(14) Å, $\beta = 96.16\ (7)°$, $V = 3525$ Å^3, and $Z = 4$. The measured density was 1.585 g/cm^3, yielding a measured formula weight of 841.2. The calculated formula weight of $[Ph_4As^+]$ III′ is 817.3.

Preparation of IV. In a typical reaction, $[Et_3BH]Li$ (6 mmol) was added to $Fe(CO)_5$ (5 mmol) in 20 mL of hexane at 0 °C and stirred for 10 min. Commercial BH_3·THF (10 mmol) was added over a period of several minutes, causing the color of the reaction solution to change from pale yellow to dark brown. After the solution was stirred at 0 °C for 1.5 h, the solvent was removed at room temperature, leaving a brown solid residue. This was acidified with H_3PO_4 (25 mL, 40% aqueous), and the neutral ferraborane and hydrocarbyl products were extracted with hexane (3 × 25 mL), yielding a brown-green solution. Subsequent extractions contained mainly $Fe_3(CO)_{12}$. The orange ferraborane IV was separated from the product mixture as the third fraction by column chromatography (hexane) carried out at −40 °C: MS, m/e P^+ 450 (−9CO), $^{56}Fe_3{}^{12}C_{10}{}^{16}O_9{}^{11}B^1H_7$ measd 449.823, calcd 449.823; IR ν_{CO} (hexane, cm^{-1}) 2095 m, 2064 sh, 2057 vs, 2044 s, 2037 vs, 2025 vs, 2015 s, 2006 m, 1982 m; ^{1}H NMR (CD_2Cl_2, −80 °C) δ 1.03 (s, 3 H), −14.6 (br, 3 H), −24.0 (s, 1 H); ^{11}B NMR (hexane, 20 °C) δ 22.1 (quintet, $J_{BH} = 40$ Hz).[34]

Preparation of IV′. Deprotonation of IV was carried out by stirring a hexane solution (20 mL) of the neutral ferraborane with a solution of Ph_4AsCl (or PPNCl) in methanol. The hexane layer was rapidly decolorized, and the methanol layer became deep red. After the methanol layer was separated, the methanol was removed and the residue extracted with ether. Removal of the ether yielded the final product: IR ν_{CO} (THF, cm^{-1}) 2045 m, 2000 vs, 1978 vs, 1956 vs, 1935 m; ^{1}H NMR ($CD_3C(O)CD_3$, 20 °C) δ 7.87 (m, 20 H), Ph_4As^+ 1.09 (s, 3 H), −12.9 (br, 3 H); ^{11}B NMR ($CD_3C(O)CD_3$, 20 °C) δ 29.3 (br q, $J_{BH} = 53$ Hz).

(34) Significant amounts of the ethyl derivative are formed as well, but little III is observed.

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Registry No. III, 92055-43-1; III′, 101810-38-2; III$[Ph_4As^+]$, 101810-39-3; IV, 101834-61-1; IV′$[Ph_4As^+]$, 101810-41-7; $[(CO)_4FeC(O)CH_3]Na$, 64867-63-6; $[(CO)_4FeC(O)CH_3]PPN$, 36464-58-1; $Fe(CO)_5$, 13463-40-6; $[Et_3BH]Li$, 22560-16-3; BH_3·THF, 14044-65-6.

Supplementary Material Available: Listing of observed and calculated structure factor amplitudes, thermal parameters, and the packing diagram (10 pages). Ordering information is given on any current masthead page.

Chiral Separation of Heterocyclic Drugs by HPLC: Solute–Stationary Phase Base-Pair Interactions

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Abstract: Hydrogen bonding between a chromatographic stationary phase and several classes of drug molecules has been explored as a means to effect HPLC chiral separation. *N,N′*-2,6-Pyridinediylbis[alkanamides] have been shown by NMR and X-ray diffraction to be complementary to the drug classes of interest and to form a highly specific triple hydrogen bond complex. A derivative of optically active *N,N′*-2,6-pyridinediylbis[(*S*)-2-phenylbutanamide] was bonded to silica gel and used in an HPLC column to separate racemic mixtures of barbiturates (**1**), glutarimides (**3**), and hydantoins (**4**). Mechanistic models of chiral resolution are suggested for these three classes of drugs. No chiral separation was effected for succinimides (**5**). Methylation of an imido nitrogen of these drugs resulted in disruption of the complementarity; therefore, such *N*-methyl derivatives were unretained by the column. This type of bonded phase would appear to offer high potential for separation of closely related species.

Hydrogen bonds are one of the key factors through which a biological system "recognizes" another system on a molecular level. For example the well-known double helix structure of double-stranded DNA is formed by hydrogen bonding between complementary pairs of purine and pyrimidine bases on the two polynucleotide strands. Pairs of these heterocyclic bases can form a hydrogen bonded complex only if there is an appropriate juxtaposition of acid/base character and if complementary functionalities are coplanar and in the correct orientation.

Broad classes of drugs have structural similarities to the bases found in nucleic acids. For example, as shown in Figure 1, glutarimides, barbiturates, succinimides, and hydantoins have similarities to uracil and thymine. These drugs form associates with adenine similar to those found in the base pairs of adenine–thymine and adenine–uracil.[1] Such associations with adenine and its derivatives have been suggested to be in part the basis of the pharmacological activity of these drugs.[2] In addition, IR studies have shown that barbiturates can displace derivatives of uracil or thymine from associates with 9-ethyladenine; however, no pairing of the barbiturates was detected with the other bases.[1] In similar studies, the glutarimides, hydantoins, and succinimides were demonstrated to complex with adenine and not with the other bases.[3] Recent studies employing IR, near IR, and proton NMR have further explored the displacement of thymine from adenine by barbiturates.[4] Such interactions have been proposed to be important in anaesthesia.[5]

The use of hydrogen bonding associates for achievement of separation in chromatography is well established, in both gas chromatography[6,7] and liquid chromatography.[8,9] Moreover,

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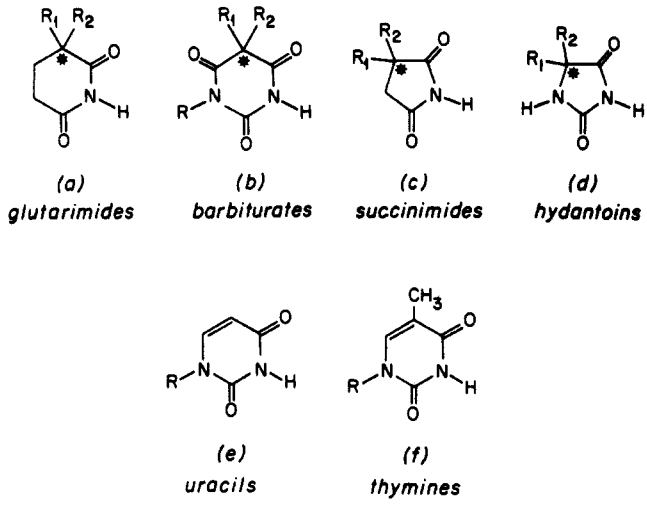

Figure 1. General structure of classes of heterocyclic compounds of pharmacological interest examined in this work, as well as the structure of bases thymine and uracil.

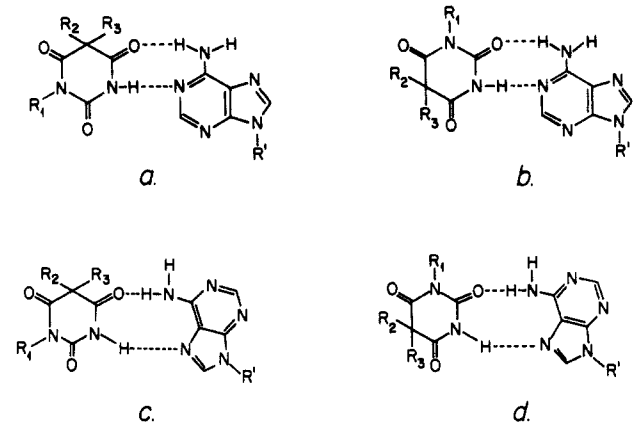

Figure 2. Four different pairing modes between 9-alkyladenine and a barbiturate.

differential hydrogen bond association of enantiomers is a well-established principle of chiral recognition.[10,11] The classes of drugs in Figure 1 have in general not been resolved as optical isomers in this manner; however, work using a polymerized chiral substituted acrylamide has been presented,[12] and enantiomers of hydantoins and succinimides have been resolved on charge-transfer chiral stationary phases.[13] In addition, no functional groups exist on these drugs to allow simple formation of diastereomeric derivatives for separation although some attempts have been carried out;[14] hence, specially designed chiral phases must be developed for separation. The purpose of this paper is to explore the possibility of using the specificity of hydrogen bonding in the HPLC chiral separation of the broad classes of drugs listed in Figure 1.

Hydrogen bond formation between the drugs and an adenine derivative leads to four possible pairing modes, each with two hydrogen bonds, as shown in Figure 2. Two of these modes, parts a and b, involve Watson–Crick pairing wherein N(1) and the C(6) amino group of adenine interact with the barbiturate. Parts c and d illustrate Hoogsteen[15] pairing, where N(7) and the C(6) amino group of adenine hydrogen bond to the barbiturate.

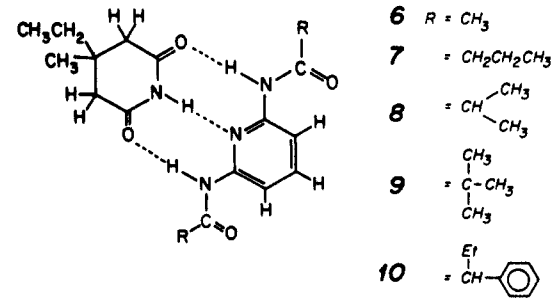

Figure 3. The triple hydrogen bonded complex formed between bemegride (**3e**) and compounds **6–10**.

In solution, all four structures can exist simultaneously, with their relative distribution depending on the various substituents of the drug and the adenine derivative. Given these four competitive possibilities, it can be postulated that the contribution of the complex between a chiral derivative of adenine and the drugs having the highest enantioselectivity might be diminished in favor of complexes of lower selectivity. In this latter case, hydrogen bonding without chiral recognition could occur, leading to a lack of enantiomer separation.

The above argument led us to seek a more specific complementary base in order to increase the possibility of chiral recognition. In particular, we decided to consider the possibility of formation of triple hydrogen bonds between molecules of the drugs in Figure 1 and complementary bases, predicated on the pairing of guanine with cytosine.[16] We selected for base pairing derivatives of *N,N'*-2,6-pyridinediylbis[alkanamide], where the possibility of a triple hydrogen bond exists (see Figure 3). When identical substitution occurs at the two amides only one hydrogen bond complex can form, thus maximizing the possibility of chiral recognition.

An optically active bonded phase attached to silica gel has been synthesized, and chiral recognition has been achieved. The basis of separation in terms of steric interactions of groups attached to the chiral centers of the base pairs is presented. The use of such tailor-made groups provides specificity not only for chiral separation but also for specific structural elements required for association to take place.

Results and Discussion

The design of a base capable of forming a hydrogen bond complex with the drugs shown in Figure 1 requires careful consideration of several factors. In order to achieve the greatest possible specificity, it is desirable first to produce the maximum number of hydrogen bonds between the base pairs, second to produce only one possible base pair structure, and third to bring the centers of chirality of each species in close proximity while still allowing hydrogen bonding to occur.

As discussed in the Introduction, we selected for base pairing derivatives of *N,N'*-2,6-pyridinediylbis[alkanamide] with which a triple hydrogen bond could, in principle, form with an imido functionality, e.g., with bemegride (**3e**) (Figure 3). The *N,N'*-2,6-pyridinediylbis[alkanamide] structure offers the possibility of introducing asymmetry through the R groups for chiral recognition, e.g., solute **10**. Moreover, when identical alkanamide groups are present the molecule possesses a C_2 axis of symmetry; the result is the formation of only one complex. The trans conformation of the amide group aids in the formation of the hydrogen bonds by removing the carbonyl groups from the zone of association; it also forces the chiral centers toward the solute as in Figure 3.

We will first demonstrate that the triple hydrogen bond does indeed form. We synthesized the series of *N,N'*-2,6-pyridinediylbis[alkanamides] listed in Figure 3 and tested for hydrogen bonding using **3e** as a model solute.

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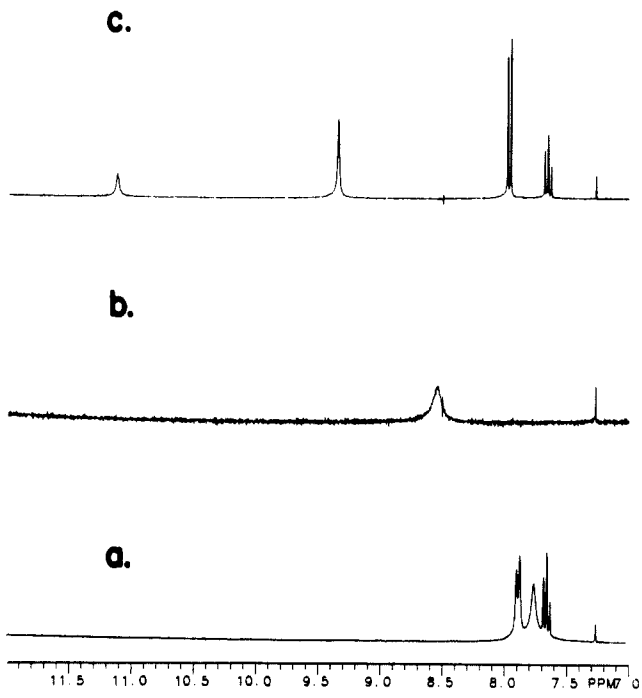

Figure 4. Chemical shifts of the protons participating in the formation of the triple hydrogen bonded complex. Conditions: 0.20 M deuterochloroform solution, 19.5 ±0.5 °C. (a) Spectrum of *N,N'*-2,6-pyridinediylbis[butanamide] (**7**), δ 7.75 (2 NH); (b) spectrum of bemegride (**3e**), δ 8.57 (NH); (c) the 1:1 mixtures **3e**:**7**, δ 9.38 (2 NH), 11.15 (NH).

NMR spectra for 1:1 mixtures of **3e** with each of the *N,N'*-2,6-pyridinediylbis[alkanamide] were measured. Figure 4 illustrates typical results in $CDCl_3$ for *N,N'*-2,6-pyridinediylbis[butanamide] (**7**) (Figure 4a), for **3e** (Figure 4b), and for a 1:1 mixture of **3e** and **7** (Figure 4c). In the mixture, shifts greater than 2 ppm were observed for signals of protons that participate in the hydrogen bonding. Thus, $\delta_{NH} = 8.57$ in **3e** and 11.15 in a mixture of 1:1 **3e**:**7**, while $\delta_{2(NH)} = 7.75$ in **7** and 9.38 in a mixture of 1:1 **3e**:**7**.

Similar deshielding of the 2 NH protons of **6**, **8**, and **10** and the NH proton of **3e** was observed in the respective 1:1 mixtures. These results are as expected for hydrogen bond formation.[17] Moreover, the simultaneous downfield shift of the three protons involved in the hydrogen bonding strongly supports the model of the formation of a triple hydrogen bond complex between **3e** and **6**, **7**, **8**, and **10**. Note that **10** has a chiral center that will be used to advantage for chiral recognition.

In the case of a 1:1 mixture of **3e** and **9** no significant downfield shift was observed. Thus, $\delta_{2(NH)} = 7.76$ in **9** and 7.85 in the 1:1 mixture of **3e**:**9**, while $\delta_{NH} = 8.57$ in **3e** and 8.85 in the 1:1 mixture of **3e**:**9**. The triple hydrogen bond does not appear to form in this case. The structural difference between **9** and the other ligands, **6**, **7**, **8**, and **10**, is in the two carbons adjacent to the amide groups. These α carbons are tertiary in **9** and either primary or secondary in the others. Evidently, these carbons must be substituted with at least one hydrogen each in order for base-pair complexation to take place.

In order to investigate further the complex formed between **3e** and **7**, crystals of a 1:1 complex of these species were grown and an X-ray analysis was conducted. The X-ray study unambiguously defines the 1:1 complex of **3e** with **7** to be held together by three hydrogen bonds. A perspective view of this complex is shown in Figure 5. The lengths of the hydrogen bonds in the complex **3e**:**7** (N···N 3.089 (3), O···N 2.943 (4), 2.942 (4) Å) are within the normal range of these types (N···N, N···O) of hydrogen bonds. They are, however, in each case longer than those found in

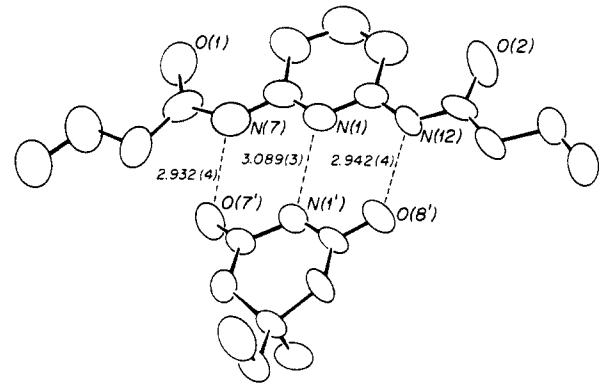

Figure 5. ORTEP drawing of non-hydrogen atoms of the complex **3e**:**7** with thermal ellipsoids drawn at the 50% probability level. Hydrogen bonds are denoted by dashed lines.

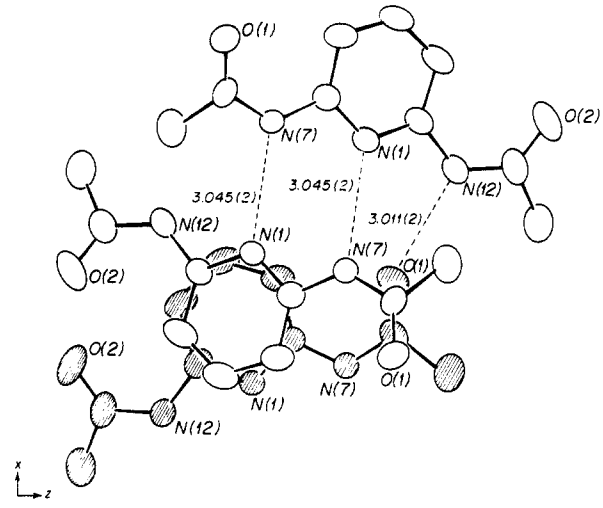

Figure 6. ORTEP drawing of a partial packing arrangement of **6** with thermal ellipsoids drawn at the 50% probability level. Hydrogen bonds are denoted by dashed lines and the lower molecule is cross-hatched for clarity.

guanylyl-3',5'-cytidine (GpC) salts,[18-20] though the estimated standard deviations for the distances in the GpC molecules are ca. 10 times those in this study. In the Na^+[16] and Ca^{2+}[17] structures of GpC, as well as in earlier studies of cytosine–guanine base pairs,[21] the N···O separations are shorter than the N···N separations, as they are in complex **3e**:**7**.

The butanamide portion of the complex is approximately planar, with each butanamide chain adopting an extended, all anti conformation. The extent of the planarity of the molecule was examined by calculation of the deviation of each atom of the butanamide chains from the mean plane of the pyridine ring. The maximum deviations are ±0.16 Å except for O(2), which lies 0.28 Å from the plane. The thermal parameters for the butanamide atoms are rather large, and reference to Figure 5 shows the thermal ellipsoids to be quite elongated in the direction perpendicular to the plane of the molecule.

The glutarimide molecule adopts a symmetrical sofa conformation with C(4) lying 0.64 Å out of the plane of C(1')–C(3'), C(5')–O(8') and the larger (ethyl) substituent adopting the equatorial position. This conformation is the normal one for glutarimide molecules that are substituted at the C(4) position.[22-26]

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Table I. Unit Cell Dimensions and Other Experimental Parameters Used in X-ray Diffraction Studies of Compound **6** and the Base Pair **3e:7**

parameter	6[a]	3e:7[b]
formula wt, amu	193.2	404.5
cryst dimen, mm	0.20 × 0.25 × 0.40	0.30 × 0.30 × 0.75
a, Å	10.624 (2)	13.110 (2)
b, Å	7.827 (1)	23.415 (3)
c, Å	22.927 (3)	7.422 (1)
β, deg	90.0	100.38 (1)
space group	*Pbcn*	$P2_1/n$
Z	8	4
d_{calcd}, g cm^{-3}	1.346	1.199
μ, cm^{-1}	8.26	6.91
min scan speed, 2θ, deg min^{-1}	4.0	2.0
no. unique reflects meas	1775	3806
no. reflectns with $I \geq 2\sigma(I)$	1272	2639
$R(I \geq 2\sigma(I))$	0.050	0.076

[a] *N,N'*-2,6-pyridinediylbis[acetamide]. [b] Complex between bemegride and *N,N'*-2,6-pyridinediylbis[butanamide].

The C–N–C–C (3.4 (3), 5.5 (3)°) and O–C–N–C (−176.2 (4), 179.5 (4)°) angles in this moiety demonstrate the near planarity of the portion of the molecule that is complementary to the attachment site on **7**.

The complexes pack as discrete, hydrogen bonded units associated only by van der Waals forces; that is, the butanamide carbonyl groups do not participate in hydrogen bonding. Molecules pack in planar arrays in the z^* direction with essentially no overlap (save unit translation). Projection onto the a,b plane shows the molecules to lie in a herringbone pattern.

In order to establish that the parameters for **7** had not been distorted by the complexation of the drug molecule, the self-association of a similar ligand, *N,N'*-2,6-pyridinediylbis[acetamide] (**6**) was studied. A partial view of the packing of the molecule is shown in Figure 6. A comparison of the bond lengths, valency angles, and torsion angles in **6** with those found in the butanamide portion of the complex shows that these parameters do not differ even though the molecules exist in quite dissimilar environments.

The molecules of **6** are held together by extensive hydrogen bonding, each molecule fulfilling its capabilities by interaction with three other molecules. Oxygen O(2) does not participate and consequently its thermal ellipsoid is much larger than that of O(1). The molecules are joined via one amido group and the pyridine nitrogen as rather loosely held cyclic dimers (N···N 3.045 (2) Å) about a center of symmetry. The second amido group interacts, again rather weakly (N···O 3.011 (2) Å), with O(1) of a different symmetry-related molecule. In the y direction the molecules are tilted 12.3° with respect to one another. There is a virtually complete overlap of the pyridine rings, albeit with a rotation of ca. 150° about this axis (see Figure 6). The center-to-center separation of these rings is 3.92 Å and the closest approach is 3.41 Å. Layers of these stacks are linked by the hydrogen bonds in the x direction. The molecules associated by NH···N hydrogen bonds are tilted at 49° with respect to one another.

In summary, the X-ray crystal structures show the ligands to exist in planar, extended conformations with trans amide linkages and demonstrate a triple hydrogen bond when the glutarimide bemegride is complexed with **7**.

Chromatographic Separation of Chiral Species. The previous section has established the formation of hydrogen bonds between the classes of heterocyclic drugs listed in Figure 1 and 2,6-pyridinediylbis[alkanamides] in nonpolar solvents. We next synthesized bonded phase **19**, the optically active isomer of a homologue of compound **10**, which was previously shown to form base pairs with **3e**. Figure 7 illustrates the bonded phase in combination with a barbiturate *S*-**1a**. Figure 8 provides a scheme for the synthesis of the silane to be bonded to the silica gel, and specific details can be found in the Experimental Section. Identical substitution of the amides, as noted previously, will yield a single complex, thereby maximizing chiral recognition. An 11-carbon spacer was placed between the silicon atom and the active ligand in order to enhance accessibility of the active site and thus hydrogen bond formation.

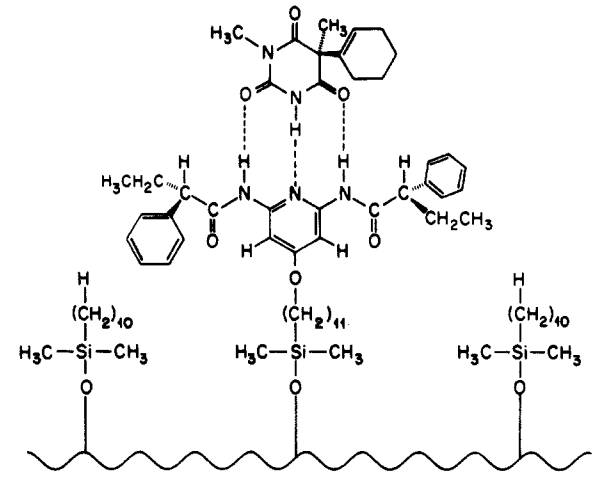

Figure 7. Structure of the complex between stationary phase **19** and the barbiturate *S*-**1a**.

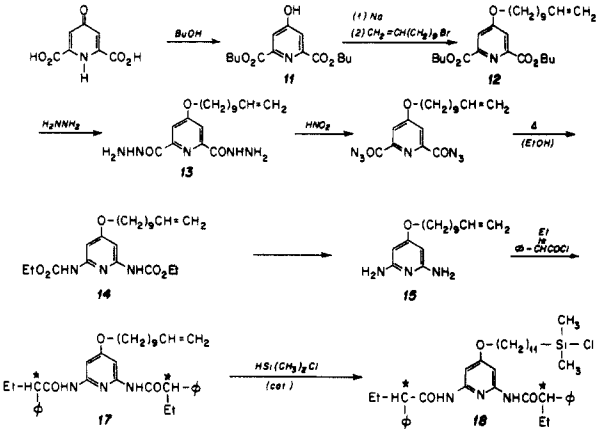

Figure 8. Synthetic scheme of the ligand **18**.

The long leash permits, in addition to the high accessibility of site, the removal of the bulky ligand from the silica gel surface and thus a relatively higher bonded phase coverage. The optical purity, determined as described in the Experimental Section, was found to be 93.4%. A second, end-capping step was performed with decyldimethylchlorosilane in order to reduce the number of unreacted silanol groups on the silica gel surface that could potentially be available for competitive hydrogen bonding with the heterocyclic drugs. The coverage by the end-capping groups was 2 μmol/m^2, yielding a total bonded phase loading of 3 μmol/m^2. Prior to bonding, the silica gel had been acid washed to remove metal impurities from the surface that could interfere with the formation of the hydrogen bond associate between the drug and active ligand.[27]

After the column was packed, it was operated at 25 °C in the normal-phase mode with a mobile phase of 2.5% 2-propanol in 1,2-dichloroethane. Table II presents results of retention and relative retention for six-membered heterocyclic compounds—barbiturates and glutarimides—and Table III for five-membered

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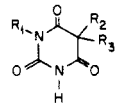
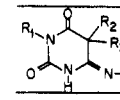
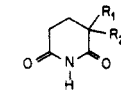
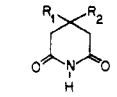
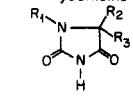
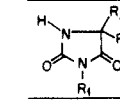
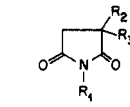
Table II. Chromatographic Characteristics of Six-Membered Heterocyclic Compounds (Mobile phase: 2.5% 2-propanol in 1,2-dichloroethane, T = 25 °C)

General Structure		R_1	R_2	R_3	F[b]	k_1'[c]	α[d]
A. Barbiturates[a]	(1a)	$-CH_3$	$-CH_3$		R	3.03	1.14
	(1b)	$-C_4H_9$	$-CH_3$		–	3.35	1.16
	(1c)	$-CH_3$	$-C_2H_5$		–	2.30	[e]
	(1d)	$-CH_3$	$-CH_2CH{=}CH_2$		–	2.69	1.11
	(1e)	$-C_2H_5$	$-CH_3$	$-N(CH_3)_2$	R	2.45	1.14
	(1f)	$-CH_3$	$-C_2H_5$	$-N(CH_3)_2$	R	2.17	1.10
	(1g)	$-CH_3$	$-C_3H_7$	$-N(CH_3)_2$	R	2.28	1.06
	(1h)		$-C_2H_5$		–	3.42	1.11
	(1i)	$-C_2H_5$	$-C_3H_7$		R	2.90	1.10
	(2)		$-CH_3$		–	4.26	1.07
B. Glutarimides[a]	(3a)	$-C_2H_5$			–	3.50	1.07
	(3b)	$-C_2H_5$		$-NHCOCF_3$	S	3.06	1.11
	(3c)	$-C_2H_5$			–	4.84	
	(3d)	$-C_2H_5$			S	5.74	1.05
	(3e)	$-CH_3$	$-C_2H_5$		–	3.23	

[a] Common names: **1a**, hexobarbital; **1c**, mephobarbital; **1d**,methohexital; **3a**, glutethimide; **3b**, N-TFA of aminoglutathimide; **3e**, bemegride. [b] F is the absolute configuration of first eluting enantiomer. [c] k' is the capacity factor of the first eluting enantiomer, $(t_r - t_0)/t_0$, where t_r is the retention time and t_0 is the unretained time. [d] $\alpha = k_2'/k_1'$, separation factor. [e] No separation observed. [f] An achiral compound.

Table III. Chromatographic Characteristics of Five-Membered Heterocyclic Compounds (Mobile phase: 2.5% 2-propanol in 1,2-dichloroethane, T = 25 °C)

General Structure		R_1	R_2	R_3	k_1'[b]	α[c]
A. Hydantoins[a]	(4a)	–H			2.44	[d]
	(4b)	–H	$-CH_3$		2.10	1.16
	(4c)	–H	$-C_2H_5$		2.27	1.16
	(4d)	$-CH_3$	–H	–H	1.85	[e]
	(4e)	$-CH_3$	$-C_2H_5$		0	[d]
B. Succinimides[a]	(5a)	–H	$-CH_3$		1.02	[d]
	(5b)	–H	$-C_2H_5$		1.38	[d]
	(5c)	–H	$-CH_3$	$-C_2H_5$	1.22	[d]
	(5d)	–H	$-CH_3$		1.24	[d]
	(5e)	$-CH_3$	–H		0	[d]
	(5f)	$-CH_3$	$-CH_3$		0	[d]

[a] Common names: **4e**, mephenytoin, **5c**, ethosuximide, **5e**, phensuximide, **5f**, methsuximide. [b] k_1' is the capacity factor of the first eluting enantiomer, $(t_r - t_0)/t_0$, where t_r is the retention time and t_0 is the unretained time. [c] $\alpha = k_2'/k_1'$, separation factor. [d] No separation observed. [e] An achiral compound.

heterocyclic compounds—hydantoins and succinimides. Chiral recognition is observed for three of the four classes of drugs, with only the succinimides yielding no separation.

As can be observed, relative retention (α) values up to 1.16 were obtained. Even though higher values are desirable, a factor of this magnitude is sufficient for base line separation with high-efficiency HPLC. This is illustrated in Figure 9, which shows the separation of various species including some pharmacologically

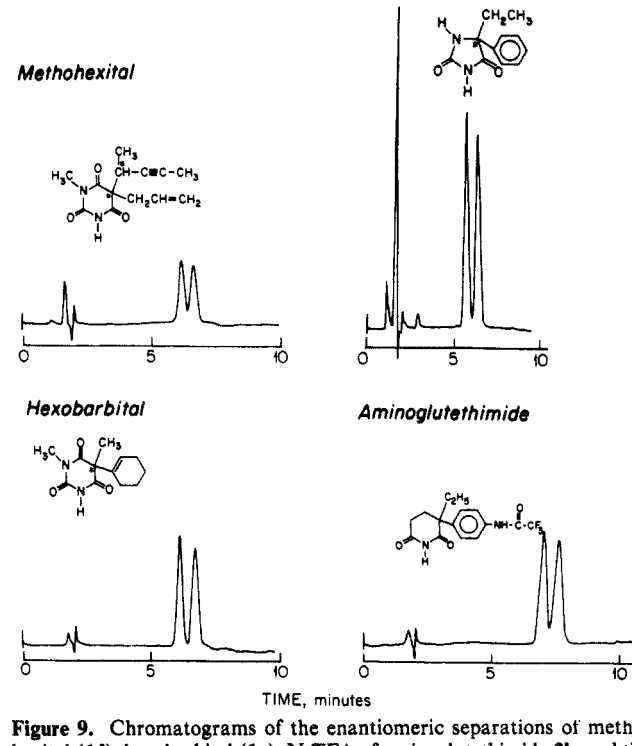


Figure 9. Chromatograms of the enantiomeric separations of methohexital (**1d**), hexobarbital (**1a**), N-TFA of aminoglutethimide **3b**, and the hydantoin **4c** on stationary phase **19**. Column, 15-cm length × 4.6-mm i.d.; mobile phase, 2.5% 2-propanol in 1,2-dichloroethane; 1.0 mL/min; 25 °C.

Table IV. Solute Enthalpy Differences between Specific Mobile Phases and the Chiral Stationary Phase[a]

solutes	$-\Delta H$, kcal/mol X = 0%	$-\Delta H$, kcal/mol X = 2.5%
barbiturate **1a**	7.68	5.23
1b		5.29
1c		5.03
1d		5.48
1h		5.45
1j		5.34
glutarimide **3a**	7.21	6.14
3b		6.87
hydantoin **4a**		5.96
4b	7.13	4.04
4c		3.43
4d		2.55
succinimide **5a**	6.73	3.76

[a] Mobile phase: X% 2-propanol in 1,2-dichloroethane.

important drugs. Presumably, improvements in the prototype bonded phase, through an understanding of the structural parameters controlling separation, will yield enhanced separation factors.

It is interesting to note that compounds **4e**, **5e**, and **5f** experience no retention and thus no separation. In the three examples the heterocyclic nitrogen flanked by the two carbonyls is substituted by a methyl group that blocks formation of the complex. The triple hydrogen bond is precluded, thereby leading to no retention for the methylated species. The high specificity inherent in the triple hydrogen bond creates a type of "affinity" site for specific binding of complementary structural units. Work is continuing on this approach to high specificity, particularly with methylated bases of nucleic acids.

The fact that methyl substitution on the heterocyclic nitrogen reduces retention to zero suggests that the major cause of retention for the drugs tested in Tables II and III is indeed hydrogen bond association. This conclusion can be reinforced by an examination of enthalpies of retention. Table IV presents $-\Delta H$ values for a number of solutes determined from van't Hoff plots of log k' vs. $1/T$. With 1,2-dichloroethane as mobile phase, $-\Delta H$ values lie

between approximately 7 and 8 kcal/mol. Interestingly, in chloroform the complexation enthalpy for 1-cyclohexyluracil:9-ethyladenine, a double hydrogen bond associate, was found to be 6.2 and 4.0–4.3 kcal/mol for their self-associates.[28]

When 2.5% 2-propanol was added to the mobile phase, all $-\Delta H$ values decrease due to the solvation of the drug in the bulk solvent and the competition of the 2-propanol for the bonded stationary phase. The barbiturates studied all have $-\Delta H$ values between 5 and 5.5 kcal/mol, whereas the glutarimides are somewhat higher at 6.3 kcal/mol. However, the five-membered hydantoins and succinimides now lie between 2.5 and 4 kcal/mol. Hence, smaller k' values are found for the solutes in Table III relative to Table II.

It is further observed in Table II that the *R* enantiomer elutes first for all the barbiturates for which an optically pure standard was available. This elution order can be rationalized with reference to Figure 7. Consider first the conformation of the bonded ligand when the hydrogen bond associate forms.

From the NMR studies it was noted that the carbon adjacent to the amide carbonyl in *N,N'*-2,6-pyridinediylbis[alkanamide] must possess at least one hydrogen for complex formation. This result suggests that free rotation about the (C=O)–CH(Et)Ph bond is restricted during complex formation and that the rotamer with the hydrogen substituent directed toward the solute molecule is preferred. This in turn requires the other two substituents at this site, Et and Ph, to lie above and below the plane of the complex (see Figure 7). This conformational stabilization and the resultant spatial orientation of the substituents are necessary for chiral recognition to occur, as described below.

Consider next the association of a barbiturate with the ligand. It is known that the heterocyclic ring is planar[29,30] and thus the three points of attachment can be coplanar with the active site of the bonded phase (see X-ray results). In the case of the *S* isomer of compound **1a**, shown in Figure 7, the bulky 1-cyclohexenyl group will now lie above and the methyl group below the plane of the complex. The *S* isomer can be expected to form the more stable hydrogen bond associate with the bonded ligand, since the larger 1-cyclohexenyl substituent is proximate to the smaller ethyl group of the ligand. On the other hand, in the *R* isomer the cyclohexenyl substituent is closer to the larger phenyl group. Similarly, for all other barbiturates where the elution order is known, the enantiomer that has its larger substituent in closer proximity to the phenyl group of the bonded ligand elutes first. Thus, the complex embodying less steric interaction between the substituents would appear to be the more stable.

That the steric difference between R_2 and R_3 is important for selectivity is demonstrated by a comparison of the α values of compounds **1e**, **1f**, and **1g**. Here, the larger substituent, R_3, is dimethylamino, while R_2 is methyl, ethyl, or propyl, respectively. The separation factor, α, decreases with a decrease in the size difference of R_2 and R_3 ($1.14 > 1.10 > 1.06$). Additionally, the only barbiturate that was not resolved was **1c**, where the larger group is phenyl. This result may be a consequence of a π–π interaction between aromatic rings of the solute and the ligand offsetting the steric hindrance. Finally, compound **2** illustrates that an imine can substitute for a carbonyl to yield retention and chiral recognition. Imine groups are known to be hydrogen bond acceptors.[31]

The results for the glutarimides differ from those for the barbiturates in that the *S* isomer is found to elute first (see Table II). As observed in Figure 5 for **3e**, glutarimides generally exist in a sofa (1,2-diplanar) conformation with C(4) lying either above or below the ring plane.[22–26] The two conformers of each enantiomer of **3d** are shown in Figure 10. The more stable conformer

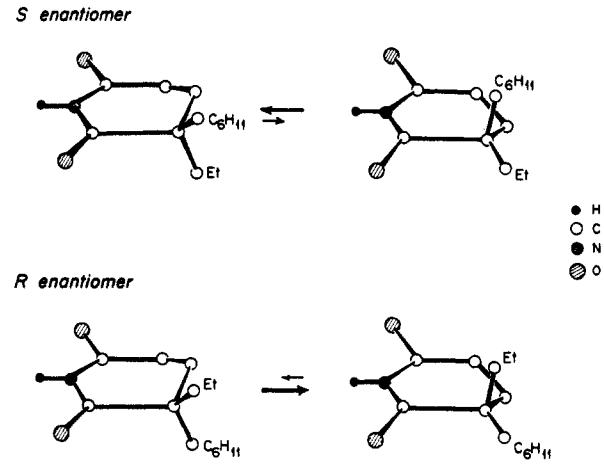


Figure 10. Sofa conformations of compound **3d**. In the predominant conformer of each enantiomer the cyclohexyl substituent is equatorial and the ethyl group is axial. The axial ethyl substituent lies below the plane for the *S* and above it for the *R* enantiomer.

is known to be the one in which the larger group occupies the equatorial position; therefore, for the *S* enantiomer, the smaller (ethyl) group lies below the plane in the axial position. This means that in the complex of the (*S*)-glutarimide with the *S* ligand, the axial ethyl group lies on the same side of the complex as does the phenyl (largest) group of the ligand. For this reason the complex with the *S*-glutarimide is less stable than that with the *R*-glutarimide and elutes first.

Turning next to hydantoins, it is known that the five-membered heterocyclic ring is planar.[32,33] Presumably, complexes analogous to that shown in Figure 7 may form having a chiral recognition mechanism similar to that of the barbiturates. Unfortunately, optically pure standards of the resolved hydantoins were not available. The fact that compound **4a** was not resolved may reflect the similar steric sizes of R_2 and R_3.

None of the succinimides tested in Table III showed chiral resolution. Even in 100% 1,2-dichlorethane, succinimides were not resolved, in spite of the increase in k'. While hydantoins and succinimides would be expected to exhibit similar structural features, e.g., O···O separations and O–C–N angles, there are electronic differences in the parent molecules due to the second heterocyclic nitrogen in the hydantoins. Examination of resonance structures suggests that there is greater negative charge localization on the carbonyl oxygens for hydantoins than for succinimides. These differences may make the hydantoins stronger Lewis bases, resulting in weaker complexation of the succinimides relative to the hydantoins. It is possible that there may be sufficient elongation of the hydrogen bonds in the complex that steric interactions between R_2 and R_3 of the drug with the bonded phase ligand is reduced to the point that chiral recognition is lost. However, more studies would be required, particularly X-ray structures of co-crystals, before more definitive statements could be made concerning the succinimides.

Conclusions

This work has shown that, in analogy to base pairing in nucleic acid chemistry, it is possible to design substrates for which hydrogen bond association with heterocyclic drugs can occur. By virtue of the coplanarity of the substrate and drug, a specific fit leading to strong binding can result. If this binding is disrupted (e.g., by methylation of nitrogen), complexation drops to zero. In addition, specific, multiple hydrogen bonding creates conformational stabilization in groups in proximity to the points of association. This stabilization allows chiral recognition to take place when groups of appropriate size differences are attached to the chiral centers.

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Experimental Section

Materials. The following derivatives of 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione[barbiturates] were studied: 1-(1-cyclohexen-1-yl)-1,5-dimethyl (**1a**); 1-butyl-5-(1-cyclohexen-1-yl)-5-methyl (**1b**); 5-ethyl-1-methyl-5-phenyl (**1c**); 1-methyl-5-(1-methyl-2-pentynyl)-5-(2-propenyl) (**1d**); 5-(dimethylamino)-1-ethyl-5-methyl (**1e**); 5-(dimethylamino)-5-ethyl-1-methyl (**1f**); 5-(dimethylamino)-1-methyl-5-propyl (**1g**); 1-cyclohexyl-5-ethyl-5-(1-piperidinyl) (**1h**); 1-ethyl-5-(1-piperidinyl)-5-propyl (**1i**); 5-(1-cyclohexen-1-yl)-4,5-dihydro-4-imino-5-methyl-1-phenyl 2,6-(1*H*,3*H*)pyrimidinedione (**2**). Several derivatives of 2,6-piperidinedione [glutarimides] were studied: 3-ethyl-3-phenyl (**3a**); 3-ethyl-3-(4-(trifluoroacetamido)phenyl) (**3b**); 3-(1-cyclohexen-1-yl)-3-ethyl (**3c**); 3-cyclohexyl-3-ethyl (**3d**), 4-ethyl-4-methyl (**3e**). Derivatives of 2,4-imidazolidinedione [hydatoins] studied were 5-(4-methylphenyl)-5-phenyl (**4a**), 5-methyl-5-phenyl (**4b**), 5-ethyl-5-phenyl (**4c**), 1-methyl (**4d**), and 1-ethyl-3-methyl-5-phenyl (**4e**). Also studied were the following derivatives of 2,5-pyrrolidinedione [succinimides]: 3-methyl-3-phenyl (**5a**); 3-ethyl-3-phenyl (**5b**); 3-ethyl-3-methyl (**5c**); 3-(1-cyclohexen-1-yl)-3-methyl (**5d**); 1-methyl-3-phenyl (**5e**); 1,3-dimethyl-3-phenyl (**5f**). These compounds were obtained from the following sources. Prof. Dr. J. Knabe (Universitat des Saarlandes, Stadtwald, W. Germany) kindly provided *RS*-, *R*-, and *S*-**1a**; *RS*-**1b**; *RS*-, *R*-, and *S*-**1c**; *RS*-, *R*-, and *S*-**1e**; *RS*-, *R*-, and *S*-**1f**; *RS*-, *R*-, and *S*-**1g**; *RS*-, *R*-, and *S*-**1h**; *RS*-, *R*-, and *S*-**1i**; *RS*-**2**; *RS*-, *R*-, and *S*-**3c**; *RS*-, *R*-, and *S*-**3d**; *RS*-, *R*-, and *S*-**5a**; *RS*-, *R*-, and *S*-**5b**; *RS*-, *R*-, and *S*-**5c**; *RS*-, *R*-, and *S*-**5d**; *RS*- and *R*-**5f**. The United States Pharmacopeia kindly provides *RS*-**1a**, *RS*-**1c**, *RS*-**1d**, *RS*-**3a**, *RS*-**4e**, *RS*-**5c**, *RS*-**5e**, and *RS*-**5f**. The compounds **3e**, *RS*-**4a**, *RS*-**4b**, *RS*-**4c**, *RS*-**4d**, acetic anhydride, butyric anhydride, 1,4-dihydro-4-oxo-2,6-pyridinedicarboxylic acid (chelidamic acid), 18-crown-6, 2,6-diaminopyridine, hexachloroplatinic acid, isobutyryl chloride, *N*-methylmorpholine, (*RS*)-2-phenylbutyric acid, and pivaloyl chloride were obtained from Aldrich Chemical Co., Milwaukee, WI. (*S*)-2-Phenylbutyric acid (97% OP) was obtained from Norse Laboratories, Newbury Park, CA. Dimethylchlorosilane was bought from Petrarch Systems Inc., Bristol, PA. ω-Undecenyl bromide was obtained from Fairfield Chemical Co., Inc., Blythewood, SC. The free base of *RS*- and *S*-**3b** was kindly obtained from Dr. H. A. Salhanic (Harvard School of Public Health, Boston, MA). Silica gel for low-pressure column chromatography and TLC plates were purchased from Analtech (Newark, DE). The silica for bonded-phase was Supelcosil 100Å, 5 μm, 162 m^2/g (Supelco, Bellefonte, PA). All solvents were HPLC grade. Other chemicals were ACS reagent grade. Elemental analysis was performed by either Galbraith Laboratories Inc., Knoxville, TN, or Multichem Laboratories, Inc., Lowell, MA.

Equipment. ^1H NMR spectra were taken with either a T-60 or a XL-300 NMR spectrometer (Varian Associates, Palo Alto, CA), melting points (uncorrected) with the Thomas–Hoover Unit Melt (Arthur H. Thomas Co., Philadelphia, PA). The gas chromatograph was a Varian Model 1200 (Varian Associates, Palo Alto, CA). The liquid chromatograph was a Beckman instrument consisting of a 420 microprocessor controller, two Model 110A single-piston reciprocating pumps, a dynamically stirred gradient mixing chamber, a Model 210 sample injection valve, a Model 160 detector with an 18.5-μL analytical flow cell for UV detection at either 214, 254, or 280 nm (Beckman Instrument, Inc., Berkeley, CA), and a linear recorder Model 500 (Linear Instruments, Reno, NV). The chromatographic data were processed with a Nelson Analytical Model 2600 chromatography software package (Nelson Analytical, Cupertino, CA) used in conjunction with an IBM XT personal computer (IBM, Boca Raton, FL). Optical rotations were determined with a Perkin-Elmer Model 241 polarimeter (Perkin-Elmer, Norwalk CT). A pneumatic Haskel pump Model DSTV 122 (Haskel, Burbank, CA) was used to pack the column.

Synthesis. Preparation of *N,N'*-2,6-Pyridinediylbis[alkanamide] 6–10. A solution of 40 mmol of 2,6-diaminopyridine and 100 mmol of the respective carboxylic anhydride or the acyl chloride in 25 mL of dry pyridine was prepared and refluxed for 2 h. The reaction mixture was concentrated under reduced pressure and dissolved in ethyl acetate. The organic layer was extracted with water, 5% tartaric acid, and 5% sodium bicarbonate. The organic layer was then dried over sodium sulfate and filtered and the solvent was stripped off. The residue was purified by column chromatography on 10-fold silica gel, utilizing as a mobile phase toluene made increasingly polar with ethyl acetate. The final product was further purified by crystallization from toluene (yield 70–80%).

***N,N'*-2,6-Pyridinediylbis[acetamide] (6).** The product precipitated when the reaction mixture was poured in ethyl acetate. The precipitate was filtered, washed with ethyl acetate, and recrystallized from chloroform to yield a white crystalline material. Mp 205–206 °C (201.5 °C phase transition). Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.84, H, 5.75; N, 21.68. ^1H NMR ($CDCl_3$) δ 2.25 (s, 2 CH_3), 7.70 (s, 2NH), 7.60–8.10 (m, C_5H_3N).

***N,N'*-2,6-Pyridinediylbis[butanamide] (7).** The product was white crystals, mp 126–127 °C. Anal. Calcd for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.86. Found: C, 62.68; H, 7.53; N, 16.86. ^1H NMR ($CDCl_3$) δ 1.01 (t, 2 CH_3 J = 7.3 Hz), 1.76 (sextet, 2 CH_2, J = 7.3 Hz), 2.35 (t, 2 CH_2, J = 7.3 Hz), 7.75 (s, 2 NH), 7.69 (t, H-4-Py, J = 7.6 Hz), 7.90 (d, 2 (H-3-Py), J = 7.6 Hz).

***N,N'*-2,6-Pyridinediylbis[2-methylpropanamide] (8).** The product was white crystals, mp 142.5–143.5 °C. Anal. Calcd as for **7**. Found: C, 62.73; H, 7.68; N, 16.81. ^1H NMR ($CDCl_3$) δ 1.26 (d, 4 CH_3, J = 6.8 Hz), 2.53 (septet, 2 CH, J = 6.8 Hz), 7.6 (s, 2 NH), 7.70 (t, H-4-Py, J = 7.7 Hz), 7.92 (d, 2 (H-3-Py), J = 7.7 Hz).

***N,N'*-2,6-Pyridinediylbis[2,2-dimethylpropanamide] (9).** The product was white crystals, mp 110–111 °C. Anal. Calcd for $C_{15}H_{23}N_3O_2$: C, 64.95; H, 8.36; N, 15.15. Found: C, 65.20; H, 8.49; N, 15.03. ^1H NMR ($CDCl_3$) δ 1.32 (s, 6 CH_3), 7.76 (s, 2 NH), 7.69 (t, H-Py, J = 8.1 Hz), 7.93 (d, 2 (H-3-Py), J = 8.1 Hz).

***N,N'*-2,6-Pyridinediylbis[2-phenylbutanamide] (10)** was prepared from *RS*-2-phenylbutyryl chloride. The crystalline material, a mixture of the meso and racemic forms, showed a double spot, R_f 0.45 and 0.49 (15% EtOAc/toluene), on a silica gel TLC plate. The melting point of such a mixture depends on the ratio of the optical isomers and therefore is not reported. Anal. Calcd for $C_{25}H_{27}N_3O_2$: C, 74.78; H, 6.78; N, 10.47. Found: C, 74.23; H, 6.77; N, 10.35. ^1H NMR ($CDCl_3$) δ 0.88 (t, 2 CH_3, J = 7.3 Hz), 1.82–2.19 (heptet, 2 CH_2, J = 7.0 Hz), 3.31 (t, 2 CH, J = 7.6 Hz), 7.28 (s, 2 C_6H_5), 7.31 (t, H-4-Py, J = 7.9 Hz), 7.61 (s, 2 NH), 7.88 (d, 2 (H-3-Py), J = 7.9 Hz).

Preparation of the Stationary Phase. The compounds **11–15** were prepared according to Markees et al.[34] with modifications. The intermediates **11–15** and compound **17** were purified by flash column chromatography as described in the preparation of **6–10**. Most of the compounds were viscous oils and their purities were verified by TLC and NMR spectrum. The steps for the synthesis of the bonded phase are shown in Figure 8.

Dibutyl 1,4-Dihydro-4-oxo-2,6-pyridinedicarboxylate (11). A 20% slurry of chelidamic acid (16.75 g) in 1-butanol containing 2% sulfuric acid was refluxed for 4 h. After cooling, the reaction mixture was filtered, most of the butanol removed from the filtrate under reduced pressure, and the residue dissolved in toluene and chromatographed: yield, 12.20 g (45%), viscous oil.

Dibutyl 4-(10-Undecenyloxy)-2,6-pyridinedicarboxylate (12). One equivalent of sodium (39.17 mmol) was dissolved in butanol and added to 11.61 g of compound **11**. The butanol was evaporated to dryness, the residue dispersed in toluene, 1.1 equiv of ω-undecenyl bromide added, and the mixture refluxed under nitrogen overnight in the presence of 18-crown-6 as catalyst. The reaction mixture was extracted with aqueous 10% sodium carbonate, followed by two water extractions. The residue of the organic layer was purified by chromatography, to yield 11.07 g (63%) of oil.

4-(10-Undecenyloxy)-2,6-pyridinedicarboxylic acid dihydrazide (13) was prepared according to a procedure described by Markees et al.[34] from compound **12**. The precipitate was filtered, washed with ether, and air-dried to yield 5.57 g (65%) of a crystalline white material, mp 140–142 °C.

Diethyl *N,N'*-[4-(10-Undecenyloxy)-2,6-pyridinediyl]bis[carbamate] (14). A suspension of 5.3 g of **13** in 110 mL of 9% aqueous hydrochloric acid was prepared, cooled to 10–15 °C, and stirred vigorously, and a solution of 4.0 g of sodium nitrite in 40 mL of water was added dropwise over 2 h. The waxy precipitate was filtered, washed with water to neutrality, and air-dried overnight. The crude diazide was dissolved in absolute ethanol and refluxed for 5 h. The reaction mixture was purified by chromatography to yield 2.6 g of a colorless solid (42%).

2,6-Diamino-4-(10-undecenyloxy)pyridine (15). Compound **14** (2.6 g) was dissolved in 50 mL of 95% ethanol containing 2.5 g of potassium hydroxide and refluxed for 3 h. Most of the alcohol was removed and the residue partitioned between ethyl acetate and water. The organic layer was washed with water, dried over sodium sulfate, and filtered, and the solvent was removed under vacuum to yield 1.45 g of **15** (85%). ^1H, NMR ($CDCl_3$) δ 1.32 (m, 7 CH_2, $W_{1/2}$ = 6 Hz), 1.6–2.4 (m, $CH_2C{=}C$), 3.82 (t, CH_2, J = 6 Hz), 4.22 (broad s, 2 NH_2, exchangable with D_2O), 4.7–5.2 (m, $CH_2{=}$), 5.38 (s, pyridino hydrogens), 5.4–6.2 (m, $CH{=}$).

(*S*)-2-Phenylbutyryl Chloride (16). A solution of 3.0 g of (*S*)-2-phenylbutyric acid [97% optically pure, $[\alpha]^{23}_D$ = +83.6° (neat)] in 55 mL of dry methylene chloride was prepared and cooled in an ice bath, and a solution of 10 mL of thionyl chloride in 20 mL of methylene chloride was added dropwise over 30 min. The solution was refluxed for 4 h and distilled: bp 97–98 °C (1.87 kPa); 2.67 g, 80%; $[\alpha]^{25}_D$ = +82.70

(34) Markees, D. G.; Dewey, V. C.; Kidder, G. W. *J. Med. Chem.* **1968**, *11*, 126–129.

(c = 2.7 in $EtCl_2$). A sample of the compound was converted to its *tert*-butylamido derivative and found to be 94.9% optically pure by GC (see section on optical purity of bonded phase).

N,N'-[4-(10-Undecenyloxy)-2,6-pyridinediyl]bis[(S)-2-phenylbutanamide] (17). A solution of 1 g of **15** and 0.9 mL of *N*-methylmorpholine in 40 mL of dry chloroform was prepared and cooled to −20 °C. A solution of 1.3 g of **16** in 10 mL of chloroform was added dropwise over 3 h and left at −15 °C overnight. The solvent was removed under reduced pressure and the residue was dissolved in ether, extracted with 5% tartaric acid and 5% sodium bicarbonate, dried over sodium sulfate, and filtered, and the solvent was stripped off. The residue (2 g) was chromatographed on 60 g of silica gel. Compound **17** (500 mg, 25%) was eluted with toluene and showed only the upper spot, R_f 0.61 (15% EtOAc/toluene), of the "doublet" on the TLC plate (see section optical purity of bonded phase). A second fraction, which eluted at 2% ethyl acetate in toluene (100 mg), contained the "double" spot, R_f 0.56 and 0.61 (15% EtOAc/toluene), with small amounts of other impurities. Rechromatographing this fraction on silica gel enriched the lower spot of the doublet, **17B**. Both separated compounds **17** and **17B**, showed the same NMR spectrum. Upper spot: mp 71.5–72.5 °C. Anal. Calcd for $C_{36}H_{47}N_3O_3$: C, 75.88; H, 8.32; N, 7.38. Found: C, 76.16; H, 8.33; N, 7.29. ^1H NMR ($CDCl_3$) δ 0.84 (t, 2 CH_3, J = 6 Hz), 1.28 (br s, 7 CH_2, $W_{1/2}$ = 6 Hz), 1.5–2.4 (m, 2 CH_2, 2 allylic), 3.22 (t, 2 PhCH, J = 7 Hz), 3.92 (t, CH_2O, J = 5.5 Hz), 4.8–5.3 (m, CH_2=), 5.4–6.1 (m, CH=), 7.12 (s, 2 C_6H_5), 7.42 (s, 2 pyridino protons), 7.58 (s, 2 NH).

A solution of 1.68 mmol of **17** was dissolved in 4 mL of dimethylchlorosilane, the solution heated to reflux, and a small crystal of platinic acid added. The reaction mixture was refluxed for 2 h. All volatiles were stripped off under high vacuum to obtain N,N'-[4-(11-(dimethylchlorosilyl)undecyloxy)-2,6-pyridinediyl]bis[2-(S)-phenylbutanamide] (**18**). The ^1H NMR spectrum showed the disappearance of the olefinic protons from **17** and the appearance of the dimethylsilyl protons.

Bonded Stationary Phase (19). Residue **18** was dissolved in 20 mL of dry pyridine, filtered through a 1-μm Millipore filter into 3.0 g of dried (200 °C, vacuum, overnight) Supelcosil. The slurry was gently homogenized and rotated for 5 h at room temperature. The mixture was then filtered and washed thoroughly with methylene chloride followed by methanol. The filtrates and washings were saved for further analysis (see below). The bonded silica was dried at 60 °C for 4 h at atmospheric pressure and 4 h under high vacuum. From carbon analysis (6.62%) the bonded ligand surface density was calculated to be 1.04 μmol/m^2. The bonded silica was dispersed again in pyridine containing dimethyldecylchlorosilane for 5 h, washed, and dried as before. Found (after C_{10} end-capping): C, 10.70. From the difference of the carbon content the density of the C_{10} ligand was estimated to be 2 μmol/m^2.

Characterization of the Washings from the Bonding. The volatiles of the previously combined filtrate and washings of **19** were removed under reduced pressure, the residue was dissolved in ethyl acetate, extracted with aqueous 5% tartaric acid followed by 5% sodium bicarbonate, and dried over sodium sulfate, and the solvent was removed under high vacuum. The residue (0.52 g) showed two main spots on a silica gel TLC plate, R_f 0.61 and 0.45 (15% EtOAc/toluene), and a tailing spot at R_f 0.35. The mixture was chromatographed on 10 g of silica gel to yield three purified compounds that were identified by NMR spectra. The first eluting material (320 mg), R_f 0.61, was found to be [4-(undecyloxy)-2,6-pyridinediyl]bis[(S)-2-phenylbutanamide] (**20**), a hydrogenated byproduct of **17**. ^1H NMR ($CDCl_3$) δ 0.82 (t, 3 CH_3, J = 6 Hz), 1.28 (br s, 9 CH_2), 1.50–2.40 (m, 2 CH_2), 3.33 (t, 2 PhCH, J = 7 Hz), 3.92 (t, CH_2O), 7.23 (s, 2 C_6H_5), 7.53 (s, 2 pyridino protons), 7.71 (br s, 2 amidic protons). The second, R_f 0.45, was found to be an oxy derivative of the silane [4-[11-(dimethylsilyl)undecyloxy]-2,6-pyridinediyl]bis[(S)-2-phenylbutanamide]. ^1H NMR ($CDCl_3$) δ 0.03 (s, 2 $SiCH_3$), 0.57 (br s, $SiCH_2$), 0.85 (t, 2 CH_3, J = 6 Hz), 1.28 (br s, 9 CH_2), 1.43–2.4 (m, 2 CH_2), 3.33 (t, PhCH, 7 Hz), 3.92 (t, CH_2O), 7.17 (s, 2 C_6H_5), 7.42 (s, 2 pyridino protons), 8.02 (br s, 2 amidic protons). A third compound (R_f 0.35), having an NMR spectrum similar to that of the second material, was isolated. From previous experience with TLC of analogous silane compounds,[35] it was assumed that the compound with R_f of 0.45 was disiloxane and that with R_f of 0.35 was a silanol derivative of **18**.

Optical Purity of the Bonded Phase. Compound **10**, which was prepared from racemic 2-phenylbutyric acid, was a mixture of the racemate (*RR* and *SS*) and the meso (*RS*) isomers and showed a double spot on a TLC plate, R_f 0.45 and 0.49 (15% EtOAc/toluene). When active compound **17** was purified by column chromatography, the last eluting fraction also contained a mixture showing a double spot, R_f 0.56 and 0.61 (15% EtOAc/toluene). This mixture was rechromatographed on silica gel to obtain a fraction containing predominantly the lower spot (fraction **17B**). The NMR spectrum of this sample was identical with that of active **17**, the first eluting compound. Moreover, compound **20** showed only one spot with the same R_f value as active **17**. If under the hydrosilylation conditions of active **17** or the bonding conditions of **18** partial racemization occurred, a meso form of **20** should be formed and the second spot of the doublet should appear, which was not the case.

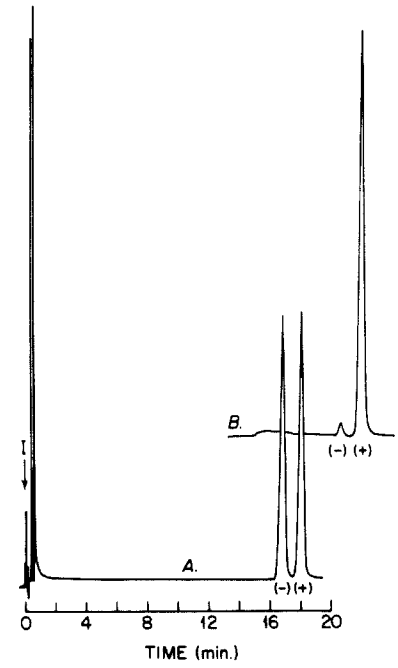

Figure 11. GC enantiomeric separation of *N*-(1,1-dimethylethyl)-2-phenylbutanamide: (A) racemic mixture; (B) obtained from the hydrolysis of **20**. Column, whisker-walled glass capillary column (8-m length × 0.35-mm i.d.) coated with *N*-((*R*)-1-naphthylethyl)dodecanamide. Conditions: temperature of the column, 140 °C; injector, 220 °C, detector, 240 °C; He, 1.5 mL/min.

The optical activity of 2-phenylbutyric acid obtained by hydrolysis of a pure active or a pure meso form of **10**, **17**, or **20** should be 100% or 0%, respectively. Compound **20** was hydrolyzed (20-h reflux in 75% trifluoroacetic acid) to produce 2-phenylbutyric acid. In addition, the sample that was predominantly the lower spot of **17** (fraction **17B**) was hydrolyzed spearately under similar conditions. After the volatiles of the hydrolysates were removed, each of the residues was dissolved in methylene chloride and the organic layer extracted with 5% sodium hydroxide. The aqueous layer was extracted with methylene chloride, acidified, and extracted back with methylene chloride. This last organic layer was dried over sodium sulfate and filtered, and the 2-phenylbutyric acid was converted to its *tert*-butylamide through the acyl chloride as for **17**. A TLC plate of the *tert*-butylamide product from **20** and from fraction **17B** showed a single spot for each product. Both had the same R_f value as pure *N*-(1,1-dimethylethyl)-2-phenylbutanamide. The optical purities of the products from **20** and from fraction **17B**, as determined by GC on a chiral stationary phase (see Figure 11), were 93.4% and 29.4%, respectively. Thus **20** was a mixture of 96.7% *SS* and 3.3% *RR* isomers, and fraction **17B** was predominantly *meso* **17**. The optical activity found in **17B** was due to incomplete purification of meso **17** from its optically active form (*SS*).

Packing of Column. The packing of the bonded phase into a 15 cm × 4.6 mm i.d. stainless steel column followed standard slurry procedures using a solution of 20% methanol in carbon tetrachloride as the slurry medium.

X-ray Diffraction. Crystals of complex **3e**:**7** suitable for diffraction were grown from a 0.02 M solution of **3e** and **7** in methylene chloride–heptane. The diacetyl compound **6** was barely soluble in methylene chloride. Its solubility increased with the addition of bemegride, but two types of crystals formed from slow evaporation of this mixture; one was the self-associated N,N'-2,6-pyridinediylbis[acetamide] and the other, hairlike crystals, was presumably bemegride. Data were collected at room temperature (21 °C) on a Syntex $P2_1$ automated diffractometer using Ni-filtered Cu Kα radiation (λ = 1.5418 Å). Cell dimensions were determined from least-squares refinement of several independently measured reflections well-separated in reciprocal space. The $\theta/2\theta$ scanning technique with variable scan rate was used to measure reflections of 2θ to 130°. Cell dimensions and other experimental parameters are given in Table I. Empirical absorption corrections were made for **6** using ψ scan data. Standard reflections for both **3e**:**7** and **6**, monitored

(35) unpublished results.

every 100 measurements, showed no diminution.

The structures were solved using MULTAN 80.[36] Non-hydrogen atoms were refined, first isotropically and subsequently anisotropically, by using full-matrix least squares using unique reflections with $I \geq 2\sigma(I)$. Hydrogen atoms for **6** were all refined isotropically. For **3e**:**7** all hydrogen atoms except those on C(10), C(11), C(16), C10′), and C(11′) were refined isotropically. Each unrefined hydrogen atom was assigned an isotropic temperature factor based on the thermal parameters of the carbon atom to which it is bonded. Some disorder was apparent at the end of each butanamide chain. Atomic scattering factors for non-hydrogen atoms were taken from ref 37, those for hydrogen atoms from ref 38. The function minimized was $\sum w(|F_o| - |F_c|)^2$, where the weights w, were determined as follows: $w^{1/2} = 1$ when $|F_o| \leq X$ and $w^{1/2} = X/|F_o| > X$. For **6** $X = 14.0$ and for **3e**:**7** $X = 9.0$.[39]

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Registry No. (*RS*)-**1a**, 7200-11-5; (*R*)-**1a**, 7245-06-9; (*S*)-**1a**, 7245-04-7; (*RS*)-**1b**, 64574-45-4; (*R*)-**1b**, 64625-35-0; (*S*)-**1b**, 64625-34-9; (*RS*)-**1c**, 2303-83-5; **1d**, 151-83-7; (*RS*)-**1e**, 101693-69-0; (*R*)-**1e**, 83128-88-5; (*S*)-**1e**, 83128-89-6; (*RS*)-**1f**, 83830-62-0; (*R*)-**1f**, 83128-90-9; (*S*)-**1f**, 83128-91-0; (*RS*)-**1g**, 101693-70-3; (*R*)-**1g**, 83128-92-1; (*S*)-**1g**, 83128-93-2; (*RS*)-**1h**, 101693-71-4; (*R*)-**1h**, 83128-76-1; (*S*)-**1h**, 83128-75-0; (*RS*)-**1i**, 83129-31-1; (*R*)-**1i**, 83541-58-6; (*S*)-**1i**, 101693-74-7; (*RS*)-**2**, 65934-66-9; (*R*)-**2**, 65981-70-6; (*S*)-**2**, 65981-69-3; (*RS*)-**3a**, 18389-24-7; (*R*)-**3a**, 17575-58-5; (*S*)-**3a**, 17575-59-6; (*RS*)-**3b**, 101630-91-5; (*R*)-**3b**, 101693-72-5; (*S*)-**3b**, 101693-75-8; (*RS*)-**3c**, 90355-50-3; (*RS*)-**3d**, 90355-75-2; (*R*)-**3d**, 90355-77-4; (*S*)-**3d**, 90355-76-3; **3e**, 64-65-3; (*RS*)-**4a**, 6322-50-5; (*RS*)-**4b**, 99571-24-1; (*R*)-**4b**, 101693-73-6; (*S*)-**4b**, 27539-12-4; (*RS*)-**4c**, 2216-93-5; (*R*)-**4c**, 65567-32-0; (*S*)-**4c**, 65567-34-2; **4d**, 616-04-6; (*RS*)-**4e**, 74007-05-9; (*RS*)-**5a**, 39122-09-3; (*RS*)-**5b**, 39122-12-8; (*RS*)-**5c**, 39122-18-4; (*RS*)-**5d**, 39122-15-1; (*RS*)-**5e**, 34367-67-4; (*RS*)-**5f**, 39122-21-9; **6**, 5441-02-1; **7**, 101630-92-6; **8**, 101630-93-7; **9**, 101630-94-8; (*meso*)-**10**, 101630-95-9; (*RS*)-**10**, 101630-96-0; **11**, 101630-97-1; **12**, 101630-98-2; **13**, 101630-99-3; **13** (diazide), 101631-00-9; **14**, 101631-01-0; **15**, 101631-02-1; **16**, 40473-35-6; (*meso*)-**17**, 101631-03-2; (*SS*)-**17**, 101693-76-9; **18**, 101631-04-3; (*RS*)-**20**, 101631-05-4; $CH_2{=}CH(CH_2)_9Br$, 7766-50-9; NH_2NH_2, 302-01-2; $HSiMe_2Cl$, 1066-35-9; (*S*)-$EtCH(Ph)CO_2H$, 4286-15-1; (±)-$EtCH(Ph)CO_2H$, 7782-29-8; 2,6-diaminopyridine, 141-86-6.

Supplementary Material Available: Tables of positional and thermal parameters, bond lengths, and valency angles and torsion angles for **6** and **3e**:**7**, all with their estimated standard deviations (12 pages). Ordering information is given on any current masthead page.

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Carbonylation of Titanocene Cyclobutenes. Synthesis and Characterization of a Titanocene–Vinylketene Complex

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Abstract: Carbonylation of several titanocene metallacyclobutene complexes yields the corresponding titanocene–vinylketene complex. The ketene complexes have been isolated as the trimethylphosphine adduct, one of which has been characterized by X-ray diffraction: $Cp_2Ti(C,O\text{-}\eta^2\text{-}OCC(C_6H_5)C(Si(CH_3)_3)CH_2)\cdot P(CH_3)_3$; space group $P2_1/c$; $Z = 4$; 6717 reflections; R_f 0.084, $I > 0$; $a = 9.625$ (2) Å, $b = 16.217$ (2) Å, $c = 16.917$ (4) Å; $\beta = 101.28$ (10)°; $V = 2589.5$ (9) Å^3. Mechanistic studies of the reaction by NMR indicate the presence of an intermediate acyl complex which has been isolated. The experimental evidence suggests that the insertion of carbon monoxide occurs into the less sterically encumbered sp^3 bond rather than the sp^2 bond of the metallacyclobutene. The rearrangement of the acyl complex to the vinylketene product may occur via a titanocene–cyclobutenone complex.

Mediation of complex organic transformations by organometallic catalysts and reagents is an important area of organic chemistry. The potential for both regio- and stereoselectivity in such reactions by the appropriate metal–ligand combinations, in addition to the ability of many organometallic systems to incorporate small organic molecules into larger more complex structures, has prompted a great deal of study in this area.[1] In particular, "Fischer" carbene complexes of Cr and Fe react with a variety of alkynes and carbon monoxide to form hydroquinones,[2] naphthols,[2] naphthoquinones,[3] or pyrones[4] and with imines to yield β-lactams.[5] The mechanistic details of these complex tranfor-

Table I. Titanocene–Vinylketene–Trimethylphosphine Complexes

compd	R	R′	yield, %
2a	Ph	Ph	82
2b	Ph	Me_2Si	92
2c	Ph	CH_3	80
2d	CH_3	CH_3	77
2e	CH_2CH_3	CH_2CH_3	70

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