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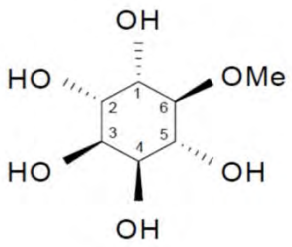
SUPRAMOLECULAR SELF-ASSEMBLY OF D-PINITOL WITH CYCLODEXTRINES

Abstract. Water-soluble mixed complexes of D-pinitol with cyclodextrins in the ratio 1:1 composition were formedby the supramolecular interaction. The structure of supracomplexeswas studied by NMR spectroscopy methods.

Keywords: D-pinitol, cyclodextrins, supramolecular complexes, NMR spectroscopy.

One of the most promising and intensively developing areas of modern supramolecular chemistry is the preparation and investigation of complexes of biologically active compounds of plant origin with cyclodextrins (CDs) [1-5]. It is known, that inclusion supramolecular complexes of CDs with biologically active compounds make it possible to regulate the solubility of the latter in water, reduce their toxicity, permit the transfer of liquid substances to solid substances, and increase the stability of substances to oxidation and hydrolysis [6-8].

The choice of D-pinitol(**1**) as a substrate of supramolecular self-assembly is due to the fact that this compound of plant origin has antidiabetic and hypoglycemic properties and it is very promising for use in pharmaceutics [9].



1

CDs are relatively affordable compounds, manufactured from renewable raw materials such as starch. The α-, β- and γ-CDs containingglucopyranose units are the most common ones. The increased interest in CDs is primarily due to their cyclic structure and the ability to form supramolecular host-guest inclusion complexes with a variety of hydrophobic guests due to the internal cavity [10, 11]. The attractiveness of CDs as host molecules in the formation of inclusion complexes is also explained by their nontoxicity.

In supramolecular chemistry, the size and shape or geometric complementarity of the interacting components play a decisive role; therefore, α-, β- and γ-CDs of various sizes of the internal cavity as well as the more hydrophilized 2-HP-β-CD (2-hydroxy-β-CD) were used to obtain complexes with the substrate.

Supramolecular complexes of **1** with α-, β-, γ- and 2-HP-β-CDs were obtained by the interaction of equimolecular amounts of substrate with receptors in ethanol solutions of reacting substances at 50°C for 5 hours followed by isolation of supracomplexes drying.

Investigation of supramolecular complexes of **1** with CDs by NMR spectroscopyis based on the determination of the difference in the values of ^{1}H chemical shifts of substrate**1** and receptors (CDs) in the free state and in the composition of complexes as a result of intermolecular interaction. One can judge the formation of internal or external complexes, respectively, according to the change of the value of chemical shifts of internal or external protons of CDs. The change in the chemical shifts of ^{1}H NMR in the spectra of the substrate makes it possible to determine the direction of entry of the latter in the cavity of CDs [12, 13].

The substrate of supramolecular self-assembly **1** was obtained from SilenebranhuicaBoiss collected in the South Kazakhstan region in natural habitats and isolated by water-ethanol and isobutanol extraction [9]. Its structurewas established based on the results of ^{1}H and ^{13}C NMR spectroscopy obtained in DMSO-d_6 (table 1). The correctness of the assignment of one-dimensional ^{1}H and ^{13}C NMR spectra of **1** was confirmed by two-dimensional correlations of the NMR spectra such as ^{1}H-^{1}HTOCSY, ^{1}H-^{1}HROESY, ^{1}H-^{13}CHMQCand^{1}H-^{13}CHMBCand coincided with the published results [9, 14, 15].

^{1}H NMR spectra data of α-, β-, γ- and 2-HP-β-CDs in the free state and supramolecular complexes on their basis with **1** obtained in D_2O are represented in tables 2 and 1.

Table 1 – The values of the chemical shifts of ^{1}Hand^{13}C NMR of **1** in the free state (δ_0, DMSO-d_6) and in the composition of the complexes (δ, D_2O), ppm

C atom No.	δ_0 (^{13}C)	δ_0 (^{1}H)	δ (^{1}H) in the complex with			
			α-CD	β-CD	γ-CD	2-HP-β-CD
1	72.52	3.34 m, 4.41 d (OH)	Signals of CDs are overlapped by signals of **1**			
2	73.12	3.60 m, 4.64 d (OH)	Signals of CDs are overlapped by signals of **1**			
3	71.45	3.47 m, 4.38 d (OH)	Signals of CDs are overlapped by signals of **1**			
4	72.92	3.60 m, 4.55 d (OH)	Signals of CDs are overlapped by signals of **1**			
5	70.61	3.34 m, 4.25 d (OH)	Signals of CDs are overlapped by signals of **1**			
6	84.33	2.97 t	3.28t	3.29t	3.28t	3.20 t
6-OCH_3	60.15	3.41s	Signals of CDs are overlapped by signals of **1**			

Table 2 – The ^{1}HNMR chemical shiftsof α-, β-, γ- and 2-HP-CDs in the free state (δ_0) and in the composition of the complexes (δ), ppm

H atom No.	α-CD			β-CD			γ-CD			2-HP-CD		
	δ_0	δ	$\Delta\delta=\delta-\delta_0$	δ_0	δ	$\Delta\delta=\delta-\delta_0$	δ_0	δ	$\Delta\delta=\delta-\delta_0$	δ_0	δ	$\Delta\delta=\delta-\delta_0$
1	4.91	5.00	0.09	4.87	5.02	0.15	4.96	5.05	0.09	4.92	4.95	0.03
2	3.49	3.58	0.09	3.45	3.60	0.15	3.51	3.60	0.09	3.46	3.48	0.02
3	3.84	3.93	0.09	3.77	3.91	0.14	3.78	3.88	0.10	3.87	3.86	-0.01
4	3.44	3.53	0.09	3.39	3.54	0.15	3.44	3.53	0.09	3.46	3.48	0.02
5	3.71	3.82	0.09	3.68	3.83	0.14	3.72	3.81	0.09	3.72	3.74	0.02
6	3.71	3.82	0.11	3.68	3.83	0.14	3.72	3.81	0.09	3.72	3.74	0.02

A comparison of the integrated intensities of the ^{1}H NMR signals of the molecule of **1** with α-, β-, γ-, and 2-HP-β-CDs in supramolecular complexes has shown that **1** forms complexes of 1:1 composition with all CDs.

Changes in the proton chemical shifts in cyclodextrin molecules Δδ occurred to an equal extent both for the internal hydrophobic protons H-3, H-5 and H-6, and for protons located in the outer hydrophilic surface H-1, H-2 and H-4at the formation of supramolecular complexes **1** with all CDs. Changes in the chemical shifts of the proton H-6in the molecule of **1** occurred to an equal extent in all the complexes formed by α-, β-, and γ-CDs. The chemical shifts of the proton H-6 in the complexes of **1** with 2-HP-β-CD were slightly different. Due to the similarity in the chemical structure of CDs with molecule **1**, almost all the proton signals of the substrate were not resolved because of the superimposition of cyclodextrin NMR responses on them. Integral intensities of the protons of CDs molecules were 6-8 times larger in magnitude than the corresponding signals of the molecule **1**. It can be assumed on the basis of the data obtained that the main interaction factors are hydrophilic interactions through hydroxyl-groups of interacting molecules with the formation of inclusion complexes, and complexes without inclusion in the supramolecular self-assembly of **1** with CDs molecules [16, 17]. The water-soluble aggregates formed thereby are able to solubilize the lipophilic molecules of substrate **1** through non-inclusive complexation [18]. This is confirmed by the good solubility of the obtained supramolecular aggregates of **1** with CDs in aqueous solutions.

In order to direct search of "candidate compounds" with the desired types of pharmacological activity, substrate **1**was tested using the PASSonline program (http://www.pharmaexpert.ru/passonline). The computer program PASSonline is based on the principle of "sliding control" of databases of chemical compounds, and allows selecting the most promising from the set of substances, i.e. with the desired pharmacological properties. The accuracy of the prediction of biological activity is 94% [19]. It is established that **1**potentially has a wide range of pharmacological properties as a result of PASS-prediction (table 3).

Table 3 – PASS prediction data of the compound **1**

Type of biologicalactivity	Probability, %	Type of biologicalactivity	Probability, %
Anti-seborrheic	86	Antidiskinetic	67
Anti-eczemic	82	Fibrinolytic	67
Vasoprotective	**77**	Anthelmintic	63
Antineoplastic	**77**	Cytoprotective	62
Analeptic	69	Anti-infectious	58
Lipotropic	67	Anti-inflammatory	58

As can be seen from table 3, antiseborrhoea and antiparasitic activities are predicted for the molecule **1** with a comparatively high probability of experimental confirmation, as well as other promising pharmacological properties.

Despite of the fact that the computer prediction data does not allow one to state absolutely exactly whether the substance under study will have predictable activity, nevertheless, the use of computer programs like PASSonline allows selecting the most promising substances for in-depth study in biological test systems *invitro* and *invivo* from the set of substances.

EXPERIMENTAL PART

The α-, β-, γ- and 2-HP-β-CDs of “Fluka”company were used in the work with a purity of 99%; The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 (**1**) and D_2O (complexes) on a JNM-ECA Jeol400 spectrometer (399.78 and 100.53 MHz, respectively). Chemical shifts are measured relative to signals of residual protons or carbon atoms of deuterated dimethyl sulfoxide.

REFERENCES

[1] Rinaldi L., Binello A., Stolle A., Curini M., Cravotto G. Efficient mechanochemical complexation of various steroid compounds with α-, β- and γ-cyclodextrin // Steroids. 2015. Vol. 98. P. 58–62. DOI: 10.1016/j.steroids.2015.02.016.

[2] Savic I.M., Nikolic V.D., Savic-GajicI., Nikolic L.B., Radovanovic B.C., Mladenovic J.D. Investigation of properties and structural characterization of the quercetin inclusion complex with (2-hydroxypropyl)-β-cyclodextrin // J. Incl. Phenom. Macrocycl.Chem. 2015. Vol. 82. P. 383-394. DOI: 10.1007/s10847-015-0500-4.

[3] Hazra S., Hossain M., Kumar G.S. Studies on α-, β-, and γ-cyclodextrin inclusion complexes of isoquinoline alkaloids berberine, palmatine and coralyne // J. Incl. Phenom. Macrocycl. Chem. 2014. Vol. 78. P. 311-323. DOI: 10.1007/s10847-013-0301-6.

[4] Wadhwa G., Kumar S., Chhabra L., Mahant Sh., Rao R. Essential oil-cyclodextrin complexes: an updated review // J. Incl. Phenom. Macrocycl. Chem. 2017. Vol. 89. P. 39-58. DOI: 10.1007/s10847-017-0744-2.

[5] Carvalho L.B., Burusco K.K., Jaime C., Venancio T., Carvalho A., F., S., Murgas L.D.S., Pinto L.M.A. Complexes between methyltestosterone and β-cyclodextrin for application in aquaculture production // Carbohydr. Polym. 2018. Vol. 179. P. 386-393. DOI: 10.1016/j.carbpol.2017.09.023.

[6] Yanga R., Chena J.-B., Dai X.-Y., Huang R., Xiao C.-F., GaoZh.-Y., Yang B., Yang L.-J., Yan S.-J., Zhang H.-B., Qing Ch., Lin J. Inclusion complex of GA-13315 with cyclodextrins: Preparation, characterization, inclusion mode and properties // Carbohydr. Polym. 2012. Vol. 89. P. 89-97. DOI: 10.1016/j.carbpol.2012.02.054.

[7] Yuan Ch., Jin Zh., Xu X. Inclusion complex of astaxanthin with hydroxypropyl-cyclodextrin: UV, FTIR, ^{1}H NMR and molecular modeling studies // Carbohydr. Polym. 2012. Vol. 89. P. 492-496. DOI:10.1016/j.carbpol.2012.03.033.

[8] Dandawate P.R., Vyas A., Ahmad A., Banerjee S., Deshpande J., Swamy K.V., Jamadar A., Dumhe-Klaire A.K. Padhye S., Sarkar F.H. Inclusion Complex of Novel Curcumin Analogue CDF and β-Cyclodextrin (1:2) and Its Enhanced In Vivo Anticancer Activity Against Pancreatic Cancer // Pharm. Res. 2012. Vol. 29. P. 1775-1786. DOI: 10.1007/s11095-012-0700-1.

[9] Almagambetov A.M., Temirgaziev B.S., Zavarzin I.V., Kachala V.V., Kudabaeva P.K., Tuleuov B.I., Adekenov S.M. New prospective herbal source of D-pinitol a possessing anti-diabetic and hydroglycemic properties // Khimija Rastitel'nogo Syr'ja. 2016. N 3. P. 79–84. DOI: 10.14258/jcprm.2016031004.

[10] Uekama K., Hirayama F., Irie T. Cyclodextrins Drug Carrier Systems // Chem. Rev. 1998. Vol. 98. P. 2045-2076. DOI: 10.1021/cr970025p.

[11] Rasheed A., Kumar A.S.K., Sravanthi V.V. Cyclodextrins as Drug Carrier Molecule: A Review // Sci. Pharm. 2008. Vol. 76. P. 567-598. DOI: 10.3797/scipharm.aut-08-04.

[12] Inoue Y. NMR Studies of the Structure and Properties of Cyclodextrins and Their Inclusion Complexes // Annu. Rep. NMR Spectrosc. 1993. Vol. 27. P. 59-101. DOI: 10.1016/S0066-4103(08)60265-3.

[13]Yamanoi T., Oda Y., Katsuraya K. NMR determination of concentration-switchable inclusion complex of a β-cyclodextrin derivative carrying a benzene grouplinked to a C,C-glucopyranoside spacer // J. Incl. Phenom. Macrocycl. Chem. 2017. Vol. 89. P. 189-197. DOI: 10.1007/s10847-017-0746-0.

[14] Mukae Sh., Ohashi T., Matsumoto Yu., Ohta Sh., Omura H. D-Pinitol in Fabaceae: an Oviposition Stimulant for the Common Grass Yellow Butterfly, Eurema Mandarina // J. Chem. Ecol. 2016. Vol. 42. P. 1122–1129. DOI: 10.1007/s10886-016-0775-y.

[15] Honda K., Minematsu H., Muta K., Omura H., Nishii W. D-Pinitol as a Keyovi position stimulant for sulfur butterfly, Coliaserate: chemical basis for female acceptance of host- and non-host plants // Chemoecology. 2012. Vol. 22. P. 55-63. DOI: 10.1007/s00049-011-0098-y.

[16] Demarco P.V., Thakkar A.I. Cyclohepta-amilose Inclusion Complexes. A Proton Magnetic Resonanse Study // J. Chem. Soc., Chem. Commun. 1970. Issue 1. P. 2-4. DOI: 10.1039/C29700000002.

[17] Hazra S., Hossain M., Kumar G.S. Studies on α-, β-, and γ-cyclodextrin inclusion complexes of isoquinoline alkaloids berberine, palmatine and coralyne // J. Incl. Phenom. Macrocycl. Chem. 2014. Vol. 78, Issue 1-4. P. 311-323. DOI: 10.1007/s10847-013-0301-6

[18] Loftsson T., Masson M., Brewster M.E. Self-association of cyclodextrins and cyclodextrin complexes // J. Pharm. Sci. 2004. Vol. 93, Issue 5. P. 1091-1099. DOI: 10.1002/jps.20047.

[19] Filimonov D.A., Lagunin A.A., Gloriozova T.A., Rudik A.V., Druzhilovskii D.S., Pogodin P.V., Poroikov V.V. Prediction of the Biological Activity Spectra of Organic Compounds Using the Pass Online Web Resource // Chem. Heterocycl. Compd. 2014. Vol. 50, Issue 3. P. 444-457. DOI: 10.1007/s10593-014-1496-1.

Резюме

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D-ПИНИТОЛДЫҢ ЦИКЛОДЕКСТРИНДЕРМЕН СУПРАМОЛЕКУЛАЛЫ ӨЗІН-ӨЗІ ҚҰРАУЫ

D-пинитолдың циклодекстриндермен супрамолекулалық әрекеттесуі арқылы олардың 1:1 қатынас құрамдағы суда еритін аралас кешендер түзілді. Супракешендер құрылысы ЯМР спектроскопия әдістермен зерттелінді.

Түйін сөздер: D-пинитол, циклодекстриндер, супрамолекулалы кешендер, ЯМР спектроскопия.

Резюме

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СУПРАМОЛЕКУЛЯРНАЯ САМОСБОРКА D-ПИНИТОЛА С ЦИКЛОДЕКСТРИНАМИ

Путем супрамолекулярного взаимодействия D-пинитола с циклодекстринами образованы водорастворимые смешанные комплексы состава в соотношении 1:1. Строение супракомплексов изучено методами спектроскопии ЯМР.

Ключевые слова: D-пинитол,циклодекстрины, супрамолекулярные комплексы, спектроскопия ЯМР.