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Strong Enantioselective Self-Recognition of a Small Chiral Molecule

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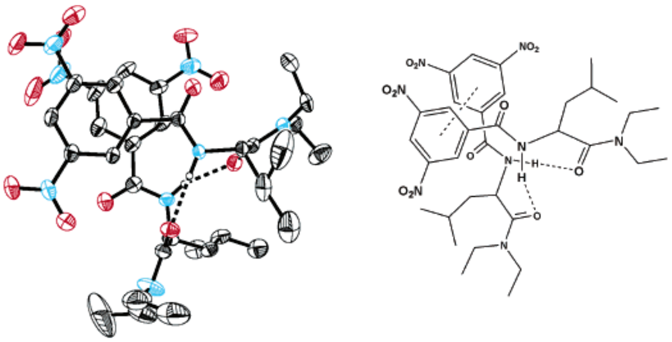
ABSTRACT



In the present report, we have crystallized a single enantiomer and the racemate of *N*-3,5-dinitrobenzoyl (DNB) leucine. In both cases, the X-ray structures show clear evidence of homochiral dimerization in the solid state. Moreover, only homochiral dimers were observed in the unit cell of the racemate, a result of solid-state enantioselective complexation. The crystal structures support a chiral recognition mechanism involving two hydrogen bonds and an offset $\pi-\pi$ interaction between the DNB rings.

Appreciating the role of chirality in molecular recognition is an important goal.[1] To this end, we have been involved in the development of simple molecular recognition systems using small chiral molecules (selectors) that interact differentially with the enantiomers of specified racemates.[2] Consequently, highly effective chiral stationary phases (CSPs)[3] and organocatalysts[4] have been prepared. Particularly intriguing, several of our and related CSPs can differentiate between the racemic precursors of these CSPs with considerable enantioselectivity, the enantiomer from the homochiral complex being more retained on the chromatography column.[5] Significant levels of enantioselective self-assembly in solution have been reported in supramolecular constructs such as hydrogen-bonded assemblies,[6] metal−ligand complexes,[7] supramolecular polymers, and molecular clips.[8] However, strong enantioselective self-association between small molecules in solution is rarely observed, likely a

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consequence of a diminished number of intermolecular interactions relative to the supramolecular assemblies.[9] Here, we explore the molecular basis of chiral self-recognition of a small-molecule chiral selector through X-ray crystallographic analysis.

We restrict our attention to the diethyl amide of 3,5-dinitrobenzoyl (DNB) leucine, **1** (see Figure 1a). A CSP derived from (*S*)-**1** can discriminate between the enantiomers of (±)-**1** with a chromatographic separation factor of approximately 6.0, corresponding to a $\Delta\Delta G$ of 1 kcal.[2] Evidence for the enantioselective dimerization of a related DNB leucine amide in solution has been reported previously.[10] The chemical shifts of many of the protons in a $CDCl_3$ solution are concentration dependent, indicative of self-association. The equilibrium constant for dimerization is estimated to be $K_{\text{dimer}} = 50 \pm 10$.[10]

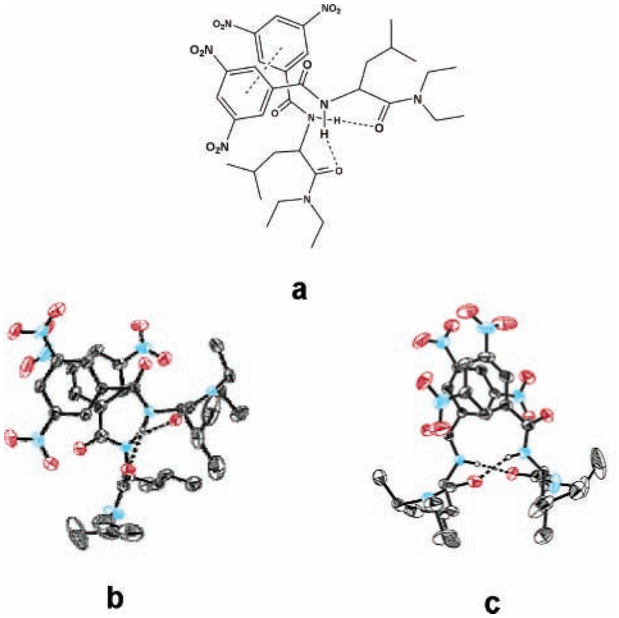

Figure 1. (a) Schematic showing the three simultaneous interactions involved in the homochiral dimer of (*S*)-**1**. (b) ORTEP plot of a (*S*,*S*)-complex viewed from the top side of the DNB rings, with dual intermolecular hydrogen bonding shown as single dashed lines. (c) Alternative view from the side of the DNB rings.

Chiral recognition models have previously been analyzed by X-ray crystallography. In general, the solid-state arrangement of components comprising the more stable diastereomeric complex is consistent with chiral recognition mechanisms advanced on the basis of spectroscopic data and nuclear Overhauser effects as well as structure activity relationships performed on CSPs.[11] Owing to the fact that chiral nonbonding interactions are strongest in the solid state, we anticipated that a single enantiomer of **1** would crystallize as a dimer or higher order aggregate, thus providing insight into the mechanism of chiral self-recognition. When (*S*)-**1** was crystallized from dichloromethane at 4 °C and the structure was analyzed by X-ray crystallography, it was found to dimerize in the solid state (space group $P2_12_12_1$). Two views of the dimeric complex are shown in parts b and c of Figure 1, with dual intermolecular hydrogen bonds shown as single dashed lines. Crystals of (±)-**1**, grown from absolute ethanol, result in a different crystal system (space group $I2/a$). Interestingly, chiral selection occurs in the solid state, as only homochiral (*S*,*S*) and (*R*,*R*) dimeric complexes are found in the unit cell (Figure 2).

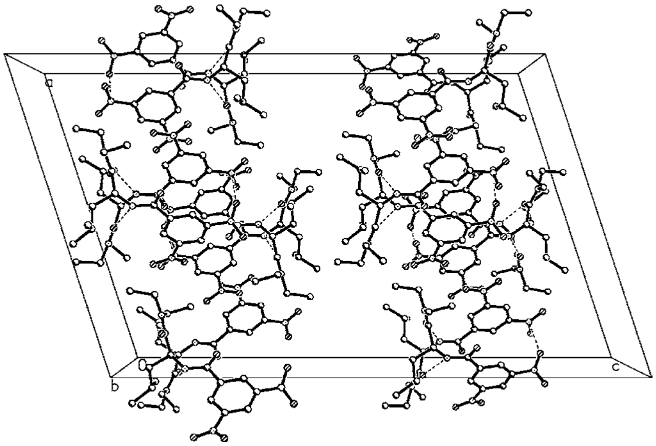

Figure 2. Unit cell of the crystals formed from (±)-**1**. Only homochiral dimers are present in the unit cell, a result of solid-state enantioselective complexation.

There are several salient features of the homochiral dimer (Figure 1) worthy of discussion. Observing the conformation of (*S*)-**1** found in the solid state, the DNB moiety is nearly planar where its carbonyl group is −6.4° out of the aromatic plane. The DNB aromatic plane bisects the stereogenic center, approximately eclipsing the methine hydrogen. The (*S*,*S*)-complex possesses a C_2 symmetry axis penetrating between the two DNB planes, as seen in Figure 1. Two intermolecular hydrogen bonds between the DNB N-Hs and the C-terminal carbonyl oxygens form a twisted 10-membered ring (Figure 1c). Such a head-to-head approach minimizes steric interactions between the two isobutyl substituents on the stereogenic centers and thus allows for chiral discrimination.

The crystal structure of (*S*)-**1** reveals that a $\pi-\pi$ interaction is a prominent feature of the chiral self-recognition mechanism. The two DNB aromatic rings in the complex are nearly parallel (7.6° out of the plane) with an interplanar distance of 3.37 Å, compelling evidence for a face-to-face $\pi-\pi$ interaction.[12] Our previous crystallographic data on

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[9] For examples of the self-discrimination of the enantiomers of small chiral molecules see: Alkorta, I.; Elguero, J. *J. Am. Chem. Soc*. **2002**, *124*, 1488−1493 and examples cited therein.

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π-donor/π-acceptor complexes show nearly identical interplanar distances but with the aromatic rings essentially stacked right on top of each other.[11] It is clear from Figure 1 that the DNB rings interact in an offset manner with a small degree of overlap, in contrast to the π-donor/π-acceptor systems. The presence of this offset $\pi-\pi$ interaction along with the dual hydrogen bonding interaction is sufficient to explain the high chromatographic separation factors and the tendency of **1** to crystallize as a dimer.

The $\pi-\pi$ interaction observed in the homochiral complex (Figure 1) can be analyzed in terms of a multitude of studies over the past 15 years which have elucidated the nature of aromatic−aromatic interactions.[13] In 1990, Hunter and Sanders proposed an electrostatic model to explain $\pi-\pi$ interactions in which a π-system was described as a positively charged σ-framework sandwiched between two regions of negatively charged electron density.[14] Consequently, identically interacting π-clouds will prefer to align themselves in an offset-stacked or face-to-edge orientation where the positively charged periphery can interact favorably with the negatively charged π-cloud.[13] Stated more formally, the offset-stacked (or face-to-edge) arrangement allows for a favorable dispersive interaction while mitigating the effects of a repulsive quadrupole−quadrupole interaction.[15] The quadrupole moment of the DNB moiety is estimated to be slightly more positive than that of hexafluorobenzene.[16] Interaction between the DNB group and an electron-rich aromatic ring results in a highly energetically favorable stacking (sandwich) interaction, consistent with our previous crystallographic data on π-donor/π-acceptor complexes.[11] For interacting DNB rings, the more energetically favorable offset-stacking arrangement is preferred, as seen in Figure 1. The strength of the offset $\pi-\pi$ interaction is surely augmented by the additional hydrogen-bonding interaction in close proximity. Likewise, the acidity of the DNB amide hydrogen is amplified owing to the electron-withdrawing capacity of the DNB ring.

Importantly, shape complementarity becomes increasingly relevant when multiple interactions are present in the host/guest assembly, complicating predictions derived from simple theoretical models.[17] For instance, the degree of offset between interacting aromatic rings will be a function of favorable electrostatics and overall shape selection. Conversely, the sterically demanding nature of the multipoint $\pi-\pi$ interaction makes it the controlling factor governing enantioselective complexation in many selector/substrate complexes.[2,3] In the present study, a favorable offset arrangement between DNB rings allows for the simultaneous formation of two hydrogen-bonding interactions only for the homochiral dimers of (±)-**1**. Hence, the offset $\pi-\pi$ interaction orients the molecules and promotes strong enantioselective dimerization. Interestingly, molecular modeling studies suggest that if the rings are perfectly stacked, the two hydrogen-bonding interactions can also be simultaneously achieved in the homochiral dimer, although the relative orientation of molecules as well as the C_2 axis of symmetry between the interacting molecules will differ from that of the crystal structure shown in Figure 2.

Although not a designed system, the chiral self-recognition mechanism described here, as suggested by X-ray crystallographic data, is consistent with π-donor/π-acceptor chiral recognition mechanisms advanced in our laboratories over the past three decades. The identification of the offset-stacking arrangement in chiral recognition is thought to be a significant finding. Interestingly, the three primary modes of $\pi-\pi$ interactions (stacked, face-to-edge, and offset-stacked) have now all been observed in chiral recognition mechanisms. The stacked orientation between electron-rich and electron-deficient rings has been the most widely used interaction in selector design.[2] Implementation of a face-to-edge interaction into a designed selector has resulted in the most versatile of our CSPs.[3] In addition to its influence on chiral self-recognition, we expect that the offset-stacked arrangement will have broad applicability toward future selector design and the development of new CSPs and chiral catalytic systems.

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Supporting Information Available: Stereoviews of Figures 1 and 2 and crystallographic data for (S)-**1** and (R,S)-**1** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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