A Simple Chiral Recognition System to Investigate Substituent Effects on $\pi-\pi$ Interactions
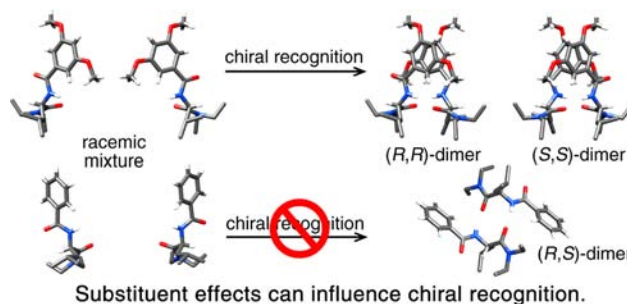
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ABSTRACT

We have used a simple molecular recognition system to study substituent effects in aromatic interactions. A series of substituted benzoylleucine diethyl amides with aromatic rings of varying electronic character were crystallized. All of the substituted dimers organized into homochiral dimers in the solid state but with pronounced differences in regard to the orientation of the aromatic rings with respect to each other. However, no homochiral dimerization was observed in the unsubstituted case.

Deciphering the nature of aromatic interactions is a longstanding goal in the field of molecular recognition.[1] Despite myriad experimental and computational studies directed at $\pi-\pi$ interactions, the molecular bases of these interactions remain controversial.[2] Simple electrostatic models such as the well-known Hunter−Sanders and polar/π models have been used to explain the mechanistic rationale driving these interactions.[3] However, more recent high-level computational studies measuring the effect of substituents on aromatic interactions have challenged the simple electrostatic models.[2,4] Surprisingly, in contrast to predictions from the Hunter−Sanders and polar/π models, these computational studies reveal enhanced interactions in the sandwich configuration of all substituted dimers relative to the unsubstituted benzene. Moreover, several studies predict that increasing the number of substituents on the aromatic moiety results in increased stabilization.[2,4i] Similar results are observed using computational models for parallel displaced $\pi-\pi$ interactions.[4c,e] A number of innovative new theories have been postulated to rationalize these results, which have

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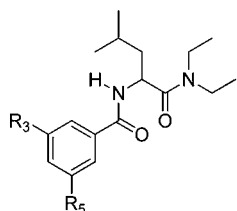
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emphasized the role of direct local interactions,[4e] dispersion effects, and charge penetration effects.[5]

There have been various innovative experimental models to study the energetics of the $\pi-\pi$ interaction, which often rely on using conformationally restrained molecules that force two aromatic rings on the molecule to interact in a particular orientation, such as a sandwich configuration or a parallel displaced configuration.[3a,b,6] However, it is not clear whether results from these systems can be generalized since the interacting rings may be oriented in a way that is energetically unfavorable within the constraints of the molecule projecting the rings but may be energetically favorable if the rings are able to assume an optimized orientation (e.g., horizontal displacement) with respect to each other. With the foregoing in mind, we postulate that simple small molecule chiral recognition systems will provide excellent models to study the nature of $\pi-\pi$ interactions and the influence of substituents on these interactions.

Indeed, $\pi-\pi$ interactions have been an essential element in the design of chiral selectors and chiral catalysts.[7] The $\pi-\pi$ sandwich interaction between a highly electron-deficient aromatic ring and a highly electron-rich ring has been designed into many chiral recognition systems.[7b] Moreover, the parallel displaced interaction between two electron-deficient rings has been observed in the solid state of several small molecule chiral recognition systems.[8] For instance, we reported the homochiral self-recognition between enantiomers of 3,5-dinitrobenzoyl (DNB) leucine amide derivatives.[8a] The chiral recognition mechanism involves a parallel displaced $\pi-\pi$ interaction between the DNB rings reinforced by two hydrogen bonds. Such homochiral self-recognition is also observed in solution and has been applied to the development of new chiral selectors for chromatographic separations.[7a,c,9]

To fully explore the influence of substituents on $\pi-\pi$ interactions, we have expanded our study of chiral self-recognition to include a variety of 3-substituted and 3,5-disubstituted benzoylleucine diethyl amides of varying electronic character. Structures of the compounds crystallized in this study are depicted in Figure 1. Our goal was to determine whether replacement of the DNB ring with aromatic rings of varying electron character would result in similar homochiral dimerization in the solid state and to determine the influence of substituents on the geometry of the $\pi-\pi$ interaction. While the dual hydrogen-bonding interactions present in the homochiral dimers (see Figure S2−S7 Supporting Information and Abstract Graphic) will likely provide some degree of steric constraint which may prevent the rings from assuming their optimal orientation with respect to each other, examination with space-filling models suggests that there is a significant amount of translational and rotational space that the rings can occupy with respect to each other while still retaining the dual hydrogen-bonding interactions. Furthermore, molecular mechanics energy minimization studies revealed that conformational minima are relatively broad for DNB amino acid derivatives and rotational barriers of the benzene ring to the benzoyl carbon are low.[7b,c] Hence, various low energy conformations are expected to be present, each of which could contribute to homochiral dimerization. As the nature of the aromatic substituent is not likely to affect the rotational barriers, the series of compounds investigated herein is also expected to be conformationally flexible.

Results of X-ray crystallographic analysis of the 3-substituted and 3,5-disubstituted benzoylleucine diethyl amides are shown in Table 1. All compounds were crystallized from hexane/dichloromethane. As shown in entries 1−5 of Table 1, all of the 3-substituted compounds organize into homochiral dimers in the solid state. Crystal structures of five different 3-substituted homochiral dimers are depicted in Figures S2a,d−g (Supporting Information). Similar to our prior study with 3,5-DNB leucine diethyl amide **1f**, the crystallographic results indicate that three intermolecular interactions are responsible for chiral self-recognition, two crossed hydrogen-bonding interactions, and a parallel displaced $\pi-\pi$ interaction.[8a,9] Notably, the sandwich configuration was not observed in any of the crystalline homochiral dimers. As in the prior study, chiral selection occurs in the unit cell of all of the 3-substituted dimers, as only homochiral (S,S) and (R,R) dimeric complexes are found. Moreover, as shown in entries 6−9 of Table 1 and in Figures S2b,h−j (Supporting Information), all 3,5-substituted compounds assemble into homochiral dimers in the solid state, including the electron-rich 3,5-dimethyl-substituted compound (entry 8 in Table 1).

Figure 1. Structure of racemic substituted benzoylleucine diethyl amides crystallized in this study.

$R_3 = NO_2$ **1a**, Me **1b**, OMe **1c**, Br **1d**, F **1e**, $R_5 = H$

$R_3 = R_5 = NO_2$ **1f**, OMe **1g**, CH_3 **1h**, F **1i**, H **1j**

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Table 1. X-ray Crystallographic Analysis of 3-Substituted and 3,5-Disubstituted Benzoylleucine Diethyl Amides

entry	compd		homochiral dimer	θ^a (deg)	R^b (Å)	I^c (Å)	α^d (deg)	space group[e]	dimer config	H-bond distance (Å)
1	**1a**	3-NO$_2$	yes	115	3.58	1.68	6.30	P2$_1$/n	R–R, S–S	2.14, 2.20
2	**1b**	3-Me	yes	128	3.36	2.65	5.34	C2/c	R–R, S–S	2.09, 2.09
3	**1c**	3-OMe	yes	114	3.52	1.56	0.06	Pbcn	R–R, S–S	2.05, 2.05
4	**1d**	3-Br	yes	135	3.20	3.21	8.65	C2/c	R–R, S–S	2.11, 2.11
5	**1e**	3-F	yes	129	3.42	2.80	5.27	C2/c	R–R, S–S	2.00, 2.00
6	**1f**	3,5-NO$_2$	yes	119	3.40	1.90	2.60	C2/c	R–R, S–S	2.01, 1.97
7	**1g**	3,5-OMe	yes	115	3.43	1.60	2.37	P2$_1$/c	R–R, S–S	2.03, 2.06
8	**1h**	3,5-Me	yes	123	3.33	2.48	0.41	C2/c	R–R, S–S	2.11, 2.11
9	**1i**	3,5-F	yes	129	3.38	2.75	4.60	C2/c	R–R, S–S	1.97, 1.97
10	**1j**	benzoyl[f]	no	NA	NA	NA	NA	P2$_1$/n	R–S	2.26, 2.26

^{a}The angle (θ) is defined by the ring-to-ring centroid to the plane of benzoyl ring (see Figure S4a, Supporting Information). ^{b}Distance (R) of ring centroid to plane defined by opposite ring (see Figure S4a, Supporting Information). ^{c}Horizontal displacement (I) between two ring centroids (see Figure S4a, Supporting Information). ^{d}Degrees (α) out of plane (see Figure S4b, Supporting Information). ^{e}Several compounds were crystallized in various other solvents such as benzene, toluene, and acetone mixtures resulting in highly similar crystal structures in identical space groups. ^{f}Additionally, no homochiral dimerization is observed when the aromatic group is replaced with a cyclohexyl group (see Figure S3, Supporting Information **1k**).

Importantly, however, as shown in entry 10 of Table 1, homochiral dimerization is not observed in the unsubstituted case (**1j**, R$_3$ = R$_5$ = H). Instead, as depicted in Figure S2c (Supporting Information) and the Abstract Graphic, the molecules organize into heterochiral dimers with the aromatic rings directed away from each other and with two parallel, hydrogen-bonding interactions in a head-to-tail approach rather than the crossed dual hydrogen bonding observed in the homochiral dimers (e.g., Figures S2a,b, Supporting Information). Interestingly, the heterochiral structure is similar to the lowest energy dimer obtained using a multiconformational docking procedure on N-(3,5-dinitrobenzoyl)valine N-hexylamide.[10] We suggest that the substituents are stabilizing the $\pi-\pi$ interaction relative to the unsubstituted benzoylleucine diethyl amide. Notably, as discussed above, results observed in the solid state are consistent with results observed in solution, which implicate a $\pi-\pi$ interaction as an element of chiral self-recognition.[7,8] As discussed with respect to the recent computational models, these results seem to implicate dispersion as an important factor in stabilizing $\pi-\pi$ interactions. However, as discussed in more detail below, there is a significant substituent effect on the degree of parallel and vertical displacement of the aromatic rings, which would appear to implicate other stabilizing forces as well.

Figures S4a,b (Supporting Information) depict the various parameters used to define the orientation of the rings with respect to each other, including the vertical displacement (R) and the horizontal displacement (I), which is a measure of offset of the interacting rings. As shown in Table 1, for the 3-substituted and 3,5-disubstituted benzoylleucine amides that crystallized as homochiral dimers, the interacting aromatic rings are essentially planar (α, the degree out of plane, is less than 10°). Surprisingly, there exists a wide range of horizontal displacement values (I) of the interacting aromatic rings, which is substituent dependent. The horizontal displacement values range from 1.56 Å for the 3-OMe **1c** dimer to 3.21 Å for the 3-Br **1d** dimer. Notably, the degree of offset does not appear to be correlated with the electron-withdrawing capacity of the substituent on the ring, as measured by either σ_m or σ_p. For instance, the horizontal displacements values of the 3-OMe **1c** and 3-NO$_2$ **1a** dimers have similar values, despite having significantly different electronic properties. The halogen-substituted dimers have the largest parallel displacement values, whereas the methyl-substituted dimers fall in between. The vertical displacement values (R) also appear to be substituent dependent, although the range of values (3.20 Å to 3.58 Å) is less pronounced than the horizontal displacement values (I).

These results suggest that a range of different stabilizing geometries are possible for the parallel displaced $\pi-\pi$ interaction and that the optimal geometry appears to be dependent on the nature of the substituents on the respective aromatic rings. The crystallographic data also indicate the flexibility of this model system, despite the constraints imposed by the crossed dual hydrogen-bonding pattern observed in all homochiral dimers. Nonetheless, the observed orientation effects are difficult to rationalize on the basis of current models of $\pi-\pi$ interactions. One might surmise, for instance, that based on the simple electrostatic models, electron-rich aromatic rings would show the largest degree of repulsion between the rings, thereby maximizing the degree of offset (I value). However, there does not appear to exist a simple correlation between the electron character of the electronic ring and the degree of offset.

A closer look at the crystal structures of the aromatic portions of the 3-NO$_2$ **1a** and 3,5-NO$_2$ **1f** dimers reveals that direct, local interactions may influence the energetics and the orientations of the aromatic rings in the respective dimers. Several different perspectives of the aromatic portions of the 3-NO$_2$ **1a** dimer and the 3,5-NO$_2$ **1f** dimer are shown in parts a and b, respectively, of Figure 2. In the

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3-NO$_2$ **1a** dimer, an oxygen on the nitro group is in close proximity (3.60 Å) and roughly parallel to an aromatic hydrogen atom on the opposing aromatic ring (Figure 2a). A similar interaction is observed in the 3,5-NO$_2$ **1f** dimer (Figure 2b). These observations suggest that there may be a stabilizing interaction between the edge hydrogen of one ring and an oxygen on the nitro group of the other ring, consistent with observations of Rashkin and Waters.[11] Furthermore, although two different rotamers for each of the 3-NO$_2$ **1a** monomers are possible, resulting in three different orientations in which the two nitro groups can arrange themselves with respect to each other, only the rotamer which results in the aforementioned stabilizing interaction is observed in the crystal structure. Notably, different rotamers are observed in the 3-NO$_2$ **1a**, 3-Me **1b**, 3-OMe **1c**, 3-Br **1d**, and 3-F **1e** dimers (see, e.g., Figures S2a,d−g, Supporting Information). In addition, only a single rotamer of 3-NO$_2$ **1a** exists in the crystal structure and is distinctly different from the 3-OMe **1c** rotamer.

The results presented in this study might lend support to the direct, local model first proposed by Wheeler and Houk and later modified by Wheeler.[4e,g] However, whether such direct, local interactions are controlling the energetics of aromatic interactions or just one of a number of factors remains an open question. Notably, as discussed above, while several of the homochiral dimers do appear to show direct interactions between local dipoles on the aromatic rings, the existence of these interactions is not as clear in other cases. For instance, in the 3-F **1e** dimer, we do not observe an interaction between the C−F and C−H dipoles of the interacting rings. It is certainly possible in this case that given the constraints imposed by the dual hydrogen-bonding interactions in the dimer, a stabilizing interaction between the C−H dipole of one molecule and the C−F dipole of the other molecule is precluded. Moreover, in aromatic rings that do not possess strong dipole moments (e.g., the 3-Me **1b** dimer), the crystal structures do not necessarily indicate the existence of direct, local interactions. Hence, other factors may be contributing to the substituent effects in aromatic interactions. As discussed above, Arnstein and Sherrill suggested that analyzing substituent effects of aromatic interactions must take into account a balancing of electrostatics, exchange repulsion, dispersion, and induction.[4c] The role that each of these factors plays in controlling the nature of aromatic interactions remain an important question in the field of molecular recognition.

In conclusion, we have shown that the solid state properties of a series of small aromatic molecules, which form homochiral dimers, can provide a wealth of information on the nature of aromatic interactions and in particular, substituent effects. The present study lends experimental support to the hypothesis that all substituents, regardless of their electronic
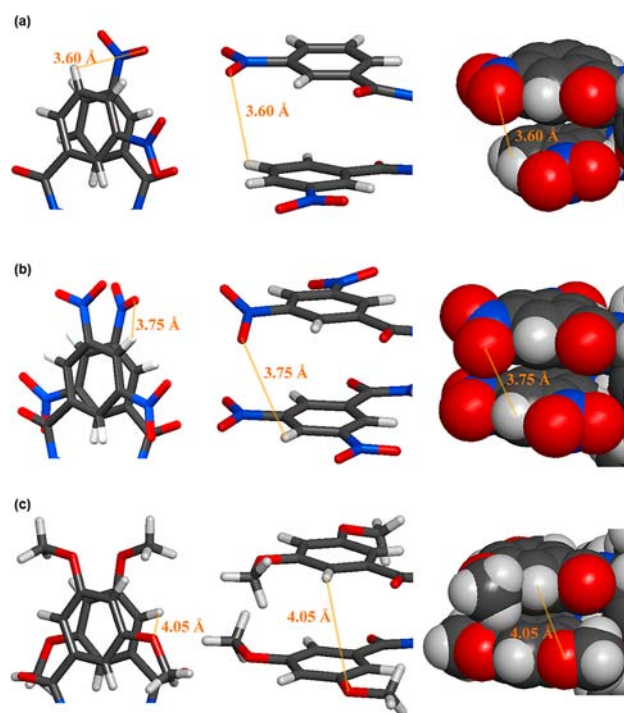

Figure 2. Various perspectives of the partial structures of (a) *N*-(3-nitrobenzoyl)leucine diethyl amide **1a**. (b) *N*-(3,5-dinitrobenzoyl)leucine diethyl amide **1f**. (c) *N*-(3,5-dimethoxybenzoyl)leucine diethyl amide **1g**. The dotted lines show potential local dipole interactions between the interacting aromatic rings of the respective dimers.

character, stabilize aromatic interactions. The results also suggest a role for direct, local interactions in aromatic interactions, although the extent to which these local interactions control overall energetics and the orientation of the interacting aromatic rings is yet to be determined. Nonetheless, we believe that it is of fundamental importance that the substituents on the aromatic rings can radically alter the orientation of interacting rings with respect to each other. Uncovering the origin of this effect can have widespread application in the fields of molecular and biomolecular recognition.

Supporting Information Available. Additional figures, synthesis, characterization, and crystallographic information files (CIF) of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.