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INFLUENCE OF ITS PRELIMINARY
SATURATION BY ENOXIL**

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WATER BINDING THROUGH POLYACRYLAMIDE HYDROGEL AND THE INFLUENCE OF ITS PRELIMINARY SATURATION BY ENOXIL

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Abstract. The state of water in a polyacrylamide gel has been studied by the ¹H NMR spectroscopy. It has been shown that water is in a strongly associated state in the form of clusters with radius is in the range of R = 0.6-30 nm. The introduction of chloroform into the gel increases the binding of absorbed water, which indicates the effect of CDCl₃ on the structure of water-filled cavities formed by the polymer linkage. Trifluoroacetic acid (TFA) reduces the interaction of the polymer with water, probably due to its binding to nitrogen-containing groups. Even more the interphase energy of water decreases in the presence of Enoxil. This decrease makes it possible to determine the free energy of the interaction of Enoxil- polyacrylamide gels, which is maximal in air and decreases in the presence of CDCl₃ and TFA.

Keywords: cluster, Enoxil, ¹H NMR spectroscopy, polyacrylamide gel, polymer linkage.

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Introduction

Polyacrylamide (PAA) gels are widely used in plastic surgery as biologically inert implants to increase the size of soft tissues [1-3]. Their main advantages are the simplicity and ease of injection, the possibility of sterilization by radiation, as well as storage stability. Gel-like state and large water content ensure the similarity of the gel to living tissues. PAA gel refers to non-toxic products, however, much attention is paid to the study of the effect of residual monomer and by-products in PAA on the state of the body tissues in contact with it [4]. One of the main methods of synthesis is homogeneous polymerization in aqueous solutions. The formation of cross-linkages between polymer chains can significantly affect the solubility of the polymer in water and its water-absorbing capacity [5,6].

One of the applications of PAA gels is their use as a reservoir providing temporary binding of hygroscopic substances, protecting them from undesirable contact with air oxygen and water vapour. Drying of such a "loaded" gel transfers it to a solid state inside of which the transported agent can remain for longer while. If necessary, such solid gels may again be saturated with water, and the stored agent transferred from them to an

aqueous or biological environment. In the manner described, systems for transdermal administration of medicaments may also be provided.

The possibility of obtaining a complex of the preparation Enoxil with hydrogel PAA was previously described [7]. The Enoxil preparation, developed by the Institute of Chemistry of the Republic of Moldova [8], is a complex of biologically active substances obtained by modification of tannins from grape seeds. The final product is a yellow-brown powder, soluble in water, with high antioxidant properties which have been proved by voltammetric studies [9]. On the basis of the biologically active complex Enoxil, new pharmaceutical preparations have been developed with curative properties for the treatment of bacteriosis and mycosis in the process of regeneration of thermal, chemical or physical ulcers and burns, in the treatment of postoperative wounds and postradiation damage in cancer patients, as well as traumatic soft tissue injuries and inflammatory lesions of maxillofacial area of children [10].

The purpose of this paper is to study the behaviour of water in the Enoxil-PAA system. ¹H NMR spectroscopy was chosen as the main method of investigation, allowing to determine the characteristics of the hydrogen bond grid that

water forms in the polymer matrix from the chemical shift, as well as to calculate the thermodynamic parameters of the bound water from the change in the freezing temperature in addition to the interfacial energy of the polymer phase with respect to its bound water [11-14].

Experimental part

Materials

In the synthesis of PAA gels, acrylamide C_3H_5NO (99.5%, Fluka), N, N'-methylene-bis-acrylamide $C_7H_{10}N_2O_2$ (99.0%, Fluka), ammonium persulfate $(NH_4)_2S_2O_8$ (98.0%, Fluka), N,N,N',N'-tetramethylethylenediamine $C_6H_{16}N_2$ (99.0%, Fluka), methyl cellulose and aqueous glucose solution were used. In detail, the synthesis of PAA for biomedical applications is described in [15]. The copolymerization of acrylamide with a cross-linking agent is carried out in an isotonic solution in the presence of ammonium persulfate at a temperature of 35°C for 2 hours. It is then thoroughly washed with an isotonic solution at 35-40°C to remove residual monomers.

PAA-Enoxil system preparation

To prepare the PAA-Enoxil system, the dry polyacrylamide (in the form of a disk, 40 mm in diameter) was placed in a wide glass beaker (600-800 mL) with an Enoxil solution (5% by weight) in distilled water. Swelling in the solution of Enoxil was carried out for 20 hours at a temperature of 26-28°C. As a result, a soft disc of a transparent orange hydrogel of PAA saturated with Enoxil solution was formed. The control sample of PAA when swollen in distilled water forms a transparent colourless hydrogel. The diameter of the discs increased to 85 mm (Figure 1(a)). In this case, the increase in the weight of the samples was 14.0 ± 0.5 g per 1 g of initial PAA. Drying of the hydrogel was carried out for 6 days at room temperature. A sample of PAA-Enoxil obtained in a 5% aqueous solution of Enoxil was additionally kept in an oven at 30°C for 4 hours. After removal of water from the hydrogel, the PAA discs recovered their original dimensions (Figure 1(b)). As a result of this procedure, a complex preparation PAA-Enoxil of red-brown colour containing ~35% by weight of Enoxil was obtained.

NMR studies

NMR spectra were recorded on a high-resolution NMR spectrometer (Varian "Mercury") at an operating frequency of 400 MHz. Eight 60° probing pulses of 1 μ s duration with a bandwidth of 20 kHz were used.

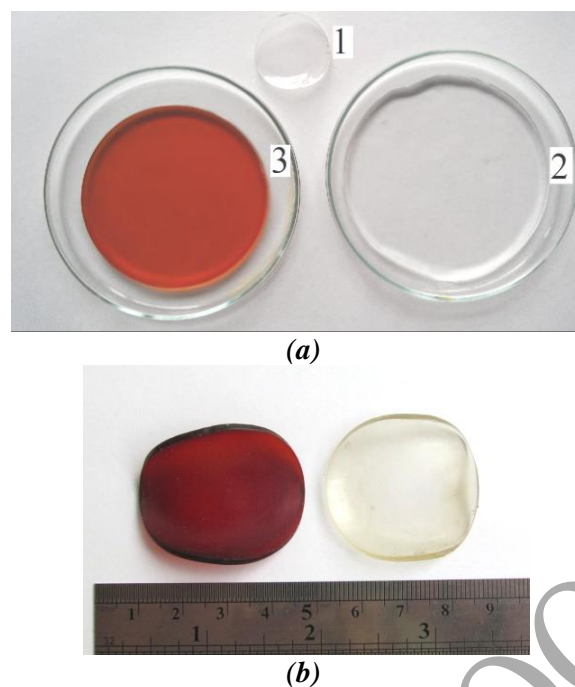


Figure 1. Photo of the samples: (a) - initial dry PAA (1), hydrogels PAA from water (2) and from aqueous solution of Enoxil (3); (b) - dry PAA-Enoxil (left) and dry PAA (right) after removed water from hydrogels at ambient conditions.

The temperature in the sensor was controlled by the Bruker VT-1000 thermal accessory with an accuracy of ± 1 deg. Signal intensities were determined by measuring the area of the peaks using the procedure for decomposing the signal into its components under the assumption of a Gaussian waveform and optimizing the zero line and phase with an accuracy that, for well-resolved signals, was not lower than 5%, and for overlapping signals $\pm 10\%$. To prevent supercooling of water in the investigated objects, measurements of the concentration of non-freezing water were carried out by heating samples previously cooled to a temperature of 210 K. Temperature dependences of the intensities of NMR signals were carried out in an automated cycle when the sample was kept at a constant temperature for 9 minutes, and the measurement time was 1 min.

For the measurements, standard 5 mm NMR vials were used. They contained crushed gel samples (0.2-0.4 g), equilibrated at 290 K with a selected amount of water (500 mg/g). The measurements were performed in air (the gaps between gel particles contained air) or organic solvents – deuteriochloroform or its mixture with deuterio-trifluoroacetic acid. Deuterated analogues were used to prevent the appearance of additional signals in the spectra due to added organic

substances. Over time, the components of the organic medium could diffuse into the polyacrylamide gel (or PAA gel saturated with Enoxil).

As the main parameter determining the structure of the grid of water hydrogen bonds, the value of the chemical shift of protons (δ_H) was used. It was assumed that water in which each molecule participates in the formation of four hydrogen bonds (two due to protons and two due to unshared electron pairs of oxygen atoms) has a chemical shift $\delta_H = 7$ ppm (realized for hexagonal ice), and weakly associated water (not involved in the formation of hydrogen bonds as a proton donor) has a chemical shift $\delta_H = 1-1.5$ ppm [11-14]. To determine the geometric dimensions of clusters of adsorbed water, the Gibbs-Thomson equation (Eq.(1)) was used that relates the radius of a spherical or cylindrical water cluster or domain (R) to the value of the freezing point depression [15,16]:

$$\Delta T_m = T_m(R) - T_{m,\infty} = \frac{2\sigma_{sl}T_{m,\infty}}{\Delta H_f \rho R} \quad (1)$$

where, $T_m(R)$ is the melting point of ice localized in pores of radius R , $T_{m,\infty}$ is the melting point of bulk ice, ρ is the density of the solid phase, σ_{sl} is the interaction energy of a solid with a liquid, and ΔH_f is the volume enthalpy of melting.

For practical application, the Eq.(1) can be used in the form $\Delta T_m = (k/R)$, in which the constant k is close to 50 deg·nm for many heterogeneous systems containing water [15,17]. The method of NMR measurements and determining the radii of clusters of interphase water is described in detail [11-14]. Polyassociates with radii $R < 2$ nm may be considered clusters, while polyassociates of a larger size - domains or nanodroplets, since they contain several thousand of water molecules [11].

The process of freezing (melting) of bound water corresponds to changes in the Gibbs free energy, due to the effects of limited space and the nature of the phase interface. The difference from the process in the volume decreases with the increase of the distance of the water layer from the surface. At $T = 273$ K water freezes, and its properties correspond to bulk water, and as the temperature decreases (without taking into account the effect of supercooling), the layers of water that are closer to the surface freeze. To change the free energy of bound water (ice), the following relation holds (Eq.(2)):

$$\Delta G_{ice} = -0.036(273.15 - T) \quad (2)$$

where, the numerical coefficient is a parameter related to the temperature coefficient of variation of the Gibbs free energy for ice [18].

Determining the temperature dependence of the non-freezing water concentration $C_{uw}(T)$ from the value of the signal intensity in accordance with the procedure detailed in [11-14], the amount of strongly and weakly bound water and the thermodynamic characteristics of these layers can be calculated.

The interfacial energy of water at the boundary with solid particles or in its aqueous solutions was determined as the modulus of the total decrease in the free energy of water due to the presence of a phase boundary by Eq.(3):

$$\gamma_s = -K \int_0^{C_{uw}^{max}} \Delta G(C_{uw}) dC_{uw} \quad (3)$$

where, C_{uw}^{max} is the total amount of non-freezing water at $T = 273$ K.

Here K is dimensional coefficient. If C_{H_2O} is measured in milligrams of adsorbed water, assigned to one gram of the adsorbent, and ΔG in kJ/mol, then to obtain the value of free surface energy expressed in mJ/m², $K = 55.6/S$, where S is the specific surface of the adsorbent. For polymer systems and systems with an unknown specific surface area, the interfacial energy refers to 1 g of dry matter. In this case, $K = 1/18$.

Results and discussion

The ¹H NMR spectra of a PAA gel containing 500 mg/g H₂O, taken at different temperatures, are shown in Figure 2a. Water that does not freeze due to adsorption interactions with the polymer network is observed in the spectra as a broadened signal, with a chemical shift $\delta_H = 4.5-6$ ppm. Its intensity decreases with diminishing temperature due to partial freezing of water absorbed by the polymer. After complete thawing of water ($T > 273$ K), two more broadened signals with chemical shifts $\delta_H = 1.5$ and 7 ppm appear in the spectra. The first of these signals can be attributed to the fusion peak related to the protons of CH₂ and CH-groups [3], and the second one to the NH₂-groups of PAA. Their appearance only after the completion of the melting process of water ice can be associated with a sharp decrease in the mobility of polymer chains in the presence of ice.

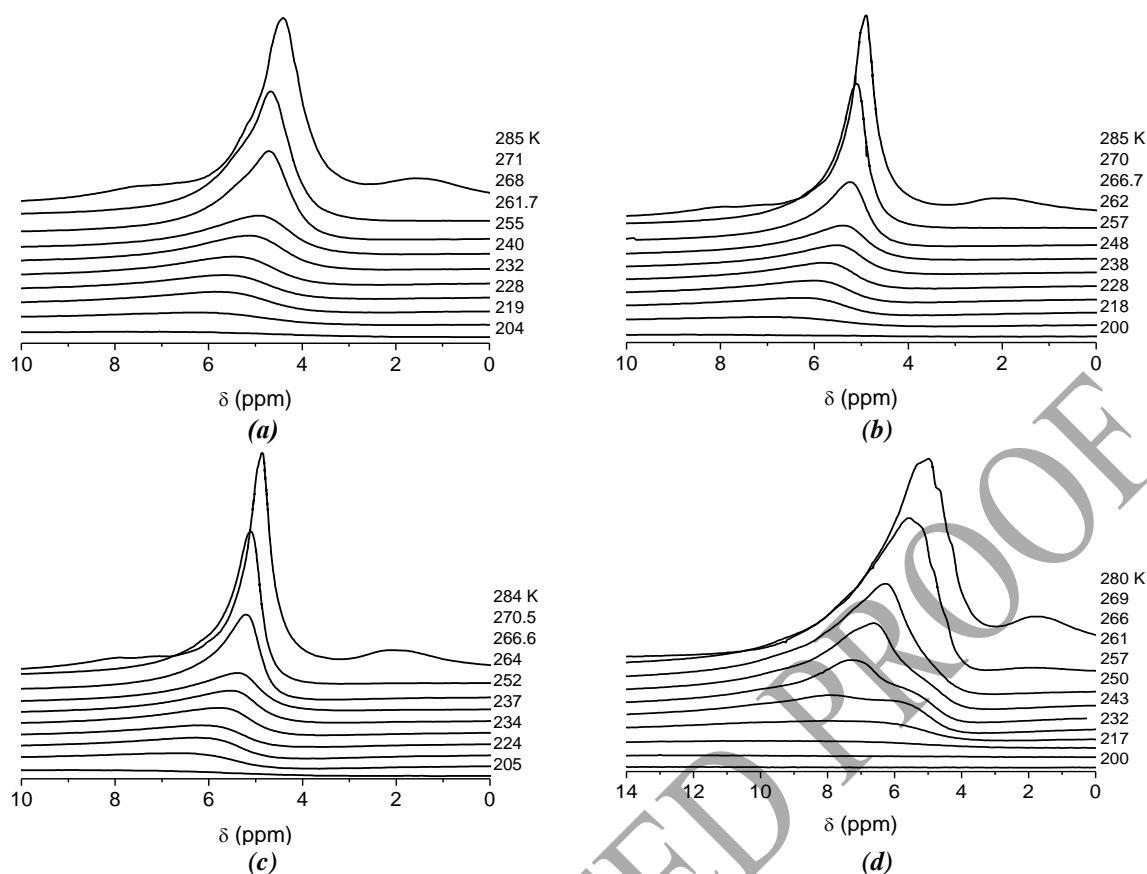


Figure 2. The ^1H NMR spectra of water-saturated hydrogels of PAA registered at different temperatures: initial, in air (a); in a CDCl_3 medium after 20 minutes (b); in a CDCl_3 medium after 60 minutes (c); in a CDCl_3 medium by adding TFA (d).

It could be expected that placing a sample of hydrogel in a medium of a weakly polar organic solvent, deuteriochloroform, will affect the binding of water by the polymer matrix, since PAA contains hydrophobic fragments - CH_2 and CH -groups. Visible changes in the form of spectra shown in Figure 2(b),(c) do not occur, but the nature of change in the intensity of water signal with temperature changes somewhat, which may indicate the presence of diffusion of chloroform inside a water-saturated polymer matrix.

The addition of 15% deuterio-trifluoroacetic acid to the chloroform medium leads to a change in the shape of the spectra (Figure 2(d)). The water signal at low temperatures is shifted to the region of weak magnetic fields (large chemical shift values). This is due to the contribution to the chemical shift of the “acidic” protons of trifluoroacetic acid, for which, in the absence of water, the chemical shift $\delta_{\text{H}} = 11$ ppm [18]. At $T < 261$ K, the water signal splits into two signals with different chemical shift values. As shown in [13,20,21], this is due to the possibility of forming several types of water clusters, which have different dissolving capability with respect to strong acids. A signal with a lower chemical shift value refers to clusters of water that weakly

dissolve the acid. In accordance with Figure 2d, the fraction of such clusters increases with decreasing temperature.

Figure 3 shows the ^1H NMR spectra of PAA gels saturated with Enoxil, registered at different temperatures: in air (a), in CDCl_3 medium after 60 minutes (b) and in CDCl_3 with 15% TFA (c). Saturation of the gel with Enoxil led to a decrease in the signal of the proton-containing polymer groups in completely thawed samples (Figure 3(a)-(c)). In the CDCl_3 medium, the temperature range, in which an unfreezing water signal is observed, has decreases (Figure 3(b)). This indicates a more efficient process of diffusion of chloroform into the sample loaded with Enoxil. In the presence of TFA (contrasting with the initial gel, Figure 2(d)), the signal of clusters of water that poorly dissolve the acid has a maximum intensity in the high-temperature region (Figure 3(c)).

Figures 4 and 5 show the temperature dependences of the non-freezing water concentration calculated from the signal intensities of the non-freezing water, provided that the completely thawed sample contains 500 mg/g of water (Figures 4(a) and 5(a)), the changes in the free Gibbs energy on the

concentration of non-freezing water, calculated in accordance with Eq.(2) (Figures 4(b) and 5(b)), and the distribution along the radii of the unfreezing water clusters, calculated from Eq.(1)

(Figures 4(c) and 5(c)) in the hydrogel of PAA (Figure 4) and the hydrogel of PAA preliminarily saturated with Enoxil (Figure 5).

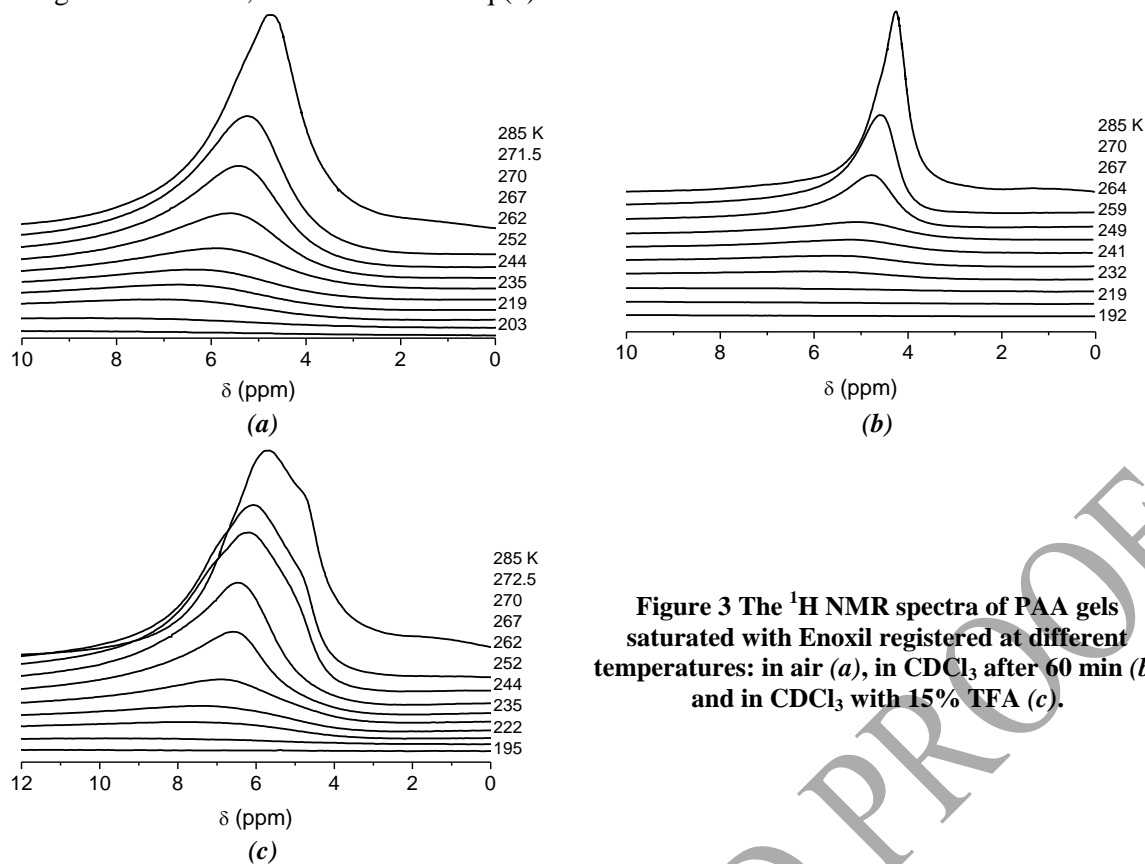


Figure 3 The ^1H NMR spectra of PAA gels saturated with Enoxil registered at different temperatures: in air (a), in CDCl_3 after 60 min (b) and in CDCl_3 with 15% TFA (c).

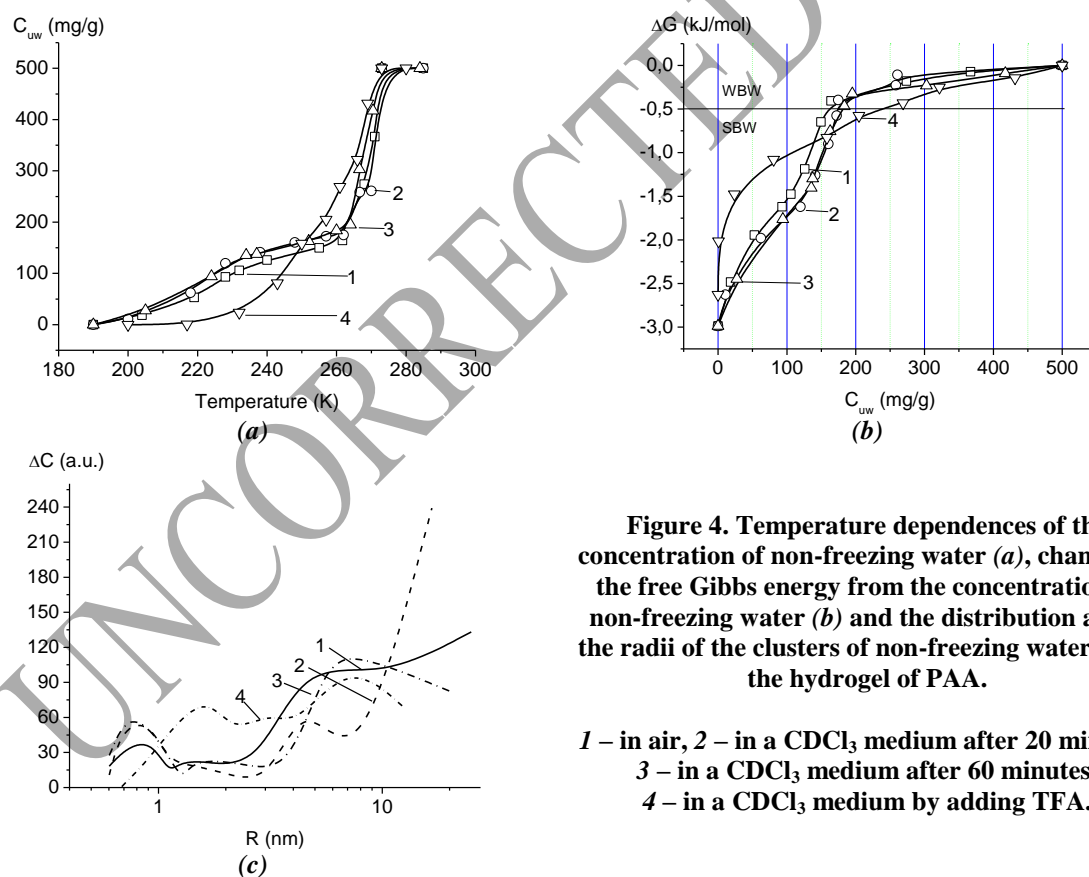


Figure 4. Temperature dependences of the concentration of non-freezing water (a), changes in the free Gibbs energy from the concentration of non-freezing water (b) and the distribution along the radii of the clusters of non-freezing water (c) in the hydrogel of PAA.

1 – in air, 2 – in a CDCl_3 medium after 20 minutes, 3 – in a CDCl_3 medium after 60 minutes, 4 – in a CDCl_3 medium by adding TFA.

Table 1 summarizes the values of the thermodynamic parameters of non-freezing water layers. In this case, the concentration of strongly (SBW) and weakly bound (WBW) water (C_{uw}^S and C_{uw}^W , respectively) were determined from the graphs of $\Delta G(C_{uw})$ dependences (Figures 4b and 5b) under the assumption that weakly bound water is that part of the water that freezes at $T > 265$ K ($\Delta G > -0.5$) [13].

The ΔG^S value determines the maximum decrease in free energy in the layer of strongly bound water. The total value of the lowering of the free energy of water, due to the presence of a polymer-water interface, is defined as the interfacial energy (γ_s). For different systems, γ_s values can only be compared for the same amount of water. Then large values of interphase energy correspond to a stronger interaction of water with polymer chains.

Based on the data shown in Figures 4, 5 and in Table 1, it can be concluded that in the PAA gels the minimum amount of strongly bound water is observed for the gel in the air medium. Penetration of a certain amount of chloroform into the gel, which improves with increasing storage time in the medium, leads to a certain increase in

C_{uw}^S and the interfacial energy value. In accordance with Figure 4(c), this is due to the relative increase in the number of clusters of water with a radius of $R = 0.8$ nm. In the presence of TFA, the amount of strongly bound water increases, while the value of γ_s decreases. At the same time, the number of small ($R < 1$ nm) and large ($R > 10$ nm) clusters of water decreases on the $\Delta C(R)$ distribution. Probably, the penetration of weakly polar substances and acids into the polymer gel greatly affects the topology of the space formed by the polymer chains.

It should be noted that in most of the systems previously studied, the presence of strong acids leads to a significant increase in the value of γ_s , which is due to the hydration of the acid molecules with water [12,20,22]. The absence of such an effect in the water-saturated PAA gel indicates that the effect of the growth of interfacial energy caused by the water solvation effect of the acid molecules is excessively compensated by the decrease in water binding caused by the preferential sorption of acid by amine and amide groups which in PAA provide the main effect of water binding.

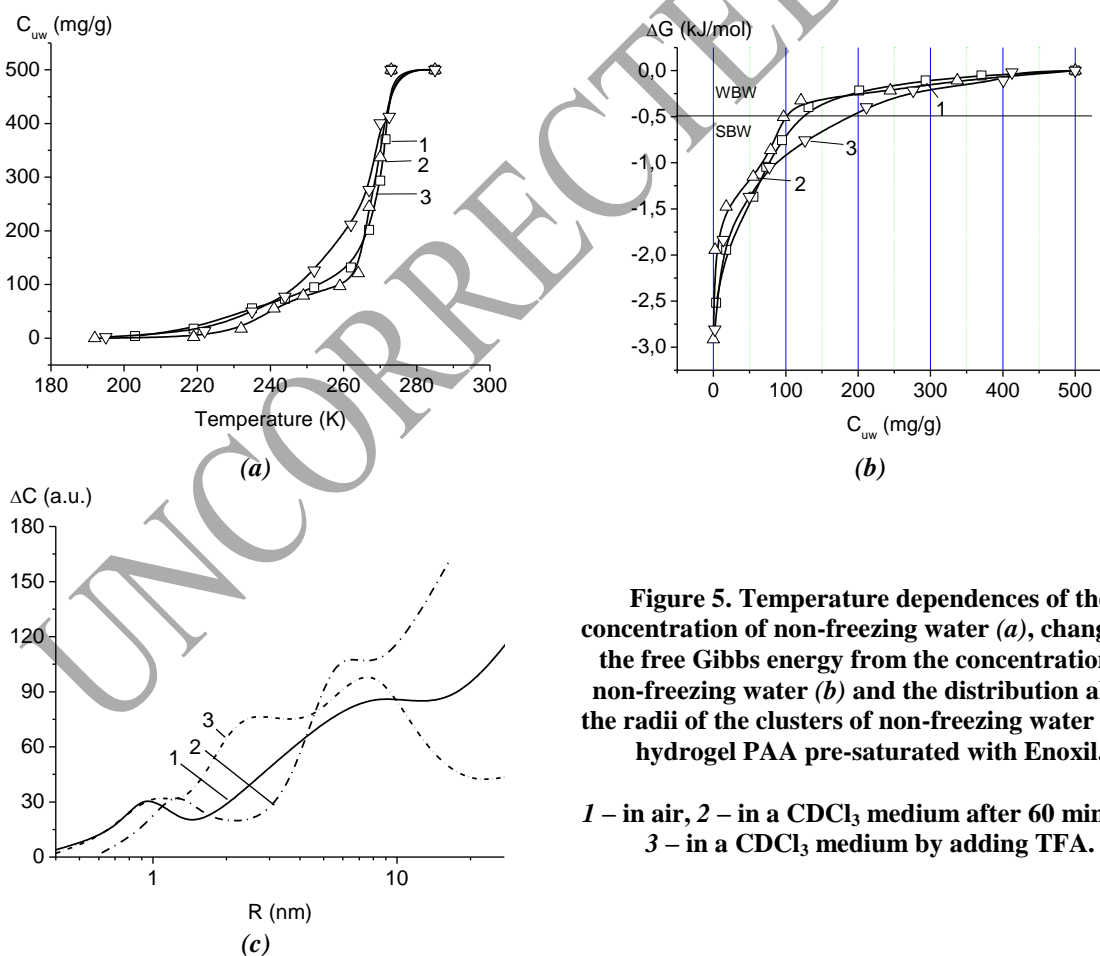


Figure 5. Temperature dependences of the concentration of non-freezing water (a), changes in the free Gibbs energy from the concentration of non-freezing water (b) and the distribution along the radii of the clusters of non-freezing water (c) in hydrogel PAA pre-saturated with Enoxil.

1 – in air, 2 – in a $CDCl_3$ medium after 60 minutes, 3 – in a $CDCl_3$ medium by adding TFA.

Characteristics of non-freezing water layers in a polyacrylamide gel, initial and saturated with Enoxil containing 500 mg/g H₂O.

Sample	Medium	C_{uw}^S (mg/g)	C_{uw}^W (mg/g)	ΔG^S (kJ/mol)	γ_s (J/g)
PAA	Air	160	340	-3	17.9
	CDCl ₃ 20 min	175	325	-3	19.6
	CDCl ₃ 60 min	180	320	-3	20.7
	CDCl ₃ +TFA	240	260	-2.75	16.6
PAA+Enoxil	Air	120	380	-3	11.2
	CDCl ₃ 60 min	90	410	-3	10.2
	CDCl ₃ +TFA	180	320	-3	14.0

The preliminary saturation of PAA by Enoxil leads to a decrease in the amount of strongly bound water and the magnitude of the interfacial energy (Figure 5(b) and Table 1). Apparently this is due to the formation of adducts between the molecular structures of Enoxil and polymer chains of PAA. The effectiveness of this type of molecular interactions can be judged from the difference in the values of the interfacial energy. Then, in the air, the interaction of Enoxil-PAA is 6.7 J/g, in the CDCl₃ medium is 9.4 J/g, and in the CDCl₃ + TFA medium is 2.2 J/g. In this case, there is a significant change in the form of the distributions along the radii of clusters of absorbed water (compare Figures 4(c) and 5(c)), which indicates the strong influence of the composition of the medium forming the liquid phase of the gel on the mutual arrangement of polymer chains with Enoxil adsorbed on them.

Conclusions

It is shown that the PAA gel can serve as a container for prolonged retention of the Enoxil preparation without changing its chemical composition. At the same time, the molecular structures of Enoxil bind strongly to polymer chains, probably due to the formation of hydrogen-bound complexes with amino and imino groups. The presence of such interactions reduces the binding of polymer chains to water molecules.

By varying the composition of the medium that fills the space between the polymer chains, it is possible to control the parameters of the interaction of the polymer with water, which should affect the processes of desorption of Enoxil into the environment.

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