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Short Communication

Chiral recognition of enantiomeric amides on a diamide chiral stationary phase by gas chromatography

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ABSTRACT

Several α-alkyl-, a-cycloalkyl- and a-aromatic-substituted ethylamine enantiomers were separated with a cross-linked polycyanoethyl vinyl siloxane–L-valine–*tert.*-butylamide fused-silica capillary column. Kováts retention indices of cyclohexane, benzene, anisole and the derivatized amines on the chiral stationary phase (CSP) were determined and compared with those on SE-30. By extrapolation of the retention behaviour, the chiial recognition mechanism of enantiomeric amides on diamide CSPs is discussed.

INTRODUCTION

Since the first successful direct resolution of enantiomers by gas chromatography (GC) in 1966 [1], a variety of enantiomeric pairs have been separated on various chiral stationary phases (CSPs) [2–5].

Amines are widely used as intermediates in the synthesis of a large number of organic compounds, including dyes, drugs, pesticides and plastics. The enantiomeric separation of chiral amines, generally derivatized as amines, has been reported by several workers [4–12]. Oi et *al.* [6] reported the direct separation of racemic amines on optically active copper(II) complexes, but the peak shapes were broad and tailing. Generally, amines are derivatized as N-perfluoroalkyl derivatives before chromatography on CSPs [13]. The enantiomeric separation of derivatized chiral amines on cyclodextrin derivatives (CD-CSPs) [4,5] and chiral hydrogen-bonding GC phases such as peptide [10], diamide [8,11,12] and even monoamide [7] CSPs has also been reported.

In this work, a-alkyl-, a-cycloalkyl- and a-aromatic-substituted ethylamines were enantiomerically separated in a cross-linked polycyanoethyl vinyl siloxane–L-valine–*tert.*-butylamide fused-silica capillary column, prepared as described previously [14]. The reasons for difference in the a-values (separation factor) of the amides were investigated.

EXPERIMENTAL

Materials

Fused-silica capillary tubes (0.25 mm I.D.) were obtained from Yongnian Optical Fibre Manufacture. 2-Aminoheptane and 2-aminooctane were purchased from Tokyo Kasei Kogyo and a-phenylethylamine from Sigma. a-Cyclo-

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hexylethylamine was synthesized from cyclohexyl methyl ketone by the Leukart reaction [15]. Methoxy-substituted a-phenylethylamines were prepared in our laboratory [12].

Derivatization

The amines were derivatized into N-trifluoroacetyl (TFA), N-acetyl (AC) or N-benzyl (Bz) derivatives [16,17].

Chromatographic conditions

Cross-linked polycyanoethyl vinyl siloxane–L-Val–*tert.*-butylamide and cross-linked SE-30 fused silica capillary columns were prepared as reported previously [14,18]. The chromatographic separation was carried out with a GC R1A gas chromatograph equipped with a split injector and a flame ionization detector.

RESULTS AND DISCUSSION

The structures, separation factors (a), peak resolution (Z?,) and capacity factors (k') of the N-TFA-amines tested are given in Table I. They have very similar structures and can all be considered as substituted N-TFA-ethylamines. The only difference among them is in the R groups of the ethylamine a-positions.

N-TFA-Zaminooctane, N-TFA-α-cyclohexylethylamine and N-TRA-a-phenylethylamine have the same carbon number. However, the difference in their a-values is considerable, and that of N-TFA-a-phenylethylamine is the highest, even at much higher temperatures.

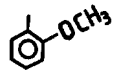
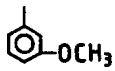
The difference in a-values between a-aromatic-substituted ethylamines and a-alkyl- or a-cycloalkyl-substituted ethylamines on monoamide CSPs has already been reported by Weinstein *et al.* [7]. In that case, the higher a-values of aromatic-substituted ethylamines were explained by an intercalation mechanism of the solutes into the parallel arrangements of aromatic rings of the monoamide CSPs. Unfortunately, this mechanism is not suitable to explain the difference in a-values in our experiments, because there is no aromatic ring in the diamide CSP used here.

For an optically active molecule, direct chiral recognition can only be effected by another chiral molecule (CSP). Although the amide

TABLE I

a, R_s AND k'(S) VALUES OF N-TFA-AMINES

Amines: $CH_3CH(R)NH_2$. a = $[t_{R(2)} - t_0]/[t_{R(1)} - t_0]$; R_s = $[t_{R(2)} - t_{R(1)}/[1/2(Wb_2 + Wb_1)]$; k'(S) = $[t_{R(2)} - t_0]/t_0$. Wb = width at base.

R	a	R_s	$k'(S)$	Temperature (°C)
n-C_5H_{11}	1.020	0.87	16.5	80
n-C_6H_{13}	1.022	1.08	32.0	80
	1.016	1.10	8.19	110
	1.026	1.76	5.78	130
	–[a]	0	8.87	130
	1.032	1.82	23.7	130
	1.033	1.95	25.4	130

[a] No separation.

groups of the derivatized amines have two strong interaction sites (oxygen and hydrogen) connected directly to the asymmetric carbon, they can only be considered as "one point" according to the "three-point" rule suggested by Dalglish [19,20]. It has also been demonstrated that one strong attraction is sufficient for chiral recognition in many instances on a diamide CSP [21]. However, it is reasonable that the enantiomeric selective interactions of other groups connected to the asymmetric atom with the CSPs will certainly affect the chiral separation.

The only difference in the N-TFA-amines is in the R group. The higher a-values of α-aromatic-substituted ethylamines might be due to the stronger interaction of the phenyl group with the CSP than that of the alkyl or cycloalkyl groups.

Kováts retention indices (I), which are greatly influenced by both structures of the solutes and solvents, are the most widely used parameters for qualitative analysis in GC. The higher the Z value, the stronger is the interaction between the solute and the solvent. The diamide CSP used is

an optically active polymeric siloxane stationary phase. The AZ values, the difference in Kováts retention indices on the diamide CSP {for enantiomers Z = [Z(S) + $I(R)$]/2} and on the dimethylsiloxane (SE-30) phase could be qualitatively assumed to be the contribution of the chiial side-chain to the Z value [22].

The Z and AZ values of the derivatized amines and the R group in their a-positions, namely cyclohexane, benzene and anisole, on the cross-linked diamide CSP and SE-30 are given in Table II. Benzene, cyclohexane and hexane have the same carbon number, but both the Z value on the CSP and the AZ value of benzene are much greater than those of cyclohexane and hexane. From Table II, it can also be seen clearly that the AZ values of all the N-TFA-α-aromatic-substituted ethylamines are much greater than those of N-TFA-a-alkyl or -a-cycloalkyl-substituted ethylamines. That is, in the derivatized amines, the interaction of a phenyl group with the CSP is much stronger than that of an alkyl or cycloalkyl group.

The introduction of a methoxy group in the *meta* and *para* positions on the benzene ring slightly improved the selectivity of enantiomers [12]. This is probably because the introduced group (methoxy) further enhanced the interaction of the benzene ring of the solutes with the CSP. The a-value of N-TFA-*o*-methoxy-a-phenylethylamine is much lower than that of the corresponding *meta* and *para* isomers owing to the intramolecular hydrogen bonding of the amide group [12]. The data in Table II show that the Z values on the CSP and SE-30 and the AZ value for N-TFA-*o*-methoxy-α-phenylethylamine are significantly lower than those for the corresponding *metu* and *para* isomers, also supporting the hypothesis of intramolecular hydrogen bonding.

The GC behaviour of N-Ac and N-Bz derivatives of a-alkyl-substituted ethylamine, 2-aminoheptane and 2-aminooctane was also studied (Tables II and III). On replacing N-TFA with N-Ac or N-Bz, the interaction of the strong interaction point, the amide group, with the CSP

TABLE II

KOVÁTS RETENTION INDICES (Z) AND DIFFERENCE IN KOVÁTS RETENTION INDICES ON THE CSP AND SE-30 (ΔI)

Solute	Z		ΔI [b]	Temperature (°C)
	SE-30	CSP[a]		
Cyclohexane	664.34	692.00	27.66	60
Benzene	657.74	760.38	102.64	60
Anisole	899.91	1060.95	161.46	60
N-TFA-Zaminoheptane	1064.62	1464.46	399.84	150
N-TFA-2-aminooctane	1160.57	1561.73	401.16	150
N-TFA-a-cyclohexylethylamine	1226.82	1644.28	417.46	150
N-TFA-a-phenylethylamine	1215.24	1724.80	509.56	150
N-TFA-*o*-methoxy-a-phenylethylamine	1386.26	1817.26	421.00	150
N-TFA-*m*-methoxy-a-phenylethylamine	1430.77	2002.14	571.37	150
N-TFA-*p*-methoxy-a-phenylethylamine	1456.36	2020.04	563.68	150
N-Ac-Zaminoheptane	1269.04	1750.48	481.44	150
N-Ac-2-aminooctane	1362 70	1852.29	489.59	150
N-Bz-2-aminoheptane	1798.59	2329.92	531.33	180
N-Bz-2-aminooctane	1896.06	2429.28	533.22	180

[a] For enantiomers on the CSP, Z = [Z(S) + $I(R)$]/2.

[b] For enantiomers, AZ= {[Z(S) + $I(R)$]/2} − Z(SE-30); Z(S), $I(R)$ and Z(SE-30) are the Kováts retention indices of the *S* or *R* configuration on the CSP and those on SE-30.

TABLE III

α, R, AND k'(S) VALUES OF N-Ac- AND N-Bz-AMINES AND N-TFA-a-PHEWINE

Solute	α	R,	k'(S)	Temperature (°C)
N-Ac-Zaminoheptane	1.017	1.21	14.55	110
N-Ac-2-aminooctane	1.021	1.50	24.23	110
N-Bz-2-aminoheptane	1.016	1.19	29.30	150
N-Bz-2-aminooctane	1.018	1.17	45.63	150
N-TFA-α-phenylethylamine	1.024	1.68	2.38	150

is enhanced and the *I* and AZ values increase, but the comparatively weak interaction point, the alkyl group (R), remains the same. The a-values of the N-Ac and N-Bz chiral alkyl-substituted ethylamines are not substantially improved whereas the volatility is greatly reduced and a much higher column temperature is needed. Although the interaction of the carbonyl groups of N-Ac and N-Bz with the CSP is stronger than that of N-TPA, the a-values of N-Ac or N-Bz chiral alkyl-substituted ethylamines are still much smaller, at the same temperature or even at lower temperatures, than that of N-TPA-1-phenylethylamine (Table III). Hence increasing the interaction strength of the relatively weak interaction point (R group) with the CSP, i.e., from an alkyl or cycloalkyl to a phenyl group, has a greater effect on chiral recognition than further increasing the strength of the strong interaction point (amide group) with the CSP.

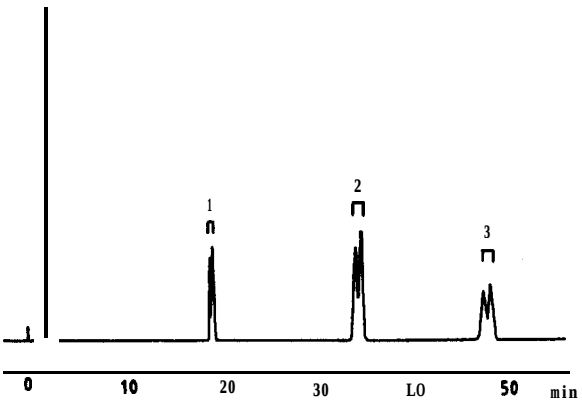
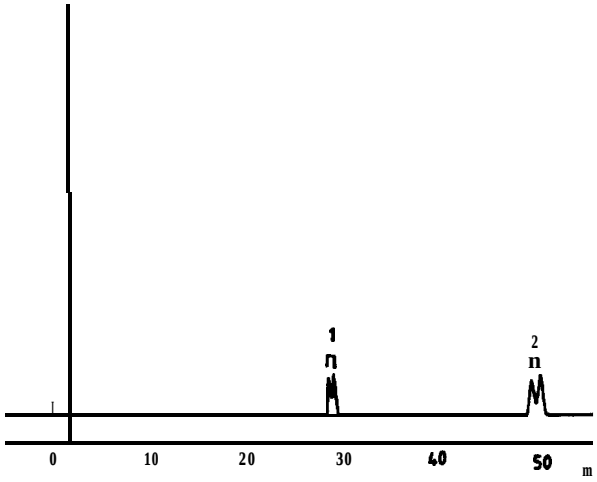


Fig. 1. Chromatogram of N-TFA-chiral α-alkyl- and α-cycloalkyl-substituted ethylamines. Column, cross-linked polycyanoethylvinylsiloxane–L-Val–*tert*.-butylamide fused-silica capillary (20 m × 0.25 mm I.D.); column temperature, 90°C; carrier gas, nitrogen. 1 = N-TFA-2-Aminoheptane; 2 = N-TFA-2-aminooctane; 3 = N-TFA-a-cyclohexylethylamine (R-enantiomers eluted first).



Fii. 2. Chromatogram of N-Ac chiral α-alkyl-substituted ethylamine. Column temperature, 110°C; other conditions as in Fig. 1. 1 = N-Ac-2-Aminoheptane; 2 = N-Ac-2-aminooctane (R-enantiomers eluted first).

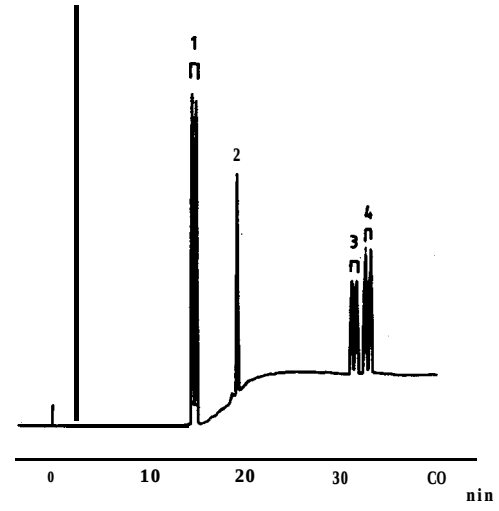


Fig. 3. Chromatogram of N-TFA chiral α-aromatic-substi- increased at 4°C/min to 150°C; other conditions same as in Fig. 1. 1 = N-TFA-cr-Phenylethylamine; 2 = N-TFA-*o*-methoxy-a-phenylethyhtmine; 3 = N-TFA-*m*-methoxy-α-phenylethylamine; 4 = N-TFA-p-methoxy-a-phenylethyl~amine (*R*-enantiomers eluted first).

The chromatograms of some amides enantiomers are shown in Figs. 1-3.

CONCLUSIONS

The separation factors (α-values) of chiral a-aromatic substituted ethylamines are much greater than those of both chiral α-alkyl- and α-cycloalkyl-substituted ethylamines, derivatized as amides, on the diamide CSP used. The Z values (Kováts retention indices) on the CSP and SE-30 and the AZ values (difference in Z values on the CSP and SE-30) of the chiral ethylamines and their substituents (R group) were tested. The higher a-values of the chiral a-aromatic-substituted ethylamines might be due to the stronger interaction of the benzene ring than the alkyl and cycloalkyl groups with the CSP.

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