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# Assessing chiral self-recognition using chiral stationary phases

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ABSTRACT

Chiral stationary phases were synthesized and their ability to separate racemic precursors from which they were derived was assessed. Taken in conjunction with homochiral recognition previously observed in the solid state, the results of this study reveal that a geometrically controlling π–π interaction has a profound influence on molecular recognition.



## 1. Introduction

An important but relatively unexplored area of small-molecule chiral recognition involves enantioselective self-assembly, often referred to as self-recognition.[1–8] Several important examples of weak small-molecule chiral self-recognition in solution involving hydrogen-bonded dimers have been reported.[9] For instance, Hara has shown that an enantioenriched sample of *N*-acetyl-*S*-valine *tert*-butyl ester exhibits self-induced NMR nonequivalence, the intensity of the signals is reflective of the enantiomeric ratio in solution.[10] Furthermore, chiral stationary phases (CSPs) derived from *N*-acetyl-*S*-valine *tert*-butyl ester and several related amino acid esters were used to show that chiral self-recognition can be used for chiral chromatographic separations, albeit with weak enantiodiscrimination.[11–13] In contrast to the weak self-association of small molecules, significant levels of enantioselective self-assembly have been reported for supramolecular constructs, such as hydrogen-bonded assemblies,[14–19] metal/ligand complexes,[20–23] and supramolecular polymers.[24] This difference reflects the larger number of intermolecular interactions composing the supramolecular assemblies relative to the small-molecule complexes.

In the course of our studies on small-molecule chiral chromatography, we have observed that several of our and related CSPs derived from amide and ester derivatives of 3,5-dinitrobenzoyl (DNB) amino acids can effectively separate the racemic precursors of these CSPs.[25,26] In all cases, the enantiomer forming the homochiral diastereomeric complex with the CSP is more retained on the chromatography column. Furthermore, enantiomerically enriched samples of the DNB-leucine amides show self-induced chemical shift nonequivalence.[27] Based on these studies, we proposed that a chiral recognition mechanism exists in solution involving three essential points of interaction: two hydrogen-bonding interactions and a controlling multipoint offset π–π interaction between the aromatic moieties. Recently, we have provided strong evidence to confirm this hypothesis through X-ray crystallographic analysis (Fig. 1).[28]

Significantly, the model not only explains the high level of chiral self-association but also reveals that the offset π–π interaction can play a prominent role in the chiral recognition of small chiral molecules. Herein, we explore the chiral self-recognition phenomenon further through chiral chromatographic analysis. The difference in free energy ($\Delta\Delta G$) of association between the homochiral complex and the heterochiral complex can be derived simply from chromatographic separation factors ($\alpha$).[3] Hence, chiral chromatography provides an effective means of studying self-recognition. Although dual hydrogen bonding drives the dimerization of 'like' molecules, we postulate that the presence of

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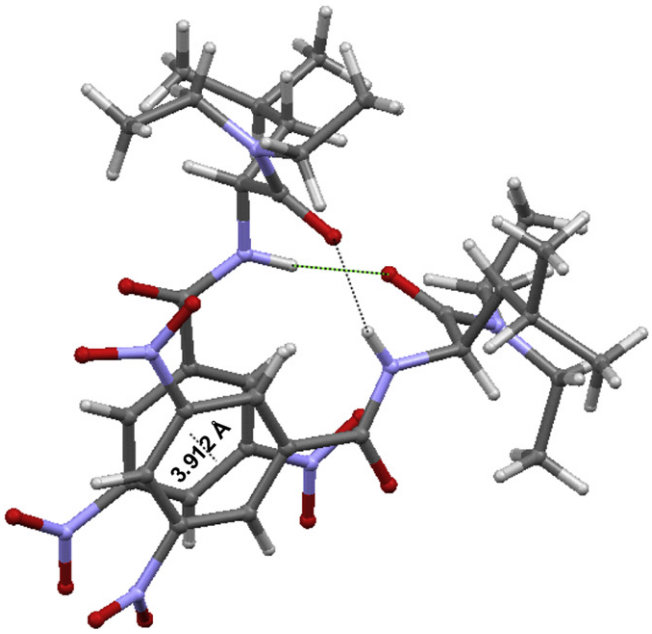


**Fig. 1.** X-ray structure of the diethyl amide of DNB leucine. Two hydrogen-bonding interactions and an offset π–π interaction account for the chiral recognition.[28]

the offset π–π interaction orients the molecules and promotes strong enantioselectivity. The results of these studies have important implications for future CSP and catalyst design as the offset π–π interaction is much more general than the π-stacking interaction between a π-acid and a π-base, an interaction designed into the majority of selector/substrate complexes.[3–5] Moreover, the results can potentially be applied to rational drug design.

## 2. Results and discussion

The structures of the CSPs and the racemic analytes used in this study are shown in Fig. 2. Notably, single enantiomers from the racemates in Fig. 2 are precursors to the four CSPs shown, requiring hydrosilyation prior to tethering to the silica support. Preparations of three commercially available CSPs (**1**, **2**, and **4**)[29,30] and compounds **5**–**10**[31] have been described earlier. The synthesis of (*S*)-CSP **3** is shown in Scheme 1. All four CSPs were initially designed to separate the enantiomers of π-basic racemic analytes suspected to interact with the CSPs through a well-established chiral recognition mechanism.[31] In each case, the essential functionalities thought to be responsible for chiral recognition are located in similar places on the backbone. CSPs **2** and **3**, derived from *tert*-butyl β-lactam and ε-caprolactam, respectively, are cyclized versions of CSPs **1** and **4** and were designed to provide a more conformationally rigid backbone, thus removing a degree of freedom at the stereocenter. Prior studies indicate that CSP **2** and CSP **4** give the highest enantioselectivities for separation of a series of π-basic racemic analytes including napthylenecarboxamides, naproxen derivatives, and benzodiazepines, while CSP **3** shows the poorest performance in all cases.[25]

The four π-acidic CSPs shown in Fig. 2 are also capable of separating the enantiomers of all of the π-acidic analytes used in this study. Chromatographic (HPLC) analysis was performed on each of the four π-acidic CSPs using a mobile phase of 20% 2-propanol in hexane (flow rate 2 mL/min). Chromatographic separation factors (α) for these racemic analytes are displayed in Table 1, with entries involving chiral self-recognition marked in bold. In all cases, the enantiomer forming the homochiral adsorbate is the more retained on the column. The butyl ester of DNB-leucine (±)-**6** shows significantly reduced α values relative to its secondary amide

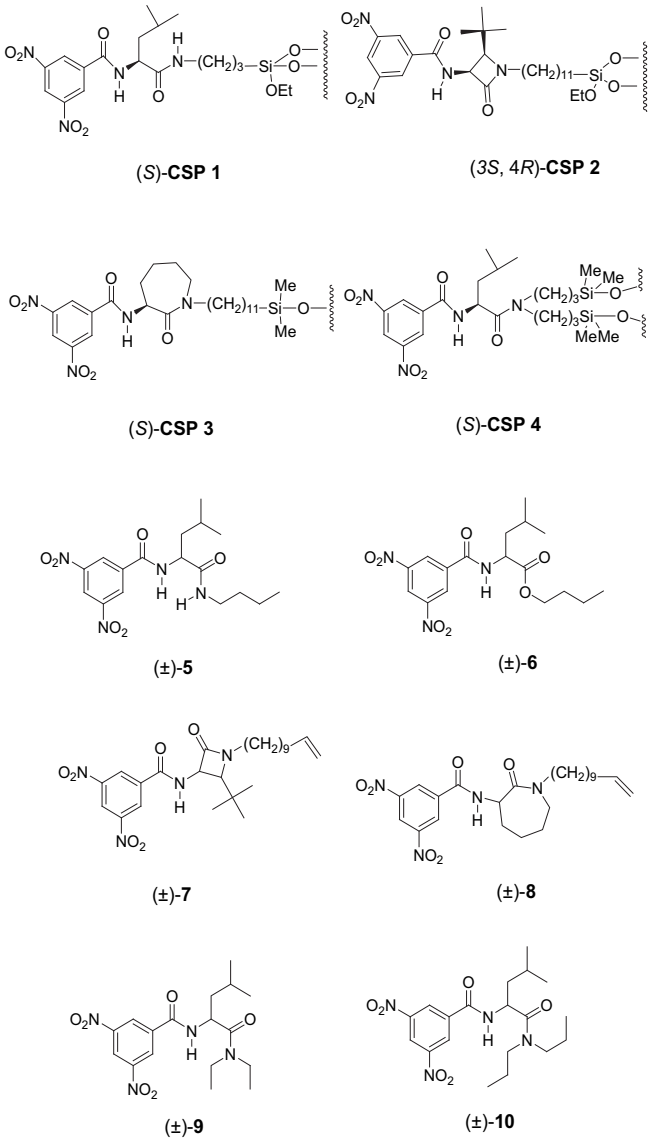


**Fig. 2.** CSPs and racemic analytes utilized in this study.

counterpart (±)-**5**, consistent with many of the previous studies involving π-donor/π-acceptor systems.[31] This result implicates the carbonyl oxygen as a hydrogen bonding acceptor in the chiral recognition mechanism owing to the increased basicity of the amide carbonyl oxygen relative to the carbonyl oxygen of the butyl ester. Furthermore, the DNB tertiary amides (±)-**9** and (±)-**10** give larger α values than the secondary *n*-butyl amide (±)-**5**. In the later case, an additional hydrogen-bonding interaction from the secondary amide hydrogen may provide a competing achiral mode of interaction that increases retention and thus diminishes enantioselectivity. The length of the alkyl chains on the *N*,*N*-dialkyl amides also affects enantioselectivity showing a modest increase from the diethyl amide (±)-**9** to the dipropyl amide (±)-**10** but then decreasing as the alkyl chains are lengthened further (data not shown). Similar effects of the length of alkyl substituents on enantioselectivity have been noted earlier and attributed to intercalation of these groups between the strands of bonded phase.[32] Separations of other racemic DNB amino acids can be accomplished on all four CSPs.

Interestingly, the ε-caprolactam derived (*S*)-CSP **3** generally outperforms the other CSPs for chromatographic resolutions of the π-acidic racemates shown in Fig. 2, despite typically giving the