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DIRECT GAS CHROMATOGRAPHIC RESOLUTION OF ENANTIOMERS ON OPTICALLY ACTIVE MESOPHASES

V. MODEL CHIRAL 3-AMINOPROPYLMETHYLSILOXANE SYSTEMS

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SUMMARY

Previous reports in this series noted unusual variations in the chromatographic separation factor, $\alpha_{R,S}$ for the series $C_6H_5(CH_2)_nCH(CH_3)NH(CF_2)_mCF_3$ with n and m when these solutes are subjected to chromatography using smectogenic stationary phases formed by members of the class carbonylbis(amino acid ester). The generality of this behavior has been further examined through the use of model polysiloxane phases of a novel type. The retention and resolution of the series of interest and other enantiomeric solutes is discussed.

INTRODUCTION

The unusual behavior of the homologous series $C_6H_5(CH_2)_nCH(CH_3)NHCO-(CF_2)_mCF_3$ using chiral stationary phases of the class carbonylbis(amino acid ester) was the subject of a recent report in this series[1]. In that work, the magnitude of the chromatographic resolution factor $\alpha_{R,S}$ was shown to alternate with increasing n. In addition, the smectogenous state of carbonylbis(S-valine isopropyl ester) (CbSV)[2–4] gave a more pronounced variation than when its isotropic liquid state served as the stationary phase. The variation in $\alpha_{R,S}$ was shown to be principally related to a departure from the anticipated linearity of $\ln k'$ *vs.* n in the case of the solute having the same configuration as the stationary phase. In addition, the value of $\alpha_{R,S}$ ($n = 0$) was seen to increase with m as it varies from 0 to 2 when the temperature of the column corresponds to the smectic state but not in the isotropic temperature range[5]. Alternation of $\alpha_{R,S}$ with n appears to be an effect which is not unique to the liquid crystalline state of the phase while the behavior of $\alpha_{R,S}$ as m is varied may be. The effect on $\ln k'$ of carbon number n was found to be small when the solute series ($n = 0, 1, 2, 3$; $m = 2$) was subjected to chromatography on the achiral polysiloxanes OV-101 and OV-17. It remained to be seen whether the behavior of these solutes on chiral station-

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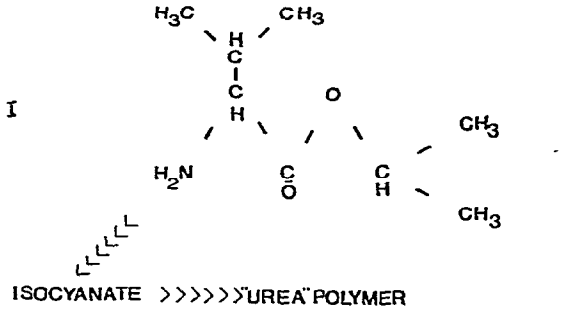
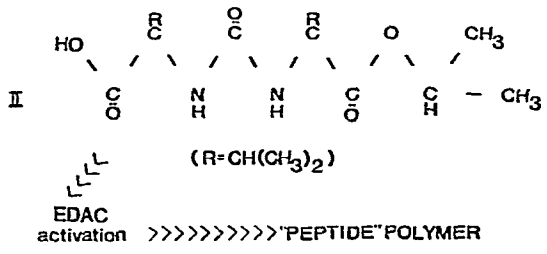
ary phases of the class of which CbSV is a member is unique to that class or a general property of chiral stationary phases capable of separating such solutes.

The work reported here represents an attempt to clarify this point and to this end, several new chiral stationary phases were synthesized which gave resolution of enantiomers. The models chosen for this work were chiral polysiloxanes formed when copolymers of dimethyl and methyl-γ-amino propyl silane were modified by reaction to include the amino bonded moeties I and II. This created a "urea"-type phase and a "peptide"-type phase of mol.wt. *ca.* 1500. In addition, the effect of "amine content" was examined by synthesizing polymers of 2–4% and 32% methylamino propyl siloxane content. Wall-coated open tubular (WCOT) columns were prepared using these novel phases and a series of solutes were studied in terms of retention and resolution.





EXPERIMENTAL

Stationary phases

A dimethylsilicone copolymer containing a nominal 2–4% of 3-aminopropylmethylsiloxane groups was obtained commercially (Petrarch System, Levittown, PA, U.S.A.; stock No. PS054). A second copolymer was synthesized[6] by base-catalyzed hydrolysis of a mixture containing 32% (w/w) of 3-aminopropylmethyldiethoxysilane in dimethyldiethoxysilane along with trimethylethoxysilane to provide capping groups[7]. The product was a viscous, clear liquid which was further conditioned at 70°C under reduced pressure (0.1 torr)/70°C for 3 h. Acetic acid–perchloric acid

titration[8] of the 32% copolymer gave 1.0 mequiv. of amine/g of polymer. The commercial 2–4% copolymer gave 0.25 mequiv. of amine/g.

S-Valine isocyanate isopropyl ester was obtained from (S)-valine as described previously[5]. (S)-Valine benzyl ester *p*-toluenesulfonate was prepared according to Greenstein and Winitz[9]. The S-valine benzyl ester, obtained from this salt, was then condensed with the isocyanate in methylene chloride. Debenzylation hydrogenation over a palladium-on-carbon catalyst in ethyl acetate yielded II.

Two to three grams of each of the two copolymers were condensed with one equivalent (based on titration) of the isocyanate of I in methylene chloride yielding III and IV. Peptidization was carried out by reacting each of the copolymers with 1.1 equiv. of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDAC)[10] and 1.1 equiv. of II in tetrahydrofuran yielding V and VI.

Solutes

The N-perfluoroacyl amine derivatives were synthesized from the amines using the appropriate perfluoro-acid anhydride[1,3]. Resolved amines were used, with the exception of 2-amino-4-phenylbutane and 2-amino-5-phenylpentane[5]. Amino acids were chromatographed as the N-trifluoroacetyl (TFA) isopropyl esters which were prepared by the method of Roach and Gerhke[11].

Gas chromatography

A Model 3700 gas chromatograph (Varian, Walnut Creek, CA, U.S.A.), equipped with a split/splitless injection system, flame-ionization detector and auto-linear temperature programming module was used. WCOT columns were prepared from 0.23 mm I.D. capillaries drawn on a capillary drawing machine from stock borosilicate glass tubing. In the case of copolymers III, IV and V, the columns were treated with barium carbonate as described by Grob and Grob[12], pre-coated with a non-extractable layer of Carbowax 20M[13], and then dynamically coated with the copolymers by the mercury-drop method[14]. For copolymer VI, a capillary was baked out at 300°C with helium gas flow, prepared with a non-extractable layer of Carbowax 20M, and then coated statically with the copolymer as described by Grob[15] and by Rutten and Rijks[16]. The columns were conditioned with normal carrier gas flow (oxygen-free helium) at 160°C for 3 h prior to use.

RESULTS AND DISCUSSION

The results obtained when the series $C_6H_5CH(CH_3)NHCO(CF_2)_mCF_3$ ($m = 0$, 1,2) was subjected to capillary chromatography on 2–4% and 32% "urea" and "peptide" phases is presented in Table I. Also presented in Table I are the results of experiments carried out using packed columns in the smectic andisotropictemperature regions of carbonylbis(S-valine isopropyl ester) using this same series. Fig. 1 is a capillary chromatogram of the ($m = 0, 1, 2$) series using the 32% peptide polymer phase. Several interesting facts are revealed in this data. First, only when the stationary phase is CbSV and then only in its smectic state does one observe an increase in α with liquid loading or film thickness. Differential scanning calorimetry studies of the coated material indicate no difference in the behavior of CbSV in the pure and coated state in terms of transition temperatures. The variation of α is not, therefore,

TABLE I

CHROMATOGRAPHIC BEHAVIOR OF PERFLUOROAMIDE SOLUTES OF TYPE $C_6H_5CH(CH_3)NH(CF_2)_mCF_3$ ON CARBONYLBIS(S-VALINE ISOPROPYL ESTER), MODEL "UREA" and "PEPTIDE" SILOXANE PHASES

CbSV = Carbonylbis(S-valine isopropyl ester); packed columns % refers to loading by weight. S = smectic; I = isotropic (100, 112°C resp.). Siloxane data 112°C; % refers to amino propyl content of polymer.

	CbSV 1%		*CbSV 5%*		*Urea*		*Peptide*	
m	*S*	*I*	*S*	*I*	*2–4%*	*32%*	*2–4%*	*32%*
0	1.08	1.09	1.42	1.11	1.01	1.01	1.03	1.03
1	1.12	1.09	1.87	1.12	1.01	1.01	1.03	1.03
2	1.14	1.09	2.21	1.13	1.01	1.02	1.03	1.03

related to textural changes in the phase. The possibility of a complex sorption mechanism, *e.g.* Gibbs isotherm behavior has been investigated in our laboratory[17]. The results indicate significant, non-bulk solution contributions to retention and will be the subject of a subsequent contribution.

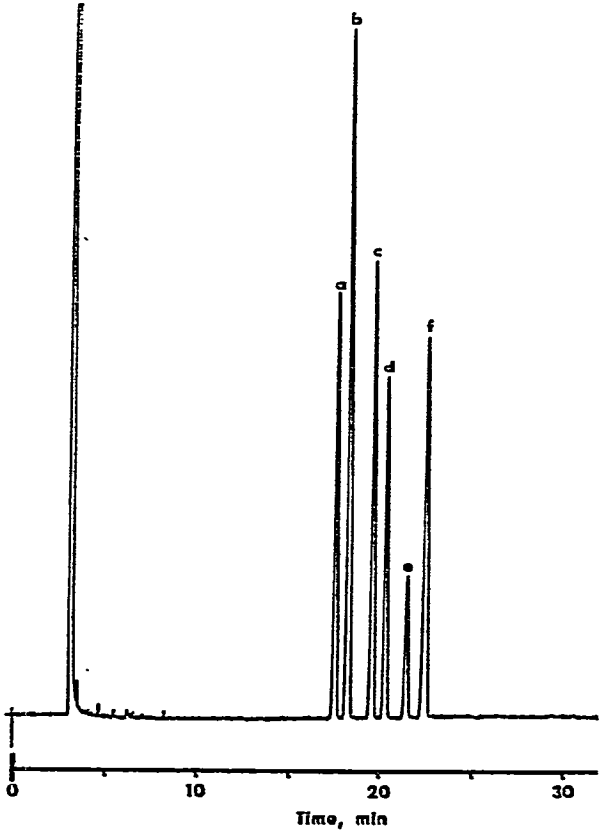


Fig. 1. Capillary gas chromatogram of the series (m = 0, 1, 2) on a WCOT column of 40 m length at 125°C (32% polymer). The notation a, b, c, d, e, f refers to chiral pairs, *e.g.* a–b.

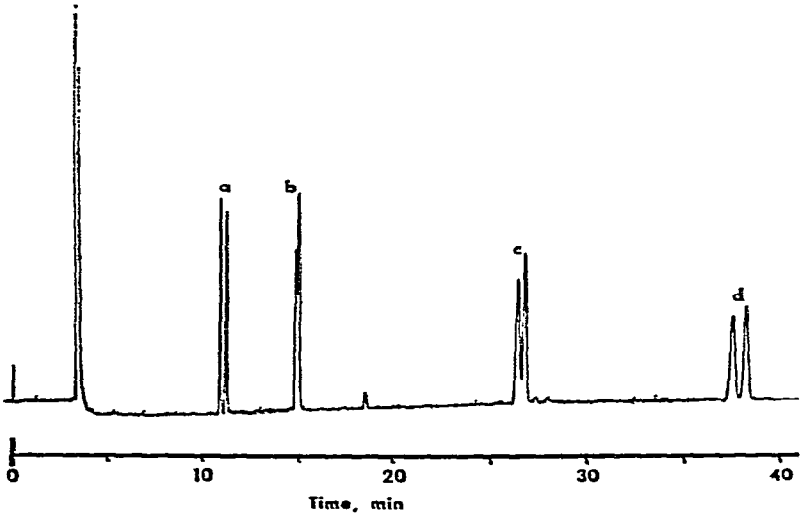


Fig. 2. Capillary gas chromatogram of the series ($m = 1$; $n = 0, 1, 2, 3$) on a WCOT column of 40 m length at 140°C (32% polymer). The notation a, b, c, d refers to series members.

Table II presents the results obtained when the series $C_6H_5(CH_2)_nCH(CH_3)$-$NHCOCF_2CF_3$ ($n = 0$–3) was examined. Only results from the "peptide"-type phase are presented for comparison although the urea phase gave qualitatively similar results. Fig. 2 is a capillary chromatogram of the series ($n = 0, 1, 2, 3$, $m = 1$) using the 32% peptide polymer phase. As can be seen the chromatographic resolution of these solutes varies with n in a like manner on both phases. In the case of the $n = 2$ solute on the 32% phase the measured value of α was always greater than for $n = 3$ but the absence of enantiomerically pure or resolved solutes precluded precise estimation of the exact magnitude. It appears then that the alternation of α value magnitude is a property of this series and is not exclusively related to the behavior of CbSV or structurally related phases of that type. The α values obtained on the 32% phase are consistently larger than for the 2–4% phase for this series in contrast to the ($m = 0, 1, 2$) series discussed previously.

TABLE II

CHROMATOGRAPHIC BEHAVIOR OF PERFLUOROPROPIONAMIDE SOLUTES OF THE SERIES $C_6H_5(CH_2)_nCH(CH_3)NHCOCF_2CF_3$ ON CARBONYLBIS(S-VALINE ISOPROPYLESTER) AND THE 2 AND 32% PEPTIDE SILOXANE PHASES IN TERMS OF RESOLUTION FACTOR α

	CbSV		*Peptide*	
n	*S*	*I*	*2%*	*32%*
0	2.45	1.13	1.02	1.05
1	1.45	1.03	1	1.10
2	2.09	1.05	1.01	1.02*
3	1.85	1.04	1.005	1.02

* The arithmetic mean of multiple measurements is significantly greater than 10.2 but less than 10.3.

Table III lists the α values obtained for a variety of solutes unrelated to the question posed in the introduction. These data are presented solely for the interest of those wishing to compare these polysiloxane phases with others that are available. The 32% "peptide" phase is moderately polar [k'(alanine) = 1.6, k'(phenylglycine) = 14 under conditions in Table III].

TABLE III

ENANTIOMERIC SEPARATION FACTORS ($\alpha_{R,S}$) FOR SEVERAL AMINE DERIVATIVES AT 100°C ON THE FOUR CHIRAL POLYSILOXANES

PFP = perfluoropropionamido; HFB = heptofluorobutyramido.

Solute	$\alpha_{R,S}$			
	Stationary phase			
	2–4% Urea (IV)	*32% Urea (V)*	*2–4% Peptide (VI)*	*32% Peptide (VII)*
N-TFA-2-Aminoheptane	1.015	1.007	1.023	1.034
N-TFA-2-Aminooctane	1.018	—	—	1.033
N-TFA-2-Aminoethylcyclohexane	1.016	1.007	1.022	1.036
N-TFA-2-Aminoethylbenzene	1.029	1.032	1.036	1.065
N-PFP-2-Aminoethylbenzene	1.030	1.047	1.027	1.050
N-HFB-2-Aminoethylbenzene	1.031	1.032	1.026	1.053

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