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NMR Spectroscopy Study of Complex Formation between Dimeric Derivative of β-Cyclodextrine and Some Pharmacologically Important Compounds

M. A. Malenkovskaya, L. K. Vasyanina, and M. K. Grachev

Institute of Biology and Chemistry of Moscow State Pedagogical University, Nesvizhskii per. 3, Moscow, 119021 Russia
e-mail: mkgrachev@yandex.ru

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Abstract—The formation of inclusion compounds of β-cyclodextrine with a series of pharmacologically important compounds was studied using ^{1}H and ^{13}C NMR spectroscopy.

Keywords: NMR spectroscopy, inclusion complexes, cyclodextrine derivatives, pharmacologically important compounds

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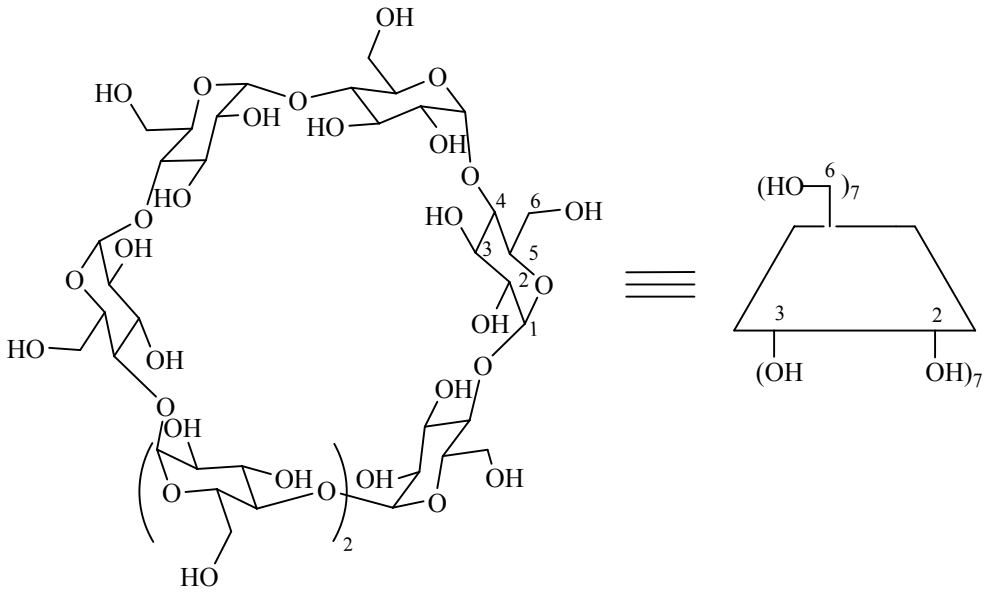
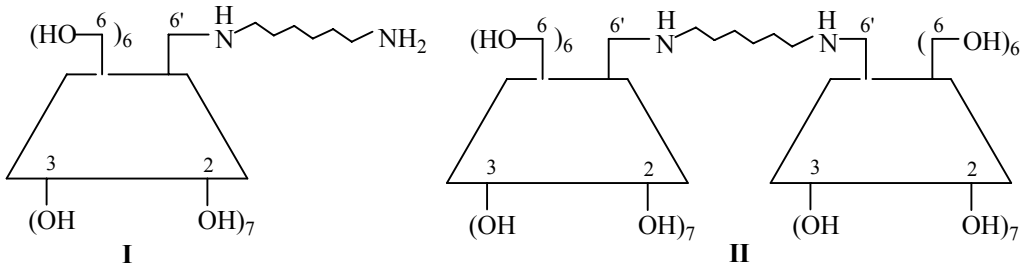
It is known that cyclodextrines found wide application in pharmacology mainly as containers for drugs due to their ability to form inclusion compounds of the *host–guest* type [1–5]. Such incapsulation often protects the drug from biodegradation, increases water solubility, and in some cases results in prolonged and targeting site delivery. Earlier we have studied the synthesis and complexing ability of the monomeric **I** and dimeric **II** amphiphilic derivatives of β-cyclodextrine with respect to 2-(4-isobutylphenyl)propionic acid (ibuprofen) [6]. Using the method of ^{1}H and ^{13}C NMR spectroscopy the possibility of inclusion of this acid (*guest*) in the hydrophobic cavity of the derivatives of β-cyclodextrine (**I, II**) (*host*) and the formation of relatively strong (in the NMR timescale) inclusion compounds was shown. It turned out that as compared to the monomeric derivative **I** the dimeric derivative **II** possesses an enhanced synergistic effect

Scheme 1.

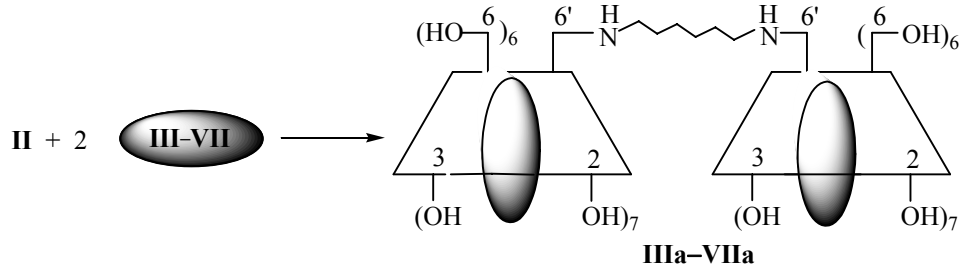


Scheme 2.

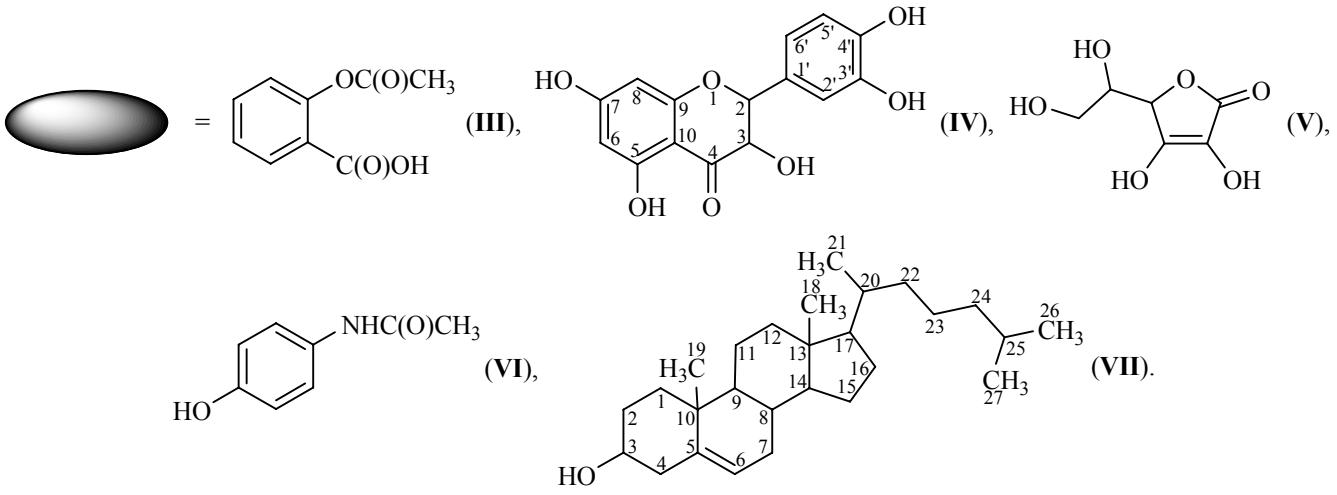


I **II**

Scheme 3.



IIIa–VIIa



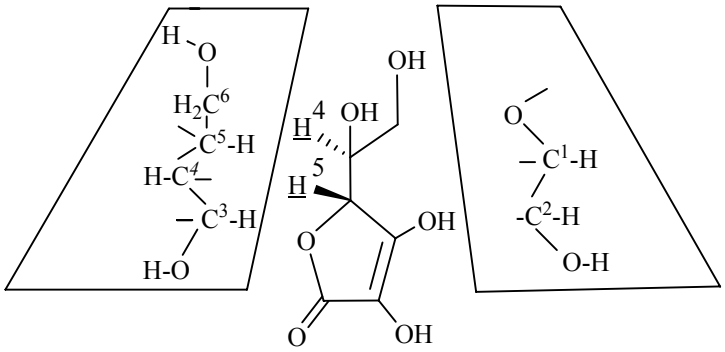
(**III**), (**IV**), (**V**), (**VI**), (**VII**).

with respect to inclusion of a *guest* into the cyclodextrine cavity that favors more effective delivery of the drug.

In the present work, using ^{1}H and ^{13}C NMR spectroscopy, we have studied the ability of the dimeric derivative **II** to form in solutions the inclusion compounds **IIIa–VIIa** with a number of pharmacologically important compounds like acetylsalicylic acid (aspirin) **III**, 3,5,7,3',4'-pentahydroxyflavone (dihydroquercetin) **IV**, γ-lactone-2,3-dihydro-L-gulonic acid (ascorbic acid) **V**, *N-(*4-hydroxyphenyl)acetamide (paracetamol) **VI**, and cholesterol **VII** (Scheme 3).

To this end to the solution of compound **II** in D_2O (9.42 mmol/L) 2 mol-equiv of compounds **III–VII** was added, stirred, and the reaction mixture was analyzed by the NMR spectroscopy. As earlier [6], taking into account the fact that when registering the ^{1}H NMR spectra the signals of residual protons of deuterated solvents often overlapped with the analytical regions of the spectra, the ^{1}H NMR spectra were taken in D_2O at different temperatures, 20 and 80°C (for correct assignment of movable hydroxyl protons and the protons at nitrogen atom), as well as in neutral and acidic medium (pH = 2). In the latter case, due to protonation and appearance of positive charge on the nitrogen atom a substantial downfield shift of the signals of adjacent protons takes place that strongly simplifies the interpretation of the spectra. The correctness of assignment of the signals positions in

Scheme 4.



the spectra was proved by the data of two-dimensional homo (HOMOCOR ^{1}H–^{1}H) and heteronuclear (HETCOR ^{1}H–^{13}C) spectroscopy. It is important to note that in the case of compounds **III–VI**[1] the dimeric water-soluble inclusion complexes **IIIa–VIa** are formed.

In the ^{1}H NMR spectra of solutions of complexes **IIIa–VIIa** an upfield shift of the signals of protons H^3 and H^5 was observed, on the average by the value of $\Delta\delta$ = 0.04 (**III**), 0.06 (**IV**), 0.05 (**V**), 0.02 (**VI**), and 0.02 ppm (**VII**) with respect to the spectrum of compound **II** taken under the same conditions [6]. This is indicative of the formation of relatively strong (in the NMR timescale) inclusion compounds of the *guest–host* type. It is known that upon the inclusion of a *guest* molecule into the hydrophobic cavity of β-cyclodextrine the signals of the protons in the 3 and 5 positions of the glycoside fragments undergo the most strong changes in the ^{1}H NMR spectra, since just these protons are oriented inward the cyclodextrine cavity [7–11] (Scheme 4).

An additional confirmation of the formation of inclusion compounds was the presence in the ^{1}H–^{1}H NMR ROESY spectrum of interactions between the protons CH_3 and C^3H (**IIIa**), $H^{2,3}$ and C^5H (**IVa**), $H^{4,5}$ and C^5H (**Va**) (see Scheme 4), CH_3 and C^3H, C^5H (**VIa**), H^6 and C^5H (**VIIa**).

In the case of complex with acetylsalicylic acid **IIIa** the data of ^{1}H NMR spectroscopy indicate, apart of the formation of inclusion compounds, also the hydrolysis of the acetyl group [12] and, as a result, the accumulation of acetic acid (δ_H = 2.40 ppm, CH_3) and salicylic acid (δ_H = 7.30–8.17 ppm, Ar) in the reaction mixture.

The performed study opens the possibility for the synthesis of dimeric complexes of β-cyclodextrine with drugs, which can be of interest for medical biological investigations.

EXPERIMENTAL

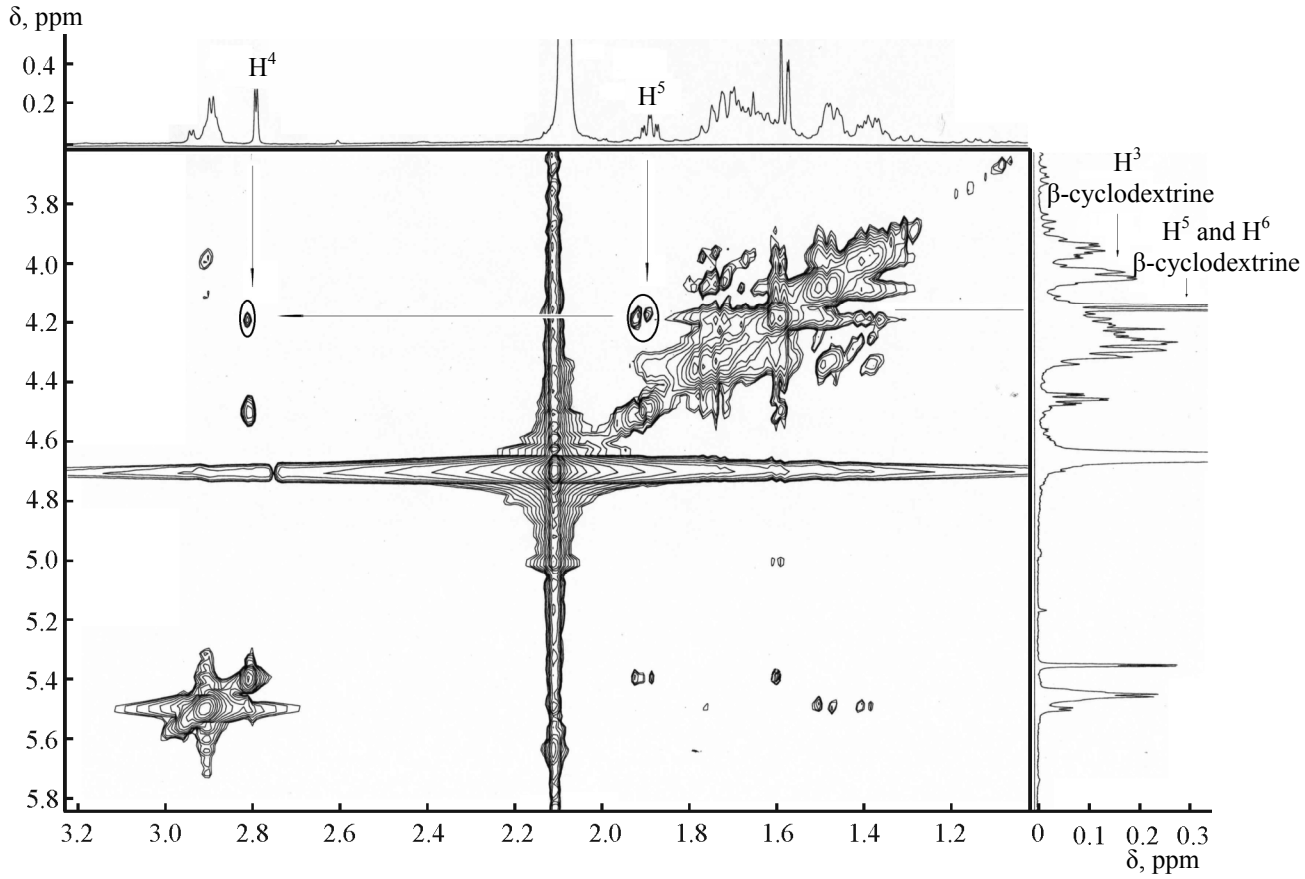
^{1}H and ^{13}C NMR spectra were registered on a Jeol ECX400 instrument at the frequencies 400 and 100.53 MHz, respectively, with respect to residual protons of D_2O (**IIIa–VIa**) and DMSO-d_6 (**VIIa**).

The synthesis of dimeric derivative **II** was described in [6].

Complex with acetylsalicylic acid (IIIa). ^{1}H NMR spectrum, δ, ppm: 1.72–1.82 m (4H, $NCH_2CH_2C\underline{H}_2$), 2.04–2.10 m (4H, $NCH_2C\underline{H}_2CH_2$), 2.70 s [6H, C(O)$CH_3$], 3.37–3.42 m (4H, $NC\underline{H}_2CH_2CH_2$), 3.93–4.15 m (28H, C^2H, C^4H), 4.21 m (28H, C^6H_2), 4.24 m (14H, C^5H), 4.27 m (14H, C^3H), 5.42 br.s (14H, C^1H), 7.49–8.12 m (8H, CH_{arom}). ^{13}C NMR spectrum, δ_C, ppm (hereinafter strokes mark the cyclodextrine carbon atoms at which the hydroxyl groups are substituted): 20.6 [C(O)CH_3], 25.3 ($NCH_2CH_2\underline{C}H_2$), 26.5 ($NCH_2\underline{C}H_2CH_2$), 39.3 and 48.1 ($N\underline{C}H_2CH_2CH_2$), 60.1 ($C^{6'}$), 60.2 ($C^6$), 71.8 ($C^5$), 71.9 ($C^2$), 72.1 ($C^3$), 81.0 ($C^4$), 81.2 ($C^{4'}$), 101.9 ($C^1$), 126.5–130.2 ($C_{arom}$), 148.2 [$COC(O)CH_3$], 160.2, 160.4 [C(O)].

Complex with dihydroquercetin (IVa). ^{1}H NMR spectrum, δ, ppm: 1.82–1.93 m (4H, $NCH_2CH_2C\underline{H}_2$), 1.95–2.12 m (4H, $NCH_2C\underline{H}_2CH_2$), 2.65–2.77 m and 2.82–2.97 m (4H, $NC\underline{H}_2CH_2CH_2$), 3.42–3.56 m (28H, C^2H, C^4H), 4.19 m (28H, C^6H_2), 4.28 m (14H, C^5H), 4.37 m (14H, C^3H), 4.88 br.s (14H, C^1H), 4.91 s and

[1] Due to very poor solubility of cholesterol **VII** in water the experiments were performed in DMSO-d_6.



ROESY spectrum of complex **Va** in D_2O.

4.92 s (4H, C^2H, C^3H), 6.82 c and 6.92 s (10H, $C^{2'}H$, $C^{5'}H$, C^6H, $C^{6'}H$, $C^{8'}H$). ^{13}C NMR spectrum, δ_C, ppm: 26.1 ($NCH_2CH_2\underline{C}H_2$), 26.6 ($NCH_2\underline{C}H_2CH_2$), 39.4 and 48.0 ($N\underline{C}H_2CH_2CH_2$), 60.1 ($C^{6'}$), 60.3 ($C^6$), 71.8 ($C^5$), 71.9 ($C^3$), 72.0 ($C^2$), 72.2 ($C^3$), 73.1 ($C^3$), 80.9 ($C^4$), 83.5 ($C^2$), 94.6 ($C^8$), 97.2 ($C^6$), 101.9 ($C^1$), 110.2 ($C^{10}$), 114.1 ($C^{6'}$), 117.5 ($C^{5'}$), 121.1 ($C^{2'}$), 129.1 ($C^{1'}$), 146.2 ($C^{3'}$), 147.5 ($C^{4'}$), 152.3 ($C^9$), 161.3 ($C^5$), 164.9 ($C^7$), 178.6 ($C^4$).

Complex with ascorbic acid (Va). ^1H NMR spectrum, δ, ppm: 1.71–1.81 m (4H, $NCH_2CH_2C\underline{H}_2$), 1.83–2.25 m (4H, $NCH_2C\underline{H}_2CH_2$), 3.38–3.36 m and 3.36–3.55 m (4H, $NC\underline{H}_2CH_2CH_2$), 3.73 m and 3.98 m (4H, C^6H_2), 3.93–4.15 m (28H, C^2H, C^4H), 4.20 m (28H, C^6H_2), 4.24 m (14H, C^5H), 4.28 m (14H, C^3H), 4.48 br.s (2H, C^5H), 5.09 br.s (2H, C^4H), 5.46 br.s (14H, C^1H). ^{13}C NMR spectrum, δ_C, ppm: 25.2 ($NCH_2CH_2\underline{C}H_2$), 26.5 ($NCH_2\underline{C}H_2CH_2$), 39.4 and 48.3 ($N\underline{C}H_2CH_2CH_2$), 60.2 ($C^{6'}$), 60.3 ($C^6$), 62.3 ($C^6$), 71.9 ($C^5$), 72.1 ($C^5$), 73.2 ($C^4$), 77.3 ($C^2$), 77.4 ($C^3$), 81.1 ($C^4$), 102.1 ($C^1$), 115.3 ($C^2$), 166.3 ($C^3$), 175.6 ($C^1$).

Complex with paracetamol (VIa). ^1H NMR spectrum, δ, ppm: 1.72–1.85 m (4H, $NCH_2CH_2C\underline{H}_2$), 1.86–2.05 m (4H, $NCH_2C\underline{H}_2CH_2$), 2.58 br.s (6H, CH_3), 3.22–3.30 m and 3.42–3.50 m (4H, $NC\underline{H}_2CH_2CH_2$), 3.95–4.08 m (28H, C^2H, C^4H), 4.23 m (28H, C^6H_2), 4.25 m (14H, C^3H), 4.28 m (14H, C^5H), 5.46 br.s (14H, C^1H), 6.71 d and 7.09 d (8H, CH_{arom}, $^3J_{HH}$ 8.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 22.5 (CH_3), 25.8 ($NCH_2CH_2\underline{C}H_2$), 26.8 ($NCH_2\underline{C}H_2CH_2$), 39.5 and 48.3 ($N\underline{C}H_2CH_2CH_2$), 60.1 ($C^{6'}$), 60.2 ($C^6$), 71.8 ($C^5$), 72.0 ($C^2$), 73.2 ($C^3$), 80.9 ($C^4$), 101.9 ($C^1$), 115.9, 124.4, 128.8, 154.8 (C_{arom}), 172.9 [C(O)].

Complex with cholesterol (VIIa). ^1H NMR spectrum, δ, ppm: 0.68–2.47 m (86H, $CH^{1,2,4,7–27}$), 1.30–1.32 m (4H, $NCH_2CH_2C\underline{H}_2$), 1.33–1.36 m (4H, $NCH_2C\underline{H}_2CH_2$), 2.46 br. m (4H, $NC\underline{H}_2CH_2CH_2$), 3.18–3.20 m (2H, C^3H), 3.23–3.42 m (28H, C^2H, C^4H), 3.60 m (28H, C^6H_2), 3.62 m (14H, C^5H), 3.64 m (14H, C^3H), 4.10 br.s (12H, C^6OH), 4.81 br.s (14H, C^1H), 5.23 br.s (2H, C^6H), 5.45 br.s (28H, C^2OH, C^3OH). ^{13}C NMR spectrum, δ_C, ppm: 19.4–3.72 ($C^{1–3, 7–13, 15–23, 25–27}$),

26.7 ($NCH_2CH_2\underline{C}H_2$), 26.9 ($NCH_2\underline{C}H_2CH_2$), 39.8 and 48.3 ($N\underline{C}H_2CH_2CH_2$), 41.8 ($C^4$, C^{24}), 56.5 (C^{14}), 58.3 (C^{17}), 60.1 ($C^{6'}$), 60.4 (C^6), 72.5 (C^5), 72.9 (C^2), 73.3 (C^3), 82.1 (C^4), 102.5 (C^1), 126.5 (C^6), 140.8 (C^5).

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