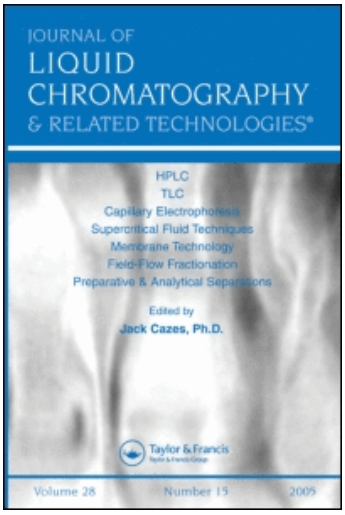

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SEPARATION OF THE ENANTIOMERS OF 3,5-DINITROPHENYL CARBAMATES AND 3,5-DINITROPHENYL UREAS

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ABSTRACT

The preparation of 3,5-dinitrophenyl carbamates and 3,5-dinitrophenyl ureas from chiral alcohols and amines and 3,5-dinitrobenzoyl azide is described. These ureas and carbamates have been observed to resolve on α-arylalkylamine based chiral stationary phases **1** and **2**. A mechanism for the resolution of these carbamates and ureas is presented and compared to the resolution and mechanism thereof for the analogous series of 3,5-dinitrobenzamides on these phases.

INTRODUCTION

Recent work in this laboratory has centered on the rational design and synthesis of chiral stationary phases (CSP's) for the direct liquid chromatographic resolution of racemates. To this end, a series of fluoroalcohol (1), amino acid (2), hydantoin (3), and α-arylalkylamine (4) derived stationary phases have been prepared and evaluated. Each class of stationary phase exhibits enantioselectivity toward a

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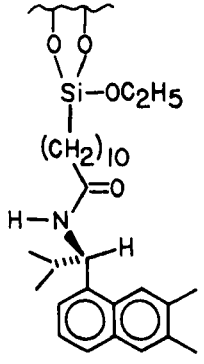
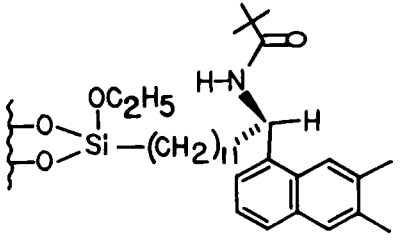
variety of analytes which, in a mechanistic sense, are of similar constitution even though they may contain a wide range of functionality.

Efforts to understand the selectivity of these chiral phases have led to the postulation of chiral recognition models (1-5). These models are intended to be used as aids to understanding which enantiomers may be separated on a given CSP and in what order the enantiomers may elute. Moreover, these models may also be used to aid in the design of CSPs of improved scope and selectivity. CSPs **1** and **2** were designed in this manner (4,5). These reciprocal CSPs typically separate the enantiomers of amines, amino acids, amino alcohols, alcohols, etc. after acylation with achiral π-acidic reagents. We commonly employ 3,5-dinitrobenzoyl chloride (DNBC) for this purpose; preparations of the enantiomers of a number of its amide and ester derivatives have been reported. (**1**, **3**, **4**, **5**).



CSP 1



CSP 2

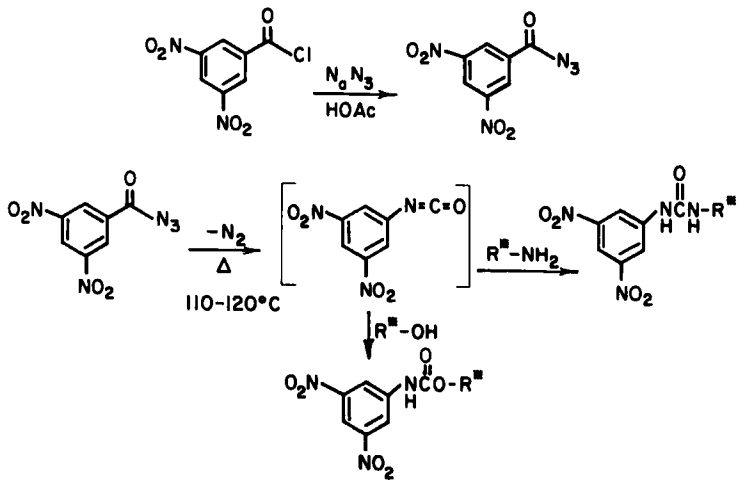
As a derivatizing agent, DNBC has several desirable properties. It is inexpensive, simple to use, affords derivatives in nearly quantitative yield, produces few (and easily removed) side products and, being achiral, affords no

optical fractionation. Other acylating agents may be used as derivatizing agents although most are inferior to DNBC in terms of product separability. An interesting alternative as an achiral π-acidic derivatizing agent is 3,5-dinitrophenyl isocyanate (DNPI). This reagent has been used by Oi and co-workers (**6**) to derivatize several enantiomeric alcohols. Oi has found that the enantiomers of the resultant carbamates are readily separable on CSPs developed in his laboratory (**7**). Since no comprehensive study of this derivatizing agent has appeared, we are moved to report the results of a systematic investigation of the separability on CSPs **1** and **2** of a series of enantiomeric dinitrophenyl carbamates (DNPC) and dinitrophenyl ureas (DNPU) derived from DNPI. Of specific interest is a comparison of the chiral recognition mechanisms involved in the separation of the various enantiomeric derivatives.

MATERIALS

The 3,5-dinitrophenyl carbamates and ureas used in this study are readily prepared from alcohols and amines by the action of DNPI. This reagent is conveniently generated *in situ* from the thermal decomposition of 3,5-dinitrobenzoyl azide (**8**) (Scheme 1), prepared by portionwise addition of one equivalent of sodium azide to DNBC dissolved in a minimum amount of glacial acetic acid. Dilution of the reaction mixture with water after 30 minutes causes 3,5-dinitrobenzoyl azide to crystallize in high yield and purity. The azide is stable to storage, survives melting, but loses nitrogen at approximately 120°C to yield DNPI.

The carbamates and ureas used in this study were prepared by heating a 10% excess of the azide in toluene under reflux for 6-10 minutes. The alcohol or amine was then added to this



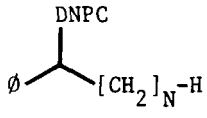
solution. These reactions were typically carried out on a small scale and the reaction mixture was analyzed without any work up beyond cooling and dilution. This procedure is quite convenient, affords derivatives with few impurities and avoids isolation of the isocyanate. Residual DNPI or azide elutes before the carbamates or ureas and does not interfere with the analysis. All of the columns employed in this study have been described (**4**, **5**, **9**).

RESULTS

Chiral stationary phases **1** and **2** were selected for this study because of the insight they were expected to provide into the mechanism of separation of the enantiomers of the carbamates and ureas. Table 1 contains data relevant to the chromatographic behaviour of homologous series of carbamate and urea analytes on CSPs **1** and **2**. Plots of α, the separability factor, versus the number of carbons in the linear alkyl portion of the analytes are shown in Figures 1-4. Essentially all of the analyte enantiomers are separable on CSPs **1** and **2**.

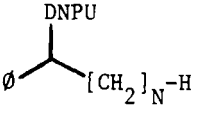
TABLE 1

Resolution of 3,5-Dinitrophenyl Carbamates[A]



	CSP 1_H		CSP 1_M		CSP 1_L		CSP 2	
N	k_i'	α	k_i'	α	k_i'	α	k_i'	α
1	1.5	1.53	1.5	1.42	1.6	1.23	14.2	1.31
2	1.4	1.47	1.5	1.48	1.6	1.17	12.5	1.35
3	1.2	1.41	1.4	1.41	1.5	1.14	11.4	1.35
4	1.1	1.40	1.3	1.40	1.4	1.14	8.2	1.46
5	1.0	1.33	1.3	1.38	1.3	1.15	8.2	1.43
7	1.1	1.27	1.2	1.31	1.6	1.15	8.2	1.50
8	1.2	1.30	1.1	1.30	1.8	1.16	8.5	1.49
9	1.2	1.26	1.1	1.30	1.6	1.19	7.0	1.61
11	1.1	1.22	1.0	1.28	1.5	1.11	6.1	1.71
13	1.1	1.17	1.0	1.20	1.5	1.11	7.0	1.64

Resolution of 3,5-Dinitrophenyl Ureas[B]



	CSP 1_H		CSP 1_M		CSP 1_L		CSP 2	
N	k_i'	α	k_i'	α	k_i'	α	k_i'	α
1	1.7	1.79	1.4	1.42	1.9	1.47	3.4	1.36
2	1.8	1.66	1.4	1.36	2.0	1.55	4.3	1.38
3	1.7	1.58	1.3	1.38	1.8	1.55	3.2	1.45
4	1.7	1.36	1.3	1.36	1.9	1.42	3.0	1.46
5	1.6	1.29	1.3	1.35	1.8	1.44	2.8	1.46
6	1.9	1.21	1.2	1.35	1.7	1.41	2.6	1.51
7	1.8	1.16	1.1	1.36	1.7	1.41	2.5	1.54
8	1.9	1.12	1.1	1.27	1.7	1.35	2.6	1.62
9	1.5	1.10	1.1	1.27	1.4	1.42	2.6	1.67
11	1.3	1.01	1.0	1.20	1.3	1.35	2.0	1.70
13	1.2	1.01	1.0	1.10	1.4	1.35	1.8	1.75

A. Analytes were isocratically eluted with 10% isopropyl alcohol in hexane at 2 ml/min.

B. Analytes were isocratically eluted with 20% isopropyl alcohol in hexane at 2 ml/min.

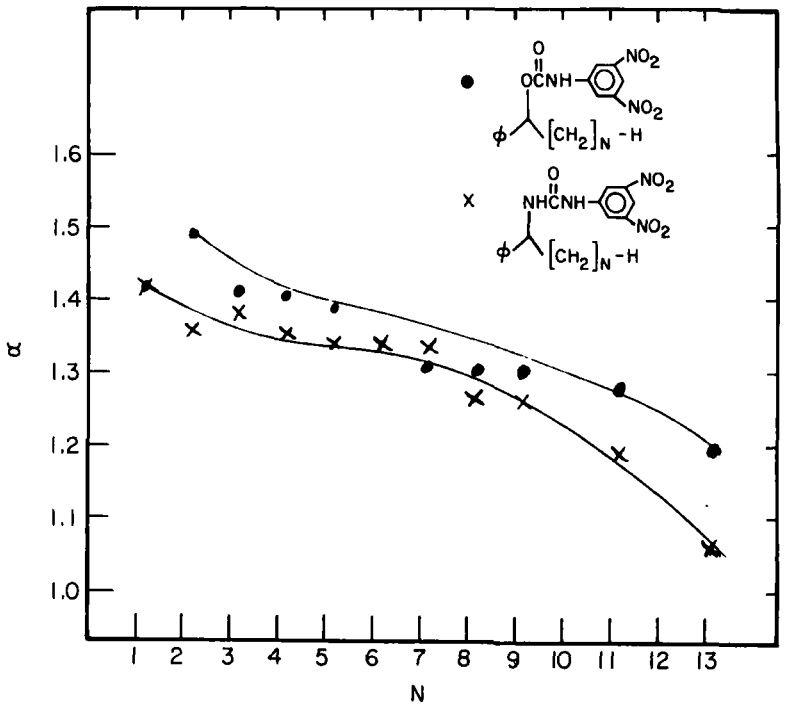


Figure 1: Separation of enantiomeric 3,5-dinitrophenyl carbamates and ureas on CSP $\mathbf{1_M}$. The carbamates and ureas were eluted at 2 ml/min using 10 and 20% isopropyl alcohol in hexane, respectively.

DISCUSSION

We previously reported for the corresponding 3,5-dinitrobenzamides that there is a competition between two chiral recognition processes of opposite enantioselectivity (5). The dominant dipole stacking process intercalates the analytes' linear alkyl substituent between adjacent strands of bonded phase **1**. As the length of the alkyl substituent is increased, the contribution from this intercalative process lessens and, by default, the contribution from the

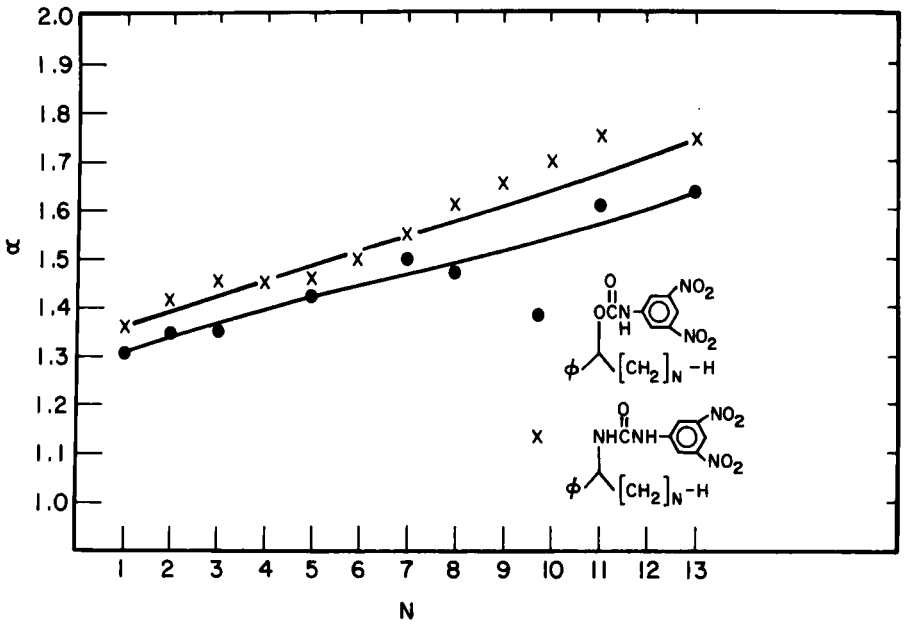


Figure 2: Separation of enantiomeric 3,5-dinitrophenyl carbamates and ureas on CSP **2**. The carbamates and ureas were eluted at 2 ml/min using 10 and 20% isopropyl alcohol in hexane, respectively.

nonintercalative hydrogen bonding process increases. Because the two processes differ in sense of enantioselectivity, the overall degree of chiral recognition is reduced. Shortening the length of the connecting arm of the CSP or reducing the spacing between adjacent strands of bonded phase has much the same effect, which, at its extreme, can invert the elution order of the enantiomers (**5**, **9**). Because the chiral amide portion of CSP **2** is oriented differently (with respect to the silica support) than that of CSP **1**, its dipole stacking process is nonintercalative while the competing hydrogen-bonding process is intercalative. Hence, lengthening the analytes alkyl

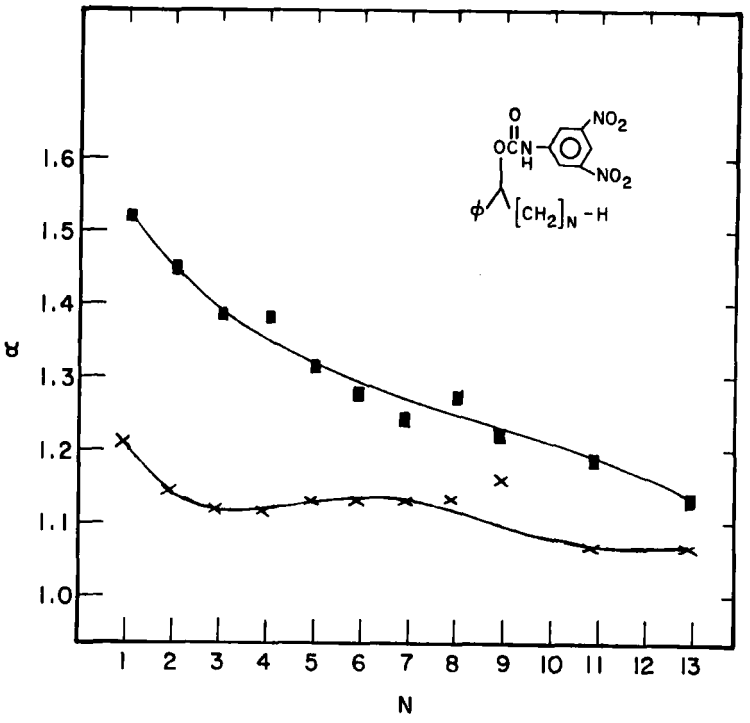


Figure 3: Separation of enantiomeric 3,5-dinitrophenyl carbamates on CSP $\mathbf{1}_H$ (✕) and CSP $\mathbf{1}_L$ (■). The carbamates were eluted at 2 ml/min using 10% isopropyl alcohol in hexane.

substituent increases the magnitude of α rather than diminishing it by increasingly favoring the already dominant process (5).

Figures 1 and 2 show the effect the length of the analytes' alkyl substituent has on the separability of enantiomeric DNPCs and DNPUs when these analytes are chromatographed on CSPs 1 and 2 respectively. These curve shapes are reminiscent of those noted for the DNBC derived analytes where the (R) analyte enantiomers are also most

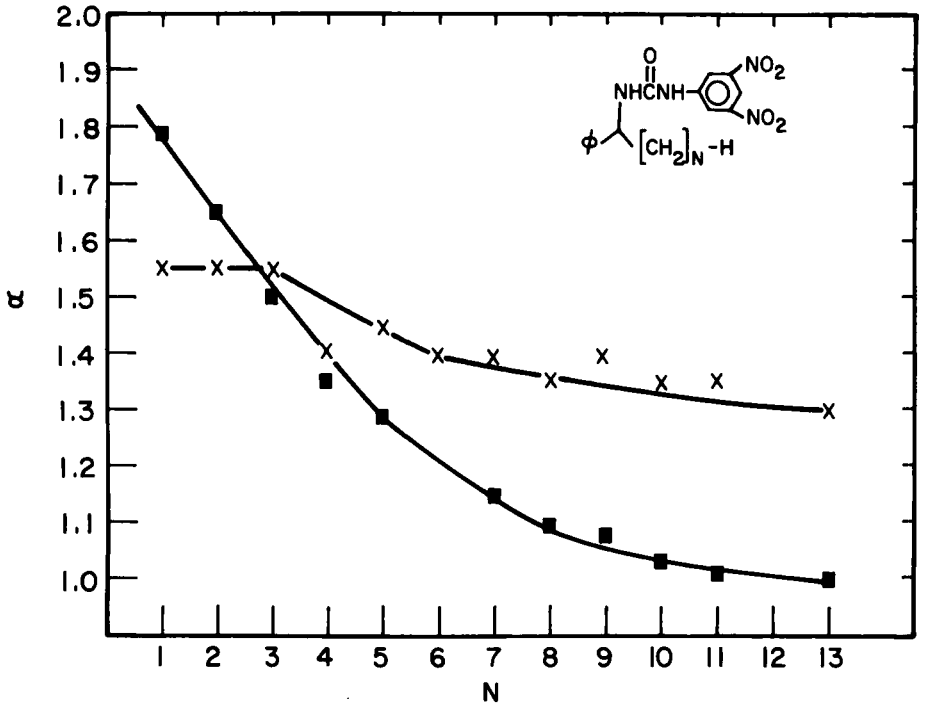


Figure 4: Separation of enantiomeric 3,5-dinitrophenyl ureas on CSP 1_H (■) and CSP 1_L (✕). The ureas were eluted at 2 ml/min using 20% isopropyl alcohol in hexane.

strongly retained (**5**). This suggests a similarity in the mechanisms of chiral recognition for the DNBC and the DNPI derived analytes. We conclude that the dominant chiral recognition process for both the carbamate and urea analytes is a variation of the previously encountered dipole stacking process. This view is further supported by Figures 3 & 4 which shows that closer spacing of the strands of CSP **1**, by disfavoring the intercalation of long alkyl substituents, reduces the contribution of the dominant dipole stacking

process. The columns used to generate the data in Figures 3 and 4 are identical except for the amount of chiral silane bonded to the silica. The column designated $\mathbf{1}_H$ is more heavily loaded with bonded phase than is column $\mathbf{1}_L$ (9). The column designated $\mathbf{1}_M$ is loaded to an intermediate degree and was used to generate the curves shown in Fig. 1.

Overall, the magnitude of the separability factors for the DNPI derived analytes is typically smaller than those noted on these columns for the corresponding DNBC derived analytes. Although this might be of some concern were one performing preparative scale resolutions, it is of reduced concern for analytical separations. Hence, Oi's introduction of DNPI as an achiral derivatizing agent is significant for it offers an alternative to DNBC and might, in some cases, offer some advantage. For example, we note for some enantiomeric aliphatic alcohols that DNPI confers greater separability than does DNBC. This aspect of our work will be described elsewhere.

ACKNOWLEDGEMENT

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