X-ray Crystallographic Evidence in Support of a Proposed Chiral Recognition Mechanism

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A new family of π-basic chiral selectors has been developed and employed in the separation of enantiomers by liquid chromatography. These chiral selectors, derived from (*S*)-proline and designed from mechanistic considerations, show high levels of discrimination between the enantiomers of *N*-(3,5-dinitrobenzoyl)amino acid esters and amides. A considerable amount of chromatographic data has been assembled, all of it consistent with the proposed chiral recognition mechanism. Moreover, this mechanism is supported by induced chemical shift differences and intermolecular NOE data previously obtained in solution with an equimolar mixture of (*S*)-**1** and (*S*)-**2**. A crystalline 1:1 complex of (*S*)-**1** and (*S*)-**2** has been obtained and analyzed by X-ray crystallography. The structure of this complex in the solid state illustrates the essential features of the mechanism proposed to account for chiral recognition between chiral stationary phase (CSP) **3** and the enantiomers of **2** and related analytes. In addition, the orientation of the two components in the solid state is in close agreement with the structure of the more stable diastereomeric complex deduced from solution-state NMR evidence relating to the same system.

Introduction

The development and evaluation of a new category of π-basic chiral stationary phases (CSPs) derived from L-proline has been reported.[1] These CSPs, while designed to distinguish between the enantiomers of *N*-(3,5-dinitrobenzoyl)amino acid esters and amides, are capable of resolving a variety of racemates which contain π-acidic functionality. The structure of one of these CSPs is shown in Figure 1.

These CSPs make use of intercalative effects to hasten the elution of the least retained enantiomer. These effects are partially responsible for the high levels of enantioselectivity displayed by these CSPs. That intercalative effects are dependent upon the orientation of the chiral selector with respect to the underlying support has been demonstrated,[2] and the absence of intercalative effects in solution-state asymmetric transformations using these chiral selectors has been noted.[3] Though useful in practice, it is important to bear in mind that the concept of differential extents of intercalation by enantiomers is but a rationalization of experimental observations and is based on mechanistic speculation about retention modes of the enantiomers. Evidence for the nature of those interactions which contribute to the retention of the more retained enantiomers has been presented, but it is difficult to obtain such evidence for the less retained enantiomers since these are complexed but a small fraction of the time. Because the (*S*)-proline-derived CSPs afford significant retention of the second eluting enantiomers of the targeted class of π-acidic analytes, information concerning the nature and structure(s) of the more stable diastereomeric complex(es) formed between these chiral selectors and the (*S*)-enantiomers of *N*-(3,5-dinitrobenzoyl)amino acid esters and amides is experimentally accessible.

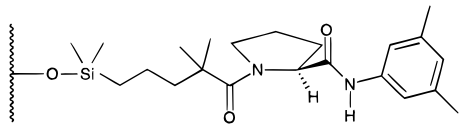

Figure 1. Structure of the (*S*)-proline-derived chiral stationary phase.

The analysis of X-ray crystallographic data has been useful in determining the solid-state arrangement of various components of molecular recognition systems[4−7] and has proven consistent with chiral recognition mechanisms advanced on the basis of UV−visible spectroscopic data and intermolecular nuclear Overhauser effects.[8] In the present instance, a 1:1 complex obtained from an equimolar solution of (*S*)-**1** and (*S*)-**2** (Figure 2) has been crystallized and the structure determined by X-ray analysis.

Experimental Section

A solution of 15.1 mg of (*S*)-*N*-pivaloylproline 3,5-dimethylanilide, (*S*)-**1**, and 17.6 mg of (*S*)-*N*-(3,5-dinitrobenzoyl)leucine dimethylamide, (*S*)-**2**, in 2 mL of warm anhydrous ethanol was allowed to cool to room temperature. When the ethanol had evaporated, one of the bright yellow crystals which had formed was selected for X-ray analysis. One previous attempt to obtain X-ray quality crystals using dichloromethane failed.

This equidimensional data crystal was mounted to a thin glass fiber using epoxy with the (−1, −7, 3) scattering planes roughly normal to the spindle axis. The data crystal was bound by the (1, 0, 0), (−1, 0, 0), (0, 1, 0), (0, −1, 0), (0, 0, 1), and (0, 0, −1) faces. The distances from the crystal center to

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(1) Pirkle, W. H.; Murray, P. G. *J. Chromatogr.* **1993**, *641*, 11−19.
(2) Pirkle, W. H.; Murray, P. G.; Burke, J. A. *J. Chromatogr.* **1993**, *641*, 21−29.
(3) Pirkle, W. H.; Murray, P. G. *J. Chromatogr.*, accepted for publication.
(4) Dobashi, Y.; Hara, S.; Iitaka, Y. *J. Org. Chem.* **1988**, *53*, 3894−3896.
(5) Cram, D. J.; Karbach, S.; Kim, H.; Knobler, C.; Maverick, E.; Ericson, J.; Helgeson, R. *J. Am. Chem. Soc.* **1988**, *110*, 2229−2237.
(6) Yabuki, T.; Yasui, M.; Tezuka, H.; Kasai, N.; Harada, S.; Tenaka, K.; Toda, F. *Chem. Lett.* **1988**, 749−752.
(7) Lee, G.; Wang, Y.; Tanaka, K.; Toda, F. *Chem. Lett.* **1988**, 781−784.
(8) Pirkle, W. H.; Burke, J. A.; Wilson, S. R. *J. Am. Chem. Soc.* **1989**, *111*, 9222− 9223.

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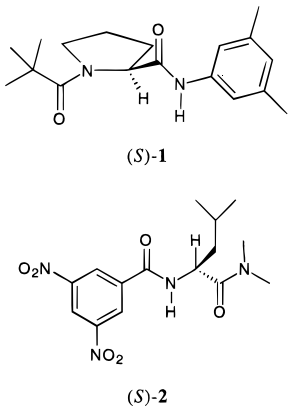

Figure 2. Structures of (*S*)-**1** and (*S*)-**2**.

these facial boundaries were 0.15, 0.15, 0.15, 0.15, 0.11, and 0.11 mm, respectively. The data were collected on an Enraf-Nonius CAD4 diffractometer at 198 K. The polarity of the four chiral molecules with respect to the *b*-axis of the crystal was evident. Periodically monitored standard intensities showed no decay. Step-scanned intensity data were reduced by profile analysis[9] and corrected for Lorentz polarization effects. No absorption correction was applied. Scattering factors and anomalous dispersion terms were taken from standard tables.[10]

The structure was solved by direct methods using SHELXS-86. The correct positions for 91 non-hydrogen atoms were deduced from an *E*-map. One cycle of isotropic least squares refinement followed by an unweighted difference Fourier synthesis revealed the positions for the remaining non-hydrogen atoms. For the disordered solvent molecule (CH_2Cl_2), C−Cl bond lengths were restrained to 1.76 Å and displacement parameters for equivalent atoms were restrained to equivalent values. Hydrogen atom positions H9 and H20 were refined with N−H bond lengths restrained to 0.91 Å. Methyl group hydrogen atoms, R−CH_3 were optimized by rotation around R−C bonds with idealized C−H, R−H, and H−H distances. Remaining hydrogen atoms were included as fixed idealized contributors. Hydrogen atoms *U* values were assigned as 1.2 times U_{eq} of adjacent non-hydrogen atoms. The maximum shift/error for the final cycle of full-matrix least squares refinement on F^2 indicated successful convergence. A final analysis of the goodness of fit between observed and calculated structure factors showed no dependence on amplitude or resolution.

Results and Discussion

The numbering system employed along with a representation of the components in the conformations they populate in the solid-state complex is given in Figure 3. A depiction of the 1:1 complex is reproduced in Figure 4, and a stereoview of the same complex is provided in Figure 5.

It is instructive to consider the conformations of the individual components before commenting on the structure of the complex. The trimethylacetyl group of the chiral selector, (*S*)-**1**, exists in the *trans*-rotamer. The 3,5-dimethylanilide group is planar and populates the *Z*-rotamer, which places H9 *syn*- to H7. The 3,5-dimethylanilide group is perpendicular to the plane of the five-member proline ring. Thus, the two amide carbonyl oxygens are *anti* to one another.

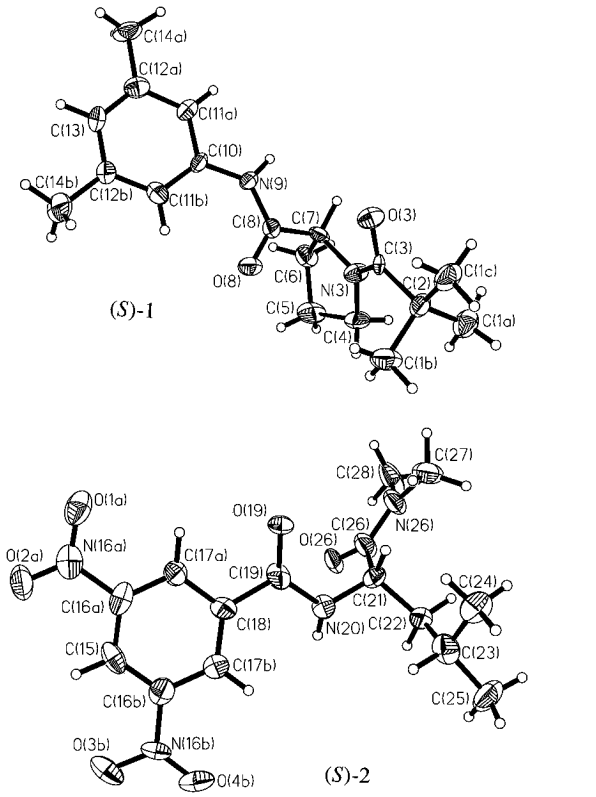

Figure 3. ORTEP diagrams showing the numbering system employed for (*S*)-**1** and (*S*)-**2**, depicting the conformations present in the solid-state complex. Thermal ellipsoids were drawn for non-carbon atoms, and most hydrogens were omitted for clarity

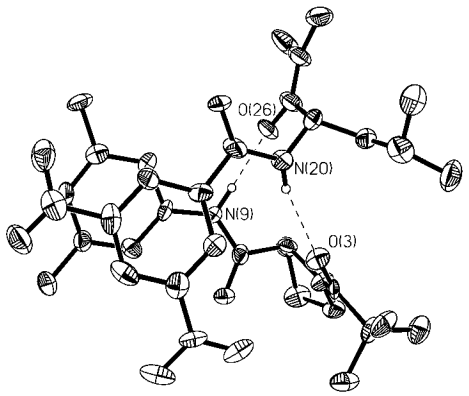

Figure 4. ORTEP plot of a 1:1 complex of (*S*)-**1** with (*S*)-**2**. Thermal ellipsoids were drawn for non-carbon atoms, and most hydrogen atoms were omitted for clarity.

The methine hydrogen, H21, of (*S*)-**2** is more or less eclipsed by O19, the carbonyl oxygen of C19. The 3,5-dinitrobenzamide group is planar and populates the *Z*-rotamer. O26 is *anti* to H21, and so the two amide carbonyl oxygens are *anti* in (*S*)-**2** as well. These conformations are those expected to be the lowest in energy for the individual components, based on the examination of space-filling models, and were expected to be maintained in the complex.

Several features of the 1:1 complex are noteworthy. The two aromatic rings are parallel and separated by 3.36 Å, compelling evidence for the face-to-face interaction deemed necessary for chiral recognition. H20 is thought to be hydrogen bonded to O3, and indeed the closeness of approach of this amide hydrogen to the C3 carbonyl

(9) Coppens, P.; Blessing, R. H.; Becker, P. *J. Appl. Crystallogr.* **1972**, *7*, 488.

(10) Wilson, A. J. C., Ed.; *International Tables for X-Ray Crystallography*, Vol. C; Kluwer Academic Publishers: Dordrecht: 1992.

(11) The interested reader should address correspondence regarding this data to Scott R. Wilson at the School of Chemical Sciences, Noyes Laboratory, University of Illinois at Urbana−Champaign, Urbana, IL 61801.

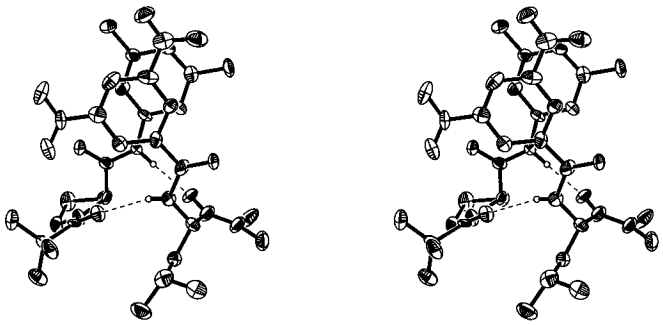

Figure 5. Stereoview of a 1:1 complex of (*S*)-**1** with (*S*)-**2**. Thermal ellipsoids were drawn for non-carbon atoms, and most hydrogen atoms were omitted for clarity.

oxygen (2.05 Å) and the N20−H20−O3 angle (171.02°) seem consistent with this notion. H9 is thought to be hydrogen bonded to O26, and in fact, this amide hydrogen and the C26 carbonyl oxygen are but 1.94 Å apart in the complex. In (*S*)-**1**, the torsional angle between the aromatic ring and the amide group is approximately 5° [C8−N9−C10−C11b = −7(3)°; C8−N9−C10−C11a = 177(14)°]. The torsional angle in the amide group is approximately 4° [O8−C8−N9−C10 = 0(3)°; C7−C8−N9−C10 = 172.2(14)°]. In (*S*)-**2**, the torsional angle between the aromatic ring and the amide group is approximately 9° [C17b−C18−C19−O19 = −175(2)°; C17a−C18−C19−O19 = 9(2)°; C17b−C18−C19−N20 = 9(3)°; C17a−C18−C19−N20 = −167.9(14)°]. The torsional angle in the amide group is approximately 3.5° [C18−C19−N20−C21 = 175(2)°; O19−C19−N20−C21 = −2(2)°].

Since chromatographic and spectroscopic data indicate that there is relatively little association between (*S*)-**1** and (*R*)-**2**, no attempt was made to obtain a crystalline complex of these compounds. Could such a complex be obtained, it seems unlikely that the solid state arrangement would be relevant to the structures of any complexes formed in solution as a consequence of the relatively weak interactions between these molecules.

All other relevant information, including bond lengths, bond angles, atomic coordinates, and torsional angles has been determined using the data derived from this experiment.[12]

Conclusion

On the basis of the examination of CPK space-filling molecular models, a family of chiral selectors was designed to distinguish between the enantiomers of π-acidic derivatives of amino acids, amines, amino alcohols, and alcohols. In practice, enantioselectivity encountered with chiral stationary phases derived from these proline-based selectors is often substantial. The interactions proposed to occur during chiral recognition in solution with these selectors is herein supported by a 1:1 crystalline complex of (*S*)-**1** and (*S*)-**2**. Moreover, the relative positions of the two components in the solid-state complex agree entirely with the conclusions drawn from induced chemical shifts and intermolecular nuclear Overhauser enhancements observed in the solution state for the same chiral selector−analyte combination (see previous paper in this issue).

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(12) There are actually two slightly different complexes present in the unit cell. The interatomic distances and torsional angles reported in the text are those from one pair and are similar but not identical to those of the second pair. Both complexes utilize the same intermolecular interactions in complex formation. The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.