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N-ACYL DERIVATIVES OF CHIRAL AMINES AS NOVEL, READILY PREPARED PHASES FOR THE SEPARATION OF OPTICAL ISOMERS BY GAS CHROMATOGRAPHY

S. WEINSTEIN, B. FEIBUSH and E. GIL-AV

Department of Organic Chemistry, Weizmann Institute of Science, Rehovot (Israel)

SUMMARY

The results reported demonstrate that it suffices for a chiral stationary phase to contain an amide group and an asymmetric carbon atom, attached to the nitrogen atom [RCONHCH(CH_3)R'], in order to show selectivity in its interaction with the enantiomers of amides such as N-trifluoroacetylamines, N-trifluoroacetylamino acid esters and α-methyl- and α-phenylcarboxylic acid amides. The best efficiency is obtained when R' is aromatic, particularly α-naphthyl, as in N-lauroyl-*S*-α-(1-naphthyl)ethylamine.

The highest resolution factors were found for aromatic solutes, such as N-trifluoroacetyl-α-phenylethylamine and α-phenylbutyric acid amides, which could be resolved readily on packed columns.

The enantiomers of α-branched carboxylic acids were separated for the first time by gas chromatography.

Based on the packing arrangement in the crystalline form of the N-acetyl homologue of N-lauroyl-*S*-α-(1-naphthyl)ethylamine, a mechanism for the resolution is proposed. It is assumed that the mode of association found in the solid state is at least partially retained in the melt through a network of hydrogen bonds. The mechanism proposed is developed with particular reference to the aromatic solute–solvent systems. It is suggested that the solute is intercalated ("sandwiched") between two solvent molecules. Arguments, based on X-ray data, are given to explain the selectivity observed.

INTRODUCTION

The optically active phases used hitherto for the separation of enantiomers by gas chromatography were characterized by the following structural features: (1) one or two asymmetric carbon atoms each linked to the nitrogen atom of an amide group; and (2) one additional function, consisting of either an ester or an amide group. Examples are N-acyl-α-amino acid esters[1], N-acyldipeptide esters[2], diamides of the formula RCONHCH(*i*-Pr)CONHR'[3,4] and carbonylbis-(N-α-amino acid esters)[5,6].

It was the purpose of the present research to examine whether stationary phases still show selectivity when their structure is simplified to contain no more than one

amide group' (*i.e.*, compounds of type $RCONHCH(CH_3)R'$). We have already reported[5] that volatile amides of this type are resolved on carbonylbis-(N-L-valine isopropyl ester) (V). Furthermore, comparison[3,4] of diamide and dipeptide phases shows that selectivity is considerably increased when the polar part of the solvent molecule is reduced to the group –CONHCH(R)CONH–.

The substituents R and R' in the solvents studied were chosen as follows. In order to impart low volatility to the phases, the long lauroyl group ($RCO=C_{11}H_{23}CO$) was used throughout for acylation. The R' radicals were phenyl (I), cyclohexyl (II), α-naphthyl (III) and α-decahydronaphthyl (IV). The solutes examined included N-TFA* derivatives of aliphatic and cyclic amines, N-TFA esters of α-amino and α-methyl-α-amino acids, and amides of α-methyl- and α-phenylcarboxylic acids.

EXPERIMENTAL

Synthesis of amides

Equimolar ice-cold solutions of freshly distilled lauroyl chloride and the corresponding chiral amine in dry chloroform were slowly mixed. A 10% excess of triethylamine was added and the solution left overnight in the cold (5–10°). The solution was washed successively with water, saturated sodium hydrogen carbonate solution, 2% hydrochloric acid and water. After drying over magnesium sulphate and evaporation, the amides were crystallized several times from chloroform–*n*-hexane**.

Synthesis of hydroaromatic amides

These amides were prepared by catalytic hydrogenation of the corresponding aromatic amides with 5% rhodium–alumina in methanolic solution at a hydrogen pressure of 60 p.s.i. for 24 h. The catalyst was filtered off, the solution evaporated and the amides were purified by column chromatography with silica gel and light petroleum–dichloromethane as the eluent.

Synthesis of N-methylamides

N-Methylamides were prepared from the amides by treatment with methyl iodide in dimethylformamide in the presence of silver oxide for several days at room temperature[7].

Carbonylbis-(N-L-valine isopropyl ester) (V). This phase was purchased from Miles-Yeda, Rehovot, Israel.

The properties of the *S*-monoamide phases were as follows:

Phase	*M.p. (°C)*	$[\alpha]_D$	*(c in $CHCl_3$)*
I	62	−66.0	(1.5)
II	86	−10.0	(1.5)
III	96–97	−59.6	(1.5)
IV	76–80	+ 6.4	(2.0)

The structures of all of the phases were confirmed by NMR and IR spectroscopy and microanalysis.

* TFA = trifluoroacetyl.

** Phase III can be obtained from Yeda, Rehovot, Israel.

Synthesis of solutes

N-TFA amines[5] and N-TFA amino acid esters[8] were synthesized as described previously.

Aliphatic α-methylcarboxylic acids were prepared from α-methyl diethylmalonate[9] by the malonic ester synthesis[10] with the corresponding alkyl bromide.

α-Phenylbutyric acid and α-phenylpropionic acid were purchased from Norse Labs., Santa Barbara, Calif., U.S.A.

The acids were converted to the amides via the acyl chlorides by treatment with the corresponding amine in the presence of a 10% excess of triethylamine.

Application of Horeau's method[11] for the determination of the configuration to l-menthol

l-Menthol (1.6 mg; 10 μmole), 50 μl of a benzene solution of *d,l*-2-phenylbutyric anhydride (3.1 mg; 10 μmole) and 20 μl of dry pyridine were mixed in a small vial and left for 20 h at room temperature. Water (40 μl) was added and the mixture shaken occasionally for 2 h. After addition of diethyl ether, the heterogeneous mixture was washed twice with 2 ml of 1 *N* hydrochloric acid. The supernatant ether solution was dried over magnesium sulphate, evaporated to dryness and the residue dissolved in 40 μl of dry benezene and treated successively with 5 μl of *tert.*-butylamine and 5 μl of triethylamine. A few drops of ethyl acetate were added after 20 min, the solution was concentrated and a sample chromatographed on a packed column under the conditions given in Fig. 3. The first peak, corresponding to *S*-α-phenylbutyric acid, was markedly larger, as expected.

Gas chromatography

The experiments were carried out with a Varian Aerograph 1200 gas chromatograph equipped with a flame-ionization detector. The stainless-steel capillary columns (400 ft. × 0.02 in. or 150 ft. × 0.02 in.) were cleaned thoroughly[12] and then coated with a 5% solution of the stationary phase in chloroform at 10–15 p.s.i.

A description of the packed column used in some experiments is given in the legend of Fig. 2.

RESULTS AND DISCUSSION

The results are given in Tables I–III and Figs. 1–3.

N-TFA amines

As can be seen in Table I, the highest selectivity was found for phase III, which contains a naphthyl group in its molecule. This solvent is, in general, as efficient* as the carbonylbis-(N-L-valine isopropyl ester) (V)[5] and its homologues[13], which were previously the only phases known to resolve amine derivatives effectively. Solvent III is also much more convenient to prepare and has the further advantage of a lower melting point (96–97°) and higher upper operating temperature (at least 150°). An example of a chromatogram illustrating the excellent separation obtained for a N-TFA-2-amino-*n*-alkane is given in Fig. 1.

The influence of the aromatic system can clearly be seen when comparing

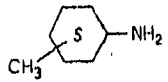
* Comparison with the behaviour on phase V and its homologues is made above the melting point of these solvents.

TABLE I

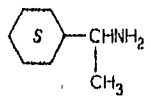
RESOLUTION OF CHIRAL N-TFA-AMINES

Compound	*Optically active stationary phase*											
	N-Lauroyl-S-α-phenylethyl-amine (I) *			*N-Lauroyl-S-α-(1-naphthyl)ethylamine (III)* *						*N-Lauroyl-S-α-(1-decahydronaphthyl)ethylamine (IV)* *		
	120°			*100°*			*130°*			*100°*		
	r(min) **	$r_{S/R}$***	R_s§	*r(min)* **	$r_{S/R}$***	R_s§	*r(min)* **	$r_{S/R}$§***	R_s§	*r(min)* **	$r_{S/R}$***	R_s§
Aliphatic amines, $CH_3CH(NH_2)R$:												
R =												
C_2H_5				25.0 25.0	1.000	—				23.0 23.0	1.000	—
n-C_3H_7				60.0 60.0	1.000	—						
n-C_4H_9	*S* 31.6 *R* 31.0	1.020	0.5	*S* 115.0 *R* 108.8	1.057	0.95	*S* 29.8 *R* 28.8	1.036	0.8	*S* 83.0 *R* 81.6	1.016	0.5
n-C_5H_{11}	*S* 55.8 *R* 54.6	1.022	0.7	*S* 221.5 *R* 210.0	1.055	1.0	*S* 53.7 *R* 51.6	1.040	0.9	*S* 131.2 *R* 128.6	1.020	0.5
n-C_6H_{13}				*S* 432.0 *R* 408.0	1.059	1.0	*S* 96.3 *R* 92.4	1.042	1.0			
$CH_2C^*H(CH_3)CH_2CH_3$				160.3 150.7	1.064	1.0	26.6 25.5	1.041	0.8			
				166.0 160.3	1.035	0.85	27.5 26.6	1.034	0.6			
$CH_2CH_2CH(CH_3)_2$	176.8 173.2	1.020	0.5	172.5 161.6	1.068	1.5	45.3 43.2	1.048	0.8	95.1 92.7	1.025	0.5
$CH_2(CH_2)_2CH(CH_3)_2$	85.8 84.3	1.018	0.3	339.3 319.3	1.063	1.3	48.6 46.8	1.038	0.7			
$CH_2C(CH_3)_3$				115.5 110.0	1.050	0.95	20.7 20.1	1.030	0.2			

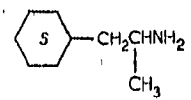
Cyclic saturated amines



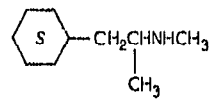
ortho	*trans-*				167.8 164.4	1.021	0.3	37.0 37.0	sh[a]	
	cis-				423.0 411.0	1.028	0.8	77.8 76.3	1.019	0.6
meta	*trans-*				209.0 204.5	1.022	0.5	49.3 48.7	1.012	0.2
	cis-				400.0 388.0	1.029	0.9	81.7 80.0	1.019	0.6



S 52.3 *R* 51.3	1.020 (140°)	0.7	*S* 649.0 *R* 608.0	1.067	2.5	*S* 89.2 *R* 85.2	1.047	0.9

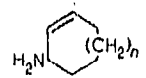


								164.6 156.4	1.052	0.95



								90.7 90.7	1.000	–

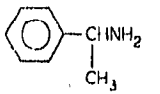
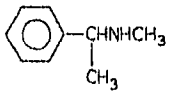
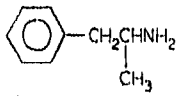
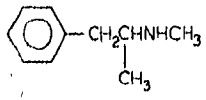
Cyclic unsaturated amines



	r_{III}[a]			r_{III}[a]	
$n = 0$	27.0 26.7	1.011	0.3	42.3 41.3	1.024	0.5
$n = 1$	60.0 ~ 60.0	sh[a]	–	96.0 94.0	1.022	0.8
$n = 2$				(+) 228.7 (–) 220.6	1.037	1.0

(Continued on p. 102)

TABLE I *(continued)*

Compound	*Optically active stationary phase*											
	*N-Lauroyl-S-α-phenylethyl-amine (I)**			*N-Lauroyl-S-α-(1-naphthyl)ethylamine (III)**						*N-Lauroyl-S-α-(1-decahydronaphthyl)ethylamine (IV)**		
	140°			*100°*			*130°*			*100°*		
	*r(min)***	$r_{S/R}$***	R_s§	*r(min)***	$r_{S/R}$***	R_s§	*r(min)***	$r_{S/R}$***	R_s§	*r(min)***	$r_{S/R}$***	R_s§
Aromatic amines												
	*S* 71.25 *R* 68.4	1.042	1.6	*S* 668.0 *R* 597.0	1.119	4.0	*S* 151.0 *R* 138.0	1.094	3.0			
				*S* 346.5 *R* 342.5	1.011							
							~ 150.0 150.0	sh§§	–			
							91.0 91.0	1.000	–			

* Chromatographed on stainless-steel columns of the following dimensions: (I) 400 ft. × 0.02 in. I.D.; (III) 400 ft. × 0.02 in. I.D.; (IV) 400 ft. × 0.02 in. I.D.

** r = corrected retention time.

*** Ratio of the corrected retention times of the *S*-enantiomer over that of the *R*-isomer. Assignment was made for a number of compounds by optically enriched mixtures (retention times marked *S* and *R*, respectively) and for the remainder by extrapolation.

§ Defined in the usual way by the expression $2d/(w_1 + w_2)$.

§§ sh = shoulder.

§§§ Ratio of the corrected retention time of the second peak over that of the first peak.

the data for III with those for its hydrogenated product IV. Thus, the $r_{S/R}$ values for the 2-amino-*n*-alkanes are, respectively, about 1.06 and 1.020. The selectivity is decreased to about the same extent for I, where R = phenyl. Finally, replacement of the benzene ring in I with a cyclohexyl group (II) results in complete loss of selectivity (*e.g.*, 2-amino-*n*-hexane, $r_{S/R} = 1.000$, not shown in Table I).

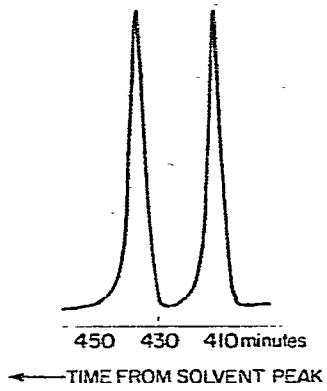


Fig. 1. Resolution of N-TFA-2-amino-*n*-octane. Phase: N-lauroyl-*S*-α-(1-naphthyl)ethylamine (III). coated on a capillary stainless-steel column, 400 ft. × 0.02 in. I.D.; temperature, 100°.

The order of emergence observed on all *S*-monoamide phases is *R*- before the *S*-solute, as on phase V. However, the effects of structural changes are very different for the two types of phases. For example, on V there is a gradual increase in the resolution coefficients ($r_{S/R}$) on lengthening the chain for the 2-amino-*n*-alkanes. In con-

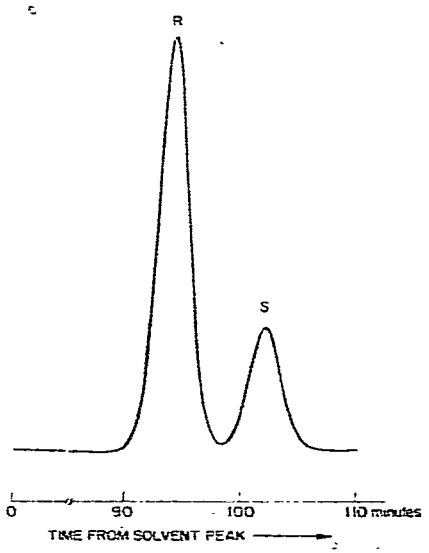


Fig. 2. Resolution of N-TFA-α-phenylethylamine. Phase: N-lauroyl-*S*-α-(1-naphthyl)ethylamine (III), 9% on Chromosorb W, HP. Column: 12 ft. × 1/8 in. I.D.; temperature, 140°.

tradistinction, on III the first two members of the series are not resolved, and for the higher homologues $r_{S/R}$ is about constant (*ca.* 1.06). The cycloolefinic amines are better separated on III than on V ($r_{S/R}$ values greater by about 0.01, although determined at a temperature higher by 10°). Perhaps the most interesting result is that N-TFA-α-phenylethylamine has a very high resolution factor ($r_{S/R} = 1.19$ at 100°; resolved on packed columns, Fig. 2), and that insertion of a methylene group between the asymmetric carbon atom and the benzene ring (amphetamine) leads to almost complete loss of selectivity (shoulder, Table I). Similar observations were made for the carbonylbis-(N-L-α-amino acid esters)*.

As hydrogen bonding is an essential feature of the mechanism of resolution, it is not surprising that the introduction of a methyl group on the nitrogen atom leads to almost complete loss of resolution for N-methyl-N-TFA-α-phenylethylamine ($r_{S/R} = 1.011$, 100°).

N-TFA-amino acid esters

The results obtained for N-TFA-amino acid esters on phase III are given in Table II. As for the amines, the solvent with the naphthyl group (III) shows a higher selectivity than the phenylic phase I (*e.g.*, $r_{L/D}$ for N-TFA-Ala-OMe = 1.025 (I), 1.053 (III); for N-TFA-Ala-O-*i*-Pr = 1.030 (I), 1.042 (III); for N-TFA-Val-OMe = 1.023 (I), 1.054 (III); all at 100°). No separation could be obtained on the hydrogenated phases II and IV for any N-TFA-amino acid ester.

The order of magnitude of the coefficients of resolution, and the fact that also α-methyl-α-amino acid esters are separated on III, illustrate the similarity to phase V[15]. However, as with the amines no systematic relationship between structure and resolution coefficient is apparent in homologous series. Also, branching of the chain of either the alcohol or the alkyl group attached to the asymmetric carbon atom shows irregular effects. Thus, isopropyl esters may have either higher or lower $r_{L/D}$ values compared with normal alcohol esters. The valine derivatives have virtually the same coefficients as those of alanine, whereas the esters of leucine are either badly resolved (O-*n*-Pr, 1.020) or not at all (OMe, OEt, O-*i*-Pr). The reversal of the order of emergence of the N-TFA-amino acid esters depending on the relative size of the alkyl group at the asymmetric carbon atom and the alcohol is a salient feature of the behaviour of phase V, but was not observed for III. Where resolution occurred, the order was always D-before the L-isomer on N-lauroyl-*S*-α-naphthylethylamine.

Proline is a difficult compound to resolve. As it contains a secondary amino function, no hydrogen is available for bonding after acylation, and hence its mechanism of resolution differs from that of amino acids with a primary amino group. On the dipeptide phases[8] and the diamides[3,4], proline is therefore one of the worst resolved amino acids. On phase III, however, the difference is much less pronounced, and the $r_{L/D}$ value of the methyl ester at 100° (1.039) is virtually the same as for the corresponding derivatives of *tert.*-leucine and α-aminobutyric acid.

On the whole, phase III is of little practical interest for the chromatography of α-amino acids, with perhaps the exception of proline. On the other hand, it could

* On a capillary column coated with V, only a shoulder was observed for amphetamine[14]; on packed columns, Lochmüller and Souter[13] did not notice any resolution with V or its homologues, either above or below the melting point of the phases.

be used with advantage for the separation of the enantiomers of α-methyl-α-amino acids, which cannot be resolved on the dipeptide and diamide phases.

α-Alkyl- and α-phenylcarboxylic acids

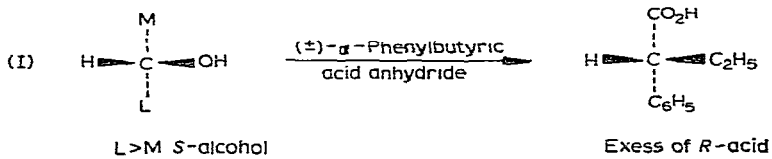
The α-alkyl- and α-phenylcarboxylic acid amides contain an asymmetric carbon atom linked to the carbonyl and not to the NH group as found in the two classes of solutes discussed above. It seemed likely that these compounds would also be separated on the monoamide phases, and we therefore examined derivatives of formula RCH(R')CONHR'', where R = methyl, ethyl or isopentyl, R' = methyl or phenyl and R'' = methyl, isopropyl or *tert.*-butyl.

The first experiments were carried out with phase V. As can be seen in Table III, resolution was obtained for α,δ-dimethylhexanoic acid, and the values for $r_{II/I}$ increased with the bulk of the alkyl group at the nitrogen atom. The *tert.*-butylamide is also the most volatile derivative.

Equally, phases I and III show the selectivity expected. The data available are as yet sparse, but it is noteworthy that α-methylbutyric acid amide is resolved on I but not on III, and that the derivatives of α,δ-dimethylhexanoic acid are best separated on III.

For the aromatic acids, III shows a relatively large selectivity, particularly for α-phenylbutyric acid *tert.*-butylamide ($r_{S/R}$ = 1.090, 130°), which can be separated on packed columns (Fig. 3). The order of emergence is the reverse of that found for the amines, namely *S*- before the *R*-isomer; this finding will be discussed in the following section*.

The ready resolution of the latter acid is of particular interest in connection with the analytical aspects of Horeau's method[11] for the determination of the configuration of secondary, optically active alcohols of structure I:



It has been found that esterification of these alcohols with an excess of racemic α-phenylbutyric acid anhydride leads to a relatively large optical enrichment of the unreacted reagent, with formation of an excess of the *R*-acid for the *S*-alcohol and *vice versa*.

The gas chromatographic determination of the enantiomeric composition of the excess of reagent will permit the Horeau method to be carried out on a microscale. A similar procedure was described by Gilbert and Brooks[16], who converted the excess of acid into a diastereomeric mixture by reaction with α-phenylethylamine. The direct resolution of enantiomers has, however, the advantage that chiral reagents (often of variable optical purity) are not required for derivatization. An example of the procedure as applied to *l*-menthol is given under Experimental.

* It is to be noted that the compounds discussed in this sub-section are the first enantiomers separated by gas chromatography that do not possess an NH group directly linked to the asymmetric carbon atom.

TABLE II

RESOLUTION OF N-TFA-AMINO ACID ESTERS ON N-LAUROYL-*S*-α-(1-NAPHTHYL)ETHYL AMINE (III)*

α-Amino acid	*t* (°C)	*Alcohol residue*							
		Me			*Et*			*n-Pr*	
		*r(min)***	$r_{L/D}$***	R_s§	*r(min)***	$r_{L/D}$***	R_s§	*r(min)***	$r_{L/D}$***
Ala	100	59.7 56.7	1.055	0.95	82.3 78.3	1.052	0.95	157.0 149.0	1.054
	120	28.8 27.6	1.043	0.9	37.5 36.0	1.042	0.9	78.4 75.0	1.045
Val	100	71.1 67.4	1.054	1.0					
	120	33.8 32.5	1.040	0.9					
Leu	100	200.0 ~ 200.0	sh§§	—	270.0 270.0	sh§§	—	549.0 538.0	1.020
	120	75.0 75.0	1.000	—	120.0 120.0	1.000	—		
tert.-Leu	100	59.1 56.5	1.044	0.9					
	130								
Pro	100	203.1 195.5	1.039	0.9					
	130	61.0 59.2	1.028	0.3					
Phenyl–Gly	130								
Phe	130	270.0 270.0	1.000	—					
α-Methyl α-amino acid									
α-Me-*tert.*-Leu	100	82.2 80.7	1.018	0.3					
α-Me-Val	100	72.9 72.3	1.008	—					
α-Me-Leu	100	60.0 60.0	1.000	—					
α-Me-Norleu	100	105.5 102.5	1.029	0.5					
α-Me-Norval	100	62.8 61.7	1.018	0.3					

* See Table I.

** See Table I.

*** Ratio of the corrected retention times of the L-enantiomer over that of the D-isomer. Assignment was made with optically enriched mixtures, except for *tert.*-leucine for which the order of emergence was deduced by extrapolation.

§ See Table I.

§§ sh = shoulder.

i-Pr			*n-Butyl*			*3-n-Pentyl*		
*r(min)***	$r_{L/D}$****	R_s§	*r(min)***	$r_{L/D}$****	R_s§	*r(min)***	$r_{L/D}$****	R_s§
85.6 82.2	1.042	0.9	303.5 288.5	1.052	1.5	86.8 83.0	1.046	1.0
39.2 37.8	1.037	0.9	126.4 120.9	1.045	1.5	37.5 36.0	1.042	1.0
104.3 98.8	1.055	0.9						
36.0 34.5	1.042	0.9						
320.0 320.0	1.000	—	1015.0 990.0	1.025	1.0			
95.0 95.0	1.000	—				80.0 80.0	1.000	—
58.2 56.1	1.034	0.3						
20.3 19.7	1.030	0.6						
170.0 166.0	1.024	0.5						
62.7 61.0	1.027	—						

TABLE III

RESOLUTION OF α-METHYL- AND α-PHENYLCARBOXYLIC ACID AMIDES

Compound	*Optically active stationary phase*							
	N-Lauroyl-S-α-phenylethylamine (I) *			*N-Lauroyl-S-α-(1-naphthyl)ethylamine (III)* *			*Carbonylbis-(N-L-valine isopropyl ester) (V)* *	
	r (min) **	$r_{III/I}$ ***	R_s §	*r (min)* **	$r_{III/I}$ ***	R_s §	*r (min)* **	$r_{III/I}$ ***
Aliphatic acids, $RCHCONHR'$ | CH_3								
$R=CH_3CH_2$ $R'=(CH_3)_3C$	45.0 45.0	1.000 (120°)	—	175.0 175.0	1.000 (100°)	—		
$R=(CH_3)_2CHCH_2CH_2$ $R'=(CH_3)_3C$	76.0 74.1	1.026 (140°)	0.7	119.6 115.3	1.037 (130°)	0.6	47.1 45.1	1.043 (120°)
				756.3 714.0	1.059 (100°)	2.0		
$R'=(CH_3)_2CH$ $R'=CH_3$	149.3 146.2	1.021 (140°)	0.4	230.5 222.7	1.035 (130°)	0.8	98.6 96.3	1.024 (120°)
							147.0 142.9	1.028 (120°)
Aromatic acids $RCHCONHC(CH_3)_3$ | C_6H_5								
$R=CH_3$	*R* 212.5 *S* 205.0	1.036 (130°)	1.5	*R* 352.5 *S* 335.5	1.051 (130°)	1.0		
$R=CH_3CH_2$				*R* 482.0 *S* 441.0	1.093 (130°)	3.0		

* Chromatographed on stainless-steel columns of the following dimensions: (I) 400 ft. × 0.02 in. I.D.; (III) 400 ft. × 0.02 in. I.D.; (V) 150 ft. × 0.02 in. I.D.

** See Table I.

*** Ratio of the corrected retention time of the second peak over that of the first peak.

§ See Table I.

Mechanism of resolution

In order to explain the selective association of enantiomers, such as the N-TFA-α- and -γ-amino acid esters with diamides, we have recently[3,4,17,18] proposed models based on the preferred conformations of the solvents (selectors*) and their

* In this section, "solvent" and "solute" will often be referred to by the equivalent terms "selector" and "selectand"; these are operational definitions first introduced by Mikeš *et al.* (see ref. 19 for a brief comment).

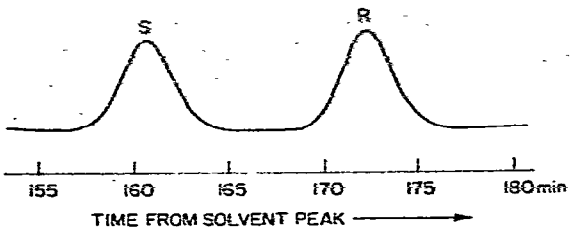


Fig. 3. Resolution of α-phenylbutyric acid *tert.*-butylamide. Chromatographic conditions as in Fig. 2; temperature, 150°.

modes of intermolecular hydrogen bonding. As a result of these considerations, the association between the solute and the solvent has been assumed to resemble the β-pleated sheet structure of peptides. An important aspect of the mechanism proposed is that the crystal structure is retained to a certain extent in the melt through intermolecular hydrogen bonding.

We have tried a similar approach to the interpretation of the present results, limiting ourselves to the strong selective effects observed for aromatic solutes and solvents.

For this purpose, the crystal structure of N-acetyl-α-(1-naphthyl)ethylamine

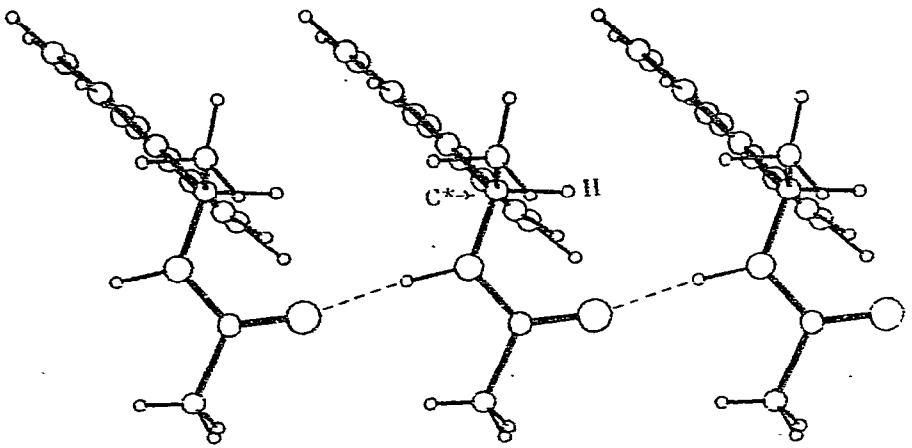
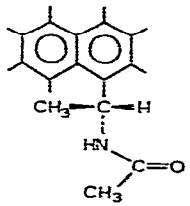


Fig. 4. Projection of hydrogen-bonded molecules of N-acetyl-*R*-α-(1-naphthyl)ethylamine, as arranged



in the crystal. The asymmetric carbon atom (C*) and the hydrogen (H) attached to it are labelled for the middle molecule of the stack.

(VI)* has been determined by X-ray crystallography[20]. Fig. 4 displays the experimentally determined packing arrangement of the molecules of (*R*)-VI along a short 4.9 Å translation axis with the hydrogen-bonded amide groups in the plane of the paper. A particularly relevant feature of the structure is that the hydrogen atom linked to the asymmetric carbon atom fits snugly between two naphthalene rings of the stack. The distance between this hydrogen atom and the nearest ring carbon atom is, in fact, only 2.6 Å, which is less than the sum of the corresponding Van der Waals radii.

A solute such as N-TFA-α-phenylethylamine, when introduced into an excess of solvent molecules, *i.e.*, under the conditions of the gas chromatographic column, will be able to implement fully its potential for hydrogen bond formation and associate with two selector molecules in a fashion similar to that shown in Fig. 4. The selectand could than readily assume a conformation analogous to that of VI in Fig. 4. If its configuration is the same as that of the selector, the chiral carbon atom with its attached hydrogen atom and methyl group, as well as the benzene ring, will replace the corresponding atoms and groups of the middle solvent molecule in the stack. This will lead to a good fit and close association.

The corresponding antipodic solute can also form hydrogen bonds with two selector molecules, but insertion into the stack of solvent molecules, in the same manner as above, will bring about inversion of the positions of the hydrogen atom and the methyl group attached to the asymmetric carbon atom. The placing of the methyl group between the aromatic rings makes stack formation impossible without considerable distortion. In fact, X-ray studies[20] of racemic crystals of VI showed that hydrogen bonding between *S*- and *R*- isomers leads to a looser structure around the hydrogen bond, which means less intermolecular contacts and a lower stability. It is thus understandable that the solute with the configuration opposite to that of the phase is less well retained.

The model of association through intercalation between two selector molecules also explains the reversal of order of emergence for the α-phenylaliphatic acid amides. In these molecules, the chiral atom –CH(R)Ph is attached to the carbonyl and not to the NH group. In order to form hydrogen bonds and, simultaneously, to maximize contacts by intercalation of the benzene between the naphthalene rings of the solvent, the amide groups of selectand and selector cannot be related by translation ("in parallel"), but have to be antiparallel. This arrangement will tend, by necessity, to place the methyl group linked to the chiral carbon between the aromatic rings in the stack, when the selectand and selector have the same configuration. On the other hand, for opposite configurations of solute and solvent, the smaller hydrogen atom will occupy this position. Thus the stability relationships discussed above for the α-phenylethylamine are reversed and, correspondingly, also the order of emergence.

The influence of the nature of the cyclic substitutent of both the selector and selectand molecules can be readily accounted for. The relatively large naphthalene ring system can form a more rigid (close fitting) stack than benzene (I), leading to higher selectivity for an intercalated solute molecule of the correct configuration. On the other hand, hydrogenation of the ring(s), as in II and IV, destroys the flat aromatic structure and makes close contacts more difficult; accordingly, these phases show little or no selectivity. Decrease in the resolution factor of α-cyclohexylethylamine,

* For III, crystals suitable for X-ray studies could not be obtained.

compared with that of α-phenylethylamine, on phase III can be interpreted in a similar manner by a reduction in the strength of the intercalation complex.

Amphetamine cannot form good contacts when inserted into the stack, and should be less well resolved than α-phenylethylamine according to the mechanism proposed. The complete loss of selectivity observed for this aromatic amine may be due to alternative non-selective associations involving the benzene ring of the solute.

The aliphatic amines $CH_3CH(NH_2)R$ show about the same $r_{S/R}$ values as α-cyclohexylethylamine. Here, too, "sandwich" associates of lesser selectivity could account for the resolution mechanism.

The importance of the intercalation-type of association is supported by the data for N-methyl-α-phenylethylamine. This compound can form only one hydrogen bond, and hence the resolution factor is very low. However, the $r_{S/R}$ value is not unity, and this result indicates that also a 1:1 complex with this type of solvent may show selectivity, which could possibly be increased by appropriate structural modifications.

For the amino acid derivatives, it must be remembered that they contain an ester group in addition to the amide function, and association with the selector could, therefore, proceed in a different fashion than for the other solutes studied.

The mechanism proposed should be considered as a working hypothesis only at this stage. The suggestive X-ray evidence must be corroborated by physical studies on association in the liquid state. However, it is gratifying to note that many of the experimental facts observed can be satisfactorily explained by the model used.

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