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MACROMOLECULAR COMPOUNDS AND POLYMERIC MATERIALS

Modification of Cellulose Acetates for Preparing Chiral Sorbents

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Abstract—Modification of cellulose acetates via sorption–desorption of vapors of mesogenic solvents in which the polymer forms a lyotropic liquid crystal phase and of mixtures of these solvents with water leads to the formation of a new chiral structure of the polymeric sample. This is manifested in a significant change in the value and even sign of the specific optical rotation of the polysaccharide system. The sorbents based on cellulose acetates that have been modified by such treatment exhibit specific affinity for definite optical antipodes. When a racemic mixture of L- and D-isomers of amino acids is passed through this sorbent, it acts as a chiral filter owing to "steric recognition" of one of the enantiomers, so that the filtrate contains an optically pure product (isomer). The revealed effects served as a basis for the development of a new procedure for preparation of optically pure stereoisomers of chiral products.

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The development of highly selective chiral sorbents and of simple procedures for separation of optical isomers of bioproducts and drugs is a topical problem for chemical, pharmaceutical, and biochemical industry and medicine [1]. The technology for the production of the majority of drugs is limited to preparation of the final product as a racemic mixture of chiral molecules. The therapeutic effect of such racemates is due, as a rule, to the action of only one of enantiomers. The other enantiomer is less active or inactive at all; furthermore, it can even exert negative pharmacological effects [2, 3].

Equimolar mixtures of levo- and dextrorotating enantiomers are separated into optical antipodes using, as a rule, chromatographic [4–7] and electrokinetic [8–10] methods. The latter methods are based on principles of capillary electrophoresis, which, in turn, is based on hydrophobic, dipole–dipole, and other interactions of stereoisomers with a chiral selector. Various cyclodextrins, acyclic oligosaccharides, anionic or cationic polysaccharide derivatives, etc., are used as such selectors.

Among chromatographic methods, high-performance liquid chromatography and affinity (or biospecific) liquid chromatography with optically active sorbents (chiral stationary phases, chiral "hosts") are the most widely used. The selectivity of the interaction of such sorbents with heterochiral substrates in the course of separation is determined by the principles of molecular recognition and steric correspondence [11]. Such sorbents are prepared by grafting of various chiral groups (fragments of optically active amines, amino acids, antibiotics, etc. [12, 13], or special "hooks" created by methods of genetic engineering [14–16]) or synthesized on the basis of crown compounds, porphyrins, or cyclodextrins as three-dimensional network structures with "chiral voids" allowing selective penetration of only one of the enantiomers [17–21]. Chiral-selective composite membranes based on cellulose [22], cellulose acetobutyrate [23], etc., are also used as stationary phases for separating optically active substances.

It should be noted that chiral selectors, sorption media, and stereoselective membranes in such approaches are

Table 1. Characteristics of cellulose acetate samples

Polymer	Producer	Amount of bound CH_3COOH γ, %	Viscosity-average molecular mass $M\eta \times 10^4$, kDa	Bulk density ρ, g cm^{-3}
CDA-1	OAO Khimvolokno, Vladimir	54.9	7.7	1.32
CDA-2	OAO Khimvolokno, Engels	55.1	8.2	1.32
CTA		62.2	7.0	1.28

prepared by multistep directional synthesis. Furthermore, despite high efficiency, both chromatography and electrophoresis are semipreparative methods requiring choice of additional methods and conditions (eluent, pH, ionic strength, etc.) for extraction the homochiral substance from the support. All these facts make the development of simpler methods for preparing stereospecific sorbents and of feasible methods for racemate separation a topical problem. In this connection, we believe that attention should be paid to the possibility of solving these problems via physicochemical modification of optically active cellulose acetates in the active vapor phase specifically interacting with the polymeric molecules.

Previous studies of the nature and formation conditions of a lyotropic liquid crystal (LC) phase of cellulose esters showed that these esters are capable to change their asymmetric structure and form stereoisomers differing in the optical activity [24–29]. For example, when cellulose acetate powders take up vapors of mesogenic solvents in which they form an LC phase or of their mixtures with water, the supramolecular and stereomeric structure of the polymer undergoes rearrangement. This is manifested in changes in the value and sign (in most cases) of the specific optical rotation of solutions of modified samples, reflecting changes in the conformation (steric arrangement) of the chiral macromolecules. The action of vapors of such solvents on the structure and optical activity of cellulose acetate is described by the dose–effect relationship. The most significant effect is exerted by small doses (no more than 10–12 wt %) of the absorbed sorbate vapor.

The discovered fact that the new sterically modified metastable structure of the cellulose ester sample is preserved upon dissolution of the polymer powder (with the sorbed vapor) in the process solvent and upon formation of the ready product opens the way to preparation of polymeric materials with new specific functional possibilities that are not exhibited by the initial polymer. For example, cellulose acetate filters and membranes capable of selective separation of optically active components of blood plasma were prepared by this procedure. These materials efficiently retain cholesterol or bilirubin, but do not retain proteins and electrolytes [30–32].

It was interesting to determine whether the steric organization of the macrochains is preserved in other procedures for further processing of the polymeric substances modified in vapors of mesogenic solvents, in particular, after desorption of the sorbate vapor taken up by the polymeric matrix directly in the powdered samples, without dissolving the polymer with the sorbed vapor in appropriate solvent (the latter procedure is used, as a rule, for the subsequent formation of the condensed polymeric material). This study was also aimed at evaluating the stereospecificity of the induced chiral structure of the obtained cellulose acetate samples for separating racemates of optically active compounds, with racemic mixtures of α-amino acids as example.

EXPERIMENTAL

We chose for our study commercial samples of cellulose acetates: diacetate (CDA) and triacetate (CTA), used for the production of acetate yarns for textiles. The sample characteristics are given in Table 1.

As sorbates we used nitromethane, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), acetic acid (AA), and their binary mixtures with distilled water (component ratio from 1 : 99 to 20 : 80). The choice of these liquids was governed by the fact that they belong to the class of mesogenic solvents in which cellulose and its derivatives form a lyotropic LC phase. In addition, as shown in

[24–32], vapors of these sorbates influence not only the supramolecular structure of cellulose acetates, but also their stereomeric structure (at its fixation with the sorbed vapors in the condensed material).

The CDA and CTA modification was performed as follows. A polymer powder sample was kept in the sorbate vapor at 20°C in a hermetically closed desiccator filled to 1/25 with the liquid medium. The sample was arranged in sieves with the pore diameter of 0.25 mm at a distance of approximately 5 cm from the liquid surface, and the sorption was performed. The desorption of the absorbed vapor was performed in air at 20 ± 2°C. The amounts of the sorbed, c_s (wt %), and desorbed, c_s^{-1} (wt %), vapor were determined by the formulas

$$c_s = \frac{m_1 - m_0}{m_0} \times 100, \quad (1)$$

$$c_s^{-1} = \frac{m_1 - m_2}{m_1} \times 100, \quad (2)$$

where m_0 is the initial sample weight (g), and m_1 and m_2 are the sample weights after the sorption and desorption, respectively (g).

Because of strong influence of small amounts of the absorbed vapors on the structure of CDA and CTA samples, the amount of the vapor sorbed by the polymer did not exceed 10–12 wt %.

The IR spectra of the CDA and CTA powders were recorded with an FSM 1201 Fourier IR spectrometer from thin layers of mulls in mineral oil between KBr windows. The ^{13}C NMR spectra of CDA and CTA solutions in DMSO-d_6 were taken with a Varian-400 NMR spectrometer (USA).

The optical activity of the control and modified samples of CDA and CTA was measured with an SM-2 circular polarimeter at the wavelength $\lambda_{Na} = 589$ nm, $T = 20$°C. We used solutions of concentration $c = 0.5$ g dL^{-1} in common process solvents: acetone–water mixture (95 : 5) for CDA and methylene chloride–ethanol mixture (90 : 10) for CTA. All the solvents were of analytically pure grade. The specific optical rotation α (deg mL dm^{-1} g^{-1}) of the solutions was determined by the formula

$$[\alpha] = \frac{(\alpha - \alpha_0) \times 100}{lc}, \quad (3)$$

where α and α_0 are the measured rotation angles for the solution and solvent, respectively (deg), l is the optical path length (dm), and c is the solution concentration (g dL^{-1}).

To evaluate structural changes that occurred in the polymeric matrix upon sorption and sorption–desorption of the sorbate, we performed comparative analysis of cellulose acetate solutions prepared by different procedures. In the first procedure, the modified samples after the dissolution were left in air for the desorption of the absorbed vapor; in the second procedure, as in [30–32], the samples with the sorbed vapors were immediately placed into the solvent.

The selectivity of the separation of racemic mixtures of optically active substances was evaluated by chromatography on a special separation cell at $T = 20 \pm 2$°C. The cell was a glass tube 17 cm long, 1 cm in diameter, with two compartments isolated from each other. The first (upper) compartment was a hollow tube 13.5 cm high, and the second (lower) compartment was a glass filter with a pore diameter of approximately 0.1 cm and a height of 3.0 cm. The sample of the powdered polymer was placed into the upper hollow tube of the column to a bed height of 3 cm and compacted, after which 20 mL of a solution of an optically active substance was passed. We used aqueous solutions (c = 0.1–0.2 g dL^{-1}) of racemic mixtures of L- and D-amino acids (1 : 1): tryptophan, serine, aspartic acid, and valine (chemically pure grade). Data on the specific optical rotation of the individual enantiomers of amino acids, $[\alpha]_e$, and of their racemic mixtures, $[\alpha]_r$, are given in Table 2.

The efficiency of separating the enantiomers was monitored by variation of the specific optical rotation of the amino acid solution before ($[\alpha]_r$) and after ($[\alpha_i]$) passing through the sorbent, taking into account $[\alpha]_e$. The separation selectivity S (%) was determined by the formula

$$S = \frac{[\alpha]_i}{[\alpha]_0} \times 100, \quad (4)$$

where $[\alpha]_i$ is the specific optical rotation of the permeate and $[\alpha]_0$ is that of either L- or D-enantiomer.

As shown in [24–26], the sorption by CDA and CTA (powder, film, fiber) from the vapor phase formed by nitromethane, DMSO, DMF, AA, and their mixtures with water (H_2O content no more than 20–25%) is not described by Fick's law and is characterized by

anomalous swelling curves. Under the same conditions, acetate yarns and films undergo spontaneous elongation and the inverse effect of spontaneous "shrinkage" of the specimens that underwent elongation on exposure to the vapor. Relaxation of internal stresses in the polymer system occurs; it is accompanied by a decrease in the misorientation angle and by an increase in the mechanical characteristics of the materials. Stable optical anisotropy in film specimens is realized [27–29]. Sorption of vapors of active mesogenic solvents also affects the optical activity of the polysaccharides under consideration, varying it within wide limits [26–32]. This fact suggests changes in the overall chiral structure of the polymer system and enhancement of its optical heterogeneity. It should be emphasized once again that all these effects are observed with cellulose acetates that have taken up vapor of a specific sorbate.

As we found, the samples modified by sorption–desorption of vapor of specific active media undergo not only changes in the absolute values of the specific optical rotation, but also the inversion of the sign of [α].

Figure 1 shows as example the dependence of the specific optical rotation [α] of solutions of CDA-1 and CTA modified by the first and second procedures on the amount of vapors of nitromethane and DMSO–water mixture (10 : 90), taken up by the polymer. For the samples modified by the first procedure, i.e., by sorption and subsequent desorption of the sorbate vapor, the quantity c_s (as in the second procedure) corresponds to the degree of vapor sorption by the polymer. The dependence

Table 2. Characteristics of aqueous solutions of amino acids

Amino acid	Specific optical rotation (λ = 589 nm), deg mL dm^{-1} g^{-1}		
	$[\alpha]_e$		$[\alpha]_r$ L : D (1 : 1)[a,b]
	L-Enantiomer[a]	D-Enantiomer[a]	
Tryptophan	–32.1	+32.9	0
Valine	–6.06	+6.42	0
Serine	–14.32	+14.45	0
Aspartic acid	–25.5	+25.5	0

[a] Reference data.
[b] Experimental data.

$[\alpha] = f(c_s)$, obtained in [29] for the system of CDA-2 with nitromethane vapor, is also shown for comparison.

The experimental data shown in Fig. 1 indicate that the control samples of CDA powders in the acetone–water solvent (95 : 5) have positive specific optical rotation, $[\alpha] = +25 \pm 1$ deg mL dm^{-1} g^{-1} for CDA-1 and $[\alpha] = +30 \pm 2$ deg mL dm^{-1} g^{-1} for CDA-2. For CDA-1 modified by the first and second procedures and for CDA-2 modified by the second procedure, the optical activity sharply changes already after the absorption of the first, relatively small (up to ~2.0 wt %) amounts of the sorbate vapor, with the change in the sign of [α] (Fig. 1a, curves *1–3*). As the amount of the vapor taken up by the polymer is increased to 4–5 (CDA-1) and 7–8 wt % (CDA-2), [α] remains negative and further increases in the absolute value. The

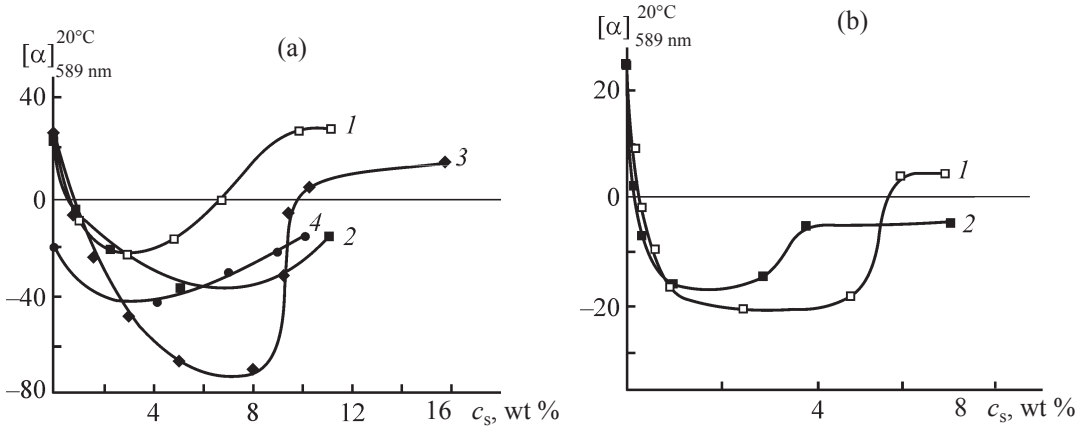

Fig. 1. Specific optical rotation $\alpha_{589\,nm}^{20°C}$ of solutions (c = 0.5 g dL^{-1}) of the initial CDA powders (points on the ordinate), CDA powders modified in 95 : 5 acetone–water mixture, and CTA powders modified in 90 : 10 methylene chloride–ethanol mixture as a function of the amount c_s of vapor of (a) nitromethane and (b) 10 : 90 DMSO–H_2O mixture. (*1, 2*) CDA-1 modified by the first and second procedures, respectively; (*3*) CDA-2 modified by the second procedure [29]; and (*4*) CTA modified by the first procedure.

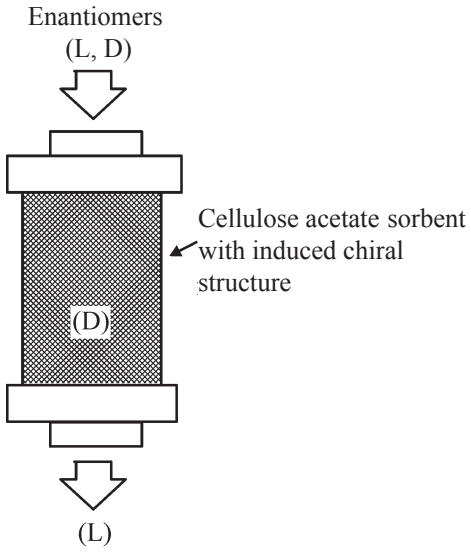

Fig. 2. Scheme of chiral filtration of racemic mixtures of α-amino acids on cellulose acetate sorbents with induced chiral structure.

uptake of still larger amounts of nitromethane by CDA-1 and CDA-2 (more than 5 and 8 wt %, respectively) results in that [α] becomes positive again. This trend is clearly manifested for CDA-1 modified by the first procedure (curve *1*) and for CDA-2 modified by the second procedure (curve *3*). Probably, similar shape of the $[\alpha] = f(c_s)$ dependence will also be observed for CDA-1 modified by the second procedure at $c_s > 13$–14 wt % (curve *2*). The same is true for other systems based on CDA-1 with the vapor phase formed by the mixtures DMSO : H_2O = 1 : 99–10 : 90 (Fig. 1b), DMF : water = 10 : 90–20 : 80, and AA : water = 5 : 95 as sorbate.

The initial samples of CTA powder in methylene chloride with ethanol (90 : 10) are characterized by negative specific optical rotation, [α] = –20 ± 2 deg mL dm^{-1} g^{-1}. The nitromethane sorption–desorption cycle is not accompanied by the inversion of the sign of [α] of CTA solutions. However, both CDA and CTA modified by the first procedure undergo changes in the value of the specific optical rotation (Fig. 1a, curve *4*). It is appropriate to note that similar dependence $[\alpha] = f(c_s)$ was also obtained for the CTA powder modified by the second procedure in vapors of nitromethane, AA, trifluoroacetic acid, and formic acid [29]. The latter two acids, like the liquids used in this study, are also mesogenic solvents for cellulose acetates.

Our results show that the dependences $[\alpha] = f(c_s)$ both for the CDA and CTA samples that sorbed the sorbate vapor and for those subjected to the sorption–desorption cycle are similar: The specific optical rotation varies in a wide range, and for CDA powder [α] also changes sign. The polymer modified by both the first (desorption of the sorbed vapor before dissolution) and second (dissolution of the sample with the sorbed vapor in the process solvent) procedures is characterized by the altered chiral structure.

There are good grounds to state that the steric structure of the polymer, modified as a result of sorption of vapors of specific media, is preserved after desorption of the sorbate vapor. The Fourier IR data for powders of CDA and CTA modified by the first procedure and the ^{13}C NMR data for solutions of these substances show that the substances do not contain mesogene molecules, i.e., that the sorbate molecules are virtually completely removed from the polymeric matrix. Thus, the desolvation of the swollen polymer powder, apparently, leads to fixation of the supramolecular structures and of the conformations that the macromolecules acquired upon interaction with the specific active medium.

Taking into account the fact that the altered steric organization of the modified polymeric sample strongly affects the properties of the materials obtained [30–32], we estimated the stereospecificity of the induced chiral structure of CDA and CTA modified by the first procedure. For this purpose, we performed chromatographic separation of racemic mixtures of L- and D-isomers of amino acids, chosen as example, with the modified cellulose derivatives. The results of chromatographic separation of aqueous solutions of racemic α-amino acids (tryptophan, valine, serine, aspartic acid) on the initial powdered cellulose acetate sorbents and on the samples with the induced chiral structure are given in Table 3.

Passing of aqueous solutions of amino acid racemates through a column packed with the initial polymer does not result in separation of the enantiomers. However, when the modified CDA or CTA powder, characterized by the induced negative [α] of polymer solutions in standard solvents, is used as stationary phase, the D-isomer is retained in the column, whereas the L-isomer passes through the sorbent (Table 3). On the contrary, when a solution of the racemic mixture is passed from the CDA sorbent with positive [α], the D-isomer passes through the column.

It engages attention that the most efficient influence on the steric structure of the polymer is exerted by small amounts of the absorbed vapor ($c_s < 5$–7 wt %) of the active medium. For example, the CDA sorbent after the uptake of 3 wt % vapor of the 1 : 99 DMSO : water

Table 3. Results of chromatographic separation of racemic mixtures of amino acid L-, D-enantiomers on cellulose acetate sorbents with induced chiral structure

Sorbent characteristics				"Adsorbate" characteristics		*S*, %
polymer	active medium	c_s, wt %	$[\alpha]_{589\ nm}$, deg mL dm^{-1} g^{-1}	amino acid	$[\alpha]_{i\ 589\ nm}$, deg mL dm^{-1} g^{-1}	
CDA-1	–	–	+25	Tryptophan	0	0
	–	–	+25	Serine	0	0
	–	–	+25	Aspartic acid	0	0
	AA : water (5 : 95)	3.0	0	Tryptophan	0	0
	"	5.0	–14	"	–32.5	100
	DMF : water:					
	10 : 90	3.0	–13	"	–30.1	94
	10 : 90	5.0	–8	"	–32.1	100
	20 : 80	5.0	–15	"	–23.9	75
	DMSO : water:					
	1 : 99	3.0	–10	"	–32.7	100
	5 : 95	5.0	–2	"	–32.5	100
	10 : 90	3.0	–15	Serine	–32.3	100
	10 : 90	4.0	–5	Tryptophan	–22.9	71
	Nitromethane	1.5	–19.5	Aspartic acid	–5.4	21
	"	1.5	–19.5	Tryptophan	–30.7	96
	"	3.5	–22	"	–32.8	100
	"	7.0	0	"	0	0
	"	11.0	+25	"	+16.6	51
CTA	–	–	–20	"	0	0
	–	–	–20	Valine	0	0
	Nitromethane	0.6	–21	Tryptophan	–25.1	78
	"	4.5	–44	Valine	–2.7	45
	"	4.5	–44	Tryptophan	–26.6	82
	"	7.0	–29	"	–32.3	100
	"	9.0	–21	"	–33.0	100

mixture, followed by its removal, separates racemic tryptophan with 100% yield of the L-isomer, and after the uptake and subsequent desorption of the same amount of the vapor of the 10 : 90 DMSO : water it separates racemic serine with 100% yield of the L-isomer (Table 3). The data obtained allow modified CDA and CTA powders to be considered as promising sorbents for separation of racemates of α-amino acids and, probably, of other optically active substances and of their heterochiral mixtures.

Thus, the cellulose acetate sample modified by appropriate treatment and characterized by the altered chiral structure exhibits specific affinity (possibly, steric complementarity) for definite optical antipodes. When passing a racemic mixture of L-, D-isomers, the sorbent actually acts as a chiral filter, which leads to "steric recognition" of one of the enantiomers and to the passing to the L- or, more seldom, D-isomer to the filtrate in the optically pure form (Fig. 2). This phenomenon can be of great practical importance, because it is well known that many organic compounds (including drugs) exhibit the maximal biological and pharmacological activity specifically in the form of their L-isomers.

The revealed effects served as the basis for developing a new procedure for preparing optically pure stereoisomers of chiral products. The procedure has been patented in the Russian Federation [33].

CONCLUSIONS

(1) Modification of cellulose acetate powder of different degrees of acetylation by sorption–desorption of vapors of individual mesogenic solvents and of their

mixtures with water involves transformations altering the overall chiral structure of the polysaccharide system. The stereomeric organization of the polymeric matrix, induced by the vapors, is preserved after the desorption of the absorbed sorbate, which is manifested in changes in the value and sign of the specific optical rotation of the solutions of the modified samples. The most significant influence on the optical activity of the polysaccharide is exerted by relatively small doses of the vapor used as sorbate.

(2) The modification process is described by the dose–effect relationship and can be completed in any step of the formation of the chiral structure of the polymer sample. The conversion can be monitored by measuring the specific optical activity of the samples.

(3) Sorbents with the altered chiral structure, optimized for preparing optically pure isomers of α-amino acids from the corresponding racemates, were prepared from cellulose diacetate and triacetate powders modified by appropriate treatment. The sorbents show high performance in "chiral recognition" of definite optical antipodes (D- or L-isomers) in the course of chromatographic separation on the powdered cellulose acetate material.

(4) The above-presented examples show that the sorbents prepared by this procedure ensure selective separation of racemates of optically active substances and predictable degree of their sorption, which can be promising and economically feasible for preparing optically pure stereoisomers of a wide range of chiral products.

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