Journal of Chromatography, 388 (1987) 307–314
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CHROM. 19 185

DIRECT CHROMATOGRAPHIC SEPARATION OF ENANTIOMERIC DIOL DERIVATIVES

W. H. PIRKLE*, GEORGE S. MAHLER, THOMAS C. POCHAPSKY and MYUNG HO HYUN
School of Chemical Sciences, University of Illinois at Urbana-Champaign, 1209 W. California, Urbana, IL 61801 (U.S.A.)
(Received September 16th, 1986)

SUMMARY

The enantiomers of a variety of aliphatic and alicyclic vicinal diols, derivatized as the bis-3,5-dinitrophenyl carbamates, have been separated on chiral stationary phases derived from either (*R*)-N-(2-naphthyl)alanine or an (*R*)-N-acylated α-aryl-α-aminoalkane. The technique has utility not only for analytical determinations of enantiomeric purity and absolute configuration but also for preparative separations as the diols may be easily recovered from the separated derivatives. Chiral recognition mechanisms are presented to account for the observed separations.

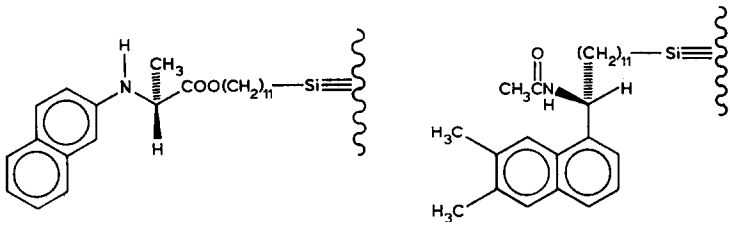
INTRODUCTION

Because of their importance as starting materials and intermediates for a variety of synthetic transformations, optically active diols have been of long standing interest to chemists. Many natural products either are themselves or are derived from diols. Thus, the determination of enantiomeric purity and absolute configuration of chiral diols has attracted the attention of several groups. Moreover, preparative separation of diol enantiomers is of interest as a convenient source of optically active diols. To date, workers interested in obtaining useful quantities of non-racemic diols have relied on separation of diastereomeric precursors or direct enzymatic synthesis[1]. While several methods for the separation of derivatized diol enantiomers on chiral stationary phases (CSPs) have been reported[2,3], these techniquies are limited to determinations of enantiomeric excess and absolute configurations of volatile analytes or require derivatizing agents of absolute enantiomeric purity.

We now report that the enantiomers of derivatized diols can be separated on either CSP 1, derived from (*R*)-N-(2-naphthyl)alanine[4], or on (*R*)-2, one of a recently reported[5] series of N-acylated α-aryl-α-aminoalkane derived CSPs. Columns packed with CSP 1 are now commercially available[6]. As discussed below, these separations have both analytical and preparative potential.

The direct liquid chromatographic (LC) separation on CSPs 1 and 2 of the enantiomers of simple chiral amines and alcohols derivatized as the 3,5-dinitrophenyl ureas and carbamates respectively has been reported recently[7,8]. Though the present

0021-9673/87/$03.50



method for preparation and separation of derivatized diols is a logical extension of this prior report, the separation of the enantiomeric diol derivatives is of mechanistic interest, both in comparison with the separations of the closely related mono hydroxy derivatives[7,8] and in terms of relating absolute configuration of the diols enantiomers to their elution order from a given CSP.

EXPERIMENTAL

The chromatographic system employed in these studies consists of an Altex 100A pump, an Altex 210 injector, and an Altex model 165 variable-wavelength detector. The CSP 1 column used in this study is commercially available. The eluent was routinely monitored at 254 and 280 nm. Signs of rotation at 589 nm were obtained by directing the eluent from the chiral column through a Rudolf Autopol III digital polarimeter equipped with a 20-cm flow cell, a digital to analogue converter and a strip chart recorder.

The diols used in this study were available commercially or were prepared either by hydration of epoxides in wet benzene containing catalytic amounts of mineral acid, or by oxidation of the appropriate alkene with performic acid followed by basic hydrolysis of the resulting hydroxy formates. Diols of known absolute configuration were prepared by hydroxy-deamination of a non-racemic amino acid ester by the method of Van Slyke[9], followed by lithium aluminum hydride reduction of the resulting hydroxy ester. The absolute configuration of the resulting diol can be related to that of the amino acid precursor. For diols which are not formally derived from amino acids, (for example, *trans*-1,2-cyclohexane-diol), enriched samples were prepared by classical methods[10].

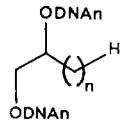
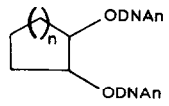
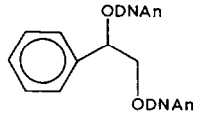
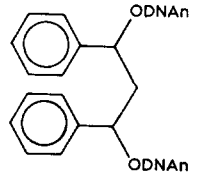
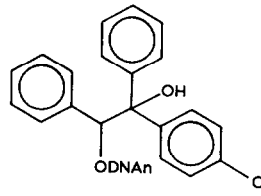
Derivatives were prepared as described previously for simple alcohols, using 3,5-dinitrobenzoyl azide[8] as a convenient source of 3,5-dinitrophenyl isocyanate[11]. The bis carbamates are readily formed as indicated by satisfactory nuclear magnetic resonance (NMR) data and the absence of O–H stretching bands in the infrared spectra of the derivatives. For diols which are sparingly soluble in toluene, derivatization may be caried out in anhydrous dioxane. For diols having a sterically hindered hydroxyl group (*e.g.* entry 12, Table I) only the less hindered hydroxyl group is derivatized even after prolonged heating with excess 3,5-dinitrophenyl isocyanate. This presents no particular difficulty as the hydroxycarbamates also resolve on CSP 1 and 2.

In several instances, samples of 0.5–1.5 g of racemic diol bis-carbamates were preparatively resolved on a medium-pressure liquid chromatographic column, 100 cm × 25 cm, packed with the (*S*)-valine analogue[3] of CSP 1. While the low solubility of these bis-carbamates complicates their preparative resolution, the chromatography

TABLE I

ALIPHATIC AND ALICYCLIC DIOLS SEPARATED ON CSPs 1 AND 2

DNAn = Dinitroanilido. For CSP 1, analytes were isocratically eluted with 10% isopropyl alcohol in hexane at 2 ml/min. For CSP 2, analytes were isocratically eluted with 20% isopropyl alcohol in hexane at 2 ml/min.

Entry	*N*	*CSP 1*			*CSP 2*		
		k'_1	α	*Most retained enantiomer**	k'_1	α	*Most retained enantiomer**
							
1	1	15.28	1.19	(+), *R*	16.35	1.35	(−), *S*
2	2	14.14	1.13	(+), *R*	15.7	1.36	(−), *S*
3	3	14.28	1.22	(+)	15.28	1.39	(−)
4	4	15.0	1.19	(+), *R*	13.7	1.36	(−), *S*
5	6	21.57	1.18	(+), *R*	10.6	1.29	(−), *S*
							
6	1	37.0	1.45	(+)	10.14	1.09	(−)
7	2	25.57	1.19	(+), 1*S*,2*S*	9.28	1.13	(−), 1*R*,2*R*
8	3	24.0	1.15	(+), 1*S*,2*S*	9.36	1.42	(−), 1*R*,2*R*
9	4	20.8	1.13	(+), 1*S*,2*S*	9.57	1.46	(−), 1*R*,2*R*
10		44.4	1.13	(+), *R*	25.14	1.66	(−), *S*
11		33.3	1.40	(−)	14.71	1.62	(+)
12		5.86	1.12	(+)	2.14	1.13	(−)

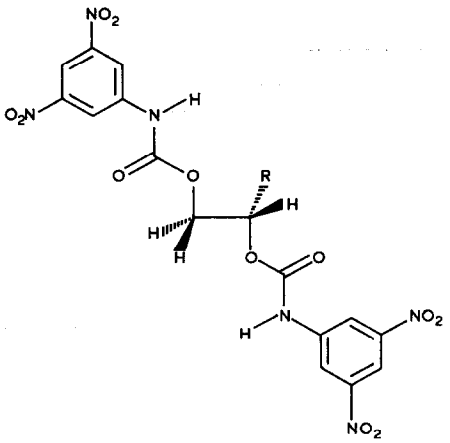
* The signs in parenthesis are the signs of rotation at 589 nm for the most strongly retained bis-carbamate enantiomer. The letters refer to the absolute configuration of the most retained bis-carbamate enantiomer.

proceeds smoothly. Retrieval of the diols from the separated bis-carbamate enantiomers also proceeds smoothly using trichlorosilane[12]. The optically active diols and bis-carbamates so obtained aided in establishing the relationship between absolute configuration and order of elution from CSPs 1 and 2. The experiments also demonstrate the potential of this approach for preparative resolution of chiral diols.

RESULTS

Table I lists data obtained from the separation on CSPs 1 and 2 of the bis-3,5-dinitroanilido carbamates of a variety of aliphatic and alicyclic diols. The signs of rotation and absolute configurations noted are those for the last eluted enantiomers. Diol samples of known stereochemistry were derived from enantiomerically pure amino esters. While the hydroxy-deamination-reduction sequence may not afford enantiomerically pure diols from enantiomerically pure amino acids, the extent of enrichment afforded is sufficient to relate the configuration of the diol to its amino acid precursor. Esters of (*S*)-amino acids yield the corresponding (*S*)-diols[13]. Complete racemization may occur during hydroxy-deamination if the reaction temperature is not maintained between 0 and +5°C. Samples of enriched cyclic diols were obtained by fractional crystallization of the menthyloxy acetate esters[14]. In several instances, absolute configurations of cyclic diols have been assigned by prior workers and we have utilized these asignments without independent verification[15].

In rationalizing the experimental data in mechanistic terms, one must first consider analyte conformation as well as configuration. We initially assert that for bis-carbamates of 1,2-diols, the preferred rotamer about the 1,2-carbon–carbon bond should, for electronic and steric reasons, be the one where both alkoxyl oxygens are essentially antiperiplanar: that is, roughly as far from one another as possible. For steric and electronic reasons, the carbonyl oxygens will, on a time averaged basis, prefer to more or less eclipse a single carbinyl hydrogen[16–18] or lie between them if there are two. Such an arrangement is shown in Scheme 1.

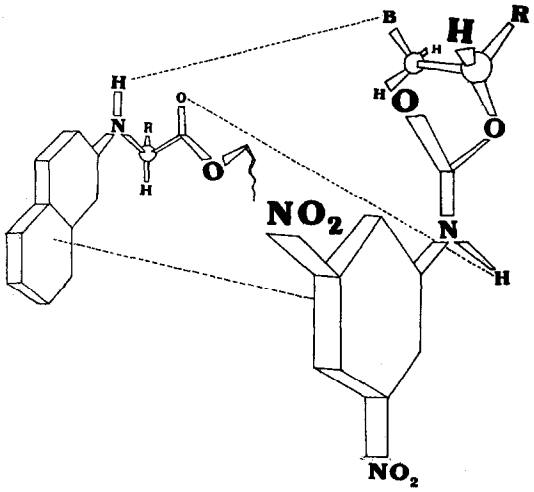


Scheme 1.

Implicit in our present and prior chiral recognition models is the tenant that chiral recognition is most efficient when the low-energy conformations of the most strongly retained analyte enantiomer and CSP are involved during interaction.

From the data in Table I, one sees that the magnitude of the separation factors for entries 1–5 are essentially independent of the length of the alkyl substituent on the chiral center of the bis-carbamates. From this, it is inferred that, during interaction with the CSP, neither analyte enantiomer requires that the alkyl substituent be intercalated between adjacent stands of the CSP. This is mechanistically informative because other types of analytes have shown a dependence of α on the length of alkyl substituents owing to the steric consequences of intercalation. In some instances, a pronounced dependence of the magnitude of the separation factors upon the length (or size) of alkyl substituents in an homologous series of analytes has been taken as indicative of the operation of chiral recognition processes of opposite enantioselectivity[5,19–21].

Note from the signs of rotation in the Table that elution orders are always different on (*R*)-CSP 2 and (*R*)-CSP 1. This is suggestive of the systematic operation of a single dominant chiral recognition process on each CSP. However, the processes are not identical. The mode of operation of CSP 1 is more readily assessed than that of CSP 2 owing to the limited number of interactions available for the analytes. The chiral recognition mechanism advanced to account for the resolution of entries 1–5 and 10 on CSP 1 is shown in Scheme 2 and is only a specific instance of a general mechanism recently described[7]. Three bonding interactions dictate the sense of chiral recognition. These are: π–π interaction between the 3,5-dinitroanilido system and the naphthyl system of the CSP, hydrogen bonding of the anilido N–*H* to the carbonyl oxygen of the CSP, and hydrogen bonding of the β-naphthylamino N–*H* to the carbonyl oxygen of the primary carbamoyl group. Both carbamoyl groups can presumably undergo these interactions. However, only when the secondary carbamoyl group is the one involved in the π–π interaction is significant chiral recognition expected. It is these interactions which are depicted in Scheme 2. Except in the case of

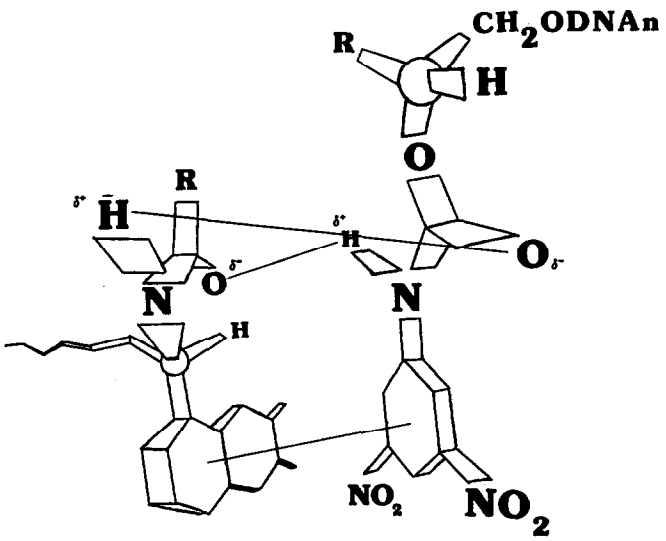


Scheme 2.

entry 6, CSP 1 affords smaller separation factors than does CSP 2, presumable because the interaction sites in the bis-carbamates are spaced too widely and one or more of the interactions essential to chiral recognition is thereby weakened. A similar situation is noted on CSP 1 for N-3,5-dinitrobenzoyl derivatives of α- and β-amino esters[22,23]. The enantiomers of the latter show smaller separation factors than do those of the former.

In the present instance, a variation of the dipole-stacking process previously reported to be the dominant chiral recognition mechanism for mono 3,5-dinitrophenyl carbamates[7] seems to adequately account for the data obtained on CSP 2 for entries 1–5 and 10. In this process, shown in Scheme 3, it is proposed that the most retained bis-carbamate enantiomer approaches the most accessible face of CSP 2 where it undergoes bonding interactions stemming from π–π interaction and "head to tail" stacking of amide dipoles. Such interactions presumably occur with either the primary or secondary 3,5-dinitroanilido groups but appreciable chiral recognition accrues only from the latter set of interactions. It is this process which is depicted. Maintaining the aforementioned conformations during interaction, it is seen from Scheme 3 that, depending on the stereochemistry of the analyte, either the alkyl group or the primary carbamoyl group will be directed toward the CSP. Chiral recognition stems from differences in the abilities of these groups to further interact with CSP 2. In the (*S*)-enantiomers, the carbonyl oxygen of the primary carbamoyl group is suggested to undergo hydrogen bonding to the amide proton of CSP 2. This interaction is analogous to one recently suggested to account for the facile separation of N-3,5-dinitrobenzoyl-β-amino esters on CSPs related to 2[22].

The assertion that appreciable chiral recognition occurs only when the 3,5-dinitroanilido group on the chiral center is involved in π–π interaction with the CSP was tested in the following way. Acylation of either racemic 1,2-hexanediol or racemic 1-phenyl-1,2-ethanediol with one equivalent of the mixed anhydride derived from



Scheme 3.

benzoic acid and N,N-dicyclohexylcarbodiimide affords principly the primary benzoates. After purification of these hydroxybenzoates, the structures of which were confirmed by NMR, acylation with 3,5-dinitrophenyl isocyanate generated the corresponding primary benzoate-secondary carbamates. Analysis of the primary benzoate-secondary carbamate of 1,2-hexanediol and 1-phenyl-1,2-ethanediol on CSP 2 gave separability factors of 1.13 and 1.26 respectively. Alternatively, reaction of the diols with one equivalent of 3,5-dinitrophenyl isocyanate with 1,2-hexanediol generates a mixture of the primary and secondary carbamates as well as the bis-carbamate. The isomeric monocarbamates, readily isolated from the reaction mixture by filtration through silica using 30% ethyl acetate in hexane, were then acylated with benzoyl chloride. Analysis on CSP 2 of the mixture of products so obtained revealed peaks previously assigned to the enantiomers of the primary benzoate-secondary carbamate as well as a third peak shown, by isolation and characterization, to stem from the non-separated enantiomers of the primary carbamate-secondary benzoate. From these studies, it is inferred that significant chiral recognition indeed requires π–π interaction between the CSP and the 3,5-dinitroanilido group on the chiral center of the 1,2-diol.

Several cyclic *trans*-1,2-diols were investigated (entries 6–9, Table I) and their enantiomers were found to be readily separable on CSP 2. From the dependence of the separation factor on ring size, it is evident that ring conformation influences the extent of chiral recognition. Elution order of enantiomers was established rigorously only for the bis-carbamates of *trans*-1,2-cyclohexanediol, *trans*-1,2-cycloheptanediol, and *trans*-1,2-cyclooctanediol. No chiral recognition model is presently advanced for the separation of the enantiomers of bis-carbamates of cyclic diols owing to uncertainty as to their conformational behaviour.

CONCLUSION

The described methodology allows for simple and practical analytical determinations of enantiomeric purity of chiral diols. For all entries in Table I, resolution factors greater than 1.5 are observed, thus permitting accurate determination of relative peak areas. It is to be noted that this technique is well suited for preparative separations as the diols are easily recovered from the resolved carbamates without racemization.

ACKNOWLEDGEMENT

This work was supported by grants from the National Science Foundation and from Eli Lilly and Company.

REFERENCES

1 L. G. Lee and G. M. Whitesides, *J. Org. Chem.*, 51 (1986) 25.
2 W. A. König, E. Steinbach and K. Ernst, *J. Chromatogr.*, 301 (1984) 129.
3 V. Schurig and D. Wistuba, *Tetrahedron Lett.*, 25 (1984) 5633.
4 W. H. Pirkle and T. C. Pochapsky, *J. Am. Chem. Soc.*, 108 (1986) 352.
5 W. H. Pirkle, M. H. Hyun and B. Bank, *J. Chromatogr.*, 316 (1984) 585.
6 Regis Chemical Company, Morton Grove, IL.

7 W. H. Pirkle, T. C. Pochapsky, G. S. Mahler, D. M. Alessi, D. S. Reno and D. E. Corey, *J. Org. Chem.*, (1986) in press.
8 W. H. Pirkle, G. S. Mahler and M. H. Hyun, *J. Liq. Chromatogr.*, 9 (1986) 443.
9 D. D. van Slyke, *Chem. Ber.*, 43 (1910) 3170.
10 N. A. B. Wilson and J. Read, *J. Chem. Soc.*, 138 (1935) 1269.
11 N. Ôi and H. J. Kitahara, *J. Chromatogr.*, 265 (1983) 117.
12 W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, 44 (1979) 4891.
13 J. B. Brewter and C. A. Ingold, *Nature (London)*, 66 (1950) 179.
14 K. Freudenberg, *Chem. Ber.*, 66 (1933) 177.
15 P. Newman (Editor), *Optical Resolution Procedures for Chemical Compounds*, Vol. 3, Optical Resolution Information Center Riverdale, NY, 1984.
16 W. H. Pirkle and C. J. Welch, *J. Org. Chem.*, 49 (1984) 138.
17 W. H. Pirkle, M. R. Robertson and M. H. Hyun, *J. Org. Chem.*, 49 (1984) 2433.
18 W. H. Pirkle, K. A. Simmons, and C. W. Boeder, *J. Org. Chem.*, 44 (1979) 4891.
19 W. H. Pirkle and M. H. Hyun, *J. Chromatogr.*, 322 (1985) 287.
20 W. H. Pirkle and M. H. Hyun, *J. Chromatogr.*, 322 (1985) 295.
21 W. H. Pirkle and M. H. Hyun, *J. Chromatogr.*, 328 (1985) 1.
22 W. H. Pirkle, A. Tsipouras, M. H. Hyun, D. J. Hart and C.-S. Lee, *J. Chromatogr.*, 358 (1986) 377.
23 O. W. Griffith, E. B. Campbell, W. H. Pirkle, A. Tsipouras and M. H. Hyun, *J. Chromatogr.*, 362 (1986) 345.