g (14 mmol, 89%) of carboxylic acid **15** as colorless crystals: mp 171-173 °C; IR (Nujol) 3358, 3300, 1721, 1649, 1220, 1174 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.68, 2.01 (br s, 15 H, adamantyl), 2.36 (m, 6 H, CH_2CO, CH_2NH), 3.10 (m, 2 H, $NHCH_2CH_2$), 7.22 (br s, 1 H, AdNH), 7.76 (br s, 1 H, CH_2NHCO).

Carboxylic acid **15** (0.500 g, 1.55 mmol), 0.39 mL (0.32 g, 3.11 mmol) of freshly distilled *N,N*-dimethyl-1,3-propanediamine (Aldrich), 0.353 g (1.71 mmol) of *N,N'*-dicyclohexylcarbodiimide,[28] and 0.975 g (6.37 mmol) of 1-hydroxybenzotriazole[29] hydrate (Aldrich) were reacted in 5 mL of *N,N*-dimethylformamide according to Martinez and Bodanszky[23] to afford 0.312 g (0.77 mmol, 51%) of pure colorless **16** (from toluene): mp 184-186 °C; IR (Nujol) 3275, 3090, 1665, 1635, 1551 cm^{-1}; ^1H NMR δ 1.30 (m, 2 H, $CH_2CH_2CH_2$), 1.68, 2.02 (s, 15 H, adamantyl), 2.26 (s, 6 H, $N(CH_3)_2$), 2.40 (m, 4 H, $COCH_2CH_2NH$, $(CH_3)_2NCH_2$), 2.50 (m, 4 H, $COCH_2CH_2CO$), 3.44 (m, 4 H, $COCH_2CH_2NH$, $CH_2CH_2CH_2N(CH_3)_2$), 5.67 (br s, 1 H, AdNH), 6.87 (br s, 1 H, NHCO).

Anal. Calcd for $C_{22}H_{38}N_4O_3$: C, 64.99; H, 9.42; N, 13.78. Found: C, 65.24; H, 9.52; N, 13.80.

Triamide **16** (0.315 g, 0.78 mmol) was added to a stirred suspension of 0.236 g (6.2 mmol) of $LiAlH_4$[30] in 10 mL of anhydrous ether. The mixture was boiled under reflux under N_2 for 30 h. After the mixture had cooled to room temperature, saturated sodium potassium tartrate solution was added dropwise until no more foaming occurred. The resulting precipitates were removed by filtration and washed with Et_2O. The filtrate and washings were transferred to a separatory funnel, and a small amount of K_2CO_3 was added to basify the solution. The layers were separated, and the aqueous layer was extracted with three 10-mL portions of Et_2O. The combined organic solution was dried over K_2CO_3 and concentrated by rotary evaporation to yield 0.268 g (0.74 mmol, 95%) of tetraamine **17** as a colorless oil: IR (film) 3296, 2916, 1442 cm^{-1}; ^1H NMR δ 1.64 (br s, 23 H, adamantyl, NH, $CH_2CH_2CH_2$, $CH_2(CH_2)_2CH_2$), 1.99 (br s, 3 H, adamantyl), 2.22 (s, 6 H, $(CH_3)_2N$), 2.59 (m, 12 H, NCH_2).

A portion of **17** was treated with excess saturated ethanolic picric acid[27] to form a yellow powder, which resisted recrystallization but was washed several times with cold EtOH and twice with acetone to afford the crystalline tetrapicrate: mp 236 °C dec.

Anal. Calcd for $C_{46}H_{56}N_{16}O_{28}$: C, 43.13; H, 4.41. Found: C, 43.81; H, 4.79.

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Registry No. **4b**, 87639-76-7; **5a**, 63066-15-9; **5b**, 87639-77-8; **5c**, 87639-78-9; **5d**, 87639-79-0; **5e**, 87639-80-3; **5f**, 87639-81-4; **5g**, 87639-82-5; **6a**, 87655-14-9; **6b**, 87639-83-6; **7a**, 87639-84-7; **7b**, 87639-85-8; **7c**, 87639-86-9; **7d**, 3728-77-6; **8a**, 87639-87-0; **8b**, 87639-88-1; **8c** (Y = Cl), 87639-89-2; **8d**, 87639-90-5; **9a**, 87639-91-6; **9b**, 87639-92-7; **10**, 87639-93-8; **12**, 87639-94-9; **13a**, 87639-95-0; **14**, 87639-96-1; **15**, 87639-97-2; **16**, 87639-98-3; **17**, 87655-15-0; **17** (tetrapicrate), 87655-16-1; *N*-(trifluoroacetyl)-β-alanine, 50632-82-1; *N*-(trifluoroacetyl)-γ-aminobutyric acid, 50632-83-2; 1-adamantylamine hydrochloride, 665-66-7; N^8-adamantylspermidine, 87639-99-4; N^8-adamantylspermidine tripicrate, 87640-00-4; *N*-(trifluoroacetyl)glycine, 383-70-0; morpholine, 110-91-8; benzylamine, 100-46-9; piperidine, 110-89-4; *N*-ethylaniline, 103-69-5; dimethylamine, 124-40-3; acrylonitrile, 107-13-1; succinic anhydride, 108-30-5; *N,N*-dimethyl-1,3-propanediamine, 109-55-7.

(28) Sheehan, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067.
(29) König, W.; Geiger, R. *Chem. Ber.* **1973**, *106*, 3626.
(30) Brown, W. G. In "Organic Reactions"; Wiley: New York, 1951; Vol. 6, pp 469-509.

Chromatographic Separation of the Enantiomers of Acylated Amines on Chiral Stationary Phases[1]

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Enantiomers of acylated amines are chromatographically resolved on a stationary phase comprised of (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine covalently bound to γ-aminopropylsilanized silica. Among the acylating agents studied, α-naphthoyl chloride generally serves well and possesses desirable chromophoric properties. The α-naphthamides of a series of primary amines, amino alcohols, and amino acid derivatives have been found to be resolvable on the chiral stationary phase. Among the amines are various substituted cyclohexylamines. A chiral recognition model consistent with present data is described to rationalize the degree of sense of the observed chiral recognition.

High-pressure liquid chromatography columns containing chiral stationary phases (CSP's) derived from the 3,5-dinitrobenzamides of α-amino acids are capable of separating the enantiomers of a great many compounds.[2-4] HPLC columns packed with CSP's derived from (*R*)-phenylglycine (i.e., **1a-b**) are commercially available[5] and, as we now report, are capable of separating the enantiomers of a great many acylated amines.[6]

Acylation of basic amines both facilitates their passage through the π-acidic CSP's, **1a-c**, and provides functionality helpful in the chiral recognition process. While acylation of these amines with a variety of acylating agents

(1) This work has been described at the 184th National Meeting of the American Chemical Society, Kansas City, MO, Sept 1982.
(2) Pirkle, W. H.; Finn, J. M.; Schreiner, J. L.; Hamper, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 3964.
(3) Pirkle, W. H.; Finn, J. M.; Hamper, B. C.; Schreiner, J. L.; Pribish, J. R. *ACS Symp. Ser.* **1982**, *No. 185*, 246.
(4) Pirkle, W. H.; House, D. W.; Finn, J. M. *J. Chromatogr.* **1980**, *192*, 143.
(5) (a) Regis Chemical Co., 8210 Austin Avenue, Morton Grove, IL 60053. (b) J. T. Baker Chemical Co., 222 Red School Lane, Phillipsburg, NJ 08865.
(6) This observation has been made independently by others as well. See: Wainer, I.; et al. *J. Chromatogr.*, in press.

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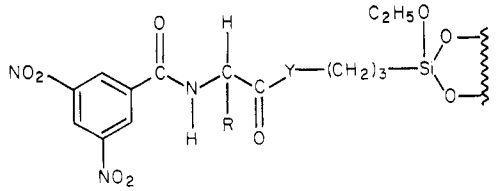


1a, Y = $O^{-+}NH_3$; R = Ph
b, Y = NH; R = Ph
c, Y = NH; R = isobutyl

affords resolvable enantiomers, we restrict the present discussion to the resolution of α-naphthamides of primary and secondary amines. The α-naphthoyl group facilitates ultraviolet detection as well as assists in the chiral recognition process and represents a reasonable "first choice" as an acylating agent.[7]

Table I contains data pertinent to the chromatographic resolution of the α-naphthamides of a variety of amines, amino acid esters, and amino alcohols. In most instances, the magnitude of α, the enantiomeric separability factor, is large enough not only to render trivial the HPLC determination of enantiomeric purity and absolute configuration but also to allow preparative resolution of the amides on larger columns of somewhat lower efficiency.[8]

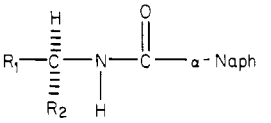
In each instance where the elution orders of the compounds in Table I have been established, it is the enantiomer of the configuration depicted in **2** which is most strongly retained.

Several potential chiral recognition mechanisms can be envisioned, and the extent to which each might contribute to the overall result will depend upon the structure of the acylated amine. It is mechanistically relevant that secondary amines may also be resolved. For example, *N*-methyl-α-phenylethylamine, as the α-naphthamide, elutes in the same order ($\alpha = 1.08$, $\kappa_1' = 3.0$) as the corresponding amide of α-phenylethylamine. As will be described elsewhere, the α-naphthamides of a number of secondary heterocyclic amines are also resovable on CSP **1b**.

Other amino acid derived chiral stationary phases have been found to resolve racemic amides, most commonly those derived from amino acids.[9] Since amides are known to associate strongly through hydrogen bonding, such interactions have usually been suggested as being important to chiral recognition. However, hydrogen bond formation may not necessarily be required for chiral recognition although it is undoubtedly involved in the overall retention process. One such process is envisioned in Figure 1 where the two components are shown in stable solution conformations, and the solute enantiomers are depicted as "stacking" onto the most accessible face (the carboxamide group is effectively smaller than the phenyl group) of the CSP. The major associative interactions are π–π bonding between the naphthyl and 3,5-dinitrobenzoyl systems and electrostatic bonding of the amide dipoles. Weak bonding of the aminyl hydrogen[9] of the solute to the carboxamide carbonyl oxygen may also aid in face selection. Chiral recognition then becomes a matter of differential interaction of R_1 and R_2 with the proximate portions of the CSP. The most stable diastereomeric absorbate will be formed from the solute enantiomer where, in Figure 1, R_2 is smaller than R_1. This will be the most strongly retained enantiomer. A similar elution order would be expected should R_2 be a polar group capable of bonding to a proximate portion of the CSP more effectively than does R_1. This model rationalizes all the elution orders reported in Table I. We hasten to point out that, should one of these groups be a strong π base, π–π interaction with the dinitrobenzoyl group can diminish the contribution of the aforementioned chiral recognition model and bring into play a still more effective process (to be described elsewhere) that usually operates in the same stereochemical sense.

In Figure 1, the α-naphthyl and carboxamide systems are depicted as being coplanar. Owing to steric interaction with the peri hydrogen, these amides must be somewhat twisted, the average extent and sense of this twist possibly being influenced by the substituents and chirality present

Table I. Resolution of α-Naphthamides of Acyclic Amines on CSP 1b



2

R_1	R_2	α[a]	κ_1[b]	retained enantiomer[c]
C_2H_5	CH_3	1.03	6.9	*S*
n-C_3H_7	CH_3	1.07	5.9	
i-C_3H_7	CH_3	1.05	6.8	
i-C_4H_9	CH_3	1.09	5.6	
t-C_4H_9	CH_3	1.05	5.3	
n-C_5H_{11}	CH_3	1.13	5.4	
n-C_6H_{13}	CH_3	1.11	5.0	*S*
Ph	CH_3	1.20	13.7	*S*
Ph	C_2H_5	1.21	9.2	*S*
Ph	*i*-C_3H_7	1.22	8.2	*S*
p-anisyl	CH_3	1.15	2.5	*S*
α-thienyl	CH_3	1.08	13.7	*S*
α-Naph	CH_3	1.66	18.5	*S*
β-Naph	CH_3	1.44	25.5	*S*
Bz	CH_3	1.05	10.5	*S*
Ph	$CO_2C_2H_5$	1.23	10.1	*R*
Bz	CO_2CH_3	1.21	12.1	*R*
i-C_3H_7	$CO_2C_2H_5$	1.20	5.4	*R*
α-Naph	CO_2-*n*-C_4H_9	1.27	11.8	
p-$HOC_6H_4CH_2$	$CO_2C_2H_5$	1.21	14.7	*R*
Ph	CH_2OH	1.32	16.8	
CH_3	CH_2OH	1.14	13.5	*R*
C_2H_5	CH_2OH	1.24	12.1	

[a] α, the chromatographic separability factor, is the ratio of the capacity ratios, κ_1' and κ_2', of the two enantiomers. [b] The mobile phase was 10% 2-propanol in hexane. [c] The retained enantiomer is the last eluted. No entry indicates that the elution order is not yet established.

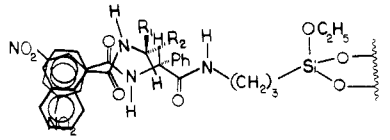


Figure 1. "Dipole-stacking" chiral recognition model.

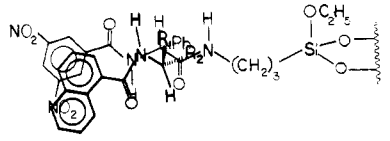


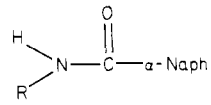
Figure 2. "Hydrogen bond" chiral recognition model. The carbonyl oxygen of the amide solute is visualized as projecting beneath the plane of the naphthyl ring.

(7) Several commercial samples of α-naphthoic acid have been found to contain β-naphthoic acid as well. Unless the latter is removed prior to conversion to naphthoyl chloride, the final α-naphthamide will be contaminated with β-naphthamide. Usually, the β-naphthamide enantiomers elute prior to those of the α isomer.

(8) Pirkle, W. H.; Finn, J. M. *J. Org. Chem.* **1982**, *47*, 4037.

(9) For a discussion of weak N–C–*H*···O bonding, see: (a) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1976**, *41*, 801. (b) Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5063.

Table II. Resolution of α-Naphthamides of Carbocyclic Amines on CSP 1b



R	α	k_1' [a]
trans-2-phenylcyclopropyl	1.14	13.7
cis-2-phenylcyclopropyl	1.04	10.3
trans-2-hydroxycyclohexyl	1.33	11.2
cis-2-hydroxycyclohexyl	1.20	13.7
trans-2-methylcyclohexyl	1.04	9.6
cis-2-methylcyclohexyl	1.05	10.6
trans-2-cyclohexylcyclohexyl	1.17	6.9
cis-2-cyclohexylcyclohexyl	1.18	7.5

[a] The mobile phase was 10% 2-propanol in hexane.

in the amine portion of the molecule. A variation of the "stacked" model is shown in Figure 2. Here, the solute is repositioned on the CSP to allow hydrogen bond formation to occur between the DNB amide hydrogen and the carbonyl oxygen of the solute. Once again, the most stable diastereomeric absorbate is the one pictured, where R_2 is smaller than R_1, or, alternatively, the one more capable of bonding to proximate portions of the CSP. Although $\pi-\pi$ bonding between the dinitrobenzoyl and naphthoyl groups can stabilize the stacking modes shown in Figures 1 and 2, $\pi-\pi$ interaction is not absolutely essential; a number of simple acyl groups (acetyl, butanoyl) may be used in place of the α-naphthoyl group. Thus, the chiral model(s) presented above can be extended to cover the elution orders reported by Dobashi et al. for acylated amino acid esters on a valine-derived CSP.[10]

The α-naphthamides of aminocycloalkanes are also resolvable on CSP **1b**. Table II provides data pertinent to the resolution of several such compounds. No elution order data is yet available for these compounds.

CSP **1c**, derived from (*S*)-leucine, is often more efficacious for the resolution of enantiomers than is CSP **1b**. However, this is typically not the case for the α-naphthamides studied, the major difference between the two CSP's being the expected difference in elution orders, since the two CSP's differ in absolute configuration.

CSP **1a** is quite similar to **1b** in its ability to resolve acylated amines. In any individual instance, **1a** may perform either slightly better or slightly worse than **1b**.

(10) For example, see: Dobashi, A.; Oka, K.; Hara, S. *J. Am. Chem. Soc.* **1980**, *102*, 7122.

Experimental Section

General Methods. Chromatography was conducted by using a Beckman 100A pump, a Model 210 injector, and a Model 165 detector and a Kipp-Zonen BD41 dual-pen recorder. A Regis Covalent Pirkle 1A column was employed. Rudolph Auto-pol III fitted with a 20-cm flow cell was used as a polarimetric detector in most instances to complement the dual wavelength (usually 254 and 280 nm) ultraviolet detector.

The amines used were available from prior studies and were acylated with α-naphthoyl chloride by using standard procedures. Since most were made from partially resolved amines, they were not crystallized prior to use. The use of dual-wavelength ultraviolet and polarimetric detection ensures that the peaks attributed to the amide enantiomers do, in fact, so arise.

Covalently Bound (*S*)-*N*-(3,5-Dinitrobenzoyl)leucine Stationary Phase (1c). To a slurry of 2 g of finely powdered (*S*)-*N*-(3,5-dinitrobenzoyl)leucine in 60 mL of dry methylene chloride was added 2 g of powdered *N*-(ethoxycarbonyl)-2-ethoxy-1,2-dihydroquinoline. The mixture was swirled until solution was complete, and the solution was suction filtered to remove any residual solids. This solution was immediately pumped through a Regis aminopropyl column at a flow rate of 2 mL/min. This solution was followed by 50 mL of methylene chloride, 100 mL of methanol, and 10% 2-propanol in hexane until the base line stabilized. Columns of this type are available from both Regis and J. T. Baker.

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α-Alkoxyallylation of Activated Carbonyl Compounds. A Novel Variant of the Michael Reaction

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Enolic or readily enolizable carbonyl compounds undergo α-alkoxyallylation upon reaction with acetals of α,β-enals or ethoxyallene at temperatures ranging from 200 °C to ambient. Whereas reactions of the highly enolic or acidic carbonyl compounds (endocyclic β-diketones, α-cyano ketones, α-nitro carbonyl compounds, and α-hydroxymethylene derivatives) occurred simply upon heating, alkylation of the less acidic exocyclic β-diketones and β-keto esters was best carried out in the presence of 1 mol % of $Ni(acac)_2$ as a catalyst. Pyridinium *p*-toluenesulfonate was employed as a catalyst for alkylations with acrolein ethylene acetal. Although ethoxyallylation of acylic substrates (e.g., ethyl acetoacetate, diethyl malonate, and ethyl cyanoacetate) with acrolein diethyl acetal proved to be slow, these and related alkylations could be conveniently accomplished by use of the corresponding α-hydroxymethylene derivatives. Unsaturated acetals bearing a methyl or phenyl substituent at C-2 can be employed for alkoxyallylation, but the reaction appears to be incompatible with a methyl group at C-3. The mechanism of these reactions probably involves either direct C-allylation of the carbonyl compound on the γ-position of an alkoxyallyl carbocation intermediate or an indirect pathway via O-allylation at the α-position of the carbocation followed by Claisen rearrangement.

The Michael reaction of β-dicarbonyl compounds with α,β-enones and other electron-deficient olefins is an important synthetic method for carbon–carbon bond formation.[1] Although typically carried out in protic solvents

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