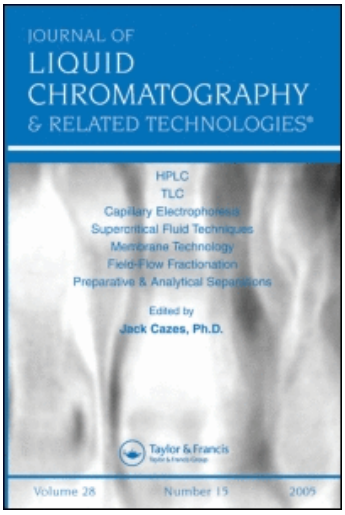


Journal of Liquid Chromatography & Related Technologies
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

Liquid Chromatographic Separation of the Enantiomers of Chiral Secondary Alcohols as Their α-Naphthyl Urethane Derivatives

William H. Pirkle[a]; John E. Mccune[a]
[a] School of Chemical Sciences University of Illinois, Urbana, Illinois

To cite this Article Pirkle, William H. and Mccune, John E.(1988) 'Liquid Chromatographic Separation of the Enantiomers of Chiral Secondary Alcohols as Their α-Naphthyl Urethane Derivatives', Journal of Liquid Chromatography & Related Technologies, 11: 9, 2165 — 2173
To link to this Article: DOI: 10.1080/01483918808069047
URL: http://dx.doi.org/10.1080/01483918808069047

JOURNAL OF LIQUID CHROMATOGRAPHY, 11(9&10), 2165-2173 (1988)

LIQUID CHROMATOGRAPHIC SEPARATION OF THE ENANTIOMERS OF CHIRAL SECONDARY ALCOHOLS AS THEIR α-NAPHTHYL URETHANE DERIVATIVES

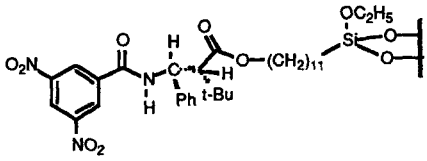
William H. Pirkle and John E. McCune
School of Chemical Sciences
University of Illinois
Urbana, Illinois 61801

ABSTRACT

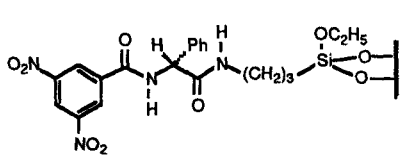
The enantiomers of α-naphthyl urethane derivatives of a wide variety of chiral secondary alcohols are separable by liquid chromatography on a chiral stationary phase derived from a conformationally restricted β-amino acid. In many instances separation factors are sufficiently great (1.5-6.5) to enable preparative separations to be effected.

INTRODUCTION

We recently described a chiral stationary phase (CSP **1**), derived from a conformationally restricted β-amino acid, which exhibits a significantly different selectivity than that noted upon its widely used phenyl glycine-derived predecessor, CSP **2** (1,2). The presence of the *t*-butyl substituent on the second stereogenic center confers considerable conformational rigidity to CSP **1**. In general, as one imposes additional restraints upon CSPs, one expects them to become more enzyme-like in their selectivity for analytes. Greater selectivity is expected for optimized analytes but the overall range of analytes for which the CSP is effective may be reduced.



CSP 1

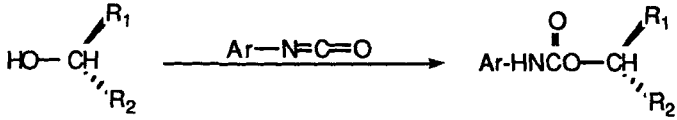


CSP 2

Urethane derivatives of chiral secondary alcohols are among the analytes having structures more complimentary to CSP **1** than CSP **2**. Aryl isocyanates are used in preparing these derivatives since they contribute to chiral recognition and enhance detectability. These urethane derivatives are easily prepared; a generalized reaction is shown in Scheme 1. Both phenyl and α-naphthyl isocyanate are commericially available and are standard derivatizing agents often used in qualitative organic analysis courses for converting alcohols to crystalline derivatives (3,4).

Crystallization of the derivatives should be avoided when the enantiomeric purity of the alcohol is to be determined, owing to the potential for selective crystallization. Similarly, samples should be totally dissolved prior to injection. For preparative resolution of these alcohols, a mild and convenient procedure employing trichlorosilane affords the unracemized alcohol from the urethane in high yield after preparative separation of the enantiomers (5).

Scheme 1



EXPERIMENTAL

Chromatography was performed with an Anspec-Bischoff model 2200 HPLC pump, Rheodyne Inc. model 7125 injector with a 20 µl sample loop, two Milton Roy Uv Monitor™ D fixed wavelength detectors (254 and 280 nm) connected in series, and a Kipp & Zonen model BD 41 chart recorder.

The general procedure for preparing urethane derivatives from alcohols with aryl isocyanates is as follows: Mix 0.5 ml of anhydrous alcohol, or 0.5 g of solid alcohol , and 0.5 ml of aryl isocyanate in a

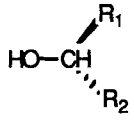
13x100 mm screw cap test tube (if desired, 0.5 ml of an inert high boiling solvent such as toluene may be added) and heat on a steam bath. Reaction times range from 5 min to 24 hrs depending on the alcohol. The progress of the reaction can be monitered by thin layer chromatography. Derivatization with 1-isocyanato-6,7-dimethylnaphthalene was catalyzed with two drops of boron trifluoride etherate and required longer reaction times.

RESULTS AND DISCUSSION

The data in Table 1 illustrate the greater enantioselectivity noted for these urethanes on CSP **1** compared to that noted on CSP **2**. The separation of enantiomeric α-naphthyl urethanes on CSP **2** has been independently noted (6). A detailed mechanistic explaination of the greater enantioselectivity of CSP **1** awaits further study, but presumbly

TABLE 1

Comparision of the Separation of the Enantiomers of Chiral Secondary Alcohols As Their α-Naphthyl Urethane Derivatives on CSPs **1** and **2**.

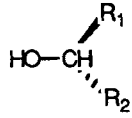


		CSP **1**		CSP **2**	
R_1	R_2	α^a	$K'_1{}^b$	α^a	$K'_1{}^b$
$-CH_3$	$-(CH_2)_3CH_3$	1.28	5.07	1.00	2.69
$-CH_2CH_3$	$-(CH_2)_3CH_3$	1.12	5.47	1.00	1.31
$-C{\equiv}CH$	$-(CH_2)_2CH_3$	2.02	4.94	1.00	2.12
$-C_6H_5$	$-(CH_2)_8CH_3$	3.39	3.94	1.15	1.69
$-CH_2C_6H_5$	$-CH_2CH_3$	1.79	5.80	1.00	2.06
$-C_6H_5$	$-CCl_3$	2.27	3.61	1.32	1.81
$-CF_3$	$-(p\text{-}CH_3)\text{-}C_6H_4$	1.91	2.80	1.16	1.56

[a]Chromatographic separation factor [b]Capacity factor for the first eluted enantiomer using 9:1 hexane - isopropyl alcohol as the mobile phase; flow rate 2 ml/min.

TABLE 2

Separation of the Enantiomers of Chiral Secondary Alcohols As Their α-Naphthyl Urethane Derivatives on CSP 1.



		Mobile Phase			
		Normal[a]		Reverse[b]	
R_1	R_2	α[c]	K'_1[d]	α[c]	K'_1[d]
$-CH_3$	$-CH_2CH_3$	1.12	5.60	~1.05	0.87
$-CH_3$	$-(CH_2)_2CH_3$	1.21	5.21	1.12	1.10
$-CH_3$	$-(CH_2)_3CH_3$	1.28	5.07	1.17	1.24
$-CH_3$	$-(CH_2)_5CH_3$	1.19	4.45	1.14	1.68
$-CH_2CH_3$	$-(CH_2)_3CH_3$	1.12	5.47	1.11	1.48
$-(CH_2)_2CH_3$	$-(CH_2)_3CH_3$	1.06	5.47	1.00	1.94
$-CH_3$	$-CH_2CH(CH_3)_2$	1.34	4.25	1.12	3.10
$-CH_3$	$-CH{=}CHCH_3$	1.55	6.71	1.26	0.88
$-C{\equiv}CH$	$-CH_3$	1.98	5.44	1.40	0.48
$-C{\equiv}CH$	$-CH_2CH_3$	2.00	5.60	1.39	0.58
$-C{\equiv}CH$	$-(CH_2)_2CH_3$	2.02	4.94	1.38	0.72
$-C{\equiv}CH$	$-(CH_2)_3CH_3$	2.00	5.50	1.32	0.84
$-C{\equiv}CH$	$-(CH_2)_7CH_3$	2.12	3.66	1.35	0.84

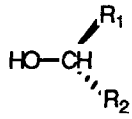
[a]Mobile phase was 9:1 hexane-isopropyl alcohol; flow rate 2 ml/min. [b]Mobile phase was. 9:1 methanol-water; flow rate 2ml/min. [c]Chromatographic separation factor. [d]Capacity factor for the first eluted enantiomer.

stems from a more complimentary "fit" between the more retained urethane enantiomers and the CSP.

Tables 2 thru 5 provide data relevant to the chromatographic separation of the enantiomers of a series of urethane derivatives. Significantly, the enantioselectivity afforded by reverse mobile phases (*e.g.* 9:1 methanol-water) is not much inferior (*ca.* 60%) to that noted with 9:1 hexane-isopropyl alcohol. This is most unusual and may possibly arise from the conformational rigidity of CSP **1** relative to prior chiral stationary phases we have investigated.

TABLE 3

Separation of the Enantiomers of a Homologeous Series of Phenyl Alkyl Carbinols As Their α-Naphthyl Urethane Derivatives on CSP 1.



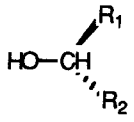
		Mobile Phase			
		Normal[a]		Reverse[b]	
R_1	R_2	α^c	$K'_1{}^d$	α^c	$K'_1{}^d$
$-C_6H_5$	$-CH_3$	2.61	5.95	1.84	1.19
$-C_6H_5$	$-CH_2CH_3$	3.19	5.72	2.16	1.19
$-C_6H_5$	$-(CH_2)_2CH_3$	3.12	5.75	1.91	1.44
$-C_6H_5$	$-(CH_2)_3CH_3$	2.96	5.15	2.01	1.65
$-C_6H_5$	$-(CH_2)_4CH_3$	3.08	5.02	2.02	1.98
$-C_6H_5$	$-(CH_2)_7CH_3$	3.24	3.88	1.90	2.62
$-C_6H_5$	$-(CH_2)_8CH_3$	3.39	3.94	1.95	3.59
$-C_6H_5$	$-(CH_2)_9CH_3$	3.21	3.91	1.91	4.19
$-C_6H_5$	$-(CH_2)_{10}CH_3$	3.24	3.63	1.88	4.96
$-C_6H_5$	$-(CH_2)_{12}CH_3$	3.36	3.27	1.88	6.90
$-C_6H_5$	$-(CH_2)_{14}CH_3$	3.36	2.95	1.91	9.38
$-C_6H_5$	$-(CH_2)_{16}CH_3$	3.35	3.07	1.90	9.56

[a]Mobile phase was 9:1 hexane - isopropyl alcohol; flow rate 2 ml/min. [b]Mobile phase was 9:1 methanol - water; flow rate 2 ml/min. [c]Chromatographic separation factor [d]Capacity factor for the first eluted enantiomer

The nature of the aryl substituent of the isocyanate plays an important role in chiral recognition. Table 6 contains data for the chromatographic separation of the enantiomers of urethanes derived from a variety of aryl isocyanates. The π-basicity of the aryl isocyanate directly affects resolution. Phenyl isocyanate affords derivatives which show less enantioselectivity than does naphthyl isocyanate. Moreover, the conformational disposition of the naphthyl substituent with respect to the remainder of the urethane also plays a role. For example, α-naphthyl isocyanate affords enantiomeric derivatives showing greater

TABLE 4

Separation of the Enantiomers of Chiral Secondary Alcohols As Their α-Naphthyl Ureathane Derivatives on CSP 1.

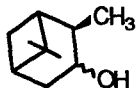
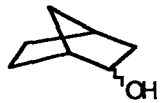
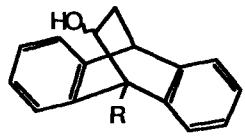


		Mobile Phase			
		Normal[a]		Reverse[b]	
R_1	R_2	α[c]	K'_1[d]	α[c]	K'_1[d]
$-CH_2C_6H_5$	$-CH_3$	1.82	5.50	1.43	1.31
$-CH_2C_6H_5$	$-CH_2CH_3$	1.79	5.80	1.44	1.44
$-C_6H_5$	$-CH_2CH(CH_3)_2$	3.28	5.13	2.06	1.84
$-C_6H_5$	$-CCl_3$	2.27	3.61	1.59	1.10
$-C_6F_5$	$-CH_3$	1.73	4.40	1.31	1.62
$-CF_3$	$-(p\text{-}CH_3)\text{-}C_6H_4$	1.91	2.80	1.54	0.81
$-CH_2CH_3$	$-CH_2SC_6H_5$	1.20	6.00	1.14	1.81
$-CH_2CH_3$	$-CH_2S(O)C_6H_5$	1.18	6.47	1.18	1.12
$-C_6H_5$	$-C(O)NH_2$	1.35	10.8	1.20	5.65
-1-Naphthyl	$-CF_3$	4.15	5.33	3.10	1.69
-9-Anthryl	$-CF_3$	6.46	6.36	3.79	2.11
-10-Benzyl-9-anthryl	$-CF_3$	4.42	4.71	2.91	4.00
-10-Methoxy-9-anthryl	$-CF_3$	3.65	8.33	3.08	4.56
-Cyclohexyl	$-CH_3$	1.33	5.12	1.21	1.75

[a]Mobile phase was 9:1 hexane - isopropyl alcohol; flow rate 2 ml/min. [b]Mobile phase was 9:1 methanol - water; flow rate 2 ml/min. [c]Chromatographic separation factor [d]Capacity factor for the first eluted enantiomer

TABLE 5

Separation of the Enantiomers of Chiral Secondary Alcohols As Their α-Naphthyl Urethane Derivatives on CSP 1.

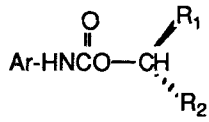
Compound	Mobile Phase: Normal[a] α[c]	Normal[a] K'_1[d]	Reverse[b] α[c]	Reverse[b] K'_1[d]
	1.06	6.38	1.07	2.81
	1.18	9.57	1.06	1.75
				
R= -H	1.17	8.78	1.12	3.15
R= $-CH_2C{\equiv}CH$	1.56	19.3	1.30	4.19

[a]Mobile phase was 9:1 hexane - isopropyl alcohol; flow rate 2 ml/min. [b]Mobile phase was 9:1 methanol - water; flow rate 2 ml/min. [c]Chromatographic separation factor [d]Capacity factor for the first eluted enantiomer

separation factors on CSP 1 than does β-naphthyl isocyanate. Conversely, urethane derivatives made from 1-isocyanato-2,3-dimethylnaphthlene show much reduced separation factors owing (presumably) to the conformational impact of the adjacent methyl groups. We expect the still unknown 1-isocyanato-6,7-dimethyl-naphthalene to afford derivatives of enhanced enantioselectivity owing to the greater π-basicity but conformational similarity to α-naphthyl isocyanate.

TABLE 6

Separation of the Enantiomers of Chiral Secondary Alcohols As Various Urethane Derivatives on CSP **1**.



Ar	R_2	R_3	α^a	$K'_1{}^b$
$-C_6H_5$	$-CH_2CH_3$	$-(CH_2)_3CH_3$	1.00	0.87
$-C_6H_5$	$-CF_3$	$-(p\text{-}CH_3)\text{-}C_6H_4$	1.31	0.87
$-C_6H_5$	$-C_6H_5$	$-CCl_3$	1.40	1.00
$-C_6H_5$	$-C\equiv CH$	$-(CH_2)_2CH_3$	1.07	1.27
$-C_6H_5$	$-CH_3$	$-(CH_2)_2CH_3$	~1.07	1.00
-2-Naphthyl	$-C_6H_5$	$-CH_3$	1.56	5.33
-2-Naphthyl	$-C_6H_5$	$-CH_2CH(CH_3)_2$	1.84	4.67
-2-Naphthyl	$-CH_3$	$-CH_2CH(CH_3)_2$	1.14	3.80
$-3,4\text{-}(CH_3)_2$-1-Naphthyl	$-C\equiv CH$	$-(CH_2)_2CH_3$	1.45	4.06
$-3,4\text{-}(CH_3)_2$-1-Naphthyl	$-CH_3$	$-CH_2C_6H_5$	1.16	4.09
$-3,4\text{-}(CH_3)_2$-1-Naphthyl	$-CF_3$	-1-Naphthyl	1.06	4.36

[a]Chromatographic separation factor [b]Capacity factor for the first eluted enantiomer using 9:1 hexane - isopropyl alcohol as the mobile phase; flow rate 2 ml/min.

CONCLUSION

Chiral secondary alcohols are readily resolved by HPLC on CSP **1** as their urethane derivatives. The enantiomeric purity of chiral secondary alcohols can be determined and in many cases preparative resolutions are feasible. Because it is readily available and convenient to use, α-naphthyl isocyanate is presently the derivatizing agent of choice.

ACKNOWLEDGEMENT

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

REFERENCES

1. Pirkle, W. H. and McCune, J. E., An Improved Chiral Stationary Phase for the Facile Separation of Enantiomers, J. Chromatogr., in press.

2. Pirkle, W. H.; House, D.W. and Finn, J. M., Broad Spectrum Resolution of Optical Isomers Using Chiral High-Performance Liquid Chromatographic Bonded Phases, J. Chromatogr., 192,143,1980.

3. Shriner, R. L.; Fuson, R. C. and Curtin, D. C., The Systematic Identification of Organic Compounds; A Laboratory Manual, 6 th ed., Wiley & Sons, New York, 1980.

4. Pasto, D. J. and Johnson, C. R., Organic Structure Determination, Prentice-Hall, Englewood Cliffs, 1969, p359.

5. Pirkle, W. H. and Hauske, J. R., Trichlorosilane Induced Cleavage: A Mild Method for Retrieving Carbinols from Carbamates, J. Org. Chem., 42, 2436, 1977.

6. Personal communcation from Qing Yang, Zeng-pei Sun, and Da-Kui Ling. Portions of this work are in press.