NEW ASPECTS IN CHEMISTRY AND CHARACTERIZATION OF POLY(ETHYLENE OXIDE) HYDROGELS

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Abstract: To extend the variability of poly(ethylene oxide) (PEO) hydrogels in their swelling behaviour, ability to bind various subjects, and possible applications, some new synthetic approaches have been elaborated recently:
(i) PEO networks with ionic and reactive groups were prepared by the reaction of P-OH groups of poly(oligoethylene glycol phosphate)s with diepoxide. The swelling degree of these hydrogels is strongly affected by salts, what is typical of polyelectrolyte networks. The structure parameters of the network evaluated from the swelling data are discussed.
(ii) A series of hydrogels with controlled structure was obtained by radical polymerization of methacrylate PEO macromonomers of various molecular weights and average functionality (0.99-1.85) in aqueous media. The networks prepared are characterized by means of elastic modulus and swelling pressure measurements as well as with the help of microparticles of liquid-crystalline dispersion of DNA as probes highly sensitive to the network structure and state.

INTRODUCTION

Poly(ethylene oxide) (PEO) is one of the most available water-soluble polymers attracting stable interest as a basis for hydrophilic networks and corresponding hydrogels. The latter in their turn are quite popular objects of scientific research and applications. As for the advantages of this kind of hydrogels, principal ones are the following:

- extremely high hydrophilicity (interaction parameter $\chi \approx 0.41$-0.42) and chain flexibility ($\sigma \approx 1.55$) what are the guarantee for high swelling;
- intrinsic nonionic nature and high resistance to the salt presence in the media;
- tolerance to biological attack and high long-term stability.

Two well-developed approaches are most frequently used to prepare these gels.
The first of them is the polyaddition reaction between OH-groups of polyethylene glycol (PEG) and multifunctional isocyanates (Ref. 1). Contrary to expectations, the possibility to

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vary the network density at the expense of PEG chain length is rather limited. As a result of that, the swelling degree of these hydrogels (Q, ml/ml) does not exceed 40. A quite negative feature of this reaction is that it has to be performed only in dry organic media, what narrows the applicability of this method. To visualize its whole potentialities, it is convenient to present the existing data (Ref. 1) in the form of correlation between elastic modulus (G_e) and swelling degree (Q_e) at the equilibrium (Fig. 1).

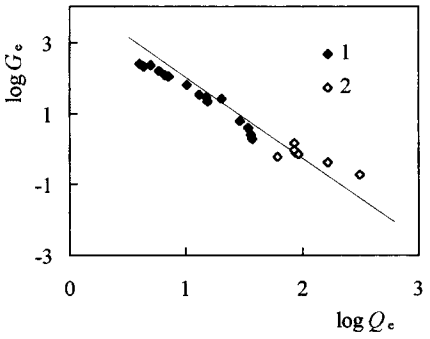


Fig. 1. Correlation between elastic modulus and swelling degree of PEO hydrogels at the equilibrium state: 1 -- end-linking of PEGs by isocyanates (Ref. 1); 2 -- radiation crosslinking of high-molecular-weight PEO in aqueous solutions (Ref. 4). Straight line has the slope equal to 2.25 characteristic of a good solvent according to Ref. 2.

The scales for modulus and swelling degree as values of practical interest are self-evident from the figure, however this plot provides a somewhat deeper insight into the thermodynamic state of the system. Indeed, according to Ref. 2 the exponent μ in the relation

$$G_e \sim Q_e^{-\mu} \qquad (1)$$

must be equal to 2.25 for a good solvent, and the corresponding straight line is shown in the figure. As is quite evident, water is really a good solvent for crosslinked PEO, what is consistent with a common point of view.

The lowest group of data points in the same diagram relates to radiation-crosslinked PEO (Ref. 3). It is another useful way to PEO hydrogel that extends the whole potentialities. It has long been known that high-molecular-weight PEO is readily crosslinked in an aqueous solution at very low radiation doses. Much higher extent of swelling (up to 300) is attainable in this case. Radiation-crosslinked PEO behaves as pure non-ionic gel and practically indifferent to salt's presence in the system. Sodium chloride affects but little the swelling degree of the gel via the salting-out, whereas in the same concentration range (up to 1 M) it drastically changes the swelling of charged networks, for example, those of polyacrylamide type.

To conclude this short survey, we can admit that PEO hydrogels can be obtained in a broad range of clue characteristics, e.g. swelling and elastic modulus. Nevertheless, there are obvious

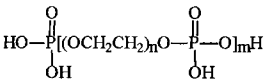
limitations in the whole preparative technique that, in particular, do not allow us:

- to build the network of controlled structure in aqueous media;
- to immobilize some subjects (chemical, biological, etc.) by binding or physical trapping;
- to introduce charged groups into the network in order to improve its swelling ability or to make it stimuli-influenced (pH, electric field, etc.).

Some results of our recent attempts to solve these problems are presented and discussed in this concise paper.

PARTLY CHARGED HYDROGELS WITH PHOSPHORIC ACID GROUPS IN NETWORK CHAINS BY THE CROSSLINKING OF PRECURSORS

It is of great interest to combine the advantages of nonionic and charged networks in PEO gels. The charges bound to a network are known to increase sharply its swelling degree, predominantly due to ionic contribution to swelling pressure. Some new attractive possibility was opened up with the synthesis of the PEG based polyphosphates of general formula **1**.



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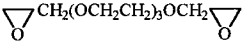

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The chain length values *m* and *n* can be to some extent varied by the choice of parent PEG and synthesis conditions (Ref. 5). The *m* values are most important because they determine the precursor functionality, which ensures the crosslinking at low conversion of reactive P-OH groups (α_P). Molecular characteristics of the precursors used are given in Tab. 1. Diepoxide **2** (diglycidyl ether of triethylene glycol) was chosen as the crosslinking agent because the reactions of epoxides with acids of phosphorus were known to proceed quite quantitatively (Ref. 7). The extent of the reaction was controlled by the crosslinking ratio CR = [Epoxide]/[P-OH], all other factors being the same (60°C, reaction time 24 hrs, in bulk).

The main idea of this work is to carry out the crosslinking reaction by using only the minor part of P-OH groups, so that the rest of them, being free and dissociated, may enhance the hydrogel swelling due to the Donnan effect. Free P-OH groups in the network chains can be considered as a strong electrolyte; for example, diethyl phosphoric acid (DEPA) as their close model has pK_a near to 1.4. As for gelation condition, it is reasonable to expect the gel point to occur at rather low values of CR or P-OH conversion: for this particular case of *m*-functional

precursor and bifunctional crosslinking agent the critical condition can be written as $\alpha_P^2 \approx CR/m$, which gives, for instance, $\alpha_P = 0.26$ at CR = 0.8 for both the precursors.

Tab. 1. Molecular Parameters of the Precursors (Ref. 6)

Code	PEG	n	m		[P-OH]·10^3, mol/g	
			Osmo-metry	^{31}P NMR[a]	calc.[b]	obs.[c]
1a	1000	22.7	12.8	14.1	0.94	1.02
1b	2000	45.5	13.1	14.7	0.49	0.53

[a] From the ratio of peak intensities of terminal (monoester) and chain (diester) P-OH groups. [b] From the structure of **1** at a given n. [c] From the potentiometric titration data.

The swelling behaviour of these new hydrogels reveals the features characteristic of the charged networks. The level of their equilibrium swelling lies much higher than in the case of PEGs end-linking (Ref. 1) and reaches 85 ml/ml at most. Besides, the Q values of all the samples drop distinctly from pure water to NaCl and then, much sharply, to K_2SO_4 solutions. In the NaCl case we deal only with the suppression of ionic part of the swelling, whereas in case of K_2SO_4 this effect is superimposed on the worsening of the solvent up to the Θ-point due to salting-out effect (Ref. 8). The equilibrium swelling degree as a function of NaCl concentration for several samples based on the precursor **1a** is displayed in Fig. 1. As compared to typical nonionic gels (for instance, Ref. 4), effect of added salt seems more considerable, and it is reasonable to suggest them to be caused mainly by the suppression of charge contribution to the swelling. Near to lower plateau the network can be considered as practically non-charged.

The analysis of salt effects is known to play an important part in characterization of hydrophilic networks. The potentialities based on the Flory approach have been recently approved as applied to some systems, i.e., partly ionic polyacrylamide gels (Ref. 9). The curves in Fig. 2 are calculated with the same algorithm, the network-average chain length x_c and the ionic content of gel β being the only fitting parameters. The data on potassium sulphate effect on swelling can be also treated in this way, and all the results of the swelling analysis are given in Tab. 2.

As is seen from Tab. 2, the swelling degree essentially decreases with CR increasing, obviously due to the growth of the network density characterized by the x_c values. It is clear, that the number of PEG blocks as well as that of non-reacted P-OH groups in a single network chain can be simply evaluated from x_c, for instance, $N_P \approx x_c/n - 1$. This way leads then to the P-OH

groups conversion into network knots $\alpha_P \approx 1/(N_P - 1)$ and finally to the values of $\beta \approx 1 - \alpha_P$. Both α_P and β are in close agreement with those evaluated from sol content and from the direct analysis of the curves in Fig. 2. Quite similar behaviour is typical for the series of hydrogels based on precursor **1b** and the detailed study of these gels is in progress now.

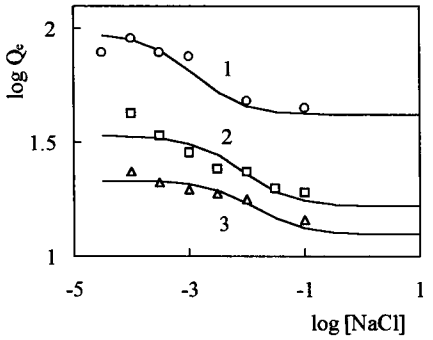


Fig. 2. Experimental swelling degree of ionic PEO hydrogels as a function of sodium chloride concentration in comparison with theoretical treatment. Precursor **1a**, the CR values are 1.05 (1), 1.10 (2), and 1.53 (3). The curves are calculated with pK_a 1.4 (DEPA) and with x_c and β values given in Tab. 2 (Ref. 6).

Tab. 2. Network Parameters of Ionic Poly(Ethylene Oxide) Hydrogels[a)]

CR	x_c [b)]	N_P [c)]	Yield of crosslinks		β [d)]	
			From N_P	From sol content	From N_P	From $Q(C_s)$ [e)]
1.05	284	11.5	(0.1)	0.32	0.92	—
1.10	76	2.2	0.31	0.41	0.69	0.49
1.53	50	1.2	0.45	0.50	0.55	0.52

[a)] Prepared from precursor **1a** by the crosslinking reaction in bulk at 60°C. [b)] From plateau values of Q with using of the χ parameters equal to 0.41 (NaCl), 0.50 (K_2SO_4); [c)] Number of free P-OH groups in a single network chain; [d)] Ionic content of hydrogel; [e)] From depression of swelling by NaCl.

To resume these data, we should emphasize, that hydrogels prepared display all the features of polyelectrolyte networks and are of perspective interest. These gels can be used for binding some agents through the reaction of free P-OH groups. Subsequent controlled delivery of these agents via the slow hydrolysis is possible.

It should be noted, however, that, contrary to previous evaluations, the crosslinking takes place only at a relative excess of the crosslinking agent. The α_P values obtained from potentiometric titration, ^{31}P NMR, and swelling data show the significant deficit in yield of both triesters and network junctions. That is just the very feature that stops from obtaining weakly crosslinked

networks with a higher content of ionizable groups. Some reasons for this anomaly have been discussed recently (Ref. 6).

NONIONIC HYDROGELS BY POLYMERIZATION OF METHACRYLATE MACROMONOMERS IN AQUEOUS MEDIA

The challenge to this work came from molecular biology. The idea was to stabilize the liquid-crystalline (LC) cholesteric dispersions of DNA by incorporating them into gel matrix, what could be the way to a new kind of biosensors (Ref. 10). Such LC dispersions were known to be formed via phase exclusion of DNA from solution by PEG. So, the only problem was to make PEG "polymerizable" in aqueous media, and the radical polymerization of methacrylate PEO macromonomers appeared to be most appropriate for this system. The whole procedure of "active" hydrogel preparation consisted of synthesis of macromonomers, their use in DNA phase exclusion followed by polymerization in the presence of LC particles. As it was then shown, neither functionalyzation of PEG nor polymerization interfered the labile structure of LC particles (Ref. 11).

It is quite evident *a priori*, that the polymer networks formed from macromonomers should differ in their structure from those prepared by end-linking reaction of PEG as precursor. The gelation proceeds here through the polymerization of terminal groups that combine to form macromolecular and multifunctional network junctions. In this particular case the part of these junctions is played by polymethacrylate chains whose length completely determines the functionality of a single junction. These chains, being obviously hydrophobic, exist in aqueous media in a rather collapsed state. In principle, it can produce problems for the gelation, as chain lengths of polymacromonomers can be as high as 50-70. Therefore, it is of interest to clear up the real situation and to evaluate the usefulness of this approach for the preparing PEO gels of a controlled structure in aqueous media.

The series of methacrylate macromonomers of PEO, prepared for this study by a direct methacrylation of corresponding PEGs, has the following molecular characteristics:

Code	A	B	C	D	E	F	G
M_n	4000	4000	4000	6000	6000	6000	12000
f_n	1.37	1.45	1.66	0.99	1.45	1.86	1.25
P_2	0.47	0.53	0.69	0.24	0.53	0.86	0.39

Here M_n is molecular weight of parent PEG and f_n is number-average functionality of macromonomers. P_2 is the fraction of dimethacrylate in them calculated from f_n on the assumption of equal reactivity of both OH groups in the esterification reaction. These macromonomers can be polymerized in aqueous solutions with common radical initiators in a broad range of polymer concentration (Refs. 11, 12). The network structure and state of hydrogels formed have been studied by several methods.

Crosslinking density of hydrogels can be evaluated from the elastic modulus according to well-known relation from the theory of rubber elasticity (Ref. 13). For the gel in the preparation state it can be essentially simplified to the following one:

$$G_o = RT\, n_c^0, \tag{2}$$

where G_o and n_c^0 are the elastic modulus and the number of elastically active chains of the gel sample in a nascent form, respectively. Both the n_c^0 and the average chain length between junction x_c are used as a measure of the crosslinking density. The simplest evaluations based on the measured moduli show that the x_c values are surprisingly close to the chain lengths of macromonomers. Particularly, for the gel sample prepared from macromonomer C at the concentration C_p = 0.193 g/ml the x_c value obtained from G_o is of the order of 100 and comparable with that found from M_n.

On the other hand, namely for the preparation state the n_c^0 values can be estimated from the composition of the polymerizing system. Indeed, if we assume that only bifunctional macromonomers become elastically active in the network formed, a simple relation can be obtained:

$$n_c^0 = (C_p/M_n) \cdot P_2 \tag{3}$$

The correlation of experimental modulus with the calculated network density is shown in Fig. 3 for the whole series of gels obtained. Omitting some details, we can conclude that the crosslinking density of the networks formed is close to that taken from the simple model. The only serious exception is represented by macromonomer D with the lowest f_n and, consequently, the highest fraction of non-functionalyzed PEG.

Correlation between elastic modulus and swelling at the equilibrium state is not less informative. It is a common practice now to consider such correlation in terms of Eq. (1) with the exponent μ depending on the thermodynamic state of the system. According to Ref. 2, the magnitudes of μ for the good, theta, and poor solvents are 2.25, 3.0, and ∞, respectively. The experimental data on elastic modulus and swelling for gels at the equilibrium are presented in the form of bilogarithmic plot in Fig. 4. For the reference, a straight line with a slope

corresponding to the good solvent is also shown here. Thus, the experimental data evidently demonstrate that water is a much poorer solvent for this kind of PEO networks than for linear or radiation-crosslinked PEO (cf., Fig. 1). It is most probably due to the already mentioned influence of hydrophobic polymethacrylate chains as junctions on the whole network state.

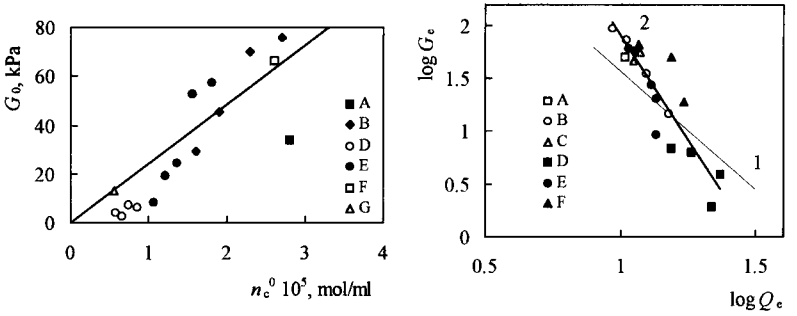


Fig. 3. Experimental modulus of PEO hydrogels in the preparation state as a function of the network density calculated from the model consideration by Eq. (3); the slope of straight line is equal to *RT*

Fig. 4. Bilogarithmic correlation between the elastic modulus and swelling degree of gels at the state of equilibrium. Straight lines: 1 - $\mu = 2.25$ (good solvent), 2 - $\mu = 3.95$ (experimental data approximation). Letters in both figures relate to macromonomer codes (Ref. 12)

This effect is supported qualitatively by our recent data (Ref. 14) on the behaviour of a luminescent probe, namely, magnesium salt of 8-anilinonaphtalene-1-sulphonic acid, especially sensitive to the fate of hydrophobic fragments. In particular, it has been shown that luminescence intensity increases sharply during gelation in the presence of this probe as well as by the diffusion of probe into a swollen gel sample.

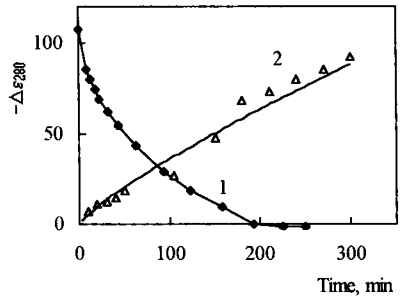
Swelling pressure of gels provides a more quantitative criterion of the state of swollen networks. Being a direct measure of the chemical potential of the solvent, it allows us to evaluate an interaction parameter χ if the network density is known from the modulus.

The swelling pressure of hydrogels was obtained by a deswelling technique, where the swelling degree of gel sample was measured in an equilibrium with a linear polymer solution whose osmotic pressure was known (Ref. 15). It was reasonable to use PEG as a compressing polymer in these experiments. The experimental data on swelling pressure were shown to obey the simple Flory formalism with the χ parameter equal to 0.462 (Ref. 12). This value is much higher as compared with 0.410-0.425 for linear polymers (Refs. 16, 17) and gives us one more evidence for the marked decrease in the solvent power upon going from the solution to

swollen PEO gel. In a practical sense this effect is obviously a negative factor because it significantly reduces the equilibrium swelling of PEO hydrogels of this kind.

Liquid-crystalline particles of DNA can be incorporated into the gel on the preparation step and turn out to be quite responsive to the gel structure. Their optical activity measured by the intensive anomalous band of the LC phase of DNA at about 275-280 nm in circular dichroism spectra provides a convenient measure of the particles state.

As it has been shown (Ref. 11), the intensity of this band ($\Delta\varepsilon$) is highly sensitive to any changes in the state of the system. In particular, it changes during gelation, that is in going from solution to gel, as well as at the swelling of a gel sample after preparation or its deswelling by osmotic compression. Fig. 5 shows how the probe particles lose their optical activity when a sample is allowed to swell and restore it in the contact with a compressing solution. Moreover, the $\Delta\varepsilon$ value of a particular sample is to some extent sensitive to its network density.



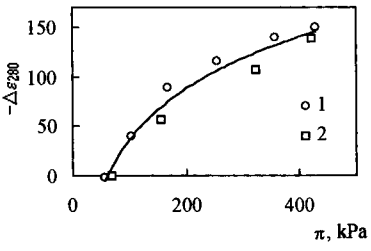


Fig. 5. Variation of the LC particles optical activity during the swelling (1) and osmotic deswelling of hydrogel (Ref. 11)

Fig. 6. The optical activity of the LC probes as a function of the pressure exerted by the outer PEO solution (1) or gel (2) (according to Ref. 12)

Some clues to this behaviour can be found in the existing theory of DNA phase exclusion and LC ordering under the action of PEG (Ref. 16). The analysis of the situation has shown (Ref. 12) that the LC particles are sensitive mainly to the pressure of the outer medium, be it an osmotic pressure of solution or swelling pressure of hydrogel. The decisive argument for this is shown in Fig. 6 in the form of the universal dependence $\Delta\varepsilon(\pi)$. So, these particles can be considered as the internal probes to swelling pressure of gels, which is of great interest. Another interesting aspect consists in the possibility of using the gel as a compressing matrix in the study of the LC ordering of DNA, because the existing data (Ref. 17) relate to much higher pressures than at the critical point in Fig. 6.

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