The latter procedure was repeated, and the precipitate was dried in a vacuum. Yield 2.71 g (77%), mp 70–71°C (73°C [7]), R_f 0.71 (A). ^{1}H NMR spectrum (CCl_4), δ, ppm (*J*, Hz): 4.18–4.22 m (4H, CH_2O), 7.01 d.d (4H, C_6H^{meta}, ^3J 7.3, 7.4), 7.11 t (2H, C_6H^{para}, ^3J 7.4), 7.64 d (4H, C_6H^{ortho}, ^3J 7.3). Found, %: C 71.05; H 5.12. $C_{16}H_{14}O_4$. Calculated, %: C 71.10; H 5.22.

b. 0.52 g of sodium benzoate was added to the solution of 0.34 g of 1,2-dibromoethane in 15 mL of DMF, and the mixture was stirred at 120°C during 3 h. The formed precipitate was filtered off, washed with diethyl ether (2 × 2 mL), dried, washed with water (2 × 2 mL), and dried in a vacuum. Yield 0.29 g (60%), mp 70–71°C, R_f 0.71 (A). ^{1}H NMR spectrum (CCl_4) coincided with that of **I** prepared via procedure *a*.

***O,O′*-Bisbenzoyl-1,3-propylenediol (II)** was prepared similarly to compound **I** (procedure *a*) from 0.49 g of 1,3-propandiol and 1.83 g of benzoyl chloride in 4 mL of pyridine. Yield 1.44 g (78%), mp 50–52°C, R_f 0.49 (B). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.24–2.27 m (2H, $CH_2C\underline{H}_2CH_2$), 4.41–4.57 m (4H, CH_2O), 7.41 d.d (4H, C_6H^{meta}, ^3J 7.3), 7.54 t (2H, C_6H^{para}, ^3J 7.3), 8.05 d (4H, C_6H^{ortho}, ^3J 7.3). Found, %: C 71.95; H 5.50. $C_{17}H_{16}O_4$. Calculated, %: C 71.82; H 5.67.

***O,O′*-Bisbenzoyl-1,4-butylenediol (III)** was prepared similarly to compound **I** (procedure *b*) from 0.73 g of 1,4-dibromobutane and 0.97 g of sodium benzoate in 15 mL of DMF. Yield 0.736 g (78%), mp 64–65°C, R_f 0.68 (A). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.90–1.98 m (4H, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 4.35 t (4H, CH_2O, ^3J 6.0), 7.51 d.d (4H, C_6H^{meta}, ^3J 7.8), 7.64 t (2H, C_6H^{para}, ^3J 7.8), 7.97 d (4H, C_6H^{ortho}, ^3J 7.8). Found, %: C 71.65; H 5.52. $C_{18}H_{18}O_4$. Calculated, %: C 72.47; H 6.08.

***O,O′*-Bisbenzoyl-2,2-dimethyl-1,3-propylenediol (IV)** was prepared similarly to compound **I** (procedure *a*) from 0.677 g of 2,2-dimethyl-1,3-propanediol and 1.83 g of benzoyl chloride in 8 mL of pyridine. Yield 1.71 g (84%), mp 40–42°C, R_f 0.44 (B). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.66 s (6H, CH_3), 4.25 s (4H, CH_2O), 7.42 d.d (4H, C_6H^{meta}, ^3J 7.3, 7.4), 7.55 t (2H, C_6H^{para}, ^3J 7.4), 8.04 d (4H, C_6H^{ortho}, ^3J 7.3). Found, %: C 72.95; H 6.50. $C_{19}H_{20}O_4$. Calculated, %: C 73.06; H 6.45.

***O,O′*-Bis(*p*-aminobenzoyl)-1,2-ethylebediol (V)** was prepared similarly to compound **I** (procedure *b*) from 0.307 g of 1,2-dichloroethane and 1.00 g of sodium *p*-aminobenzoate in 15 mL of DMF. Yield 0.69 g (74%), mp 198–199°C, R_f 0.58 (A). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 4.40 br.s (4H, CH_2O), 5.95 s (4H, NH_2), 6.49–6.52 d (4H, C_6H^{meta}, ^3J 8.7), 7.57–7.60 d (4H, C_6H^{ortho}, ^3J 8.7). Found, %: C 64.05; H 5.42; N 9.25. $C_{16}H_{16}N_2O_4$. Calculated, %: C 63.99; H 5.37; N 9.33.

***O,O′*-Bisnicotinoyl-1,2-ethylenediol (VI)** was prepared similarly to compound **I** (procedure *b*) from 0.31 g of 1,2-dichloroethane and 0.92 g of nicotinic acid sodium salt in 15 mL of DMF. Yield 0.61 g (71%), mp 125–126°C, R_f 0.64 (A). ^{1}H NMR spectrum (DMSO-d_6),

δ, ppm (*J*, Hz): 4.64 br.s (4H, CH_2O), 7.53–7.56 m [2H, NCHCHCHCC(O)], 8.24–8.27 m [2H, NCHCH·CHCC(O)O], 8.76–8.79 m [2H, NCHCHCHCC(O)], 9.05 d [2H, NCHCC(O), ^4J 1.6]. Found, %: C 61.86; H 4.30; N 10.05. $C_{14}H_{12}N_2O_4$. Calculated, %: C 61.76; H 4.44; N 10.29.

***O,O′*-Bisnicotinoyl-1,4-butylenediol (VII)** was prepared similarly to compound **I** (procedure *b*) from 0.544 g of 1,2-dibromobutane and 0.73 g of nicotinic acid sodium salt in 15 mL of DMF. Yield 0.59 g (78%), mp 97–98°C, R_f 0.61 (A). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.83–1.88 m (4H, CH_2CH_2), 4.34 br.s (4H, CH_2O), 7.51–7.53 d.d [2H, NCHCHCHCC(O), ^3J 7.3, 7.8], 8.24 d [2H, NCHCH·CHCC(O)O, ^3J 7.8], 8.77 d [2H, NCHCHCHCC(O), ^3J 7.3], 9.04–9.05 d [2H, NCHCC(O), ^4J 1.6]. Found, %: C 62.85; H 5.30; N 9.45. $C_{16}H_{16}N_2O_4$. Calculated, %: C 63.99; H 5.37; N 9.33.

***O,O′*-Bis(isonicotinoyl)-1,2-ethylenediol (VIII)** was prepared similarly to compound **I** (procedure *b*) from 0.208 g of 1,2-dichloroethane and 0.61 g of isonicotinic acid sodium salt in 15 mL of DMF. Yield 0.45 g (79%), mp 165–166°C, R_f 0.53 (A). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 4.71 br.s (4H, CH_2O), 7.81–7.84 m (4H, NCHCH), 8.79–8.82 m (4H, NCH). Found, %: C 61.90; H 4.28; N 10.15. $C_{14}H_{12}N_2O_4$. Calculated, %: C 61.76; H 4.44; N 10.29.

***O,O′*-Bis(isonicotinoyl)-1,4-butylenediol (IX)** was prepared similarly to compound **I** (procedure *b*) from 0.41 g of 1,2-dibromobutane and 0.55 g of isonicotinic acid sodium salt in 15 mL of DMF. Yield 0.43 g (75%), mp 137–138°C, R_f 0.51 (A). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.89–1.93 m (4H, CH_2CH_2), 4.40–4.43 m (4H, CH_2O), 7.82–7.83 d (4H, NCHCH), 8.79–8.81 d (4H, NCH). Found, %: C 64.25; H 5.25; N 9.43. $C_{16}H_{16}N_2O_4$. Calculated, %: C 63.99; H 5.37; N 9.33.

Inclusion complex of β-cyclodextrin with *O,O′*-bisbenzoyl-1,2-ethylenediol (X). 0.024 g of diol I was added while stirring at 70°C to the solution of 0.20 g of β-cyclodextrin in 4 mL of water, and the mixture was stirred at 70°C during 1 h. The reaction mixture was cooled to room temperature, the formed precipitate was filtered off after 20 h, washed with acetone (3 × 3 mL), and dried in a vacuum at 1 mmHg during 4 h at 50°C. Yield 0.13 g (58%), mp 251–253°C (decomp.), R_f 0.75 (C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): β-cyclodextrin, 3.34–3.68 m (84H, C^2H–C^5H, C^6H_2), 4.15–4.18 m (14H, C^6OH), 4.85–4.86 br.s (14H, C^1H), 5.44–5.47 br.s (28H, C^2OH, C^3OH); diol **I**, 4.65 br.s (4H, CH_2O), 7.52 t (4H, C_6H^{meta}, ^3J 7.8), 7.64–7.67 t (2H, C_6H^{para}, ^3J 7.8), 7.98 d (4H, C_6H^{ortho}, ^3J 7.7). Found, %: C 47.35; H 6.12. $C_{100}H_{154}O_{74}$. Calculated, %: C 47.28; H 6.11.

Inclusion complex of β-cyclodextrin with *O,O′*-bisbenzoyl-1,4-butylenediol (XI) was prepared similarly from 0.34 g of β-cyclodextrin and 0.045 g of diol **III** in 10 mL of water. Yield 0.21 g (55%), mp 201–202°C (decomp.), R_f 0.72 (C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): β-cyclodextrin, 3.32–3.68 m (84H, C^2H–C^5H, C^6H_2), 4.19–4.21 m (14H, C^6OH), 4.85–4.86 br.s (14H, C^1H), 4.48–5.49 br.s (28H, C^2OH, C^3OH); diol **III**, 1.87–1.93 m (4H, $CH_2CH_2CH_2CH_2$), 4.38 br.s (4H, CH_2O), 7.52 t (4H, C_6H^{meta}, ^3J 7.8), 7.65 t (2H, C_6H^{para}, ^3J 7.8), 7.98 d (4H, C_6H^{ortho}, ^3J 7.7). Found, %: C 47.60; H 6.12. $C_{102}H_{158}O_{74}$. Calculated, %: C 47.70; H 6.20.

Inclusion complex of β-cyclodextrin with *O,O′*-bisnicotinoyl-1,4-butylenediol (XII) was prepared similarly from 0.34 g β-cyclodextrin and 0.045 g of diol **VII** in 10 mL of water. Yield 0.12 g (31%), mp 302–303°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): β-cyclodextrin, 3.32–3.68 m (84H, C^2H–C^5H, C^6H_2), 4.16–4.18 m (14H, C^6OH), 4.85–4.86 br.s (14H, C^1H), 5.45–5.47 br.s (28H, C^2OH, C^3OH); diol VII, 1.91–1.95 m (4H, CH_2CH_2), 4.41 br.s (4H, CH_2O), 7.54–7.56 d.d [2H, NCHCHCHCC(O), ^3J 5.6, ^4J 0.8], 8.27–8.29 d.d [2H, NCHCHCHCC(O)O, ^3J 7.9, ^4J 2.1], 8.79–8.82 d.d [2H, NCHCHCHCC(O), ^3J 5.9, ^4J 1.6], 9.09 d [2H, NCHCC(O), ^4J 1.6]. Found, %: C 46.63; H 6.05; N 1.15. $C_{100}H_{156}N_2O_{74}$. Calculated, %: C 46.73; H 6.12; N 1.09.

Inclusion complex of β-cyclodextrin with *O,O′*-bis(isonicotinoyl)-1,2-ethylenediol (XIII) was prepared similarly from 0.49 g of β-cyclodextrin and 0.0459 g of diol **VIII** in 10 mL of water. Yield 0.186 g (34%), mp 284–285°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): β-cyclodextrin, 3.33–3.70 m (84H, C^2H–C^5H, C^6H_2), 4.71–4.88 m (14H, C^6OH), 4.85–4.86 br.s (14H, C^1H), 5.45–5.48 br.s (28H, C^2OH, C^3OH); diol VIII, 4.17 br.s (4H, CH_2O), 7.82–7.83 d (4H, NCHCH, ^3J 4.5), 8.80 d (2H, NCH, ^3J 4.5). Found, %: C 46.48; H 6.28; N 1.15. $C_{98}H_{152}N_2O_{74}$. Calculated, %: C 46.30; H 6.03; N 1.10.

Inclusion complex of β-cyclodextrin with *O,O′*-bis(isonicotinoyl)-1,4-butylenediol (XIV) was prepared similarly from 0.50 g of β-cyclodextrin and 0.066 g of diol **IX** in 10 mL of water. Yield 0.17 g

(30%), mp 277–278°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): β-cyclodextrin, 3.34–3.68 m (84H, C^2H–C^5H, C^6H_2), 4.15–4.17 m (14H, C^6OH), 4.85–4.86 br.s (14H, C^1H), 5.44–5.47 br.s (28H, C^2OH, C^3OH); diol IX, 1.90–1.94 m (4H, $CH_2C\underline{H}_2$), 4.43–4.45 m (4H, CH_2O), 7.81–7.82 m (4H, NCHC$\underline{H}$), 8.79–8.80 m (4H, NCH). Found, %: C 46.83; H 6.15; N 1.05. $C_{100}H_{156}N_2O_{74}$. Calculated, %: C 46.73; H 6.12; N 1.09.

Inclusion complex of β-cyclodextrin with *O,O′*-bisbenzoyl-1,3-propylenediol (XV) was prepared similarly from 0.227 g of β-cyclodextrin and 0.0284 g of diol **II** in 10 mL of water. Yield 0.078 g (55%), mp 254–256°C (decomp.), R_f 0.68 (C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): β-cyclodextrin, 3.32–3.71 m (42H, C^2H–C^5H, C^6H_2), 4.38–4.51 m (7H, C^6OH), 4.73–4.79 br.s (7H, C^1H), 5.59–5.68 br.s (7H, C^3OH), 5.69–5.73 br.s (7H, C^2OH); diol II, 2.12–2.21 m (2H, $CH_2C\underline{H}_2CH_2$), 4.39–4.41 m (4H, CH_2O), 7.45 t (4H, C_6H^{meta}, ^3J 7.8), 7.61 t (2H, C_6H^{para}, ^3J 7.3), 7.93 d (4H, C_6H^{ortho}, ^3J 7.3). Found, %: C 50.05; H 6.20. $C_{59}H_{86}O_{39}$. Calculated, %: C 49.93; H 6.11.

Inclusion complex of β-cyclodextrin with *O,O′*-bisbenzoyl-2,2-dimethyl-1,3-propylenediol (XVI) was prepared similarly from 0.227 g of β-cyclodextrin and 0.0312 g of diol **IV** in 4 mL of water. Yield 0.068 g (47%), mp 272–274°C (decomp.), R_f 0.51 (C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): β-cyclodextrin, 3.21–3.69 m (42H, C^2H–C^5H, C^6H_2), 4.42–4.45 m (7H, C^6OH), 4.77–4.83 br.s (7H, C^1H), 5.61–5.75 br.s (7H, C^3OH); 5.76–5.80 br.s (7H, C^2OH); diol **IV**, 1.08 s (6H, CH_3), 4.17 s (4H, CH_2O), 7.48 t (4H, C_6H^{meta}, ^3J 7.8), 7.62 t (2H, C_6H^{para}, ^3J 7.8), 7.95 d (4H, C_6H^{ortho}, ^3J 7.3). Found, %: C 50.75; H 6.17. $C_{61}H_{90}O_{39}$. Calculated, %: C 50.62; H 6.27.

Inclusion complex of β-cyclodextrin with *O,O′*-bisnicotinoyl-1,2-ethylenediol (XVII) was prepared similarly from 0.363 g of β-cyclodextrin and 0.0436 g of diol **VI** in 10 mL of water. Yield 0.092 g (41%), mp 306–307°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): β-cyclodextrin, 3.32–3.68 m (42H, C^2H–C^5H, C^6H_2), 4.20–4.22 m (7H, C^6OH), 4.85–4.86 br.s (7H, C^1H), 5.49–5.52 br.s (14H, C^2OH, C^3OH); diol **VI**, 4.70 br.s (4H, CH_2O), 7.55–7.58 d.d [2H, NCHC$\underline{H}$CHCC(O), ^3J 4.9], 8.28–8.30 d.d [2H, NCHCHC$\underline{H}$CC(O)O, ^3J 7.9, ^4J 2.1], 8.81–8.82 d.d [2H, NC$\underline{H}$CHCHCC(O), ^3J 7.9, ^4J 1.7], 9.10 d [2H, NC$\underline{H}$CC(O), ^4J 1.7]. Found, %: C 47.91; H 5.77; N 1.89. $C_{56}H_{82}N_2O_{39}$. Calculated, %: C 47.80; H 5.87; N 1.99.

ACKNOWLEDGMENTS

This work was financially supported by Russian Foundation for Basic Research (project no. 12-03-00147a).

REFERENCES

1. Kurochkina, G.I., Kudryavtseva, N.A., Grachev, M.K., Lysenko, S.A., Vasyanina, L.K., and Nifant'ev, E.E., *Russ. J. Gen. Chem*., 2007, vol. 77, no. 3, p. 442; Senyushkina, I.A., Kurochkina, G.I., Grachev, M.K., Grinberg, V.A., Batalova, T.A., and Nifant'ev, E.E., *Russ. J. Gen. Chem*., 2009, vol. 79, no. 6, p. 1167; Grachev, M.K., Senyushkina, I.A., Kurochkina, G.I., Lysenko, K.A., Vasyanina, L.K., and Nifant'ev, E.E., *Russ. J. Gen. Chem*., 2010, vol. 46, no. 10, p. 1933.
2. Sergievich A.A., Grachev, M.K., Kurochkina, G.I., Batalova, T.A., and Plastinin, M.L., *Yakut. Med. Zh.*, 2011, no. 1, p. 101; Batalova, T.A., Dorovskikh, V.A., Grachev, M.K., Kurochkina, G.I., Charaev, A.A., Plastinin, M.L., and Sergievich, A.A., *Vopr. Eksp. Biol. i Med*., 2011, no. 1, p. 42.
3. Grachev, M.K., Charaev, A.A., Kurochkina, G.I., Batalova, T.A., Soboleva, N.O., Vasyanina, L.K., and Nifant'ev, E.E., *Russ. J. Gen. Chem*., 2011, vol. 81, no. 10, p. 2129.
4. Geze, A., Aous, S., Baussane, I., Putaux, J.L., Defaye, J., and Wouessiddjewe, D.G., *Int. J. Pharm*., 2002, vol. 242, p. 301.
5. Rajewski, R.A. and Stella, V.J., *J. Pharm. Sci*., 1996, vol. 85, p. 1142.
6. Sliwa, W. and Grizek, T., *Chem. Heterocycl. Comp*., 2005, vol. 41, no. 11, p. 1343.
7. Bourne, J.E., Stacey, M., Tatlow, J.C., and Tedder, J.M., *J. Am. Chem. Soc*., 1949, vol. 69, p. 2976.