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Chiral recognition in the solid state: crystallographically characterized diastereomeric co-crystals between a synthetic chiral selector (Whelk-O1) and a representative chiral analyte

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Abstract—Designed to distinguish between the enantiomers of compounds possessing commonly occurring structural features, the chiral selector used in the chiral stationary phase (CSP) **1** (Whelk-O1) is broadly applicable. In an effort to further the understanding of the mechanism of chiral recognition with this chiral selector, both diastereomeric combinations of selector **1** and a representative analyte, the pivalamide of *p*-bromo-α-phenylethylamine, **2**, were successfully co-crystallized and characterized by single crystal X-ray diffraction. The crystal corresponding to the complex that is more stable in solution is consistent with our previously reported chiral recognition model. The aromatic portion of **2** is in the cleft of selector **1**, displaying both face-to-face and face-to-edge π–π interactions as well as a hydrogen bond between the benzamide proton of the selector and the carbonyl oxygen of the analyte. For the crystal corresponding to the complex, which is less stable in solution, the aromatic portion of **2** is not in the cleft of selector **1**, having approached from the opposite face of the π-acidic dinitrobenzamide moiety so as to undergo face-to-face π–π and hydrogen bonding interactions. Comparisons of these structures and their relevance to enantioselective chromatography are also discussed.

1. Introduction

We have been concerned with the design, development, and evaluation of low molecular weight chiral selectors used in enantioselective chromatography. The selector used in chiral stationary phase (CSP) **1** was originally designed to differentiate the enantiomers of naproxen and other non-steroidal anti-inflammatory drugs.[1–3] It has since been shown that it is capable of resolving the enantiomers of a wide variety of chiral analytes using a range of chromatographic conditions.[4–7] In general, analytes with an aromatic ring and a hydrogen bond acceptor near a stereogenic center are candidates for enantiodifferentiation by CSP **1**. From systematic chromatographic studies, a model accounting for the manner in which the selector interacts with the more retained enantiomer of numerous analytes has been reported.[8–16] The selector is thought to have a cleft-like binding site formed by the planes of the naphthyl and dinitrobenzamide rings. CSP **1** preferentially retains the analyte enantiomer, which without departing substantially from a low energy conformation, can undergo simultaneous face-to-face π–π interaction with the dinitrobenzamide portion of the selector as well as a hydrogen bonding interaction with the amide proton of the selector. Additionally, a face-to-edge π–π interaction will enhance the affinity of the selector for the more retained enantiomer of the analyte. The analyte enantiomer, which is less retained, is unable to achieve these same analyte–selector interactions without unfavorable torsional and/or steric destabilization. This model for chiral recognition is consistent with the chromatographic data and accounts for observed elution orders for the enantiomers of analytes in cases where the absolute configuration of the analyte is known. When applied properly, this model can even allow the assignment of absolute configuration.[17] The model is also consistent with NMR data determined for these complexes using soluble analogues of CSP **1**.[18,19] Additionally, this model is consistent with recent computational modeling studies between an analogue of CSP **1**, and derivatives of *N*-pivaloyl-α-phenylethylamine.[20]

Herein, we report the solid state structures of a 1:1 complex for each diastereomeric pair formed from a CSP **1** analogue compound, **1**, and the pivalamide of

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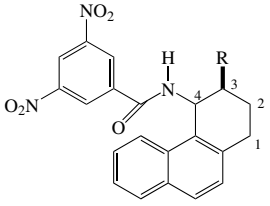
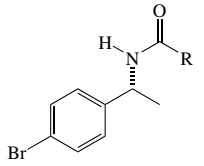
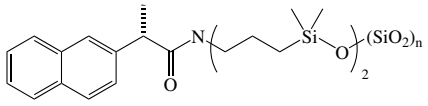
p-bromo-α-phenylethylamine, **2**.[21–24] Since it is the difference in energy of the two diastereomeric adsorbates, which determines the extent of enantioselectivity, structural modifications, which increase this energy difference will increase the chromatographic separation factor whether it is by increasing the affinity of the selector for the more retained analyte enantiomer or by decreasing the affinity of the selector for the less retained enantiomer of the analyte. A detailed understanding of how the selector interacts with each analyte enantiomer should allow design modifications for selectors of improved scope and/or selectivity (Fig. 1).



(3*R*,4*S*)-CSP **1** R = $(CH_2)_3Si(CH_3)_2$-$(SiO_2)_n$
(3*S*,4*S*)-**1** R = CH_3



(*R*)-CSP **2** R = $NH(CH_2)_3$-$(SiO_2)_n$
(*R*)-**2** R = *t*-Bu



(*S*)-CSP **3**

Figure 1. Chiral stationary phases and analytes used herein.

2. Results and discussion

2.1. Chromatographic chiral recognition

From analysis of the proposed chiral recognition model for selector **1**, (3*R*,4*S*)-CSP **1** was expected to preferentially retain the (*S*)-enantiomer of **2**. Indeed this was the case (Table 1). Additionally, a chiral stationary phase derived from (*R*)-*p*-bromo-α-phenylethylamine (CSP **2**) preferentially retains the (3*R*,4*R*)-enantiomer of **1** consistent with the proposed model. In an effort to avoid confusion, it should be pointed out that the (3*R*,4*S*) CSP **1** and (3*S*,4*S*)-**1** possess the same relative stereochemistry about the partially saturated ring of the selector—in both cases the substituent at the 3-position is *cis* to the dinitrobenzamide moiety. There is a change in the Cahn–Ingold–Prelog priority at the 3-position when propyl silyl moiety is exchanged for a methyl group, which accounts for the stereochemical descriptor at this position being (*R*)- for the CSP and (*S*)- for the soluble selector when the stereochemical descriptor at the 4-position is *S* in both cases.

Table 1. Chromatographic data

	2 on (3*R*,4*S*) CSP **1**	**1** on (*R*) CSP **2**
Mobile phase	40% Isopropanol/ hexanes	20% Isopropanol/ hexanes
Retention factor 1: k_1	0.59	0.92
Retention factor 2: k_2	6.91	5.85
Separation factor: α	11.63	6.36
More retained	(*S*)	(3*R*,4*R*)

Conducted at ambient temperature with a nominal flow rate of 2 mL/min.

The chromatographic separation factor (α) is related to the difference in free energy of the adsorption of the two enantiomers by the equation: $\Delta\Delta G = RT\ln\alpha$. From the separation of the enantiomers of **2** on CSP **1**, the energy difference between the two diastereomeric adsorbates is 1.44 kcal/mol at 25 °C. From the reciprocal chromatographic experiment, the difference in energy of the two diastereomeric adsorbates formed with the enantiomers of **1** and CSP **2** is 1.08 kcal/mol at 25 °C. It should be borne in mind that these values are weighted averages influenced by all processes, which retain the enantiomers on the CSP and are minimum values of the true differences in energy.

The chiral recognition model derived from chromatographic and NMR studies is of value in anticipating when resolutions can be expected, the order of elution, and, to some degree, in providing rough estimates of the separation factors which might be expected. However, it provides a first approximation of the relative orientations of the selector and the more retained enantiomer of the analyte. In order to gain a better understanding of the manner in which chiral selector **1** interacts with the enantiomers of an analyte, a more detailed picture of the manner in which selector **1** interacts with each enantiomer is needed.

2.2. Homochiral complex

The (3*R*,4*R*)-enantiomer of selector **1** and the (*R*)-enantiomer of **2** crystallized as a methylene chloride solvate in a 2:2:1 ratio, respectively. The complexed pairs are generally well separated from other interacting pairs in the solid state with only one notable exception (vide infra). In the solid state there are actually two selector–analyte pairs in the unit cell. The measurements (bond lengths, angles, etc.) for the two pairs are similar but not identical. Both utilize the same intermolecular interactions in the complex formation. Measurements are quoted for both pairs and in a consistent order.

Depictions of the two components illustrating the conformations they adopt in the 1:1 co-crystal, along with the numbering system employed, are presented in Figure 2. Before considering the structure of the complex, it is instructive to consider the conformation of each component separately. The saturated six-membered ring of selector **1** adopts a half-chair conformation placing the methyl group in a pseudo-equatorial position and the dinitrobenzamide moiety in a pseudo-axial position. The pseudo-axial disposition of the dinitrobenzamide moiety sets up the cleft between it and the naphthyl ring, which is thought to be essential for effective chiral recognition with this selector. The aryl portion of the dinitrobenzamide moiety shows a slight deviation from planarity with respect to the amide portion [dihedral

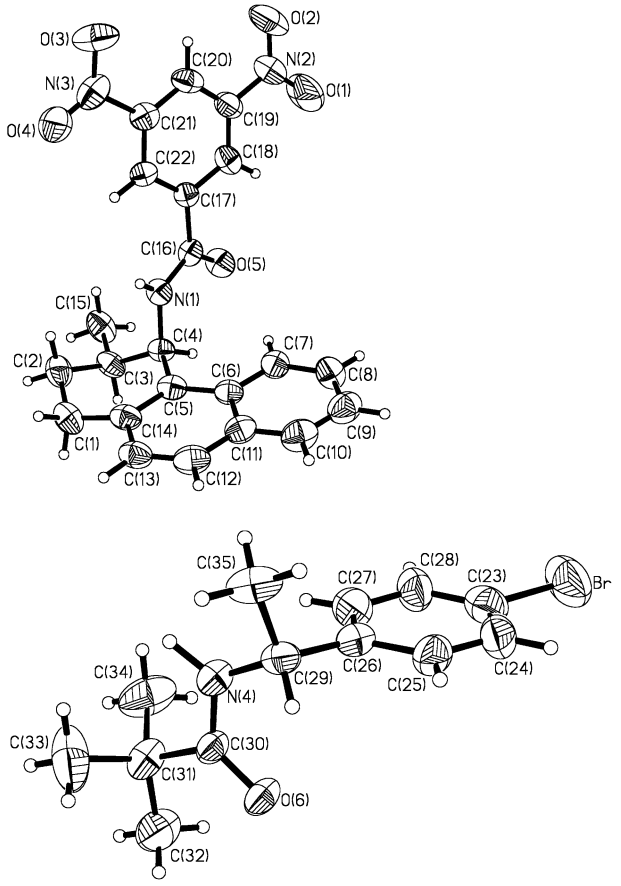


Figure 2. ORTEP diagrams of the components of the homochiral complex, with numbering. Thirty five percent probability thermal ellipsoids are shown for non-hydrogen atoms and circles of arbitrary size for hydrogen atoms.

angles: O5–C16–C17–C18 −16.8° (13.5°); N1–C16–C17–C18 163.8° (166.6°)]. This deviation from planarity directs the benzamide proton toward the cleft of the selector and is probably a consequence of hydrogen bonding to **2**.

The amide portion of **2** is nearly planar and populates the (*Z*)-rotomer about the amide nitrogen–carbon bond [dihedral angles: O6–C30–N4–C29 −1.0° (−2.5°); C31–C30–N4–C29 179.5° (177.0°)]. The methyl group attached to the stereocenter of **2** is nearly perpendicular to the plane of the aryl ring, thus leaving the nitrogen (and the methine hydrogen) ca. 30° out of the plane of the aryl ring (dihedral angles: C35–C29–C26–C27 −91.1° (−94.9°); N4–C29–C26–C27 31.2° (31.5°)).

A depiction of the 1:1 complex is shown in Figure 3. The aryl portion of the dinitrobenzamide moiety of **1** and the aryl ring of **2** are nearly parallel, with a 3.3° (8.1°) angle between mean planes and a separation of 3.6 Å (3.6 Å). Projections of the complex orthogonal to both aryl rings of **1** are shown in Figure 4. The aryl portion of the dinitrobenzamide moiety of **1** and the aryl portion of **2** are offset from one another, as is common to many observed face-to-face π–π interactions between aryl rings. Additionally, the close approach of the benzamide nitrogen of **1** and the carbonyl oxygen of **2** is suggestive of a hydrogen bonding interaction (Table 2).

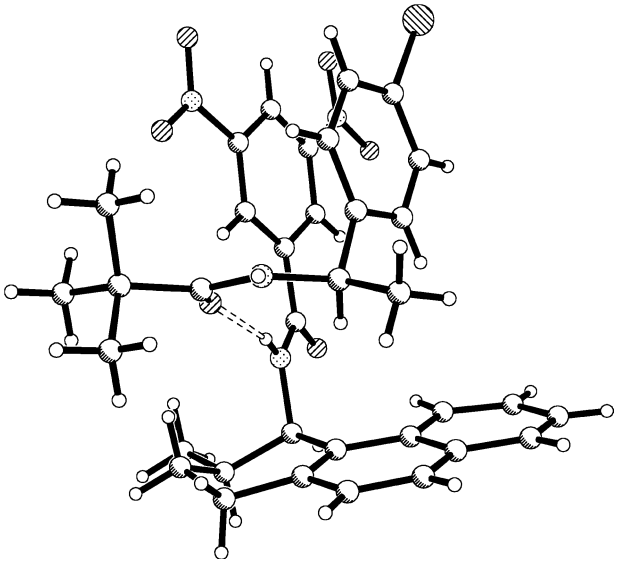


Figure 3. Depiction of the 1:1 homochiral complex in the solid state. Shown as a ball-and-stick diagram for clarity.

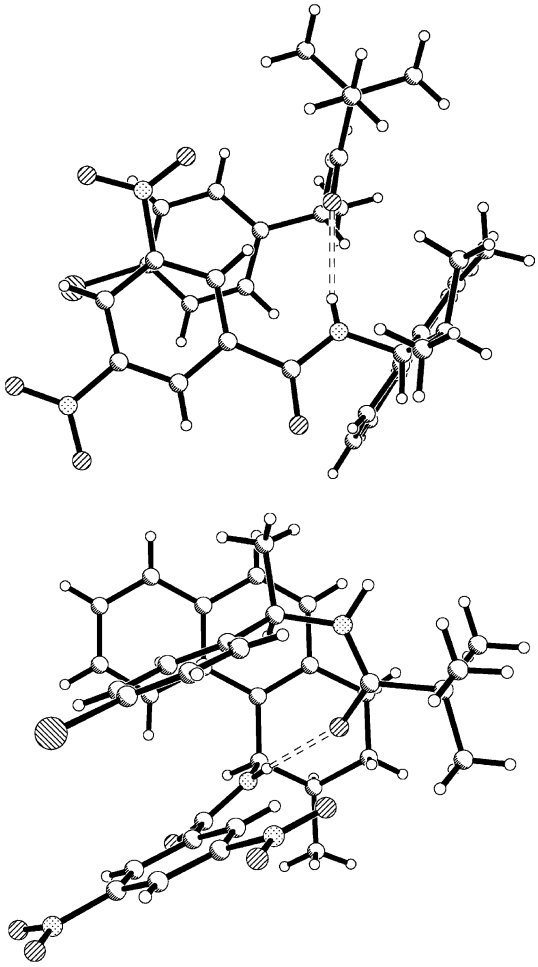


Figure 4. Projections of the 1:1 homochiral complex orthogonal to the dinitrobenzoyl aryl portion of **1** and the naphthyl portion of **1**, illustrating the geometry of the π–π interactions.

Table 2. Hydrogen bonding details[a]

	Homochiral		Heterochiral	
	Intra-complex	Inter-complex	Intra-complex	Inter-complex
N–H bond length	0.74 (0.65)	0.98 (0.71)	0.760	0.841
N–O distance	2.90 (2.86)	3.02 (2.98)	2.916	3.095
H–O distance	2.16 (2.26)	2.12 (2.35)	2.174	2.284
N–H–O angle	168° (153°)	153° (152°)	166°	162°

[a] Distances are in angstroms.

In addition to the face-to-face π–π and hydrogen bonding interactions, the close approach of the aryl group of **2** to the naphthyl portion of selector **1** is suggestive of additional stabilizing face-to-edge π–π interaction and possibly indicates a weak hydrogen bonding interaction of the methine hydrogen of **2** to the electron-rich naphthyl portion of the selector. The angle between the planes of the naphthyl ring of **1** and the aryl ring of **2** is near perpendicular, 80.1° (78.0°). The distance from the center of the aryl ring of **2** to the naphthyl ring of **1** is 5.4 Å (4.9 Å), while the distance of C25 from the naphthyl ring is 4.1 Å (3.6 Å). Additionally, the distance from the carbon at the stereogenic center of **2** (C29) to the naphthyl ring is 3.6 Å (3.7 Å).

In addition to the aforementioned interactions, all of which are consistent with the model for chiral recognition by selector **1**, there is one additional inter-complex interaction present in the solid state. The close contact of the amide nitrogen of **2** and the benzamide oxygen of selector **1** in the adjacent complex in the unit cell is suggestive of a hydrogen bonding interaction (Table 2). This 'one-point' interaction likely aids in the crystallization, but is not thought to be important in chiral recognition in solution, although it could very well occur as a minor achiral interaction between selectors **1** and **2**. While it has previously been shown that removal of extraneous sites for achiral interaction generally leads to greater enantiodifferentiation by a chiral selector,[9] in this case, modification of either of these sites would undoubtedly lead to other undesired consequences.

2.3. Heterochiral complex

The (3*S*,4*S*)-enantiomer of selector **1** and the (*R*)-enantiomer of **2** are crystallized in a 1:1 ratio. It should be noted that the absolute configuration of the components is irrelevant; it is the *relative* configuration of **1** and **2** that is important. The crystallographic data for the complex between (3*S*,4*S*)-**1** and (*R*)-**2** is merely the mirror image of the complex between (3*R*,4*R*)-**1** and (*S*)-**2**, both being diastereomeric to the homochiral complex. The complexed pairs are generally well separated from other interacting pairs in the solid state with the exception of one interaction. As with the homochiral complex, there is one additional 'inter-complex' interaction. The close contact of the amide nitrogen of **2** and the benzamide oxygen of selector **1** is suggestive of a hydrogen bonding interaction (Table 2).

Depictions of the two components illustrating the conformation they adopt in the 1:1 co-crystal, along with the numbering system are shown in Figure 5. The saturated six-membered ring of selector **1** adopts a half-chair conformation placing the methyl group in a pseudo-equatorial position and the dinitrobenzamide moiety in a pseudo-axial position. The aryl portion of the dinitrobenzamide shows a rather significant deviation from planarity with respect to the amide portion (dihedral angles: O5–C16–C17–C22 −32.2°; N1–C16–C17–C22 148.2°). This deviation from planarity directs the benzamide proton away from the cleft of the selector and is probably a consequence of hydrogen bonding to **2**.

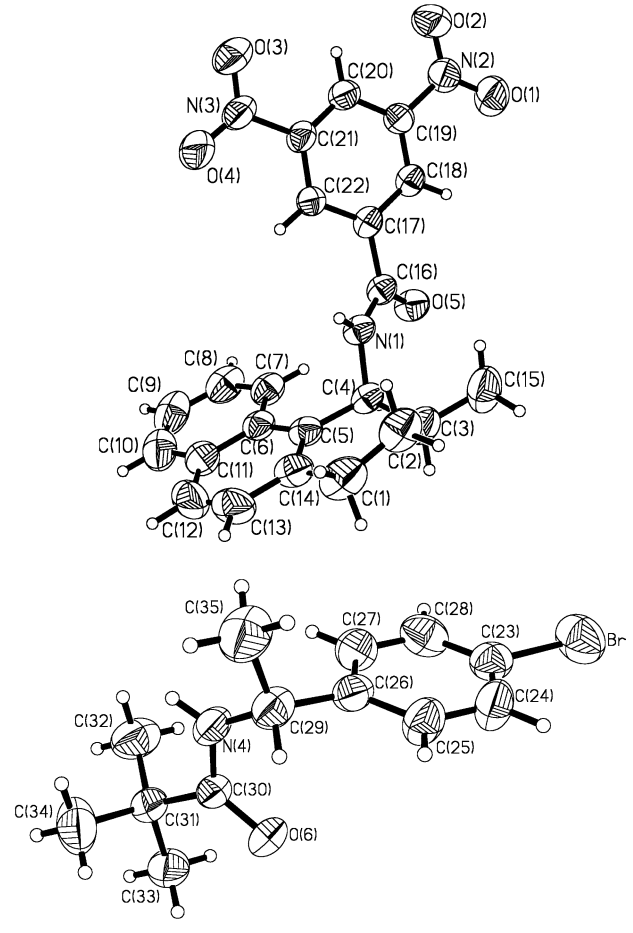


Figure 5. ORTEP diagrams of the components of the heterochiral complex, with numbering. Thirty five percent probability thermal ellipsoids are shown for non-hydrogen atoms and circles of arbitrary size for hydrogen atoms.

The amide portion of **2** is nearly planar and populates the (*Z*)-rotomer about the amide nitrogen–carbon bond

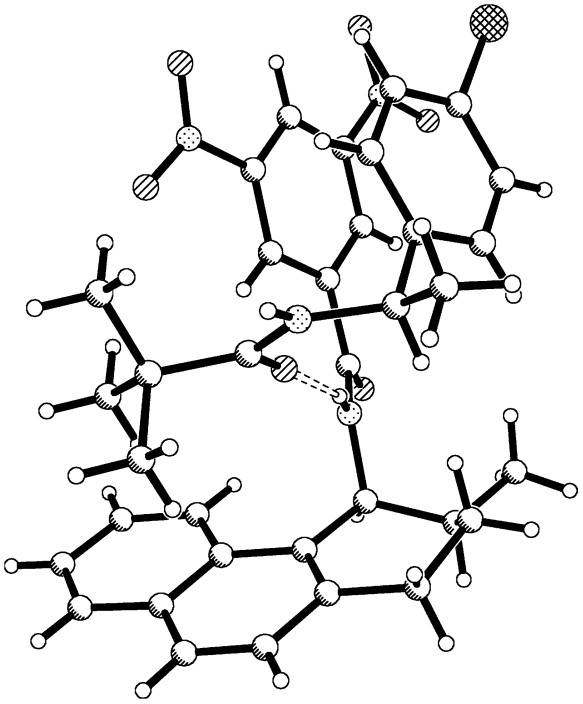


Figure 6. Depiction of the 1:1 heterochiral complex in the solid state. Shown as a ball-and-stick diagram for clarity.

(dihedral angles: O6–C30–N4–C29 −4.3°; C31–C30–N4–C29 174.4°). The methyl group at the stereocenter of **2** is nearly perpendicular to the plane of the aryl ring with the nitrogen ca. 43° out of the plane of the aryl ring (dihedral angles: C35–C29–C26–C27 −80.8°; N4–C29–C26–C27 43.3°).

A depiction of the 1:1 complex is shown in Figure 6. The aryl ring of the dinitrobenzamide moiety of selector **1** and the aryl ring of **2** are in close proximity, suggestive of a face-to-face π–π interaction. The angle between the mean planes of the two rings is 15.4° with a separation of 3.6 Å. A projection of the complex orthogonal to the aryl ring of **2** is shown in Figure 7. The two rings are offset from one another, as is commonly observed for many face-to-face π–π interactions between aryl rings. Additionally, the close approach of the benzamide nitrogen of **1** and the carboxyl oxygen of **2** is suggestive of a hydrogen bonding interaction (Table 2).

2.4. Comparison of the solid state structures

For the heterochiral diastereomer, the aromatic portion of compound **2** is not in the cleft of selector **1**. This is not unexpected from the chiral recognition model for selector **1**. It is evident that in order for the (*R*)-enantiomer of **2** to undergo simultaneous face-to-face π–π interaction as well as a hydrogen bonding interaction in the cleft of the (3*S*,4*S*)-enantiomer of selector **1**, compound **2** must undergo a conformational change. This conformational change would place the methyl group of **2** near the plane of the aryl ring and the methine hydrogen near perpendicular to the aryl plane. This is expected to be an energetically much less favorable conformation.

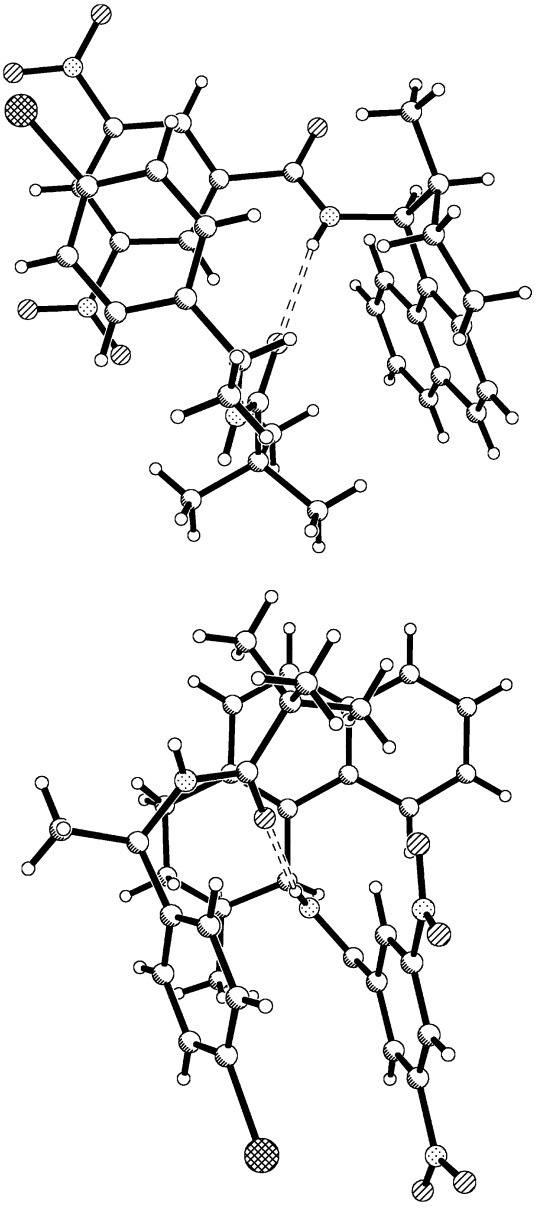


Figure 7. Projection of the 1:1 heterochiral complex orthogonal to the dinitrobenzoyl aryl portion of **1** showing the offset geometry of the face-to-face π–π interaction, and orthogonal to the naphthyl portion of **1**.

Additionally, the methyl group of **2** would be directed toward the naphthyl ring of selector **1**, something which would tend to sterically destabilize this mode of complexation.

3. Conclusions

The two diastereomeric complexes between chiral selector **1** and compound **2** have been characterized in the solid state. Both display a face-to-face π–π interaction between the dinitrobenzoyl aromatic ring of **1** and the *p*-bromophenyl ring of **2**, as well as a hydrogen bonding interaction between the benzamide proton of **1** and the carbonyl oxygen of **2**. The relative orientations of **2** with respect to chiral selector **1** are different for the two

diastereomeric complexes. The more stable homochiral diastereomeric pair (as judged from chromatographic elution order) interacts in such a way that the aryl moiety of **2** is in the cleft of selector **1**. The spatial complementarity of these two allows complexation in this cleft without a substantial deviation from a low energy conformation for either component. Additionally, while in the cleft, the total energy of the complex is lowered by additional bonding interactions with the π-electron rich naphthyl ring of selector **1**. The less stable heterochiral diastereomeric pair interacts in a manner such that the aryl portion of **2** is not within the cleft of selector **1**. Rather, the aryl moiety of **2** is alongside the 'back face' of the dinitrobenzamide moiety and over the saturated portion of the tetrahydrophenanthrene ring system of the selector. The saturated ring of selector **1** is sterically more demanding than the planar naphthyl portion of the selector and this tends to reduce the stability of this complex. Additionally, this 'back face' complex cannot enjoy any additional bonding interactions with the naphthyl portion of the selector as does occur in the homochiral complex.

Herein, we have reported two different modes of chiral recognition observed in the solid state for the diastereomeric complexes formed from each of the enantiomers of chiral selector **1** and the (*R*)-enantiomer of **2**. The homochiral diastereomeric complex is consistent with numerous chromatographic studies as well as NMR chemical shift data of complexes as well as observed intermolecular nuclear Overhauser enhancements. Additional evidence is needed to determine the importance of the mode of chiral recognition displayed by the heterochiral diastereomeric pair. Although, even without any additional solution state evidence, this complex does suggest possible modifications to CSP **1**, which would increase enantiodifferentiation by decreasing the extent of binding in this manner; namely, restricting the analyte approach from the 'back face' of the selector.

4. Experimental

4.1. General

Analytical chromatography was carried out with a commercial version of (3*R*,4*S*)-CSP **1** [250 × 4.6 mm, available from Regis Technologies under the name (*S*,*S*)-Whelk-O1]. (*R*)-CSP **2** (250 × 4.6 mm) was available from a previous study. Compound **1** was prepared as previously reported.[3] Compound **2** was obtained by acylation of *p*-bromo-α-phenylethylamine with pivaloyl chloride as previously reported.[11] HPLC grade solvents were obtained from EM Science. Melting points are uncorrected. The terms homochiral and heterochiral are meant only to relate the relative configuration of **1** and **2**. The term homochiral is used for the diastereomeric combination, in which the Cahn–Ingold–Prelog stereochemical descriptor is the same for both **1** and **2** [i.e., (*R*,*R*)-**1** and (*R*)-**2**]. Heterochiral refers to the diastereomeric combination in which the stereochemical descriptors are not the same [i.e., (*R*,*R*)-**1** and (*S*)-**2**].

4.2. Enantiomer resolutions

Selector **1** was resolved using a preparative chiral stationary phase derived from *N*,*N*-diallyl-(*S*)-naproxen[25] (CSP **3**: 900 × 25 mm) eluting with 25% THF in hexanes with a flow rate of 35 mL/min. Injection of 700 mg of racemate yielded 331 mg of the (3*S*,4*S*)-(−)-enantiomer (>99% ee) followed by 312 mg of the (3*R*,4*R*)-(+)-enantiomer (97.5% ee) in a single pass through the column.

Compound **2** (mp 120.0–122.0 °C) was resolved using a commercial version of (3*R*,4*S*)-CSP **1** (250 × 21 mm) eluting with 40% THF in hexanes with a flow rate of 5 mL/min. Injection of 179 mg of racemate yielded 70 mg of the (*R*)-(+) enantiomer (mp 130.5–131.5 °C, >99% ee) followed by 72 mg of the (*S*)-(−) enantiomer (mp 132.0–133.0 °C, 98% ee).

4.3. Crystallization

4.3.1. Homochiral complex. The enantiomer of **1** (20 mg, 49 μmol), which is more retained on (*S*)-CSP **3** and the enantiomer of **2** (14 mg, 49 μmol) first eluted from (3*R*,4*S*)-CSP **1,** were dissolved in CH_2Cl_2 (1 mL). Diethyl ether vapor was then allowed to diffuse into this solution, leading to slow crystallization. After 4 days, the remaining solvents were decanted and a suitable crystal chosen for X-ray analysis (colorless crystals, mp >200 °C).

4.3.2. Heterochiral complex. The enantiomer of **1** (20 mg, 49 μmol) first eluted from (*S*)-CSP **3** and the enantiomer of **2** (14 mg, 49 μmol) first eluted from (3*R*,4*S*)-CSP **1** were dissolved in CH_2Cl_2 (1 mL) and Et_2O (3 mL). The solvents were allowed to slowly evaporate. After 21 days the solvent volume had decreased to ca. 1 mL. The remaining solvents were decanted and a suitable crystal chosen for X-ray analysis (light yellow crystals, mp 186.5–187.5 °C).

4.4. X-ray analysis[†]

A portion of the data crystal was mounted using epoxy to a thin glass fiber. The data were collected on a Siemens Platform diffractometer at 293 K. Crystal data are given in Table 3. Structure solution and refinement were carried out with the use of the SHELXTL family of programs. Hydrogens thought to undergo hydrogen bonding interactions were independently refined (H1 and H4). Methyl hydrogen positions were optimized by rotation about R–C bonds with idealized C–H, R–H and H–H distances. Remaining hydrogen atoms were included as fixed idealized contributors. Hydrogen atom *U* values were assigned as 1.2 times U_{eq} of adjacent non-hydrogen atoms. The maximum shift/error for the final

[†] Crystallographic data (excluding structure factors) for the structures herein have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 273851 (heterochiral complex), and CCDC 273852 (homochiral complex). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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. Analysis of the absolute structure parameter indicated the absolute configuration to be (3*R*,4*R*)-**1** and (*R*)-**2** for the homochiral diastereomer and (3*S*,4*S*)-**1** and (*R*)-**2** for the heterochiral diastereomer.

Table 3. Crystallographic data

	Homochiral crystal	Heterochiral crystal
Formula	$C_{35.5}H_{38}BrClN_4O_6$	$C_{35}H_{37}BrN_4O_6$
Formula weight	732.06	689.60
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a, Å	18.192(4)	8.884(2)
b, Å	19.186(4)	19.471(4)
c, Å	21.085(4)	20.263(4)
Z	8	4
λ, Å	1.54178 (Cu K_α)	1.54178 (Cu K_α)
R_1	0.0810	0.0411
wR_2	0.2324	0.1175
Goodness of fit	1.076	1.067
Absolute structure parameter	0.01(4)	−0.02(2)

Acknowledgments

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