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# PREPARATION AND EVALUATION OF A CHIRAL STATIONARY PHASE BEARING BOTH π-ACIDIC AND -BASIC SITES

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## SUMMARY

A new chiral stationary phase has been prepared and evaluated. It contains both π-acidic and -basic sites. When used to chromatograph racemic analytes which also contain π-acidic and -basic sites, two simultaneous π–π interactions occur. The impact of such interactions on the chromatographic behavior of the enantiomers of several homologous series of analytes was determined and is explained in terms of competing chiral recognition mechanisms.

## INTRODUCTION

The use of chiral stationary phases for the analysis of enantiomeric purity by high-performance liquid chromatography (HPLC) is now a well established technique. Moreover, preparative separations of enantiomers are being similarly conducted in a number of laboratories. However, the view that the elution order from a chiral stationary phase (CSP) can be used to assign absolute configurations to enantiomers will be slow to gain general acceptance. To assign correctly absolute configurations from elution orders from a given CSP of known absolute configuration, one must clearly understand the mechanism(s) by which the separations occur. For some time now, our laboratory has been addressing the mechanisms of chiral recognition on CSPs. In these studies, we have used the concept of reciprocality of chiral recognition. For example, the N-(3,5-dinitrobenzoyl)-α-amino acid derivative 1 (itself developed from a consideration of chiral recognition mechanisms) has been used to resolve many chiral analytes bearing a π-basic group together with other suitably placed functionalities[1,2]. From such studies, "reciprocal" 1-aryl-1-amino alkane-based derivatives such as 2 or 3, and N-arylamino acid-based derivatives such as 4, have evolved[1–4]. These have proven to be quite effective for the resolution of chiral analytes containing π-acidic groups in conjunction with other appropriately situated functionalities. Usually, π-acidic group such as 3,5-dinitrobenzoyl or 3,5-dinitroanilido are most effective. Other π-acidic groups may also suffice, albeit with

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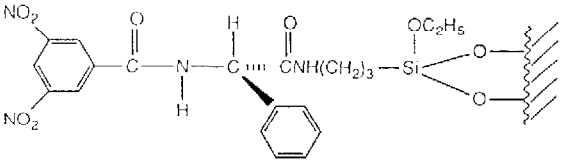

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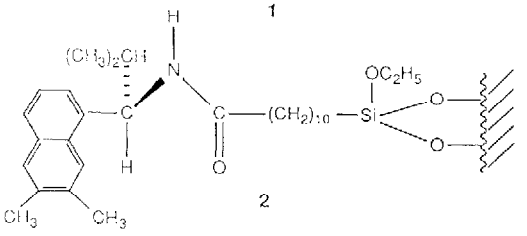

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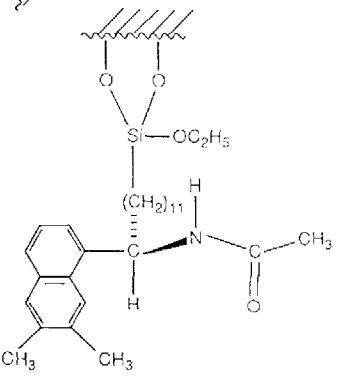

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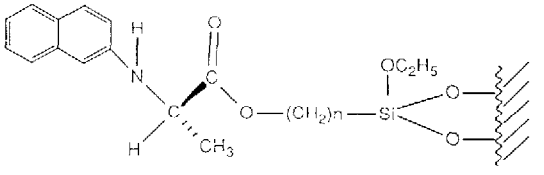

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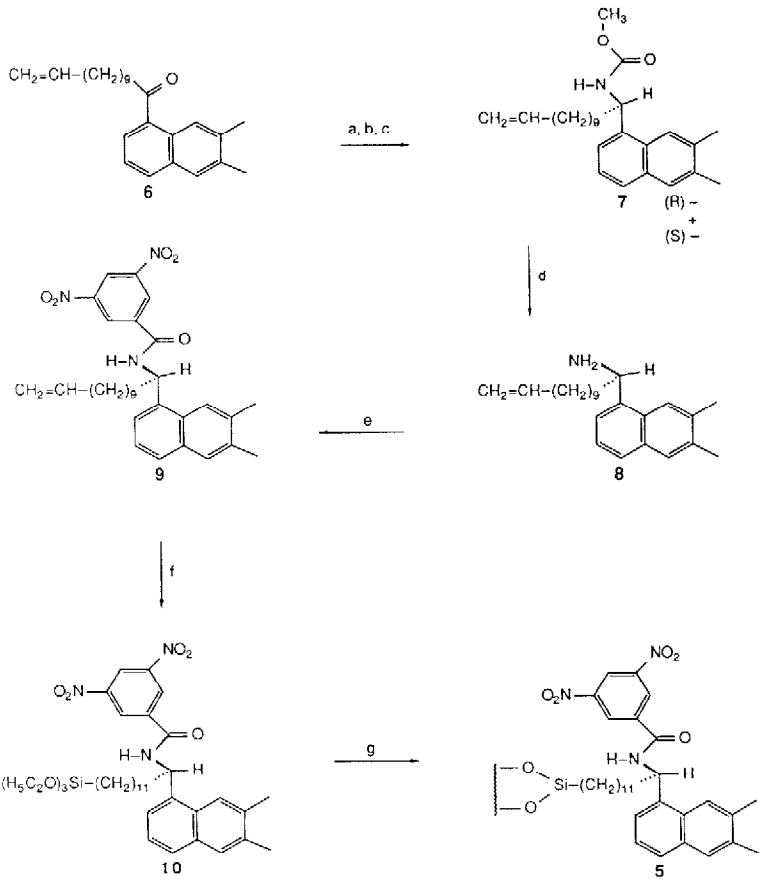
reduced levels of chiral recognition. The occurrence of $\pi$–$\pi$ interactions, in combination with other interactions, is common in most enantiomer separations afforded by CSPs 1–4, although some exceptions are known. That is, $\pi$–$\pi$ interactions are important to the functioning of these CSPs, although not always essential.

One can readily envisage a CSP containing both $\pi$-acidic and -basic sites which might be expected to give two simultaneous $\pi$ $\pi$ interactions for analytes containing appropriately located $\pi$-basic and -acidic sites. In this paper, we describe the preparation (Scheme 1) and evaluation of CSP 5 which bears both a $\pi$-acidic N-3,5-dinitrobenzoyl group and a $\pi$-basic 1-(6,7-dimethyl)naphthyl group.

## EXPERIMENTAL

### *General*

$^1$H NMR spectra were recorded on a Varian EM 390 or on a Varian XL-200



Scheme 1. (a) $NaCNBH_3$, $CH_3CO_2NH_4$, $CH_3OH$, reflux; (b) $CH_3OO(O)Cl$, triethylamine, $CH_2Cl_2$, room temperature (R.T.); (c) Resolution on chiral stationary phase 1; (d) $(CH_3)_3SiI$, $CHCl_3$, 55°C, then methanol–water; (e) 3,5-dinitrobenzoyl chloride, triethylamine, $CH_2Cl_2$, R.T.; (f) (1) $HSiCl_3$, $H_2PtCl_6$, reflux, (2) $C_2H_5OH$, triethylamine, $CH_2Cl_2$; (g) 5 μm silica gel, benzene, reflux.

spectrometer, IR spectra on a Perkin-Elmer 1320 or Nicolet 7199 FT-IR spectrometer. Microanalyses were performed by the Microanalytical Laboratory, University of Illinois at Urbana-Champaign. High-resolution mass spectra were obtained on a Varian 731 mass spectrometer. Optical rotations were observed at 589 nm at room temperature using a Rudolph Autopol III polarimeter.

Chromatography was performed using an Altex 100 A pump, an Altex 210 injector, an Altex Model 152 dual wavelength (254 and 280 nm) or an Altex Model 165 variable-wavelength detector and a Kip-Zonen BD 41 recorder. All solutes used were available from previous studies[1].

*Methyl N-1-[1-(6,7-dimethyl)naphthyl]-11-dodecenylcarbamate (7)*

This carbamate was prepared in two steps by reductive amination of the ketone 6 with sodium cyanoborohydride as described[1] and, without isolation, treatment of

the amine with methyl chloroformate. After work-up and flash chromatography, carbamate 7 was isolated in 65% yield as a white solid, m.p. 109–111°C. $^1$H NMR (deuterochloroform): $\delta$ 1.13–1.50 (m, 14 H), 1.70–2.13 (m, 4 H), 2.40 (s, 3 H), 2.44 (s, 3 H), 3.63 (s, 3 H), 4.80–5.08 (m, 3 H), 5.30–5.48 (m, 1 H), 5.50–6.00 (m, 1 H), 7.20–7.30 (m, 2 H), 7.50–7.68 (m, 2 H), 7.84 (s, 1 H). IR (potassium bromide): 3330, 2920, 2855, 1704, 1566 cm$^{-1}$. Analysis (%): calc. for $C_{26}H_{37}NO_2$ C, 78.94; H, 9.43; N, 3.54; found C, 79.08; H, 9.17; N, 3.66.

*Resolution.* This carbamate was resolved on a previously reported preparative chiral column containing CSP 1[5]. High-$R_F$ enantiomer, (*R*)-7: m.p. 123–124°C; $[\alpha]_D$ + 5.04 (*c* 0.58, dichloromethane). Low-$R_F$ enantiomer, (*S*)-7: m.p. 125–126°C; $[\alpha]_D$ − 3.46 (*c* 0.81, dichloromethane). In this instance, the low-$R_F$ enantiomer fraction was of reduced enantiomeric purity owing to tailing of the high-$R_F$ enantiomer band. However, the high-$R_F$ enantiomer was of >98% enantiomeric purity.

*(R)-1-[1-(6,7-Dimethyl)naphthyl]-11-dodecenylamine (8)*

Carbamate (*R*)-7 (1.6 g, 0.0041 mol) was dissolved in 30 ml of chloroform and then trimethylsilyl iodide (1.12 g, 0.0056 mol) was added. After heating the mixture to 55°C for 2 h, the complete disappearance of the methoxy group was observed by NMR spectroscopy. The mixture was cooled to room temperature and the solvent was removed under vacuum. The residue was treated with 10 ml of methanol and 100 ml of water. After removing the methanol, the aqueous solution was made strongly basic with potassium hydroxide pellets. This solution was extracted twice with diethyl ether. The ether extracts were pooled, dried over magnesium sulphate and then evaporated to dryness to afford 1.38 g of a dense pale yellow liquid (crude yield 100%). This crude amine was used for the next reaction without further purification.

*(R)-N-(3,5-Dinitrobenzoyl)-1-[1-(6,7-dimethyl)naphthyl]-11-dodecenylamine (9)*

Crude amine 8 (1.38 g), obtained as above, and triethylamine (0.84 ml, 0.006 mol) were dissolved in 200 ml of dichloromethane. To this stirred solution was added 3,5-dinitrobenzoyl chloride (1.39 g, 0.006 mol). The mixture was vigorously stirred for 20 min at room temperature (R.T.) and then washed with 1 *M* sodium hydroxide solution, 1 *M* hydrochloric acid solution and water. After drying over magnesium sulphate and flash chromatography, 2.07 g of amide 9 were obtained [overall yield 95% from carbamate (*R*)-7]. Yellow solid, m.p. 140–143°C. $^1$H NMR (deuterochloroform): $\delta$ 1.10–1.40 (m, 14 H), 1.83–2.07 (m, 4 H), 2.27 (s, 3 H), 2.32 (s, 3 H), 4.70–4.97 (m, 2 H), 5.43–5.90 (m, 2 H), 7.10–7.55 (m, 5 H), 7.70 (s, 1 H), 8.67–8.80 (m, 3 H). IR (potassium bromide): 3300, 3100, 2925, 2855, 1640, 1545 cm$^{-1}$. Analysis (%): calc. for $C_{31}H_{37}N_3O_5$ C, 70.03; H, 7.02; N, 7.90; found C, 69.62; H, 7.04; N, 7.70. High-resolution mass spectrum: calc. 531.2733; found 531.2730. $[\alpha]_D$ − 61.33 (*c* 1.58, dichloromethane).

*(R)-N-(3,5-Dinitrobenzoyl)-1-[1-(6,7-dimethyl)naphthyl]-12-triethoxysilyldodecylamine (10)*

This compound was prepared from the reaction of amide 9 with trichlorosilane using chloroplatinic acid as a catalyst as described[1]. Yellow viscous oil, yield 68%. $^1$H NMR (deuterochloroform): $\delta$ 0.50–0.74 (m, 2 H), 1.10–1.50 (m, 27 H), 1.42 (s,

6 H), 1.83–2.13 (m, 2 H), 3.80 (q, 6 H), 5.77–6.03 (m, 1 H), 7.13 (d, 1 H), 7.20–7.38 (m, 2 H), 7.48–7.67 (m, 2 H), 7.82 (s, 1 H), 8.78–8.85 (m, 2 H), 8.90–9.00 (m, 1 H). IR (neat): 3300, 3100, 2980, 2930, 2860, 1637, 1548 $cm^{-1}$. High-resolution mass spectrum: calc. for $C_{37}H_{53}N_3O_8Si$ 695.3601; found 695.3605. $[\alpha]_D$ – 53.3 (*c* 0.33, dichloromethane).

*Chiral stationary phase 5*

A 4.5-g portion of 5-μm Spherisorb silica gel was slurried with benzene and then water was removed azotropically using a Dean–Stark trap. After complete removal of water, 2 g (0.003 mol) of the chiral organosilane 10 were added and heated to reflux for 36 h under a nitrogen atmosphere with continuous stirring. The modified silica gel was collected by filtration and washed with benzene, ethyl acetate, methanol, acetone, diethyl ether and pentane. This chiral absorbent was packed into a 250 mm × 4.6 mm I.D. stainless-steel column as a methanol slurry by conventional means. Analysis: found C, 7.26; H, 0.99; N, 0.56; Si, 41.78%; calc. 0.13 mmol of 10 per g of stationary phase (based on N), 0.18 mmol of 10 per g of stationary phase (based on C).

## RESULTS AND DISCUSSION

The chiral phase 5 was prepared from ketone 6 as shown in Scheme 1. The intermediate amine was not isolated but converted directly into carbamate 7 by the action of methyl chloroformate. Purification and optical resolution of racemic 7 was effected by chromatography on a preparative column containing CSP 1[5]. The (*R*)-enantiomer of carbamate 7 was converted to amine (*R*)-8 by the action of trimethylsilyl iodide and subsequent quenching with methanol–water. Treatment of amine (*R*)-8 with 3,5-dinitrobenzoyl chloride affords amide (*R*)-9. Hydrosilylation of this amide with trichlorosilane, catalyzed by chloroplatinic acid, and subsequent treatment with ethanol–triethylamine, gave the (*R*)-enantiomer of compound 10. Reaction of 10 with 5-μm Spherisorb silica affords CSP (*R*)-5.

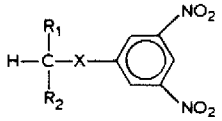
CSP 5 is structurally similar to CSP 3, a 3,5-dinitrobenzoyl group being present rather than acetyl. Consequently, CSP 5 was expected to provide chromatographic performance somewhat similar to that of CSP 3 but modified in instances where a second π–π interaction might occur.

Table I summarizes the chromatographic data for the resolution of a number of N-3,5-dinitrobenzoyl derivatives of α-amino esters, α-amino amides, amines and amino alcohols, as well as the 3,5-dinitroanilides of several chiral carboxylic acids. All these compounds are also resolvable on CSP 3 for which similar data have been reported elsewhere[1]. The elution orders and general chromatographic trends noted on the two CSPs are the same, consistent with an overall similarity in the fundamental mechanisms of chiral recognition. However, none of the compounds in Table I contains strongly π-basic substituents. Hence, the similar behavior of CSPs 3 and 5 is not unexpected. However, the behavior of CSP 5 towards analytes containing more effective π-basic sites differs considerably from that of CSP 3.

In Fig. 1A, the effect of the length of the alkyl "tail" upon the magnitude of α, the separation coefficient for the enantiomers noted on CSP 3, is shown for one of several homologous series of N-(3,5-dinitrobenzoyl)-1-aryl-1-aminoalkanes (11)

TABLE I

SEPARATION OF THE ENANTIOMERS OF N-(3,5-DINITROBENZOYL) AMINES AND AMINO ACID DERIVATIVES ON CSP 5



| $R_1$ | $R_2$ | $\alpha$ | $k_1'$* | *Configuration*** |
|---|---|---|---|---|
| X = –NH–C– | | | | |
| $CH_3$ | $COOCH_3$ | 1.57 | 4.7 | *R* |
| *iso*-$C_3H_7$ | $COOCH_3$ | 2.01 | 4.3 | *R* |
| *iso*-$C_4H_9$ | $COOCH_3$ | 2.33 | 3.3 | *R* |
| Phenyl | $COOCH_3$ | 1.79 | 9.1 | *R* |
| | $COOC_5H_{11}$-*n* | 1.64 | 6.0 | *R* |
| | $COOC_{10}H_{21}$-*n* | 1.40 | 4.8 | *R* |
| Benzyl | $COOCH_3$ | 2.19 | 6.5 | *R* |
| | $COOC_4H_9$-*n* | 2.12 | 4.4 | *R* |
| | $COOC_{10}H_{21}$-*n* | 1.72 | 3.4 | *R* |
| *iso*-$C_3H_7$ | $CONHC_4H_9$-*n* | 1.40 | 1.0 | *R* |
| *iso*-$C_4H_9$ | $CONHC_4H_9$-*n* | 1.36 | 1.1 | *R* |
| Phenyl | $CONHC_4H_9$-*n* | 1.10 | 2.7 | *R* |
| Benzyl | $CONHC_4H_9$-*n* | 1.39 | 1.6 | *R* |
| $CH_3$ | $CH_2CH_3$ | 1.14 | 4.2 | *S* |
| $CH_3$ | $(CH_2)_5CH_3$ | 1.16 | 3.3 | |
| $CH_3$ | *iso*-$C_4H_9$ | 1.21 | 3.3 | |
| $CH_2CH_3$ | $CH_2OH$ | 1.10 | 2.5 | *R* |
| *iso*-$C_3H_7$ | $CH_2OH$ | 1.17 | 2.0 | *R* |
| Phenyl | $PO(OC_2H_5)_2$ | 1.62 | 4.9 | |
| 4-Methoxyphenyl | $PO(OC_2H_5)_2$ | 1.64 | 8.4 | |
| X = C NH | | | | |
| Phenyl | $CH_2CH_3$ | 1.30 | 2.3 | |
| Phenoxy | $CH_3$ | 1.11 | 4.6 | |
| 2-Phenoxyethyl | $CH_3$ | 1.08 | 2.9 | |

* Capacity ratio for the enantiomer eluted first at room temperature. Mobile phase: isopropanol–hexane (20:80); flow-rate 2 ml/min.

** Absolute configuration of the enantiomer eluted second.

used in this study. The series in Fig. 1A utilizes a 1-naphthyl group as an effective $\pi$-base. While the $\alpha$ *vs.* *n* curves for the series where the 1-aryl substituent is phenyl, *p*-anisyl or 2-naphthyl are not shown, these curves are qualitatively quite similar in shape and $\alpha$ values to the curve in Fig. 1A. Evidently, the 1-aryl group simply serves as an effectively larger substituent than the alkyl tail, thus determining the elution orders. The length of the alkyl tail influences the magnitude of $\alpha$.

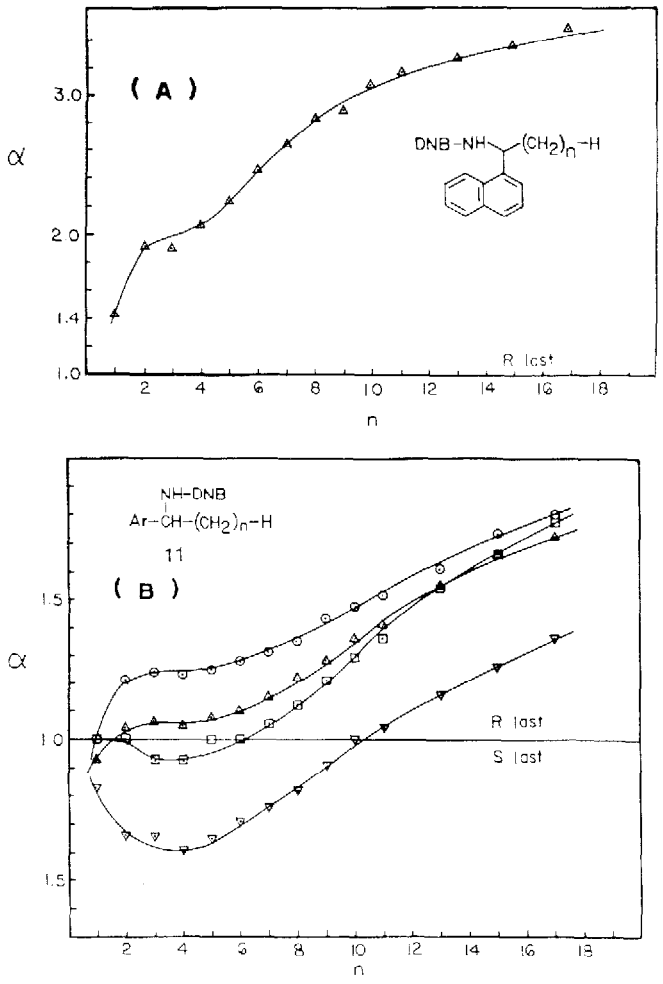



Fig. 1. Relationship between $n$ and the chromatographic separation factor, $\alpha$, for the enantiomers of an homologous series analytes. (A) Chromatography on CSP (*R*)-3 using 20% isopropanol in hexane as a mobile phase; (B) chromatography on CSP (*R*)-5 using the same mobile phase. Ar = Phenyl (⊙), 4-methoxyphenyl (△), 1-naphthyl (▽), 2-naphthyl (□).

It has been suggested that, on CSP 3, the dominant chiral recognition process, termed a dipole-stacking process, does not require that the alkyl tail of the most retained analyte enantiomer intercalate between adjacent strands of the bonded phase[1]. From a study of models, we infer that the initial segment of the alkyl tail is, for the most strongly retained (*R*)-enantiomer, in the vicinity of the acetyl methyl group of CSP 3. The competing "hydrogen bonding" process expresses a preference for the opposite sense of enantioselectivity[1]. During this process on CSP 3, the preferentially retained (*S*)-enantiomer must intercalate its alkyl tail between adjacent strands of bonded phase. In non-polar mobile phases, this intercalation is sterically disfavored. Hence, the longer the alkyl tail, the more severe is the steric interaction

and the less the retention of the (*S*)-enantiomer by the hydrogen-bonding process. Since, owing to the dominance of the dipole-stacking process, the (*S*)-enantiomer is the first eluted, further hastening of its elution increases $\alpha$. Hence, the shape of the $\alpha$ *vs.* *n* curve in Fig. 1A[1].

During dipole stacking, the preferentially retained (*R*)-enantiomer places the initial segment of its alkyl tail near the acyl group of the CSP. When similarly "stacked", the (*S*)-enantiomer places its 1-aryl substituent near this acyl group. Consider the consequences of replacing the acyl group with a $\pi$-acidic group. In such an instance, *i.e.*, CSP 5, one might anticipate enhanced retention of the (*S*)-enantiomers owing to the occurrence of $\pi$–$\pi$ bonding between the CSP $\pi$-acidic acyl group and the (*S*)-enantiomer 1-aryl substituent. This effect should increase as the $\pi$-basicity of the 1-aryl substituent increases. Were it sufficiently strong, this additional $\pi$–$\pi$ interaction might even reverse the usual elution order of the enantiomers.

Examination of Fig. 1B shows that the $\alpha$ *vs.* *n* curves of homologeous series of type 11 analytes are indeed influenced by the $\pi$-basicity of the aryl substituent. The curves seemingly indicate a superpositioning of the effect of the second $\pi$–$\pi$ interaction upon the usual blend (dipole stacking dominant, hydrogen bonding subordinate) of chiral recognition mechanisms. The extent of the contribution made by the additional $\pi$–$\pi$ interaction clearly increases as the $\pi$-basicity of the aryl group increases. The greater ability of the 1-naphthyl substituent to undergo this effect compared to the 2-naphthyl substituent is suggested to be conformational in origin. The *peri*-hydrogen confers a degree of conformational preference and rigidity upon the 1-naphthyl substituent that is lacking for the 2-naphthyl substituent. Conformational rigidity may either enhance or reduce the degree of chiral recognition, depending upon the conformation preferred. It may be that even the 1-naphthyl substituent is not optimally placed so as to facilitate the second $\pi$ $\pi$ interaction. Other types of analytes bearing $\pi$-basic substituents may be better able to interact with the 3,5-dinitrobenzoyl group of CSP 5.

## CONCLUSIONS

The curves in Fig. 1B, when compoared to that in Fig. 1A, clearly indicate the occurrence of a second $\pi$–$\pi$ interaction, when type 11 analytes are chromatographed on CSP 5. The magnitude of this additional $\pi$–$\pi$ interaction increases with the $\pi$-basicity of the analyte's aryl substituent. These curves demonstrate the type of mechanistic information to be had from systematic studies of the effect of structure upon the sense and magnitude of chiral recognition on a CSP. This type of information is essential if one is to understand chiral recognition sufficiently well so as reliably to relate the elution order to the absolute configuration. It should be manifest that such understanding is an essential aid in designing improved CSPs.

## ACKNOWLEDGEMENTS

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