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Carbon Enterosorbents Modified by Biologically Active Substances: Synthesis, Properties, and Application

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Abstract

To improve biospecific properties of carbon enterosorbents for purposes of veterinary medicine methods of chemical modification of their surface were proposed. The first area is modification of carbon surfaces by the method of polycondensation of biologically active substances (arginine) and in situ formation of polymers (directly on the surface of carbon sorbents). Another method is impregnating into a porous matrix of carbon carrier nanodispersed betuline in a water soluble form. To study physicochemical characteristics of veterinary preparations synthesized the following methods were used: scanning electron microscopy (SEM) (relief and morphology); X-Ray phase analysis (phase composition); the method of low-temperature nitrogen adsorption-desorption (texture studies); X-Ray microanalysis and CHNOS Elemental Analysis (elemental composition): IR spectroscopic analysis, Kjeldahl method, H. P. Boehm's method and X-ray photoelectron spectroscopy (XPS) (surface functional composition of the synthesized samples). Study results of physicochemical properties of carbon sorbents before and after modification that confirm the presence of polyarginine and betuline in the composition of the resulting samples are presented..

Kew words: carbon sorbent, arginine, polyarginine, betuline, impregnation, modification, physicochemical properties

INTRODUCTION

Enterosorption relates to sorption therapy methods based on binding and removing from the gastrointestinal tract of various nature toxins [1–4]. The major mechanism of action of sorptive preparations is binding toxic substances in the gastrointestinal tract by adsorption, sorption, ion exchange, complex formation.

Enterosorbents have a special importance in veterinary practice. This is due to the extensive dissemination of gastrointestinal tract disorders in animals. Young growth is especially susceptible to them, since its protective mechanisms including the microbiological bowel system are formed later. It is also known that a human, as the final link in the food chain, is subjected to a significant risk by consuming livestock products with elevated amounts of toxins that are accumulated in organs and tissues of animals [5–7].

The requirements for the quality of enterosorbents for animals are like the criteria for enterosorbents for medical purposes [2]. En-

terosorbents based on silica, carbon, lignin, chitin, and its derivatives and mineral enterosorbents (bentonites, zeolites, vermiculites *etc.*) find broad application [8, 9].

The most known enterosorbents of domestic production in veterinary practice are Zoocarb (Omsk); Tsamax (Moscow Region, Zheleznodorozhny-5 city); Polyphepanum (St. Petersburg); activated carbon (Yekaterinburg); Enterosgel (Saratov); Polysorb VP (Chelyabinsk) *etc.* [10–20].

It is noteworthy that there are no enterosorbents of prolonged and biospecific action in the veterinary pharmaceutical market. This is due to the complexity of their production and a high cost. In this regard, creating new efficient modified carbon sorbents for detoxification of the organism of humans and animals that do not exert negative actions on them, convenient in practical applications to treat a broad range of diseases, as well as allowing improving the quality of foods of animal origin is relevant.

To improve biospecific properties of carbon sorbents two areas are used in the work: 1) surface chemical modification by the method of arginine polycondensation and *in situ* polymers formation (directly on the surface of carbon sorbents); 2) impregnation of carbon carrier nanodispersed betuline in a water soluble form into a porous matrix. Currently, similar processes have been almost unstudied.

BIOLOGICALLY ACTIVE SUBSTANCES AS PROMISING MODIFIERS FOR CARBON MATERIALS

Modifiers used for elaborating medical purpose sorbents should meet the following requirements: nontoxicity, a good biocompatibility; solubility in aqueous solutions; the availability in the structure of functional groups capable of entering into a polycondensation/polymerization reaction with the formation of oligomeric/polymeric chains that determine low mobility of a modifier in pores of the carrier, accessibility.

Literature analysis conducted allowed highlighting a number of substances for modification of carbon surface. Betuline and arginine were used as modifiers in this work (Table 1). They possess valuable biological properties and have in their composition active functional groups (COOH–, OH–, NH_2–) with hydrophilic properties and a hydrophobic $(CH_2)_n$ chain. Such a structure ensures the optimum balance between hydrophilic and hydrophobic interactions at contacting with toxic substances. The betuline and arginine molecules are small by their sizes (average diameter is less than 1 nm) and comparable with the sizes of macro- and mesopores of carbon sorbent.

Arginine (1-amino-4-guanidinovaleric acid, 2-amino-5-pentanoic acid) used as a modifier in the work is an aliphatic basic α-amino acid. It is optically active, exists as *D*- and *L*-isomers. This acid has a formula of $C_6H_{14}N_4O_2$; its molecular mass is 174.2 g/mol, represents colourless crystals. For *D*,*L*-arginine, *D*-arginine and *L*-arginine, the melting point values are equal to 220–222, 235–240 and 244 °C, respectively (all isomers melt with decomposition); pK_a = 2.18, 9.09, 13.2; p*I* = 10.76. The amino acid in an aqueous solution shows mainly basic properties. Arginine is unstable to alkalies and decomposed in weak alkaline solutions to citrulline, and in concentrated – to ornithine [21–23].

In the organism, arginine is present in a free form and in the composition of proteins (there

TABLE 1

Properties of modifiers

Indicators	Betuline	Arginine
Molar mass, g/mol	442.7	174.2
Appearance	White needle-like crystals	White granular powder
Estimated average diameter of the molecule, nm	1.4	0.8
Melting point, °C	251–261	238
Solubility, g/100 g:		
water	Insoluble	Soluble
ethanol	0.9 (20 °C)	Slightly soluble
	4.3 (78 °C)	

is a lot of arginine in protamines). It is the major source of nitrogen oxide (NO) in the organism; all its biological functions are associated precisely with this.

Betuline is a natural compound, a triterpene alcohol of the lupane series. It is contained in the birch bark, hazel bark, calendula and in other drug plants. Betuline determines the white colour of birches. Its contents in the external bark is varied from 10 to 35 % depending on the birch species, place and growing conditions, tree age, season [24, 25].

Betuline is $C_{30}H_{50}O_2$ (molar mass is 442.7 g/mol), a creamy or white crystalline powder. It is poorly soluble in water, alcohol, fatty bases. Biological properties of betuline were known as early as in the 19th century. Thus, in 1899, Wheeler pointed out at antiseptic properties of betuline, owing to which it began to be applied for sterilization of wounds, cuts in the form of patches.

Betuline and its derivatives have pharmacological activity: antiviral, immunostimulating, anti-inflammatory, oncoprotective, and antibacterial. This explains prospects of its use in the pharmaceutical industry. It was proven that betuline was nontoxic, did not have cancerogenic, mutagenic, allergenic, and skin-irritating properties. Betuline is safe for animals, has the gastroprotective effect [25, 26].

EXPERIMENTAL

A research object is mesoporous carbon enterosorbent Zoocarb. A carbon sorbent sample corresponded to technical specifications TU 9318-003-71069834−2006 and represented black or silver, shiny, odourless, spherical granules with a diameter from 0.1 to 1.0 mm. The carbon mass fraction in the sample was no less than 99.5 %; the mass loss at drying − no more than 0.10 %; the residue after calcination − no more than 0.5 %; the adsorption activity for methylene blue − no less than 30 μg/g, according to the results of sieve analysis, the residue on the sieve with a diameter of openings of 1.0 mm and came through a sieve with a diameter of openings of 0.1 mm did not exceed 0.5 %.

To modify the mesoporous carbon sorbent surface there were applied:

− biologically active component betuline (M = 442.7 g/mol; average diameter of 1.4 nm) obtained at the Institute of Chemistry and Chemical Technology, SB RAS (Krasnoyarsk); ethyl alcohol rectified industrial State Standard GOST 18300 (Osha LVZ OOO, Omsk); glycerine GOST 6259−75 (Zhirovoy Kombinat OAO, Saratov);

− L-arginine, M = 174.2 g/mol average diameter of 0.8 nm (Panreac, Spain).

The morphology and relief of the sorbent samples tested were studied by SEM using a JEOL JSM-6460 LV electron microscope (Akishima, Japan) at the Boreskov Institute of Catalysis, SB RAS (Novosibirsk).

The adsorption method studied the texture of the samples by low-temperature nitrogen adsorption desorption at −195.7 °C using a Sorptomatic-1900 volumetric static vacuum setup (Carlo Erba, Italia) and a Gemini 2380 analyzer (Micromeritics, USA). The samples were preliminarily trained under vacuum at a temperature of 300 °C (initial sample) and 40−60 °C (modified samples) for 6−8 h. The thermal training temperature of modified samples was selected considering the melting points of the modifiers and the polymers formed as a result of polycondensation.

The specific surface was determined by the BET method (S_{BET}, calculation in the region of P/P_0 = 0.05−0.33). The pore volume V_{Σ_1} and V_{Σ_2} at the values of P/P_0 = 0.999 and P/P_0 = 0.996, respectively, was calculated according to nitrogen adsorption data in the region of nitrogen vapour partial pressures $P/P_0 = 10^{-4}$−10^{-1}. The adsorbate density was considered equal to that of the normal fluid density ($\rho_{N_2/d}$ = 0.808 g/cm^3). Specific macropore volume (V_{macro}) values were assessed according to difference V_{Σ_1} − $V_{\Sigma_2;}$ mesopores (V_{meso}) − according to difference $V_{\Sigma_2} - V_{micro}$ at the condition that V_{micro} is the micropore volume (comparative t-method).

CHNOS analysis was carried out on a Vario EL Cube Elementar elemental analyzer (the Omsk Center for Collective Use, SB RAS). When conducting elemental analysis, samples were automatically supplied to the combustion area using an autosampler equipped with a ball valve. The content of elements was determined using a detector on thermal conductivity (katharometer).

Quantitative analysis of functional samples on the surface of carbon sorbent samples was

carried out by infrared spectroscopy (IRS) on a Nicolet 5700 FTIR spectrometer (Intertech Corp., the USA) at the Omsk Center for Collective Use, SB RAS. Research technique consisted in the preparing a sample as a very thin layer homogeneous layer sprayed by the sedimentation method of small particles in a glass cylinder with a height of 25 cm onto BaF_2 plate. Studies were carried out in a spectral range of 750–7000 cm^{-1} with a resolution of 4 cm^{-1} and 32 scans. Small portions of carbon material were injected through an opening in the upper part of the cylinder and after sedimentation of large particles (during 2–3 min), BaF_2 plate was placed into the cylinder. Sedimentation of small particles proceeds about 1 h. The procedure was repeated 5–7 times to obtain the necessary layer thickness. Registering IR spectra was carried out afterwards. The spectra were processed in ORIGIN software (baseline correction and smoothing).

To carry out X-Ray photoelectron spectroscopy (XPS) an ES-300 Kratos Analytical device was used. Before conducting measurements, the bond energy scale (E_b) was preliminarily calibrated according to the position of peaks Au4$f_{7/2}$ (E_b = 84.0 eV) and Cu2$p_{3/2}$ (932.7 eV) [27]. Spectra are given without corrections for recharge because of high sample conductivity. Before measurements, the samples were grinded in an agate mortar and secured on the holder using adhesive vacuum tape. Extraneous impurities on the sample were not detected according to survey spectra [28].

The total nitrogen content in the carbon enterosorbent structure was determined by the Kjeldahl method [29].

The Boehm titration method studied the composition and content of oxygen-containing groups [30, 31].

RESULTS AND DISCUSSION

Synthesis of composite veterinary preparation Betuline in Carbon Microsphere

When elaborating modification methods of the carbon sorbent with betuline, one of the major tasks consisted in developing technological techniques that ensure betuline transfer in a water-soluble state when varying its dispersion.

Ethanol and a mixture of ethanol and glycerine (92 vol. %/ 8 vol. %, respectively) were used as solvents. Deposition of betuline dissolved in glycerine on the hydrophobic carrier surface contributed to its completed desorption into the biological medium of the animal organism. The selection of the solvent and physicochemical parameters on the impregnation process by nanodispersed betuline of the carbon sorbent have been described earlier [32].

Stages of the preparation process of the carbon sorbent impregnated with betuline:

1. The preparation of a 1 % ethanol-glycerine solution of betuline: the mass ratio of betuline/glycerine/ethanol components = 0.07 : 0.14 : 1.

2. The impregnation stage of the mesoporous carbon sorbent with an alcoholic solution of betuline and glycerine: performed at a mass ratio of solution components of betuline/carbon carrier = 0.4 : 1.

3. The isolation stage of ethanol from the reaction mixture: carried out in an impregnator reactor at the end of the sorbent impregnation process.

4. Drying the preparation: performed at a temperature of 150 °C.

5. Packaging of preparation Betulin in Carbon Microsphere (BCM) pilot batches: the dried preparation is cooled to room temperature and packaged.

Synthesis of enterosorbent modified with polyarginine

Modification of the carbon sorbent with arginine was carried out in several stages.

Stage 1. Impregnation of the carbon sorbent sample for 1 h with an 15 % aqueous arginine solution (pH 10.76) at a ratio of sorbent/modifier solution of 1 : 5 and a temperature of (20±2) ° with continuous stirring.

Stage 2. Thermal treatment of the impregnated sorbent at a temperature of (105±2) °C until the constant mass.

Stage 3. High temperature polycondensation of the sorbent sample in a silica boat in a flow of an inert gas. The sample was aged in a flow-through furnace for 15 min at a temperature of (160±2) °C under an argon atmosphere (for firmer attachment of the modifier to the carbon material).

Stages 4, 5. Repeated impregnation and drying the sorbent under conditions similar to stages 1–3.

Monomers that did not enter into the polycondensation reaction were removed by washing in distilled water during 1 h with continuous stirring the suspension.

Physicochemical characteristics of modified enterosorbents

Studying morphology, relief, and textural characteristics of carbon sorbents. Surface morphology and relief of the tested carbon sorbents was studied using the SEM method (Fig. 1).

It was found that betuline and glycerine used as modifiers were distributed under selected conditions locally with filling holes, channels, and pores. Betuline was deposited on the sorbent in the form of fine particles.

Impregnation with a solution of arginine followed by modifier polycondensation on the carbon sorbent surface at selected modification parameters led to the local (insular) distribution of a polymer film in the form of outgrowths or layers on the sorbent surface. At modification of carbon material, filling the porous space with a modifier occurs, herewith, specific surface and total pore volume are accordingly reduced.

Textural characteristics of the samples under study are represented in Table 2.

X-Ray phase analysis confirmed that the modification process of the carbon enterosorbent with selected modifiers did not change the carbon sorbent structure.

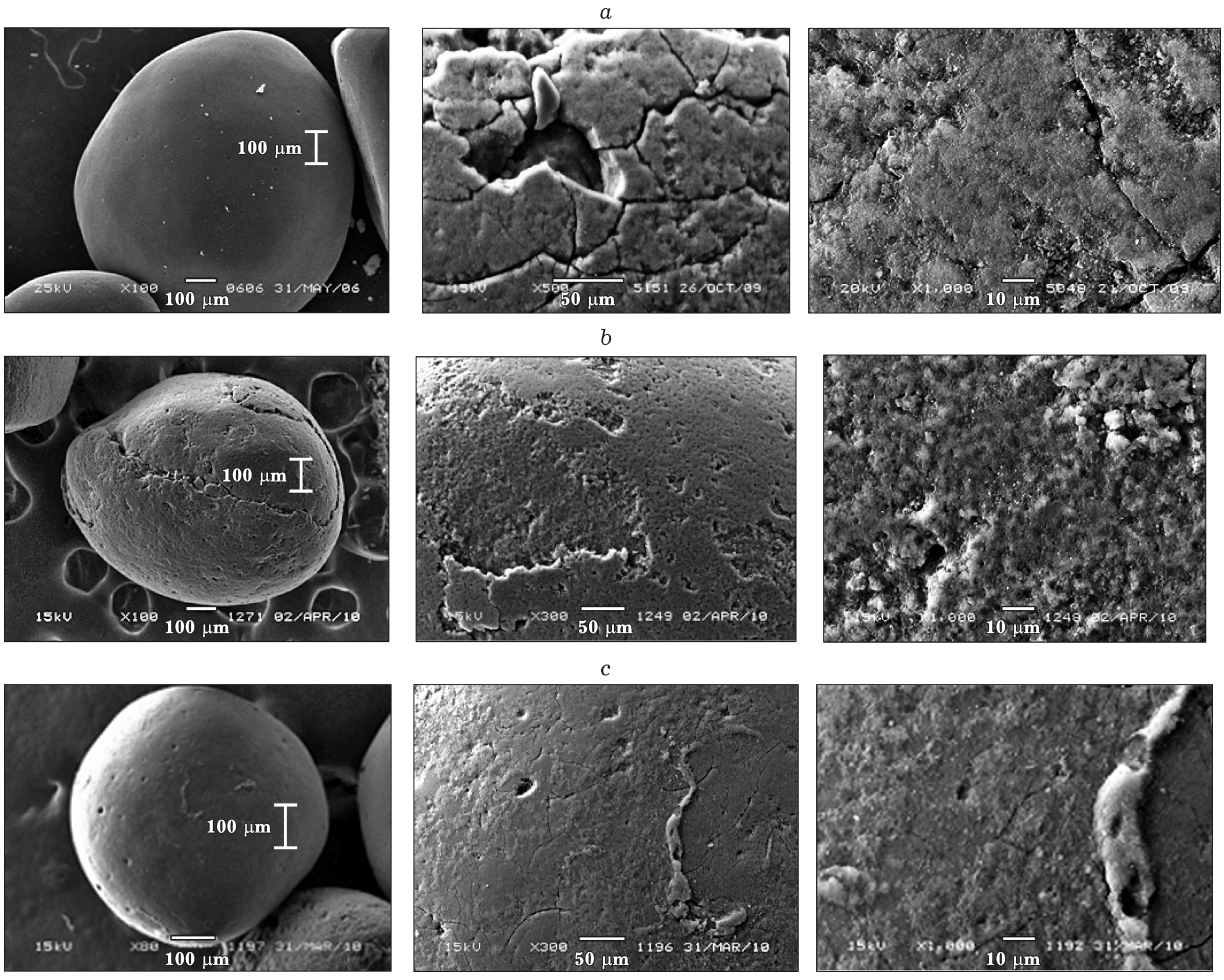

Fig. 1. Electron microscope images of the granules and surface of the tested samples of mesoporous carbon materials: *a* – initial (magn.: 100×, 500×, 1000×, respectively); *b* – impregnated with betuline (magn.: 100×, 300×, 1000×, respectively); *c* – modified with polyarginine (magn.: 80×, 300×, 1000×, respectively).

TABLE 2

Textural characteristics of the carbon sorbent samples under study

Carbon sorbents	S_{BET}, m^2/g	Total pore volume, cm^3/g	Pore volume, cm^3/g		
			Micropores	Mesopores	Macropores
Initial	306±12	0.398	0.016	0.351	0.031
Modified with betuline	228±6	0.363	–	0.335	0.028
Modified with polyarginine	212±4	0.249	–	0.229	0.020

Note. Dash indicates there are no micropores.

Consequently, all material properties driven by its nature (mesoporous structure, firmness, biocompatibility *etc*.) are preserved.

Volumetric elemental composition of samples. Analysis of the data obtained using a CHNOS elemental analyzer (in the material volume) demonstrated that modifier deposition affected the elemental composition of samples. When modifying the carbon sorbent with betuline the total carbon content is reduced from (98.46±0.26) to (97.50±0.09) %, but the contents of hydrogen (from (0.27±0.08) to (0.37±0.01) %) and oxygen (from (0.96±0.07) to (1.25±0.06) %) are increased.

Polycondensation of arginine on the carbon sorbent surface leads to a decrease in the total carbon content from (98.46±0.26) to (90.89±0.29) %, an increase in hydrogen content (from (0.27±0.08) to (0.95±0.08) %), oxygen (from (0.96±0.07) to (4.78±0.04) %) and appearance of nitrogen in the sample composition – up to (93.18±0.090) %.

Qualitative composition of surface functional groups. Spectra of modifiers of the initial sorbent and modified samples were obtained using IR spectroscopy.

An adsorption band in the region of 1735 cm^{-1} corresponding to vibrations of carbonyl, carboxyl groups disappeared at impregnation of the carbon sorbent with betuline. A significant increase of adsorption bands in the

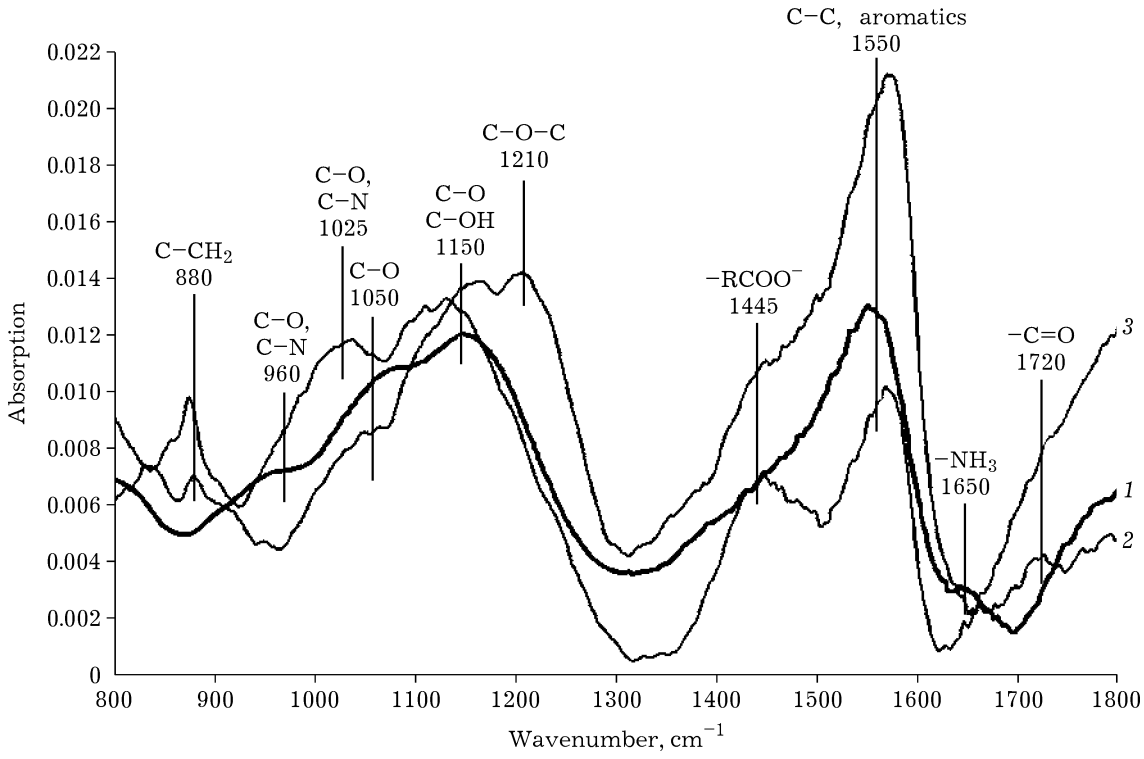

Fig. 2. IR spectra of the initial sorbent (*1*) modified with betuline (*2*) and polyarginine (*3*).

region of 1000–1200 cm^{-1} corresponding to valence fluctuations of the C–O bond in alcohols and phenols (Fig. 2).

The observable redistribution of functional groups on the sorbent surface can be explained by introducing into its porous structure a modifier that has in its structure a double CH_2=C bond and appropriate functional groups (CH_3, CH_2, CH). Analysis of IR spectra of arginine demonstrated that the amino acid is found in the ionized state, *i. e.* in the form of bipolar ions (zwitter ions). Adsorption bands of a unionized C=O group are observed. At modification of carbon material with polyarginine, an increase in intensity of adsorption bands at 1157 and 1205 cm^{-1}, as well as the appearance of adsorption bands at 1065 and 965 cm^{-1} corresponding to vibrations of C–O and C–N bonds are observed, which may point out at modification by the corresponding amino acid (see Fig. 2). One should note the appearance of an adsorption band at 1651 cm^{-1} in samples containing arginine as a modifier. This adsorption band may correspond primarily to both asymmetric deformational vibrations of NH_3^+, and the C=O group conjugated with the ring, Thus, IR spectroscopy results demonstrate that modification of the carbon sorbent with biologically active substances leads to a change in the qualitative composition of functional groups.

Survey X-Ray photoelectron spectra (XPS) of samples of the initial carbon sorbent, arginine modifier and samples modified with arginine are presented in Fig. 3, *a*.

The appearance of a spectral line N1*s* in a region of 400.3 eV is due to functionalization of the carbon sorbent surface by arginine. Figure 3, *b* demonstrates narrow spectral regions C1*s*, O1*s* and N1*s* recorded with a high precision for different carbon sorbent samples. Spectral analysis in the region of C1*s* demonstrated that line intensity significantly decreased during the modification process and a gradual shift of the peak from 282.8 to 284.5 eV occurs, which is associated with shielding the carbon sorbent surface by the modifier. It can be seen from spectra that intensities of appropriate lines in modified samples increase, especially for sample *3* (see Fig. 3, *b*). A peak in the region of 530.7–531.9 eV can be related to carbon atoms bound with the OH group in alco-

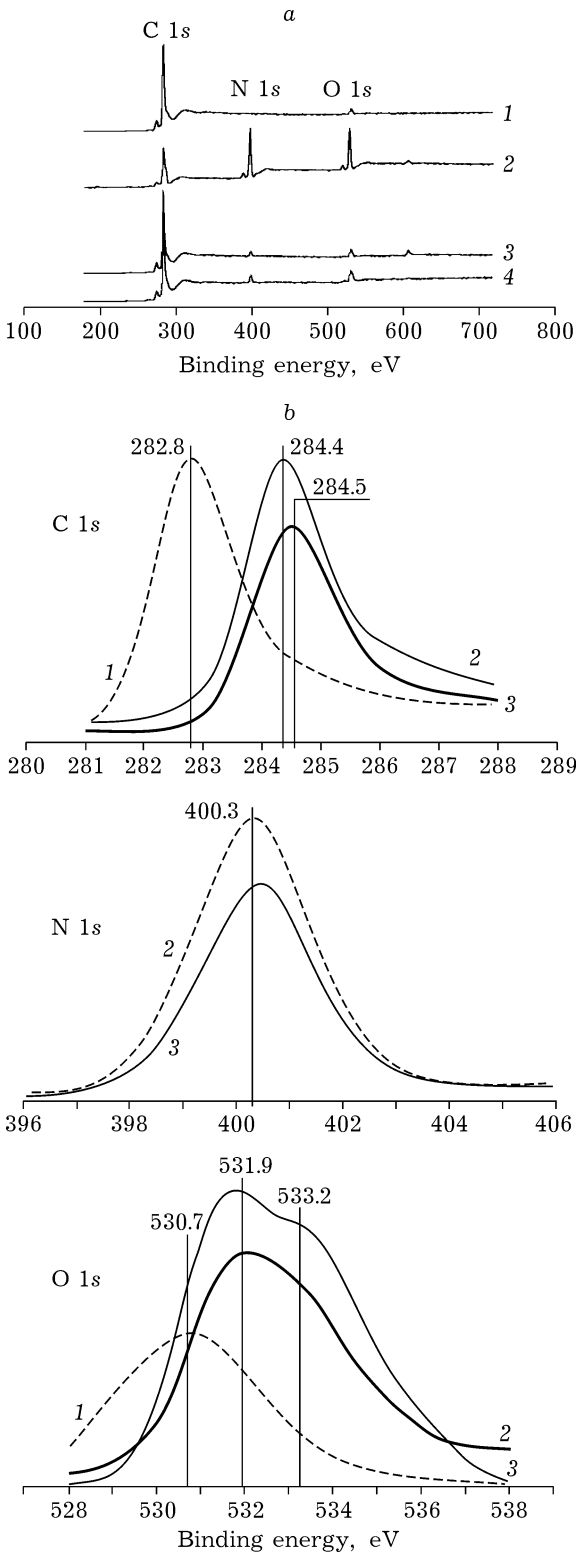

Fig. 3. Survey XPS spectra (*a*) and C1*s*, O1*s* and N1*s* narrow spectral regions (*b*) of the investigated samples of carbon sorbent: *a* – initial (*1*), arginine (*2*), modified with arginine after the first (*3*) and second (*4*) impregnation and polycondensation; *b* – initial (*1*), modified with arginine, after the first (*2*) and second (*3*) impregnation and polycondensation.

TABLE 3

Content of oxygen-containing groups in the samples studies

Carbon sorbents	Nitrogen content, %	Content of groups, meq/g			
		Oxygen			Basic
		Total	Carboxyl	Phenol	
Initial	–	0.087±0.003	0.051±0.004	0.036±0.002	–
Modified with betuline	–	0.098±0.005	0.037±0.005	0.061±0.003	–
Modified with polyarginine	3.12±0.62	0.329±0.002	0.282±0.006	0.047±0.004	0.272±0.008

Note. Dash indicates not identified by this method.

holic groups of Ph–OH groups. An intense line in the region of 533.2 eV characterizes the energy of the O=C–OH bond.

XPS spectral analysis in the region of N1*s* demonstrated that modification of the initial sorbent led the appearance of a peak in the region of 400.3 eV, which corresponds to the peptide C–NO bond. The line intensity increases for the sample *3* (see Fig. 3, *b*), which is due to the completeness of the technological process.

Thus, the effect of the sorbent modification process with polyarginine on the structure and the composition of surface functional groups is confirmed by the XPS method based on the character and intensity of spectral lines in the regions of C1*s*, O1*s* and N1*s*.

Titrimetric determination of total nitrogen. Determination of total nitrogen conducted by the Kjeldahl method allowed finding that nitrogen appears in the structure of the modified sample, nitrogen content is (3.12±0.62) %. This indicates that as a result of chemical modification with the selected amino acid, changes in the composition and content of functional groups on the carbon sorbent surface occur.

Titrimetric determination of oxygen-containing groups. It was found that the total number of oxygen-containing groups on the surface of the sample modified with polyarginine increased in 4 times, carboxyl groups – in 5.6 times, phenol groups – in 1.3 times (Table 3).

The total number of oxygen-containing groups in the sample modified with betuline is somewhat higher in comparison with the initial sample, the amount of phenol groups increases in 1.7 times. Analysis results confirm application of modifiers onto the sorbent surface.

CONCLUSIONS

Modification methods of carbon enterosorbent Zoocarb were elaborated, modification of the carbon surface was carried out by the method of polycondensation of arginine and impregnation into the porous matrix of carbon carrier nanodispersed betuline in the water-soluble form.

Physicochemical characteristics of the developed modified sorbents were studied. The study of textural characteristics of modified carbon sorbents demonstrated that filling the porous space of the material with a modifier occurred. Herewith, the specific surface and total pore volume change. The mesoporous nature of the surface is preserved. The study results confirm the appearance of the local coating of the sorbent surface: betuline is applied on the sorbent in the form of fine particles, polyarginine – as polymer films with various shapes.

Analysis of the qualitative and quantitative composition of functional groups on the carbon sorbent allowed finding that modification processes of sorbents with betuline and polyarginine led to an increase in oxygen-containing groups: phenol – in 1.3–1.7 times, carboxyl groups – in 5.6 times. The revealed regularity complies with the literature data on the study of the effect of oxygen-containing modifiers (oxygen, hydrogen peroxide, *etc.*) on acid-base properties of carbon materials.

The results obtained allow suggesting that local application of modifiers on carbon sorbent samples and an elevated content of surface oxygen- and nitrogen-containing groups will have a positive impact on adsorption properties of the synthesized materials in relation to low and medium molecular mass substances.

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