

Supramolecular Complex of 20-Hydroxyecdysone-3-acetate with β -Cyclodextrin and Its Biological Activity

B. I. Tuleuov^{a,*}, B. S. Temirgaziev^{a,b}, A. M. Kozhanova^a, R. B. Seydakhmetova^a,
K. M. Turdybekov^b, T. M. Seilkhanov^c, O. T. Seilkhanov^c, P. Drasar^d, and S. M. Adekenov^a

^a International Scientific and Production Holding “Phytochemistry,” Karaganda, 100009 Kazakhstan

^b E.A. Buketov Karaganda State University, Karaganda, 100028 Kazakhstan

^c Sh. Ualikhanov Kokshetau State University, Kokshetau, 020000 Kazakhstan

^d University of Chemistry and Technology, Prague, 16628 Czech Republic

*e-mail: info@phyto.kz

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Abstract—In order to obtain new potentially bioactive substances and to investigate the effect of bulky functional groups on the formation of supramolecular complexes, 20-hydroxyecdysone triacetate has been synthesized, its spatial structure has been determined, and its complexation with β -cyclodextrin has been studied by means of NMR. The anti-inflammatory activity of the obtained water-soluble complex has been assessed.

Keywords: 20-hydroxyecdysone triacetate, β -cyclodextrin, supramolecular complex, X-ray diffraction analysis, NMR spectroscopy

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Formation of supramolecular complexes of phytoecdysteroids with cyclodextrins affords encapsulated forms of the drug, improves its stability against external factors (light, heat, or air oxygen), and enhances its solubility [1–3]. In view of this, the use of the most common α -, β -, and γ -cyclodextrins for the preparation of novel inclusion complexes of biologically active compounds, pharmaceuticals, and drugs is among the major trends in supramolecular chemistry [4–6].

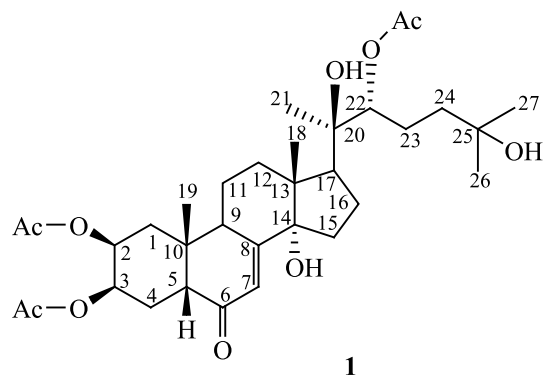
We have earlier synthesized a series of novel cyclodextrin complexes with 20-hydroxyecdysone and other phytoecdysteroids [7, 8], but preparation of supramolecular water-soluble complexes based on their modified derivatives has not been described. Herein we report the first attempt of the synthesis of novel supramolecular complexes based on vicinal-substituted polyoxysteroid.

The choice of 20-hydroxyecdysone triacetate [2,3,22-acetoxy-14,20,25-hydroxy-5,9(*H*)-cholest-7-en-6-one] **1** (Scheme 1) as the synthon and the substrate of the supramolecular self-assembly with β -cyclodextrin was due to the fact that 20-hydroxyecdysone exhibited wound

healing ability which could be significantly enhanced by the incorporation in liposomes and were poorly water-soluble [9].

To obtain novel potentially bioactive compounds, elucidate the effect of bulky functional groups on the formation of supramolecular complexes, and to enhance their solubility in water, we investigated the fine structure of the starting synthon. 20-Hydroxyecdysone triacetate was studied by means of X-ray diffraction analysis in the form of crystal hydrate **2** (**1**·2.5 H₂O). General view

Scheme 1.



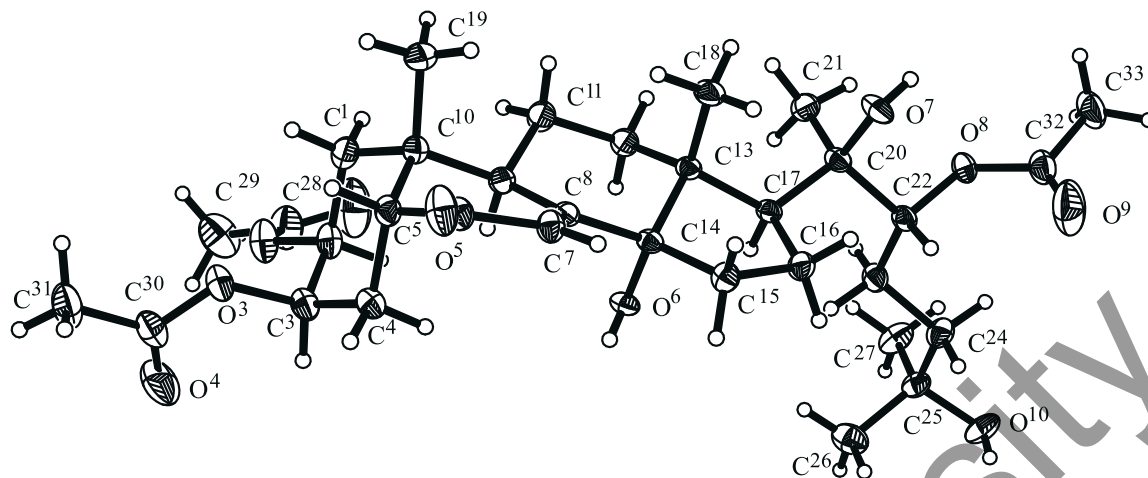


Fig. 1. General view of a molecule of [2,3,22-acetoxy-14,20,25-hydroxy-5,9(*H*)-cholest-7-en-6-one] **1**.

of 20-hydroxyecdysone triacetate **1** molecule is shown in Fig. 1.

Bond lengths and bond angles in the crystal hydrate **2** were close to the ordinary ones [10]. Conformation of the C¹C²C³C⁴C⁵C¹⁰ cycle (A) was close to the ideal *chair* (minimal asymmetry parameter $\Delta C_3^3 = 0.4^\circ$, the transannular torsion angles are collected in Table 1). Conformation of cycle B containing the C⁷=C⁸ double bond deviated from the ideal *5 α ,10 β -semichair* towards *5 α -sofa* ($\Delta C_8^8 = 16.0^\circ$ and $\Delta C_7^{7,8} = 9.3^\circ$) due to the presence of the C⁶=O double bond and conjugation with two 6-membered carbocycles. Conformation of the C⁸C⁹C¹¹C¹²C¹³C¹⁴ cycle (C) significantly deviated from the ideal *chair* ($\Delta C_9^9 = 3.7^\circ$) due to the fusion with the unsaturated cycle B. Conformation of the 5-membered carbocycle D

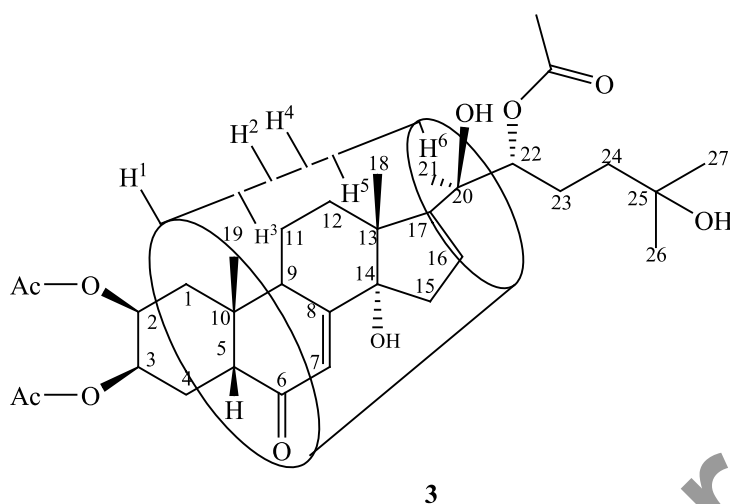
corresponded to *14 α ,13 β -semichair* ($\Delta C_2^{13,14} = 5.4^\circ$), significant distortion of which was due to the repulsion of the methyl groups at the C¹³ and C²⁰ atoms. The distance between the C¹⁸ and C²¹ atoms was 3.612 Å, whereas the van der Waals radius of methyl group was 2.0 Å [11]. Overall, distortion of cycles A–D was close to that observed in the crystal of 20-hydroxyecdysone and its crystal hydrate [12]. The Flack parameter was close to zero [0.05(12)] [13], and therefore *2 β ,3 β ,22R*-acetoxy-14 α ,20*R*,25-hydroxy-5 β ,9 α (*H*)-cholest-7-en-6-one structure was assigned to compound **1**.

Molecule of compound **1** and water molecules in the crystal formed the following hydrogen bonds: O⁷–H(*x, y, z*) \cdots O⁵ (1.5–*x*, 0.5+*y*, 1–*z*) [O \cdots O 2.896(2) Å, H \cdots O 2.19(3) Å, O–H \cdots O 158(3)°], O⁶–H \cdots O^{2w} (*x, y, z*)

Table 1. Transannular torsion angles in crystal hydrate **2**

Angle	τ , deg	Angle	τ , deg
Cycle A		Cycle C	
C ¹⁰ C ¹ C ² C ³	56.5(2)	C ¹⁴ C ⁸ C ⁹ C ¹¹	–48.8(2)
C ¹ C ² C ³ C ⁴	–52.1(2)	C ⁸ C ⁹ C ¹¹ C ¹²	46.5(2)
C ² C ³ C ⁴ C ⁵	51.7(2)	C ⁹ C ¹¹ C ¹² C ¹³	–52.0(3)
C ³ C ⁴ C ⁵ C ¹⁰	–56.1(2)	C ¹¹ C ¹² C ¹³ C ¹⁴	57.0(2)
C ⁴ C ⁵ C ¹⁰ C ¹	56.4(2)	C ¹² C ¹³ C ¹⁴ C ⁸	–60.0(2)
C ² C ¹ C ¹⁰ C ⁵	–56.6(2)	C ⁹ C ⁸ C ¹⁴ C ¹³	57.1(2)
Cycle B		Cycle D	
C ¹⁰ C ⁵ C ⁶ C ⁷	–47.9(2)	C ¹⁷ C ¹³ C ¹⁴ C ¹⁵	45.8(2)
C ⁵ C ⁶ C ⁷ C ⁸	15.4(3)	C ¹³ C ¹⁴ C ¹⁵ C ¹⁶	–35.3(2)
C ⁶ C ⁷ C ⁸ C ⁹	5.6(3)	C ¹⁴ C ¹⁵ C ¹⁶ C ¹⁷	10.5(2)
C ⁷ C ⁸ C ⁹ C ¹⁰	6.6(3)	C ¹⁵ C ¹⁶ C ¹⁷ C ¹³	17.6(2)
C ⁸ C ⁹ C ¹⁰ C ⁵	–38.1(2)	C ¹⁴ C ¹³ C ¹⁷ C ¹⁶	–38.0(2)
C ⁶ C ⁵ C ¹⁰ C ⁹	58.3(2)		

Scheme 2.



[2.714(3), 1.95(3) Å, 174(3)°], O¹⁰-H···O^{1w} (1.5-x, -0.5+y, -z) [2.737(3), 1.90(4) Å, 169(3)°], O^{1w}-H···O⁶ (x, y, z) [2.832(2), 1.95(6) Å, 159(4)°], O^{1w}-H···O⁴ (1-x, y, -z) [2.847(3), 1.94(5) Å, 176(4)°], O^{2w}-H···O² (x, -1+y, z) [2.785(2), 1.96(3) Å, 161(3)°], O^{2w}-H···O¹⁰ (1.5-x, -0.5+y, -z) [2.737(3), 1.91(5) Å, 172(4)°], O^{3w}-H···O² (1-x, y, -z) [O···O 2.878(3) Å], and O^{3w}-H···O^{3w} (1-x, y, -z) [O···O 2.839(3) Å], thus forming three-dimensional network.

Since size and structure of the interacting components are determinative factors in supramolecular chemistry, supramolecular complexes of ecdysone **1** were prepared with β-cyclodextrin. The complexes were obtained via the interaction of equimolecular amounts of 20-hydroxyecdysone triacetate **1** and cyclodextrin in an aqueous-ethanolic solution at 50°C during 8 h.

Investigation of the structure of supramolecular complexes by means of NMR spectroscopy is based on the change in the ¹H chemical shifts of substrate **1** and β-cyclodextrin in the complex in comparison with the components in the free state. The values of the chemical shift change for the inner and outer protons of cyclodextrin reflect the formation of inner, outer, and mixed complexes. The change in the ¹H and ¹³C chemical shifts in the spectra of the substrate allows elucidation of the details of the substrate incorporation in the cyclodextrin cavity [14–16].

The structure of compound **1** was elucidated by means of ¹H and ¹³C NMR spectroscopy in DMSO-*d*₆ (Table 2). Assignment of the signals in the 1D ¹H and ¹³C NMR spectra was confirmed by the data of ¹H-¹H

COSY, ¹H-¹H ROESY, ¹H-¹³C HMQC, and ¹H-¹³C HMBC two-dimensional correlations (Table 2). From the data in Table 2 it is to be seen that the most prominent change in the chemical shifts of the glucopyranose units was observed for the H³ and H⁵ protons in the inner part of the truncated cyclodextrin cone (Scheme 2). That fact suggested the incorporation of molecules of substrate **1** in the cavity if β-cyclodextrin with the formation of the inclusion complex **3** (Scheme 2). Complex **3** was relatively water-soluble. Comparison of the integral intensities of the proton signals of substrate **1** and β-cyclodextrin in the complex revealed that their ratio was 1 : 1.

Bioscreening (investigation of the anti-inflammatory activity) of 20-hydroxyecdysone triacetate **1** and its complex with β-cyclodextrin **3** revealed anti-inflammatory activity of the complex (dose 25 mg/kg) on the model of acute exudative reaction, and the activity was comparable to that of the reference drug sodium diclofenac, whereas the parent 20-hydroxyecdysone triacetate exhibited only weak anti-inflammatory activity at the same dose.

In summary, 20-hydroxyecdysone triacetate was prepared, and its structure was confirmed by means of X-ray diffraction analysis and NMR spectroscopy data. Its supramolecular complex with β-cyclodextrin exhibited anti-inflammatory activity.

EXPERIMENTAL

β-Cyclodextrin (99%) was purchased from Fluka.

¹H and ¹³C NMR spectra were recorded using a Jeol JNM-ECA 400 spectrometer (399.78 and 100.53 MHz for

Table 2. Chemical shifts of ^1H and ^{13}C nuclei in free substrate **1** and β -cyclodextrin (δ_0) and in their complex **3** (δ)

Atom no.	Group	δ_0 , ppm		δ , ppm		$\Delta\delta = \delta - \delta_0$	
		^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
Substrate 1							
$1_{ax}1_{eq}$	CH_2	1.65–1.70 m 2.11–2.22 m	37.19	1.65–1.70 m 2.11–2.20 m		0.00	
2	CH	4.95 d, $^3J = 12.0$ Hz	68.75	4.94 d		-0.01	
3	CH	5.17 br. s	67.34	5.16		-0.01	
$4_{ax}4_{eq}$	CH_2	1.65–1.70 m 1.90–1.93 m	31.41	1.65–1.70 m 1.90–1.92 m		0.00 -0.01	
5	CH	2.11–2.22 m	51.10	2.11–2.20 m		0.02	
6	$>\text{C}=\text{O}$	–	201.32	–			
7	CH	5.65 s	121.07	5.66		0.01	
8	$>\text{C}<$	–	165.83	–			
9	CH	3.02–3.08 m	34.09	3.02–3.08 m		0.00	
10	$>\text{C}<$	–	38.24				
$11_{ax}11_{eq}$	CH_2	1.65–1.70 m 1.78–1.81 m	21.37	1.65–1.70 m 1.76–1.82 m		0.00 0.01	
$12_{ax}12_{eq}$	CH_2	1.90–1.93 m 2.44–2.48 m	30.81	1.90–1.92 m 2.44–2.48 m		-0.01 0.00	
13	$>\text{C}<$	–	47.34	–			
14	$>\text{C}<$	–	83.51	–			
$15_{ax}15_{eq}$	CH_2	1.91 s 2.11–2.22	33.52	1.90 s 2.11–2.20		-0.01 -0.02	
$16_{ax}16_{eq}$	CH_2	2.11–2.22 m 2.44–2.48	21.70	2.11–2.20 2.44–2.48		-0.02 0.00	
17	CH	3.02–3.08	49.58	3.02–3.08		0.00	
18	$-\text{CH}_3$	0.88 s	23.90	0.88 s		0.00	
19	$-\text{CH}_3$	0.73 s	17.68	0.72 s		-0.01	
20	$>\text{C}<$	–	79.11	–			
21	$-\text{CH}_3$	1.13 s	23.91	1.12 s		-0.01	
22	CH	4.63 d, $^3J = 10.0$ Hz	81.86	4.63 d		0.00	
$23_{ax}23_{eq}$	CH_2	1.78–1.81 m 2.11–2.22 m	26.54	1.76–1.82 m 2.11–2.20 m		0.01 -0.02	
$24_{ax}24_{eq}$	CH_2	1.78–1.81 m 2.11–2.22 m	40.63	1.76–1.82 m 2.11–2.20 m		0.01 -0.02	
25	$>\text{C}<$	–	75.24	–			
26	$-\text{CH}_3$	1.28 s	26.29	1.27 s		-0.01	
27	$-\text{CH}_3$	1.33 s	29.09	1.32 s		-0.01	
2	$-\text{OOC}-\text{CH}_3$	1.88 s	170.31	1.87 s		-0.01	
3	$-\text{OOC}-\text{CH}_3$	1.98 s	170.18	1.97 s		-0.01	
22	$-\text{OOC}-\text{CH}_3$	2.05 s	172.92	2.04 s		-0.01	
β-Cyclodextrin							
1	CH	4.77 d, $^3J = 4.0$ Hz	102.40	4.78 d	102.45	0.01	0.05
2	CH	3.26 d, $^3J = 12.1$ Hz	72.83	3.26 d	72.92	0.00	0.09
3	CH	3.58 t, $^3J = 8.3$ Hz	73.54	3.60 t	73.56	0.02	0.02
4	CH	3.28 t, $^3J = 10.0$ Hz	81.98	3.28 t	82.03	0.00	0.05
5	CH	3.50 s	72.50	3.53 s	72.55	0.03	0.05
6	CH_2	3.58 s	60.42	3.59 s	60.42	0.01	0.00

^1H and ^{13}C , respectively) in DMS)- d_6 solution at room temperature. Chemical shifts were measured relative to residual protons or carbon atoms of the solvent.

X-ray diffraction analysis. Unit cell parameters and intensities of 55472 reflections (8130 independent ones, $R_{\text{int}} = 0.0363$) were measured using a Bruker Kappa APEX2 CCD diffractometer (Mo K_{α} , graphite monochromator, φ, ω -scanning, $2.33 \leq \theta \leq 27.48^\circ$) at 180 K. The crystals were monoclinic, $a = 31.052(6)$, $b = 7.995(2)$, $c = 15.196(3)$ Å, $\beta = 110.55(3)^\circ$, $V = 3533(1)$ Å 3 , $Z = 4$ ($\text{C}_{33}\text{H}_{50}\text{O}_{10} \cdot 2.5\text{H}_2\text{O}$), space group $C2$, $d_{\text{calc}} = 1.242$ g/cm 3 , $\mu = 0.095$ mm $^{-1}$. The intensity data were processed (including account for absorption) using SAINT [17] and SADABS [18] routines of APEX2 software package.

The structure was solved via direct method. The positions of nonhydrogen atoms were refined under anisotropic approximation by means of full-matrix least squares method. The hydrogen atoms of the hydroxyl groups and two crystal hydrate water molecules ($\text{O}^{1\text{w}}$ and $\text{O}^{2\text{w}}$) were located from the differential synthesis, and their positions were refined under isotropic approximation. Hydrogen atoms of the third water molecule ($\text{O}^{3\text{w}}$) could not be located, since its population was 1/2 molecule per a unit cell. Other hydrogen atoms were put in the geometric positions and refined under isotropic approximation with constant position and heat parameters (*rider* model). 7591 reflections with $I \geq 2\sigma(I)$ were processed, the number of refined parameters being 451. Final divergence factors: $R_1 = 0.0476$, $wR_2 = 0.1010$ (over reflections with $I \geq 2\sigma(I)$), $R_1 = 0.0414$, $wR_2 = 0.1032$ (over all reflections), GooF 1.046. Peaks of residual electronic density: $\Delta\rho = 0.667$ and -0.337 e/Å 3 . The structure was solved and refined using SIR-97 [19] and SHELXL-2018/3 [20], respectively. The structural data were deposited at the Cambridge Crystallographic Data Centre (CCDC 1919742).

Complex 3. was prepared via the interaction between equimolar amounts of compound **1** with β -cyclodextrin. A solution of 0.094 g (0.83 mmol) of β -cyclodextrin in 4 mL of distilled water was added to a solution of 0.050 g (0.83 mmol) of compound **1** in 3 mL of anhydrous ethanol and the mixture was stirred at 50°C during 8 h. The precipitate was filtered off, washed with ethanol, and dried in a vacuum oven at 40°C. White powder, mp 267° (decomp.). IR spectrum (KBr), ν , cm $^{-1}$: 579, 609, 707, 757, 858, 947, 1029, 1081, 1157, 1254, 1216, 1254, 1336, 1371, 1426, 1660 (C=O), 1742, 2928, 3445 (OH), UV spectrum, λ_{max} : 245 nm.

Investigation of anti-inflammatory activity. The experiments were performed using 32 white outbred rats of both sexes, body mass 250–320 g. The anti-inflammatory action was assessed using a model of acute exudative inflammatory reaction (peritonitis). The anti-exudative activity was estimated from the volume of exudate formed in the abdominal cavity. The acute exudative reaction (peritonitis) was induced via intra-abdominal administration of 1% solution of AcOH (1 mL per 100 g of the rat mass). The experiment was performed as described elsewhere [21]. The considered compounds were studied in the dose of 25 mg/kg (peroral administration as starch slime). Reference drug (sodium diclofenac) was used in the dose of 25 mg/kg. The control animals received the same volume of starch slime. The drugs were administered once, 1 h prior to administration of 1% solution of AcOH.

Statistical processing of the data was performed using Statistica 6.0 software package. Between-groups difference was estimated using nonparametric Mann–Whitney U -test. The significance level was $p < 0.05$. The animals were divided into 4 groups, the body mass was as follows: “Control” ($n = 8$) 293.0±15.4; “Sodium diclofenac” ($n = 8$) 319.5±25.9; “**1**” ($n = 8$) – 275.3±17.7; “**3**” ($n = 8$) – 263.8±12.9.

The experiment revealed that sample **3** in the dose of 25 mg/kg exhibited anti-inflammatory activity (exudate volume 4.9±0.5 mL) comparable to sodium diclofenac (exudate volume 4.4±0.7 mL). Sample **1** in the same dose exhibited weak anti-inflammatory activity (exudate volume 6.5±1.2 mL)

This study was performed in compliance with applicable international, national, and institutional regulations for the experiments involving animals.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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