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ARTICLE TYPE

Anti-parallel sheet structures of side-chain-free γ-, δ-, and ε-dipeptides stabilized by benzene-pentafluorobenzene stacking†

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This paper describes intermolecular benzene/pentafluorobenzene stacking-promoted anti-parallel arrangement of side-chain-free γ-, δ-, and ε-dipeptides. Three diamides have been prepared from γ-, δ-, and ε-amino acids with a benzene ring and a pentafluorobenzene ring being attached to their *C*- and *N*-terminals, respectively. Their crystal structures showed that all the compounds formed intermolecular benzene/pentafluorobenzene stacking, which guided the molecules to arrange in a ruler-styled pattern and the aliphatic backbones to adopt extended sheet-like conformations. Shorter control compounds also gave rise to similar intermolecular aromatic stacking, but the central aliphatic amide chains adopted different conformations.

Introduction

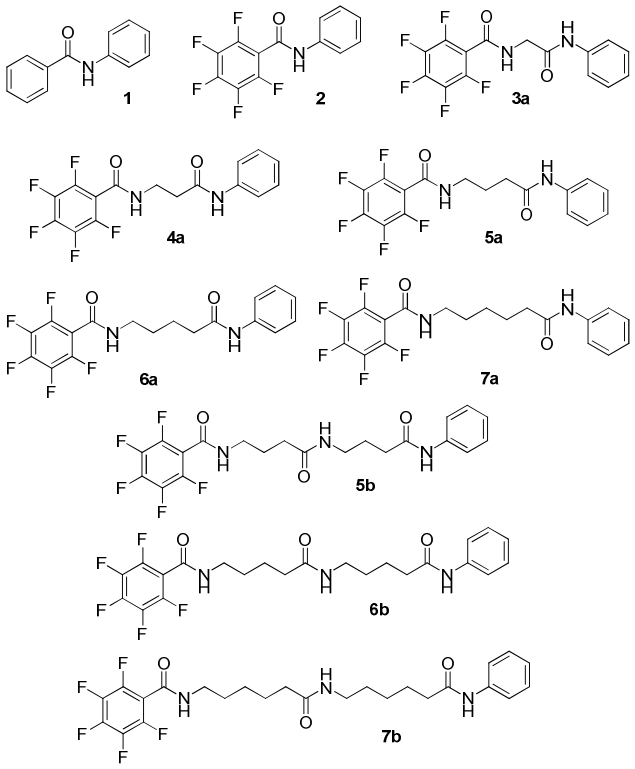
For peptides and proteins, helices and sheets are the only two types of secondary structures with long-range order. To mimic these ordered structures and their functions, in the past decades, chemists have designed various unnatural amino acids to construct a large amount of foldamers, the artificial sequences that can spontaneously form well-defined compact conformations driven by discrete non-covalent forces.[1-5] To date, great efforts have been devoted to the generation of β-peptides, α/β-peptides and their analogues,[4-8] which can form both helical or sheet secondary structures depending on the structures of the monomeric units and their arrangement in the sequences and/or rationally designed inducing segments. γ-Peptides had been proposed to represent the natural next step for the generation of new amide-based foldamers.[9] Currently, many γ-peptides, hybrid α/γ- or β/γ-peptides or their analogues have been revealed to form helical conformations.[10-12] Although by making use of rigid cyclopropane subunits to rigidify the sequences or with the help of turn-promoting residues,[13,14] γ-peptides can be forced to afford parallel sheet structures, both experimental and computational studies indicated that this family of backbones and related hybrid α/γ- or β/γ-peptides prefers to adopt helical conformations.[10,15-19] Investigations on the hexameric series of different amino acids suggested that the helical conformation of γ-peptides are even more stable than that of α- and β-peptides.[20] With further homologation of the monomeric units, it is expected that corresponding δ- or ε-peptides can also be constructed. However, the increased degrees of freedom in the longer monomeric units of these backbones, as compared to those of the β- and γ-series, should lead to increased backbone variations and thus reduce the stability of any regular secondary structures, making it a challenge to control the backbones to adopt a specific compact conformation. Early studies revealed that nylon 6, the polymer of 6-aminohexanoic acid, prefers to form sheet-like structures,[21] while naturally occurring γ-D-glutamic acid polymers adopt ordered helical conformations.[22] Theoretical calculations on glutaramide,[23] adipamide,[24] and several ε-amino acid oligomers[25] showed that these oligomers all favour folded or helical conformations. However, to the best of our knowledge, no experimental investigations on the control of the secondary structures of oligomers of these long ω-amino acids have been reported in the literature.

Stacking between benzene and perfluorobenzene features the face-to-face orientation stabilized by the quadrupole interaction,[26] which can be utilized to control the photochemical reactions in the solid state.[27] More recently, Gao and co-workers have introduced this interaction to explore novel mechanisms of molecular recognition that do not exist in native proteins by preparing fluorinated aromatic amino acids.[28] In this paper, we describe that by introducing benzene and pentafluorobenzene rings to the two ends of dipeptides of 4-aminobutanoic acid, 5-aminopentanoic acid, and 6-aminohexanoic acid, the linear molecules can be controlled to form anti-parallel sheet-like extended structures in the solid state.

Results and discussion

Compounds **1**–**7** were prepared to investigate their structures in the solid state. Compounds **1** and **2** were used to reveal the mutual influence of the amide hydrogen bonding and the intermolecular stacking between the benzene and pentafluorobenzene rings, while **3a**–**7a** were designed to study the intrinsic tendency of the aliphatic amide segment in forming a specific conformation, particularly the extended one. Compounds **5b**–**7b** were designed as new unnatural ω-dipeptides. A comparison of their structures with those of the shorter analogues in the solid state would reveal the effectiveness of the intermolecular benzene/pentafluorobenzene stacking in

promoting the formation of anti-parallel sheet structures. For all the compounds, no side chains were introduced in order to avoid the effect of additional steric or van der Waals interactions. The crystal structures of the compounds, except that of **6a**, were obtained. The crystal data and structure refinements for these compounds were summarized in ESI.



Crystal structures of compounds 1 and 2

The crystal structures of compounds **1** and **2** are provided in Fig. 1. Compound **1** stacked in parallel mode. As shown in Fig. 1a, both the *N*- and *C*-terminal benzene rings were in offset stacking and the distance between the centroids of the neighboring benzene rings was 5.35 Å. The value is slightly longer than the average distance (5.05 Å) between the centroids of benzene rings appended in the side chains of proteins which were reported to stabilize their 3D structures,[29] and the distance between two corresponding parallel arranged phenyl ring planes was 2.75 Å. Though the H···O distance between amide proton and carbonyl oxygen of two neighbouring molecules was 2.41 Å, much longer than general intermolecular N–H···O=C hydrogen bonding length, this intermolecular interaction forced the amide unit to distort from the *N*- and *C*-terminal benzene rings by 31.4 and 31.7°, respectively (Fig. 1b). Different from **1**, compound **2** stacked in anti-parallel mode (Fig. 1c). The hydrogen bond H···O distance length is 2.02 Å, which is much shorter than that of **1**. Three geometric parameters[30] were used to define the orientation of the two interacting aromatic rings (Fig. 2). It can be found that, for **2**, the benzene and pentafluorobenzene rings of the neighbouring molecules stacked alternately and the distance between the centroid (*d*) of the benzene and pentafluorobenzene rings are 4.78 and 4.54 Å, respectively, both of which are shorter than that between the stacked benzene rings of **1**. Thus, it is reasonable to propose that the intermolecular hydrogen bonding and the benzene/pentafluorobenzene stacking stabilized each other. The torsion angles between the amide unit and the benzene and pentafluorobenzene rings are 31.8 and 73.5°, respectively (Fig. 1d). The obviously larger torsion of the pentafluorobenzene ring, which was also observed for other compounds (vide infra), should be mainly attributed to the repulsion of the fluorine atoms at the 2- and 6-positions.

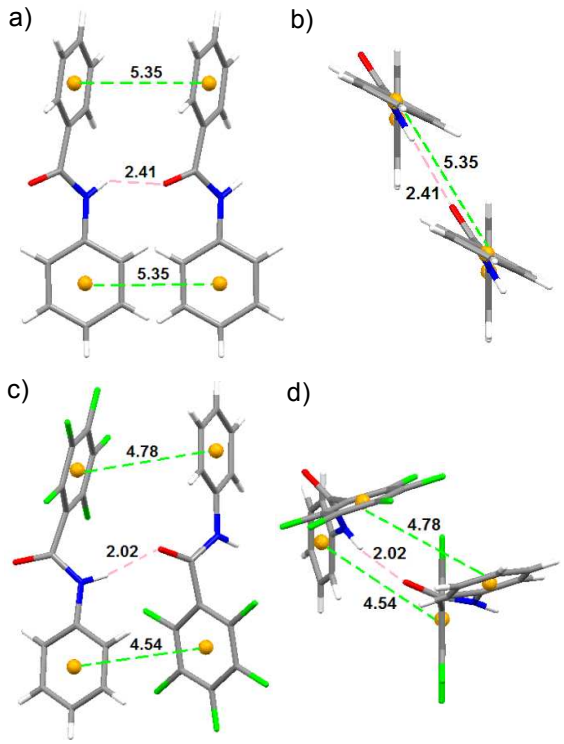


Fig. 1 Crystal structures of **1** and **2**: a) parallel stacking of **1**, b) view along the benzene ring plane of **1**, c) anti-parallel stacking of **2**, and d) view along *N*-terminal pentafluorobenzene ring plane of **2**. The data (Å) represent the hydrogen bonding length and the distance between the centroids of the neighbouring benzene rings.

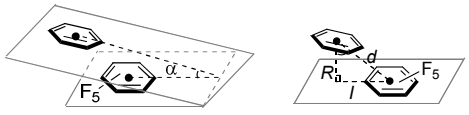


Fig. 2 Geometric parameters used to define the orientation of the two interacting aromatic rings

For compound **2**, the pentafluorobenzene ring plane of one molecule has a tilt angle (α) of 15.8° to the benzene ring plane of the neighbouring molecule, which reveals that two molecules preferred to possess an offset-stacked version rather than the T-shaped mode conformation which would have a tilt angle near 90°. The distance of the benzene ring centroid to the plane defined by the opposite pentafluorobenzene ring (*R*) was 3.64 and 3.79 Å, which is comparable to the experimental and theoretical calculation data reported in the literatures.[31] The distance of the horizontal displacement (*I*) of the two interacting rings is much shorter than that of **1** (2.50 Å *vs.* 4.59 Å), which also suggests that strong stacking interaction occurred between the electron-

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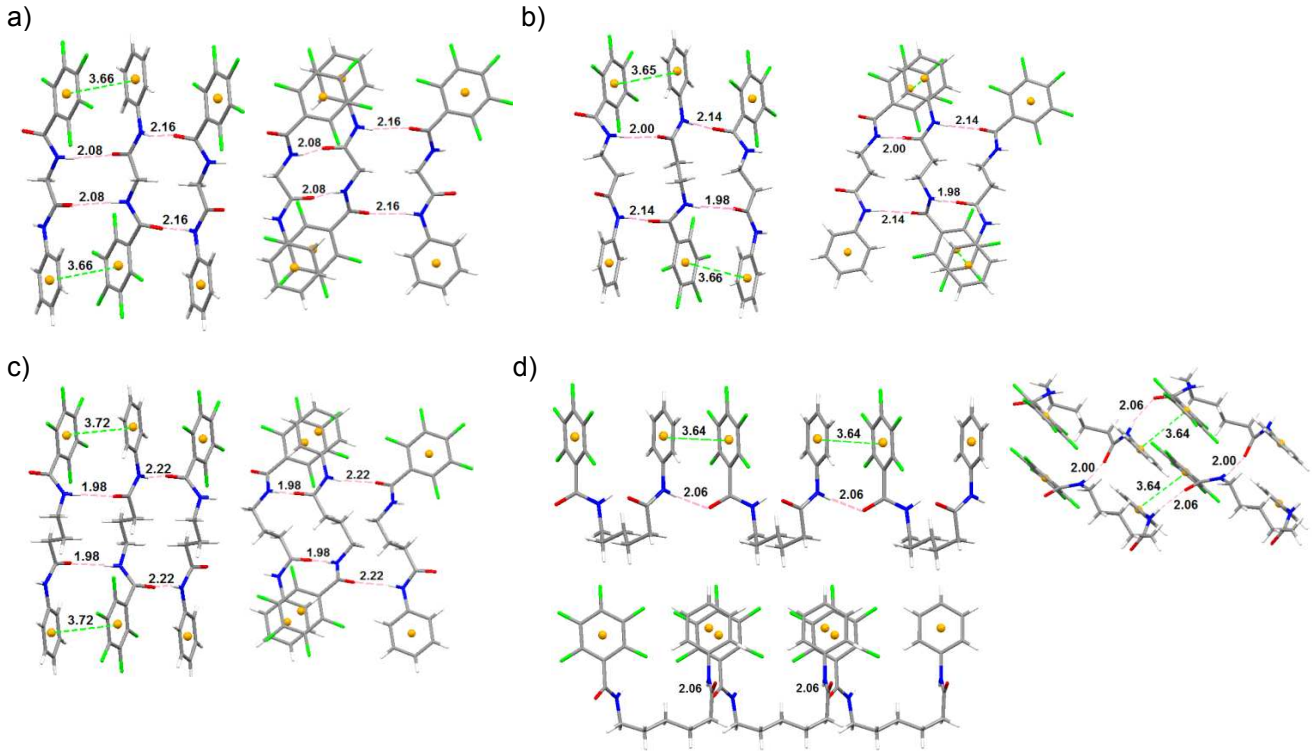


Fig. 3 Crystal structures and stacking patterns of compounds a) **3a**, b) **4a**, c) **5a**, and d) **7a**. The data (Å) represent the hydrogen bonding length and the distance between the centroid of the neighboring benzene and pentafluorobenzene rings.

deficient pentafluorobenzene ring and electron-rich aniline benzene ring. This interaction should play a key role in fixing the anti-parallel orientation of the neighbouring molecule and also strengthen the intermolecular N–H···O=C hydrogen bonding.

Crystal structures of compounds 3a, 4a, 5a, and 7a

The crystal structures of these four diamides are shown in Fig. 3. For **3a** which contains a glycine residue, the molecules were also arranged in anti-parallel mode. In contrast, its analogue, acetylglycine *N*-methylamide (Ac-Gly-NHMe, **8**) adopted a disordered conformation in the solid state.[32] Two anti-parallel-arranged molecules formed a close dimer which was stabilized by two short intermolecular N–H···O=C hydrogen bonds (the H···O distance: 2.08 Å) and intermolecular benzene/pentafluorobenzene stacking. The tilt angle (α) of the stacked benzene and pentafluorobenzene is 5.8° and the distance between the centroid (*d*) of the two stacking aromatic rings is 3.66 Å. Both values are much smaller than that observed for **2**, reflecting the increased stacking of the benzene and pentafluorobenzene rings. In accordance with this, the amide plane was distorted by 17.6° from the *C*-terminal benzene ring and 40.4° from the *N*-terminal pentafluorobenzene ring, both of which are also smaller than the corresponding values of **2**. Every molecule further formed two intermolecular N–H···O=C hydrogen bonds (the H···O distance: 2.16 Å) with another neighbouring molecule, but no benzene/pentafluorobenzene stacking occurred between them. The distance of the horizontal displacement (*l*) of the two interacting rings is 1.45 Å, which is smaller by 1.05 Å than that observed for **2**, indicating an increased overlapping between the two aromatic rings (Fig. 3a, right). This enhanced stacking should not only direct the molecules to arrange in the anti-parallel manner but also significantly strengthen the N–H···O=C hydrogen bonding.

The crystal structure of compound **4a**, which bears an *h*Gly unit, is shown in Fig. 3b. Different from those of **3a**, the molecules of **4a** lined up in a head-to-tail zigzag form in the crystal and the benzene ring interacted with the pentafluorobenzene ring of the following molecule. As a result, only one set of benzene/pentafluorobenzene stacking interaction existed between one pair of molecules. The two carbonyl groups were oriented to the same direction and thus the neighbouring molecules also adopted anti-parallel arrangement, which was stabilized by two sets of intermolecular N–H···O=C hydrogen bonds (the H···O distance: 1.98, 2.14, 2.00, and 2.14 Å, respectively). The tilt angle (α) is 6.1°, the distance between the centroid (*d*) of the two paired aromatic rings is 3.65 Å, and the distance of their horizontal displacement (*l*) is 1.35 Å. The torsion angles of the benzene and pentafluorobenzene rings from the connected amide units are 17.0 and 41.9°, respectively. All

these values are quite close to those of **3a**, implying their benzene/pentafluorobenzene stacking contributed comparably to the stabilization of the extended conformation of the central aliphatic amide segment.

In the crystal of **5a** which contains a GABA (γ-amino acid) unit, the molecules existed as a symmetric dimer with the two molecules also being arranged in an anti-parallel manner (Fig. 3c). The two amide units formed two strong intermolecular N–H···O=C hydrogen bonds (the H···O distance: 1.98 Å) and the two pairs of benzene/pentafluorobenzene units stacked closely. Thus, the two different non-covalent forces should also promote each other. The two carbonyl groups were oriented to the opposite sides of the backbone, which is similar to that observed for **3a**. However, the trimethylene chain formed a torsion, which shortened the length of the backbone, probably for the avoidance of the existence of large unfilled space. Every molecule also formed another pair of N–H···O=C hydrogen bonds with another neighboring molecule, but the H···O distance is notably longer (2.22 Å). The tilt angle (α) of the two stacked aromatic rings is 6.0° and the distance between the centroid (*d*) of the stacked benzene and pentafluorobenzene rings is 3.72 Å, which corresponds to a 1.29 Å distance of horizontal displacement (*I*). These values are also close to the related ones of **3a**, even though its trimethylene chain adopted a turn conformation.

The crystal structure of ε-amino acid derivative **7a** is provided in Fig. 3d. Different from **3a**–**5a**, the backbone of this longer diamide formed a dislocated, turn-like structure. The benzene and pentafluorobenzene rings of every molecule stacked with the pentafluorobenzene or benzene ring of neighbouring molecules to produce a ladder-like array. The centroid distance (*d*) of the two stacked rings is 3.64 Å, which corresponded to a tilt angle (α) of 2.1°. The distance of their horizontal displacement (*I*) is only 0.66 Å, indicating that the two aromatic rings were nearly superimposed. The two amides formed two intermolecular N–H···O=C hydrogen bonds, with the H···O distance being 2.00 and 2.06 Å, respectively. These two strong hydrogen bonds forced the amides to strongly distort from the connected pentafluorobenzene and benzene rings. As a result, the torsion angles are as high as 80.3 and 81.8, respectively. Although **7a** did not exhibit an extended conformation, it still formed the benzene/pentafluorobenzene stacking, reflecting the strength of this interaction. We thus further prepared longer dipeptides (triamides) **5b**, **6b** and **7b** to investigate their conformation in the solid state.

Crystal structures of compounds 5b, 6b, and 7b

The crystal structure of **5b** displayed two extended conformers (Fig. 4a). For both conformers, the benzene ring stacked with the pentafluorobenzene ring of another molecule and thus gave rise to folded ruler-styled packing structures. As a result, the neighbouring molecules were arranged in an anti-parallel manner and held by three intermolecular N–H···O=C hydrogen bonds. For conformer **1** (Fig. 4a, left), the H···O distances are 2.13, 2.01, and 2.02 Å, respectively, and the tilt angle (α) is 3.0°, while the distance of the horizontal displacement (*I*) of the two stacking aromatic rings is 1.23 Å and the distance between their centroids (*d*) is only 3.56 Å, which indicated that highly efficient stacking occurred between the two aromatic rings. Conformer 2 also adopted the similar anti-parallel packing (Fig. 4a, right). For both conformers, the amide carbonyl groups were oriented to the opposite directions alternately, as displayed by the extended structure of α-peptides.

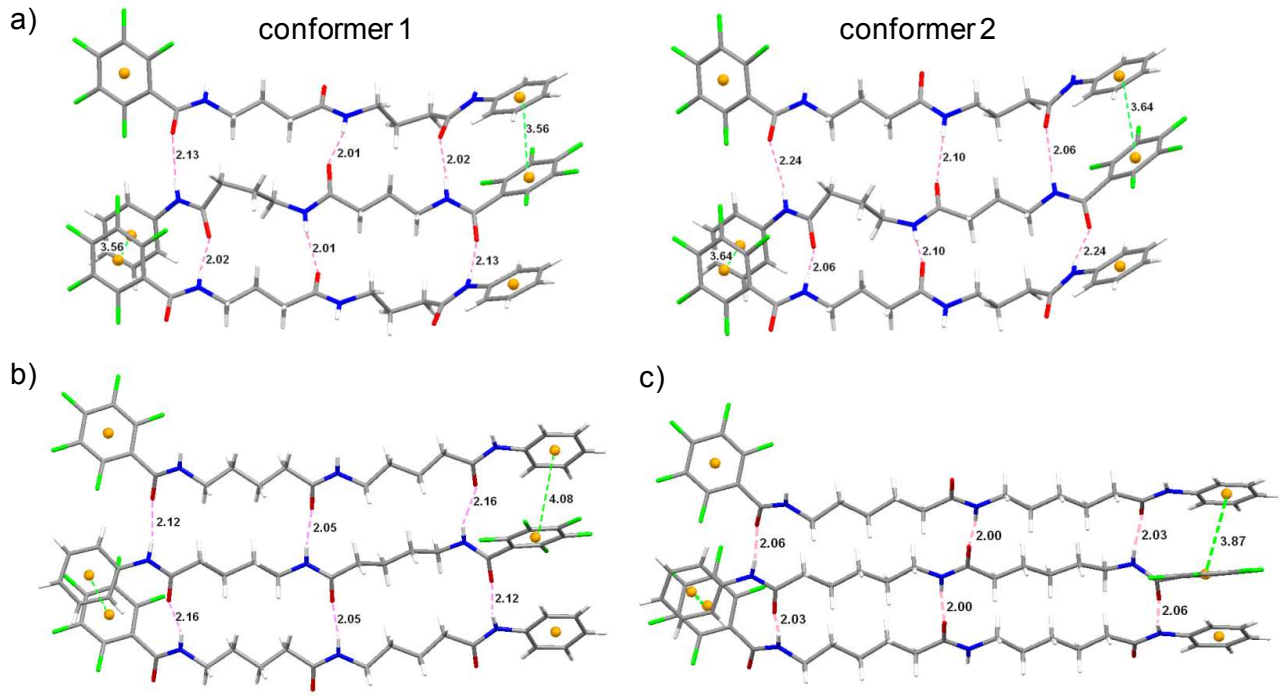


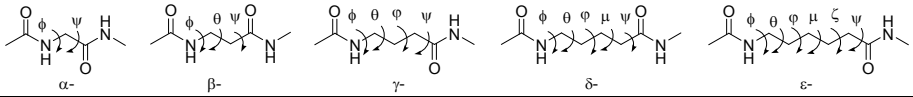
Fig. 4 Crystal structures of compounds a) **5b**, b) **6b**, and c) **7b**, showing the anti-parallel molecular packing of the extended backbone. The data represent the O···H distance and the centroid distance of the two stacking aromatic rings (Å).

The crystal structure of compound **6b** is provided in Fig. 4b. As revealed for **5b**, **6b** also adopted an extended conformation and the benzene ring stacked with the pentafluorobenzene ring of another molecule to form a ruler-styled anti-parallel array. The two tetramethylene segments were both in the *anti* conformation. As a result, the three amide carbonyl groups were all oriented to the same direction to form three strong intermolecular N–H···O=C hydrogen bonds. Such an arrangement of the carbonyl groups is similar to that observed for β-peptide sheet structures, suggesting that the tetramethylene segment in the *anti* conformation resembles the ethylene segment in controlling the orientation of the connected amide units. Compared to that revealed for **5b**, the centroid distance (*d*, 4.08 Å) of the stacking benzene and pentafluorobenzene rings of **6b** is notable longer and the tilt angle (α, 19.5°) is also larger. This may be attributed to the increased co-planarity of the anti-parallel-arranged aliphatic backbone with the benzene ring and the distortion of the pentafluorobenzene ring from the plane due to the steric repulsion of the connected carbonyl oxygen with the fluorine atoms at 2- and 6-positions.

The longest dipeptide **7b** also existed in the extended conformation and the intermolecular stacking of the benzene and pentafluorobenzene units forced the backbone to pack in the anti-parallel arrangement. This result is different from that of **7a** (Fig. 3d), which formed a turn conformation. This difference may reflect the fact that in this anti-parallel arrangement, the three intermolecular N–H···O=C hydrogen bonds could stabilize each other. However, the benzene/pentafluorobenzene stacking should also help to facilitate this arrangement, because otherwise the parallel arrangement might also occur for the triamide backbone, which also could enable the formation of three intermolecular N–H···O=C hydrogen bonds. As observed for **6b**, the aliphatic backbone of **7b** was also remarkably coplanar and the tilt angle (α, 18.6°) is quite large, compared with that of compound **5b**, leading to the relatively long centroid distance (*d*, 3.87 Å) of the two stacked aromatic rings.

The torsion angles of the amino acid residues of the above di- and triamides were further analyzed, partially by comparing with reported structures. The data of the di- and triamides are summarized in Table 1. The conformation of the aliphatic backbone of **3a** is similar to that of Ac-Gly-NHMe (**8**),[32] whose torsion angle is 109° (*gauche*) for ϕ and –21° (*anti*) for ψ. Compound **3a** also has a *gauche*/*anti* conformation and the angle between the two peptide bond planes is 35.3°. However, this angle is 97° for **8**. This almost perpendicular geometry induced it to form a disordered sheet structure, while the benzene/pentafluorobenzene stacking of **3a** should help to reduce the torsion angle between its two peptide bond planes and thus promote the formation of the extended sheet structure. Diamide **4a** exhibited an extended all-*anti* conformation, while the longer analogues **5a** and **7a** formed several *gauche* dihedral angles (θ and ψ for **5a** and ϕ, θ, ζ and ψ for **7a**). The angles (30–40°) between the two peptide bond planes of **3a**, **4a**, **5a** and **7a** were quite similar, which probably reflects the comparable influence of their intermolecular hydrogen bonding and benzene/pentafluorobenzene stacking in keeping the planarity of the central aliphatic segment. The *N*-terminal residue of dipeptide **5b** possessed all-*anti* conformations, while in the *C*-terminal residue the angle ϕ and φ were *gauche*. Dipeptide **6b** exhibited all-*anti* conformations except the angle ϕ of the *N*-terminal residue which had a nearly eclipsed conformation, while for **7b**, the dihedral angles of the backbone were all-*anti* conformation. These observations suggest that, with the elongation of the aliphatic chains, the stretching tendency of the backbone was also increased. Given that linear backbone tends to keep their extended conformation in the crystal, the above difference may reflect the decreased stacking of the benzene and pentafluorobenzene rings in the longer molecules. However, this

Table 1. The torsion angles of the amino acid residues of diamides **3a–5a**, and **7a** and triamides **5b–7b** in the solid state



compound	ϕ [°]	θ [°]	φ [°]	μ [°]	ζ [°]	ψ[°]	$\angle_{pep}$ [a)] [°]
3a	–144.9					171.7	35.3
8[31]	109					–21	97
4a	162.6	–179.8				164.2	31.2
5a	137.1	–64.7	–179.4			79.4	39.4
5b-1	–177.3	–178.7	–178.9			161.0	14.0
	–94.4	–175.2	64.3			–157.0	29.3
5b-2	–179.9	–173.9	–176.2			179.1	15.3
	–103.1	–173.4	64.1			–160.3	40.6
6b	126.1	–173.2	179.5	–176.8		–139.6	16.1
	159.2	–175.8	–179.4	–175.2		–166.1	16.2
7a	–93.0	–61.9	178.6	–173.0	62.5	–117.4	39.0
7b	142.8	–169.8	–173.6	–176.4	–170.1	–176.6	23.8
	178.0	178.2	–176.3	–177.7	–174.3	–173.8	13.5

a) The angle between two peptide bond planes.

interaction was still strong to be able to direct the molecules to arrange in the *anti*-parallel manner.

Conclusions

We have demonstrated that, by introducing intermolecular benzene/pentafluorobenzene stacking interaction, we can control γ-, δ-, and ε-amino acid-based dipeptides to arrange in the anti-parallel manner in the solid state. For all the compounds, the amide units are engaged in intermolecular N–H···O=C hydrogen bonding and the backbones adopt an extended sheet conformation. It is also noteworthy that in all the crystal structures, including those of the short analogues, no stacking between the identical aromatic rings or N–H···π or C–H···π interaction is observed.[33] Thus, the benzene/pentafluorobenzene stacking interaction does not weaken or break the intrinsic non-covalent interactions of the aliphatic amide chains. Further works will point to peptides to which the benzene and/or pentafluorobenzene unit is incorporated at the inner positions and sequences that consist of chiral amino acid residues.

Acknowledgments

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Notes and references

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† Electronic Supplementary Information (ESI) available: Synthetic procedure and charicterizations of compounds **1**, **2**, **3a**–**7a**, and **5b**–**7b**, X-ray crystallographic files in CIF format for the structural determinations. See DOI: 10.1039/b000000x/

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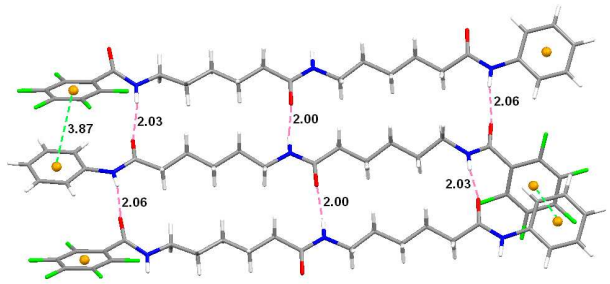
Table of Contents Graphic

Benzene/pentafluorobenzene stacking can guide ω-amino acid dipeptides to arrange in an anti-parallel manner.



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Benzene/pentafluorobenzene stacking can guide ω-amino acid dipeptides to arrange in an anti-parallel manner.