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Acrylamide polymers with covalently linked zinc(II)tetraphenylporphyrin groups: synthesis and complexation with amino acids

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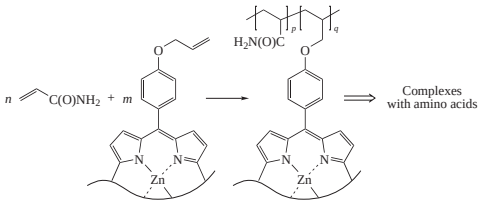
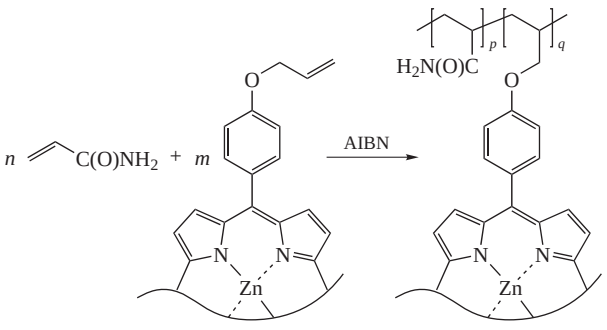
New copolymers of acrylamide with zinc 5,10,15,20-tetrakis-(4-allyloxyphenyl)porphyrinate were synthesized and tested as cysteine and histidine sensors.



Cysteine and histidine are essential amino acids responsible for functioning of human organism.[1–8] Diagnostics of diseases requires identification of low amounts of biomarkers. However, known methods for such identification[9–19] are not universal. In recent years attention has been paid to development of optical sensors based on polymers because polymer sensors enable both detection of analytes and enhancing their signals. The process of manufacturing such devices is simple. Therefore, the aim of this work was the synthesis of water-soluble porphyrin-tethered acrylamide polymers and estimation of their functionality as optical sensors for detection of histidine and cysteine.

The copolymers of acrylamide with zinc(II) 5,10,15,20-tetrakis(4-allyloxyphenyl)porphyrinate (ZnAOPP) were prepared by radical copolymerization (AIBN as the initiator) of the monomers (Scheme 1).† The electron absorption and fluorescence spectra of the synthesized polymers are of the same type irrespectively of content of Zn(II)tetraphenylporphyrin groups. As an example, Figure 1 demonstrates the spectra of Pol10. In comparison with the porphyrin exhibiting two bands, the fluorescence spectrum of the polymer reveals three emission bands. In the long-wave region of the UV-VIS spectrum, an abnormal broad band with higher intensity than that of the band at 560 nm is detected. Similar phenomenon has been observed for polymers with covalently linked porphyrin compounds,[20] which is explained by π–π self-aggregation of the porphyrin chromophores into conformationally flexible polymer chains. However, the absence of changes in the electron absorption spectra of the synthesized polymers with increasing content of zinc(II)tetraphenylporphyrin groups makes the supposition on π–π self-aggregation of the porphyrin chromophores[20] doubtfull. The results of titration of the polymer



Scheme 1

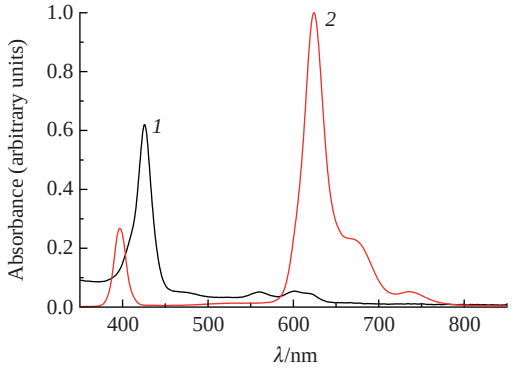


Figure 1 (*1*) Electron absorption and (*2*) fluorescence spectra of Pol10 aqueous solution (0.1 wt%).

† The synthesis was carried out in 1.4-dioxane using a microwave system Discover LabMate (CEM Corporation; 2.45 GHz, 300 W) in 10 ml flask. ZnAOPP (5, 10 or 20 mg) and azobisisobutyronitrile (AIBN) (1 mg) were added to a solution of acrylamide (100 mg) in 1,4-dioxane (5 ml). The copolymerization was performed at 75 °C under continuous microwave irradiation (25 W) for 50 min. The precipitate formed was filtered, washed with chloroform and dried at 50 °C until the constant weight of the product. The yields of the product at ratios of acrylamide–ZnAOPP (mg): 100 : 5, 100 : 10 and 100 : 20 were 92%, 88% and 67%, respectively. The obtained polymers were denoted Pol5, Pol10 and Pol20.

The molecular weights of the copolymers were measured using an Agilent 1200 Series liquid chromatograph equipped with refractometric detector at 25 °C. The 0.1 M aqueous solution of $NaNO_3$ was used as an eluent. The estimated average molecular weights of the prepared polymers were in the range of 19000–22000. The obtained samples were polydisperse (M_w/M_n = 2–3). The polydispersity is explained by precipitation of increasing polymer macromolecules due to their limited solubility in 1,4-dioxane during the process leading to loss of possibility to participate in further reaction of copolymerization.

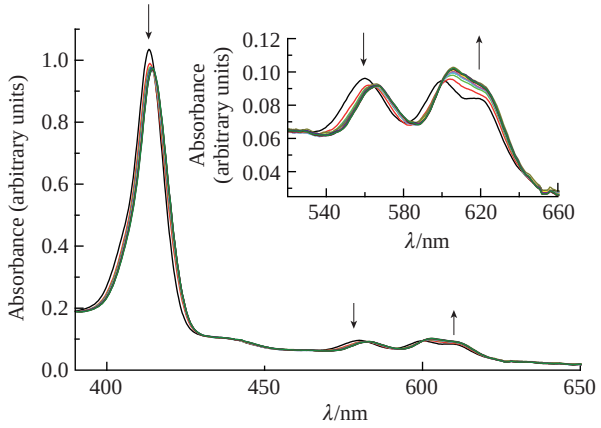


Figure 2 Electron absorption spectra of Pol20 aqueous solution (0.061 wt%) with increasing concentration of pyridine (0–0.15 mol dm^{-3}).

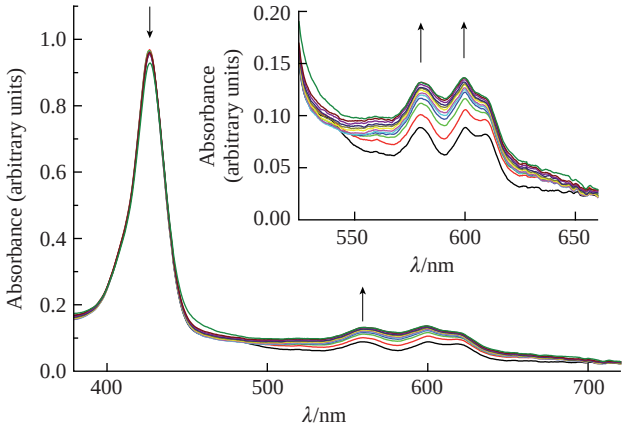


Figure 3 Electron absorption spectra of Pol20 aqueous solution (0.047 wt%) with increasing concentration of cysteine (0–0.10 mol dm^{-3}).

solutions by pyridine bring more evidence of the absence of the π–π self-aggregation.

Figure 2 demonstrates red shift of the Soret band and decrease in its intensity. The spectral changes may be attributed to axial coordination of pyridine on zinc atom of the porphyrin. If the coordination occurred on the associates of the chromophore, the spectral changes would be opposite.[21,22] Thus, the porphyrin fragments in the synthesized polymers (up to 0.12 wt%) do not aggregate irrespective of their content in the polymers. Therefore, it is likely that the band at 625 nm in the electron absorption spectrum and three emission bands in the range of 625–750 nm can be due to the presence of chlorin structures along with the porphyrin fragments in the synthesized polymers. The fitting spectral data in the range of 580–660 nm using published extinction coefficients of chlorin[23] showed that a portion of chlorin structures is not greater that 10%.

The absence of self-aggregation of the porphyrin fragments is a positive factor from the viewpoint of potential sensor properties of the polymers because there are no additional equilibria, π–π associated molecules blocking access to the central metal atom. Nevertheless, it should be noted that competitive interactions occur. A shift of the Soret band to long-wave region by 2 nm at titration of the polymer solutions by pyridine shows that the fifth coordination position on the zinc atom is occupied by nitrogen of amide group of the polymer.

We also studied complexation properties of the synthesized polymers towards amino acids (methionine, arginine, histidine and cysteine), dipeptides (alanyl-alanine, glycyl-alanine, alanyl-valine), bovine serum albumin and DNA. Among the listed bioactive compounds, the synthesized polymers interact specifically only with histidine and cysteine forming thermodynamically stable complexes (Table 1). Note also that the obtained binding constants are apparent because they incorporate dissociation of zinc(II)porphyrin–polymer amide group complex. The binding of the indicated amino acids leads to the spectral changes (Figure 3) which are detected visually, particularly in the case of cysteine (Figure S1, see Online Supplementary Materials).

Comparative analysis of the obtained results allowed us to ascertain binding sites of amino acids with the synthesized polymers. Methionine and cysteine are sulfur-containing amino acids having similar structure. However, only cysteine binds to the polymers, and the binding occurs only at pH > 5. The isoelectric point of cysteine (pH) is 5.02. At higher pH values, cysteine becomes negatively charged. Therefore, the amino acid coordination on the porphyrin fragments does not proceed due to sulfur atom of cysteine (because no specific interaction with methionine was observed) and cysteine carboxyl group (because no specific interaction with cysteine was observed at pH < 5). Thus, cysteine coordination on the zinc(II)porphyrin fragments of the polymers occurs due to its amino group.

Comparing electron donating ability of cysteine and methionine amino groups, it seems reasonable to surmise that it will be greater for methionine NH_2 group because in this amino acid the distance from oxygen and sulfur atoms to nitrogen atom is longer than that in cysteine and, hence, their negative inductive effect will be lower. Taking into account the absence of donor–acceptor interaction of methionine with the porphyrin fragments of the polymers, it may be concluded that one more binding site is required for complex formation between the polymers and the sulfur amino acid. Thus, the investigated polymers form complex with cysteine through two binding sites. The first site is donor-acceptor interaction between zinc atom of the porphyrin fragments of the polymers and amino group of cysteine. The second site is interaction between amide group of the polymers and SH group of cysteine. Elongation of alkyl spacer on transition from cysteine to methionine has negative effect on the binding of the amino acid to the polymer. The complexes with histidine are weaker but formed by analogous way. Unlike the other investigated amino acids, histidine has short spacer between its amino group and heterocycle.

Thus, cysteine and histidine are capable of complementary interacting with the porphyrin containing acrylamide polymers. This effect may be detected visually.

Table 1 Binding constants (K) of histidine (HIS) and cysteine (CYS) to the synthesized polymers.

System	K/dm^3 mol^{-1}	System	K/dm^3 mol^{-1}
Pol5–CYS	1428	Pol5–HIS	200
Pol10–CYS	1656	Pol10–HIS	213
Pol20–CYS	1231	Pol20–HIS	120

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.03.016.

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