ORIGINAL ARTICLE

IR, UV and NMR studies of *β*-cyclodextrin inclusion complexes of kazcaine and prosidol bases

U. Kemelbekov · Y. Luo · Z. Orynbekova ·
Zh. Rustembekov · R. Haag · W. Saenger ·
K. Praliyev

Abstract The interaction of the analgesic prosidol [1-(2-ethoxyethyl)-4-phenyl-4-propionyl-oxypiperidine] and the anaesthetic kazcaine [1-(2-ethoxyethyl)-4-ethynyl-4-benzoyloxypiperidine] with *β*-cyclodextrin (*β*-CD) in aqueous solutions has been studied by nuclear magnetic resonance (NMR), ultraviolet (UV) and infrared (IR) spectroscopy. The composition and structure of the formed guest:*β*-CD inclusion complexes have been determined and were found to have a molar ratio of 1:2, with the guest molecule located in the cavity formed by two *β*-CD molecules in head-to-head orientation, with the O(2), O(3) rims interacting. The phenyl and ethoxyethyl substituents of the guests are in contact with the *β*-CD molecules. In contrast to prosidol–base and kazcaine–base the complexes with *β*-CD show a higher analgesic and local anaesthetic activity.

Keywords Kazcaine and prosidol base · Cyclodextrin · Anaesthetic and analgesic · 2D NMR · ¹H NMR · UV and IR-spectroscopy

U. Kemelbekov (✉) · Z. Orynbekova · Zh. Rustembekov · K. Praliyev
Institute of Chemical Sciences of MES RK, Kazakhstan Sh. Ualihanov Str., 106, Almaty 050010, Kazakhstan
e-mail: k_ulan@rambler.ru

Y. Luo (✉) · R. Haag
Institut für Chemie und Biochemie/Organishe Chemie, Freie Universität Berlin, Takustrasse 3, 14195 Berlin, Germany
e-mail: yingfu05@hotmail.de

W. Saenger
Institut für Chemie und Biochemie/Kristallographie, Freie Universität Berlin, Takustrasse 6, 14195 Berlin, Germany

Introduction

Since the pain syndrome relief is a basic problem in medical practice, the development of novel and highly effective medications with analgesic and anaesthetic actions attracts attention. Prosidol–base [1-(2-ethoxyethyl)-4-phenyl-4-propionyl-oxypiperidine] is analgesic drug acting on the central nervous system, and kazcaine–base [1-(2-ethoxyethyl)-4-ethynyl-4-benzoyl piperidine] (Scheme 1) is a local anaesthetic and antiarrhythmic drug. Both compounds were first synthesized by the group of Prof. Praliev [1–3] at the A. B. Bekturov Institute of Chemical Sciences of the Republic of Kazakhstan. At present, the analgesic prosidol has been approved for industrial production and medical application, and the anaesthetic kazcaine undergoes final stages of clinical trials [3, 4]. Since the free bases of prosidol and kazcaine are poorly soluble in water, the hydrochlorides with better solubility are frequently used (prosidol–HCl), (kazcaine–HCl), Scheme 1.

For the biologically active prosidol and kazcaine, scientific studies have been initiated with the aim to create new formulations based on different polymer compositions [5, 6]. The results suggested various polymeric pharmaceutical forms of prosidol and kazcaine, which allowed to optimize the concentration in the body and to reduce the consumption of active ingredients, as well as increasing the time of action.
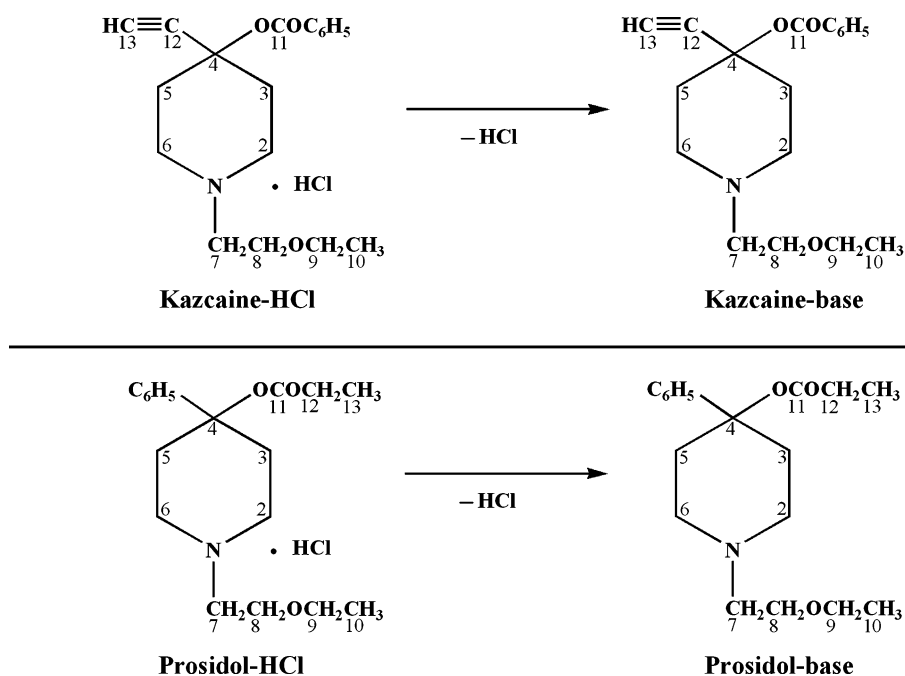
Besides hydrochlorides and polymer modifications, the use of inclusion complexes of biologically active substances with naturally occurring cyclic oligosaccharides, the α-, β-, γ-cyclodextrins, is a prospective way for creating new forms of drugs. The use of inclusion complexes of biologically active substances with the naturally occurring cyclic oligosaccharides α-, β-, γ-cyclodextrins may increase the solubility of drugs in water. Moreover, the

Scheme 1 Scheme of the formation of water soluble salt forms of kazcaine and prosidol

Kazcaine-HCl   **Kazcaine-base**

Prosidol-HCl   **Prosidol-base**

transition of drugs from the liquid to solid state (when inclusion complexes are formed) can improve the chemical stability and biological availability and reduce side effects of drugs [7–9]. Therefore, this method is widely applied in modern pharmaceutical industry and is a prospective way for creating new forms of drugs [10, 11]. Among the natural cyclodextrins, β-cyclodextrin (β-CD) is most often used due to its availability and low price. For the above reasons, inclusion complexes of the poorly water soluble analgesic prosidol and the anaesthetic kazcaine with β-CD may be of importance for the production of new drug forms.

The research presented here deals with the production of inclusion complexes of β-CD with free bases of kazcaine and prosidol (Scheme 1) and describes methods for their identification.

Experimental

Materials

Prosidol and kazcaine were synthesized and purified according to published procedures [3, 4]. β-cyclodextrin (β-CD) from SIGMA was used to produce inclusion complexes by co-precipitation from aqueous-ethanol solutions.

Synthesis of complexes formed by β-cyclodextrin with bases of kazcaine and prosidol

To produce the inclusion complex of *kazcaine–base with β-CD* or of *prosidol–base with β-CD* the co-precipitation

method from aqueous-ethanol solution was used. 50 mL of a 20 mM aqueous solution of β-CD was added to 25 mL of a 40 mM ethanol solution of kazcaine–base or of prosidol–base, heated to 65 °C during 15 min and allowed to cool to room temperature. The formed precipitate was separated from the mother liquor, washed with distilled water and left at room temperature for 24 h to dry, yielding 1.437 g (86.7%) and 0.8750 g (38.8%) β-CD inclusion complexes with kazcaine–base and prosidol–base, respectively, as crystalline powder.

Physicochemical analysis of the formed complexes

IR spectroscopy

IR spectra were recorded at 25 °C with a Nicolet Avator 320 FT-IR spectrometer on solid samples prepared as KBr pellets.

UV-spectroscopy

UV spectra were recorded on a JAS.co Model 7850 UV/VIS spectrophotometer at 25 °C.

^{1}H NMR spectroscopy

The ^{1}H NMR spectra of the compounds in a mixture of methanol-d$_4$ and D$_2$O (1:2) were recorded with an ECX-400 MHz spectrometer. The proton chemical shifts of β-CD and of the guest compounds were characterized [12, 13]. The 2D NOESY spectra of the complexes in a

mixture of methanol-d_4 and D_2O (1:2) were recorded with a Delta JEOL Eclipse (700 MHz) spectrometer at 25 °C.

Results and discussion

Complex formation studied by IR spectroscopy

The formation of an inclusion complex between β-CD and a guest substance is accompanied by changes in their IR spectra as compared with the individual components [14, 15]. Figure 1 shows the IR spectra of β-CD, kazcaine–base, their complex, and a physical mixture (1:1, molar ratio) in the solid state that were recorded within 750–2,000 and 2,750–3,750 cm^{-1} at 25 °C. Significant differences of C–H and C=O vibration modes are indicated.

In the aliphatic C–H region, the peaks are not only shifted after complex formation, but the shapes of peaks are also changed at 25 °C. As compared to the multi-peaks within 2,804–2,974 cm^{-1} for individual kazcaine–base, the aliphatic C–H vibration in the complex with β-CD becomes broader and is located at wavenumber 2,928 cm^{-1}, suggesting an interaction between kazcaine–base and β-CD. This is not detected in the physical mixture (Fig. 1), in which only a superposition of peaks of the two individual components is observed. The C=O absorption band is the most informative one and appears for individual kazcaine–base and for the physical mixture at 1,713 and 1,714 cm^{-1}, respectively. In the inclusion complex with β-CD this band shifts to 1,726 cm^{-1}. The changes in C–H and C=O bands indicate that both, the aromatic moiety and the ethoxyethyl substituent of kazcaine, are located in the cavity of β-CD.

Figure 2 shows the solid state IR spectra recorded within 750–2,000 and 2,750–3,750 cm^{-1} for β-CD, prosidol–base, their complex, and physical mixture (1:1, molar ratio).
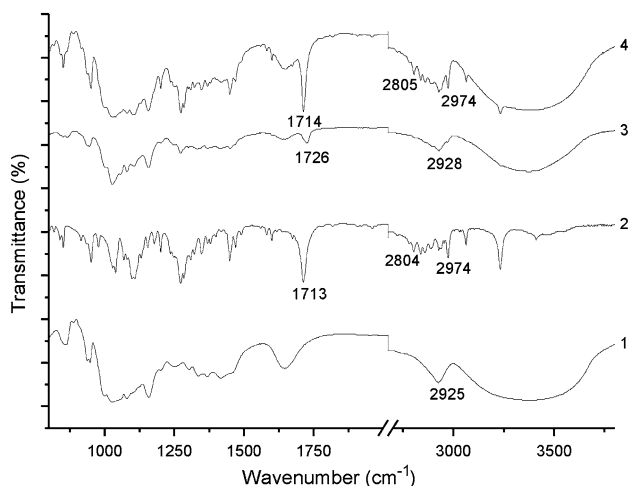

Fig. 1 Solid state FT-IR spectra of β-CD (1), kazcaine–base (2), complex (3), and physical mixture (1:1, mol%) (4)
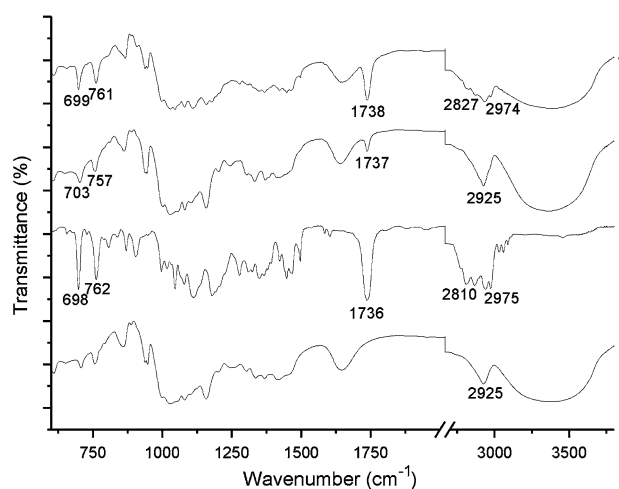

Fig. 2 Solid state FT-IR spectra of β-CD (1), prosidol–base (2), inclusion complex (3), and physical mixture (1:1, mol%) (4)

Differences of the aliphatic C–H and C=O vibrations and of the monosubstituted benzene are indicated.

The IR-spectrum of prosidol–base shows absorption bands of the monosubstituted benzene at 698, 762 cm^{-1}, the aliphatic group at 2,810–2,975 cm^{-1}, and the C=O group at 1,736 cm^{-1}. In the IR spectrum of the inclusion complex formed by β-CD and prosidol–base, the absorption band of monosubstituted benzene is shifted to 703, 757 cm^{-1} in comparison with the spectrum of the initial compound, indicating that the phenyl ring interacts with β-CD.

Furthermore, the absorption bands of C–H$_{aliph}$ become simpler and the intensity of the peak of the C=O group is significantly decreased in the spectrum of the complex which additionally confirms that a "host–guest" inclusion complex has been formed.

Determination of compositions of the complexes by UV-spectroscopy

Because *kazcaine–base* and *prosidol–base* are poorly soluble in water, the better soluble salt forms of *kazcaine–HCl* and *prosidol–HCl* were used to determine calibration curves. The obtained data were re-calculated by taking into account the used quantities of *kazcaine–base* and *prosidol–base,* each containing 0.089, 0.059, 0.044, 0.036 and 0.029 mg/mL, respectively. The UV-spectra were measured at 25 °C within the range of 200–400 nm. The intensities of the absorption bands were evaluated at the spectral maxima, 237.8 nm for *kazcaine–HCl* and 257.9 nm for *prosidol–HCl*. The calibration graphs and resulting data are presented in Figs. 3, 4 and Tables 1, 2.

To determine the compositions of the complexes by UV spectroscopy, the following solutions were prepared: 3.7 mg of the complex *prosidol–base/β-CD* and 4.3 mg of

Fig. 3 Calibration curve for *kazcaine–base*, absorption A measured at 237.8 nm
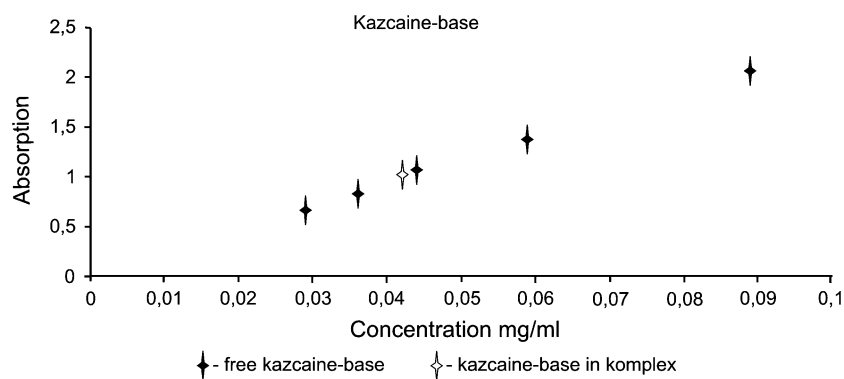

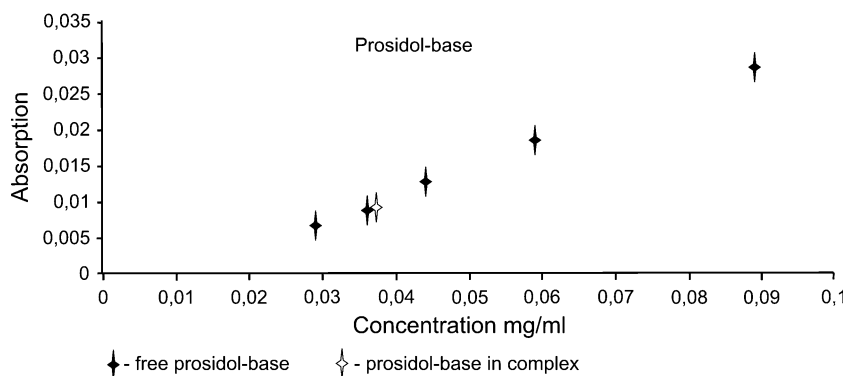**Fig. 4** Calibration curve for *prosidol–base*, absorption A measured at 257.9 nm

Table 1 Results obtained from UV-spectroscopy for the complex of the kazcaine–base with β-CD at 25 °C

x, y/dilution	10 times	15 times	20 times	25 times	30 times	Kazcaine–base in β-CD
mg, m	0.089	0.059	0.044	0.036	0.029	0.042
Absorption at 237.8 nm	2.050	1.367	1.065	0.829	0.654	1.024

Complex kazcaine–base with β-CD

Name	mol	m, mg	%
Complex	1	0.43	100
Kazcaine–base	1	0.042	9.77
β-CD	2	0.318	73.95
H_2O	27	0.070	16.28

Table 2 Results obtained from UV-spectroscopy for the complex of the prosidol–base with β-CD at 25 °C

x,y/dilution	10 times	15 times	20 times	25 times	30 times	Prosidol–base in β-CD
mg, m	0.089	0.059	0.044	0.036	0.029	0.037
Absorption at 257.9 nm	0.029	0.019	0.013	0.009	0.007	0.009

Complex prosidol–base with β-CD

Name	mol	m, mg	%
Complex	1	0.37	100
Prosidol–base	1	0.037	10.00
β-CD	2	0.276	74.6
H_2O	25	0.057	15.4

the complex *kazcaine–base*/β-CD were dissolved in 10 mL distilled water at 25 °C. The calibration graph showed that the concentration of kazcaine–base and prosidol–base are 0.042 and 0.037 mg/mL, respectively.

The compositions of the complexes were calculated according to formula:

$$\frac{v_{CD}}{v_{drug}} = \frac{\frac{m_{CD}}{M_{CD}}}{\frac{m_{drug}}{M_{drug}}}$$

where: m_{CD}—mass of β-CD, m_{drug}—mass of drug, M_{CD} and M_{drug} molar masses of β-CD and drug, respectively.

For the complex kazcaine–base/β-CD:

$$\frac{v_{CD}}{v_{drug}} = \frac{\frac{m_{CD}}{M_{CD}}}{\frac{m_{drug}}{M_{drug}}} = \frac{\frac{0.388}{1,135}}{\frac{0.042}{301}} = \frac{0.000342}{0.00014} = \frac{2.44}{1} = 2.44$$

For the complex prosidol–base/β-CD:

$$\frac{v_{CD}}{v_{drug}} = \frac{\frac{m_{CD}}{M_{CD}}}{\frac{m_{drug}}{M_{drug}}} = \frac{\frac{0.333}{1,135}}{\frac{0.037}{305}} = \frac{0.000293}{0.000121} = \frac{2.42}{1} = 2.42$$

According to above given formula we determined the molar ratio of drugs with β-CD in the complexes. This showed that in both complexes the ratio of the drug and β-CD are the same, 1:2. Knowing that in the complex, except for drug and β-CD, the key component is water; its concentration was deduced from the excess molar mass of β-CD. The estimates are given in Tables 1 and 2. The calculation was performed according to the formula:
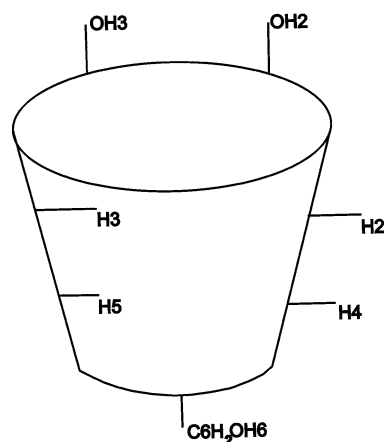
$$X = (C/m) * 100,$$

where C—is the concentration of drug in solution, mg/mL, which was obtained from the calibration graph;

m—is the amount of the test sample, mg.

Thus, UV-spectroscopy at 25 °C shows that the complex of kazcaine–base with β-CD consists of 1 molecule of kazcaine–base, 2 molecules of β-CD and about 27 molecules of H_2O, and the complex of prosidol–base with β-CD consists of 1 molecule prosidol–base, 2 molecules of β-CD and about 25 molecules of H_2O. The ratio of drugs to β-CD is 1:2, in agreement with results obtained by NOESY and ^{1}H NMR spectroscopy shown below.

Complexation in aqueous solutions characterized by ^{1}H NMR spectroscopy

Taking into account the problem of low solubility of the free bases in water, the proton NMR spectroscopy of kazcaine–base, prosidol–base, β-CD (Scheme 2) and their complexes were characterized in a mixture of methanol-d$_4$ and D_2O (1:2) at 25 °C. After complex formation, changes of chemical shifts of protons not only in β-CD but also in kazcaine–base and prosidol–base were observed; see Tables 3, 4 and 5, respectively. In Table 3, the protons at

Scheme 2 Schematic view of β-CD with average orientation of the most important atoms and OH groups

H3, H5 and H6 suffer maximum screening, indicating that the drug molecules are located in the cavity of β-CD.

In Tables 4, 5 the differences in ^{1}H NMR spectra for both *kazcaine–base* and *prosidol–base* in presence and absence of β-CD are presented, respectively.

In the ^{1}H NMR spectra of kazcaine–base axial and equatorial protons of the piperidine ring appear as multiplets near 2.25 and 2.69 ppm at 25 °C (Table 4). Proton signals of two methylene and one methyl groups in the ethoxyethyl substituent appear as triplets located near 2.62 (H-7), 3.59 (H-8) and 1.11 (H-10) ppm, and another methylene proton (H-9) is shown as quartet with a chemical shift of 3.49 ppm. The proton signal of the ethynyl substituent at C-4 shows a singlet near 3.15 ppm, and proton signals of the benzoyloxy group are located at 7.97 (H-o[b]), 7.64 (H-p[b]) and 7.49 (H-m[b]) ppm.

The changes $\Delta\delta^d$ observed indicate that β-CD has an effect on all protons of kazcaine–base, especially for the ethynyl (H-13), ethoxyethyl (H-9, H-10), and benzoyl (H-o[b], H-p[b]) substituents. This suggests that complexes have been formed with a molar ratio of β-CD to kazcaine–base of 2:1, in which one kazcaine–base molecule is enclosed in the hydrophobic cavities formed by two β-CD (Table 4), in agreement with a crystal structure analysis accepted for publication [16]. Furthermore, the ^{1}H NMR signals of the piperidine protons in spectra of the kazcaine–base and the complex formed with β-CD are broad and have no fine structure.

^{1}H NMR spectra of prosidol–base show that the protons of the piperidine ring give rise to separate signals, and the chemical shifts of axial protons of prosidol–base are located as usual in a stronger field, contrasting equatorial ones. Thus, equatorial protons H-2,6 (2.85 ppm) and equatorial H-3,5 (2.39 ppm) resonate as a doublets of triplets, while the axial protons H-2,6 (2.50 ppm) and axial H-3,5 (2.03) resonate as triplets of doublets. This
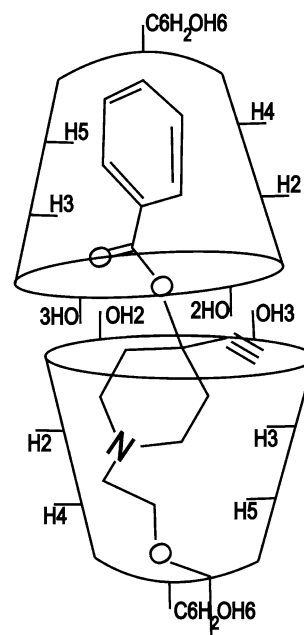
Table 3 Difference between proton chemical shifts of β-cyclodextrin and its complexes with kazcaine and prosidol at 25 °C

Protons of β-CD	H1	H2	H3	H4	H5	H6
$\Delta\delta$, β-CD/(kazcaine–base)	−0.0202	−0.0180	−0.0240	−0.0172	−0.0615	−0.0418
$\Delta\delta$, β-CD/(prosidol–base)	−0.1234	−0.1234	−0.1529	−0.1169	−0.1536	−0.1314

The difference ($\Delta\delta$) was calculated as ($\Delta\delta$) = ($\delta - \delta_o$), where δ_o is the chemical shift of β-CD protons, δ is the chemical shift of β-CD protons in complex with drug

Table 4 Difference between proton chemical shifts of kazcaine–base and its complex with β-CD at 25 °C

Protons		δ_o	δ	$\Delta\delta^c$
H-2,6	Ax.	2.6984 m.[b]	2.7088 m.	0.0104
	Eq.			
H-3,5	Ax.	2.2574 m.	2.2806 m.	0.0232
	Eq.			
H-7		2.6201 t.[b]	2.6236 t.	0.0035
H-8		3.5995 t.	3.6076 t.	0.0081
H-9		3.4911 qu.[b]	3.5044 qu.	0.0133
H-10		1.1194 t.	1.1312 t.	0.0118
H-13		3.1507 s.[b]	3.1739 s.	0.0232
H-o[a]		7.9767 d.[b]	7.9575 d.	−0.0192
H-м[a]		7.4943 t.	7.4966 t.	0.0023
H-p[a]		7.6456 t.t.[b]	7.6645 t.t.	0.0189

Schematic description of the complex formed between β-CD and *kazcaine–base*

Difference ($\Delta\delta$) was calculated as ($\Delta\delta$) = ($\delta - \delta_o$), where δ_o is the chemical shift of kazcaine–base, δ is the chemical shift of kazcaine–base in complex with β-CD

[a] Protons in ortho, meta-, para position of the benzyl group

[b] s., d., t., qu., m., t.d., and d.t. mean singlet, doublet, triplet, quartet, multiplet, triplet of doublets, doublet of triplets, respectively

[c] Difference between the proton chemical shifts of kazcaine–base and its complex with β-CD

multiplicity of signals clearly indicates that the piperidine ring in prosidol–base has a fixed chair conformation.

In prosidol, protons of the propionyloxy group at C-4 are observed as quartet and triplet at 2.35 and 1.13 ppm. Signals of protons of the phenyl ring form superimposed multiplets in the range of 7.25 to 7.35 ppm at 25 °C.

Chemical shifts of protons of the ethoxyethyl substituent of prosidol–base and kazcaine–base behave similarly (Tables 4, 5).
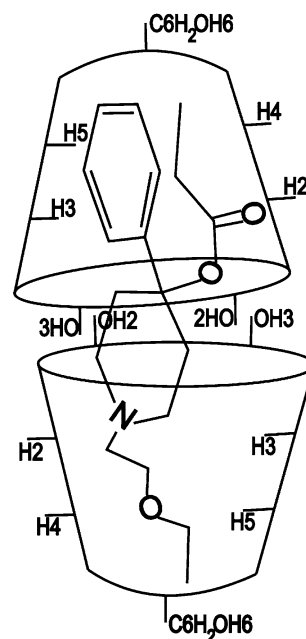
The ^{1}H NMR spectrum of the β-CD inclusion complex with prosidol–base contrasts the spectrum of pure prosidol–base at 25 °C, because the proton signals of the piperidine

ring, the ethoxyethyl substituent at N and substituents at C4 (propionyloxy group, phenyl ring) shift to stronger field (Table 5) and show signals of β-CD protons. We conclude that all the prosidol–base molecules were located in the cavity formed by two β-CD molecules (Table 5).

Thus, the analysis of ^{1}H NMR spectra of the complexes formed between β-CD and kazcaine–base or prosidol–base allowed to determine the composition and structure of the complexes in solution. Differences between chemical shifts of protons, integral intensities, and considering the size of the inner cavity of β-CD indicate that kazcaine–base and prosidol–base can interact with β-CD in molar ratios of 1:2.

Table 5 Difference between proton chemical shifts of prosidol–base and their complexes with β-CD at 25 °C

Protons		δ_o	δ	$\Delta\delta^c$
H-2,6	Ax.	2.5038 t.d.[b]	2.4353 t.d.	−0.0685
	Eq.	2.8588 d.t.[b]	2.7571 d.t.	−0.1017
H-3,5	Ax.	2.0393 t.d.	2.0116 t.d.	−0.0277
	Eq.	2.3959 d.t.	2.3775 d.t.	−0.0184
H-7		2.6331 t.	2.5384 t.	−0.0947
H-8		3.6175 t.	3.5108 t.	−0.1067
H-9		3.5126 qu.	3.4118 qu.	−0.1008
H-10		1.0318 t.	0.9499 t.	−0.0819
H-12		2.3517 qu.	2.2954 qu.	−0.0563
H-13		1.1344 t.	1.0474 t.	−0.087
H-o[a]		7.3548* m.	7.2798 d.	−0.075
H-м[a]		7.3490 m.	7.2542 t.	−0.0948
H-p[a]		7.2542* m.	7.1818 t.	−0.0724

Schematic description of the complex formed between β-CD and *prosidol–base*

Difference ($\Delta\delta$) was calculated as ($\Delta\delta$) = ($\delta - \delta_o$), where δ_o is the chemical shift of prosidol–base, δ is the chemical shift of prosidol–base in complex with β-CD

[a] Protons in ortho, meta-, para position of the benzyl group

[b] s., d., t., qu., m., t.d., and d.t., mean singlet, doublet, triplet, quartet, multiplet, triplet of doublets, doublet of triplets, respectively

[c] Difference between the proton chemical shifts of prosidol–base and its complex with β-CD

Geometry analysis of inclusion complex by NOESY spectroscopy

NOESY experiments are often performed to investigate the geometry of inclusion complexes of organic molecules with CDs. Figure 5a shows a two-dimensional NOESY spectrum of the complex formed by kazcaine–base and β-CD at 25 °C. NOEs are observed between H-o[b], H-m[b], H-p[b] (aromatic ring) and H3, H5, H6 (β-CD). The proton at the ortho-position (H-o[b]) has cross peaks with all of the three protons in the β-CD cavity, the meta-proton (H-m[b]) has cross peaks with H5 and H6, while the para-proton (H-p[b]) only has a cross peak with H6. Taking into account the 3D structure of β-CD (Scheme 2), we conclude that the phenyl moiety enters the wide rim of the β-CD cavity and protrudes from the narrow rim, which is consistent with the results obtained from 1D ^{1}H NMR measurements.
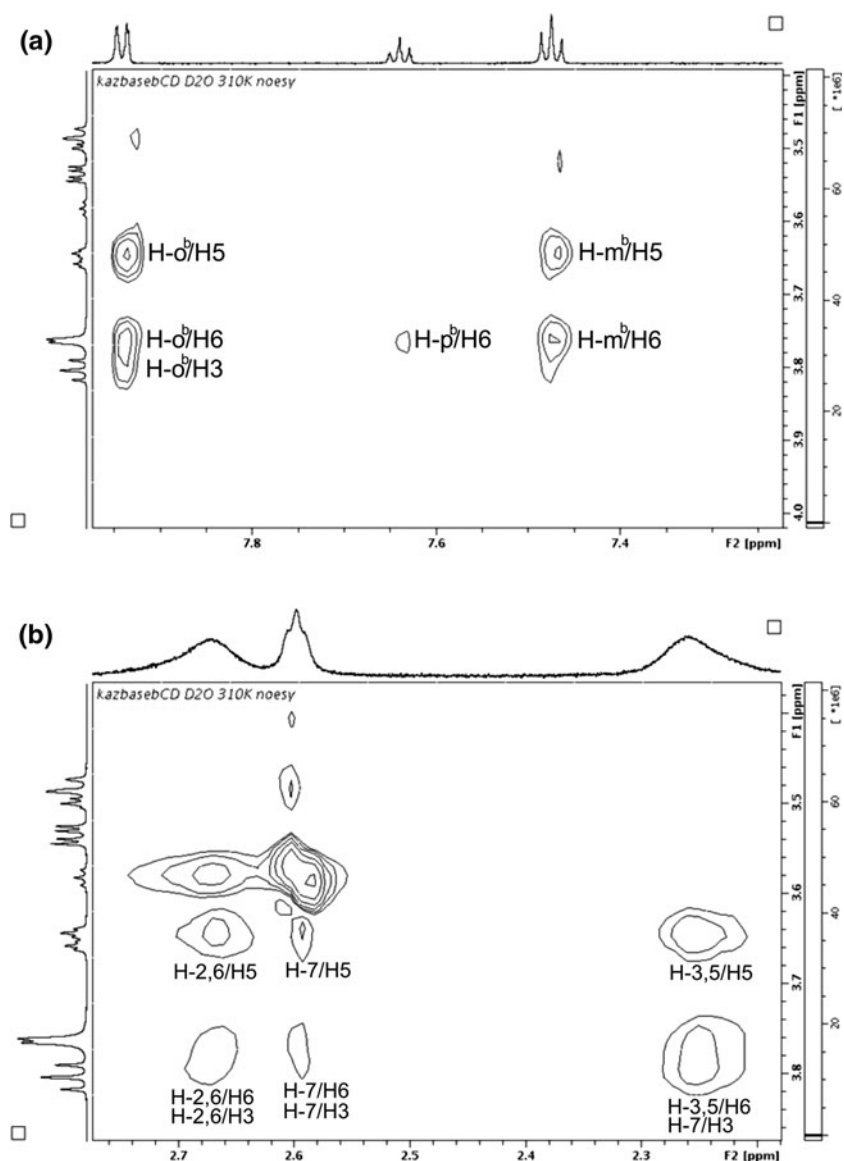
Moreover, we also found cross peaks of H-3,5, H-2,6, and H-7 with H3, H5 and H6 (Fig. 5b). Therefore, we conclude that the piperidine ring is located in the β-CD cavity as well. The complex between kazcaine–base and β-CD is formed by one kazcaine–base molecule and two of β-CD.

The NOESY spectrum of the complex formed by prosidol–base and β-CD (Fig. 6a) shows that protons of H-o[b], H-m[b] and H-p[b] of the phenyl substituent interact with protons H3 and H5 of β-CD. Moreover, the NOESY spectrum of the complex formed by prosidol–base and β-CD at 25 °C (Fig. 6b) demonstrates that H-3,5 and H-2,6 of the piperidine ring, and protons H-7, H-9, H-10 of the ethoxyethyl substituent interact with protons H3 and H5 of β-CD, and proton H-13 of the propionyloxy substituent interacts with proton H6 of β-CD as well.

Therefore, the NOESY spectra of the complex formed by prosidol–base and β-CD show that the composition of the β-CD inclusion complex of prosidol–base consists of one molecule of prosidol–base and two molecules of β-CD.

Fig. 5 (a) Two-dimensional NOESY spectrum (X: 7.3–8.3 ppm, Y: 3.5–4.0 ppm) of the kazcaine–base–β–CD complex in methanol-d$_4$ and D$_2$O (1:2) at 25 °C. The *signals* denoted as H-o^b, H-m^b, and H-p^b are due to protons of the kazcaine phenyl ring at ortho-, meta-, and para-positions, respectively. **b** Two-dimensional NOESY spectrum (X: 1.0–4.0 ppm, Y: 1.0–4.0 ppm) of the kazcaine–base–β–CD complex in methanol-d$_4$ and D$_2$O (1:2 vol/vol)

These results are consistent with the IR, UV and 1D ^{1}H NMR data.
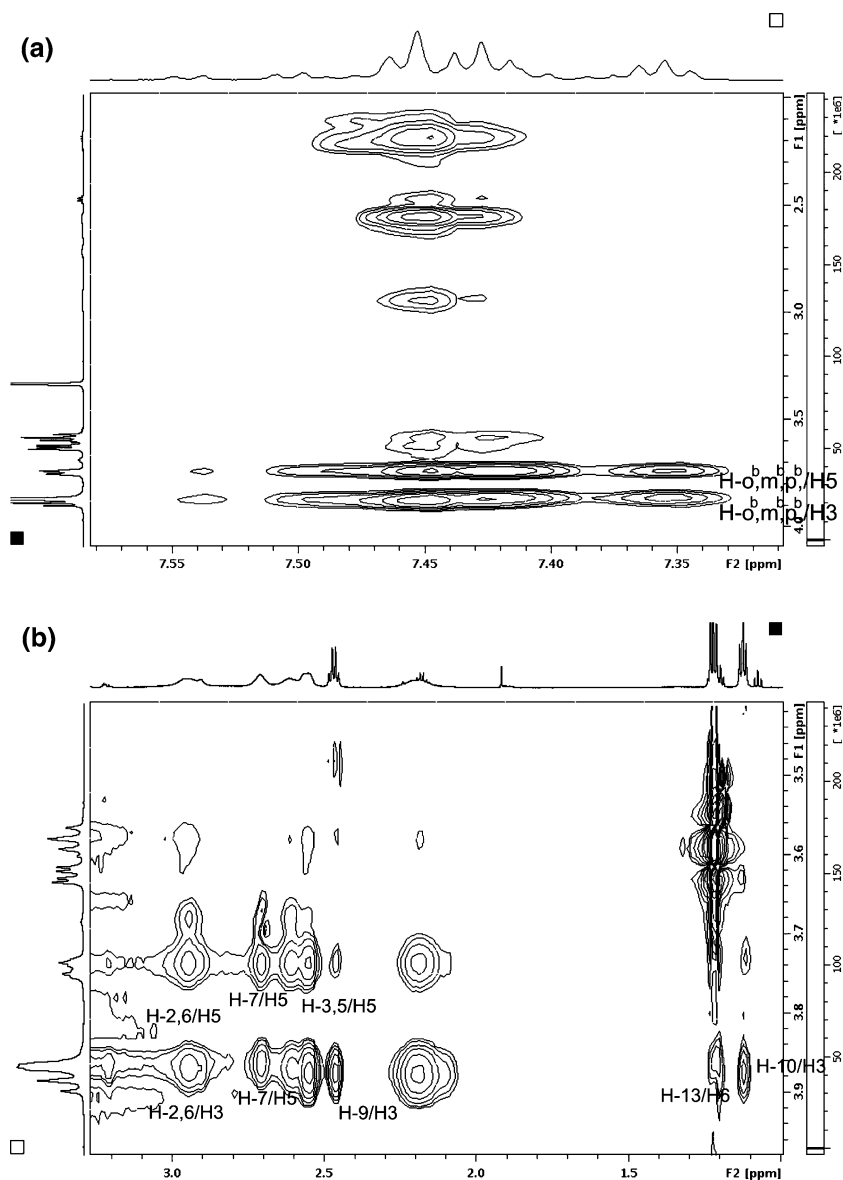
Pharmacological tests

Pharmacological tests carried out by the research groups of the Veterinary Institute (Almaty, Kazakhstan) and the Research Chemical-Pharmaceutical Institute (Novokuznetsk, Russia) showed that the complex of kazcaine–base with β-CD reveals a highly effective anaesthetic action during infiltration and conductor anesthesia. While the complex of prosidol–base with β-CD has a similar activity and index of pharmacological action width; at the same time it causes less depression of peristalsis than prosidol that is used in practice. In addition the formed complexes

are less toxic than the individual drugs, and wider pharmacological tests have been recommended. These results will be published elsewhere.

Conclusions

The successful formation of solid powders of "host–guest" inclusion complexes of kazcaine–base or prosidol–base with β-CD was confirmed by IR, UV and solution 1D ^{1}H NMR studies. Geometrical analyses of the inclusion complexes were performed by 2D NOESY measurements, which revealed that one drug molecule is encapsulated by two β-CD cavities arranged in head-to-head configuration. The main point of this work is the

Fig. 6 a Two-dimensional NOESY spectrum (X: 6.8–8.1 ppm, Y: 1.8–4.0 ppm) of the complex formed by prosidol–base and β-CD in methanol-d_4 and D_2O (1:2) at 25 °C. The β-CD signals are denoted as H-n. **b** Two-dimensional NOESY spectrum (X: 0.6–4.4 ppm, Y: 0.8–4.0 ppm) of the complex formed by prosidol–base and β-CD in methanol-d_4 and D_2O (1:2 vol/vol)

conclusion of the Professional Veterinary Institute that further biological studies of inclusion complexes of kazcaine–base with β-CD as a highly effective anesthetic for infiltration and conduction anesthesia should be performed, and screening studies of the complex of β-CD with prosidol–base carried out by research groups of the Chemical-Pharmaceutical Institute showed that this combination is promising and indicated differences from the original analgesic prosidol that require future in-depth pharmacological studies.

References

1. Patent RK 527 (Patent RU N 1,262,908, Patent Switzerland 6,786,224, Patent Italy 1,232,984, Patent Britain 2,234,241, Patent France 2,650,999 F, Patent FRG DE 3,924,466) hydrochloride 1-(2-ethoxyethyl)-4-phenyl-4-propionyl-oxypiperidine, possesses analgesic activity Praliev, K.D., Yu, V.K., Sokolov, D.V., Bosyakov, Y.G., Kurilenko, V.M., Hlienko, Jh.N., Moiseeva, L.M., Chetverikov, V.N., Tetenchuk, E.V., Nurahov, S.N. Byull. Izobret. Resp. Kazakhstan, No. 1 (1994)

2. Praliev, K.D., Yu, V.K., et al.: Synthesis of 1-(2-ethoxyethyl)-4-phenyl-4-propionyloxypiperidine hydrochloride (prosidol)–new

high effective analgesic. In: Biological Active Substances. Nauka, Alma-Ata, vol. 1, pp. 3–10 (1988)

3. Praliev, K.D., Yu, V.K., Poplavskaya, I.A.: Target synthesis of pharmacologically active derivatives of 4-ethynyl-4-hydroxypiperidine. In: Kartsev, V.G., Tolstikov, G.A. (eds.) Monograph Nitrogen-Containing Heterocycles and Alkaloids, vol. 1, pp. 454–457. IBS Press, Moscow (2001)

4. Praliev, K.D., Isin, Zh., Yu, V.K., Tarakov, S.A., Bosyakov, Yu.G., Utepbergenova, R.K., Shin, S.N., Kadyrova, D.M.: Hydrochloride of 1-(2-ethoxyethyl)-4-ethynyl-4-benzoyloxy-piperidine possesses anesthetic activity. Patent Ru., 1704415 (1996)

5. Batyrbekov, E.O., Iskakov, R.M., Boldyrev, D.Y., Yu, V.K., Praliyev, K.D., Zhubnov, B.A.: Segmented polyurethanes for controlled delivery of anaesthetics. Architecture and Application of Biomaterials and Biomolecular Materials. Symposium Proceeding, vol. EXS-1, pp. 433–435. MRS, Warrendale, PA, USA (2004).

6. Zhubanov, B.A., Praliev, K.D., Nurmukhambetova, B.I., Batyrbekov, E.O., Rukhin, L.B., Yu, V.K., Markin, B.A., Khromov, V.N.: Buccal medication forms of the analgesic drug prosidol. Pharm. Chem. J. **31**(8), 428–430 (1997)

7. Szejtli, J.: Past, present, and future of cyclodextrin research. Pure Appl. Chem. **76**(10), 1825–1845 (2004)

8. Saenger, W.: Cyclodextrin inclusion compounds in research and industry. Angew. Chem. Int. Ed. Engl. **19**, 344–362 (1980)

9. Dodziuk, H.: Cyclodextrins and their Complexes. WILEY-VCH Verlag GmbH and Co. KgaA, Weinheim (2006)

10. Wen, X., Tan, F., Jing, Z., Liu, Z.: Preparation and study the 1:2 inclusion complex of carvedilol with beta-cyclodextrin. J. Pharm. Biomed. Anal. **34**(3), 517–523 (2004)

11. Liu, F.-Y., Kildsig, D.O., Mitra, A.K.: Beta-cyclodextrin/steroid complexation: effect of steroid structure on association equilibria. Pharm. Res. **7**(8), 869–873 (1990)

12. Leyva, E., Moctezuma, E., Strouse, J., Garcia-Garibay, M.A.: Spectrometric and 2D NMR studies on the complexation of chlorophenols with cyclodextrins. J. Incl. Phenom. Macrocycl. Chem. **39**(1–2), 41–46 (2001)

13. Fan, Y., Li, J., Dong, C.: Preparation and study on the inclusion complexes of two tanshinone compounds with beta-cyclodextrin. Spectrochim. Acta Part A: Molecular and Biomolecular Spectroscopy. **61**(1–2), 135–140 (2005)

14. Hudson, R.L., Moore, M.H., Cook, A.M.: IR characterization and radiation chemistry of glycolaldehyde and ethylene glycolices. Adv. Space Res. **36**, 184–189 (2005).

15. Choi, S.-H., Kim, S.-Y., Ryoo, J.J., Park, J.Y., Lee, K.-P.: FT-Raman and FT-IR spectra of the non-steroidal antiinflammatory drug ketoprofen included in cyclodextrins. Anal. Sci. **17**, 1785–1788 (2001)

16. Kemelbekov, U.S., Hagenbach, A., Lentz, D., Imachova, Sh.O., Pichkhadze, G.M., Rustembekov, Zh.I., Beketov, K.M., Praliev, K.D., Gabdulkhakov, A., Guskov, A., Saenger, W.: Pharmacology and structures of the free base of the anaesthetic kazcaine and its complex with b-cyclodextrin. J. Incl. Phenom. Macrocycl. Chem. (2010). doi:10.1007/s10847-010-9791-7.