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The Effects of Substituents on the Geometry of π–π Interactions

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Dedicated to William H. Pirkle on the occasion of his 78th birthday

Abstract: We have designed and utilized a simple molecular recognition system to study the substituent effects in aromatic interactions. Recently, we showed that 3- and 3,5-disubstituted benzoyl leucine diethyl amides with aromatic rings of varying electronic character organized into homochiral dimers in the solid state through a parallel displaced π–π interaction and two hydrogen bonds, but no such homochiral dimerization was observed for the unsubstituted case. This phenomenon supports the hypothesis that substituents stabilize π–π interactions regardless of their electronic character. To further investigate the origin of substituent effects for π–π interactions, we synthesized and crystallized a series of 4-substituted benzoyl leucine diethyl amides. Surprisingly, only two of the 4-substituted compounds formed homochiral dimers. A comparison among the 4-substituted compounds that crystallized as homochiral dimers and their 3-substituted counterparts revealed that there are differences in regard to the geometry of the aromatic rings with respect to each other, which depend on the electronic nature and location of the substituent. The crystal structures of the homochiral dimers that showed evidence of direct, local interactions between the substituents on the aromatic rings also displayed nonequivalent dihedral angles in the individual monomers. The crystallographic data suggests that such "flexing" may be the result of the individual molecules orienting themselves to maximize the local dipole interactions on the respective aromatic rings. The results presented here can potentially have broad applicability towards the development of molecular recognition systems that involve aromatic interactions.

Keywords: homochirality · molecular recognition · pi–pi interactions · stacking interactions · substituent effects

Introduction

Aromatic interactions (e.g., π–π interactions) are amongst the most well studied and least understood of all interactions in the field of molecular recognition.[1] Simple electrostatic models have traditionally been employed to explain the nature of these interactions.[2] However, over the past decade, results derived from advanced computational calculations, have challenged the simple electrostatic models and shed new light on the effects of substituents on π–π interactions.[3]

There have been several new theories that have attempted to rationalize these computational results. Wheeler and Houk hypothesized that although dispersive interactions stabilize the interaction of substituted benzene rings in a sandwich configuration relative to the unsubstituted case, substituent effects can be explained primarily in terms of direct interactions between the substituent and the other ring, not π-polarization effects.[3e] Recently, Wheeler expanded upon this model, hypothesizing that substituent effects may be explained in terms of direct, local interactions, such as the interaction between local dipoles.[3a] Rashkin and Waters had earlier provided experimental support that direct, local interactions between substituents on interacting benzene rings in a parallel displaced arrangement may contribute to stabilizing π–π interactions.[4] Arnstein and Sherrill also hypothesized that local interactions may contribute to stabilizing parallel displaced π–π interactions, but emphasized that substituent effects should be viewed as a balancing of at least four fundamental components including electrostatics, exchange repulsion, dispersion, and induction.[3f] Ringer and Sherrill argued that the model proposed by Wheeler and Houk significantly de-emphasized the role played by dispersion interactions.[3d] Furthermore, Sherrill et al. suggested that both electron-withdrawing and electron-donating groups are able to stabilize the electrostatic component of π–π interactions through increased charge penetration effects.[5] Nonetheless, deciphering the role of the various intermolecular forces that control aromatic interactions, and substituent effects, remains highly controversial. Hence, there is a strong need for experimental models that can validate these recent computational studies.

We propose that chiral recognition systems that use small molecules will provide exceptional models to investigate the

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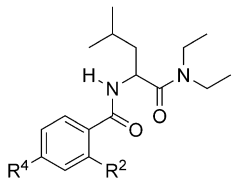
nature of π–π interactions, particularly the influence of substituents on π–π interactions. Small-molecule chiral recognition systems have been studied in detail for more than two decades and have served as the basis for the design of a multitude of chiral chromatographic stationary phases, chiral solvating agents, and catalysts.[6] A number of crystal structures has been solved involving a 1:1 complex between the chiral selector and a molecule that interacts with the selector.[7] Invariably, these solid-state data have been consistent with results derived from chromatographic and NMR spectroscopic studies.[6c,d,8] Moreover, these crystal structures have been used in the design of new generations of chiral selectors and catalysts. Small-molecule chiral recognition systems are simplistic, and require minimal interactions. Thus, they provide an ideal opportunity to study molecular interactions, in particular complex aromatic interactions, which is the goal of the present manuscript. Additionally, as discussed in detail below, we postulate that significant differences in the orientation of interacting aromatic rings induced by substituents can best be ascertained through crystallographic studies. Such orientation effects will be of fundamental importance to computational modelers that are trying to elucidate the nature of aromatic interactions.

Recently, we demonstrated that all racemic 3-substituted and 3,5-disubstituted benzoyl leucine diethyl amides, regardless of the electronic nature of the substituent, undergo homochiral self-recognition in the solid state, whereas the unsubstituted compound does not.[9] The homochiral recognition system is minimalist in nature in that it requires only three interactions, including a π–π interaction and two hydrogen-bonding interactions.[10] Furthermore, unlike some of the early innovative models that involved interacting rings that were spatially fixed with respect to each other,[2a–i,11] we showed that the aromatic rings in the substituted dimers have significant translational freedom, and thus can interact in various orientations. We hypothesized that compounds with aromatic rings involved in an energetically favorable π–π interaction are capable of forming homochiral dimers in the solid state. We further pointed out that the results provided experimental support to the hypothesis that all substituents, regardless of their electronic character, stabilize π–π interactions.[5,9] The crystallographic data also revealed that the orientation of the interacting aromatic rings is profoundly influenced by the nature of the substituent on the respective rings. For instance, the degree of horizontal displacement (i.e., offset) and vertical displacement between the interacting rings varies dramatically, in a substituent-dependent manner. In particular cases, we observed evidence of interactions between local dipoles on the rings, which appear to influence the orientation. These results suggested that a range of different stabilizing geometries is possible for the parallel displaced π–π interactions and that the optimal geometry appears to be dependent on the nature of the substituents on the respective aromatic rings.

To enhance our understanding of the influence of substituents on the orientation of the interacting aromatic rings, a series of 2- and 4-substituted benzoyl leucine diethyl amides was prepared and crystallized. We hypothesize that simple crystallographic systems such as those described herein provide a means of uncovering the extent to which small changes in the substitution pattern of interacting aromatic rings can influence the nature of the π–π interaction.

Results and Discussion

Structures of various racemic 2- and 4-substituted benzoyl leucine diethyl amides crystallized in this study are depicted in Figure 1. All of the compounds investigated in this study



1a: R^2 = H, R^4 = NO_2
1b: R^2= H, R^4 = F
1c: R^2 = H, R^4 = Me
1d: R^2 = H, R^4 = CN
1e: R^2 = H, R^4 = OMe
1f: R^2 = H, R^4 = Cl
1g: R^2 = H, R^4 = Br
1h: R^2 = H, R^4 = H
1i: R^2 = NO_2, R^4 = H
1j: R^2 = Me, R^4 = H
1k: R^2 = F, R^4 = H

Figure 1. Structures of the racemic substituted benzoyl leucine diethyl amides crystallized in this study.

were crystallized from hexane/dichloromethane. Additionally, we crystallized several compounds in additional solvents such as toluene, benzene, and acetone mixtures resulting in largely similar structures in identical space groups.

A diverse set of geometric parameters has been used to describe the spatial orientation between a pair of aromatic compounds.[1e,3f,12a–g] For a rigorous geometric description of the spatial orientation of a pair of interacting aromatic compounds, see Moore et al.[12f] Common and simplistic parameters used to define the offset face-to-face interaction include the distance between the ring-to-ring centroids (d), the distance of the horizontal (I) and vertical (R) displacements of the two interacting rings, the displacement angle (θ), and the tilt angle (α). These parameters are depicted in Figure 2.[9,12e] If the aromatic rings are stacked (i.e., sandwich configuration) the displacement angle θ is equal to 90°, and the horizontal displacement I is equal to 0 Å. Tilt angles less than 20° are considered as stacked or displaced-stacked pairs.[12a] If the rings are parallel, the tilt angle α is equal to 0°. If the rings are perpendicular, the tilt angle α is equal to 90° and the rings assume a T-shaped configuration, as opposed to a sandwich configuration or an offset stacked configuration. Data displayed in Tables 1 and 2 are within typical values for horizontal (I) and vertical (R) displacements

Table 1. X-ray crystallographic analysis of 2- and 4-substituted benzoyl leucine diethyl amides.

	Compound		Homochiral dimer	θ[a] [°]	d[a] [Å]	R[a] [Å]	I[a] [Å]	α[a] [°]	Space group[d]	Hydrogen bonds lengths[Å]
1	**1a**	4-NO_2[b]	yes	107.37	3.78	3.61	1.13	14.29	*C*2/*c*	2.05, 1.89
2	**1b**	4-F[c]	yes	130.06	4.51	3.45	2.90	8.60	$P2_1$	1.97, 2.03
3	**1c**	4-Me	no	NA[e]	9.89	NA	NA	0	$P2_1/c$	2.19, 2.19
4	**1d**	4-CN	no	NA	9.65	NA	NA	0	$P2_1/n$	2.07, 2.07
5	**1e**	4-OMe	no	NA	7.31	NA	NA	65.38	*Pbca*	2.06, 2.06
6	**1f**	4-Cl	no	NA	7.40	NA	NA	54.74	*Pbca*	2.12, 2.12
7	**1g**	4-Br	no	NA	7.38	NA	NA	56.58	*Pbca*	2.15, 2.15
8	**1h**	4-H	no	NA	10.25	NA	NA	0	$P2_1/n$	2.26, 2.26
9	**1i**	2-NO_2	no	NA	8.35	NA	NA	0	$P2_1/n$	1.97, 1.97
10	**1j**	2-Me	no	NA	9.21	NA	NA	0	$P2_1/c$	2.03, 2.03
11	**1k**	2-F	no	NA	8.99	NA	NA	0	$P2_1/c$	2.05, 2.05

[a] See the legend of Figure 2 for an definitions of θ, d, R, I, and α. [b] Compound **1a** crystallizes as a racemate containing homochiral dimers. [c] Compound **1b** crystallizes as a single enantiomer, that is a conglomerate. [d] We crystallized several compounds in additional solvents such as toluene, benzene, and acetone mixtures resulting in largely similar structures in identical space groups. [e] NA = not available.

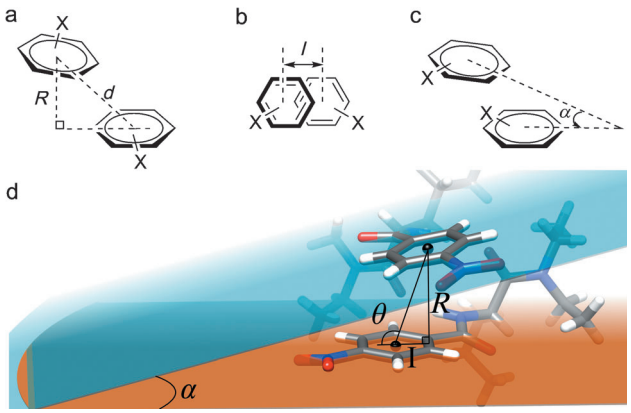


Figure 2. Geometric parameters used to define the orientation of two interacting aromatic rings. a) The distance R of the ring centroid to the plane defined by the opposite ring, and the ring-centroid-to-ring-centroid distance (d). b) The horizontal displacement I between two ring centroids. c) The tilt angle α. d) The displacement angle θ is defined by the smaller of the two angles defined by the ring-to-ring centroids to the plane of the benzoyl rings.

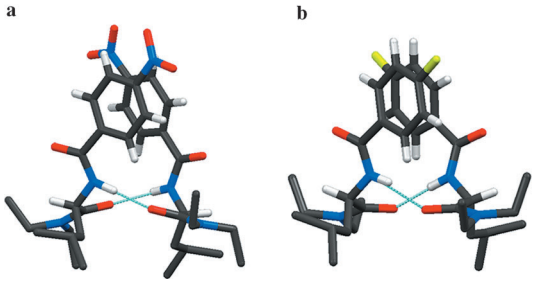


Figure 3. Crystal structures of a) 4-NO_2 **1a** and b) 4-F **1b**, which crystallized as homochiral dimers with two hydrogen bonds (shown as cyan lines) and a parallel displaced π–π interaction.

of two interacting rings in the solid state. Typical values reported in the literature range from 1–3 Å for I and approximately 3.5 Å for R.[12d] In addition, data shown in Tables 1 and 2 are in the range of d values reported in the literature, which are as low as approximately 3 or as high as about 7 Å.[12a,e,f,h]

Seven different 4-substituted benzoyl leucine diethyl amides were crystallized and analyzed. Crystallographic data are provided in Table 1. As indicated in Table 1, the 4-NO_2 **1a** (Table 1, entry 1) and the 4-F compound **1b** (Table 1, entry 2) form homochiral dimers in the solid state (shown in Figure 3). These two dimers are characterized by two crossed hydrogen-bonding interactions and an offset stacked π–π interaction, similar to the crystal structures of their 3-substituted counterparts.

However, the other 4-substituted benzoyl leucine diethyl amides (4-Me **1c**, 4-CN **1d**, 4-OMe **1e**, 4-Cl **1f**, and 4-Br **1g** (Table 1, entries 3–7)) do not self-assemble into homochiral dimers in the solid state, in contrast to their 3-substituted counterparts. Moreover, the aromatic rings of these compounds are not involved in a π–π interaction. Notably, the compounds 4-Me **1c** and 4-CN **1d** form heterochiral dimers in the solid state with their aromatic rings directed away from each other, similar to the unsubstituted benzoyl leucine diethyl amide **1h**.[9] A comparison between the crystal structures of the 3-Me and 4-Me **1c** benzoyl leucine diethyl amides is shown in Figure 4. The 4-OMe **1e**, 4-Cl **1f**, and 4-Br **1g** compounds form non-stacked, one dimensional heterochiral chains through a single hydrogen bond from the leucine amide of one monomer to the benzoyl oxygen atom of the other monomer. A comparison between the crystal structures of the 3-OMe and the 4-OMe **1e** benzoyl leucine diethyl amide is shown in Figure 5.

The results presented above suggest that there may be differences in the stability of the π–π interaction between the 3- and the 4-substituted benzoyl leucine diethyl amides. Because all of the 3-substituted compounds readily form homochiral dimers in the solid state by using a geometrically controlling π–π interaction as an element of molecular recognition, whereas the majority of the 4-substituted compounds failed to self-assemble as such, the π–π interactions in the 3-substituted compounds may be energetically more favorable than the π–π interactions in the corresponding 4-substituted compounds. Additionally, because the electron densities on the rings of the 3-Me-, 3-OMe-, and 3-Br-substitued benzoyl leucine diethyl amides are similar to that of their 4-substitut-

Table 2. X-ray crystallographic analysis of 4-NO_2 **1a**, 3-NO_2, 4-F **1b**, and 3-F dimers.

	Compound	Homochiral dimer	θ[a] [°]	d[a] [Å]	R[a] [Å]	I[a] [Å]	α[a] [°]	Space group	Hydrogen bond lengths [Å]
1	4-NO_2	yes	107.37	3.78	3.61	1.13	14.29	$C2/c$	2.05, 1.89
2	3-NO_2[b]	yes	115.17	3.96	3.58	1.68	6.30	$P2_1/n$	2.14, 2.20
3	4-F	yes	130.06	4.51	3.45	2.90	8.60	$P2_1$	1.97, 2.03
4	3-F[b]	yes	129.28	4.42	3.42	2.80	5.27	$C2/n$	2.00, 2.00

[a] See the legend of Figure 2 for an definitions of θ, d, R, I, and α. [b] For syntheses and crystal structures, see reference [9].

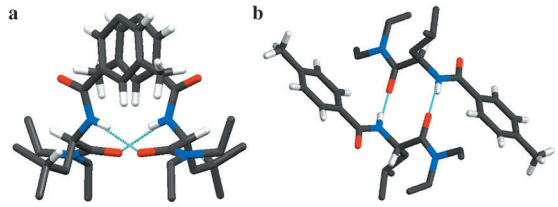


Figure 4. Crystal structures of a) 3-Me and b) 4-Me **1c** benzoyl leucine diethyl amides. The 3-Me compound self-assembled into homochiral dimers in the solid state, whereas the 4-Me compound **1c** failed to do so.

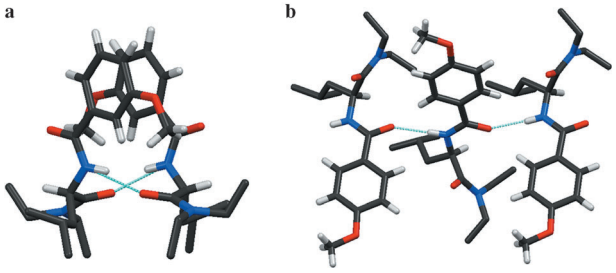


Figure 5. Crystal structures of a) 3-OMe and b) 4-OMe **1e** benzoyl leucine diethyl amides. The 3-OMe compound self-assembled into homochiral dimers in the solid state, whereas the 4-OMe compound **1e** failed to do so.

ed counterparts, factors other than the electron density appear to be contributing to the enhanced π–π interactions of the 3-substituted compounds. To elucidate the difference between the 3- and 4-substituted benzoyl leucine diethyl amides, we compared the crystallographic data of the two 4-substituted benzoyl leucine diethyl amides that did self-assemble into homochiral crystals (compounds **1a** and **1b**) with their 3-substituted counterparts. The relevant crystallographic data for the 4-NO_2 **1a**, 3-NO_2, 4-F **1b**, and 3-F dimers are summarized in Table 2. The crystal structure of the 3-NO_2 and the 4-NO_2 **1a** dimers show significant differences, particularly with respect to the interacting aromatic rings. For instance, compared with the 3-NO_2 dimer, the horizontal displacement I observed between the aromatic rings in the 4-NO_2 **1a** dimer is significantly smaller. In fact, the 4-NO_2 **1a** dimer shows the most overlap between the aromatic rings of any of the compounds crystallized in this and our previous work.[9] Moreover, unlike the 3-NO_2 and 3,5-NO_2 dimers, where the rings are essentially planar, the aromatic rings of the 4-NO_2 **1a** dimer are substantially out of plane ($\alpha = 14.29°$). Considering only the electronics of the aromatic rings, one would not predict significant differences in the orientation between the aromatic rings of the 3-NO_2 and the 4-NO_2 **1a** benzoyl leucine diethyl amide dimers. A closer look at the crystal structures of the aromatic portions of the 3-NO_2 and the 4-NO_2 **1a** dimer reveals that direct, local interactions may explain the discrepancy between the orientations of the rings in the two dimers. The aromatic portions of the 3-NO_2 and the 4-NO_2 **1a** dimer are shown in Figures 6a and b, respectively. Several different vantage points

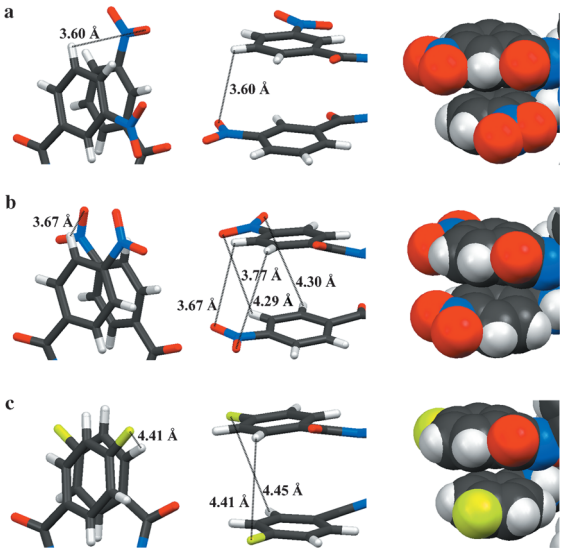


Figure 6. The partial structures of a) 3-NO_2,[9] b) 4-NO_2 **1a**, and c) 4-F **1b** benzoyl leucine diethyl amides. The potential local dipole interactions are displayed through dotted lines between two interacting aromatic rings.

for each dimer are shown. For the 3-NO_2 dimer, a nitro group oxygen atom is neighboring and approximately parallel to an aromatic hydrogen atom on the opposing aromatic ring (Figure 6a). Consistent with observations of Rashkin and Waters[4] and as discussed in our previous study,[9] this orientation may suggest a stabilizing interaction between the edge hydrogen atom of one ring and a nitro group oxygen atom of the other ring.

Indeed, two different rotamers for each of the 3-NO_2 monomers are possible, which would result in three different orientations in which the two nitro groups can arrange themselves with respect to each other. However, only the rotamer, which results in the above-mentioned stabilizing interactions, is present in the crystal structure. In the 4-NO_2

1a dimer, the oxygen atoms of the nitro groups are approximately parallel and nearby to two ring hydrogen atoms on the opposing ring (Figure 6b). Hence, there are at least four direct, local stabilizing interactions when the rings are oriented as shown in Figure 6b. This added stabilization may explain why the 4-NO_2 **1a** dimer self-assembles, whereas the majority of the other 4-substituted compounds, including the similarly electron-deficient 4-CN **1d**, fail to do so. In contrast to the significant discrepancies observed between the 3-NO_2 and the 4-NO_2 **1a** benzoyl leucine diethyl amide dimers, the crystal structures of the 3-F and the 4-F **1b** benzoyl leucine diethyl amides are highly similar. For instance, as shown in Table 2, the aromatic rings of 3-F and 4-F **1b** have similar *I*, *R*, and θ values. Additionally, the 4-F **1b** dimer shows evidence of a direct local interaction between the C–F dipole on one ring and the C–H dipole on the other ring (Figure 6c).

However, there is a confounding difference between crystal structure of the 3-F and the 4-F **1b** benzoyl leucine diethyl amides. The 3-F dimer crystallizes as a racemate in which homochiral dimers are found in the unit cell. In contrast, 4-F **1b** crystallizes as a conglomerate in a chiral space group. It should be noted that of all the 3-, 4-, and 3,5-disubstituted benzoyl leucine diethyl amides investigated in this and our prior study,[9] only compound 4-F **1b** crystallizes as a conglomerate rather than as a racemic compound. Figure 7 depicts the crystal packing showing the unit cell content of the 4-F **1b** conglomerate. The origin of this effect is currently being investigated.

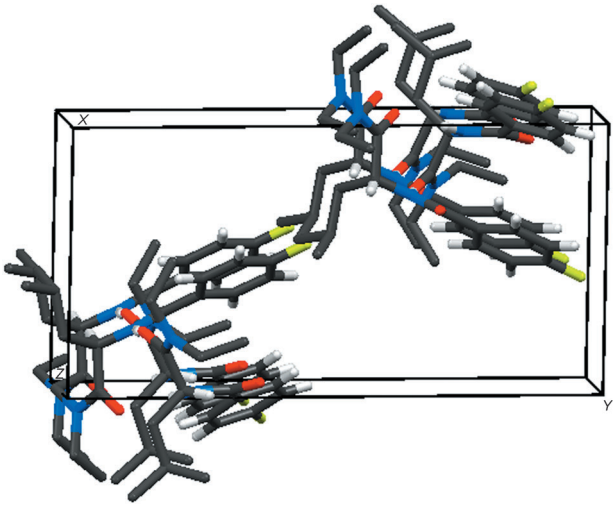
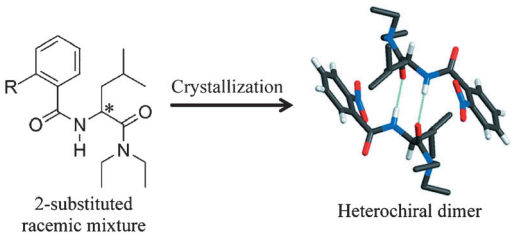


Figure 7. Unit cell of (*R*)-4-F **1b** benzoyl leucine diethyl amide.

In addition to the 4-substituted benzoyl leucine diethyl amides described above, we also prepared a series of 2-substituted benzoyl leucine diethyl amides (see Table 1). None of the 2-substituted compounds form homochiral dimers in the solid state. Instead, the compounds form heterochiral dimers without a π–π interaction, similar to the unsubstituted compound **1h** (see graphical abstract and Scheme 1 for a configurational summary of the 2- and 4-substituted compounds). In the 2-substituted compounds prepared in this study, the aromatic ring is significantly out-of-plane with the adjacent carbonyl group, presumably to minimize steric interactions. Hence, a π–π interaction is likely precluded.

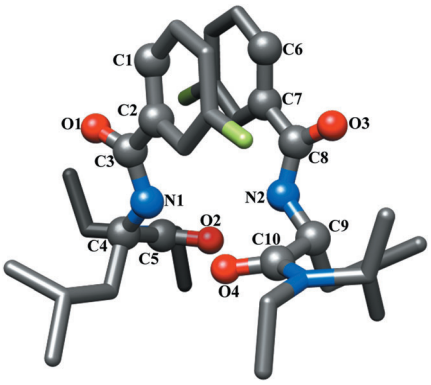


Scheme 1. 2-substituted benzoyl leucine diethyl amides form heterochiral dimers with two hydrogen bonds (shown as cyan lines) in the solid state.

As discussed above, we suggest that local interactions may have a profound influence on the orientation of interacting aromatic rings involved in a π–π interaction. If local interactions between dipoles are influencing the stacking between the rings, the molecules may assume conformations to optimize these interactions. Although it is often assumed that small molecules will interact with each other only in their lowest energy conformations, there is a possibility that the presence of one molecule can influence the conformational state of the interacting molecule, and vice versa. For instance, Lipkowitz performed molecular modeling studies on 3,5-dinitrobenzoyl amino acid as chiral stationary phases (CSPs) reacting with various analytes.[13] Lipkowitz pointed out that just as in the pharmaceutical sciences where it is recognized that the bio-active conformation of a drug molecule need not be in the global minimum, the most effective binding shape of the CSP and the analyte need not be the lowest energy structures either. Moreover, Zehnacker and Suhm reviewed studies on chiral recognition between neutral molecules in the gas phase.[14] The authors noted that the observed gas-phase complexes of the interacting molecules are not always made from the most stable conformers of each individual molecule and that the structures of the molecules adapt to each other in a concerted way to optimize the interaction energy.

In Table 3, three sets of dihedral angles are shown for the 4-NO_2 **1a** and the 4-F **1b** homochiral dimers. Additionally, the 3- and 3,5-disubstituted homochiral dimers of the previous study[9] and the dihedral angles of each of the molecules forming the dimer are tabulated. As the (*R*,*R*)- and (*S*,*S*)-dimers have identical dihedral angles, only values for the (*R*,*R*)-dimers are tabulated. It is first noted that when comparing the dihedral angles of the various homochiral dimers, there are some interesting differences. For instance, the dihedral angle O1-C3-C2-C1, which indicates the deviation from planarity of the aromatic ring with respect to the amide portion, shows a slight to moderate deviation from planarity ranging from −5.8–−19.9°, which is dependent upon the substitution on the aromatic ring. Similar discrepancies are observed in the N1-C3-C2-C1 and O4-C10-C9-N2 dihedral angles. As discussed above, molecular mechanics

Table 3. Dihedral angles of the individual molecules comprising the homochiral dimers crystallized in the present study. The bold, red, and green colors represent compounds with nonequivalent dihedral angles in the individual molecules of the dimer.



	Compounds	Molecule 1			Molecule 2		
		O1-C3-C2-C1	N1-C3-C2-C1	O2-C5-C4-N1	O3-C8-C7-C6	N2-C8-C7-C6	O4-C10-C9-N2
1	4-NO_2	**−18.4**	162.9	30.4	**−14.9**	164.0	41.2
2	4-F	**−16.7**	164.2	33.4	**−24.7**	155.4	37.6
3	3NO_2[a]	**−10.6**	170.5	32.5	**−13.4**	167.3	34.4
4	3-Me[a]	−17.7	163.1	35.8	−17.7	163.1	35.8
5	3-OMe[a]	−12.0	168.5	31.7	−12.0	168.5	31.7
6	3-Br[a]	−19.9	160.4	35.7	−19.9	160.4	35.8
7	3-F[a]	−18.8	162.1	38.6	−18.8	162.1	38.6
8	3,5-NO_2[a]	**−5.8**	174.0	34.1	**−8.8**	170.0	35.2
9	3,5-OMe[a]	**−11.3**	169.9	33.0	**−9.0**	172.4	31.4
10	3,5-Me[a]	−13.6	167.4	34.3	−13.6	167.4	34.3
11	3,5-F[a]	−16.0	164.6	37.5	−16.0	164.6	37.5

[a] These compounds were synthesized in our previous study.[9]

studies suggested that substituted benzoyl leucine compounds are considerably conformationally flexible, which is consistent with results observed here. However, why is the substituent on the aromatic ring influencing conformational preferences?

We postulate that the respective molecules comprising each dimer are aligning themselves to maximize the favorable local interactions and/or minimize the repulsive local interactions. Particularly telling is the fact that in several cases, the individual molecules comprising the dimer show nonequivalent dihedral angles and we refer to this phenomenon as "flexing". Cases where there is flexing of the individual molecules of the dimer are marked in bold in Table 3. It is noteworthy that the five cases that show the most pronounced flexing of the respective molecules in the dimer are 4-NO_2 **1a**, 4-F **1b**, 3-NO_2, 3,5-NO_2, 3,5-OMe dimers. In each of these cases, the crystal structures show evidence of direct local interactions between the negative end of the N–O or C–F dipole on one ring, and the positive end of the C–H dipole on the other (see Figure 6).

It would appear then, that the rings are orientating themselves to maximize these interactions. This may be most readily seen in the 4-NO_2 **1a** dimer (Figure 6b), where the rings appear to be orientating themselves to align four dipoles simultaneously. The same degree of overlap would not exist if the molecules comprising the dimer exhibited identical torsion angles. It is also noteworthy, that in the 4-NO_2 **1a** dimer, the aromatic rings are 14.29° out-of-plane with respect to each other (shown in Figure 8), which is larger than the tilt angle (α) observed for the interacting aromatic rings of other homochiral dimers. We suggest that the deviation from planarity observed in the rings of the 4-NO_2 **1a** dimer (and perhaps the other homochiral dimers), is the result of

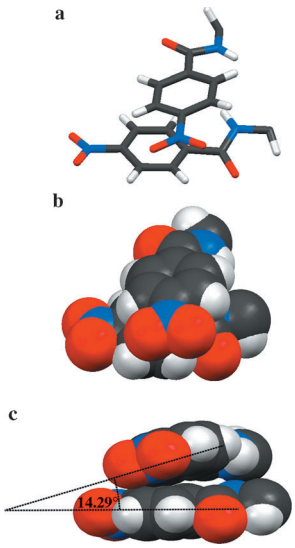


Figure 8. Partial structure of the 4-NO_2 **1a** benzoyl leucine diethyl amide: a) top view, capped sticks; b) top view, space-filling model; c) side view, space-filling model, α of **1a** is 14.29°.

maximizing the degree of overlap between the local dipoles of the interacting rings.

The results presented herein may support the direct, local model proposed by Wheeler and Houk.[3a–e] Nevertheless, whether these direct, local interactions are controlling the energetic of aromatic interactions remains an open question. Although several of the homochiral dimers appear to exhibit direct interactions between local dipoles on the aromatic rings, the existence of these interactions is not obvious in all homochiral dimers. For example, an interaction between the C–F and C–H dipole of the interacting rings was observed for the 4-F **1b** dimer but not for the corresponding 3-F dimer. Additionally, with respect to the 4-F **1b** dimer, although their appears to be a local dipole interaction between the C–F bond on one ring and the C–H dipole on the other, the centroid distance is one of the largest (4.51 Å) observed for all compounds that were crystallized in this and the previous study.[9] If local interactions were the dominating factor, one might surmise that the interacting rings would have a higher degree of overlap. Furthermore, in compounds that do not possess strong dipole moments such as the 3-Me dimer, the crystal structures do not clearly display direct, local interactions. Consequently, there may be other factors influencing substituent effects in aromatic interactions. Arnstein and Sherrill suggested that analyzing substituent effects of aromatic interactions must take into account at least four components including electrostatic forces, exchange repulsion, dispersion, and induction.[3f] The contribution from each of these components in controlling the nature of aromatic interactions remains an important question.

Conclusion

In conclusion, we have shown that the position of a substituent on an aromatic moiety can have a profound effect on π–π interactions. In our prior study, a series of 3- and 3,5-disubstitued benzoyl leucine diethyl amides of varying electronic character was crystallized and characterized in the solid state. All of the 3- and 3,5-disubstituted dimers self-assembled into homochiral dimers in the solid state, with a parallel displaced π–π interaction stabilizing each dimer. However, no homochiral dimerization was observed in the unsubstituted case. In the present study involving 4-substituted benzoyl leucine diethyl amides, only two of the compounds, 4-NO_2 **1a** and 4-F **1b**, formed homochiral dimers with stabilizing parallel displaced π–π interactions. The crystallographic data suggest that local interactions between dipoles may stabilize the interaction in the 4-NO_2 **1a** and the 4-F **1b** dimers and provide a driving force for homochiral dimerization. However, the origin of the enhanced stabiliza-

Table 4. Crystal structure analysis for compounds **1a**–**1f**.

	1a	**1b**	**1c**	**1d**	**1e**	**1f**
empirical formula	$C_{17}H_{25}N_3O_4$	$C_{17}H_{25}FN_2O_2$	$C_{18}H_{28}N_2O_2$	$C_{18}H_{25}N_3O_2$	$C_{18}H_{28}N_2O_3$	$C_{17}H_{25}ClN_2O_2$
M_w	335.40	308.39	304.42	315.41	320.42	324.84
T [K]	110(2)	110(2)	110(2)	110(2)	110(2)	110(2)
λ [Å]	0.71073	1.54178	0.71073	0.71073	0.71073	0.71073
crystal system	monoclinic	monoclinic	monoclinic	monoclinic	orthorhombic	orthorhombic
space group	*C*2/*c*	$P2_1$	$P2_1/n$	$P2_1/n$	*Pbca*	*Pbca*
a [Å]	19.2534(7)	10.2718(2)	10.0166(3)	9.4313(3)	10.1124(2)	10.1373(3)
b [Å]	19.3811(8)	17.6424(4)	9.8877(3)	10.4584(4)	16.0981(4)	15.6596(4)
c [Å]	21.0097(7)	10.8798(2)	17.5286(5)	18.3036(7)	21.7719(6)	22.0323(6)
α [°]	90	90	90	90	90	90
β [°]	102.664(4)	116.793(3)	92.004(3)	98.284(4)	90	90
γ [°]	90	90	90	90	90	90
V [Å^3]	7649.1(5)	1759.96(6)	1734.99(9)	1786.56(11)	3544.26(15)	3497.54(17)
Z	16	4	4	4	8	8
ρ_{calcd} [Mg m^{-3}]	1.165	1.164	1.165	1.173	1.201	1.234
μ [mm^{-1}]	0.084	0.681	0.076	0.078	0.082	0.227
F(000)	2880	664	664	680	1392	1392
crystal size [mm^3]	0.40×0.30×0.25	0.72×0.52×0.35	0.48×0.32×0.20	0.68×0.54×0.50	0.60×0.46×0.42	0.52×0.46×0.43
θ [°]	1.51–25.95	4.55–71.66	2.90–29.17	2.93–29.26	3.03–29.12	2.76–29.30
index ranges	$-15 \le h \le 23$	$-12 \le h \le 12$	$-13 \le h \le 13$	$-12 \le h \le 12$	$-12 \le h \le 10$	$-12 \le h \le 13$
	$-23 \le k \le 23$	$-18 \le k \le 21$	$-12 \le k \le 13$	$-14 \le k \le 13$	$-20 \le k \le 21$	$-17 \le k \le 19$
	$-25 \le l \le 25$	$-13 \le l \le 13$	$-15 \le l \le 23$	$-24 \le l \le 25$	$-29 \le l \le 24$	$-29 \le l \le 21$
reflns collected	16053	14482	8329	15466	11571	10351
independent reflns	7320	6090	4028	4241	4166	4093
R(int)	0.0334	0.0316	0.0211	0.0266	0.0292	0.0222
completeness [%] to θ [°]	98.0/25.95	99.0/71.66	99.9/26.00	99.8/26.00	99.9/26.00	99.9/26.00
max/min transmission	1.00000/0.76940	1.00000/0.80448	1.00000/0.99723	1.00000/0.97033	1.00000/0.98634	1.00000/0.99126
data/restraints/parameters	7320/0/441	6090/1/399	4028/0/215	4241/0/212	4166/0/212	4093/0/203
GooF on F^2	0.985	1.181	1.092	1.039	0.964	0.997
$R1$, w$R2$ [$I > 2\sigma(I)$]	0.0635, 0.2015	0.0585, 0.1592	0.0390, 0.0749	0.0393, 0.0988	0.0399, 0.0994	0.0363, 0.0900
$R1$, w$R2$ (all data)	0.0997, 0.2284	0.0620, 0.1625	0.0599, 0.0772	0.0582, 0.1032	0.0598, 0.1038	0.0564, 0.0938
diff. peak/hole [e Å^{-3}]	0.389/−0.244	0.721/−0.598	0.251/−0.236	0.306/−0.203	0.363/−0.214	0.305/−0.290

Table 5. Crystal structure analysis for compounds **1g**–**1k**.

	1g	**1h**	**1i**	**1j**	**1k**
empirical formula	$C_{17}H_{25}BrN_2O_2$	$C_{17}H_{26}N_2O_2$	$C_{17}H_{25}N_3O_4$	$C_{18}H_{28}N_2O_2$	$C_{17}H_{25}FN_2O_2$
M_w	369.30	290.40	335.40	304.42	308.39
T [K]	297(2)	297(2)	110(2)	297(2)	110(2)
λ [Å]	0.71073	1.54178	0.71073	1.54178	0.71073
crystal system	orthorhombic	monoclinic	monoclinic	monoclinic	monoclinic
space group	*Pbca*	$P2_1/c$	$P2_1/n$	$P2_1/c$	$P2_1/c$
a [Å]	10.2088(5)	10.3265(5)	10.3883(3)	8.7443(2)	8.7136(3)
b [Å]	15.9887(11)	9.9356(5)	14.8162(4)	17.3141(4)	16.9065(5)
c [Å]	22.2875(11)	19.3787(8)	11.6216(3)	12.3464(3)	12.2036(4)
α [°]	90	90	90	90	90
β [°]	90	118.669	92.258(3)	109.958(3)	108.497(4)
γ [°]	90	90	90	90	90
V [Å^3]	3637.9(4)	1744.50(14)	1756.98(7)	1756.98(7)	1704.92(10)
Z	8	4	4	4	4
ρ_{calcd} [Mg m^{-3}]	1.349	1.106	1.151	1.151	1.201
μ [mm^{-1}]	2.268	0.573	0.590	0.590	0.086
F(000)	1536	632	664	664	664
crystal size [mm^3]	0.54×0.28×0.17	0.78×0.55×0.48	0.76×0.62×0.42	0.76×0.62×0.42	0.72×0.62×0.45
θ [°]	2.99–29.09	5.15–71.79	4.59–72.19	4.59–72.19	2.98–29.32
index ranges	$-8\le h\le 13$	$-12\le h\le 11$	$-9\le h\le 10$	$-9\le h\le 10$	$-11\le h\le 11$
	$-7\le k\le 20$	$-10\le k\le 11$	$-11\le k\le 21$	$-11\le k\le 21$	$-20\le k\le 23$
	$-22\le l\le 29$	$-23\le l\le 23$	$-14\le l\le 15$	$-14\le l\le 15$	$-14\le l\le 15$
reflns collected	10880	13273	6834	6834	8241
independent reflns	4295	3350	3376	3376	3954
R(int)	0.0329	0.0189	0.0173	0.0173	0.0253
completeness [%] to θ [°]	99.9/26.00	98.8/71.00	99.2/26.00	99.270.00	99.8/26.00
max/min transmission	1.00000/0.94998	1.00000/0.86644	1.00000/0.85058	1.00000/0.85058	1.00000/0.98531
data/restraints/parameters	4295/0/187	3350/1/194	3376/0/222	3376/0/222	3954/0/222
GooF on F^2	1.097	1.463	1.029	1.029	0.966
$R1$, w$R2$ [$I>2\sigma(I)$]	0.0440, 0.0863	0.0999, 0.3522	0.0530, 0.1488	0.0530, 0.1488	0.0590, 0.1667
$R1$, w$R2$ (all data)	0.1281, 0.0916	0.1225, 0.3757	0.0579, 0.1534	0.0579, 0.1534	0.0954, 0.1791
diff. peak/hole [e Å^{-3}]	0.647/−0.607	0.695/−0.635	0.490/−0.412	0.490/−0.412	0.959/−0.469

tion of the 3- and 3,5-disubstituted benzoyl leucine diethyl amides is not clear and will require further investigation.

Experimental Section

General procedure for the synthesis of substituted benzoyl leucine acids: The substituted benzoyl acid chloride was added to D,L-leucine that was suspended in tetrahydrofuran. (±)-Propylene oxide was added under Ar (or N_2) at RT. The reaction mixtures were stirred no more than 24 h. Unreacted D,L-leucine was removed by filtration and the solutions were concentrated in vacuum. The crude products were purified by recrystallization from acetonitrile or by flash chromatography.

General procedure for the synthesis of substituted benzoyl leucine amides: Substituted benzoyl leucine diethyl amide derivatives were prepared as follows: *N*,*N*′-Diisopropylcarbodiimide (DIC) was added dropwise to a stirred suspension of the substituted benzoyl leucine in CH_2Cl_2 for 10–15 min under Ar at 0 °C. Next, diethylamine was added dropwise to the solution and the mixture was stirred overnight. The resulting solid was removed by filtration and the filtrate was quenched with 5% aqueous $KHSO_4$, 5% aqueous $NaHCO_3$, and saturated aqueous NaCl solution. The organic layer was dried over $MgSO_4$ and concentrated in vacuum. The crude product was purified by flash chromatography and the pure solid was recrystallized from hexane/dichloromethane. The products were characterized by using ^{1}H NMR, ^{13}C NMR, IR, and UV spectroscopy, HRMS, HPLC, and X-ray crystallography. See the Supporting Information for detailed methods and characterizations of new compounds. To produce single crystals suitable for X-ray structure determination, the respective diethyl amide (40–45 mg) was added to CH_2Cl_2 (1 mL), followed by *n*-hexane (4 mL) and the solution was allowed to sit undisturbed at RT for several days. Tables 4 and 5 contain selected crystallographic data for compounds **1a**–**1k**. A semiempirical absorption correction was applied to all compounds with the exception of **1g**. The data for all compounds were refined by full-matrix least-squares methods on F^2. CCDC 887495 (**1a**), 887496 (**1b**), 887497 (**1c**), 887498 (**1d**), 887499 (**1e**), 887500 (**1f**), 887501 (**1g**), 887505 (**1h**), 887502 (**1i**), 887503 (**1j**), and 887504 (**1k**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[1] a) H.-J. Schneider, *Angew. Chem.* **2009**, *121*, 3982–4036; *Angew. Chem. Int. Ed.* **2009**, *48*, 3924–3977; b) T. Yajima, R. Takamido, Y. Shimazaki, A. Odani, Y. Nakabayashi, O. Yamauchi, *Dalton Trans.* **2007**, 299–307; c) M. Gray, A. J. Goodman, J. B. Carroll, K. Bardon, M. Markey, G. Cooke, V. M. Rotello, *Org. Lett.* **2004**, *6*, 385–388; d) R. Faraoni, M. Blanzat, S. Kubicek, C. Braun, W. B. Schweizer, V. Gramlich, F. Diederich, *Org. Biomol. Chem.* **2004**, *2*, 1962–1964;

e) E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem.* **2003**, *115*, 1244–1287; *Angew. Chem. Int. Ed.* **2003**, *42*, 1210–1250; f) M. L. Waters, *Curr. Opin. Chem. Biol.* **2002**, *6*, 736–741; g) S. L. McKay, B. Haptonstall, S. H. Gellman, *J. Am. Chem. Soc.* **2001**, *123*, 1244–1245; h) S. Lavieri, J. A. Zoltewicz, *J. Org. Chem.* **2001**, *66*, 7227–7230; i) M. S. Cubberley, B. L. Iverson, *J. Am. Chem. Soc.* **2001**, *123*, 7560–7563; j) R. R. Gardner, S. L. McKay, S. H. Gellman, *Org. Lett.* **2000**, *2*, 2335–2338; k) L. F. Newcomb, S. H. Gellman, *J. Am. Chem. Soc.* **1994**, *116*, 4993–4994.

[2] a) F. Cozzi, R. Annunziata, M. Benaglia, K. K. Baldridge, G. Aguirre, J. Estrada, Y. Sritana-Anant, J. S. Siegel, *Phys. Chem. Chem. Phys.* **2008**, *10*, 2686–2694; b) S. L. Cockroft, J. Perkins, C. Zonta, H. Aams, S. E. Spey, C. M. R. Low, J. G. Vinter, K. R. Lawson, C. J. Urch, C. A. Hunter, *Org. Biomol. Chem.* **2007**, *5*, 1062–1080; c) S. L. Cockroft, C. A. Hunter, *Chem. Soc. Rev.* **2007**, *36*, 172–188; d) S. K. Cockroft, C. A. Hunter, K. R. Lawson, J. Perkins, C. J. Urch, *J. Am. Chem. Soc.* **2005**, *127*, 8594–8595; e) F. Cozzi, R. Annunziata, M. Benzglia, M. Cinquini, L. Raimondi, K. K. Baldridge, J. S. Siegel, *Org. Biomol. Chem.* **2003**, *1*, 157–162; f) C. A. Hunter, K. R. Lawson, J. Perkins, C. J. Urch, *J. Chem. Soc. Perkin Trans. 2* **2001**, 651–669; g) F. Cozzi, J. S. Siegel, *Pure Appl. Chem.* **1995**, *67*, 683–689; h) F. Cozzi, M. Cinquini, R. Annuziata, J. S. Siegel, *J. Am. Chem. Soc.* **1993**, *115*, 5330–5331; i) F. Cozzi, M. Cinquini, R. Annunziata, T. Dwyer, J. S. Siegel, *J. Am. Chem. Soc.* **1992**, *114*, 5729–5733; j) C. A. Hunter, J. K. M. Sanders, *J. Am. Chem. Soc.* **1990**, *112*, 5525–5534.

[3] a) S. E. Wheeler, *J. Am. Chem. Soc.* **2011**, *133*, 10262–10274; b) M. Watt, L. K. E. Hardebeck, C. C. Kirkpatrick, M. Lewis, *J. Am. Chem. Soc.* **2011**, *133*, 3854–3862; c) S. E. Wheeler, K. N. Houk, *Mol. Phys.* **2009**, *107*, 749–760; d) A. L. Ringer, C. D. Sherrill, *J. Am. Chem. Soc.* **2009**, *131*, 4574–4575; e) S. E. Wheeler, K. N. Houk, *J. Am. Chem. Soc.* **2008**, *130*, 10854–10855; f) S. A. Arnstein, C. D. Sherrill, *Phys. Chem. Chem. Phys.* **2008**, *10*, 2646–2655; g) M. O. Sinnokrot, C. D. Sherrill, *J. Phys. Chem. A* **2006**, *110*, 10656–10668; h) A. L. Ringer, M. O. Sinnokrot, R. P. Lively, C. D. Sherrill, *Chem. Eur. J.* **2006**, *12*, 3821–3828; i) M. O. Sinnokrot, C. D. Sherrill, *J. Am. Chem. Soc.* **2004**, *126*, 7690–7697; j) M. O. Sinnokrot, C. D. Sherrill, *J. Phys. Chem. A* **2003**, *107*, 8377–8379.

[4] M. J. Rashkin, M. L. Waters, *J. Am. Chem. Soc.* **2002**, *124*, 1860–1861.

[5] E. G. Hohenstein, J. Duan, C. D. Sherrill, *J. Am. Chem. Soc.* **2011**, *133*, 13244–13247.

[6] a) S. E. Snyder, J. R. Carey, W. H. Pirkle, *Tetrahedron* **2005**, *61*, 7562–7567; b) W. H. Pirkle, T. C. Pochapsky, *Chem. Rev.* **1989**, *89*, 347–362; c) W. H. Pirkle, T. C. Pochapsky, *J. Am. Chem. Soc.* **1987**, *109*, 5975–5982; d) G. Tárkányi, P. Király, S. Varga, B. Vakulya, T. Soós, *Chem. Eur. J.* **2008**, *14*, 6078–6086; e) A. Matsuzawa, A. Nojiri, N. Kumagai, M. Shibasaki, *Chem. Eur. J.* **2010**, *16*, 5036–5042.

[7] a) M. E. Koscho, P. L. Spence, W. H. Pirkle, *Tetrahedron: Asymmetry* **2005**, *16*, 3147–3153; b) W. H. Pirkle, P. G. Murray, S. R. Wilson, *J. Org. Chem.* **1996**, *61*, 4775–4777; c) W. H. Pirkle, J. A. Burke, S. R. Wilson, *J. Am. Chem. Soc.* **1989**, *111*, 9222–9223.

[8] a) M. H. Hyun, J.-J. Ryoo, W. H. Pirkle, *J. Chromatogr. A* **2000**, *886*, 47–53; b) M. H. Hyun, Y. D. Kim, S. C. Han, J. B. Lee, *J. High Resolut. Chromatogr.* **1998**, *21*, 464–470; c) W. H. Pirkle, P. G. Murray, D. J. Rausch, S. T. McKenna, *J. Org. Chem.* **1996**, *61*, 4769–4774; d) W. H. Pirkle, P. G. Murray, *J. Chromatogr. A* **1996**, *719*, 299–305; e) W. H. Pirkle, T. C. Pochapsky, *J. Am. Chem. Soc.* **1986**, *108*, 5627–5628; f) W. H. Pirkle, C. J. Welch, *J. Org. Chem.* **1984**, *49*, 138–140; g) W. H. Pirkle, M. H. Hyun, *J. Org. Chem.* **1984**, *49*, 3043–3046.

[9] S. E. Snyder, B.-S. Huang, Y.-T. Chen, H.-S. Lin, J. R. Carey, *Org. Lett.* **2012**, *14*, 3442–3445.

[10] a) W. Lee, S. E. Snyder, P. I. Volkers, W. H. Pirkle, D. A. Engebretson, W. A. Boulanger, H.-S. Lin, B.-S. Huang, J. R. Carey, *Tetrahedron* **2011**, *67*, 7143–7147; b) S. E. Snyder, P. T. Volkers, D. A. Engebretson, W. Lee, W. H. Pirkle, J. R. Carey, *Org. Lett.* **2007**, *9*, 2341–2343; c) J. R. Carey, E. Kim, J. H. Hong, J. S. Kang, W. H. Pirkle, W. Lee, *Bull. Korean Chem. Soc.* **2011**, *32*, 4423–4426.

[11] a) J. L. Xia, S. H. Liu, F. Cozzi, M. Mancinelli, A. Mazzanti, *Chem. Eur. J.* **2012**, *18*, 3611–3620; b) B. W. Gung, B. U. Emenike, C. N. Alverez, J. Rakovan, K. Kirschbaum, N. Jain, *Tetrahedron Lett.* **2010**, *51*, 1648–1650; c) B. W. Gung, X. Xue, H. J. Reich, *J. Org. Chem.* **2005**, *70*, 3641–3644; d) B. W. Gung, B. U. Emenike, M. Lewis, K. Kirschbaum, *Chem. Eur. J.* **2010**, *16*, 12357–12362; e) B. W. Gung, M. Patel, X. Xue, *J. Org. Chem.* **2005**, *70*, 10532–10537.

[12] a) M. Chourasia, G. M. Sastry, G. N. Sastry, *Int. J. Biol. Macromol.* **2011**, *48*, 540–552; b) I. Geronimo, E. C. Lee, N. J. Singh, K. S. Kim, *J. Chem. Theory Comput.* **2010**, *6*, 1931–1934; c) J.-I. Seo, I. Kim, Y. S. Lee, *Chem. Phys. Lett.* **2009**, *474*, 101–106; d) Y. S. Chong, W. R. Carroll, W. G. Burns, M. D. Smith, K. D. Shimizu, *Chem. Eur. J.* **2009**, *15*, 9117–9126; e) C.-Y. Kim, P. P. Chandra, A. Jain, D. W. Christianson, *J. Am. Chem. Soc.* **2001**, *123*, 9620–9627; f) A. S. Shetty, J. Zhang, J. S. Moore, *J. Am. Chem. Soc.* **1996**, *118*, 1019–1027; g) P. Hobza, H. L. Selzle, E. W. Schlag, *J. Physi. Chem.* **1996**, *100*, 18790–18794; h) Z.-G. Wang, B.-H. Zhou, Y.-F. Chen, G.-D. Yin, Y.-T. Li, A.-X. Wu, L. Issacs, *J. Org. Chem.* **2006**, *71*, 4502–4508.

[13] K. B. Lipkowitz, *J. Chromatogr. A* **2001**, *906*, 417–442.

[14] A. Zehnacker, M. A. Suhm, *Angew. Chem.* **2008**, *120*, 7076–7100; *Angew. Chem. Int. Ed.* **2008**, *47*, 6970–6992.

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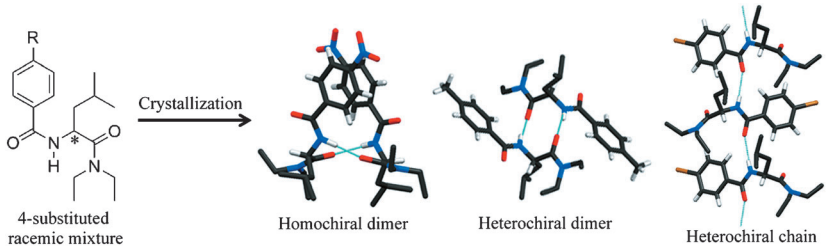
π–π Interactions



To dimerize or not to dimerize? The position of a substituent on an aromatic moiety can have a profound effect on π–π interactions. In the present study, involving 4-substituted benzoyl leucine diethyl amides, only certain compounds formed homochiral dimers with a stabilizing parallel displaced π–π interaction (see figure). The crystallographic data suggest that local interactions between dipoles may provide a driving force for self-assembly and for homochiral dimerization.

A series of benzoyl leucine amides…
…of varying electronic character were prepared. All of the 3- and 3,5-disubstituted compounds assembled into homochiral dimers in the solid state. However, no homochiral dimerization was observed in the unsubstituted case and in several 4-substituted cases (shown in yellow). The crystallographic data suggests that local interactions between the dipoles may stabilize the interaction in several of the dimers (shown in red) and provides a driving force for homochiral dimerization. For more details see the Full Paper by J. R. Carey et al. on page ■ ■ ff.