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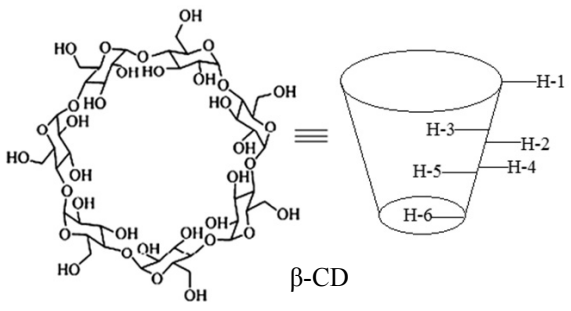
Study of supramolecular inclusion complexes of pseudoephedrine, lupinine, anabasine and cytisine with β-cyclodextrin by NMR spectroscopy

The ^{1}H, ^{13}C and DEPT one-dimensional NMR and two-dimensional spectroscopy methods COSY (^{1}H-^{1}H), HMQC (^{1}H-^{13}C) and TOCSY (^{1}H-^{1}H) were used to study the alkaloids pseudoephedrine, lupinine, anabasine and cytisine and their supramolecular inclusion complexes with cyclic polysaccharide β-cyclodextrin. The proton-proton correlation patterns are presented through three bonds and the proton-carbon correlation patterns through one bond, namely COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C) in the molecules of the alkaloids under study. The use of the capabilities of two-dimensional spectroscopy COSY (^{1}H-^{1}H), HMQC (^{1}H-^{13}C) and TOCSY (^{1}H-^{1}H) to identify the studied alkaloids allowed us to correctly and unambiguously identify the structure of substrates of the supramolecular self-assembly with a cyclic polysaccharide receptor. Homonuclear and heteronuclear correlation NMR COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C) is also used to identify and confirm the structure and structure of the cyclic polysaccharide β-cyclodextrin. The chemical shifts of the aliphatic and hydroxyl protons of the inner and outer surfaces of the receptor were determined. A comparative analysis of the ^{1}H and ^{13}C NMR spectra of pseudoephedrine, lupine, anabasine and cytisine, β-cyclodextrin and their supramolecular inclusion complexes was carried out. Changes in the chemical shifts of ^{1}H and ^{13}C nucleus of pseudoephedrine, lupinine, anabasine, and cytisine, and β-cyclodextrin in inclusion complexes were determined. The proton integral intensities of the substrate and receptor in the ^{1}H NMR spectra determined that the supramolecular interaction of the studied pseudoephedrine, lupinine, anabasine and cytisine with β-cyclodextrin is accompanied by the entry of hydrophobic fragments of 1 substrate molecule into the inner cavity 1 of the receptor molecule.

Keywords: pseudoephedrine, lupinine, anabasine, cytisine, β-cyclodextrin, inclusion complexes, NMR spectroscopy.

Introduction

NMR spectroscopy is currently one of the most informative methods for studying the structure and intermolecular interactions in inclusion complexes [1]. Therefore, this research method was chosen to study the supramolecular inclusion complexes of pseudoephedrine **1**, lupine **2**, anabasine **3** and cytisine **4** with β-cyclodextrin (β-CD). The inclusion of alkaloids **1**–**4** in the cavity of the host molecule will increase the solubility of the substance, improve bioavailability and physico-chemical stability, and protect against biodegradation [2]. Among the currently known biologically active compounds, encapsulating receptors such as cucurbiturils, crown ethers, calixarenes, and others, β-CD [3] has a number of remarkable properties due to its structure. This is a relatively readily available compound derived from a renewable source, namely starch. β-CD is a cyclic oligosaccharide containing 7 glucopyranose units. The β-CD molecule has the shape of a truncated cone, on the inner surface of which hydrophobic binding protons H-3 and H-5 are located, and on the outer surface — H-2 and H-4.



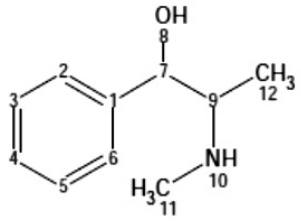
β-CD

The most important feature of β-CD is its ability to hydrophobically bind the guest molecule in its cavity in an aqueous medium.

Results and Discussion

The study by NMR spectroscopy of supramolecular inclusion complexes 5–8 obtained respectively on the basis of alkaloids 1–4 and β-CD is based on determining the difference in the values of chemical shifts of ^{1}H and ^{13}C substrates (1–4) and receptor (β-CD) in free condition and composition of complexes as a result of intermolecular interaction. According to the magnitude of chemical shifts of internal or external protons of β-CD, one can judge the formation of internal or external complexes, respectively. The change in the chemical shifts of ^{1}H and ^{13}C in the spectra of substrates makes it possible to determine the direction of the latter entering the β-CD cavity [4].

Interpretation of the ^{1}H NMR spectrum of the pseudoephedrine 1 molecule in the free state showed the presence of strong-field signals in the form of a three-proton doublet with ^{3}J 6.4 Hz at 0.67 ppm and three-proton singlet at 2.26 ppm, which can be attributed to the protons of the methyl groups H-12, 12, 12 and H-11, 11, 11, respectively.



1

One-proton quintet signal at 2.53 ppm from ^{3}J 6.4 Hz can be correlated to protons H-9. One-proton doublet at 4.19 ppm from ^{3}J to 7.2 Hz corresponds to the methane hydrogen atom H-7. Protons of the phenyl radical resonate in the low-field region of the spectrum. Proton H-4 was detected in the form of one-proton multiplet at 7.17–7.22 ppm. The remaining protons of the aromatic nucleus H-2, 6, 3, 5 resonate as multiplet at 7.26–7.27 (4H) ppm. Hydroxyl and imine protons H-8 and H-10 fell into the region of resonance of residual protons of the solvent and appeared along with them as broadened singlet at 3.25 ppm. Similar signals are observed in the PMR spectrum of the pseudoephedrine complex with β-CD 5.

In the carbon NMR spectrum of an individual pseudoephedrine, signals of methyl atoms C-12 and C-13 are observed in the strong field region at 15.77 and 33.90 ppm, respectively. Asymmetric carbon atoms C-9 and C-7 correspond to doublet signals with chemical shifts of 61.10, 61.30 and 76.72–76.94 ppm, respectively. Aromatic carbon atoms resonate at 127.35 (C-3, 5), 128.07 (C-4), 128.44 (C-2, 6) and 144.10 (C-1) ppm. In the supramolecular complexes of pseudoephedrine with β-CD in comparison with the free substrate, the signals of ^{13}C nuclei ($\pm\Delta\delta$) are shifted both to the weak and strong fields (Table 1). This is due to the disshielding and shielding of carbon nuclei during the formation of supra complexes when the interacting nuclei approach each other.

Table 1

Chemical shifts NMR ^{1}H and ^{13}C 1 and β-CD in the free state and in complex 5

Atom number	Group	The value of δ_0 in the free state, ppm		The value of δ in the complex, ppm		Change in chemical shift $\Delta\delta(\delta - \delta_0)$, ppm	
	CH_x	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1	2	3	4	5	6	7	8
Pseudoephedrine							
1	=C<	–	144.10	–	144.02	–	-0.08
2	=CH-	7.27	128.44	7.27	128.48	0	0.04
3	=CH-	7.26	127.35	7.26	127.35	0	0
4	=CH-	7.20	128.07	7.20	128.09	0	0.02
5	=CH-	7.26	127.35	7.26	127.35	0	0
6	=CH-	7.27	128.44	7.27	128.48	0	0.04
7	>CH-	4.19	76.94	4.19	76.88	0	-0.06

Continuation of Table 1

1	2	3	4	5	6	7	8
9	>CH-	2.53	61.10	2.53	57.03	0	-4.07
11	$-CH_3$	2.26	33.90	2.26	33.82	0	-0.08
12	$-CH_3$	0.67	15.77	0.67	15.71	0	-0.06
β-cyclodextrin							
1	>CH-	4.77	102.43	4.79	102.68	0.02	0.25
2	>CH-	3.27	72.87	3.29	72.92	0.02	0.05
3	>CH-	3.49	73.54	3.59	73.68	0.10	0.14
4	>CH-	3.30	82.00	3.34	82.14	0.04	0.14
5	>CH-	3.45	72.52	3.55	72.65	0.10	0.13
6	$-CH_2-$	3.57	60.40	3.61	60.57	0.04	0.17

The NMR spectrum of an individual β-CDD (Fig. 1) is characterized by the manifestation of six groups of signals in the region 3.23–3.32; 3.45–3.60; 4.47–4.49; 4.77–4.78; 5.66; 5.71–5.73 ppm.

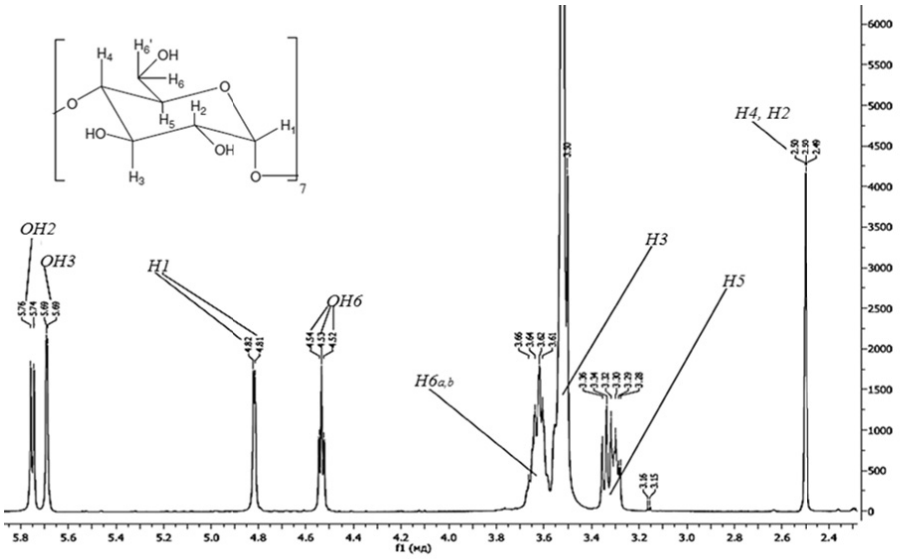


Figure 1. ^{1}H NMR spectrum β-CD

The lowest-field doublet signal in the range of 5.71–5.73 ppm with the splitting of 4 Hz belongs to the proton of the hydroxyl group at the C-2 atom. Also in the weak field region, the proton of the OH group of the neighboring atom (OH-3) resonates in the internal cavity of the β-CD molecule (δ = 5.66 ppm, doublet). The doublet signal in the region of 4.77–4.78 ppm corresponds to the proton H-1 β-CDD. The location of the indicated proton in a weaker field compared to the protons of other CH groups is due to the influence of the oxygen atom. The hydroxyl group OH-6 resonates splitting into a triplet with a center at 4.48 ppm. In the field of a strong field at 3.49–3.60 ppm signals of protons H-6a, b of the methylene group are observed. High intensity signal at 3.45 ppm corresponds to the protons H-3 and H-5 of glucopyranose link. In the range from 3.23 to 3.32 ppm metinic protons H-2 and H-4 appear.

The β-CD NMR spectrum (Fig. 2) consists of six signals from ^{13}C nuclei of the elementary link.

The signal of carbon atom C-6 appears at 60.41 ppm in the high-field part. The signals at 72.49, 72.85 and 7351 ppm resonate due to the C-5, C-2 and C-3 atoms, respectively. Signals of carbon atoms C-4 and C-1, respectively, are observed in the weaker field at 82.02 and 102.41 ppm, which are directly connected with the neighboring glucopyranous unit through the oxygen bridge.

The study of the one-dimensional spectra of β-CD in the free and bound state (Table 1) made it possible to identify the pattern of displacement of all ^{1}H and ^{13}C signals of the host molecule to the weak field, which confirms non-valent binding to the guest. For proton spectra, the greatest difference in the chemical shift values (Δδ=+0.10 ppm) is characteristic of the H-3 and H-5 inner-sphere protons, on the basis of which it can be concluded that an internal (inclusive) complex with pseudoephedrine is formed. In the case of the carbon spectrum, the difference is more significant and ranges from 0.05–0.25 ppm.

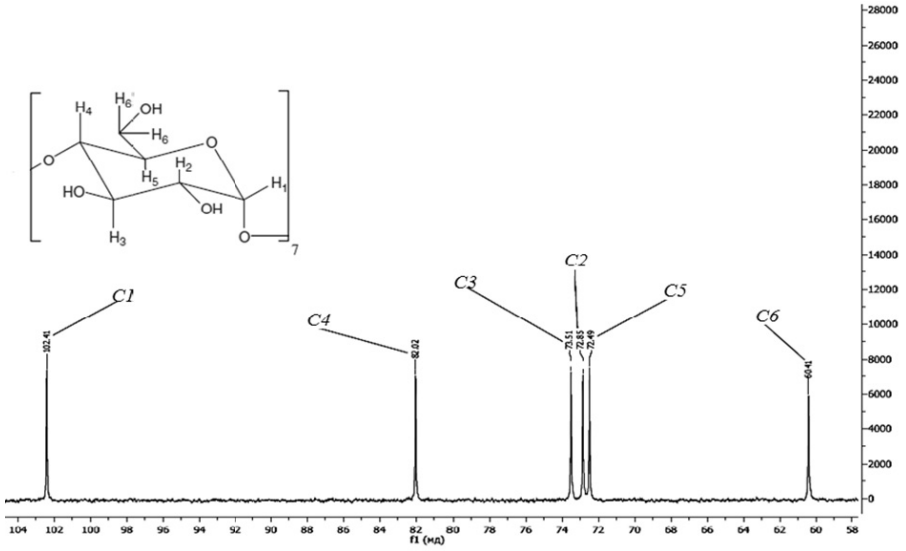


Figure 2. ^{13}C NMR spectrum β-CD

Analysis of two-dimensional NMR spectra in COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C) formats (Fig. 3 and 4) allowed us to establish homo- and heteronuclear interactions in pseudoephedrine molecules in both the free state 1 and in the composition of the supramolecular inclusion complex 5.

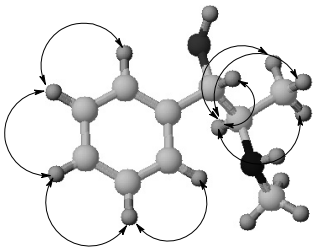


Figure 3. Correlations of COSY (^{1}H-^{1}H) in molecule 1

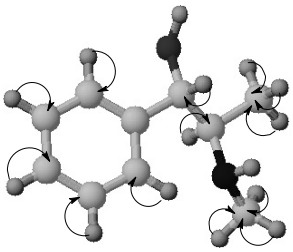
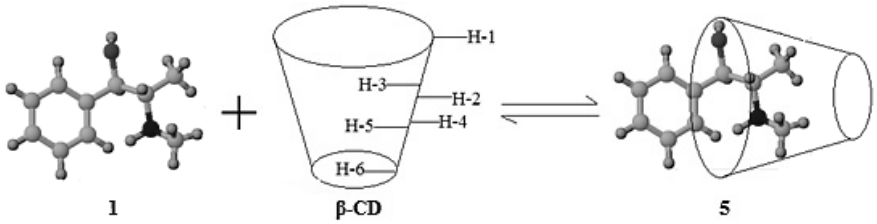


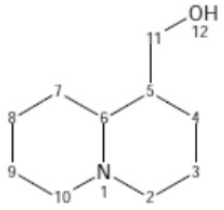
Figure 4. Correlations of HMQC (^{1}H-^{13}C) in molecule 1

Thus, the formation of supramolecular inclusion complexes is confirmed on the basis of changes in the chemical shifts of NMR of the substrate and receptor atoms. Comparison of the integral intensities of the ^{1}H signals of the receptor molecules and the substrate in individual and encapsulated forms showed that there was 1 receptor molecule in the inclusion complexes 5 per 1 substrate molecule. Considering that the greatest displacements of atoms in the substrate molecule are observed for the aliphatic fragment, we can assume the following picture of the inclusion of pseudoephedrine in the internal cavity of β-CD (Scheme 1):



Scheme 1. The formation of the inclusion complex 1 with β-CD

In the spectra of free lupinine in the strong field at 1.03–1.64 and 1.75–1.91 ppm multiplet signals with an intensity of 10H and 4H, respectively, of protons H-6, 4, 4, 3, 3, 8, 8, 5, 7, 7, and H-9, 9, 2, 2 condensed ring systems are observed. The doublet-like multiplet signal at 2.65–2.67 ppm with integral 2H can be attributed to the protons H-10, 10. The two-proton multiplet at 3.47–3.59 ppm belongs to the methylene protons H-11, 11. Hydroxyl protons H-11 resonated with a broad one-proton singlet at 4.23 ppm.



2

Carbon atoms resonate at 21.62 (C-3), 25.40 (C-8), 25.75 (C-6), 27.40 (C-7), 29.35 (C-4), 41.00 (C-5) in the ^{13}C NMR spectrum of substrate 2. The weakest field signals are at 57.28, 60.45 and 64.66 ppm can be attributed to carbon atoms with a nitrogen heteroatom of C-2, 10, C-9 and secondary C-11, respectively.

Analysis of the two-dimensional spectra of COSY (^1H-^1H) and HMQC (^1H-^{13}C) (Fig. 5, 6) allowed us to establish homo- and heteronuclear interactions in the substrate molecule. The COSY correlations carried out through three bonds are determined between the protons of the system of condensed nuclei of the lupinine molecule.

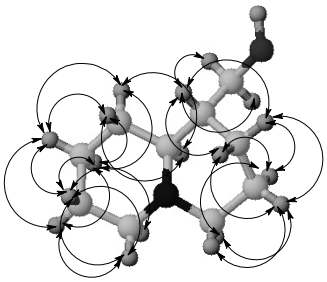


Figure 5. Correlations of COSY (^1H-^1H) in molecule 2

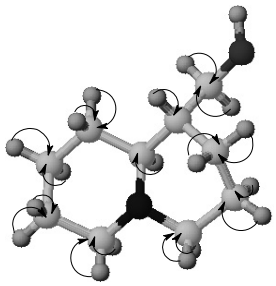


Figure 6. Correlations of HMQC (^1H-^{13}C) in molecule 2

Nonvalent bonding of atoms occurs in the process of supramolecular interaction. This is reflected in the chemical shifts of the interacting nuclei. Equivalent signals of protons of condensed nuclei of lupinine appear in the spectrum of the inclusion complex with β-CD (6) in the ranges 1.00–1.62 and 1.76–1.92 ppm. The signal of the methylene proton in the OH group as a result of complexation shifts to 3.49–3.50 ppm.

For β-CD protons, the formation of an inclusion complex is accompanied by the displacement of all ^1H nuclei into the region of a weak field. The largest difference in chemical shift values (Δδ=+0.10–0.12 ppm) is characteristic of the H-3 and H-5 inner-sphere protons, on the basis of which it can be concluded that an internal β-CD complex is formed lupinine (Table 2).

In the case of carbon spectra of substrate 2, the receptor and their complex 6, a more significant shift of signals is observed. To the carbon atoms of the condensed system, lupinine molecules correspond to signals at 21.59, 25.40, 27.35 and 29.33 ppm. The C-6 signal of the methine group is observed at 25.69 ppm. The weak field signals of the C-2, 10, C-9 and C-11 atoms also underwent slight shifts on the chemical shift scale and appear at 57.28, 64.62 and 60.56 ppm, respectively. The difference in the values of changes in chemical shifts ranges from 0.03–0.25 ppm for carbon atoms of β-CD (Table 2).

Table 2

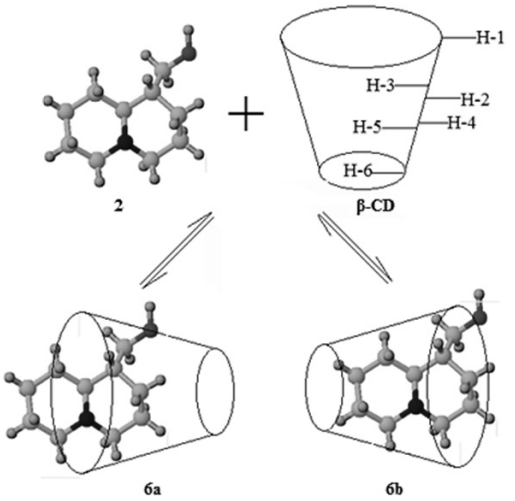
Chemical shifts NMR ^1H and ^{13}C 2 and β-CD in the free state and as part of complex 6

Atom number	Group	The value of δ_0 in the free state, ppm		The value of δ in the complex, ppm		Change in chemical shift $\Delta\delta(\delta-\delta_0)$, ppm	
	CH_x	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
1	2	3	4	5	6	7	8
Lupinine							
2	$-CH_2-N$	1.90	57.29	1.92	57.28	0.02	-0.01
3	$-CH_2-$	1.36	21.62	1.34	21.59	-0.02	-0.03
4	$-CH_2-$	1.34	29.35	1.32	29.33	-0.02	-0.02
5	>CH-	1.58	41.01	1.57	41.03	-0.01	0.02
6	>CH-	1.17	25.58	1.20	25.69	0.03	0.11
7	$-CH_2-$	1.65	27.40	1.64	27.42	-0.01	0.02

Continuation of Table 2

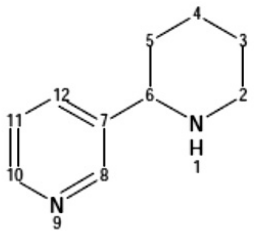
1	2	3	4	5	6	7	8
8	-CH_2-	1.37	25.40	1.38	25.40	0.01	0
9	-CH_2-	1.82	64.66	1.83	64.62	0.01	-0.04
10	-CH_2-N	2.66	57.29	2.66	57.28	0	-0.01
11	-CH_2OH	3.56	60.45	3.55	60.49	-0.01	0.04
β-cyclodextrin							
1	>CH-	4.77	102.43	4.79	102.68	0.02	0.25
2	>CH-	3.27	72.87	3.30	72.90	0.03	0.03
3	>CH-	3.49	73.54	3.61	73.69	0.12	0.15
4	>CH-	3.30	82.00	3.33	82.15	0.03	0.15
5	>CH-	3.45	72.52	3.55	72.66	0.10	0.14
6	-CH_2-	3.57	60.40	3.61	60.56	0.04	0.16

Thus, the formation of supramolecular inclusion complexes is confirmed on the basis of changes in chemical shifts of the characteristic atoms of the substrate and receptor. Comparison of the integral intensities of the ^{1}H NMR signals of the receptor molecules and the substrate in the free and encapsulated forms showed that in the 6 per 1 inclusion molecule complexes there is 1 receptor molecule. Taking into account that the greatest displacements of atoms in the substrate molecule are observed uniformly for the atoms of the entire lupinine molecule, the following variants of encapsulating lupinine into the β-CD cavity can be assumed (Scheme 2).



Scheme 2. Possible options for encapsulating 2 in β-CD

In the spectrum of molecular anabasine **3** in the range from 1.25 to 1.52 ppm NMR ^{1}H observed signals 4 protons, which can be correlated to the CH_2-groups with atoms of C-4 and C-5 of the piperidine system. The protons of two neighboring methylene groups of the heterocycle resonate at 1.76 (H-3, multiplet), 2.61 (H-2ax, triplet of doublets, ^{2}J 11.7, ^{3}J .7 Hz) and 2.99 (H-2eq, doublet, ^{2}J 13.7 Hz) ppm. Proton H-6 was manifested by a one-proton doublet of doublets at 3.54 with ^{2}J 10.8 and ^{3}J 2.5 Hz. In the weak-field region of the spectrum, protons of the pyridine cycle at 7.26 (H-11), 7.68 (H-12), 8.38 (H-10) and 8.50 (H-10) ppm manifested themselves in the multiplet signals.



3

In the case of the carbon spectrum of anabasine, a similar picture is noted — the signals of ^{13}C nuclei of the piperidine fragment are observed in the region of a strong field, while the pyridine cycle gives signals in the weak-field part. Methylene atoms C-2, C-3, C-4 and C-5 of a saturated heterocycle are signals with chemical shifts at 47.20, 25.97, 25.81 and 35.38 ppm, respectively. The methine atom C-6 resonates at 59.37 ppm. Carbon atoms in the *o*-position of the pyridine ring give signals in the region of 148.26–148.86 ppm *m*-Atoms C-7 and C-11 resonate at 141.60 and 123.66 ppm, respectively. The carbon atom C-12 appeared at 134.52 ppm. It should be noted that the presence of asymmetric carbon atoms in the molecule 3 leads to the splitting of ^{13}C NMR signals due to the presence of antipodes in the molecules studied.

Homo- and heteronuclear correlations in the anabasine molecule were established using the two-dimensional spectra of COSY (^1H-^1H) (Fig. 7) and HMQC (^1H-^{13}C) (Fig. 8).

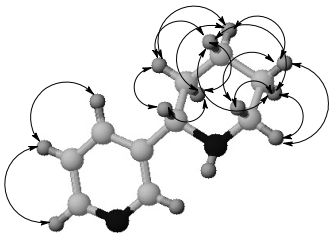


Figure 7. Correlations of COSY (^1H-^1H) in molecule 3

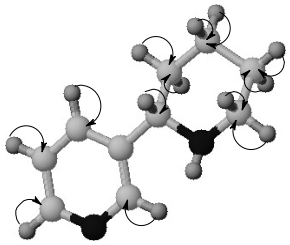


Figure 8. Correlations of HMQC (^1H-^{13}C) in molecule 3

An insignificant strong-field shift was observed ($\Delta\delta$ = –0.01 ppm) for protons of the piperidine ring of molecule 3 during complexation. In the supracomplex, the signals of the protons of the pyridine system are observed at 7.27, 7.68, 8.38 and 8.49 ppm. Since the signals of the piperidine fragment of the substrate underwent the greatest change in the process of complexation, the assumption was made that the protons were bound to the protons of β-CD.

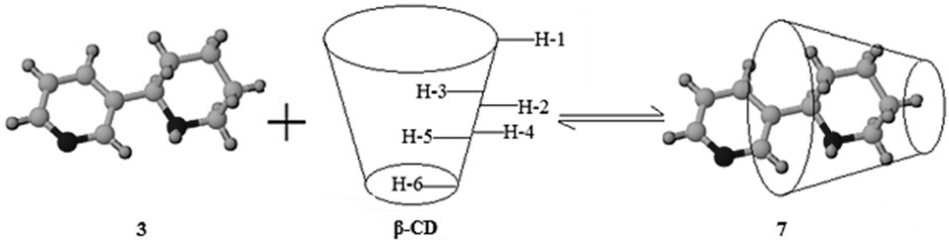
For ^1H cyclodextrin cone nuclei, the formation of a complex is accompanied by a shift of all signals to the weak field region. The largest difference in the chemical shift values ($\Delta\delta$=+0.11–0.12 ppm) is characteristic of the protons of the internal cavity H-3 and H-5, on the basis of which it can be concluded that the formation of the supramolecular inclusion complex 7 of the cyclic polysaccharide with molecule 3 (Table 3).

Table 3

Chemical shifts NMR ^1H and ^{13}C 3 and β-CD in the free state and as part of complex 7

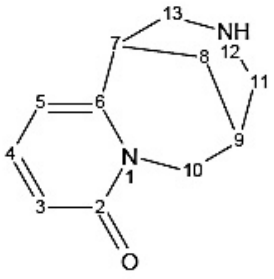
Atom number	Group	The value of δ_0 in the free state, ppm		The value of δ in the complex, ppm		Change in chemical shift $\Delta\delta(\delta-\delta_0)$, ppm	
	CH_x	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
Anabasine							
2	$-CH_{ax}$	2.61	47.20	2.61	47.16	0	-0.04
	$-CH_{eq}$	2.99		2.99		0	
3	$-CH_2-$	1.76	25.97	1.75	25.95	-0.01	-0.02
4	$-CH_2-$	1.45	25.51	1.44	25.48	-0.01	-0.03
5	$-CH_2-$	1.38	35.24	1.37	35.21	-0.01	-0.03
6	>CH-	3.54	59.37	3.56	59.33	0.02	-0.06
7	>C=	–	141.60	–	141.57	–	-0.03
8	-CH=N	8.50	148.26	8.49	148.28	-0.01	0.02
10	-CH=N	8.38	148.62	8.38	148.62	0	0
11	-CH=	7.26	123.66	7.27	123.70	0.01	0.04
12	-CH=	7.68	134.52	7.68	134.66	0	0.14
β-cyclodextrin							
1	>CH-	4.77	102.43	4.79	102.66	0.02	0.23
2	>CH-	3.27	72.87	3.30	72.96	0.03	0.09
3	>CH-	3.49	73.54	3.61	73.68	0.12	0.14
4	>CH-	3.30	82.00	3.34	82.16	0.04	0.16
5	>CH-	3.45	72.52	3.56	72.65	0.11	0.13
6	$-CH_2-$	3.57	60.40	3.63	60.57	0.06	0.17

Based on the values of the integral intensities of the signals of the protons of CD, consisting of seven glucopyranose units and 6–7 water molecules released during complexation, it can be assumed that one molecule 3 is inserted into the internal cavity of one β-CD molecule with the piperidine fragment of the substrate entering the internal cavity of the receptor (Scheme 3):



Scheme 3. The formation of the inclusion complex 3 with β-CD

The cytisine 4 alkaloid in the low-field part of the proton spectrum exhibits two doublet at 6.00 (1H, H-5, ^{3}J 6.8 Hz) and 6.16 (1H, H-3, ^{3}J 6.8 Hz) ppm and one triplet signal at 7.27 (1H, H-4, ^{3}J 6.8 Hz) of the pyridine core. In the area of 3.63–3.80 ppm (2H) the resonances of the protons H-10ax and H-10eq are noted, and the signal of the axial proton is shifted to the strong-field part of the spectrum. Four protons H-11, 11, 13, 13 methylene groups associated with the NH-group, and the methine proton H-7 give signals in the range of 2.73–2.90 ppm (5H), splitting under the influence of neighboring atoms into triplets and a multiplet, respectively. Widened singlet signals in the high-field part of the spectrum at 1.77 (2H) and 2.20 (1H) ppm correspond to protons H-8 and H-9.



4

Analysis of the DEPT format spectra indicated the presence of four CH_2-signals and five CH-group signals in the carbon spectrum. Spectra at 139.19, 115.60 and 104.36 ppm correspond to the C-4, C-3 and C-5 atoms of the methine groups of the α-pyridine system. Two other signals of tertiary carbon atoms appear in the region of 35.33 and 27.75 ppm and are due to C-7 and C-9 atoms, respectively.

The signals of the methylene groups of the bicyclic system appeared at 26.41 (C-8), 49.98 (C-10), 53.16 (C-11) and 54.07 (C-13) ppm. In the weakest field at 152.95 and 162.85 ppm low-intensity signals of quaternary carbon atoms C-6 and C-2, respectively, appear.

The results of the analysis of two-dimensional spectra in the formats COSY (^{1}H-^{1}H), TOCSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C) indicating homo- and heteronuclear interactions in molecule 4 are presented in the diagrams below (Fig. 9–11).

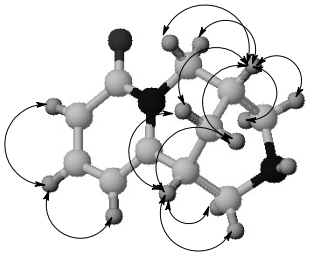


Figure 9. Scheme of the COSY (^{1}H-^{1}H) correlations in molecule 4

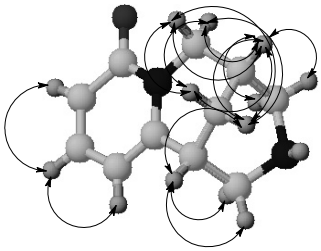


Figure 10. Scheme of TOCSY (^{1}H-^{1}H) correlations in molecule 4

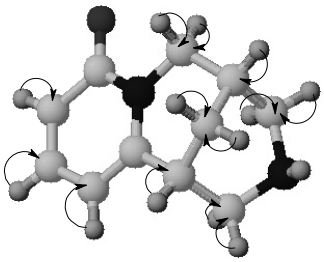


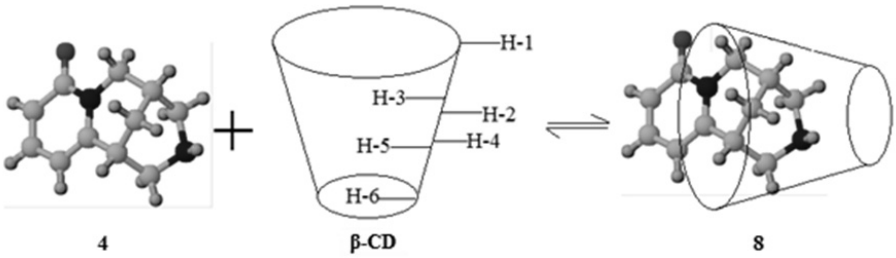
Figure 11. Scheme of HMQC (^{1}H-^{13}C) correlations in molecule 4

According to Table 4, it can be noted that all protons of the glucopyranose β-CDA link in the complex are shifted towards a weaker field compared to similar protons of the individual receptor, with the largest difference in chemical shift values ($\Delta\delta(^1H)$=0.15 m.e.) are observed in the protons of the internal cavity of the toroidal molecule H-3 and H-5. That serves as evidence of the formation of an inclusion complex 8. Comparison of the proton integral intensities of the substrate and receptor indicate the formation of a supramolecular complex of 1:1 composition (Scheme 4).

Table 4

Chemical shifts NMR ^1H and ^{13}C 4 and β-CD in the free state and as part of complex 8

Atom number	Group	The value of δ_0 in the free state, ppm		The value of δ in the complex, ppm		Change in chemical shift $\Delta\delta(\delta-\delta_0)$, ppm	
	CH_x	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
Cytisine							
2	>C=O	–	162.85	–	162.92	–	0.07
3	=CH-	6.16	115.60	6.17	115.62	0.01	0.02
4	=CH-	7.27	139.19	7.28	139.27	0.01	0.08
5	=CH-	6.00	104.36	6.01	104.51	0.01	0.15
6	>C=	–	152.95	–	152.89	–	-0.06
7	>CH-	2.76	35.33	2.76	35.27	0	-0.06
8	$-CH_2-$	1.77	26.41	1.78	26.35	0.01	-0.06
9	>CH-	2.20	27.75	2.21	27.69	0.01	-0.06
10	$-CH_2-$	3.76	49.98	3.76	49.98	0	0
11	$-CH_2-$	2.84	53.16	2.86	53.08	0.02	-0.08
13	$-CH_2-$	2.80	54.07	2.81	54.01	0.01	-0.06
β-cyclodextrin							
1	>CH-	4.77	102.43	4.79	102.49	0.02	0.06
2	>CH-	3.27	72.87	3.29	72.97	0.02	0.10
3	>CH-	3.45	73.54	3.60	73.60	0.15	0.06
4	>CH-	3.30	82.00	3.31	82.12	0.01	0.12
5	>CH-	3.45	72.52	3.60	72.59	0.15	0.07
6	$-CH_2-$	3.57	60.40	3.62	60.49	0.05	0.09



Scheme 4. The formation of the inclusion complex 4 with β-CD

Conclusions

From the above results, it follows that all the alkaloids studied enter supramolecular self-assembly with β-cyclodextrin with the formation of 1:1 inclusion complexes with the occurrence of the hydrophobic part of substrates in the inner region of the receptor. This will increase the solubility of substrates in water. The resulting supra complexes of alkaloids are essentially nanocomplexes of the latter and can be further implemented in nanomedicine.

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Псевдоэфедрин, лупинин, анабазин және цитизиннің β-циклодекстринмен супрамолекулалық қосылу кешендерін ЯМР спектроскопия әдісімен зерттеу

Бірөлшемді ^{1}H, ^{13}C, DEPT және екіөлшемді COSY (^{1}H-^{1}H), HMQC (^{1}H-^{13}C) және TOCSY (^{1}H-^{1}H) ЯМР спектроскопиялары әдістері арқылы псевдоэфедрин, лупинин, анабазин және цитизин алкалоидтары, сонымен қатар құрамында циклдық полисахариды бар β-циклодекстрин қосылу кешендері зерттелді. Зерттеліп отырған алкалоид молекулаларындағы протондармен үш байланыс арқылы біріккен протондардың корреляция сызбасы және COSY (^{1}H-^{1}H) және HMQC (^{1}H-^{13}C) бір байланысты көміртек атомдары протондарының корреляциясы келтірілген. Зерттеліп отырған алкалоидтарды сәйкестендіру кезінде COSY (^{1}H-^{1}H), HMQC (^{1}H-^{13}C) және TOCSY (^{1}H-^{1}H) екіөлшемді спектроскопия мүмкіндіктері циклдік полисахаридты рецепторы бар супрамолекулалық өздік жинақталған субстраттардың құрылымын дұрыс әрі нақты сәйкестендіруге мүмкіндік берді. Сонымен қатар COSY (^{1}H-^{1}H) және HMQC (^{1}H-^{13}C) ЯМР-тың гомо- және гетероядролы корреляциясы β-циклодекстрин циклдік полисахаридтың құрылымы мен құрылысын сәйкестендіруге және растауға қолданылды. Псевдоэфедрин, лупинин, анабазин, цитизин, β-циклодекстриннің және олардың қосылу кешендерінің ЯМР спектрлеріне салыстырмалы талдау жүргізілді. Псевдоэфедрин, лупинин, анабазин, цитизин, β-циклодекстриннің және олардың қосылу кешендеріндегі ^{1}H және ^{13}C ядролардың химиялық жылжу мәндерінің өзгеруі анықталды. ЯМР ^{1}H спектрлеріндегі субстрат пен рецептордың протондық интегралдық қарқындылықтарының мәні бойынша зерттеліп отырған псевдоэфедрин, лупинин, анабазин және цитизиннің β-циклодекстринмен супрамолекулалық әрекеттесуі молекула 1 гидрафобты фрагментінің рецептор молекуласының 1 ішкі қуысына енуімен жүреді.

Кілт сөздер: псевдоэфедрин, лупинин, анабазин, цитизин, β-циклодекстрин, қосылу кешені, ЯМР спектроскопиясы.

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Исследование супрамолекулярных комплексов включения псевдоэфедрина, лупинина, анабазина и цитизина с β-циклодекстрином методом спектроскопии ЯМР

Методами ЯМР одномерной ^{1}H, ^{13}C и DEPT и двумерной спектроскопии COSY (^{1}H-^{1}H), HMQC (^{1}H-^{13}C) и TOCSY (^{1}H-^{1}H) исследованы алкалоиды псевдоэфедрин, лупинин, анабазин и цитизин, а также их супрамолекулярные комплексы включения с циклическим полисахаридом β-циклодекстрином. Представлены схемы корреляций протонов с протонами через три связи и схемы корреляций протонов с углеродными атомами через одну связь COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C) в молекулах исследуемых алкалоидов. Использование при идентификации изучаемых алкалоидов возможностей двумерной спектроскопии COSY (^{1}H-^{1}H), HMQC (^{1}H-^{13}C) и TOCSY (^{1}H-^{1}H) позволило правильно и однозначно идентифицировать строение субстратов супрамолекулярной самосборки с циклическим полисахаридным рецептором. Гомоядерная и гетероядерная корреляция ЯМР COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C) применена также для идентификации и подтверждения строения и структуры циклического полисахарида β-циклодекстрина. Были определены химические сдвиги алифатических и гидроксильных протонов внутренней и внешней поверхности рецептора. Проведен сравнительный анализ спектров ЯМР ^{1}H и ^{13}C псевдоэфедрина, лупинина, анабазина и цитизина, β-циклодекстрина и их супрамолекулярных комплексов включения. Определены изменения значений химических сдвигов ядер ^{1}H и ^{13}C псевдоэфедрина, лупинина, анабазина и цитизина, а также β-циклодекстрина в комплексах включения. По величине протонных интегральных интенсивностей субстрата и рецептора в спектрах ^{1}H ЯМР было определено, что супрамолекулярное взаимодействие исследуемых псевдоэфедрина, лупинина, анабазина и цитизина с β-циклодекстрином сопровождается вхождением гидрофобных фрагментов 1 молекулы субстрата во внутреннюю полость 1 молекулы рецептора.

Ключевые слова: псевдоэфедрин, лупинин, анабазин, цитизин, β-циклодекстрин, комплексы включения, спектроскопия ЯМР.