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Aromatic β-sheet foldamers based on tertiary squaramides†

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The preference of *N,N*-aryl, alkyl tertiary amides for *cis* conformations has been exploited through the use of tertiary squaramides as hairpin turn units that promote the folding of aromatic β-sheets. Head-to-head aromatic arrangements were shown to prevail in sufficiently long bent aromatic sequences.

Aromatic face-to-face stacking is associated with both structural order and electronic properties in systems as diverse as DNA, organic reactions, dye assemblies and solids for organic electronics.[1] To decipher and program these systems, strategies to produce aromatic stacks with a defined number of rings in solution are very useful. Thus, the controlled self-assembly of discrete aromatic stacks has been reported using coordination cages, pseudo-rotaxanes, macrocycles or interdigitated structures.[2] The folding of aromatic oligomers into multi-turn helices also promotes face-to-face stacking.[3] When the aromatic rings have an inherent tendency to stack in an ordered way, *e.g.* in donor–acceptor pairs, connecting them with flexible covalent linkers gives rise to folded aromatic pillars.[4] Some of these stacks have shown engaging charge transport properties.[5] Of special interest are covalent linkers that can promote hairpin turns and favour stacking between adjacent aromatic rings, *e.g.* ferrocene (Fig. 1a),[6] 1,8-naphthylene (Fig. 1b),[7] bis-*o*-phenol ethers,[8] tertiary imides,[9] proline,[10] 4-amino-butyric acid,[11] *o*-aminomethyl-aniline,[12] and 4,6-dinitro-1,3-phenylenediamine (Fig. 1c).[14] We have previously

made use of the latter in multi-turn sequences that fold into linear or bent aromatic sheets.[15] Here, we introduce tertiary squaramides as a new‡[16] hairpin turn unit to construct aromatic β-sheets. Specifically, the easy synthetic access – three steps – of Boc-amino methyl ester **1** (Fig. 1e) makes it an attractive building block for incorporation into aromatic amide foldamer sequences.[17]

The design of **1** was based on the conformational preference of *N,N'*-diaryl squaramides.[13,18] *N,N'*-dimethylation of these compounds favours *cis,cis* conformations (Fig. 1d), as for benzanilides and *N,N'*-diaryl-ureas.[19] Thus, the two aryl rings of **1** are close to parallel (angle of 15°, compared to *ca.* 60° and 30° for *N*-methylbenzanilide and *N,N'*-dimethyl-*N,N'*-diphenylurea, respectively). An important aspect is the orientation of the protected amine and acid functions of **1**. The structure in Fig. 1d reveals a twist of the four-membered ring conducive to a 60° relative rotation of the phenyl groups. Substitution at
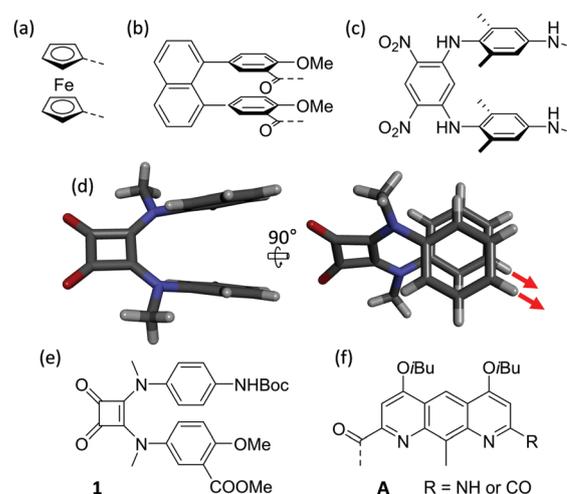

Fig. 1 (a–c) Examples of hairpin turns that promote aromatic face-to-face stacking. (d) Side and top views of the crystal structure of *N,N'*-dimethyl-*N,N'*-diphenyl-squaramide.[13] (e) Tertiary squaramide-based turn unit **1**. (f) 1,8-Diaza-anthracene monomers **A**. Both amino acid and diacid monomers were used in this study.

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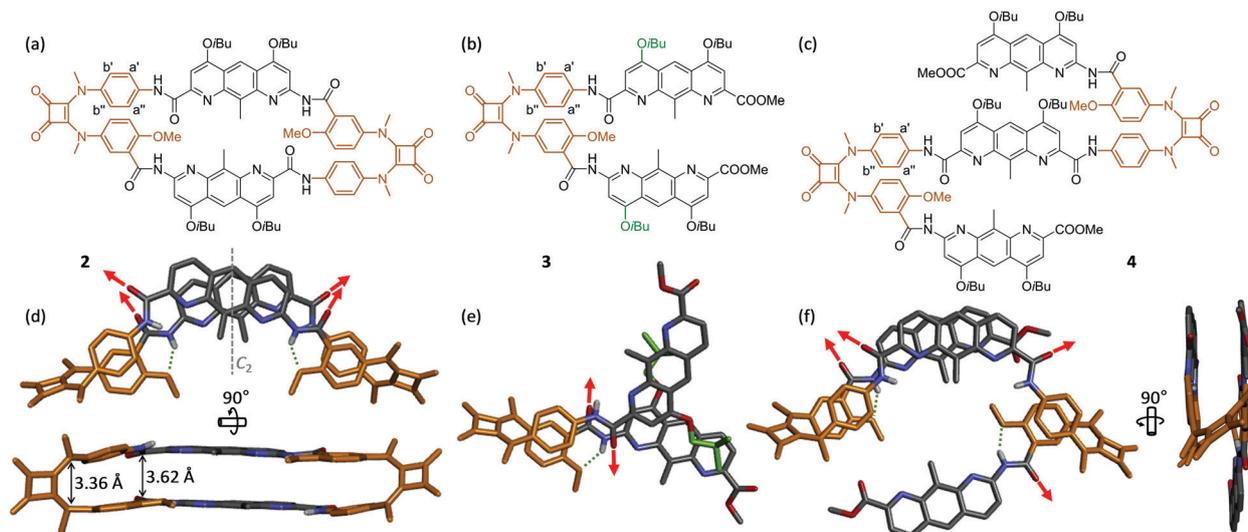[d] *Department of Chemistry, Ludwig-Maximilians-Universität, Butenandtstraße 5-13, D-81377 München, Germany*

Fig. 2 Chemical structures (a–c) and crystal structures (d–f) of compounds **2–4**. Some 1,8-diaza-anthracene units derive from an amino acid, others from a diacid. In the crystal structures the non-polar hydrogen atoms are omitted for clarity. iBu side-chains are also omitted except in (e), where two of them are shown in green. In (d–f) red arrows show the orientation of the amides adjacent to the squaramide turn. Green dotted lines indicate hydrogen bonds within the turn unit.

para and *meta* positions is required for substituents to point in the same direction. In addition, a methoxy group adjacent to the ester of **1** controls the orientation of a secondary amide at that position *via* hydrogen bonding.[17] Such a control is unneeded in the paraphenylene diamine unit since rotation of the phenyl ring is degenerate. Compound **1** was easily prepared by sequential aminolysis of diethyl squarate with one aniline, then the other, followed by *N*-methylation of the amides and a single final chromatographic step (see ESI†).

Compounds **2** and **3** (Fig. 2a and b) were prepared as models to assess the capability of the new hairpin turn to promote β-sheet formation in aromatic oligoamides (see ESI†). They comprise 1,8-diaza-anthracenes (**A**, Fig. 1f) as large aromatic units.[20] The distance ($\sim$9 Å) and angle ($\sim$120°) between connection sites at positions 2 and 7 is expected to result in some curvature, leading to variations of the surface involved in face-to-face stacking depending on whether **A** units are in a head-to-head or head-to-tail arrangement.[15b] In contrast with **3** which has one turn, **2** is a macrocycle with two turns. Cyclization should allow for only one conformation of **2** with *cis–cis* squaramides and **A** units oriented face-to-face in a head-to-head orientation. This prediction was confirmed by a crystal structure showing tight aromatic stacking (Fig. 2d) and the expected orientation of the phenyl rings. The twist of the squaramide plane confers inherent chirality;§ macrocyclization of **2** is possible only when both turns have the same handedness, resulting in overall C_2-symmetry. Solution NMR studies also reflected chirality under the form of anisochronous diastereotopic CH_2 protons of iBu side chains (Fig. 3a). At 298 K in CDCl$_3$ the four phenylene protons (a′, b′, a″, b″ in Fig. 2a) were also anisochronous, meaning that the rotation of this ring is slow on the NMR time scale. Upon heating to 339 K in C$_2$D$_2$Cl$_4$, the signals of b′ and b″ coalesced $\left(\Delta G_2^\ddagger = 68.5 \pm 0.4 \text{ kJ mol}^{-1}\right)$.¶[21] This relatively

high energetic barrier is the consequence of the tight π–π contacts seen in the crystal. Yet, fast exchange between diastereotopic protons was not observed, showing that chirality inversion remains slow, if it takes place at all. Consistently, the fluorescence of **2** is dominated by excimer fluorescence (Fig. S50, ESI†).

Compound **3** possesses additional degrees of conformational freedom because it is not cyclic. Its ^{1}H NMR spectrum shows one set of signals (Fig. 3b). The resonances of its *N*-methyl protons at 3.76–3.80 ppm are similar to those of **2**, suggesting that it also exclusively adopts a *cis–cis* conformation. In this case, however, fast rotation of the *p*-phenylenediamine ring was observed at room temperature, indicating a less tightly packed structure. Broadening and then splitting of the signals of b′ and b″ occured upon cooling to 239 K. The rotational barrier $\left(\Delta G_3^\ddagger = 47.8 \pm 0.4 \text{ kJ mol}^{-1}\right)$¶ is thus lower than that of macrocycle **2**, and similar to that of **1** $\left(\Delta G_1^\ddagger = 44.4 \pm 0.4 \text{ kJ mol}^{-1}\right)$.¶ A structure of **3** in the solid state showed the expected arrangement of the turn conformation and the resulting face-to-face stacking of aromatic groups (Fig. 2e). The two **A** units were found to be head-to-tail, which resulted in a minimal overlap between them. Such conformations have been shown to be favoured in linear aromatic β-sheets[15b] as they allow favourable attractive interactions between local dipoles such as the amide groups of the turn in this case (red arrows in Fig. 2e). Yet in bent β-sheets, head-to-head arrangements were shown to prevail despite dipolar repulsions.[15b] The structure of **3** showed reduced π–π contacts but instead extensive overlap between each **A** unit and an iBu chain of the other **A** (Fig. 2e, in green), which may also be favourable. In solution, some aliphatic NMR signals are upfield-shifted with respect to those of **2** (Fig. 3b, red rectangle), hinting at ring current effects
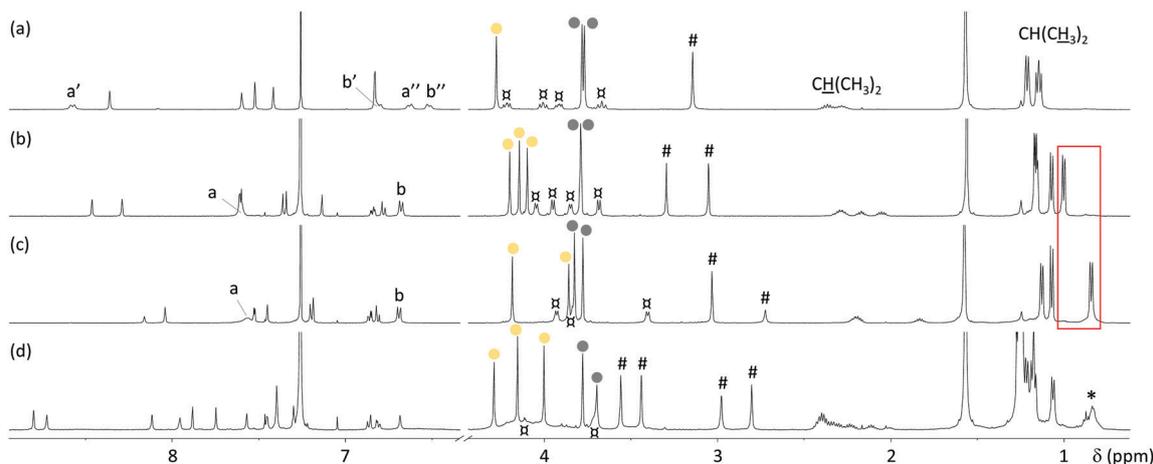
Fig. 3 ^{1}H NMR (CDCl$_3$, 298 K) of compounds (a) **2**, (b) **3**, (c) **4** and (d) **5**. The methoxy group of the turn and the terminal methyl esters (yellow spots); the two methyl groups of the turn (gray spots); the OCH$_2$ of the side chains (¤); and the Ar–CH$_3$ of the **A** monomer (#) are assigned (full assignment in the ESI†). Aliphatic impurity (*). A red box indicates upfield shifted signals of methyl protons.

consistent with the crystal structure, and suggesting that the solid state conformation is populated in solution.

Next, **4** was designed to investigate the effect of an additional aromatic layer (Fig. 2c). This compound has an overall C_2-symmetry that was reflected in the multiplicity of its ^{1}H NMR spectrum (Fig. 3c). The presence of only one set of signals showed that exchange between different conformations is fast on the NMR timescale at 298 K; slow exchange between b′ and b″ protons was observed below 237 K $\left(\Delta G_4^{\ddagger} = 47.5 \pm 0.4\ \text{kJ mol}^{-1}\right)$.¶ In addition, upfield-shifted aliphatic signals indicated that the head-to-tail conformation seen in **3** is also populated in **4**. The crystal structure of **4** is not symmetrical (Fig. 2f). One turn leads to a head-to-head arrangement of adjacent **A** units whereas the other turn does not promote sheet formation. Its N- and C-termini are not pointing in the same direction but instead at a *ca.* 120° angle. In addition, the turn is flipped 180° in such a way that the terminal **A** units are co-planar. This is likely favoured by crystal packing as the large aromatic surface generated is involved in intermolecular interactions in the crystal lattice (see Fig. S48 in the ESI†). The fluorescence of **4** showed both monomer and excimer fluorescence (Fig. S50, ESI†).

In short, tertiary squaramide turns do organize aromatic units face-to-face, but head-to-head bent β-sheets, if they are not locked in a macrocycle, co-exist with other conformations. We then designed compound **5** (Fig. 4a) to study the effect of extended aromatic strands. Remarkably, its ^{1}H NMR spectrum at 298 K shows well defined and sharp aromatic signals except for those of the *p*-phenylenediamine ring which are broad and not distinguishable from the baseline (Fig. 3d). Furthermore, no aliphatic signal was found upfield-shifted in the spectrum of **5**. A VT-NMR study in CDCl$_3$ (see ESI†) revealed a coalescence temperature for protons b′ and b″ of *ca.* 303 K. In this case the $\Delta G_5^{\ddagger}$ of *p*-phenylenediamine rotation could not be determined (see ESI†), yet the much higher coalescence temperature of compound **5** compared to those of **3** and **4** (ΔT of *ca.* 65 K)

suggests a more stable conformation. Because **3** and **5** differ through additional **A** units far away from the phenyl ring, we inferred that these units must interact, which is only possible in a head-to-head sheet conformation. The prevalence of this conformation was unambiguously demonstrated by 2D NOESY NMR (Fig. 4b). Several NOEs could be assigned to interstrand correlations involving methyl groups of **A** units and amide NHs. Consistently, excimer fluorescence prevails again in **5** (Fig. S50, ESI†).

We have thus established a simple synthesis and conditions for folding of new aromatic β-sheets. These add to the short list of sheet-like foldamers. One can speculate that their folding may be favoured by solvophobic effects in protic solvents.
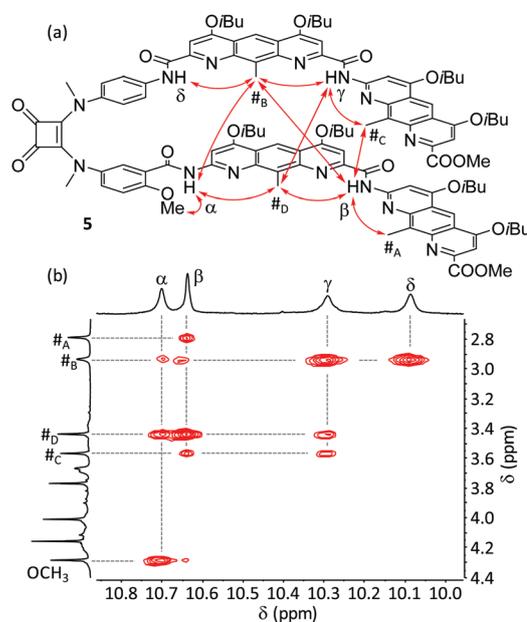

Fig. 4 (a) Chemical structure of compound **5** in its head-to-head arrangement. Observed NOE correlations are indicated with red arrows. (b) Partial 2D NOESY (800 MHz, CDCl$_3$, 298 K) of compound **5** (region where the correlations between NH and Ar–CH$_3$ signals are shown).

Testing of this hypothesis is underway and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ Secondary squaramides have previously been introduced as a hairpin turn in peptides, see ref. 16.

§ Compounds **2–4** crystallized in centro-symmetrical space groups. Unit cells contain both enantiomeric conformers. See ESI.†

¶ Activation energy of the rotation of the phenyl ring, $\Delta G^{\ddagger}$, at the temperature of coalescence. See the corresponding VT-NMR experiments in the ESI.†

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