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Dimeric Diaminocationic β–Cyclodextrin Derivatives

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Dimeric β-cyclodextrins derivatives being of interest as potential carriers (inclusion compounds and conjugates) of drugs for pharmacological studies in various directions have been obtained using various alkylenediamines and monohalogen substituted β-cyclodextrin derivatives. The position of substituents in carbohydrate fragments of CDs was unambiguously determined by various variants of ^{1}H and ^{13}C NMR spectroscopy and by elemental analysis.

Keywords: Dimeric derivatives, cationic cyclodextrins, regiodirected synthesis, ^{1}H and ^{13}C NMR spectroscopy.

Димерные диаминокатионные производные β–циклодекстрина

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С использованием различных алкилендиаминов и моногалогензамещенных производных β-циклодекстрина получены димерные производные, представляющие интерес как потенциальные носители (соединения включения и конъюгаты) лекарственных средств для фармакологических исследований в разных направлениях. Строение полученных димерых циклодекстриновых производных надежно подтверждено различными вариантами спектроскопии ЯМР ^{1}H и ^{13}C, а также элементным анализом.

Ключевые слова: Димерные производные, катионные производные, регионаправленный синтез, ^{1}H и ^{13}C ЯМР спектроскопия.

Introduction

Cyclodextrins (CDs) and some their derivatives have found wide practical application mainly due to the unique ability to form inclusion compounds of the "guest–host" type with numerous "guests".[1-4] Earlier, we turned our attention to the dimeric cyclodextrins derivatives, in which two residues of the β-cyclodextrin (Figure 1) are connected by a bridge.[5,6] In comparison with native CDs and monomodified CDs, dimeric CDs exhibit the significantly high binding abilities and molecular selectivity through the cooperative binding of two adjacent CD units.[7] This fascinating property enables them to be employed successfully in several areas of chemistry as an excellent model system mimicking substrate-specific interaction of enzymes.[8,9] Consequently, a number of dimeric β-CDs have been designed and synthesized to examine and compare the molecular binding affinity of native β-CD and dimeric β-CDs and also to gain insights into factors governing the inclusion complexation phenomena between the host dimeric β-CDs and guest molecules.[10,11] Moreover, the linker can supply a well-organized pseudo-cavity that in turns provides additional binding interactions with accommodated guest molecules.[11] Thus, dimeric CDs could be successfully utilized in carriers,[12] catalysis,[8] templated synthesis,[13] photochemical materials,[14,15] solubilizers,[16] *etc.* The dimeric complex, in com-

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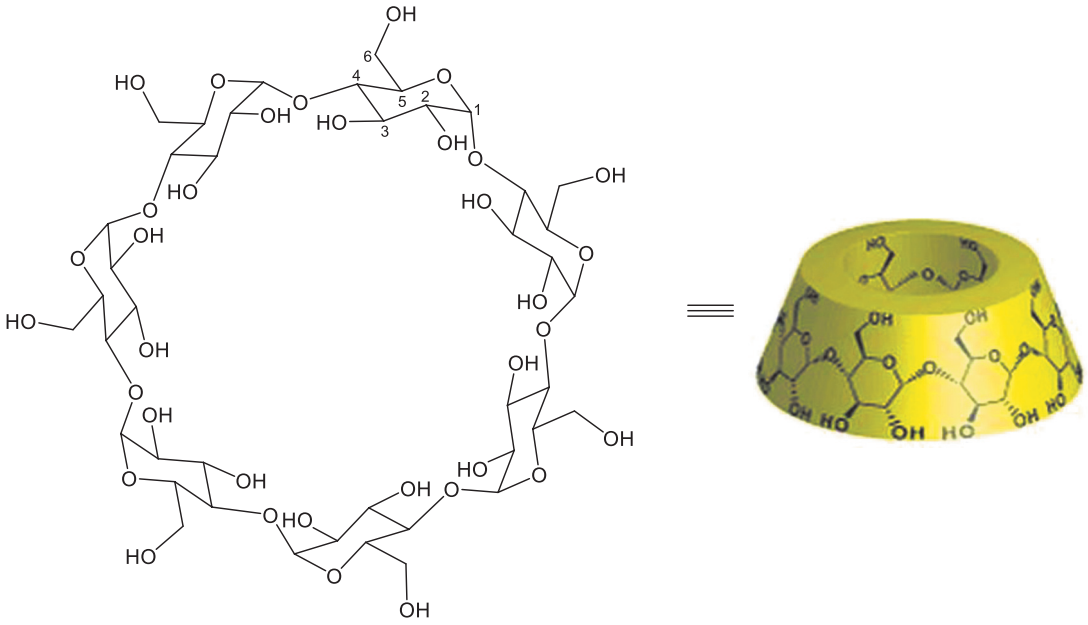

Figure 1. Chemical structure of β-cyclodextrin.

parison with the monomeric complex, has an enhanced synergistic effect on the inclusion of "guests" in its cyclodextrin cavity,[17-19] which could help for more efficient and targeting site delivery.

Cationic cyclodextrin derivatives, in which one or more hydroxyls are replaced by a group bearing a positive charge, could enhance the ability of native CDs to penetrate biological barriers, *e.g.* the blood-brain barrier,[20] to embed in biological membranes,[21,22] and serve as carriers for DNA delivery (vectorization) under gene therapy.[23-26] These properties of cationic cyclodextrins, after the formation of inclusion complexes or conjugates with pharmacologically important compounds, are used in pharmacology for more efficient and targeting site delivery of the drug (prodrug) (see, for example,[27]).

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. Elemental analyses were performed on a FlashEA 1112 HT instrument. Thin layer chromatography was performed on aluminum plates with fixed layer of SiO_2 (Silufol UV-254), eluent: acetonitrile:chloroform (1:1). Commercial β-cyclodextrin "Wacker" (USA) was dried in vacuum (1 Torr) for 10 h at 90 °C over P_2O_5 prior to use.

*Di-6,6'-dideoxy-6,6'-(propane-1,3-diyldiaminium)-β-cyclodextrin iodide (**6**).* To a solution of 1.00 g (0.80 mmol) of mono(6-iodo-6-deoxy)-β-cyclodextrin **1** in 15 mL of DMF was added at stirring 0.030 g (0.40 mmol) of propane-1,3-diamino **2**. The solution was stirred for 40 h at 120–130 °C. The reaction mixture was concentrated to 5 mL, diluted with 25 mL of acetone, the mixture was stirred, the separated precipitate was filtered off, washed successively with chloroform (2×5 mL), ethanol (2×5 mL), acetone (2×5 mL), ethyl ether (2×5 mL), and dried in a vacuum (1 mm Hg) for 4 h at 80 °C. Yield 0.75 g (66 %). M.p. 259–261°C (decomp.). R_f = 0.71. Found, %: C 40.81, H 5.93, N 1.19. $C_{87}H_{148}I_2N_2O_{68}$. Calculated, %: C 40.76, H 5.82, N 1.09. ^{1}H NMR ([D6]DMSO) δ_H ppm: 1.82 m (2H, NCH_2CH_2), 2.16 m (4H, NCH_2), 3.17–3.74 m (84H, C^2H–C^5H, C^6H_2), 4.48 br.s (12H, C^6OH), 4.78 br.s (14H, C^1H), 5.73 br.s (32H, N^+H_2, C^2OH–C^3OH). ^{13}C NMR ([D6]DMSO) δ_C ppm: 29.6 (NCH_2CH_2), 37.5 (NCH_2), 49.9 ($C^{6'}$), 60.4 (C^6), 70.1 ($C5'$), 72.5 (C^5), 72.9 (C^2), 73.4 (C^3), 82.0 (C^4), 102.4 (C^1).

*Di-6,6'-dideoxy-6,6'-(butane-1,4-diyldiaminium)-β-cyclodextrin iodide (**7**)* was prepared similarly to compound **6** from mono(6-iodo-6-deoxy)-β-cyclodextrin **1** (1.00 g, 0.80 mmol) and butane-1,4-diamino **3** (0.035 g, 0.40 mmol). Yield 0.75 g (66 %). M.p. 261–263 °C (decomp.). R_f = 0.67. Found, %: C 41.11, H 5.73, N 1.12. $C_{88}H_{150}I_2N_2O_{68}$. Calculated, %: C C 41.00, H 5.87, N 1.09. ^{1}H NMR ([D6]DMSO) δ_H ppm: 1.38 m (4H, NCH_2CH_2), 2.53 m (4H, NCH_2), 3.17–3.74 m (84H, C^2H–C^5H, C^6H_2), 4.48 br.s (12H, C^6OH), 4.78 br.s (14H, C^1H), 5.73 br.s (32H, N^+H_2, C^2OH–C^3OH). ^{13}C NMR ([D6]DMSO) δ_C ppm: 25.3 (NCH_2CH_2), 46.3 (NCH_2), 49.9 ($C^{6'}$), 60.4 (C^6), 70.1 ($C5'$), 72.6 (C^5), 73.0 (C^2), 73.6 (C^3), 82.0 (C^4), 102.4 (C^1).

*Di-6,6'-dideoxy-6,6'-(pentane-1,5-diyldiaminium)-β-cyclodextrin iodide (**8**)* was prepared similarly to compound **6** from mono(6-iodo-6-deoxy)-β-cyclodextrin **1** (1.00 g, 0.80 mmol) and pentane-1,5-diamino **4** (0.040 g, 0.40 mmol). Yield 0.80 g (70 %). M.p. 264–266 °C (decomp.). R_f = 0.63. Found, %: 41.27, H 5.83, N 1.18. $C_{89}H_{152}I_2N_2O_{68}$. Calculated, %: C 41.24, H 5.91, N 1.08. ^{1}H NMR ([D6]DMSO) δ_H ppm: 1.29 m (2H, $NCH_2CH_2CH_2$), 1.40 m (4H, NCH_2CH_2), 2.53 m (4H, NCH_2), 3.17–3.74 m (84H, C^2H–C^5H, C^6H_2), 4.48 br.s (12H, C^6OH), 4.78 br.s (14H, C^1H), 5.73 br.s (32H, N^+H_2, C^2OH–C^3OH). ^{13}C NMR ([D6]DMSO) δ_C ppm: 27.3 ($NCH_2CH_2CH_2$), 35.2 (NCH_2CH_2), 46.3 (NCH_2), 49.9 ($C^{6'}$), 60.4 (C^6), 70.1 ($C5'$), 72.6 (C^5), 73.0 (C^2), 73.6 (C^3), 82.0 (C^4), 102.4 (C^1).

*Di-6,6'-dideoxy-6,6'-(hexane-1,6-diyldiaminium)-β-cyclodextrin iodide (**9**)* was prepared similarly to compound **6** from mono(6-iodo-6-deoxy)-β-cyclodextrin **1** (1.00 g, 0.80 mmol) and hexane-1,6-diamino **5** (0.035 g, 0.40 mmol). Yield 0.94 g (89 %). M.p. 268–270 °C (decomp.), R_f = 0.60. Found, %: C 41.32, H 5.89, N 1.01. $C_{90}H_{154}I_2N_2O_{68}$. Calculated, %: C 41.48, H 5.96, N 1.07. ^{1}H NMR ([D6]DMSO) δ_H ppm: 1.20 m (4H, $NCH_2CH_2CH_2$), 1.32 m (4H, NCH_2CH_2), 2.60 m (4H, NCH_2), 3.17–3.74 m (84H, C^2H–C^5H, C^6H_2), 4.48 br.s (12H, C^6OH), 4.78 br.s (14H, C^1H), 5.73 br.s (32H, N^+H_2, C^2OH–C^3OH). ^{13}C NMR ([D6]DMSO) δ_C ppm: 26.7 ($NCH_2CH_2CH_2$), 29.7 (NCH_2CH_2), 37.5 (NCH_2), 49.9 ($C^{6'}$), 60.4 (C^6), 70.1 ($C5'$), 72.5 (C^5), 72.9 (C^2), 73.4 (C^3), 82.0 (C^4), 102.4 (C^1).

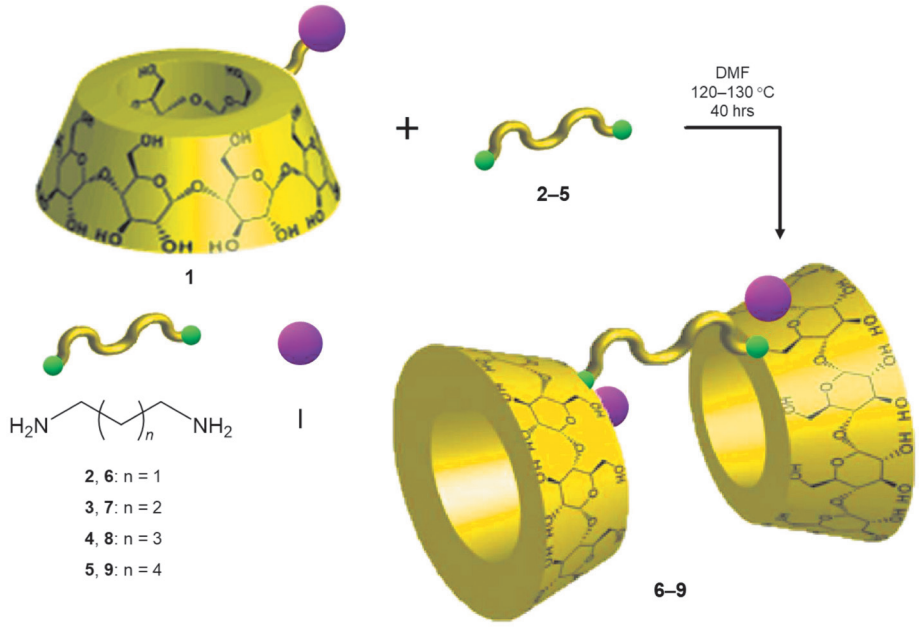

Figure 2. Scheme of the syntheses of dimeric diaminocationic β-cyclodextrin derivatives **6–9**.

Results and Discussion

In the present work, we have considered the possibility of synthesizing dimeric diaminocationic β-cyclodextrin derivatives. For this we used the procedure proposed for the synthesis of monocathionic derivatives:[28] iodo derivative **1** alkylated the diamines **2–5** with different number of methylene units to obtain dimeric diaminocationic β-cyclodextrin derivatives **6–9**, respectively (Figure 2). The syntheses were carried out in DMF at 120–130 °C for 40 h to receive in high yield compounds **6–9** with the positive charge on the side of the primary hydroxy groups of the cyclodextrin scaffold. It is interesting to note the dependence of the increase in the melting point and the decrease in chromatographic mobility with an increase in the number of methylene units in the bridge between the two cyclodextrins (see Experimental).

The structure of compounds **6–9** was confirmed by ^{1}H and ^{13}C NMR data. For example, for compound **9**, the central hexamethylene diamine bridge binds the same cyclodextrin substituents, and therefore the methylene fragments at positions 1 and 6, 2 and 5, 3 and 4 are pairwise equivalent, which is reflected in the form of three broadened singlets in the ^{1}H NMR spectrum. The regiodirection of the substitution of the primary hydroxy groups was revealed from the ^{13}C NMR data. To be able to integrate the carbon signals in the ^{13}C NMR spectra of compounds **6–9** the registration was performed at a large delay between the pulses (8 s). The ^{13}C NMR spectra of compounds **6–9** contain the signals of nuclei of unsubstituted C-6 atoms at δ 60.4 ppm and characteristic minor upfield signals of C-6' nuclei bearing the N^{+} substituent at δ 49.9 ppm. 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 **6–9** was additionally confirmed by the analysis of 2D NMR spectra of homo- (HOMOCOR {^{1}H–^{1}H}) and heteronuclear (HETCOR {^{1}H–^{13}C}) correlations (Figure 3) and registering in the DEPT mode.

Conclusions

Thus, the obtained dimeric derivatives are of interest as potential carriers (inclusion compounds and conjugates) of drugs for pharmacological studies in different directions. This research reveals possible ways of obtaining dimeric complexes of β-cyclodextrin with important pharmaceutical preparations.

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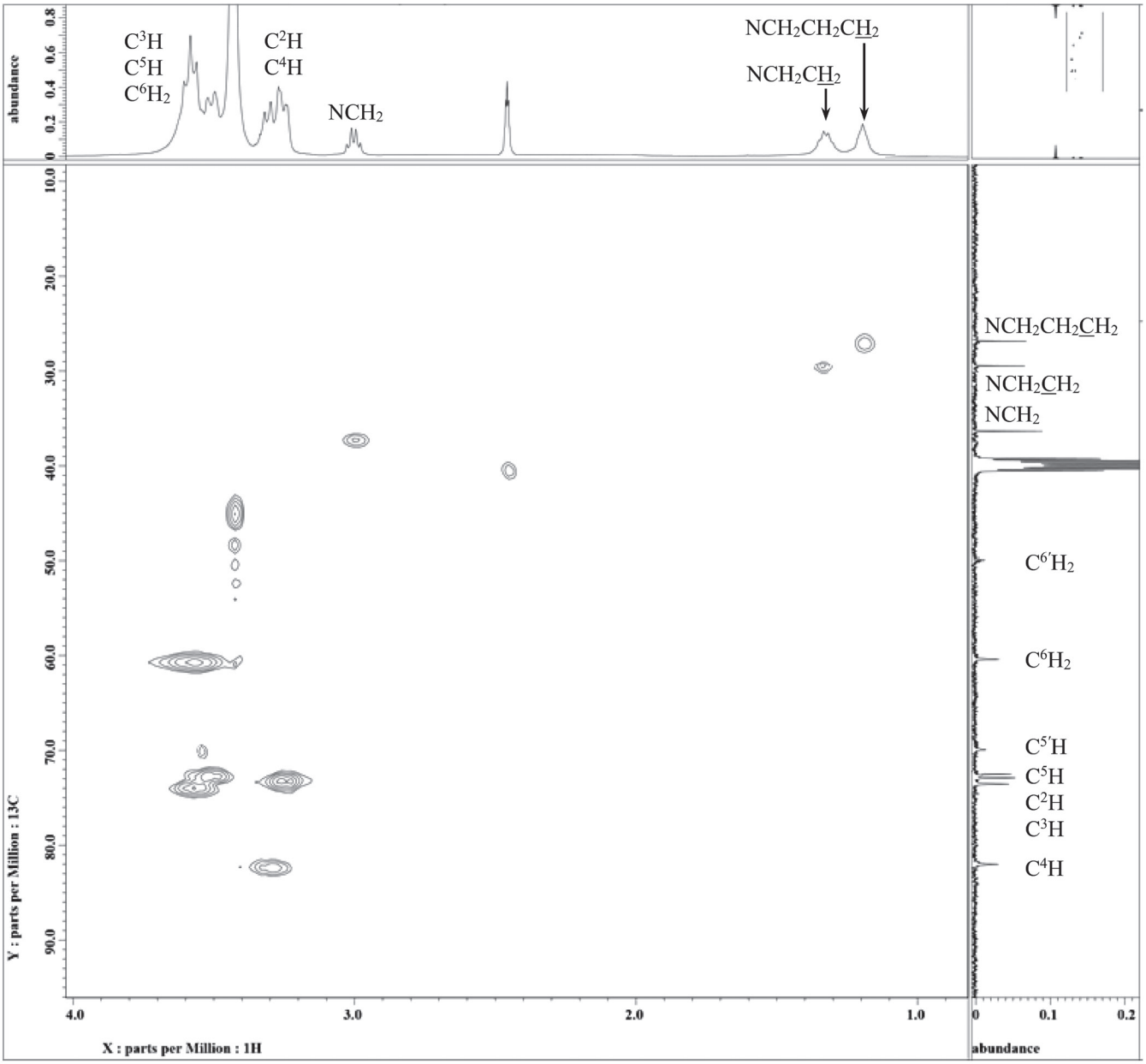

Figure 3. 2D NMR spectra of heteronuclear (HETCOR {^{1}H–^{13}C}) correlations of derivative **9** (fragment).

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