INTERACTION OF CARBOXYL-CONTAINING POLYMERS
WITH DEOXYPEGANINE

E. I. Pereverzeva,[a] A. Karimov,[a] U. N. Musaev,[a]
L. V. Molchanov,[b] É. L. Kristallovich,[b] and
Kh. N. Aripov[b]

Polymeric complexes of deoxypeganine hydrochloride with a number of carboxyl-containing polymers have been synthesized and investigated. It has been found that in the interaction of polymers with deoxypeganine both hydrogen bonds and electrostatic bonds arise.

The alkaloid deoxypeganine (DOP) in the form of its hydrochloride is a drug with the anticholinesterase type of action that promotes restoration of nerve-muscle conduction, raises the tonus of the smooth musculature, and enhances salivation [1].

It is known that a promising approach to broadening the spectrum of the pharmacological action of drugs and decreasing their toxicity is the use of their complexes with synthetic and natural carboxyl-containing polymers [2]. In view of this, we have studied the interaction of DOP with polymethacrylic acid (PMAA), pectic acid (PA), and carboxymethylcellulose (CMC). The capacity of DOP for forming complexes with d-metals has been shown in [3].

The complex-forming process was studied in an aqueous medium by potentiometry, IR and UV spectrocopy, and microcalorimetry.

The formation of salt bonds between the positively charged ions of protonated DOP and the carboxy groups of polymers is readily detected by potentiometric titration [4]. It has been shown that the degree of electrostatic binding depends on he nature of the polymer, and for the rigid-chain PA and CMC it amounts to 35%, while for PMAA it is 17%. It is obvious that this is due to the greater accessibility of the carboxy groups in these polymers. In order to study the binding of organic ions with polymers and also the mechanism of their interaction it is necessary to know the factors influencing the course of the reaction. One of them is the change in pH, since the degree of electrostatic binding of polyelectrolytes with diphilic ions depends on charge density, which is determined by the pH of the solution.

The results of the investigations have shown that the interaction of DOP with ionogenic polymers takes place in the narrow pH interval of 3.5-5, and this reveals the high cooperativeness of these reactions. At pH < 4 the degree of electrostatic binding is small, which is due to the liberation of HCl in the course of the reaction, leading to a decrease in the ionization of weak polyacids. On neutralization with a mineral acid, the yield of the polycomplexes increases.

One of the main questions in the binding of organic molecules by polymers is the elucidation of the nature of the bonds involved and of possible centers ensuring interaction. Such information has been obtained with the aid of IR spectroscopy.

The IR spectra of the polymeric complexes PMAA+DOP and PA+DOP showed a shift of the absorption bands corresponding to the vibrations of the carboxy group in the low-frequency direction by 15-20 cm^{-1} relative to that in PMAA and PA and the appearance of absorption bands in the region of active hydrogen at 3220 and 3400 cm^{-1}. This experimental fact permits the assumption of the formation of the hydrogen bonds $NH^+ \cdots O = C$ (3220 cm^{-1}) and $NH^+ \cdots OH$ (3400 cm^{-1}), while, in the latter association, in the case of PA+DOP the participation both of the OH groups of the PA and of the hydroxy groups of the water of hydration is possible. In the IR spectrum of CMC+DOP a shift of the maximum corresponding to the asymmetric vibrations of the carboxylate ion (COO^-) into the low-frequency region (1590 cm^{-1}) can probably be explained by the appearance of the electrostatic interaction $NH^+ \cdots O^- = C$.

TABLE 1. Kinetic Parameters, Obtained by Schwartz's Method, of the Binding of Polymers with DOP

Complex	Proportion of nonbound DOP in the complex	$K_{bd} \cdot 10^{-5}$	Number of active centers in the polymer	Cooperativity parameter
PMAA+DOP	0.52	10.0	1.7	2–30
CMC+DOP	0.58	11.2	2.1	2–29
PA+DOP	0.43	3.2	2.5	2–29

TABLE 2. Change in the Thermodynamic Parameters of the Binding of Polymers on their Interaction with DOP

Complex	η	K_{eq}, liters/mole	ΔH^c	$-\Delta G^c$	ΔS°, J/mole·K
			kJ/mole		
PMAA+DOP	8	1.81	12.20	4.7	55.0
CMC+DOP	7	1.73	1.83	43.6	147
PA+DOP	5	6.21	4.63	13.0	144

Thus, hydrogen bonds and electrostatic bonds are realized during the interaction of these polymers with DOP, and the active center participating in the formation of the complexes is the most basic nitrogen atom, i.e., the atom having a double bond $-N=C-$.

For the quantitative estimation of binding we used Schwartz's method [8], based on the quantitative changes in the UV spectra of the complexes in comparison with the spectrum of pure DOP, which is characteristic for the "mild" interaction of polyacids with organic substances, during which no appreciable changes take place in the structure of the drug [5].

The calculated values of the binding constants K_{bd} (Table 1) show a stronger binding of DOP with PMAA and CMC, apparently mainly as the result of electrostatic interactions, which have a reversible nature as is shown by the presence of some proportion of nonbound DOP base. For PA+DOP the proportion of nonbound DOP is somewhat lower, which indicates the formation of more stable associates. However, K_{bd} for this complex has a lower value in spite of the fact that, according to the results of potentiometric titration, a fairly large number of salt bonds are formed. This is obviously due to the formation of a more complex system of hydrogen bonds, as was shown by an IR-spectroscopic investigation.

To confirm this hypothesis, the K_{bd} values and other kinetic and thermodynamic parameters were found by another, independent, method — microcalorimetric titration, which enables information to be obtained on energy changes in systems during the binding process [6]. Calorimetric titration conducted at a fixed temperature [7] is a convenient procedure for determining thermodynamic parameters of interaction for the binding of small molecules with polymers by a simple Langmuir mechanism. When the polymer molecule includes several monotypical active centers (η), with the aid of a calorimetric titration curve it is possible to calculate the heat and constant of interaction of a small molecule with one such center, the value of η, and the entropy and enthalpy of binding.

As expected, the equilibrium constant of binding for PA+DOP proved to be considerably higher than for the other complexes (Table 2). The interaction of carboxyl-containing polymers with DOP takes place spontaneously, as is shown by the decrease found in the free energy of the systems. Its value is the highest for the case of CNC+DOP, which agrees with the results obtained previously. This polymeric complex is readily formed, mainly through electrostatic interactions, which, however, rapidly break down.

The binding of polymers with DOP is accompanied by an increase in the total entropy of the systems, the greatest change being observed for the less polar compounds (CMC and PA). Such a change in entropy is due to the breakage of intramolecular bonds in the macromolecular coils under the action of intruding organic ions and to the disruption of the hydrate shells of the polymer and of the organic ion. The positive contribution of the factors listed obviously more than covers the fall in entropy due to the decrease in the conformational mobility of the macromolecules on their binding of the counter-ions.

Thus, the binding of polymeric acids with deoxypeganine takes place as a consequence of electrostatic and hydrophobic interactions, and the complex-forming process has a weakly cooperative nature. Binding is accompanied by the absorption of heat, apparently because of the large contribution of the hydrophobic interactions. A decrease in the free energy of the system is due to an increase in its total entropy. It has been found that the strongest polymeric complex is formed on the interaction of PA and DOP.

The polymeric complexes obtained have been sent for pharmacological trials.

EXPERIMENTAL

Potentiometric titration was conducted in aqueous solutions with the aid of an I-130 pH-meter. Viscosities of solutions of PMAA and of the polycomplexes were measured in an Ubbelohde viscometer. UV spectra were taken on a Specord M-40 spectrophotometer (H_2O, λ_{max} 274.7 nm), and IR spectra on a Specord UR-75 spectrometer (KBr).

Polymethacrylic acid (PMAA) with MM 140,000 was obtained by a known method [8].

Pectic acid was obtained by the alkaline hydrolysis of commercial beet pectin [9]. Its degree of esterification was 60%, and the number of free carboxy groups 7.2%.

The sodium salt of carboxymethylcellulose with a degree of substitution of 80 and a MM of 126,500 was purified by extraction with ethanol.

To obtain the polymeric complexes, solutions of the polymers and of DOP, each with a concentration of 0.1 M, were prepared with continuous stirring and heating, after which the DOP solution was added dropwise to the polymer solution, and the mixture was stirred for 1-2 h. The complexes obtained were water-soluble amorphous powders.

REFERENCES

1. N. Tulyaganov, S. Yu. Yunusov, M. V. Telezhenetskaya, F. Sadritdinov, and Kh. N. Khakimov, USSR Inventor's Certificate No. 605614 (1978); Byull. Izobret., No. 17 (1978).
2. G. A. Pkhakadze, Biodegradable Polymers [in Russian], Kiev (1990).
3. K. D. Sargazakov, L. V. Molchanov, B. Tashkhodzhaev, and Kh. N. Aripov, Khim. Prir. Soedin., 862 (1991).
4. N. I. Bystrova, V. A. Kemenova, A. B. Zezin, and V. A. Kabanov, Khim.-Farm. Zh., No. 4, 464 (1984).
5. B. A. Zhubanov, S. V. Moshkevich, and Yu. É. Kirsh, Izv. Akad. Nauk KazSSR, Ser. Khim., No. 6, 18 (1990).
6. W. Slouga, Trans. Faraday Soc., **58**, 480, 2360 (1982).
7. I. Ya. Erukhimovich and M. A. Landau, Zh. Fiz. Khim., **59**, No. 2, 457 (1982).
8. L. A. Bimendina, V. V. Roganov, and E. A. Bekturov, Vysokomol. Soedin., **A12**, 2810 (1974).
9. G. Karakolev, I. Oganesov, and M. Marinov, Pectin Substances [in Russian], Sofia (1956).