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Behaviour Peculiarities of Some Dimeric β-Cyclodextrin Derivatives under Reaction with Organic Acids of Various Nature

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During the attempts to obtain inclusion compounds of "guest-host" type of dimeric β-cyclodextrin derivatives, formed by the ether bond bridge, with organic acids of various nature an unusual easy cleavage of ether bond occurrs with the formation of inclusion compound of β-cyclodextrin with corresponding acid. Dimeric dicationic β-cyclodextrin derivatives form corresponding inclusion compounds with molecular ratio of 1:1. The possible mechanisms of such behavior are proposed. The structure of inclusion compounds was confirmed by ^{1}H and ^{13}C NMR spectroscopy, and elemental analysis.

Keywords: Cyclodextrins, dimeric derivatives, inclusion compounds, guest, host, molecular containers, ether bond, NMR spectroscopy.

Особенности поведения некоторых димерных производных β-циклодекстрина при реакции с органическими кислотами разной природы

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При попытке получения соединений включения типа «гость-хозяин» димерных производных β-циклодекстрина, образованных мостиком из простой эфирной связи, с органическими кислотами разной природы неожиданно произошел легкий гидролиз простой эфирной связи с образованием соединений включения β-циклодекстрина с соответствующей кислотой. Димерные дикатионные производные β-циклодекстрина образовывали соответствующие соединения включения молекулярного отношения 1:1. Предложены возможные механизмы такого поведения. Строение полученных соединений включения подтверждено спектроскопией ЯМР ^{1}H, ^{13}C и элементным анализом.

Ключевые слова: Циклодекстрины, димерные производные, соединения включения, гость, хозяин, молекулярные контейнеры, простая эфирная связь, спектроскопия ЯМР.

Introduction

It is well known that α-, β-, and γ-cyclodextrins (CDs) (Figure 1) are unique objects which have found wide application in various fields of science and technics (see, for instance, monograph[1]). The main interest in cyclodextrins is caused by their cyclic structure and the presence of an internal hydrophobic cavity capable of forming *guest–host* inclusion compounds with various organic substrates. This CDs property attracts much attention in pharmacology where they used as molecular containers for numerous drugs. Such encapsulation usually enhances bioaccessibility, solubility in water and protects drugs from biodegradation.

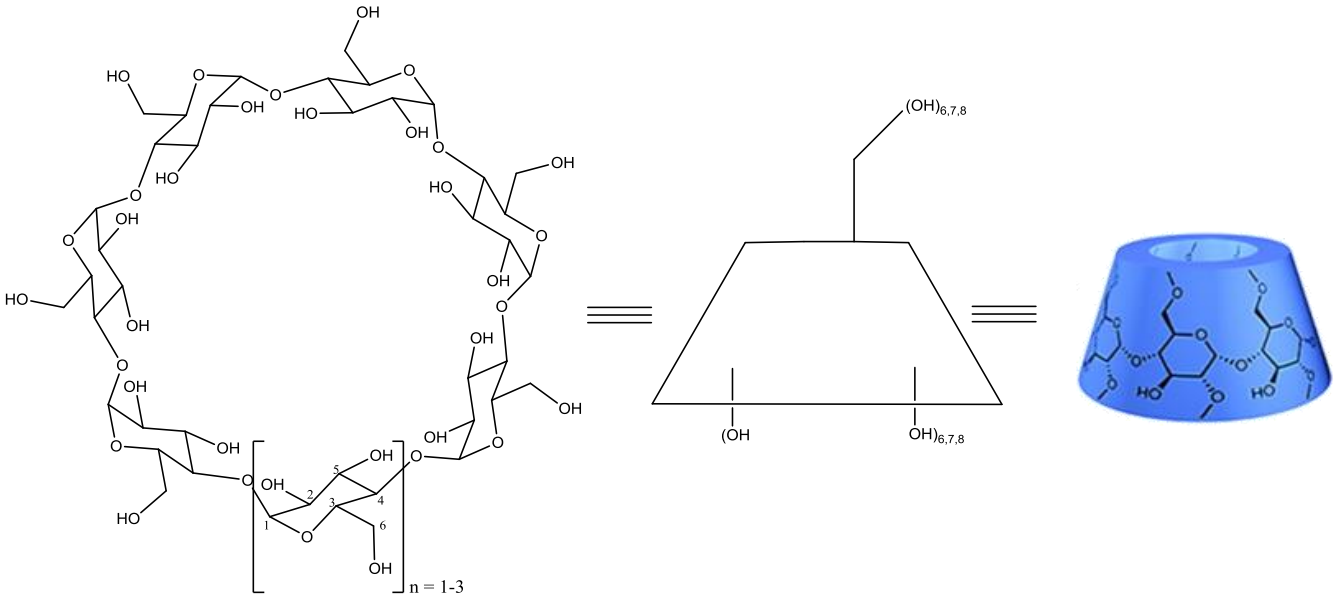

Figure 1. Chemical structure of α-, β-, and γ-cyclodextrins (n = 1, 2, 3, respectively).

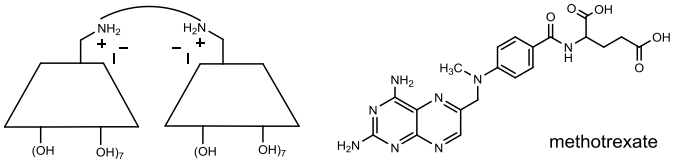

Figure 2. Dimeric dicationic β-CD and methotrexate.

Recently, we paid our attention to dimeric derivatives of β-CD, which due to the presence of two internal cyclodextrin cavities in one molecule, their spatial proximity and other properties of these derivatives, have an increased so-called *cooperative* (not *additive*) effect with respect to the inclusion of numerous guests.[2] Thus, for example, dimeric dicationic derivative of β-CD (Figure 2), as a ditopic *host*, easily forms more strong inclusion compound with the well-known antitumour compound *methotrexate* than original monomeric β-CD **1**.[3,4]

It is important that primary hydroxyl groups of β-CD are easily undergo etherification by alcohols and glycols with the formation of corresponding monomeric and dimeric CD derivatives containing ether bond.[5] This reveals high opportunities for the direct synthesis (with no using protective groups) of numerous β-CD dimeric derivatives.

Another little-known but important aspect of dimeric CDs application is that they can be represented as so-called *bolaamphiphiles*, *i.e.*, amphiphilic molecules with two hydrophilic groups at the ends of the relatively long hydrophobic hydrocarbon chain. The presence of the second hydrophilic head dramatically increases the solubility in water, increases the critical concentration of the micelle formation, which allows these bolaamphiphiles to form a variety of ensembles in water, *i.e.*, spheres, cylinders, disks, vesicles, *etc*. Therefore, it was of a special interest to consider the application opportunity of some dimeric CD derivatives as *hosts* for *guests* representing practical interest.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECX-400 spectrometer at the frequencies 399.78 and 100.53 MHz, respectively. The ^{1}H and ^{13}C chemical shifts are presented relative to tetramethylsilane in a solution of [D6]DMSO. Elemental analyses were performed on a FlashEA 1112 HT instrument. For compounds **6**, **10** – **18** thin layer chromatography was performed on aluminum plates with fixed layer of SiO_2 (Silufol UV-254), eluent: acetonitrile-chloroform (1:1).

*Di-6,6′-dideoxy-6,6′-(1-methylethane-1,2-diyldiammonium)-β-cyclodextrin diiodide (**6**).* 0.0296 g (0.40 mmol) of 1-methyl-1,2-diamine were added at stirring to a solution of 1.00 g (0.80 mmol) of mono(6-iodo-6-deoxy)-β-cyclodextrin[6] in 15 mL of DMF. The solution was stirred for 40 hrs at 120-130 °C. The reaction mixture was concentrated in a vacuum to 5 mL, diluted with 5 mL of acetone, the mixture was stirred, the separated precipitate was filtered off, washed consecutively with acetone (2×5 mL), diethyl ether (2×5 mL), and dried in a vacuum (1 mm Hg) for 4 hrs at 80 °C. Yield: 0.73 g (71%); m.p. 252-254 °C (decomp.); R_f =0.69. Found, %: C 40.35, H 5.76, N 1.04. $C_{87}H_{148}I_2N_2O_{68}$ requires C 40.76, H 5.82, N 1.09. ^{1}H NMR δ_H ppm: 1.05 t (3H, CH_3, ^3J = 6.8 Hz), 2.45-2.48 m (1H, NC*H*(CH_3)), 2.51 d (2H, NCH_2, ^3J = 7.3 Hz), 3.29-3.32 m (28H, C^6H_2), 3.57-3.59 m (56H, C^2H-C^5H), 4.44 br.s (12H, C^6OH), 4.78-4.83 m (14H, C^1H), 5.72 br.s (28H, C^2OH, C^3OH), 7.43 s (4H, $(NH^+_2)_2$). ^{13}C NMR δ_C ppm: 19.2 (CH_3), 30.1 (CH), 37.5 (NCH_2), 56.3 ($C^{6'1}$), 60.4 (C^6), 69.2 ($C^{5'}$), 72.5 (C^5), 72.9(C^2), 73.6 (C^3), 82.0 (C^4), 84.0 ($C^{4'}$), 102.5 (C^1).

*Inclusion compound **10**. A)* 0.056 g (0.27 mmol) of 2-(4-isobutylphenyl)propionic acid **7** were added at stirring to a solution of 0.212 g (0.09 mmol) of dimer **2** in 5 mL of H_2O. The solution was stirred for 4 hrs at 70 °C and stood overnight at 20 °C. The separated precipitate was filtered off, washed consecutively with water (5 mL), acetone (5 mL), and dried in a vacuum (1 mm Hg) for 4 hrs at 80 °C. Yield: 0.122 g; m.p. 251-254 °C (decomp.);

[1] Hereinafter strokes mark the CD C6' carbon atoms of a glycoside unit at which the hydroxyl groups are substituted; C5' and C4' carbon atoms do not contain substituents, but, in NMR ^{13}C spectra, they respond to the presence of substituents at C6' in the same glycoside unit.

R_f = 0.69. Found, %: C 48.76, H 6.55. $C_{55}H_{88}O_{37}$ requires C 49.25, H 6.61. ^{1}H NMR δ_H ppm: *β-cyclodextrin* ***1***: 3.29-3.32 m (14H, C^6H_2), 3.57-3.59 m (28H, C^2H-C^5H), 4.44 br.s (7H, C^6OH), 4.78-4.79 m (7H, C^1H), 5.67 br.s (14H, C^2OH, C^3OH); *2-(4-isobutylphenyl)propionic acid* ***7***: 0.82 d (6H, $(CH_3)_2$, ^3J = 6.4 Hz), 1.29 d (3H, CH_3, ^3J = 7.3 Hz), 1.76 (m, 1H, CH), 2.37 d (2H, CH_2, ^3J = 6.9 Hz), 3.75 s (1H, C*H*(CH_3)COOH), 7.06 d (2H, $C_{arom}H$, ^3J = 7.8 Hz), 7.14 d (2H, $C_{arom}H$, ^3J = 8.3 Hz), 12.21 s (1H, COOH). ^{13}C NMR δ_C ppm: *β-cyclodextrin* ***1***: 60.4 (C^6), 72.5-73.6 (C^2, C^3, C^5), 82.0 (C^4), 102.5 (C^1); *2-(4-isobutylphenyl)propionic acid* ***7***: 19.3 (CH_3), 22.7 ($(CH_3)_2$), 30.0 (CH), 39.9 (*C*H(CH_3)COOH), 40.6 (CH_2), 127.8 (C^3_{arom}, C^5_{arom}), 129.9 (C^2_{arom}, C^6_{arom}), 139.2 (C^4_{arom}), 140.1 (C^1_{arom}), 176.1 (COOH). *B*) Inclusion compound **10** was prepared similarly to method *A* from 0.0526 g (0.255 mmol) of 2-(4-isobutylphenyl)propionic acid (**7**) and 0.20 g (0.085 mmol) of dimer **3**. Yield: 0.102 g; m.p. 248-251 °C (decomp.); R_f = 0.70. Data of ^{1}H and ^{13}C NMR spectra were similar to those registered for the inclusion compound **10** obtained by method *A*.

Inclusion compound ***11*** was prepared similarly to inclusion compound **10** from 0.0311 g (0.255 mmol) of benzoic acid **8** and 0.20 g (0.085 mmol) of dimer **3**. Yield: 0.060 g; m.p. 219-222 °C (decomp.); R_f = 0.56. Found, %: C 46.35, H 6.03. $C_{49}H_{76}O_{37}$ requires C 46.82, H 6.09. ^{1}H NMR δ_H ppm: *β-cyclodextrin* ***1***: 3.32-3.58 m (14H, C^6H_2), 3.59-3.62 m (28H, C^2H-C^5H), 4.44 br.s (7H, C^6OH), 4.78-4.79 m (7H, C^1H), 5.67 br.s (14H, C^2OH, C^3OH); *benzoic acid* ***8***: 7.47 d (2H, $C_{meta}H$, ^3J = 7.8 Hz), 7.89 d (1H, $C_{para}H$, ^3J = 7.6 Hz), 7.91 d (2H, $C_{orto}H$, ^3J = 6.8 Hz), 12.95 s (1H, COOH). ^{13}C NMR δ_C ppm: *β-cyclodextrin* ***1***: 60.4 (C^6), 72.5-73.6 (C^2, C^3, C^5), 82.0 (C^4), 102.5 (C^1); *benzoic acid* ***8***: 129.1 (C_{meta}), 129.8 (C_{para}), 131.3 (C_{ortho}), 133.4 (C_{ipso}), 167.9 (COOH).

Inclusion compound ***12*** was prepared similarly to inclusion compound **10** from 0.0133 g (0.13 mmol) of valeric acid **9** and 0.10 g (0.0433 mmol) of dimer **3**. Yield: 0.053 g; m.p. 217-220 °C (decomp.), R_f = 0.59. Found, %: C 45.17, H 6.45. $C_{47}H_{80}O_{37}$ requires C 45.63, H 6.52. ^{1}H NMR δ_H ppm: *β-cyclodextrin* ***1***: 3.29-3.31 m (14H, C^6H_2), 3.58-3.62 m (28H, C^2H-C^5H), 4.43 br.s (7H, C^6OH), 4.78-4.79 m (7H, C^1H), 5.67 br.s (14H, C^2OH, C^3OH); *valeric acid* ***9***: 0.84 t (3H, CH_3, ^3J = 7.3 Hz), 1.23-1.25 m (2H, CH_3CH_2), 1.42-1.44 m (2H, CH_2CH_2COOH), 2.15 d (2H, CH_2COOH, ^3J = 7.3 Hz), 11.94 s (1H, COOH). ^{13}C NMR δ_C ppm: *β-cyclodextrin* ***1***: 60.4 (C^6), 72.5-73.6 (C^2, C^3, C^5), 82.0 (C^4), 102.5 (C^1); *valeric acid* ***9***: 14.0 (CH_3), 22.2 (CH_3CH_2), 26.9 (CH_2CH_2COOH), 33.8 (CH_2COOH), 178.1 (COOH).

Inclusion compound ***13*** was prepared similarly to inclusion compound **10** from 0.0241 g (0.117 mmol) of 2-(4-isobutylphenyl)propionic acid **7** and 0.10 g (0.039 mmol) of dimer **6**. Yield: 0.0551 g (51%); m.p. 248-250 °C (decomp.), R_f = 0.53. Found, %: C 43.00, H 5.90, N 0.95. $C_{100}H_{166}N_2I_2O_{70}$ requires C 43.36, H 6.04, N1.01. ^{1}H NMR δ_H ppm: *dimer* ***6***: 1.07 t (3H, CH_3, ^3J = 6.8 Hz), 2.45-2.48 m (1H, NC*H*(CH_3)), 2.52 d (2H, NCH_2, ^3J = 7.3 Hz), 3.29-3.32 m (28H, C^6H_2), 3.57-3.59 m (56H, C^2H-C^5H), 4.44 br.s (12H, C^6OH), 4.78-4.83 m (14H, C^1H), 5.72 br.s (28H, C^2OH, C^3OH) 7.41-7.45 m (4H, $(NH^+_2)_2$); *2-(4-isobutylphenyl)propionic acid* ***7***: 0.80 d (6H, $(CH_3)_2$ ^3J = 6.4 Hz), 1.34 d (3H, CH_3, ^3J = 6.8 Hz), 1.74-1.79 m (1H, CH), 2.38 d (2H, CH_2, ^3J = 6.9 Hz), 3.79 s (1H, C*H*(CH_3)COOH), 7.07 d (2H, $C_{arom}H$, ^3J = 8.2 Hz), 7.16 d (2H, $C_{arom}H$, ^3J = 7.8 Hz), 12.14 s (1H, COOH). ^{13}C NMR δ_C ppm: *dimer* ***6***: 30.0 (CH_3), 32.5 (NCH(CH_3)*C*H$_2$N), 56.3 ($C^{6'}$), 57.1 (CH), 60.4 (C^6), 69.2 ($C^{5'}$), 72.5 (C^5), 72.9(C^2), 73.6 (C^3), 82.0 (C^4), 84.0 ($C^{4'}$), 102.5 (C^1); *2-(4-isobutylphenyl)propionic acid* ***7***: 19.2 (CH_3), 22.7 ($(CH_3)_2$), 30.1 (CH), 40.5 (*C*H(CH_3)COOH), 44.8 (CH_2), 126.0-127.6 (C^3_{arom}, C^5_{arom}), 128.6-129.4 (C^2_{arom}, C^6_{arom}), 139.3 (C^4_{arom}), 139.9 (C^1_{arom}), 176.3 (COOH).

Inclusion compound ***14*** was prepared similarly to inclusion compound **10** from 0.0151 g (0.124 mmol) of benzoic acid **8** and 0.106 g (0.0413 mmol) of dimer **6**. Yield: 0.0532 g (48%); m.p. 223-227 °C (decomp.); R_f = 0.68. Found, %: C 41.61, H 5.72, N 0.99. $C_{94}H_{154}N_2I_2O_{70}$ requires C 42.03, H 5.78, N 1.04. ^{1}H NMR δ_H ppm: *dimer* ***6***: 1.05 t (3H, CH_3, ^3J = 6.8 Hz), 2.44-2.47 m (1H, NC*H*(CH_3)), 2.51 d (2H, NCH_2, ^3J = 7.3 Hz), 3.31-3.33 m (28H, C^6H_2), 3.57-3.62 m (56H, C^2H-C^5H), 4.48 br.s (12H, C^6OH), 4.79-4.87 m (14H, C^1H), 5.71 br.s (28H, C^2OH, C^3OH), 7.05-7.08 m (4H, $(NH^+_2)_2$); *benzoic acid* ***8***: 7.44 d (2H, $C_{arom}H$, ^3J = 7.5 Hz), 7.55 d (1H, $C_{arom}H$, ^3J = 6.9 Hz), 7.90 d (2H, $C_{arom}H$, ^3J = 5.9 Hz), 12.51 s (1H, COOH). ^{13}C NMR δ_C ppm: *dimer* ***6***: 30.1 (CH_3), 32.6 (NCH(CH_3)*C*H$_2$N), 56.3 ($C^{6'}$), 57.2 (CH), 60.4 (C^6), 69.0 ($C^{5'}$), 72.6-73.6 (C^2, C^3, C^5), 82.0 (C^4), 102.5 (C^1); *benzoic acid* ***8***: 126.0 (C_{meta}), 128.7 (C_{para}), 129.7 (C_{ortho}), 132.7 (C_{ipso}), 168.6 (COOH).

Inclusion compound ***15*** was prepared similarly to inclusion compound **10** from 0.0724 g (0.351 mmol) of 2-(4-isobutylphenyl)propionic acid **7** and 0.30 g (0.117 mmol) of dimer **5**. Yield: 0.188 g (58%); m.p. 239-241 °C (decomp.); R_f = 0.75. Found, %: C 42.92, H 5.98, N 0.97. $C_{100}H_{166}N_2I_2O_{70}$ requires C 43.36, H 6.04, N 1.01. ^{1}H NMR δ_H ppm: *dimer* ***5***: 1.05 t (2H, CH_2, ^3J = 6.9 Hz), 2.46 d (4H, $(NCH_2)_2$ ^3J 7.3 Hz), 3.29-3.32 m (28H, C^6H_2), 3.57-3.59 m (56H, C^2H-C^5H), 4.44 br.s (12H, C^6OH), 4.78-4.83 m (14H, C^1H), 5.72 br.s (28H, C^2OH, C^3OH), 7.42-7.45 m (4H, $(NH_2^+)_2$); *2-(4-isobutylphenyl)propionic acid* ***7***: 0.81 d (6H, $(CH_3)_2$, ^3J = 6.4 Hz), 1.32 d (3H, CH_3, ^3J = 7.3 Hz), 1.74-1.79 m (1H, CH), 2.36 d (2H, CH_2 ^3J = 6.9 Hz), 3.77 s (1H, C*H*(CH_3)COOH), 7.06 d (2H, $C_{arom}H$, ^3J = 8.2 Hz), 7.14 d (2H, $C_{arom}H$, ^3J = 7.8 Hz), 12.19 s (1H, COOH). ^{13}C NMR δ_C ppm: *dimer* ***5***: 29.9 ($NCH_2CH_2CH_2N$), 37.5 ($(NCH_2)_2$), 56.3 ($C^{6'}$), 60.4 (C^6), 69.2 ($C^{5'}$), 72.5 (C^5), 72.9 (C^2), 73.6 (C^3), 82.0 (C^4), 84.0 ($C^{4'}$), 102.5 (C^1); *2-(4-isobutylphenyl)propionic acid* ***7***: 19.2 (CH_3), 22.7 ($(CH_3)_2$), 30.1 (CH), 40.5 (*C*H(CH_3)COOH), 44.8 (CH_2), 126.0-127.6 (C^3_{arom}, C^5_{arom}), 128.6-129.4 (C^2_{arom}, C^6_{arom}), 139.3 (C^4_{arom}), 139.9 (C^1_{arom}), 176.3 (COOH).

Inclusion compound ***16*** was prepared similarly to inclusion compound **10** from 0.0147 g (0.12 mmol) of benzoic acid **8** and 0.103 g (0.04 mmol) of dimer **5**. Yield: 0.0486 g (45%); m.p. 269-273 °C (decomp.), R_f = 0.60. Found, %: C 41.61, H 5.72, N 0.98. $C_{94}H_{154}N_2I_2O_{70}$ requires C 41.03, H 5.78, N 1.04. ^{1}H NMR δ_H ppm: *dimer* ***5***: 1.06 t (2H, CH_2, ^3J = 6.9 Hz), 2.46 t (4H, $(NCH_2)_2$, ^3J = 7.3 Hz), 3.31-3.34 m (28H, C^6H_2), 3.51-3.59 m (56H, C^2H-C^5H), 4.43 br.s (12H, C^6OH), 4.78-4.79 m (14H, C^1H), 5.74 br.s (28H, C^2OH, C^3OH), 7.04-7.08 m (4H, $(NH^+_2)_2$); *benzoic acid* ***8***: 7.44 d (2H, $C_{arom}H$, ^3J = 8.8 Hz), 7.55 d (1H, $C_{arom}H$, ^3J = 6.9 Hz), 7.91 d (2H, $C_{arom}H$, ^3J = 9.2 Hz), 12.18 s (1H, COOH). ^{13}C NMR δ_C ppm: *dimer* ***5***: 30.1 ($NCH_2CH_2CH_2N$), 37.5 ($(NCH_2)_2$), 56.3 ($C^{6'}$), 60.4 (C^6), 69.2 ($C^{5'}$), 72.5-73.6 (C^2, C^3, C^5), 82.0 (C^4), 102.5 (C^1); benzoic acid ***8***: 126.1 (C_{meta}), 128.6 (C_{para}), 129.9 (C_{ortho}), 132.5 (C_{ipso}), 168.6 (COOH).

Inclusion compound ***17*** was prepared similarly to inclusion compound **10** from 0.0237 g (0.115 mmol) of 2-(4-isobutylphenyl)propionic acid **7** and 0.10 g (0.0383 mmol) of dimer **4**. Yield: 0.0653 g (61%); m.p. 272-275 °C (decomp.); R_f = 0.47. Found, %: C 43.55, H 6.10, N 0.96. $C_{103}H_{172}N_2I_2O_{70}$ requires C 43.99, H 6.16, N 1.00. ^{1}H NMR δ_H ppm: *dimer* ***4***: 1.05-1.09 m (4H, $(NCH_2CH_2CH_2)_2$), 2.18-2.25 m (4H, $(NCH_2CH_2)_2$), 3.01-3.03 m (4H, $(NCH_2)_2$), 3.29-3.32 m (28H, C^6H_2), 3.57-3.59 m (56H, C^2H-C^5H), 4.44 br.s (12H, C^6OH), 4.78-4.83 m (14H, C^1H), 5.72 br.s (28H, C^2OH, C^3OH), 7.41-7.44 m (4H, $(NH^+_2)_2$); *2-(4-isobutylphenyl)propionic acid* ***7***: 0.83 d (6H, $(CH_3)_2$, ^3J = 6.4 Hz), 1.33 d (3H, CH_3, ^3J = 7.3 Hz), 1.75-1.78 m (1H, CH), 2.35 d (2H, CH_2 ^3J = 6.9 Hz), 3.79 s (1H, C*H*(CH_3)COOH), 7.05 d (2H, $C_{arom}H$, ^3J = 8.2 Hz), 7.11 d (2H, $C_{arom}H$, ^3J = 7.8 Hz), 12.20 s (1H, COOH). ^{13}C NMR δ_C ppm: *dimer* ***4***: 26.4 ($(NCH_2CH_2CH_2)_2$), 29.4 ($(NCH_2CH_2)_2$), 37.5 ($(NCH_2)_2$), 48.6 ($C^{6'}$), 60.4 (C^6), 72.5 (C^5), 72.7 ($C^{5'}$), 72.9 (C^2), 73.6 (C^3), 82.0 (C^4), 84.0 ($C^{4'}$), 102.5 (C^1); *2-(4-isobutylphenyl)propionic acid* ***7***:19.1 (CH_3), 22.5 ($(CH_3)_2$), 30.2 (CH), 40.4 (*C*H(CH_3)COOH), 44.6 (CH_2), 126.1-127.5 (C^3_{arom}, C^5_{arom}), 128.7-129.3 (C^2_{arom}, C^6_{arom}), 139.2 (C^4_{arom}), 139.8 (C^1_{arom}), 176.8 (COOH).

Inclusion compound ***18*** was prepared similarly to inclusion compound **10** from 0.0465 g (0.381 mmol) of benzoic acid **8** and 0.33 g (0.127 mmol) of dimer **4**. Yield: 0.175 g (50%); m.p. 241-243 °C (decomp.), R_f = 0.62. Found, %: C 42.28, H 5.85, N 0.97. $C_{97}H_{160}N_2I_2O_{70}$ requires C 42.71, H 5.91, N 1.03. ^{1}H NMR δ_H ppm: *dimer* ***4***: 1.04-1.07 m (4H, $(NCH_2CH_2CH_2)_2$), 2.21-2.29 m

(4H, (NCH_2CH_2)$_2$) 3.02-3.04 m (4H, (NCH_2)$_2$), 3.31-3.57 m (28H, C^6H_2), 3.59-3.81 (м, 56H, C^2H-C^5H), 4.43 br.s (12H, C^6OH), 4.78-4.84 m (14H, C^1H), 5.72 br.s (28H, C^2OH, C^3OH), 7.41-7.44 m (4H, (NH^+)$_2$); *benzoic acid* ***8***: 7.04 d (2H, C_{arom}H, ^3J = 8.2 Hz), 7.45 d (1H, C_{arom}H, ^3J = 7.5 Hz), 7.89 d (2H, C_{arom}H, ^3J = 9.2 Hz), 12.01 s (1H, COOH). ^{13}C NMR δ_C ppm: *dimer* ***4***: 30.1 (($NCH_2CH_2CH_2$)$_2$), 31.2 ((NCH_2CH_2)$_2$), 32.6 ((NCH_2)$_2$), 56.3 ($C^{6'}$), 60.4 (C^6), 69.0 (C^5), 72.5-73.6 (C^2, C^3, C^5), 82.0 (C^4), 102.5 (C^1); *benzoic acid* ***8***: 126.4 (C_{meta}), 128.8 (C_{para}), 129.9 (C_{ortho}), 132.4 (C_{ipso}), 161.5 (COOH).

Results and Discussion

In the present work we consider the opportunity to use some CD dimeric derivatives **2**–**5**[5] and **6**[2], previously synthesized by us, as *hosts* for the formation of inclusion complexes with *guests* representing carbonic acids of aliphatic and aromatic nature: 2-(4-isobutylphenyl)propionic acid **7** (medicinal compound of drug *Ibuprofen*), benzoic acid **8** and valeric acid **9** (Figure 3). In all experiments the obtaining of inclusion compounds were performed according to a standard procedure. To a water solution of one molar equivalent of *host* (CD dimeric derivatives **2** – **6**) three molar equivalents of corresponding *guest* were added. The resulting solution was heated under stirring for 4 hours at 70 °C and was kept for the night at 20 °C. The resulting precipitate was filtered off, washed with water, acetone and dried in vacuum at P_2O_5. The structure and composition of thus obtained products **10**-**16** were analyzed with ^{1}H and ^{13}C NMR spectroscopy. The OH proton positions were identified by their considerable shift (by 0.3 – 0.8 ppm) at elevated temperature (80 °C). The correctness of the signals assignment of all obtained compounds was additionally assigned with the aid of ^{1}H-^{1}H homonuclear double resonance and ^{1}H-^{13}C 2D correlation techniques.

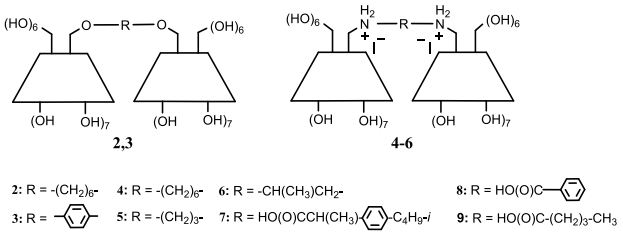

Figure 3. Compounds **2**-**9**.

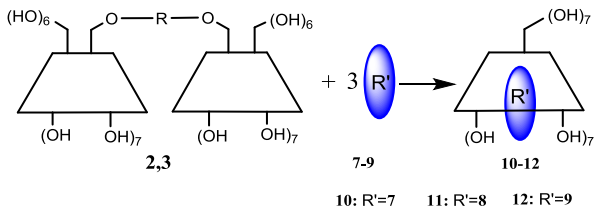

Figure 4. Hydrolysis and inclusion compounds formation of dimeric derivatives **2** and **3** with acids **7**-**9**.

[2] Dimer **6** was not previously synthesized, so its obtaining is described in this paper (see Experimental).

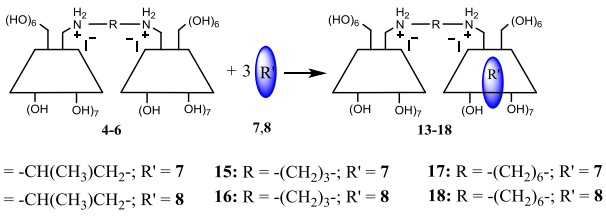

Figure 5. Formation of inclusion compounds **13**-**18** with *guests* **4**-**6**.

It turned out, that dimeric derivatives **2** and **3**, which contain ether bond between C^6 carbon atoms at the narrow rim of a CD frame, are easily undergone hydrolysis of bridged ether bond with the formation of inclusion compounds **10**-**12** consisting of native β-CD **1** and corresponding guests **7**-**9** (Figure 4).

Hydrolysis of ether bond of compounds **2** and **3** was confirmed by disappearance in spectra ^{13}C NMR downfield signals at δ 65.7 ppm of carbon atoms $C^{6'}$ bounded with ether bond at compounds **2** and **3** (see Experimental). By the special experiment[3] we have shown that in the same conditions the hydrolysis of ether bond without guests **7**-**9** does not occur. Consequently, just like monomeric CD derivatives,[7] hydrolysis of ether bond of dimers **2** and **3** occurs as a result of preliminary inclusion of a corresponding *guest* into CD cavity. Thus, dimeric CD derivatives, containing ether bond, turned out to be similar to the corresponding monomeric derivatives as regards to easy hydrolysis of ether bond under action of acidic *guests*.

As we should expect, the dimeric dicationic derivatives **4**-**6** with more firm bridge bond in similar conditions were not hydrolysed and formed inclusion compounds but, according to ^{1}H NMR data, only with one molecule of *guests* **7** and **8** (Figure 5).

The absence of hydrolysis by analogy with above described was confirmed by the remaining of carbon signals C6' at δ 56.3 ppm at ^{13}C NMR spectra, whereas molar ratio *guest-host* 1:1 was determined on the basis of ^{1}H NMR spectra (see Experimental). Inclusion of only one, but not two *guests* by dimeric **4**-**6** was apparently caused by some unusual property of dimeric CD. Thus, depending on the rigidity (or flexibility), nature and length of the bridge, they can form pseudorotaxanes by self-inclusion of one or two ends of the bridge into the cavity of CD due to the 360° reversible rotation around the 1,4-interglycoside bond of one or two glucoside fragments that carry the bridge substituent. This transition depends also on the nature of the solvent and leads to the formation of dimers with the *head-to-tail* or *tail-to-tail* configurations.[8-11] It is important that such self-inclusion of CD dimers limits the ability of dimers to include other guests.

Conclusions

Thus, we discovered that during the obtaining of inclusion compounds of some CD dimeric derivatives with

[3] We performed experiments with dimers **2**, **3** as it described for obtaining inclusion compounds **10** – **12**, but with no acids **7** – **9**. In this case we do not observed the formation of precipitate of inclusion compounds **10** – **12**.

aliphatic and aromatic carbonic acids it is necessary to take into consideration the possibility of easy hydrolysis of bridged ether bonds and possible self-inclusion of CD dimeric derivatives.

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