SYNTHESIS AND BIOLOGICAL TESTING OF NITROGEN–PHOSPHORUS-CONTAINING POLYCOMPLEXONES

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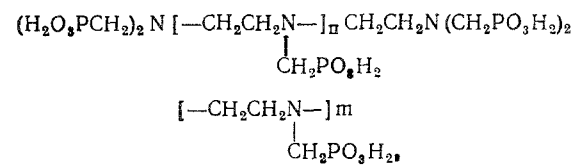
Much attention is being given in recent years to complexones containing aminomethylphosphonic groups in their composition. According to literature data [1, 2], these compounds possess complexing properties and are used to accelerate the separation of radioactive and toxic metals from the organism.

For the purpose of prolonging the effect of complexones we synthesized nitrogen–phosphorus-containing complexones of polymeric nature. The synthesis of polycomplexones was carried out by reaction of polyethylenepolyamine (PEPA) and polyethylenimine (PEI) of various molecular weights with phosphorous acid and formaldehyde in the presence of hydrochloric acid. The monomeric complexone ethylenediaminetetramethylphosphonic acid (EDTPh) was obtained for comparison by an analogous method from ethylenediamine. As a result of the research polycomplexones were obtained of the following general formula:



where n = 6-8 (I), 10-11 (II); m = 40 (III), 400 (IV).

A brief characterization of the polycomplexones is presented in Table 1. Elemental analysis and IR spectral data confirm the structure of the compounds. Bands appear in the IR spectra of polycomplexones in the regions of 945-950 and 1165-1170 cm^{-1}, which were assigned to deformation vibrations of the P–OH bond and stretching vibrations of the P=O bond [3]. The molecular weight of the compounds was calculated from results of elemental analysis.

The ability of polycomplexones to form complex compounds was determined potentiometrically. Potentiometric titration curves of polycomplexone III in the presence of equimolar amounts of the indicated metals are presented in Fig. 1. The neutralization curves are shifted to the acidic region, which indicates formation of complex compounds in solution. The most stable complexes are formed by Cu^{2+}, Cd^{2+}, Y^{3+}. Complexes of the alkaline-earth metals Ca^{2+} and Sr^{2+} are of low stability. Formation of unstable complexes with Ca^{2+} and of stable complexes with a series of metals makes it possible to draw a conclusion on the expediency of studying polycomplexones in a biological experiment to accelerate separation of radioactive isotopes from the organism.

The effect of the synthesized polycomplexones on the behavior of radioisotopes in the organism was studied in rats. Experimental groups of animals consisted of five to six rats (average weight 205.1 ± 6.8 g), into which indicator doses (3 μCi) of $Y^{91}Cl_3$ solution were injected intraveneously. Polycomplexone solutions in a dose of 20 μmole were also intro-

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TABLE 1. A Brief Characterization of the Polycomplexones

Compound	Mol. wt.	Phosphorus content, %		Nitrogen content, %		Carbon content, %		Hydrogen content, %	
		found	calculated	found	calculated	found	calculated	found	calculated
I	800	16,80	17,80	8,82	8,10	24,60	24,00	7,23	5,20
II	1 200	17,20	17,80	8,40	8,10	24,60	24,00	7,00	5,20
III	3 000	17,00	17,80	8,30	8,10	25,00	24,00	6,90	5,20
IV	70 000	14,30	17,80	8,33	8,10	26,01	24,00	7,29	5,20

TABLE 2. Effect of Polycomplexones on the Behavior of Y^{91} in the Rat*

Compound	Mol. wt.	Distribution of Y^{91} in the organism		
		liver	kidneys	spleen
EDTPh	436	0,728±0,081	0,405±0,019	0,011±0,001
I	800	1,235±0,123	0,494±0,032	0,030±0,006
II	1 200	1,237±0,156	0,560±0,071	0,020±0,003
III	3 000	0,963±0,117	0,484±0,017	0,022±0,004
IV	70 000	4,490±1,277	0,536±0,053	0,382±0,024
Control	—	5,671±0,366	2,394±0,398	0,069±0,026

Compound	Mol. wt.	Distribution of Y^{91} in the organism			
		skeleton	soft tissues	urine	feces
EDTPh	436	26,473±2,219	5,802±1,210	64,021±1,180	2,566±1,288
I	800	18,160±1,563	5,385±0,414	72,983±1,977	1,275±0,282
II	1 200	14,833±1,198	3,316±1,112	78,975±1,271	1,060±0,391
III	3 000	16,833±1,488	5,016±1,864	75,305±2,501	1,376±0,676
IV	70 000	16,847±1,835	14,831±0,632	61,570±1,0107	1,344±0,124
Control	—	62,187±4,858	12,871±6,975	15,486±1,914	1,232±0,280

*Results are given in % of the balance, amounting to 101.894 ± 1.916.

duced intravenously 1 min after incorporation of the isotope. The results are presented in Table 2. As is seen from Table 2, nitrogen–phosphorus-containing polycomplexones provide for a significant acceleration of removal of Y^{91} from the organism. Percent separation of Y^{91} with polycomplexones (II, III, IV) (72, 983; 78, 975; 75, 305%, respectively) is higher than with the monomeric complexone EDTPh (64, 0.21%; P = 0.22-0.003) and much higher than the natural removal of radioisotope. The dependence of separation of Y^{91} on the molecular weight of the complexones has extremal character with a washed out maximum in the region of molecular weight 1200 (Fig. 2); the effect of complexones on precipitation of Y^{91} in the internal organs (see Fig. 2) is in the same accord; the Y^{91} content decreases particularly significantly in the bone tissue (P = 0.02-0.03). The optimal value of molecular weight of the polycomplexones is thus in the range of 1000-3000. An increase in molecular weight to more than 3000 leads to a significant decrease in removal of the radioisotope and to an increase of its precipitation in the internal organs and tissues.

EXPERIMENTAL

Potentiometric titration was carried out using a LPU-01 pH meter with a glass electrode and acid and metal concentrations of 10^{-3} M in the presence of 0.1 M potassium chloride at 20°.

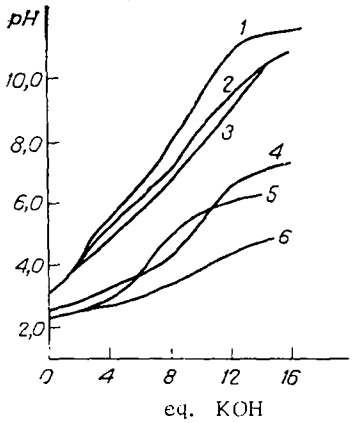

Fig. 1

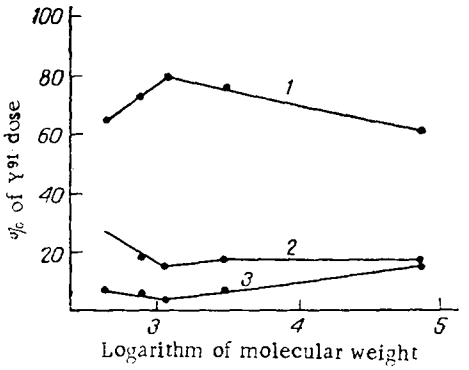

Fig. 2

Fig. 1. Neutralization curves of polycomplexone III: 1) polycomplexone III, 10^{-3} mole/liter; 2-6) polycomplexone III in the presence of equimolar amounts of Sr^{2+}, Ca^{2+}, Cd^{2+}, Y^{3+}, Cu^{2+}, respectively.

Fig. 2. Dependence of the amount of removal with urine and prevention of precipitation in the tissues of Y^{91} on molecular weight of the polycomplexones: 1) urine; 2) skeleton; 3) soft tissues.

Polyethylenepolyamine-N-methylphosphonic Acid (III). A solution of 10 g of PEPA in 20 ml of water, 36 g of phosphorous acid, and 20 ml of concentrated hydrochloric acid was heated to 100°; over 1 h 85 ml of formalin (32% solution) was added in drops and then the mixture was boiled an additional 2 h. The reaction mass was cooled, evaporated to a syrup consistency, and poured into a fivefold excess of alcohol. The amorphous yellow-colored precipitate was filtered, purified by repeated reprecipitation from aqueous solution into alcohol, washed with absolute ether, and dried over phosphorus pentoxide. The yield was 15 g (85%). The remaining polycomplexones were obtained by an analogous method.

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