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RESOLUTION OF α-HALOGENOCARBOXYLIC ACIDS BY GAS CHROMATOGRAPHY ON (*R*)-N-LAUROYL-α-(1-NAPHTHYL)ETHYLAMINE

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SUMMARY

α-Fluoro-, α-chloro and α-bromo C_3–C_6 carboxylic acids were separated efficiently into their enantiomers, after conversion into *tert.*-butylamides, on a whisker-walled glass capillary column (40 m × 3.5 mm I.D.) coated with (*R*)-N-lauroyl-α-(1-naphthyl)ethylamine. The resolution coefficients (α) of the derivatives of the α-F, α-Cl and α-Br acids were 1.04, 1.05–1.08 and 1.08–1.13, respectively, at 100°C. The retention indices (*I*) and differential Gibb's free energies of solution $\Delta(\Delta G)$ were calculated and both were found to increase for the acids in the order F < Cl < Br, i.e. in the same order as the C–X covalent radii. The order of emergence was found to be *R*- after the *S*-solute on the *R*-phase. An intercalation model to interpret the stereoselective solute-solvent interactions is proposed.

INTRODUCTION

Recently, the characteristics of chiral diamide stationary phases, $R_1CONHCH(R_2)CONHR_3$, in which R_2 varied, was reported[1,2]. In the course of this investigation, α-halogenocarboxylic acids, the resolution of which had not been examined before, received special attention[3].

Hydrogen bonding between α-halogeno acids and the above diamides is obviously of an entirely different type than the interaction assumed to occur with α-amino acid derivatives, which are of particularly high stereoselectivity on these phases (see Fig. 1).

In fact, lower resolution coefficients were observed for the α-halo acids than the α-amino derivatives. Further, it was found that N-lauroyl-(*S*)-proline-*tert.*-butylamide, which is not a typical diamide of the above type as it does not possess a CONH group, gave the best results. Nearly baseline separation was achieved for many of the solutes examined with this phase.

For solutes that possess only the CONH group, capable of hydrogen donating and accepting, the monoamide phases, such as N-lauroyl-(*R*)-α-(1-naphthyl)ethylamine (I)[4], are particularly suitable. This has been demonstrated[4] by the good resolution obtained on these phases for solutes such as N-TFA-(±)-α-phenylethylamine and N-TFA-(±)-α-phenylpropanoic and -*n*-butanoic acid amides, and to a lesser extent

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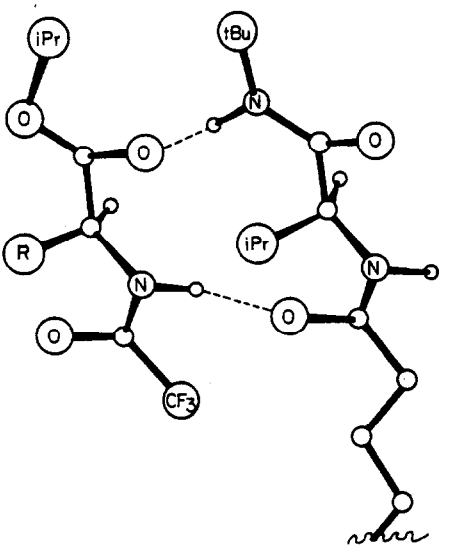


Fig. 1. "C_5–C_7" hydrogen-bonded ring between N-TFA-(*S*)-α-amino acid isopropyl ester and N-lauroyl-(*S*)-valine-*tert.*-butylamide.

for corresponding aliphatic derivatives. The mechanism of the resolution in these instances is assumed to involve an intercalation complex, as shown in Fig. 2.

As the α-halogenocarboxylic acid amides have a structure that to a great extent is analogous to that of the latter solutes, the study of their behaviour on phase I seemed promising. We report here the results obtained with a whisker-walled glass capillary column, coated with I, for a series of α-fluoro, α-chloro and α-bromo aliphatic carboxylic acids, derivatized to their *tert.*-butylamides.

EXPERIMENTAL

Gas chromatography

A Varian Aerograph Model 1200 gas chromatograph equipped with a flame-ionization detector was slightly modified to accommodate the glass capillary columns.

Whisker-walled glass capillary column. The whisker-walled glass capillary columns were prepared by the method reported previously[3,5]. The column was washed with acetone and dichloromethane and dried with nitrogen. Coating was performed with 10–15% solutions of N-lauroyl-(*R*)-α-(1-naphthyl)ethylamine (I) by the dynamic method. Before sample injection the column was preconditioned for 1 day at 160°C. The dimensions were 40 m × 0.35 mm I.D. for analysis of α-halogenocarboxylic acid and 7 m × 0.35 mm I.D. for optical purity analysis of phase I.

N-Lauroyl-(R)-α-(1-naphthyl)ethylamine. The stationary phase was available in the laboratory[4]. The optical purity of the solvent was checked as follows. The phase was hydrolysed in 6 *N* hydrochloric acid at 110°C for 4 h and, after removing the solvent, α-(1-naphthyl)ethylamine was derivatised with trifluoroacetic anhydride for 1 h at room temperature. The N-TFA derivative was injected onto the *R*-phase

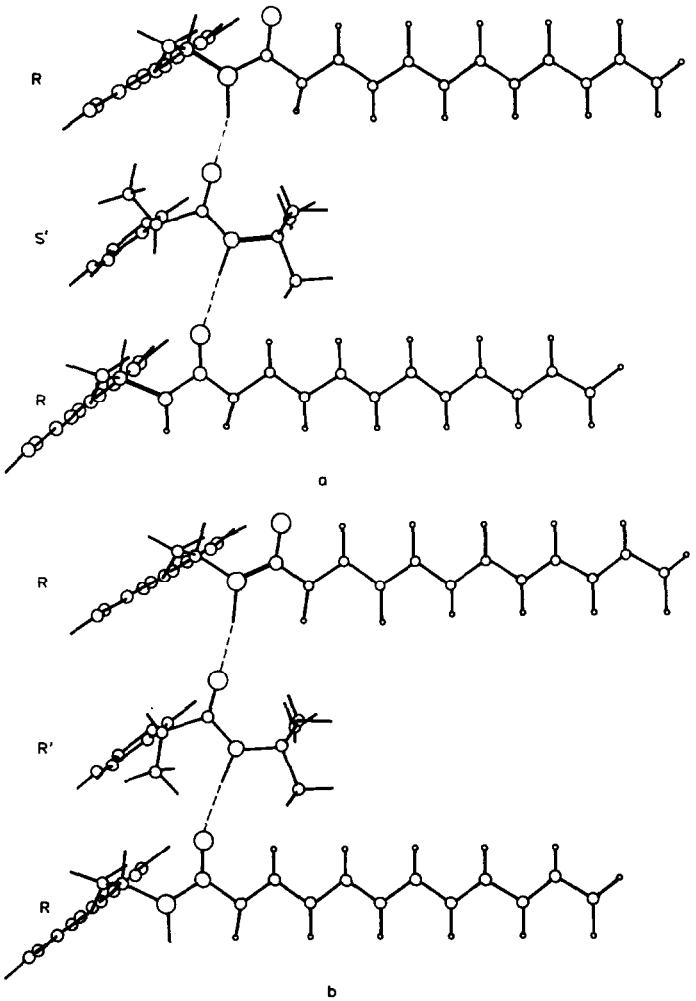


Fig. 2. Intercalation complexes of a molecule of α-phenylpropionic acid *tert.*-butylamide, of configuration *S* or *R* (labelled S' and R'), inserted in to a hydrogen-bonded stack of N-lauroyl-(*R*)-α-(1-naphthyl)ethylamine. (a) RS'R; (b) RR'R. It is found that, when an α-phenylcarboxylic acid amide is the solute, the (*R*-solvent)-(*S*-solute)-(*R*-solvent) combination is the most stable, and the *S*-solute is more strongly retained by the stationary phase.

whisker-walled glass capillary column and the peak areas were measured. The optical purity found was 99%.

Reproducibility of the retention measurements. Table I, which gives the data for eleven experiments, shows a narrow spread from the mean values. For the retention time the standard deviation was 0.05–0.067 min, and for the resolution coefficient (α) 0.002 unit. The coefficients of variation (CV) were 0.50% and 0.35% for the L- and the D-isomers, respectively, and for the resolution coefficient (α) the CV was 0.20%.

TABLE I

REPRODUCIBILITY OF RETENTION DATA

Sample: α-chloropropanoic acid *tert.*-butylamide at 115°C.

Run	*Retention time (min)*		*Resolution coefficient*
	S-isomer	*R-isomer*	
1	13.32	14.22	1.06_8
2	13.28	14.20	1.06_9
3	13.30	14.20	1.06_8
4	13.24	14.16	1.06_9
5	13.34	14.22	1.06_6
6	13.38	14.24	1.06_4
7	13.24	14.16	1.06_9
8	13.22	14.14	1.07_0
9	13.20	14.14	1.07_1
10	13.14	14.08	1.07_1
11	13.22	14.12	1.06_8
Average	13.26	14.18	1.06_8
Standard deviation*	0.067	0.050	0.002
CV (%)	0.50	0.35	0.20

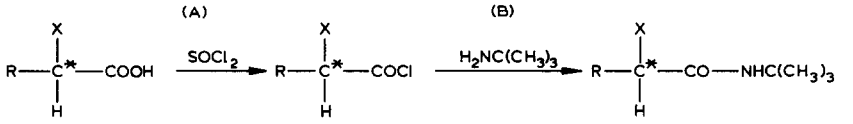
$$* \quad \sigma_{n-1} = \frac{\sqrt{\Sigma (x_i - \bar{x})^2}}{n - 1}$$

α-Halogenocarboxylic acids

The racemic α-bromo and α-chloro compounds were commercial products available as the free acids, whereas (±)-α-fluoroisopentanoic acid was obtained from the commercial ethyl ester by saponification. The optically pure or enriched samples of the α-Cl and α-Br acids were synthesized from optically pure α-amino acids by reaction with potassium bromide (or chloride), sulphuric acid and sodium nitrite according to Izumiya and Nagamatsu[6] (see also ref. 3). Some of the optically active α-chloro acids were prepared in the laboratory of Prof. V. F. Schurig, University of Tubingen, F.R.G. The optically active α-fluorobutanoic acid was obtained by enzymatic hydrogenation of the corresponding α,β-unsaturated α-fluoro acid, and was a gift from Prof. H. Simon of the Technische Universität München, F.R.G.

Derivatization

The halogenocarboxylic acids were derivatized for chromatography in two steps:



For α-bromoisopentanoic acid as an example, the detailed procedure was as follows.

Step A: thionyl chloride dissolved in diethyl ether was cooled in an ice- or

water-bath. α-Bromo acid in diethyl ether was dropped into the thionyl chloride solution and stirred for 1 h, then the ether was removed using a vacuum pump.

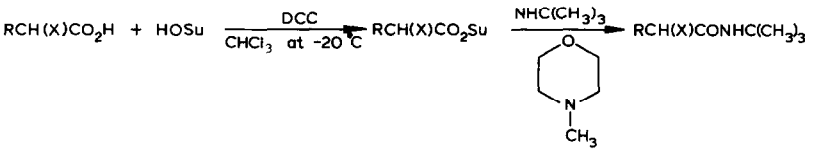
Step B: α-bromoisopentanoyl chloride in diethyl ether was cooled in water, ice, etc., according to the temperature desired. A diethyl ether solution of *tert.*-butylamine was added in one portion or dropwise and the mixture was stirred at various temperatures (−20, −10, 0 or +20°C). The solvent was removed and the residue taken up in diethyl ether. The solution was filtered to remove *tert.*-butylamine hydrochloride salt. After again removing the solvent, the α-bromoisopentanoic acid *tert.*-butylamide formed was dissolved in dichloromethane for injection into the chromatograph.

Derivatization by steps A and B may involve some racemization and we therefore examined the influence of the various reaction conditions. The experiments were carried out with (*R*)-α-bromoisopentanoic acid, which preliminary tests had shown to possess an optical purity of 99–100%.

In step A an increase in temperature from 0 to 20°C, under otherwise similar conditions (including the addition of a 1% solution of *tert.*-butylamine at 0°C in step B) did not change the results (optical purity 99% at 0°C and 98.8% at 20°C). On the other hand, in step B the same change in temperature gave optical purities differing by 0.8% (99.0% at 0°C and 98.2% at 20°C); at −10°C the optical purity was 99.26%. Further, it was found that an excess of *tert.*-butylamine can cause racemization (5% base gave, *e.g.*, an optical purity of 76.6% at room temperature).

Hence the conditions chosen for derivatization were as above, but maintaining the following conditions: for step A, 0°C (and use of a 2% solution of thionyl chloride, reaction time 1 h), and for step B, 0 to −10°C and dropwise introduction of a 2% solution of *tert.*-butylamine in the course of 1 h. Under these conditions the optical purity measured for (*R*)-α-Br-isopentanoic acid was 99.32%. Much of the L-isomer found is to be ascribed to a stereochemical leak during the synthesis from the corresponding amino acid[3,6], or even to some enantiomeric impurity in the starting material.

For many purposes, a maximum amount of 0.5% of antipode introduced by the derivatization procedure will not interfere with the analytical objective. Where the amount of racemization must be further reduced, an alternative procedure should be tried[3], *e.g.*



where Su = succinimide and DCC = dicyclohexyl dicarbodiimide.

RESULTS AND DISCUSSION

The experimental data and the parameters derived from them are given in Tables II–IV. The resolution coefficients (α) of the enantiomers (Table II) were calculated from the capacity ratios given in Table III. The magnitude of the α values for the α-fluoro, α-chloro and α-bromo acids were 1.04, 1.05–1.08 and 1.08–1.13,

TABLE II

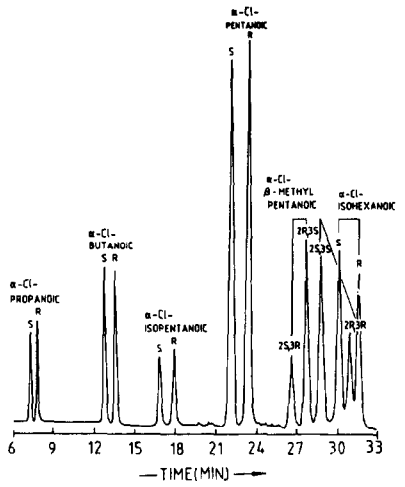
RESOLUTION COEFFICIENTS OF α-HALOGENOCARBOXYLIC ACID *tert.*-BUTYLAMIDES ON N-LAUROYL-(*R*)-α-(1-NAPHTHYL)ETHYLAMINE AT 100–150°C

The resolution coefficient is defined as the ratio of the retention time (corrected for dead volume) of the second peak to that of the first peak.

tert.-Butylamide	*100°C*	*110°C*	*120°C*	*130°C*	*140°C*	*150°C*
α-Br-propanoic acid	1.13_4	1.09_7	1.08_6	1.07_4	1.06_7	1.05_5
α-Br-butanoic acid	1.10_9	1.09_2	1.08_0	1.07_3	1.06_2	1.05_4
α-Br-isopentanoic acid	1.09_5	1.08_3	1.07_4	1.06_6	1.05_9	1.05_4
α-Br-*n*-pentanoic acid	1.08_8	1.08_1	1.07_1	1.06_1	1.05_6	1.04_8
α-Br-isohexanoic acid	–	–	1.04_7	1.04_4	–	1.03_6
α-Cl-propanoic acid	1.07_2	1.07_3	1.06_3	1.06_1	1.05_1	1.04_7
α-Cl-butanoic acid	1.07_8	1.06_6	1.06_4	1.05_6	1.05_0	1.04_5
α-Cl-isopentanoic acid	1.07_7	1.06_8	1.06_4	1.06_1	1.04_8	1.04_0
α-Cl-*n*-pentanoic acid	1.07_3	1.06_5	1.06_0	1.05_2	1.04_9	1.04_2
α-Cl-β-methylpentanoic acid*	1.05_0	1.04_7	1.04_1	1.03_6	1.03_4	1.02_7
α-Cl-β-methylpentanoic acid**	1.09_2	1.08_3	1.07_4	1.07_1	1.06_1	1.04_6
α-Cl-isohexanoic acid*	1.05_8	1.05_1	1.04_7	1.04_1	1.03_8	1.04_1
α-F-butanoic acid	1.03_8	–	–	–	–	–
α-F-isopentanoic acid	1.04_5	–	–	–	–	–

* Derivatized from alloisoleucine.
** Derivatized from isoleucine.

respectively, at 110°C. They are significantly higher than those obtained on the diamide phases, including N-lauroyl-(*S*)-proline-*tert.*-butylamide[3]. On the whisker-walled glass capillary column baseline separation could be obtained for all compounds (Figs. 3–5), except the α-fluoro acid derivative (Fig. 6). It should be pointed out that on the



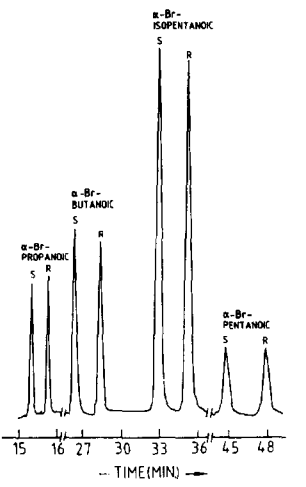


Fig. 3. Chromatogram of α-chlorocarboxylic acid *tert.*-butylamides on phase I at 115°C.

Fig. 4. Chromatogram of α-bromocarboxylic acid *tert.*-butylamides on phase I at 115°C.

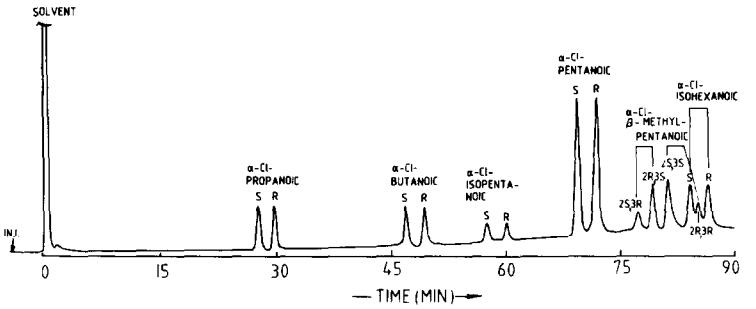


Fig. 5. Chromatogram of α-chlorocarboxylic acid *tert.*-butylamides on phase I by using temperature programming: 100°C for 20 min, increased at 2°C/min to 130°C.

diamide phases only partial separation of the enantiomers of α-chlorocarboxylic acids and no separation of α-fluorocarboxylic acids were obtained.

On phase I, a sample of α-fluorobutanoic acid, obtained by enzymatic reduction of the corresponding α,β-unsaturated α-fluoro acid was found to have an optical purity of only about 20%. This has been ascribed to the use of an enzyme preparation that contained simultaneously an *R*- and an *S*-orienting hydrogenase[7].

Temperature programming can improve the separation still further for some of the compounds, as seen in Fig. 5. For the mixture of the amides of α-chloro-β-methylpentanoic and α-chloroisohexanoic acid, which may be present simultaneously in certain samples, overlap may occur between the (2*R*,3*R*)-α-chloroβ-methylpentanoic and (*R*)-α-chloroisohexanoic acid amides above 120°C and, on the other hand, with the (*S*)-α-chloroisohexanoic acid amide isomer below 110°C. A temperature of 115°C was found to be the best compromise for the separation of this mixture (Fig. 3).

As generally found, the retention times and resolution coefficients decrease with increase in the temperature for α-chlorocarboxylic and α-bromocarboxylic acids

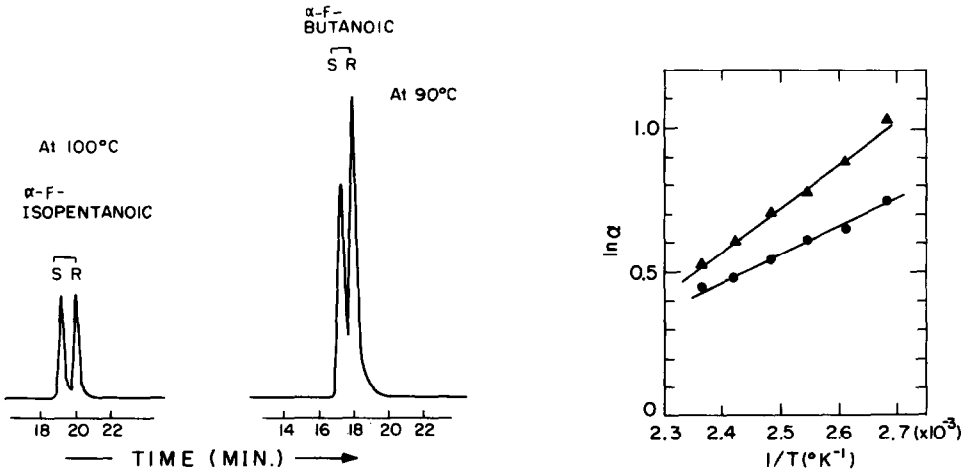


Fig. 6. Chromatograms of α-fluorobutanoic and isopentanoic acid *tert.*-butylamides on phase I.

Fig. 7. Plot of the logarithmic resolution coefficient of α-chloro- and α-bromo-*n*-butanoic acid *tert.*-butylamides *versus* 1/*T*.

TABLE III

CAPACITY RATIOS (k') AND RETENTION INDICES (I) FOR α-HALOGENOCARBOXYLIC ACID *tert.*-BUTYLAMIDES AT VARIOUS TEMPERATURES

*tert.-Butylamide**	*Isomer*	*k'***						*I*					
		100°C	*110°C*	*120°C*	*130°C*	*140°C*	*150°C*	*100°C*	*110°C*	*120°C*	*130°C*	*140°C*	*150°C*
α-Cl-propanoic acid	*S*	8.75	5.26	3.84	2.72	1.83	1.38	1257	1264	1257	1263	1268	1268
	R	9.38	5.64	4.08	2.89	1.92	1.45	1266	1275	1267	1271	1278	1277
α-Cl-butanoic acid***	*S*	16.02	9.33	6.60	4.59	2.97	2.09	1344	1353	1347	1353	1357	1355
	R	17.28	9.94	7.02	4.84	3.12	2.27	1356	1365	1356	1363	1366	1364
α-Cl-isopentanoic acid	*S*	21.58	12.40	8.74	5.97	3.83	2.79	1388	1394	1392	1399	1403	1403
	R	23.24	13.24	9.30	6.33	4.01	2.90	1400	1405	1402	1409	1412	1411
α-Cl-*n*-pentanoic acid***	*S*	29.93	16.71	11.50	7.75	4.86	3.46	1436	1441	1437	1444	1446	1444
	R	32.12	17.79	12.90	8.14	5.10	3.61	1447	1451	1447	1453	1455	1454
α-Cl-β-methylpentanoic acid§	2*S*, 3*R*	35.49	19.96	13.87	9.32	5.89	4.24	1462	1471	1467	1476	1483	1484
	2*R*, 3*S*	37.26	20.90	14.44	9.67	6.10	4.36	1469	1476	1473	1483	1487	1491
α-Cl-β-methylpentanoic acid§§	2*S*, 3*S*	39.68	21.96	15.02	9.96	6.23	4.46	1478	1484	1481	1487	1493	1495
	2*R*, 3*R*	43.34	23.79	16.13	10.67	6.61	4.62	1492	1496	1493	1494	1503	1503

α-Cl-isohexanoic	*S*	43.34	24.48	15.77	10.33	6.37	4.46	1492	1491	1487	1489	1496	1495
acid	*R*	56.86	24.67	16.51	10.75	6.61	4.64	1499	1501	1498	1495	1503	1506
α-Br-propanoic	*S*	23.18	13.01	9.24	6.22	3.93	2.83	1398	1403	1400	1405	1409	1407
acid	*R*	26.29	14.27	10.03	6.68	4.19	2.99	1416	1415	1414	1416	1419	1418
α-Br-butanoic	*S*	41.83	22.63	15.57	10.17	6.25	4.38	1484	1487	1487	1493	1494	1493
acid***	*R*	46.38	24.72	16.81	10.91	6.64	4.61	1503	1502	1501	1504	1504	1502
α-Br-isopentanoic	*S*	52.47	28.39	19.35	12.60	7.69	5.36	1517	1523	1523	1527	1534	1517
acid	*R*	57.47	30.75	29.78	13.43	8.14	5.67	1534	1535	1534	1541	1541	1542
α-Br-*n*-pentanoic	*S*	78.47	40.89	26.95	17.09	10.20	6.94	1578	1577	1577	1583	1582	1577
acid***	*R*	85.45	44.20	30.96	18.14	10.77	7.28	1592	1592	1588	1595	1592	1586
α-Br-isohexanoic	*S*	–	–	37.36	22.99	–	8.53	–	–	1632	1634	–	1619
acid	*R*	–	–	39.12	24.04	–	8.84	–	–	1639	1641	–	1624

* Peak assignment made by comparison with optically active samples of known configuration, except those marked***.
** $k' = t_x - t_0$, where t_x = net retention time and t_0 = retention time corresponding to dead volume of column.
*** Peak assignment by extrapolation.
§ Derivatized from alloisoleucine.
§§ Derivatized from isoleucine.

TABLE IV

DIFFERENTIAL GIBBS' FREE ENERGIES OF SOLUTION, $-\Delta(\Delta G)$, OF ENANTIOMERS OF α-HALOGENOCARBOXYLIC ACID *tert.*-BUTYLAMIDES IN PHASE I

$-\Delta(\Delta G) = RT \ln \alpha$.

tert.-Butylamide	$-\Delta(\Delta G)$ *(cal/mole)*					
	100°C	*110°C*	*120°C*	*130°C*	*140°C*	*150°C*
α-Br-propanoic acid	93.2	70.5	64.5	57.2	53.2	45.2
α-Br-*n*-butanoic acid	76.7	67.0	60.1	56.4	49.4	44.2
α-Br-isopentanoic acid	67.3	60.7	55.8	51.2	47.1	44.2
α-Br-*n*-pentanoic acid	62.5	59.3	53.6	47.4	44.7	39.4
α-Br-isohexanoic acid	–	–	35.9	34.5	–	29.8
α-Cl-propanoic acid	51.5	53.6	47.7	47.7	40.8	38.6
α-Cl-*n*-butanoic acid	55.7	48.7	48.5	42.9	40.1	37.0
α-Cl-isopentanoic acid	55.0	50.1	48.5	47.4	38.5	33.0
α-Cl-*n*-pentanoic acid	52.2	53.6	45.5	40.6	39.5	34.6
α-Cl-β-methylpentanoic acid*	36.2	35.0	31.4	28.3	27.4	22.4
α-Cl-β-methylpentanoic acid**	62.3	60.7	55.8	54.9	48.6	37.8
α-Cl-isohexanoic acid	41.8	37.8	35.9	31.4	30.6	33.8
α-F-*n*-butanoic acid	27.7	–	–	–	–	–
α-F-isopentanoic acid	32.6	–	–	–	–	–

* Derivatized from alloisoleucine.
** Derivatized from isoleucine.

(Tables II and III). Typical plots for α-chloro- and α-bromobutanoic acids of ln α *versus* $1/T$ is nearly linear, as shown in Fig. 7.

The retention indices for the solutes examined are given in Table III. Between 110 and 150°C, the values are almost constant, so that they can serve well for structural correlations. Retention indices increase, as expected, by about 100, on passing to the next homologue, *e.g.*, from α-chloropropanoic to α-chlorobutanoic acid and from α-bromoisopentanoic to α-bromoisohexanoic acid. The nature of the halogen influences the retention index as follows: on replacing chlorine with bromine, the retention index increases by about 140, and on replacing fluorine with chlorine, the increase is still larger and amounts to 215 for butanoic acid and to about 180 for isopentanoic acid.

The Gibbs' free energies of solution for the various solutes in the *R*-phase were calculated by the equation $-\Delta(\Delta G) = RT \ln \alpha$, and are listed in Table IV. With increase in temperature, the values decrease owing to the decrease in α.

There is a marked difference in the magnitude of the $-\Delta(\Delta G)$ values for the different halo substituents. As can be seen by comparing the *n*-butanoic acid derivatives at 100°C, $-\Delta(\Delta G)$ was 27.7, 55.7 and 76.7 cal/mole for the α-F, α-Cl and α-Br derivatives, respectively. For isopentanoic acid the respective values were 32.6, 55.0 and 67.3 cal/mole. However, as the temperature increased, these differences became less and less pronounced, as can be seen by examining the data for the α-chloro and α-bromo derivatives (Table IV).

Thus, in the series of the α-halogenocarboxylic amides, the resolution coeffi-

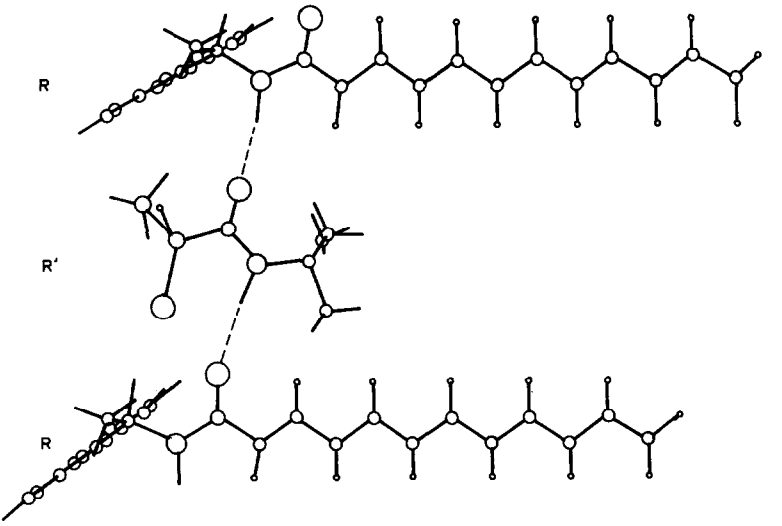


Fig. 8. Intercalation complex of an (*R*)-α-chloropropanoic acid *tert.*-butylamide inserted into a stack of N-lauroyl-(*R*)-α-(1-naphthyl)ethylamine molecules.

cients, the retention indices and the free energies of solution all show an increase in selectivity in the order F < Cl < Br, *i.e.* the same order as the covalent radius of the C–X bond. The fluorine derivatives have the lowest selectivity and, as mentioned above, are the most difficult to resolve.

The order of emergence was determined for seven of the thirteen compounds by comparison with optically active samples of known configuration, and was found to be first the *S*- and then the *R*-isomer on the *R*-phase. This is the same order as observed previously on diamide phases[3]. By extrapolating these findings, we have assigned to a sample of (+)-α-fluorobutanoic acid, obtained by enzymatic hydrogenation[8] (see above), the *R*-isomer structure. No literature data were available to correlate the sign of rotation of this compound with its configuration.

The order of emergence can be interpreted by an intercalation structure, as shown in Fig. 8, similar to that in Fig. 2. The intercalated α-halogenocarboxylic acid amide is given a conformation in which the C–X bond is oriented close to the NH group, as supported by the findings for the analogous N-methyl-α-chloroacetamide[9,10] (skew conformation a in Fig. 9). In this position, as can also be seen by inspection of CPK models, the fit for the solute is better when it has the same configuration as the solvent. Indeed, the hydrogen at the asymmetric carbon of the solute

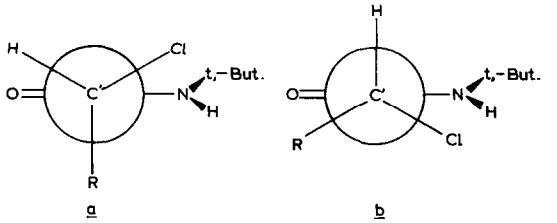


Fig. 9. Newman projection formulae of skew conformations of α-chlorocarboxylic acid *tert.*-butylamide.

is then directed towards the naphthyl group of the phase, where only little free room is available. For the antipode, in contrast, the larger R group would end to be placed in that same space near the aromatic ring, resulting in a worse fit and, hence, a shorter retention time.

If the C–X bond is rotated into the alternative skew position b (Fig. 9), the stereoselective consequences would be opposite to those mentioned above. However, because the negative end of the C–X dipole would then be directed towards the π electrons of the aromatic moiety of the phase molecule, this orientation would appear to be less favoured. In addition, for the larger halo atoms (particularly bromine, which, as mentioned, leads to the largest α values) considerable steric hindrance would occur.

CONCLUSIONS

N-Lauroyl-(*R*)-α-(1-naphthyl)ethylamine (I) gave higher resolution factors for α-halogenocarboxylic acid amides than previously obtained on diamides. α-Fluoro derivatives were separated into their enantiomers for the first time.

The resolution coefficients increased with increasing atomic radius of the halo atom, namely in the order F < Cl < Br. The order of emergence throughout is *R*(D)- after the *S*(L)-isomer on the *R*-phase, and is explained by an intercalation complex.

The model proposed to account for the mechanism of resolution is based on an analogy for the stereoselective interaction of α-phenylcarboxylic acid amides with I, and literature data for the conformation of N-methyl-α-chloroacetamide, an analogue of the α-halogenocarboxylic acid *tert.*-butylamides.

A study was made of the conditions under which racemization during the derivatization reaction acid → acid chloride → acid *tert.*-butylamide is minimal, and does not exceed a maximum of 0.3–0.4% inversion for the model compound used (α-bromoisopentanoic acid).

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