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Direct Esterification of the Hydroxyl Groups of β-Cyclodextrin with Some Aromatic Monocarboxylic Acids

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Abstract—A possibility of the direct monoesterification of β-cyclodextrin with benzoic, *p*-aminobenzoic, 2-(4-isobutylphenyl)propionic, nicotinic, and isonicotinic acids was shown. Regioselectivity of substitution on the primary hydroxyl groups was confirmed by the means of ^{1}H and ^{13}C NMR spectroscopy.

Keywords: β-cyclodextrin, esterification, NMR spectroscopy, aromatic monocarboxylic acids

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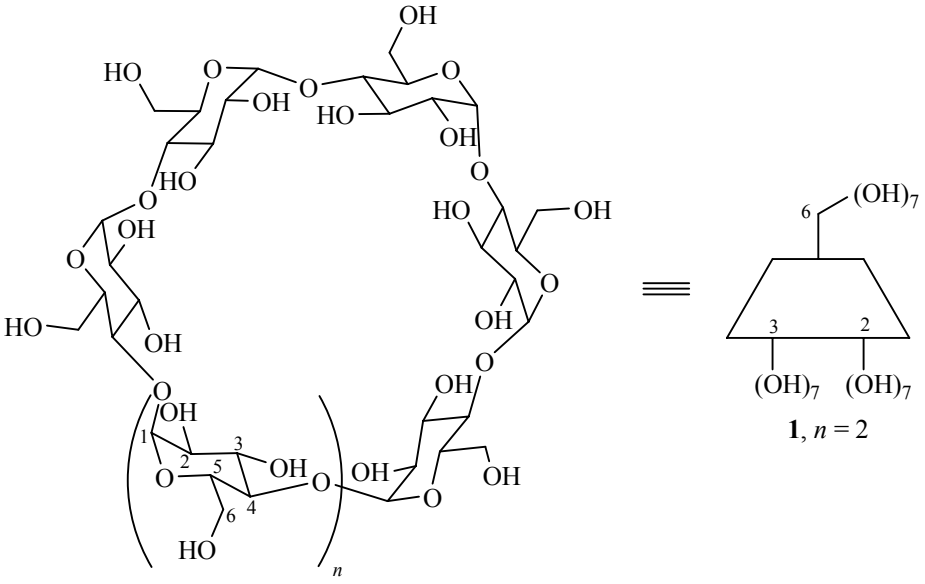
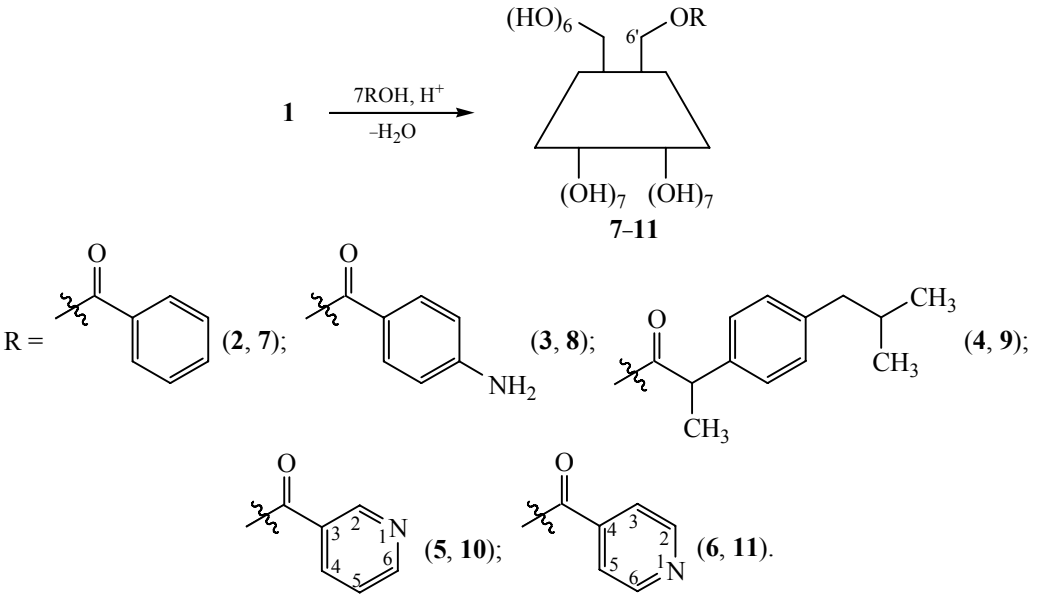
It is known that regioselective modification of cyclodextrins is an experimental challenge due to the presence of different by nature hydroxyl groups: for example, β-cyclodextrin **1** possesses seven primary and fourteen secondary ones, which are located on a narrow and wide sides of the cyclodextrin skeleton respectively. In synthetic practice for this goal usually the following procedure is being applied: introduction of protective groups to the necessary hydroxyl groups, functionalizing of the rest of hydroxyl groups and finally removing of the protective groups with the formation of the target compound [1–4]. For preparation of the monosubstituted β-cyclodextins on the primary hydroxyl groups, monotosylation and following substitution of the tosyl fragment with the appropriate nucleophilic reagent containing labile hydrogen atom is most often applied [3, 4] (Scheme 1).

Scheme 1.



Scheme 2.



Recently, a possibility of esterification of unsubstituted (without any protective groups) β-cyclodextrin with the chlorides of a number of practically valuable monocarboxylic acids was demonstrated that opened promising synthetic possibilities for the regioselective monofunctionalizing of cyclodextrins [5, 6]. In the present work we investigated a possibility of the direct esterification of β-cyclodextrin **1** with free aromatic pharmacologically valuable monocarboxylic acids such as benzoic acid **2** (model compound), *p*-aminobenzoic acid **3** (Vitamin B10), 2-(4-isobutylphenl) propionic acid **4** (active substance of Ibuprofen drug), nicotinic acid **5** (Vitamin PP, Vitamin B3), and isonicotinic acid **6** (Scheme 2).

The esterification was done in DMF solution at 120–130°C for 3 h. It was found that the use even 7 molar equivalents of the named acids led to the formation of monosubstituted on the primary hydroxyl groups products **7–11** only, which were isolated in high yield (see Experimental).

Monosubstitution was confirmed by the data of ^{1}H NMR spectroscopy; regioselectivity of the substitution was proven by ^{13}C NMR spectroscopy. To integrate the carbon nuclei signals the ^{13}C NMR spectra of compounds **7–11** were additionally registered with large delay between impulses (8 s).

In ^{13}C NMR spectra of compounds **7–11** the signals of nuclei of unsubstituted atoms C^{6} at 60.4 ppm were observed together with the typical down-field minor signals of carbon nuclei $C^{6'}$ [1] bearing substituent OR at 65.3 ppm. Appearance of the additional signals of nuclei of C^{2} and C^{3} atoms was not registered therefore the secondary hydroxyl groups were not involved into the esterification process. Positions of the hydroxyl protons were refined by significant shifting the signal (by 0.3–0.8 ppm) at recording of the spectrum of the solution of the same sample at increased temperature (80°C); correctness of the signal positions attribution in ^{1}H and ^{13}C NMR spectra was additionally confirmed by two-dimensional NMR HOMOCOR {^{1}H–^{1}H} and HETCOR {^{1}H–^{13}C} spectroscopy.

It is interesting to note that the attempts of more profound acylation under the discussed conditions occurred to be unsuccessful and led to accumulation of by-products in the reaction mixture only. This fact confirmed earlier observations [5–7] stated on preliminary incapsulation of an acid (*guest*) by hydrophobic cavity of cyclodextrin (*host*) before acylation as was mentioned in [8]. It should be noted that in synthetic practice for the direct esterification of primary hydroxyl group water-removing catalysts are usually used such as dicyclohexylcarbodiimide, and the others. In our case due to a possibility of inclusion of such catalysts into a cavity of the cyclodextrin,

[1] Here and further the carbon atoms of carbohydrate fragments of the cyclodextrin, at which hydroxyl groups have been substituted, are depicted as dashed.

esterification in the presence of sulfuric acid occurred to be more preferable.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were registered on a JEOL ECX-400 instrument at 399.78 and 100.53 MHz, respectively. Chemical shifts of proton and carbon nuclei were given against the signal of $SiMe_4$. Elemental analysis was performed on a FlashEA 1112HT apparatus. Aluminum plates coated with silica gel (Silufol UV-254) were used for TLC, eluent – ethanol–hexane, 3 : 1. β-Cyclodextrin by Fluka (USA) was used in the work.

Mono-6-*O*-benzoyl-β-cyclodextrin (7). Benzoic acid **2** (0.75 g, 6.17 mmol) and conc. sulfuric acid (0.12 g) were added to a solution of β-cyclodextrin (1.00 g, 0.88 mmol) in 15 mL of DMF at stirring. The mixture was stirred at 120–130°C for 3 h, then cooled to 20°C, and kept for 24 h. The reaction mixture was neutralized with a solution of calcium hydroxide, the solution was filtered off, and the filtrate was evaporated to dryness in vacuum. Solid precipitate was triturated with 5 mL of diethyl ether, filtered off, washed with diethyl ether (2×5 mL), and dried in vacuum. Yield 0.88 g (81%), mp 296–298°C (decomp.), R_f 0.68. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.11–3.93 m (42H, C^2H–C^5H, C^6H_2), 4.34 br.s (6H, C^6OH), 4.79 br.s (7H, C^1H), 5.55 br.s (14H, C^2OH–C^3OH), 7.25–7.67 br.s (3H, *m*-CH, *p*-CH), 7.91 d (2H, *o*-CH, *J* 7.8 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 60.4 (C^6), 65.3 ($C^{6'}$), 72.6 (C^5), 73.0 (C^2), 73.6 (C^3), 82.0 (C^4), 102.4 (C^1), 129.0 (*m*-CH), 129.8 (*o*-CH), 131.2 [Ar$\underline{C}^{ipso}$OC(O)], 133.3 (*p*-CH), 168.3 (C=O). Found, %: C 47.76; H 5.90. $C_{49}H_{74}O_{36}$. Calculated, %: C 47.50; H 6.02.

Mono-6-*O*-*p*-aminobenzoyl-β-cyclodextrin (8) was prepared similarly from β-cyclodextrin (1.00 g, 0.88 mmol) and *p*-aminobenzoic acid **3** (0.85 g, 6.17 mmol). Yield 0.98 g (89%), mp 216–218°C (decomp.), R_f 0.73. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.02–3.91 m (42H, C^2H–C^5H, C^6H_2), 4.43 br.s (6H, C^6OH), 4.78 br.s (7H, C^1H), 5.43–6.11 br.s (16H, C^2OH–C^3OH, NH_2), 6.49 d (2H, *m*-CH, *J* 8.2 Hz), 7.56 d (2H, *o*-CH, *J* 8.2 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 60.4 (C^6), 65.3 ($C^{6'}$), 72.6 (C^5), 73.0 (C^2), 73.6 (C^3), 82.0 (C^4), 102.5 (C^1), 113.0 (*m*-CH), 117.4 [Ar$\underline{C}^{ipso}$OC(O)], 131.8 (*o*-CH), 153.7 (*p*-CH), 168.0 (C=O). Found, %: C 47.09; H 5.95; N 1.04. $C_{49}H_{75}NO_{36}$. Calculated, %: C 46.93; H 6.03; N 1.12.

Mono-6-*O*-2-(4-isobutylphenyl)propionyl-β-cyclodextrin (9) was prepared similarly from β-cyclodextrin (1.00 g, 0.88 mmol) and 2-(4-isobutylphenyl)-propionic acid **4** (1.27 g, 6.17 mmol). After evaporation the solid residue was triturated with 5 mL of acetone, filtered off, washed with acetone (2 × 5 mL), and dried in vacuum. Yield 0.87 g (75%), mp 260–262°C (decomp.), R_f 0.70. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.79 d [6H, $CH(C\underline{H}_3)_2$, *J* 6.9 Hz], 1.28 d (3H, $CHC\underline{H}_3$, *J* 6.9 Hz), 1.74 m [1H, $C\underline{H}(CH_3)_2$], 2.34 d (2H, CH_2, *J* 6.9 Hz), 3.13–3.96 m [43H, C^2H–C^5H, C^6H_2, CHC(O)], 4.45 br.s (6H, C^6OH), 4.78 s (7H, C^1H), 5.70 br.s (14H, C^2OH–C^3OH), 7.03 d (2H, *m*-CH, *J* 8.2 Hz), 7.13 d (2H, *o*-CH, *J* 8.2 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 19.1 ($CH\underline{C}H_3$), 22.7 [$CH(\underline{C}H_3)_2$], 30.1 [$\underline{C}H(CH_3)_2$], 40.1 [$\underline{C}HC(O)$], 44.7 (CH_2), 60.4 (C^6), 65.3 ($C^{6'}$), 72.6 (C^5), 73.0 (C^2), 73.6 (C^3), 82.0 (C^4), 102.1 (C^1), 129.6 (*m*-CH), 131.8 (*o*-CH), 138.4 [Ar$\underline{C}^{ipso}$OC(O)], 140.3 (*p*-CH), 175.0 (C=O). Found, %: C 50.08; H 6.44. $C_{55}H_{86}O_{36}$. Calculated, %: C 49.92; H 6.55.

Mono-6-*O*-nicotinoyl-β-cyclodextrin (10) was prepared similarly from β-cyclodextrin (1.00 g, 0.88 mmol) and nicotinic acid **5** (0.76 g, 6.17 mmol). After evaporation the solid residue was triturated with 5 mL of ethanol, filtered off, washed with ethanol (2 × 5 mL), and dried in vacuum. Yield 0.95 g (87%), mp 220–222°C (decomp.), R_f 0.69. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (here and further the protons and carbons of substituents R are highlighted with *italic*): 3.18–3.89 m (42H, C^2H–C^5H, C^6H_2), 4.44 br.s (6H, C^6OH), 4.78 br.s (7H, C^1H), 5.76 br.s (14H, C^2OH–C^3OH), 7.38 m (1H, C^5H), 8.16 d (1H, C^4H, *J* 8.0 Hz), 8.58 d (1H, C^6H, *J* 3.9 Hz), 9.00 br.s (1H, C^2H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 60.4 (C^6), 65.3 ($C^{6'}$), 72.6 (C^5), 73.0 (C^2), 73.6 (C^3), 82.0 (C^4), 102.4 (C^1), 123.9 (C^5), 131.6 (C^3), 137.1 (C^4), 151.0 (C^2), 151.8 (C^6), 169.0 (C=O). Found, %: C 46.37; H 6.08; N 1.20. $C_{48}H_{73}NO_{36}$. Calculated, %: C 46.49; H 5.93; N 1.13.

Mono-6-*O*-isonicotinoyl-β-cyclodextrin (11) was prepared similarly from β-cyclodextrin (1.00 g, 0.88 mmol) and isonicotinic acid **6** (0.76 g, 6.17 mmol). Yield 0.93 g (85%), mp 191–193°C (dec.), R_f 0.69. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.07–3.85 m (42H, C^2H–C^5H, C^6H_2), 4.45 br.s (6H, C^6OH), 4.79 br.s (7H, C^1H), 5.61 br.s (14H, C^2OH–C^3OH), 8.11 d (2H, C^3H, C^5H, *J* 5.0 Hz), 8.92 d (2H, C^2H, C^6H, *J* 5.0 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 60.4 (C^6), 65.3 ($C^{6'}$), 72.00–74.00 m (C^5, C^2, C^3), 82.1

(C^4), 102.4 (C^1), 125.4 (C^3, C^5), 143.2 (C^4), 147.1 (C^2, C^6), 165.4 (*C*=O). Found, %: C 46.32; H 6.12; N 1.21. $C_{48}H_{73}NO_{36}$. Calculated, %: C 46.49; H 5.93; N 1.13.

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