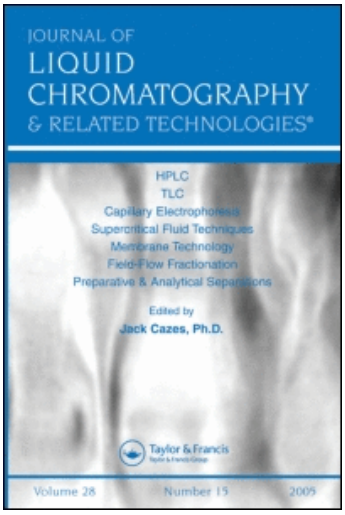

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W. H. Pirkle[a]; J. Andrew Burke[a]; K. C. Deming[a]
[a] School of Chemical Sciences, University of Illinois, Urbana, Illinois

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THE ROLE OF SPATIAL COMPLEMENTARITY IN CHIRAL RECOGNITION

W. H. PIRKLE, J. ANDREW BURKE, AND K. C. DEMING
School of Chemical Sciences
University of Illinois
Urbana, Illinois 61801

ABSTRACT

3,5-Dinitrobenzoyl chloride and the cis and trans isomers of 3,5-dinitrocinnamoyl chloride were used to acylate a variety of amines.The chromatographic behavior of these derivatives on several π-basic CSPs suggests that a correspondence in the size of the π-basic and π-acidic groups is an important factor in the observed enantioselectivity. As the size of the π-basic group in the CSP increases, the observed enantioselectivity of the *N*-(3,5-dinitrocinnamoyl) derivatives also increases.

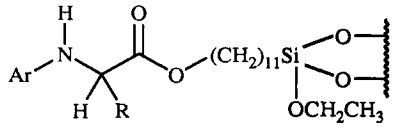
INTRODUCTION

Liquid chromatographic chiral stationary phases, CSPs, are used routinely for analytical and preparative scale separations of enantiomers.[1,2] While more than a hundred CSPs have been

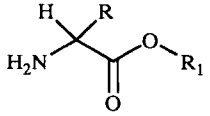
reported and at least fifty are commercially available, the mechanistic details of how these CSPs distinguish between analyte enantiomers are but little understood in most instances. Exceptional in this regard are some brush-type CSPs where mechanistic hypotheses have not only aided in the design of robust CSPs of enhanced scope and enantioselectivity, but also afford insight into which CSP should be used for a given analyte and in which order the enantiomers will elute.[3]

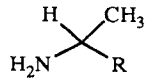
To simplify mechanistic studies, CSPs should contain only those functional groups necessary for chiral recognition. For example, CSPs **1** and **2**, designed to separate the enantiomers of π-acidic derivatives of amino acids and amines, utilize combinations of π-π interactions, hydrogen bonds and steric effects to "recognize" the stereochemistry of the analyte.[4,5,6] To be distinguished, not only must the analyte enantiomers contain the requisite interaction sites to complement those of the CSP, one of the enantiomers must present these sites to the CSP in such a manner as to allow them to be used. In other words, "spatial complementarity" strongly influences enantioselectivity.

In this paper, π-basic CSPs **1-5** are used to chromatograph the enantiomers of the derivatives of several chiral amines and amino acids, **6-13**, after these have been *N*-acylated with π-acidic groups of differing sizes and geometries. The intent of the study was to use the observed retention and enantioselectivities to afford insights into the "spatial complementarity" of the various CSP-analyte combinations.

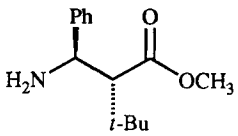


CSP	Ar	R
1	1-naphthyl	$CH_2CH(CH_3)_2$
2	2-naphthyl	CH_3
3	1-naphthyl	CH_3
4	2-anthryl	CH_3
5	2-fluorenyl	CH_3





Analyte	R	R_1	Analyte	R
6	CH_3	CH_3	**10**	C_6H_5
7	*i*-Bu	CH_2CH_3	**11**	4-$C_6H_4OCH_3$
8	$CH_2C_6H_5$	CH_3		
9	C_6H_5	CH_3		



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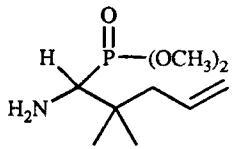

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MATERIALS AND METHODS

Apparatus

Two HPLC systems were used. System one consists of a Rainin HPX solvent delivery system and pressure monitor, a Rheodyne 7125 injector with a 20 μL sample loop, a Milton Roy LDC Monitor D fixed

wavelength detector operated at 254 nm and a Kipp and Zonen BD 41 recorder. System two consists of an Anspec isocratic HPLC pump, a Rheodyne 7125 injector with a 20 μL sample loop, a Milton Roy LDC Monitor D fixed wavelength detector operated at 254 nm and an HP 3394A recording integrator. The void volumes were determined using tri-*t*-butyl benzene.[7]

Materials

Columns containing CSPs **1** and **2** used in this study are available from Regis Chemical Company, Morton Grove, IL and CSPs **3-5** have been described.[8] The 3,5-dinitrocinnamic acid was prepared using the method of Yates[9] and converted to 3,5-dinitrocinnamoyl chloride using thionyl chloride. The *N*-3,5-dinitrocinnamoyl derivatives of **6-13** were prepared using 3,5-dinitrocinnamoyl chloride under Schotten-Baumann conditions.

The *trans* 3,5-dinitrocinnamoyl (*trans*-DNCIN) derivative of **9** was prepared for characterization. After recrystallization from ethyl acetate:hexane. mp. 164-5°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.78 s 3H; 5.26 d (J=7 Hz) 1H; 6.77 d (J=15.6 Hz) 1H; 6.92 d (J=7 Hz) 1 H; 7.2-7.5 m 5 H; 7.74 d (J=15.6 Hz) 1 H; 8.64 m 2 H; 9.08 m 1 H. MS *m/z*(relative intensity) 385(1.2); 353(3.8) 221(22), 164(23) 106(100). Anal. Calcd for $C_{18}H_{15}N_3O_7$: C, 56.11; H, 3.92;N, 10.90. Found: C, 55.75; H, 4.05; N, 10.60.

The DNB derivatives of **6-13** were available from prior studies.

RESULTS AND DISCUSSION

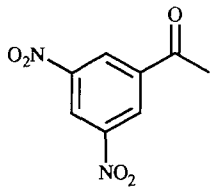
Amines **6-13** were each *N*-acylated with 3,5-dinitrobenzoyl chloride and the *cis* and *trans* isomers of 3,5-dinitrocinnamoyl

chloride. The resulting derivatives, termed DNB, *cis*-DNCIN and *trans*-DNCIN respectively, were chromatographed on CSPs **1-5** using a hexane-2-propranol mixture (Tables 1-2). The selectors used in CSPs **2-5** are identical *save for the π-basic N-aryl substituent*. On mechanistic grounds, the DNB and DNCIN derivatives are expected to behave similarly. In those instances where elution orders were determined, they are consistent with the mechanistic rationale which requires the elution from (*S*) CSPs **1-5** to be (*R*) before (*S*) for the amino acid derivatives but (*S*) before (*R*) for the aminophosphonate derivatives (owing to a different Cahn-Ingold-Prelog priority sequence).[5,6]

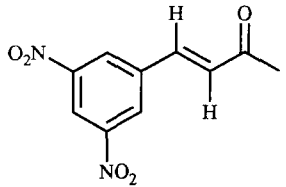
In CSPs **2-5**, the dimensions and the π-basicity of the aryl substituent differ as do the angular orientations of these groups relative to the remainder of the CSP. Similarly, the three π-acidic aryl groups differ in their dimensions, π-acidicity and angular disposition relative to remainder of the analyte. How will these changes influence the strength and stereochemical dependence of the face to face π-π interaction in the various CSP-analyte combinations?

For the *N*-(3,5-dinitrobenzoyl) derivatives, the greatest enantioselectivity is always afforded by the leucine-derived CSP **1** and, in six of the eight instances, CSP **1** affords the least retention of the least retained enantiomers of these analytes. This comes, presumably, as a consequence of CSP **1**'s greater conformational rigidity and a more favorable preorganization. The latter favors retention of the more retained enantiomer whereas the former discriminates against retention of the least retained enantiomer.

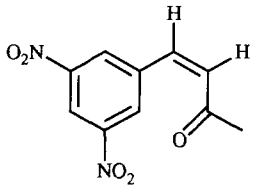
TABLE 1: Comparision of the Ability of CSPs **1-5** to Separate the Enantiomers of the DNB and DNCIN Derivatives of **6-9.**



DNB



t -DNCIN



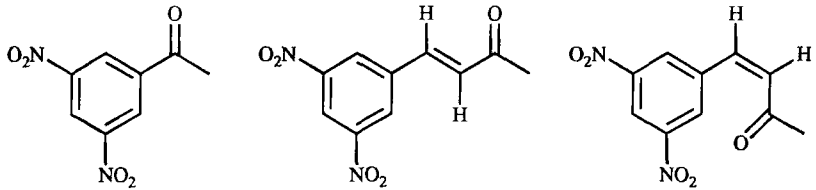
c -DNCIN

		(*S*)-CSP 1		(*R*)-CSP 2		(*R*)-CSP 3		(*S*)-CSP 4		(*R*)-CSP 5	
	deriv	k_1'[a]	α[b]	k_1'[a]	α[b]	k_1'[a]	α[b]	k_1'[a]	α[b]	k_1'[a]	α[b]
6	DNB	3.47	6.85	5.43	2.99	5.07	2.82	4.96	1.98	4.89	2.60
6	*t*-DNCIN	4.56	1.51	8.32	1.82	7.03	1.11	11.4	2.00	8.89	2.07
6	*c*-DNCIN	2.38	1.25	4.05	1.13	5.06	1.07	5.19	1.00	4.17	1.12
7	DNB	2.30	12.4	2.99	5.04	2.74	5.05	2.08	3.01	2.43	4.00
7	*t*-DNCIN	3.06	1.70	4.85	2.17	3.61	1.17	5.05	2.75	4.93	2.68
7	*c*-DNCIN	1.40	1.36	2.30	1.17	2.56	1.12	2.50	1.00	2.27	1.18
8	DNB	5.05	9.41(S)	6.92	3.89(R)	6.84	3.25(R)	5.87	2.35(S)	6.37	3.07(R)
8	*t*-DNCIN	6.49	1.80(S)	13.25	2.11(R)	9.53	1.16	14.7	2.69(S)	13.5	2.38(R)
8	*c*-DNCIN	2.85	1.27(S)	5.32	1.15(R)	5.88	1.04	5.76	1.00	5.25	1.16
9	DNB	5.91	4.73	10.2	2.18	7.36	2.26	7.71	1.66	8.38	2.02
9	*t*-DNCIN	6.37	1.39	13.5	1.64	8.82	1.09	16.3	1.88	13.7	1.80
9	*c*-DNCIN	3.11	1.25	5.80	1.14	6.32	1.08	6.02	1.00	5.60	1.12

[a] The capacity factor for the first eluted enantiomer using 20% isopropyl alcohol in hexane as the mobile phase. Flow rate: 2 ml per minute.

[b] The separation factor for the enantiomers. The letter refers to the absolute configuration of the more retained enantiomer.

TABLE 2: Comparision of the Ability of CSPs **1-5** to Separate the Enantiomers of the DNB and DNCIN Derivatives of **10-13.**



DNB *t*-DNCIN *c*-DNCIN

		(*S*)-CSP 1		(*R*)-CSP 2		(*R*)-CSP 3		(*S*)-CSP 4		(*R*)-CSP 5	
	deriv	k_1'[a]	α[b]	k_1'[a]	α[b]	k_1'[a]	α[b]	k_1'[a]	α[b]	k_1'[a]	α[b]
10	DNB	3.26	1.44(S)	5.09	1.31(R)	5.56	1.07(R)	4.77	1.12(S)	4.92	1.25(R)
10	*t*-DNCIN	3.22	1.00	5.87	1.10(R)	6.04	1.00	7.57	1.06(S)	6.58	1.12(R)
10	*c*-DNCIN	2.09	1.00	3.67	1.00	5.20	1.00	4.38	1.00	3.97	1.00
11	DNB	4.26	1.47	6.94	1.39	7.67	1.10	6.89	1.17	6.97	1.27
11	*t*-DNCIN	4.38	1.00	8.51	1.12	8.77	1.00	11.2	1.15	9.42	1.13
11	*c*-DNCIN	2.78	1.00	5.10	1.00	7.12	1.00	6.22	1.00	5.43	1.00
12	DNB	2.38	2.40	3.34	2.01	4.89	1.36	3.21	1.58	3.09	1.66
12	*t*-DNCIN	3.49	1.00	5.62	1.17	5.77	1.00	6.24	1.29	5.59	1.21
12	*c*-DNCIN	1.72	1.00	3.17	1.00	4.10	1.00	3.32	1.00	3.07	1.06
13	DNB	1.85	4.48(R)	2.71	3.61(S)	2.56	2.29(S)	2.29	2.23(R)	2.32	2.84(S)
13	*t*-DNCIN	2.78	1.18(R)	4.62	2.10(S)	3.85	1.07	5.37	3.00(R)	4.68	2.49(S)
13	*c*-DNCIN	1.74	1.22(R)	3.00	1.32(S)	3.38	1.00	4.50	1.00	3.18	1.00

[a] The capacity factor for the first eluted enantiomer using 20% isopropyl alcohol in hexane as the mobile phase. Flow rate: 2 ml per minute.

[b] The separation factor for the enantiomers. The letter refers to the absolute configuration of the more retained enantiomer.

For the *N-trans*-3,5-dinitrocinnamoyl derivatives, the greatest enantioselectivity is always observed for either CSP **4** or CSP **5**. Evidently, an "extended" π-acidic substituent requires an "extended" π-basic substituent on the CSP to afford a strong face to face π-π interaction. With but one negligible exception (analyte **10**, CSP **1**) the least retained enantiomer of a *trans*-DNCIN derivative is more strongly retained than the least retained enantiomer of a DNB derivative. Strong retention on the π-acidic CSPs of the least retained analyte enantiomer has been noted when the analyte contains a large π-basic (*e.g.* pyrenyl) substituent. This presumably occurs because the larger π-basic group enables the less retained enantiomer to somehow participate (albeit less effectively) in the bonding interactions enjoyed by the more retained enantiomer. The present situation with the larger π-acidic groups seems to be similar. Strong retention of the least retained enantiomer typically reduces enantioselectivity. Certainly, the enantioselectivies observed for the *trans*-DNCIN derivative of a given analyte on CSP **4** or CSP **5** are always less than those observed for the corresponding DNB derivatives on CSP **2**, all these CSPs being derived from alanine.

The *N-cis*-3,5-dinitrocinnamoyl derivatives typically show lower levels of enantioselectivity than their *trans* counterparts and, with but one exception (analyte **12**), show greater enantioselectivity on CSP **1** and CSP **2** than on CSP **4** and CSP **5**. The retention of these derivatives is less than that for either of the other derivatives and may stem from the nonplanarity of the *cis*-DNCIN system. The ultraviolet-visible absorption spectra of the cis and trans systems differ and, interestingly, *trans*-derivatives are photoisomerized to the

cis by room light, much as *trans*-azobenzene is photoisomerized to the less absorptive *cis* isomer.

CONCLUSION

We have frequently observed that use of large π-basic substituents, pyrenyl rather than naphthyl, for example will increase retention but diminish enantioselectivity when the analytes are chromatographed on a π-acidic CSP. This seems to be true of the converse situation as well. However, enantioselectivity can be improved if, for a given π-acidic substituent, a CSP having a π-basic substituent with the proper "spatial complementarity" is used.

ACKNOWLEDGEMENTS

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