Journal of Chromatography, 289 (1984) 53–63
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CHROMSYMP. 300

EXTENSION OF THE SCOPE OF GAS CHROMATOGRAPHIC SEPARATION OF ENANTIOMERS ON CHIRAL PHASES

RESOLUTION OF α-HALOGENOCARBOXYLIC ACIDS

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SUMMARY

The present scope of application of chiral hydrogen-bonding gas chromatographic phases to the resolution of various classes of optical isomers is briefly reviewed. A recent extension of this approach to the separation of the enantiomers of α-halogenocarboxylic acids via their *tert.*-butyl amides is then reported. The phases employed were diamides, $R_1CONHCH(R_2)CONHR_3$, derived from L-alanine, L-leucine and L-proline. Best peak resolution was obtained on N-lauroyl-L-proline *tert.*-butylamide. In four cases peak assignment was made, and the order of elution was found to be D- before the L-isomer on L-phases. This behaviour is assumed to be valid for closely related members of the series and can serve for the determination of the configuration of unknowns. The analytical procedures developed are of particular interest for the study of stereospecific reactions involving α-halogenocarboxylic acids.

INTRODUCTION

The application of chiral phases to the chromatographic separation of enantiomers has increased rapidly in recent years, and has led to the introduction of many new procedures. An important aspect of the progress made is the widening of the range of compounds which can be resolved. In the present paper we survey briefly these developments, and then consider in some detail the extension of gas chromatography (GC) on chiral phases to α-halogenocarboxylic acids.

Resolution by chiral phases depends on the formation of diastereomeric complexes between the solute chiral and reagent. If such complexes are formed rapidly and reversibly, and differ sufficiently in their stability constants, separation can be achieved. Depending on the type of interaction occurring in the association process, different classes of compounds or different derivatives of the same compounds can be separated into their enantiomers.

0021-9673/84/$03.00

For instance, hydrogen bonding permits the resolution of α-amino acids via their N-acyl esters by GC on stationary phases, themselves derivatized from α-amino acids[1,2]. On the other hand, coordination to metals, complexed to one or more chiral ligands, leads to highly efficient enantiomer separation of free amino acid[3,4] and their dansyl derivatives[5]. The extension of the scope of resolution by stationary phases containing transition metals coordinated to chiral β-diketones has been reviewed[6], and details on the application of these chiral reagents to underivatized alcohols and ketones were recently given[7].

Another stereoselectively efficient interaction is charge transfer (CT) complexation, which, combined with high-performance liquid chromatography (HPLC), opens up many new possibilities of enantiomer separation. A notable example is the resolution of overcrowded, optically active polyaromatic hydrocarbons, such as the helicenes on 2-(2,4,5,7-tetranitro-9-fluorenylideneaminooxy)propionic acid[8,9]. By incorporating into the stationary phase a chiral charge transfer reagent also capable of hydrogen bonding, such as 2,2,2-trifluoro-1-[(10-methyl)-9-anthryl]ethanol, it is possible to resolve a great variety of compounds, which either contain a CT complexing moiety, *e.g.*, aromatic sulphoxides and lactones, or possess a function through which such a moiety can be introduced, *e.g.*, alcohols, amines, amino alcohols, amino acids, hydroxy acids and esters and mercaptans[10].

In other systems, ionic forces are involved in the intermolecular interactions leading to chiral recognition, as, for instance, in ion-pairing chromatography of underivatized amino alcohols* with (+)-10-camphorsulphonic acid[11].

Many additional examples could be cited to illustrate how by the appropriate choice of the nature of the solute–solvent (more generally, selectand–selector[8]) association and of the chromatographic mode, more and more classes of substances have been brought within the scope of the approach to resolution discussed here. Within the context of this article, however, we limit discussion to the consideration of pertinent developments in GC and to systems in which the solute–solvent interactions occur through hydrogen bonding.

Corresponding phases, studied thus far, are derived from either optically active amines or α-amino acids, and have as an essential structural feature an amide group directly linked to the asymmetric carbon –CONH–C–. The most important examples are: diamides[2,12], $R_1CONHCH(R_2)CONHR_3$; N-acyl-dipeptide esters[13], trifluoroacetic acid (TFA)-NHCH(R)CONHCH(R)CO_2R'; carbonylbis(N-L-amino acid esters) such as $CO[NHCH(iso\text{-}Pr)CO_2(iso\text{-}Pr)]_2$[14] and monoamides, *e.g.*, N-lauroyl-*S*-α-(1-naphthyl)ethylamine[15]. Recently, hydrogen-bonding phases have been developed with multiple dipeptide, tripeptide or diamide moieties, linked covalently to either a central ring system[16] or a polymeric backbone[17–19].

The compounds initially resolved on these phases were amines, amino alcohols and α-, β- and γ-amino acids, containing a primary amine linked, in general, directly** to the asymmetric carbon (for the case of proline, see below). For chromatography, derivatization had to be carried out, with conversion of the amino into an amide function, –CONH–. Resolution is explained by assuming stereoselective hydrogen

* In this case association is further strengthened by hydrogen bonding.

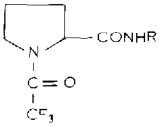
** Resolution of some compounds where the nitrogen is linked to the carbon vicinal to the asymmetric centre has also been reported.

bonding involving the amide groups of both the solute and the solvent. Depending on the particular class of solutes and phases, such associations can be of different types, *e.g.*, hydrogen-bonded ring formation[12,20] or intercalation of a solute between two solvent molecules[15].

A second family of substances resolvable on hydrogen-bonding phases does not intrinsically possess a primary amine, but has a function which can be derivatized to a nitrogen-containing moiety with both an acceptor and a donor site.

TABLE I

COMPOUNDS RESOLVABLE ON HYDROGEN-BONDING PHASES AFTER INTRODUCTION OF A NITROGEN-CONTAINING MOIETY

Compounds	*Derivative chromatographed*	*Phase*	*Ref.*
RCH(X)CO₂H	*Solutes derivatized into amides*		
X = Alkyl or phenyl	RCH(X)CONH(*tert.*-Bu)	Monoamide (Carbonylbis-N-L-valine isopropyl ester)	15, 22 23
X = –NH– as in Pro	 R = iso-Pr	Tripeptide (OA-300)	16
	R = *tert.*-Bu	Diamide (OA-400)	16
		Diamide*	22
X = OH, OAc	$CH_3CH(OH)CONHR$	Dipeptide (OA-200) R Tripeptide (OA-300)	24
	$CH_3CH(OAc)CONHC_6H_{11}$	Diamide (Chirasil-Val)	17
Alcohols	*Solutes with a functional group derivatized into a carbamate*		
Aliphatic, aromatic and monoterpenic	ROCONH(iso-Pr)	Diamide [XE-60-L-Val-(–)-phenylethylamine]	26
α-Hydroxy acids (aliphatic and aromatic)	RCH[OCONH(iso-Pr)]CO_2R' (R' = Me, iso-Pr)		27
β-Hydroxy acids** (aliphatic)	RCH[OCONH(iso-Pr)]CH_2CONH(iso-Pr)		28
*N-Methyl-α-amino acids***	*Solutes with a functional group derivatized into an ureide* iso-PrNHCON(CH_3)CH(R)CONH(iso-Pr)***		28
Ketones (aliphatic, C_5 and C_6 cycloalkanic)	*Solutes with a C=O group derivatized into an oxime* RC=NOH (*syn* plus *anti* isomers)		29

* If not specified, the diamides used were of type $R_1CONHCH(R_2)CONHR_3$, derived from neutral α-amino acids, with R_1, R_3 = alkyl; for details, see references.

** For resolution, the carboxylic acid has, in addition, to be converted into an amide group.

*** This type of derivative may in some cases be of advantage for the resolution of compounds with X = NH_2, *e.g.*, α-methyl-α-amino acids[25].

Successful resolution was first demonstrated for carboxylic acids, $RCH(X)CO_2H$, with X = alkyl or phenyl, after conversion into amides by reaction with either *tert.*-butyl- or isopropylamine[15]. The propensity for stereoselectivity in amide–amide interactions was again demonstrated.

Various types of α-substituted acids, which were separated into enantiomers by this approach, are listed in Table I. It should be noted that in the corresponding derivatives the asymmetric carbon is linked to the carbonyl of the amide and not to the NH group, as in the case of the first family of solutes. A reversal of the elution order may result from this structural change, and a model has been proposed to explain such behaviour on the monoamide type of phases[21].

For proline, where X=–NH–, derivatization to N-TFA esters, as normally practised for α-amino acids, does not leave a hydrogen on the nitrogen of the amide formed. As a result, only very low $r_{L/D}$ values (1.03–1.05) are found. Proline is, in fact, one of the most difficult amino acids to resolve, and on many phases no separation of the enantiomers is possible. On the other hand, when an amide function is introduced through the carboxylic group to form, *e.g.*, N-TFA-Pro-NH(*tert.*-Bu), markedly high chiral recognition is observed[16,22].

Furthermore, α-hydroxy acids can be resolved in the form of their amides, as has been shown for lactic acid (Table I). The alcohol function can remain free (X = OH) or be derivatized into an ester group (X = OAc, where Ac = acetyl).

Derivatives containing a modified amide group, such as $-NHCO_2-$ (carbamates) or –NHCONH– (ureides), also show stereoselective interactions with hydrogen-bonding phases. Such moieties can be introduced through reaction with isocyanates. By this device, N-methylated α-amino acids, alcohols and hydroxy acids have been resolved (Table I). Investigations of the use of isocyanate reagents for improving and extending procedures for the separation of optical isomers, as well as for examining its limitations, are being actively pursued[28].

The last entry in Table I is of special interest. It has recently been demonstrated that ketones can be resolved when converted into oximes. It should be noted that the hydrogen donor in this case is an OH and not an NH group. *Syn* and *anti* isomers form simultaneously on derivatization, and both are resolved. The appearance of four peaks for one pair of enantiomers has both advantages and drawbacks.

Resolution of α-halogenocarboxylic acids

The new data which we present in this article refer to α-substituted acids for which X = Br, Cl. The objective of our work was further to explore the resolution of solutes of type $RCH(X)CO_2H$ via derivatization of the acid to an amide function, and to scrutinize the experimental data for systematic structure–stereoselectivity relationships. Furthermore, it is obvious that novel, convenient and sensitive procedures for the measurement of the optical purity of these substances will contribute to the study of their properties. In particular, such new methods will facilitate the accurate determination of their optical rotation and the degree of retention or inversion of configuration in reactions in which they are formed[31,32] or serve as starting material[33].

EXPERIMENTAL

Materials

The preparation and properties of N-lauroyl-L-alanine *tert.*-butylamide (phase I) and N-lauroyl-L-leucine *tert.*-butylamide (phase II) have been described previously[12]. N-Lauroyl-L-proline *tert.*-butylamide (phase III) and N-docosanoyl-L-leucine *tert.*-butylamide (phase IV) were synthesized by the same procedure as I and II. Phase III: oil; n_D^{25} 1.4719; $[\alpha]_D^{25}$ − 87.2 (*c* 5 in chloroform); optical purity, 99%. Phase IV: m.p. 85–86.5°C; optical purity, 99%.

α-Halogenocarboxylic acids

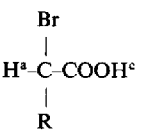
The racemic compounds used were commercial products, whereas the optically pure or enriched samples were prepared from α-amino acids by reaction with potassium bromide (or chloride), sulphuric acid and sodium nitrite. These reagents lead to replacement of the amino by a halogeno group with retention of configuration[32,33]. A typical preparation was a follows[34].

The α-amino acid (0.05 mol) and potassium bromide (0.2 mol) were dissolved in sulphuric acid (0.25 mol). The mixture was cooled in an ice-bath, sodium nitrite (0.1 mol) solution added and after stirring at room temperature for 1 h the mixture was extracted three times with diethyl ether. The ether extract was washed three times with 5% sodium thiosulphate and dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure and the residue further purified by chromatography on silica gel, to which 6% water was added. Elution was started with *n*-hexane and the polarity then gradually increased with ethyl acetate.

D-α-Bromopropanoic acid, D-α-bromoisopentanoic acid, L-α-bromoisohexanoic acid and α-chloroisopentanoic acid enriched in the L-isomer were prepared in

TABLE II

PROPERTIES OF THE OPTICALLY ACTIVE α-BROMOCARBOXYLIC ACIDS SYNTHESIZED



	D-α-*Bromopropanoic* $R = CH_3^b$	D-α-*Bromo-isopentanoic* $R = CH^b(CH_3)_2$	L-α-*Bromoisohexanoic* $R = CH_2^b\,CH(CH_3)_2$
Formula	$C_3H_5BrO_2$	$C_5H_9BrO_2$	$C_6H_{11}BrO_2$
M.p. (°C)	–	42–43	–
n_D^{27}	1.4652	–	1.4640
$[\alpha]_D^{24}$ in $CHCl_3$ (°)	+29.6 (*c* 1.3)	+21.1 (*c* 1)	−56.1 (*c* 1.2)
Optical purity (%)*	96	99.6	92.5
^{1}H-NMR (ppm) H^a	4.40 (q, J = 6.8 Hz)	4.08 (d, J = 7.6 Hz)	4.29 (t, J = 7.5 Hz)
H^b	1.85 (d, J = 6.8 Hz)	2.26 (m)	1.91 (m)
H^c	10.45 (s)	9.47 (s)	9.83 (s)

* Determined by chromatography as the *tert.*-butylamide on phase III, and also on *S*- and *R*-N-lauroyl-α-(1-naphthyl)ethylamine[36].

this manner. The characteristics of the α-bromo compounds are summarized in Table II.

Derivatization

The α-halogenocarboxylic acids were derivatized to amides by one of the following procedures, described in more detail previously[22]: (1) conversion into the acid chloride (at room temperature) followed by reaction with the desired alkylamine (at 0°C); or (2) esterification with N-hydroxysuccinimide and subsequent reaction of the product with an alkylamine (both steps at −5°C to −10°C).

Chromatographic conditions

Stainless-steel capillary columns (for dimensions see footnotes to Table II and Fig. 1) were coated by the plug method with 5 ml of a 5% solution of stationary phase in dichloromethane, under 0.75–0.8 atm N_2. They were mounted in a Varian Series 2700 chromatograph, provided with a splitter and a flame ionization detector. The temperature of the injector and the detector was 240°C; for column temperatures see Table III. The helium flow-rate was 3 ml/min.

RESULTS AND DISCUSSION

The experimental data are presented in Table III and Fig. 1.

For the solutes examined, with the exception of α-chloropropanoic acid on phase II, chiral differentiation was observed on all phases listed. The data in Table III, determined at different temperatures, cover the relatively narrow range of $r_{L/D}$ = 1.017–1.075. For optimal separation, appropriate choice of the column operating temperature is of primary importance. The proline phase (III) gives the best results as far as peak resolution is concerned (Fig. 1), although somewhat higher coefficients are found in a few cases on II.

Comparison of the data for the α-bromo derivatives reveals certain effects of the structure of the phases $R_1CONHCH(R_2)CONHR_3$ on resolution. For the alanine phase (I), where R_2 is small (Me), the coefficients are always less than for II and III. Compared with II, with phase IV decreased $r_{L/D}$ values are obtained, in accord with the "diluting effect"[35] of its longer N-acyl group (N-docosanoyl *versus* N-lau-

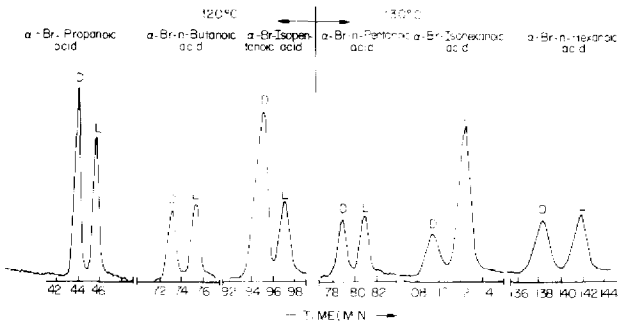


Fig. 1. Chromatograms of *tert.*-butylamides of α-bromocarboxylic acids on N-lauroyl-L-proline *tert.*-butylamide (III). Column: 50 m × 0.55 mm I.D., stainless-steel capillary coated with phase III. The times are given from the solvent peak.

royl). Experiments with diamides derived from phenylalanine and phenylglycine showed that a phenyl group in the substituent R_2 brings about annulment of chiral recognition.

The excellent separations obtained with the proline phases (III) lead to the suggestion that two –CONH– groups in the solvent molecule might not only be unnecessary, but possibly even deleterious by causing peak tailing. Indeed, recent preliminary experiments with a monoamide phase have given very good results[36].

An interesting observation is that on phase I enantiomer separation was observed about 20°C below the melting point of the phase, *i.e.*, at 65°C (Table III). This behaviour is ascribed to supercooling and does not occur when heating the cold column from room temperature to 65°C[37].

The following trends in the influence of the structure of RCH(X)CONHR′ emerge. The effect of changing the nature of R can be assessed for the bromo derivatives. It is seen that the variation in the structure of this substituent is of little consequence. In fact, for a given phase and temperature, the deviation from the average $r_{L/D}$ value of the bromo compounds is, in general, small ($\approx$ 0.002–0.006) and only rarely reaches $\approx$0.01.

As for R′, in one case (α-chloropropanoic acid) derivatives of both the isopropyl- and *tert.*-butylamine were prepared, and it was found that the former gave a much lower resolution coefficient (on I at 90°C: $r_{L/D}$ = 1.018 and 1.047 respectively). Finally, the data for α-chloropropanoic and α-chloroisopentanoic acid, when compared with the corresponding bromo compounds, show that there is a decrease in stereoselectivity as the size of the halogen atom decreases. In keeping with this behaviour, attempts to resolve an α-fluorocarboxylic acid through its amide failed under the experimental conditions.

In summary, diamide phases I–IV have been found suitable for the resolution of α-bromo- and α-chlorocarboxylic acids derivatized to amides. It expected that phases of the same type, including polymeric ones, will give analogous results. However, it should also be pointed out that these derivatives, which apart from –CONH– do not possess another appropriately placed hydrogen-bond receptor, do not belong to the classes of solutes which show highest chiral recognition on diamides. As mentioned in the discussion of the behaviour of the proline phase (III), resolution on other types of phases for the enantiomeric analysis of α-halogenocarboxylic acids is being pursued.

Applications

Determination of configuration. In four cases (Table III), peak assignment was made by injection of samples enriched in one enantiomer of known configuration. The order of elution found was always L- after the D-isomer on the L-phases. Based on relevant experience in other systems involving hydrogen-bonding chiral solutes and solvents[1,2,12,15,17], it was concluded that this behaviour is generally valid in the series studied. Obviously, caution has to be exercised when making predictions for structures which differ greatly from that of the reference compounds. Until more experimental assignments have been made, application of this rule is, therefore, recommended only where R = alkyl (see the case of α-chlorophenylacetic acid, Table III).

The chromatographic method of configurational assignment has the advantage

TABLE III

GC RESOLUTION OF α-HALOGENOCARBOXYLIC ACIDS ON CHIRAL DIAMIDE STATIONARY PHASES

Phases: N-lauroyl *tert.*-butylamides of alanine (I), leucine (II), proline (III) and N-docosanoyl-L-leucine *tert.*-butylamide (IV); I and II coated on stainless-steel capillary columns (33 m × 0.5 mm I.D.), as were III and IV (50 m × 0.5 mm I.D.). r = Retention time (minutes) corrected for the dead volume. $r_{L/D}$ = resolution factor = ratio of the corrected retention time of the L- to that of the D-enantiomer. Where peak assignment could not be made, the symbol used is $r_{II/I}$.

α-Bromo tert.-butylamide of		*I*			*II*			*III*			*IV*		
		r	$r_{L/D}$	*T*(°C)	r	$r_{L/D}$	*T*(°C)	r	$r_{L/D}$	*T*(°C)	r	$r_{L/D}$	*T*(°C)
Propanoic acid*	D	55.00	1.075	65		–		61.80	1.047	110	17.68	1.026	90
	L	59.10						71.30			18.14		
	D	20.00	1.055	90		–		44.30	1.041	120	8.60	1.023	110
	L	21.10						46.12			8.80	(shoulder)	
	D	12.24	1.046	100	10.40	1.029	130		–			–	
	L	12.80			10.70								
	D	10.90	1.031	110	9.00	1.022	140		–			–	
	L	11.44			9.20								
n-Butanoic acid**	D	36.80	1.042	90		–			–		33.60	1.034	90
	L	38.34									34.76		
	D	21.40	1.035	100	18.00	1.031	120	73.40	1.030	120	15.86	1.025	110
	L	22.14			18.56			75.64			16.26		
	D	16.10	1.029	110	17.20	1.035	130		–			–	
	L	16.56			17.80								
	D		–		13.40	1.033	140		–			–	
	L				13.84								
Isopentanoic acid*	D	49.30	1.039	90		–		144.70	1.032	110	21.60	1.038	110
	L	51.20						148.90			22.46		
	D	29.26	1.036	100	25.40	1.043	120	95.24	1.022	120		–	
	L	30.10			26.50			97.30					
	D	21.50	1.034	110	23.70	1.050	130	59.14	1.023	130		–	
	L	22.24			24.88			60.60					
	D		–		18.24	1.047	140		–			–	
	L				19.10								

n-Pentanoic acid**	D	68.20	1.044	90		–			–		26.60	1.030	110
	L	71.20									27.40		
	D	38.56	1.037	100	30.54	1.033	120		–			–	
	L	40.00			31.54								
	D		–		21.90	1.034	140	78.90	1.025	130		–	
	L				22.64			80.90					
Isohexanoic acid*	D	50.60	1.047	100	40.40	1.050	120		–			–	
	L	53.00			42.40								
	D	34.10	1.038	110	36.60	1.055	130	109.50	1.029	130		–	
	L	35.40			38.60			112.70					
	D		–		30.40	1.038	140	71.40	1.022	140		–	
	L				31.50			73.00					
n-Hexanoic acid**	D	72.60	1.034	100	53.00	1.038	120		–		50.00	1.029	110
	L	75.10			55.00						51.46		
	D	45.00	1.032	110	47.20	1.042	130	138.12	1.026	130		–	
	L	46.40			49.20			141.70					
	D		–		38.46	1.037	140	90.00	1.024	140		–	
	L				39.90			92.22					
α-Chloro tert.-butyl-amide of													
Propanoic acid**	D	23.14	1.050	65		–			–			–	
	L	24.30											
	D	12.28	1.051	80	26.24	1.000	80		–			–	
	L	12.90			26.24								
	D	9.00	1.047	90		–			–			–	
	L	9.42											
	D	6.50	1.030	100		–		26.66	1.029	110		–	
	L	6.70						27.44					
Isopentanoic acid*	D		–			–		44.00	1.018	130		–	
	L							44.74					
α-Phenylacetic*** acid	I	71.88	1.018	140		–			–			–	
	II	73.16											

* Peak assignment made by injection of optically enriched samples.
** Assignment made by extrapolation.
*** Assignment not yet made (see text).

that it requires only minute amounts of material; a sample of the racemic compound is, of course, necessary for coinjection with pure enantiomers. Such correlations will increase confidence in assignments made in other ways, as, *e.g.*, by the empirical rule that "α-amino and corresponding α-bromo acids are of the same configuration, when having opposite signs of rotation"[38].

Stereospecific reactions involving α-halogenocarboxylic acids. The stereospecific replacement of an α-amino by a halogeno group, which proceeds with retention of configuration, has received renewed attention in recent years[39]. Four compounds were prepared in the course of the present research by this reaction (Experimental), and the degree of stereospecificity obtained was measured for three α-bromocarboxylic acids (Table II) by enantiomeric analysis of the products. For D-α-isopentanoic acid, synthesized from D-valine, almost 100% retention was observed, whereas for D-α-bromopropanoic acid (ex D-alanine) and L-α-bromoisohexanoic acid (ex L-leucine) the optical purity was only 96% and 92.5%, respectively. These deviations from complete retention could be due to the reaction conditions, or to the effect of the substituent R. However, it has still to be established that no racemization occurred in the derivatization of the α-bromocarboxylic acids, $RCHBrCO_2H$, to amides. The data illustrate the contribution which the analytical procedures developed could make to the study of the stereospecific reactions involving α-halogenocarboxylic acids.

CONCLUSIONS

In recent years it has been demonstrated on more and more examples that a nitrogen function in the solute is not a condition *sine qua non* for resolution. Pertinent published reports deal almost exclusively with substances containing one or more alcohol groups, which may or may not be derivatized. Compounds resolved without protecting the alcohol function include some aromatic alcohols[40] (on OA-350 and OA-400, see Table I), menthol[41] (on a monoamide phase), lactate esters[24] (on OA-200 and OA-400) and a whole series of α-hydroxy esters[30] on Chirasil-Val coated on fused-silica capillaries. The contribution of the free hydroxy group to hydrogen bonding with the solvent plays an important rôle in the resolution process[24]. However, it has also been shown that when only hydrogen-bond receptors are present in the solute, stereoselective interaction with the hydrogen-bonding phases also occurs. Thus, aromatic diols[17] and sugars[42] were separated into their enantiomers, when converted into perfluoroacyl derivatives. It is noteworthy that in the case of the trifluoroacyl-β-pyranoside of mannose, a resolution coefficient as high as 1.247 [at 130°C on XE-60–L-valine-(−)-phenylethylamide] was obtained[42].

Many other variants of solute–solvent interactions remain to be investigated, and it is expected that a further extension of the scope of application of hydrogen-bonding phases will result from such work.

ACKNOWLEDGEMENT

S-C. C. thanks the Chung-Shan Institute of Science and Technology, Taiwan, for the grant of a scholarship.

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