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Enantiomeric separation of α-phenylethylamine and its substituted isomers by gas chromatography

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ABSTRACT

α-Phenylethylamine, *o*, *m*, *p*-methoxy-α-phenylethylamines and *o*, *m*, *p*-methyl-α-phenylethylamines were enantiomerically separated with four different diamide chiral stationary phases (CSPs) [monobenzyl succinate-L-Val-*tert*.-butylamide (CSP-1), undecenoyl-L-Val-*S*-α-phenylethylamide (CSP-2), undecenoyl-L-Val-*R*-α-phenylethylamide (CSP-3) and cross-linked polycyanoethyl vinyl siloxane-L-Val-*tert*.-butylamide (CSP-4)] using capillary gas chromatography. The *ortho*-effect of the methoxy group on the enantiomeric separation was investigated. The elution order of the enantiomers on CSP-3 is reversed with respect to that on the other CSPs studied. The enantiomeric separation of α-phenylethylamine and its methoxy- and methyl-substituted isomers is illustrated.

INTRODUCTION

α-Phenylethylamine and its derivatives can be used for the syntheses of anti-cancer drugs and asymmetric catalysts [1–3]. The enantiomeric separation of these compounds is of great importance in biochemistry, asymmetric synthesis and pharmacology. Racemic amines can be enantiomerically separated using chiral stationary phases (CSPs) [4,5], although the separation of substituted α-phenylethylamine enantiomers has not yet been fully investigated. It has been reported that the methoxy group shows a considerable *ortho*-effect in the enantiomeric separation of N-trifluoroacetyl (TFAc)-*o*-methoxy-α-phenylethylamine [6]. This paper reports an investigation of the mechanism of this *ortho*-effect.

EXPERIMENTAL

Materials

Fused-silica capillary tubes (0.25 mm I.D.) were obtained from Yongnian Optical Fibre Manufacture (China). Monobenzyl succinate-L-Val-*tert*.-butylamide (CSP-1) was kindly supplied by Professor X. Xu (Shanghai Institute of Materia Medica, Academia Sinica, Shanghai, China). The preparations and properties of undecenoyl-L-Val-*S*-α-phenylethylamide (CSP-2), undecenoyl-L-Val-*R*-α-phenylethylamide (CSP-3) and polycyanoethyl vinyl siloxane-L-Val-*tert*.-butylamide (CSP-4) have been described previously [7,8].

Syntheses of the solutes

Syntheses of methyl-substituted acetophenones. For the synthesis of *o*-and *m*-methylacetophenones, Grignard reagents of *o*- and *m*-halotoluenes were reacted with acetonitrile and hydrolysed in acid solution [9]. The Friedel–Crafts reaction of toluene was used to prepare *p*-methylacetophenone [10].

Syntheses of methoxy-substituted acetophenones. Fries rearrangement of phenyl acetate was used to prepare *o*- and *p*-methoxyacetophenones, which then reacted with dimethylsulphate in alkaline solution [11]. *m*-Methoxyacetophenone was prepared by the methylation of *m*-hydroxyacetophenone [12].

Syntheses of methyl- and methoxy-substituted α-phenylethylamines. All six of the amines were synthesized by the Leukart reaction of their methyl- and methoxy-substituted acetophenones with am-

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monium formate [13]. *d,l-p*-Methoxy-α-phenylethylamine was partly resolved with l-tartaric acid in methanol [14].

Derivatization

The amines were derivatized with trifluoroacetyl anhydride according to the method of Feibush and Gil-Av [15]. The mass spectra of the derivatized amines are shown in Fig. 1.

Chromatographic conditions

Fused-silica capillary columns were coated or cross-linked as described previously [7,16]. The chromatographic separations were carried out with a GC R1A gas chromatograph equipped with a split injector and a flame ionization detector. The elution order of the amine enantiomers was determined by comparison with the retention times of chirally pure standards.

RESULTS AND DISCUSSION

The structures of the amines studied are shown in Fig. 2. The capacity factors (k') and separation factors (α) of N-TFAc-α-phenylethylamine and its methoxy and methyl-substituted isomers are listed in Table I. The elution order of the enantiomers on CSP-3 is reversed with respect to the other CSPs studied. CSP-2 and CSP-3 have two asymmetric centres and are diastereoisomers. On CSP-2 and CSP-3 the α-values of N-TFAc-*m*-methoxy-α-phenylethylamine are slightly larger than those of the *p*-isomer, and on CSP-1 and CSP-4 the α values are almost equal. Except for the *p*-isomers on CSP-3, the α values of *m*- and *p*-N-TFAc-methoxy-α-phenylethylamines are slightly larger than those of the corresponding *m*- and *p*-N-TFAc-methyl-α-phenylethylamines. All the α values of *o*-, *m*-, *p*-methyl-substituted and *m*-, *p*-methoxy-substituted N-TFAc-α-phenylethylamines, except for the *p*-isomers on CSP-3, are not less than the α values of unsubstituted N-TFAc-α-phenylethylamine. N-TFAc-*o*-methoxy-α-phenylethylamine has the lowest α values of the amines tested and is eluted faster than its *m*- and *p*-isomers.

From these results, the following conclusions can be made:

(1) For CSP-2 and CSP-3, the configuration of the α-phenylethylamide moiety of the CSPs determines the elution order of the enantiomers. On CSP-3, the two chiral centres have opposite rotational directions and the solutes show lower α values than those on its diastereoisomer, CSP-2.

(2) Except for N-TFAc-*o*-methoxy-α-phenylethylamine and CSP-3, none of the methyl-and methoxy-substituted isomers showed lower α values than those of unsubstituted N-TFAc-α-phenylethyl amine.

(3) The *o*-methoxy group shows a pronounced *ortho*-effect on the α and k' values on the four CSPs studied.

In the *o*-position of a benzene ring, a methyl group shows greater steric hindrance than a methoxy gorup. However, the α values of N-TFAc-*o*-methyl-α-phenylethylamine are comparable with those of its *m*- and *p*-isomers and are much larger than those of N-TFAc-*o*-methoxy-α-phenylethylamine. In this instance the steric hindrance cannot reasonably be used to explain the lowest α values of N-TFAc-*o*-methoxy-α-phenylethylamine listed in Table I.

It is suggested that, in the N-TFAc-*o*-methoxy-α-phenylethylamine molecule, the oxygen atom of the methoxy group and the hydrogen atom of the amide group are at such positions that they could form a six membered ring through intramolecular hydrogen bonding (see Fig. 3). This intramolecular hydrogen bonding considerably decreases the hydrogen bonding of the N-TFAc-*o*-methoxy-α-phenylethylamine with the CSPs, resulting in much lower α values and faster elution than its *m*- and *p*-isomers.

It has been reported that chiral amines can be separated on monoamide CSPs such as N-lauroyl-*S*-α-(1-naphthyl)ethylamine. The separation mechanism suggests that the solute is intercalated between two solvent molecules [4]. If this mechanism is assumed, the interaction between the amide groups of the solute and solvent is very important for chiral recognition.

When the amide groups of the solutes cannot sufficiently interact with the diamide CSPs, such as for N-TFAc-*o*-methoxy-α-phenylethylamine, very low α values or even no separation is obtained. This implies that the amide group of the N-TFAc chiral amine is also an important interaction site for chiral recognition on diamide CSPs. The introduction of a methyl group to *o*-, *m*-, *p*-position and a methoxy

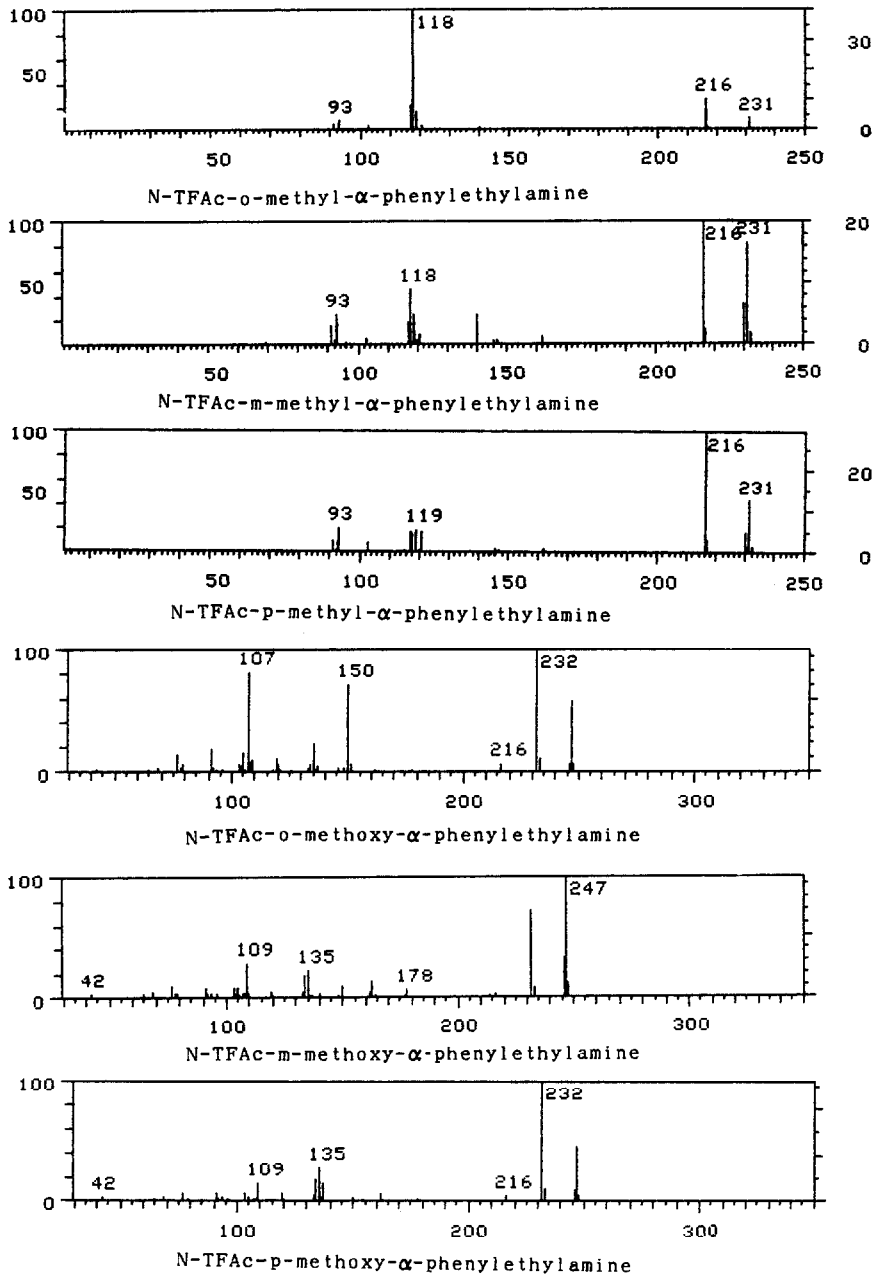
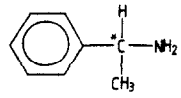


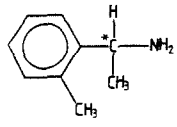
Fig. 1. Mass spectra of the N-TFAc-amines.

group to *m*, *p*-position on the benzene ring of N-TFAc-α-phenylethylamine slightly improved the selectivity of enantiomers on CSP-1, CSP-2 and CSP-4. This is probably because the introduced group (methyl or methoxy) enhances the interaction of the benzene ring of the solutes with the CSPs.

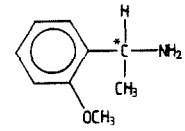
The enantiomeric separation of the amines on the four CSPs is shown in Fig. 4. Except for N-TFAc-*o*-



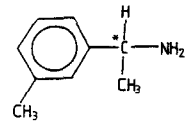
α-phenylethylamine



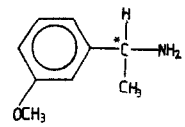
o-methyl-α-phenylethylamine



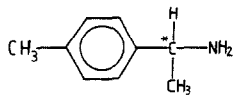
o-methoxy-α-phenylethylamine



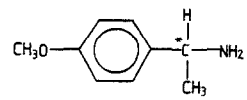
m-methyl-α-phenylethylamine



m-methoxy-α-phenylethylamine



p-methyl-α-phenylethylamine



p-methoxy-α-phenylethylamine

Fig. 2. Structures of racemic amines examined.

TABLE I

α- AND *k'* VALUES OF N-TFAc-α-PHENYLETHYLAMINE AND ITS METHOXY- AND METHYL-SUBSTITUTED ISOMERS

Isomer	Temperature (°C)	CSP-1		CSP-2		CSP-3		CSP-4	
		α	*k'* (*S*)	α	*k'* (*S*)	α	*k'* (*R*)	α	*k'* (*S*)
α-Phenylethylamine									
	130	1.044	5.74	1.045	9.24	1.028	5.98	1.026	5.78
	150	1.039	2.68	1.040	4.34	1.023	2.98	1.024	2.38
Methyl-substituted α-phenylethylamine									
o-Isomer	130	1.044	6.14	1.048	10.9	1.029	7.08	1.025	6.05
	110	1.049	14.9			1.036	15.8	1.030	16.2
m-Isomer	130	1.046	6.98	1.048	12.2	1.028	7.93	1.030	6.62
	110	1.055	17.2			1.034	18.1	1.034	18.2
p-Isomer	130	1.050	7.45	1.051	13.1	1.024	8.50	1.032	6.93
	110	1.058	18.3			1.032	19.2	1.038	19.2
Methoxy-substituted α-phenylethylamine									
o-Isomer	130	–[a]	9.59	1.015	14.2	–[a]	10.2	–[a]	8.87
	150	–[a]	4.28	1.013	6.88	–[a]	4.88	–[a]	3.62
m-Isomer	130	1.053	22.7			1.040	23.3	1.032	23.7
	150	1.045	10.9	1.052	16.7	1.032	11.6	1.024	8.44
p-Isomer	130	1.053	24.5			1.022	24.3	1.033	25.4
	150	1.046	12.0	1.047	18.1	1.018	12.6	1.026	9.08

[a] No separation.

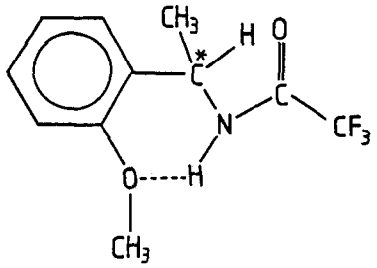


Fig. 3. Intramolecular hydrogen bonding of N-TFAc-*o*-methoxy-α-phenylethylamine.

methoxy-α-phenylethylamine, all the amines can be readily separated into their antipodes on CSP-1, CSP-2 or CSP-4.

CONCLUSIONS

The methoxy group of N-TFAc-*o*-methoxy-α-phenylethylamine shows a considerable *ortho*-effect on the selectivity of enantiomers, probably due to the formation of intramolecular hydrogen bonding

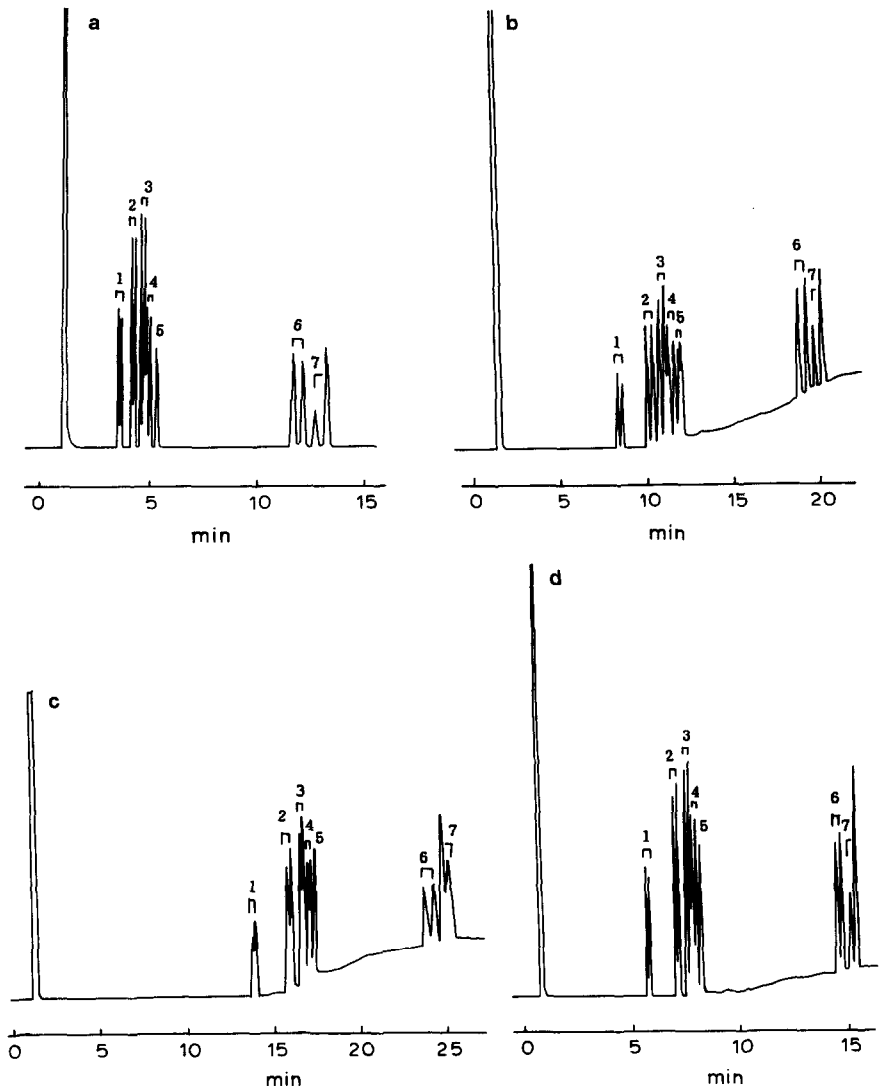


Fig. 4. Chromatogram of N-TFAc-chiral amines. Fused-silica capillary column (20 m × 0.25 mm) coated as given for each part. (a) Coated with CSP-1; temperature 150°C; carrier gas hydrogen; *R*-enantiomers eluted first. (b) Coated with CSP-2; temperature 130°C (5 min), then 4°C/min to 150°C; carrier gas hydrogen; *R*-enantiomers eluted first. (c) Coated with CSP-3; temperature 110°C (10 min), then 4°C/min to 150°C; carrier gas hydrogen; *S*-enantiomers eluted first. (d) Cross-linked with CSP-4; temperature 130°C (5 min), then 4°C/min to 150°C; carrier gas hydrogen; *R*-enantiomers eluted first. Peaks: 1 = *d,l*-α-phenylethylamine; 2 = *d,l-o*-Methyl-α-phenylethylamine; 3 = *d,l-m*-methyl-α-phenylethylamine; 4 = *d,l-p*-methyl-α-phenylethylamine; 5 = *d,l-o*-methoxy-α-phenylethylamine; 6 = *d,l-m*-methoxy-α-phenylethylamine; 7 = *d,l-p*-methoxy-α-phenylethylamine.

between the oxygen atom in the methoxy group with the hydrogen atom in the amide group. Both substituents and their positions in the benzene ring can to some extent affect the α-values of substituted-α-phenylethylamine antipodes. The amines tested, except for *o*-methoxy-α-phenylethylamine, can be readily separated into their enantiomers in a single run on CSP-1, CSP-2 or CSP-4 under selected conditions.

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