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Chromatographic Resolution of Several Racemates by Means of Optically Active Acidic Polymers Derived from α-Amino Acids

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The chromatographic resolution of several racemic amines was investigated by using three types of copolymers composed by *N*-acroylated α-amino acid and *N,N'*-dimethacroylhexamethylenediamine. The anilides of DL-phenylalanine and DL-valine, and of DL-phenylglycine and DL-1,2-diphenylethylamine, were partially resolved. The combination of substrate and sorbent giving the most efficient resolution was anilide of phenylglycine and the copolymer involving L-phenylalanine.

There have been a number of reports[1-11] concerning the use of synthetic optically active polymers as adsorbents for the chromatographic resolution of racemate.

Most such polymers have been synthesized by either one of the following two methods. The first is the method in which an optically active group is introduced into an optically inactive "reactive polymer"[7] (*e.g.*, chloromethylated polystyrene[4,5,7-9] and polymethacryl chloride[3]). The second method[1,2,6,11] includes the homogeneous copolymerization of an optically active monomer with some suitable crosslinking agent.

In a previous paper,[1] the syntheses of three types of optically active polymers by the second method and some of the results on the chromatographic resolution of racemate were reported.

This article will describe some more successful examples of resolution with DL-1,2-diphenylethylamine and with the anilides of DL-phenylalanine, DL-phenylglycine, and of DL-valine as substrates. In practice, these substrates were transformed into the corresponding acetates before the runs for resolution. The polymer sorbents used were the same as have been reported earlier[1,12] [crosslinking agent (CA): *N,N'*-dimethacroylhexamethylenediamine; copolymers A (acroyl phenylalanine-CA), B (acroyl valine-CA), and C (acroyl tryptophan-CA)].

Results and Discussion

Of course, the fraction with the highest specific rotation came out at the earliest stage of the elution

TABLE 1. OPTICAL RESOLUTION OF RACEMATES BY MEANS OF SYNTHESIZED POLYMERS

Acetates of racemic amines		Copolymer A	Copolymer B	Copolymer C
1,2-Diphenylethylamine	$[\alpha]_D$(°)	−11	0	−5
	C	0.1N	0.1N	0.1N
	O.P.(%)	16	0	7
Phenylalanine anilide	$[\alpha]_D$(°)	−49	0	−5
	C	0.1N	0.1N	0.1N
	O.P.(%)	52	0	5
Phenylglycine anilide	$[\alpha]_D$(°)	−85	−1	—
	C	0.01N	0.01N	—
	O.P.(%)	63	0.7	—
Valine anilide	$[\alpha]_D$(°C)	−15	0	—
	C	0.001N	0.1N	—
	O.P.(%)	21	0	—

C, acid concentration of eluent. O.P., Optical purity.

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TABLE 2. RESULT OF RESOLUTION OF ACETATE OF DL-PHENYLALANINE ANILIDE (200 mg) WITH COPOLYMER A

Fraction No.	Weight (mg)	c	α_D	$[\alpha]_D(°)$	α_{Hg}	$[\alpha]_{Hg}(°)$
1— 20	3	0.10	−0.049	−49	−0.063	−63
21— 40	10	0.33	−0.068	−20	−0.092	−27
41— 60	10.4	0.34	−0.039	−11	−0.060	−18
61— 90	15	0.50	−0.029	− 6	−0.036	− 7
91—200	50	1.66	0.000	0	0.000	0
201—300	26	0.86	+0.023	+ 2	+0.027	+ 3
301—400	20	0.66	+0.026	+ 4	+0.031	+ 4
401—500	15	0.50	+0.035	+ 7	+0.038	+ 8
501—600	11	0.33	+0.034	+10	+0.039	+11
601—700	8	0.26	+0.031	+11	+0.026	+10
701—800	3	0.10	+0.018	+18	+0.026	+26
last fractions	12	0.40	+0.101	+25	+0.127	+32

The wavelength of Hg-line is 546 mμ.

of the resolved substrate. However, 20—60 fractions had to be combined to obtain a sufficient amount of eluted substrate for the observation of specific rotation. Table 1 illustrates the observed values of specific rotation for the earliest combined fractions, along with those of the optical purity and the acid concentration of the eluent solvent.

In the case of copolymer A, the anilides of DL-phenylalanine and DL- phenylglycine were satisfactorily separated into their antipodes, whereas the resolutions of DL-1,2-diphenylethylamine and DL-valine anilide were rather poor. Only DL-phenylglycine anilide was resolved by copolymer B under similar conditions. Copolymer C, which is of interest because of its structure, with three adsorption centers per monomer unit, resolved DL-1,2-diphenylethylamine and DL-phenylalanine anilide with efficiencies next to those of copolymer A. The resolution ability was not examined extensively for this sorbent, since it was instable under acidic conditions. The results of the resolution of DL-phenylalanine anilide with copolymer A are given in detail in Table 2.

In order to investigate the dependence of the degree of optical resolution on the acid concentration of the eluent solvent, several resolutions of DL-valine anilide on copolymer A were carried out by changing the molarity of acetic acid from 0.1 N to 0.001 N (Table 3).

TBBLE 3. THE DEPENDENCE OF THE DEGREE OF OPTICAL RESOLUTION ON ACID CONCENTRATION OF THE ELUENT SOLVENT

Acid concentration	$[\alpha]_D(°)$	$[\alpha]_{Hg}(°)$	Optical purity (%)
0.1 N	0	0	0
0.01 N	−9	−13	13—15
0.001 N	−15	−17	20—22

The data may be interpreted as follows. In the case of a low acid concentration, the racemate would be more strongly adsorbed on the surface of the sorbent, and hence one antipode would be more susceptible to influences from the asymmetric field of the sorbent than the other. A higher acid concentration would cause a more insufficient resolution.

It may be useful to discuss the interrelation between the substrate-sorbent and the degree of optical resolution on the basis of the results shown in Table I.

1) Roberts and Haigh7) examined the partial resolution (22%) of DL-methionine on poly-[S-(ar-vinylbenzyl)-L-cysteine], a method which was employed on the basis of the assumption that the structual similarity between a substrate and the asymmetric site of a polymer must be a potent factor in efficient resolution.

Although a much higher resolution (52%) of DL-phenylalanine anilide on copolymer A seems to give an additional example of how their principle actually works in the adsorption process, the failure of the resolution (0%) of valine anilide on copolymer B suggests that some other factors also govern the resolution efficiency.

2*a*) Remarkable differences in optical purity are noticed between the resolved acetate of valine anilide and those of phenylalanine and phenylglycine anilides. These differences may be principally attributed to the difference in the bulkiness of the substituents on the asymmetric carbon atom of the molecule. The difference in the electronic characters of the substituents may also play a role.

2*b*) In comparing the data for the acetate of phenylglycine anilide with those for the acetate of 1,2-diphenylethylamine, it may be pointed out that the racemate involving the −CO·NH− group is much more efficiently resolved than is that having the $-CH_2-$ group in the corresponding moiety of the molecule. This is apparently due to the higher adsorption suitability of the former group.

2*c*) The resolution ability of copolymer A with an asymmetric carbon atom carrying a benzyl group, is also higher than that of copolymer B which carries an isopropyl group, and which gave, at the highest of four examples, only a 0.7% resolution.

These results (2a—2c) are in accord with the general rules on asymmetric adsorption proposed by Krebs[13] and Dalgliesh,[14] both of whom studied sorbent polymers with some polysaccharides.

Experimental

The Syntheses of Optically Active Acidic Polymers. The optically active polymers were synthesized according to the method reported earlier.[1]

The Syntheses of the Acetates of α-Amino Acid Anilides. *N*-phthaloyl-α-amino acid anilides obtained by the ordinary method[15–17] were treated with hydrazine hydrate to give α-amino acid anilides.[15] When acetic acid was added to the ether solution of these anilides, white precipitates were formed. The recrystallization of the filtrated precipitates from ethanol or ethyl acetate gave the pure acetates of anilides. The specific rotations of these salts were determined in 0.1N-*aqueous* acetic acid.

The physical and analytical data of the several new racemates thus obtained are:

Acetate of DL-phenylalanine anilide. Mp 110—113°C. $[\alpha]_D=+93°$, $[\alpha]_{Hg}=+155°$ (*c* 1) in L-form. Found: C, 68.35; H, 6.89; N, 9.37%. Calcd for $C_{17}H_{20}N_2O_3$: C, 68.00; H, 6.66; N, 9.33%.

Acetate of DL-phenylglycine anilide. Mp 100—105°C. $[\alpha]_D=+133°$, $[\alpha]_{Hg}=+166°$ (*c* 0.56) in L-form. Found: C, 67.13; H, 6.35; N, 9.68%. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78%.

Acetate of DL-valine anilide. Mp 139—141°C. $[\alpha]_D=+74°$, $[\alpha]_{Hg}=+90°$ (*c* 1) in L-form. Found: C, 61.87; H, 8.06; N, 11.09%. Calcd for $C_{13}H_{20}N_2O_3$: C, 61.90; H, 7.93; N, 11.19%.

Acetate of DL-1,2-diphenylethylamine. Mp 125—130°C. $[\alpha]_D=-68°$, $[\alpha]_{Hg}=-83°$ (*c* 0.5) in L-form. Found: C, 74.91; H, 7.56; N, 5.88%. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44%.

Column Chromatography. An Example with Copolymer A. Copolymer A (80 g) suspended in a sufficient volume of *aqueous* acetic acid was poured into a column (2.5 cm in diameter; 150 cm in length; *ca.* 100 cm, the final length of the packed polymer).

Racemate (200—500 mg) dissolved in a suitable volume (*ca.* 10 m*l*) of *aqueous* acetic acid (0.1, 0.01, or 0.001N) was adsorbed on the upper zone of the sorbent and then eluted with the same solvent at room temperature. The flow rate of the solvent was *ca.* 6 m*l*/hr under atmospheric pressure. 8 m*l* portions of the eluent were collected automatically, and the concentration of the sample in each fraction was estimated by UV absorption by using a Hitachi EPS-2-spectrometer. 20—60 consecutive fractions were combined when the observed concentration was too low to determine the optical rotation. The optical rotation of the evaporated residue was determined in 0.1N *aqueous* acetic acid by a Rex-automatic polarimeter.

The chromatographic resolution of racemates on copolymers B and C were also carried out by a procedure similar to that described above.

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