Tetrahedron Letters No. 16, pp 1417 - 1420, 1977. Pergamon Press. Printed in Great Britain.

DIRECTED RESOLUTION OF ENANTIOMERS VIA LIQUID CHROMATOGRAPHY OF DIASTEREOMERIC DERIVATIVES III. A CONVENIENT METHOD TO DETERMINE THE ABSOLUTE CONFIGURATION OF CARBOXYLIC ACIDS $R^1R^2HCCOOH$[1)]

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(Received in UK 15 February 1977; accepted for publication 7 March 1977)

Some time ago we introduced the term "directed resolution of enantiomers" to denote a method capable of simultaneous (a) separation of enantiomers, (b) determination of enantiomeric purity and (c) determination of absolute configuration of chiral compounds. In papers I[2)] and II[3)] of this series it was shown that directed resolution of carboxylic acids and amines can generally be achieved by forming diastereomeric secondary amides and separating them by liquid chromatography on silica gel. Condition (b) is met by high performance liquid chromatography (HPLC)[4)], condition (c) is fulfilled by a model which correlates elution order and configuration of the diastereomers. This model was previously restricted to amides $R^1R^2XCCONHCHA^1A^2$, X being a group internally hydrogen bonded to the amide proton and thereby determining the conformation of the acyl group[2)].

We have since extended our investigations to include the following aspects of the directed resolution method: (a) definition of the scope of applicability, (b) measurement of precise separation factors by HPLC, (c) quantitative prediction of separation factors (Ugi-Ruch stereochemical analogy model) and (d) preparative separation of enantiomers. We now report our observations concerning its application to amides of carboxylic acids $R^1R^2HCCOOH$, a class containing numerous compounds which are frequently encountered and often of pharmacological and stereochemical importance.

Our method is based on the following concepts[5)]:

(1) Secondary amides adopt essentially the same conformations in polar solutions and in the adsorbed state (on silica gel).

(2) In the adsorbed state a parallel alignment of the planar amide group and the surface of the silica gel is preferred (the latter is supposed to be planar in micro regions[6)]).

(3) Apolar groups (alkyl, aryl) outside the amide plane cause a disturbance of this preferred arrangement in proportion to their steric bulk in a direction perpendicular to the amide plane[7)]. Such groups are classified as large and small by indices L and S, respectively.

(4) That member of a diastereomeric pair in which <u>both</u> faces of the amide plane are more shielded than the least shielded face in the other member is eluted first.

(5) There is an attractive interaction between small polar groups and the silica gel, particularly, if they are hydrogen bond donors not internally bonded to the amide group. Formally, such groups are assigned to the S (small) class.

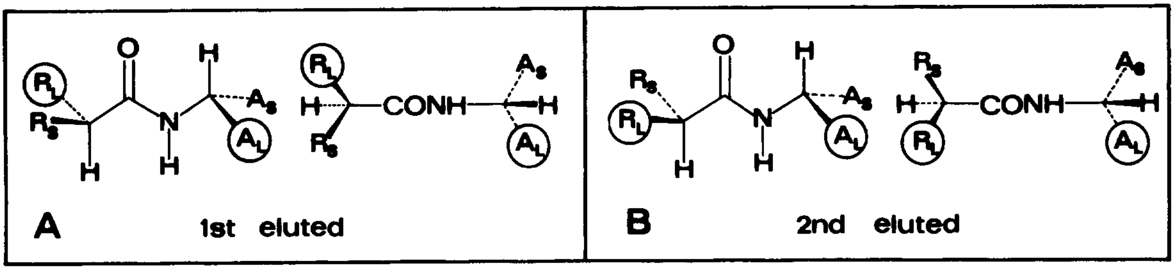
On the basis of these points, specific rules can be formulated for various classes of secondary amides if their conformations can be defined independently of the individual properties of the groups referred to under (3)-(5). Fortunately, the conformation of the carbinylimine moiety is always the same:

(1a) Amides $RCONHCHA^1A^2$ (as well as corresponding esters) have invariably been found to adopt a conformation characterized by an approximately antiplanar arrangement of the fragment HNCH (see the figures below). This statement is substantiated by numerous experimental observations[2)8)] and by quantum chemical calculations[9)].

A statement of such generality is not possible with respect to the conformation of the acyl group because the variety of the functional groups to be considered is much larger. However, for several types of acyl groups constant conformations are also found:

(1b) If there are no hydrogen bonds between R^1 or R^2 and the amide group the average conformation of amides $R^1R^2HCCONHR$ is characterized by an antiplanar disposition of the fragment HCC=O (see the figures below). This conformational assignment has been discussed before[10)] and has since been corroborated by extensive NMR investigations[11)], x-ray crystallography[12)] and quantum chemical calculations[9)].

Combination of the concepts (1)-(5), in conjunction with the observations presented in (1a) and (1b), provides the foundation to the rule illustrated by the figure: A is eluted before B (and the enantiomer of A is eluted before the enantiomer of B). This rule, of course, also applies to diastereomers derived from enantiomeric amines: A is eluted before the enantiomer of B (and the enantiomer of A is eluted before B).



RESULTS. The validity of this rule has been checked with a large number of diastereomeric pairs of known configuration. A subset is given in the table. Configurations were determined by synthesis (S) from components of known[13)] configuration or by our recently developed PNMR method (PNMR)[10)] which in the meantime has also been extended to carboxylic acids[11)]. Each compound was characterized individually by spectral data and by elemental analysis.

Table. High performance liquid chromatographic separation [a] of diastereomeric amides A and B.

No.	Config. [b]	R_S	R_L	A_S	A_L	α [c]	$-\Delta(\Delta G)$ [cal] [c]	temp. [°C]
1a,b	S/PNMR	CH_3	C_6H_5	CH_3	C_2H_5	1.27	139	23.0
2a,b	PNMR	CH_3	C_6H_5	CH_3	n-C_6H_{13}	1.70	313	22.9
3a,b	S/PNMR	CH_3	C_6H_5	CH_3	t-C_4H_9	1.70	312	23.0
4a,b	S/PNMR	CH_3	C_6H_5	CH_3	C_6H_5	1.81	349	23.0
5a,b	PNMR	CH_3	C_6H_5	CH_3	Ferrocenyl	1.34	173	23.0
6a,b		CH_3	C_6H_5	$COOCH_3/CH_3$		1.0	0	23.0
7a,b	S/PNMR	CH_3	C_6H_5	$COOCH_3$	$CH_2C_6H_5$	1.21	110	23.0
8a,b	PNMR	CH_3	C_6H_5	$COOCH_3$	C_6H_5	1.54	253	23.0
9a,b	S/PNMR	C_2H_5	C_6H_5	CH_3	C_6H_5	1.51	242	23.0
10a,b	S/PNMR	C_2H_5	C_6H_5	CH_3	1-naphthyl	1.48	233	23.5
11a,b	S/PNMR	C_2H_5	C_6H_5	CH_3	2-naphthyl	1.69	308	23.0
4a,b	S/PNMR	CH_3	C_6H_5	CH_3	C_6H_5	1.81	349	23.0
9a,b	S/PNMR	C_2H_5	C_6H_5	CH_3	C_6H_5	1.51	242	23.0
12a,b	PNMR	t-C_4H_9	C_6H_5	CH_3	C_6H_5	1.07 [d]	42	23.0
13a,b	S/PNMR	CH_3	C_2H_5	CH_3	C_6H_5	1.30	153	23.0
14a,b	PNMR	CH_3	n-C_9H_{19}	CH_3	C_6H_5	1.80	347	23.0
15a,b	S/PNMR	CH_2OAc	C_6H_5	CH_3	C_6H_5	2.06 [e]	424	23.0
16a,b	S/PNMR	CH_2CH_2OH	C_6H_5	CH_3	C_6H_5	2.90 [f]	626	23.4

[a] Eluens: hexane-ethyl acetate 8+2 if not otherwise stated; pressure: 100 bar; apparatus: as described in 3). [b] See text (Discussion).

[c] $\alpha = t_{R(2)}-t_o/t_{R(1)}-t_o$; $t_{R(1)}$, $t_{R(2)}$ = retention time of 1st and 2nd eluted component, respectively; t_o = ret. time of a non-ads. subst. (pentane); $\Delta(\Delta G) = -RT\ln\alpha$; 5-10 measurements were performed with each sample; maximal standard deviation for α and $\Delta(\Delta G)$ 0.01 and 4 cal., respectively; the values of α and $\Delta(\Delta G)$ are rounded off separately. [d] Pressure: 50 bar. [e] Pressure: 200 bar.

[f] Eluens: l.b. petroleum ether-ethyl acetate 1+1.

DISCUSSION. The results presented in the table are in excellent agreement with the concepts we have delineated. A number of points deserve special comment: (a) For the sake of convenience we have used hexane-ethyl acetate as the eluent throughout this investigation, however, in many cases other solvents give better separation. Of particular value are mixtures of hydrocarbons (alkanes, benzene) with polar aprotic solvents (ethyl acetate, chloroform, tetrahydrofurane). Protic solvents seem to have a detrimental effect. (b) HPLC is only necessary for the determination of enantiomeric purity. TLC is adequate for the determination of elution order and optimization of separations. (c) Highest separation factors have been obtained with 1-(2-naphthyl)-ethylamine. This compound is an excellent reagent as it is crystalline, has a high UV absorption and is easily prepared in an enantiomerically pure state. Because of their ready availibility 1-phenylethylamine, phenylglycine methyl ester and other amino acid esters are also useful reagents. (d) Experimentally, the determination of absolute configuration is extremely simple: A mixture of diastereomeres and a pure or enriched sample has to be prepared from racemic and optically active components, respectively, and the order of TLC spots has to be established. Our experience shows that preparation of amides via acid chlorides (oxalylic chloride) or imidazolides is particularly advantageous and possible on a micro scale. (e) The pairs 15a, b and 16a, b show exceptionally high separation effects (see concept (5)). Furthermore, amides of type 16 are easily hydrolized by dilute acids. The development of enantiomer separation reagents on the basis of these findings is under active investigation by us[14]. (f) In order to examine the efficiency of our method for enantiomer separations[15] all the pairs of the table with $\alpha > 1.05$ were separated on a preparative scale (1-20 g) by chromatography with MERCK-LOBAR columns or a similar preparative low pressure technique developed in our laboratory[16].

1) Support of this research by the Deutsche Forschungsgemeinschaft is gratefully acknowledged. This work has been presented in part in lectures (Regensburg, 22.4.75 and 31.3.76 (Chemiedozenten-Tagung); Aachen, 20.1.77).
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4) 3) and footnote 13 of 2); for applications of this method see: 4a) R. Eberhardt, C. Glotzmann, H. Lehner, K. Schlögl, Tetrahedron Lett. 1974, 4365, 4b) C.G. Scott, M.J. Petrin, T. McCorkle, J. Chromatography 125, 157 (1976).
5) It is to be emphasized that these concepts are based only on experience with silica gel.
6) L.R. Snyder, "Principles of Adsorption Chromatography", Marcel Dekker, New York, 1968, p. 159.
7) We assume that this arrangement is due to double hydrogen bonding of the type: Si-OH···O=C-N-H··· O(H)-Si . This assumption is supported by the observation that separation factors of diastereomeric esters are generally smaller than those of corresponding amides.
8) W.H. Pirkle, J.R. Hauske, J. Org. Chem. 41, 801 (1976).
9) L. Pavlidou, G. Helmchen, to be published (PCILO method).
10) G. Helmchen, Tetrahedron Lett. 1974, 1527.
11) G. Helmchen, to be published.
12) A.T. Hagler, L. Leiserowitz, M. Tuval, J. Am. Chem. Soc. 98, 4600 (1976).
13) Contrary to a statement in 4a), the absolute configuration of 1-(1-naphthyl)-ethylamine is securely known: M.G.B. Drew, Acta Cryst. B 25, 1320 (1969).
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