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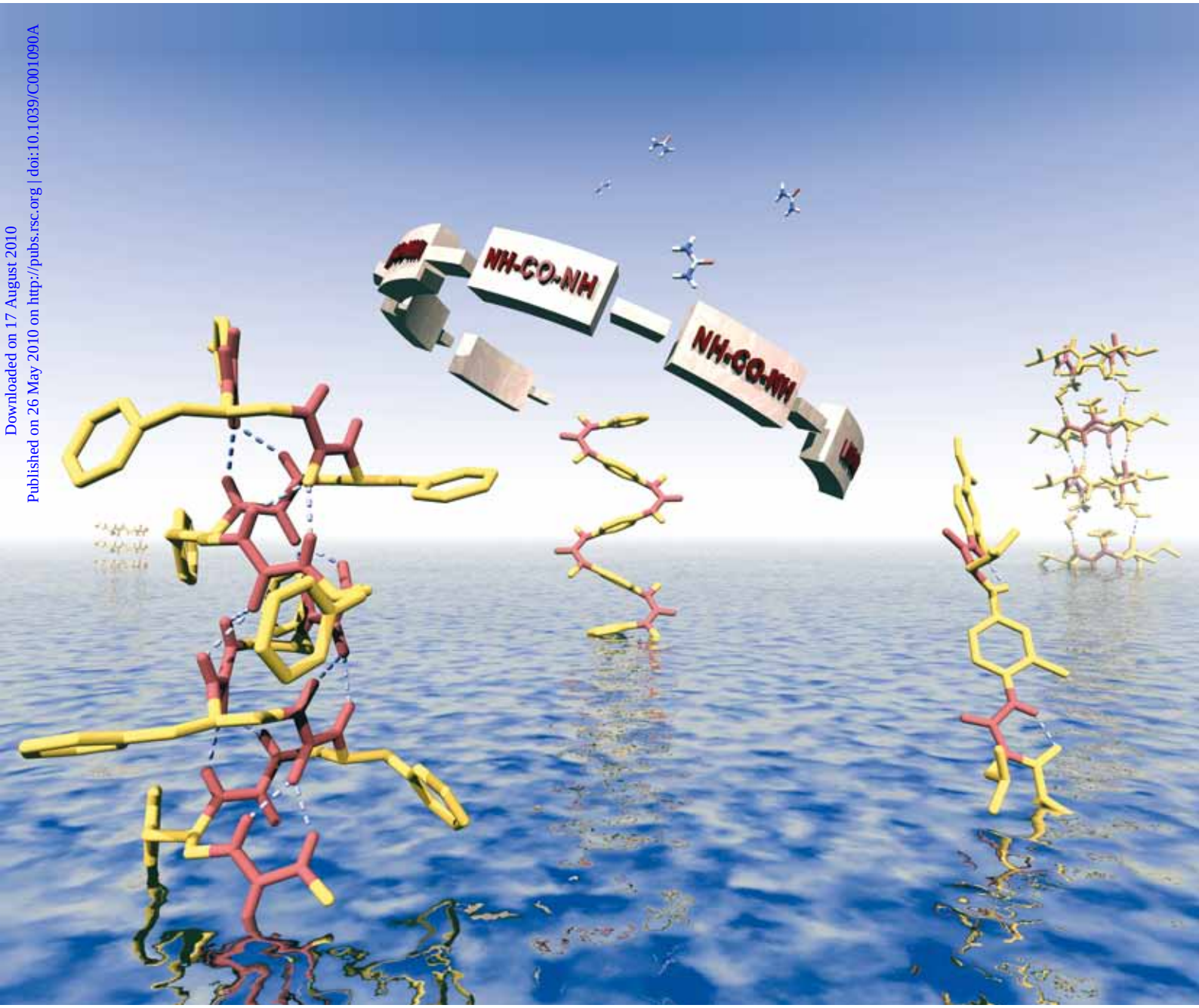

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Folding and self-assembly of aromatic and aliphatic urea oligomers: Towards connecting structure and function

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Folding and self-assembly of biomacromolecules has inspired the development of discrete, non-natural oligomers that fold and/or self-assemble in a controlled manner. Though aromatic and aliphatic oligoamides remain unmatched for structural diversity and synthetic versatility, oligomers based on amide bond surrogates, such as urea backbones, also demonstrated a propensity for folding and self-assembly. In this Perspective, we review the advances in the design of oligomeric aromatic and aliphatic urea sequences (essentially *N*,*N*′-linked) that fold and/or self-assemble. Whenever applicable, the relationship between structure and function will be highlighted.

1. Introduction

Nature has developed a strategy of folding and hierarchical structure formation to adjust and control the dimensions, shapes and functionalities of macromolecules (*e.g.* proteins, nucleic acids) operating at the cellular level. For example, functions fulfilled by proteins (*e.g.* molecular recognition, sensing, transport, catalysis) essentially depend on the ability of intrinsically flexible chains to fold correctly into well-ordered and compact structures and eventually to assemble into quaternary structures. Multiple approaches at the interface between biology, synthetic organic and polymer chemistries have been used to develop synthetic systems with protein-like structures and functions. The design of discrete non-natural oligomers (*i.e. foldamers*) with predictable and well-characterized folding patterns akin to naturally occurring helices, turns and linear strands has attracted considerable attention over the last decade.[1–7] Today, the possibility to integrate and convert high resolution structural data into a functional outcome is being actively explored. For instance, biomedical applications of foldamers include the development of antimicrobials, cell penetrating agents and inhibitors of protein–protein interactions.[8,9] Non-natural aromatic and aliphatic oligoamide backbones have proven to be extremely well suited for the design of robust secondary structures,[6] as well as more sophisticated tertiary structural motifs[10] and quaternary arrangements.[11,12] Macrocyclic and linear oligoamides have also been shown to be reliable building units for the fabrication of *self-assembled nanostructures* (*e.g. nanotubes*, *nanospheres*, *fibrils*,…)[13–20] with potential applications in biotechnology. The reasons for the dominance of the amide linkage in the design of non-natural oligomers used to reproduce

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Gilles Guichard was born in Orléans (France) in 1969. He studied chemistry at the Ecole Nationale Supérieure de Chimie in Toulouse and at the University of Montpellier. He received his PhD from the University Louis Pasteur in Strasbourg (1996). After post-doctoral research with Prof. Dieter Seebach at the ETH in Zürich (1997), he joined the Institut de Biologie Moléculaire et Cellulaire in Strasbourg as a CNRS Chargé de Recherche (1998). Since 2006 he has been a CNRS Research Director. In 2009, he moved as a new group leader to the Institut Européen de Chimie et Biologie (IECB) in Bordeaux. His current research focuses on biomimetic chemistry of peptides, folding, self-assembly and biomolecular recognition.

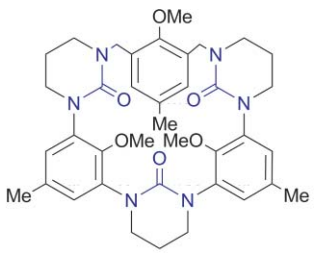
protein-like structures lies in part in the relative ease of amide bond formation and in the robustness of hydrogen bonding interactions mediated by secondary amides. These help to stabilize folded conformations (through either remote or local intrastrand interactions) and to drive self-assembly. Even oligomers consisting exclusively of tertiary amides, which lack H-bond donors and display lower rotational barriers about the C–N bond can be enforced to fold (*e.g.* oligomers of *N*-substituted glycine, so called "peptoids" with chiral side chains[21]). In this case, folding results primarily from non-covalent forces such as steric repulsion, $n \rightarrow \pi^*$ interactions,[22,23] hydrophobic and solvophobic interactions[6] and combinations thereof.

At first glance, the creation of peptidomimetics with non-amide backbones endowed with the potential to fold and self-assemble to an extent rivalling that of oligoamides, may appear difficult. In an effort to meet this challenge, a variety of amide bond surrogates have been probed, with varying degrees of success. Despite receiving far less attention than their amide counterparts, oligomers with a urea-type backbone (–[RNHCONH]$_n$–) have gradually made their mark in the field. The urea-linkage shares a number of desirable features (*i.e.* rigidity, planarity, polarity, and hydrogen bonding capacity) with the amide group. A closer look, however, reveals subtle differences between the two that are likely to become significant when designing and utilizing oligomers with self-assembling and/or folding propensity: (*i*) The dipole moment of ureas exceeds that of amides. (*i.e.* 4.8–4.9 D for simple symmetrical aliphatic ureas[24] *versus* 3.7–3.9 D for simple amides[25] in dioxane at 30 °C). (*ii*) As a result of competitive conjugation, the double bond character of the CONH bond is significantly reduced in ureas compared to amides. Experimentally determined barriers for rotation ($\Delta G^{\ddagger}$) for ureas are typically around 10–12 kcal mol^{-1} (*versus* 16–20 kcal mol^{-1} for amides) and urea motifs with significant deviation from planarity are likely to be observed. (*iii*) Due to the presence of one additional NH-group, *N*,*N*′-disubstituted ureas have a propensity to form three-centred H-bonds, a property which has been largely exploited in the solid state to create highly directional H-bonded assemblies of chains, ribbons and layers.[26–28]

This Perspective will illustrate a number of representative examples of the principles that guided the design of aliphatic and aromatic urea oligomers (essentially *N*,*N*′-linked) with the propensity for folding and/or self-assembly. Whenever applicable, the relationship between structure and function as well as the parallel with their oligoamide counterparts will be discussed. Section 2 is dedicated to H-bond-mediated self-assembly of macrocyclic oligomers and their applications. Sections 3–6 are related to approaches aimed at promoting folding over self-assembly in open chain oligomers. Finally, Section 7 is focusing on early efforts to design folding urea-based oligomers with function.

Together, urea, thiourea and their derivatives have been playing a central role in the field of supramolecular chemistry since the 1940s–1950s, when urea itself was recognized to form self-assembled tunnel host structures, so-called urea inclusion compounds in the presence of appropriate guest molecules (*e.g. n*-alkane chains).[29] The use of urea derivatives as binding elements for molecular recognition was pioneered by *Cram* who made extensive use of macrocyclic systems incorporating cyclic tetrasubstituted urea units (*e.g.* **1**) for alkali metal, ammonium and alkylammonium ions recognition as well as to mimic serine protease activity.[30] The last 20 years have seen the spectacular development of *N*,*N*′disubstituted (thio)ureas as receptors for neutral H-bond acceptors[31,32] and anions,[33–35] as well as their applications in H-bond-mediated organocatalysis.[36–41]

Intermolecular interactions involving H-bonds can be further strengthened and controlled by utilizing molecules containing multiple urea functional groups. For example, bis ureido compounds which give rise to collectively stronger H-bonding interactions have been used to form stable duplexes (*e.g.* **2**),[42] organo-[43–45] and hydro-gels[46] as well as microfibrillar foams and supramolecular polymers.[47–51] Larger arrays of ureas have been introduced by *Rebek*[52] and *Bohmer*[53] as zippers to drive the formation of self-assembled capsules useful for host–guest chemistry. For example, in calix[4]arenes containing four urea groups connected at the upper rim (*e.g.* **3**), a dimeric capsule is formed by interdigitation of all eight ureas in a head-to-tail directional array of 16 H-bonds.[54] Other urea-based dimeric systems that deviate from the calixarenes have also been studied.[55–57] In the field of synthetic carbohydrate receptors,[58] porphyrins with multiple urea appendages have been shown to bind pyranosides in organic solvents.[59] Glycoluril-based systems including cucurbit[n]urils and congeners (*e.g.* **4**) are yet another fascinating family of tetrasubstituted urea-based materials with multiple applications in host–guest chemistry.[60,61] Although they are of high interest and immediately relevant in the context of this review, it is not our intention to cover the



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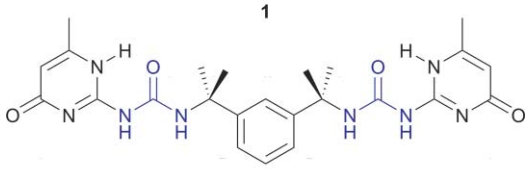

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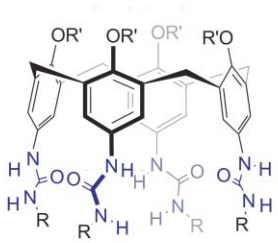

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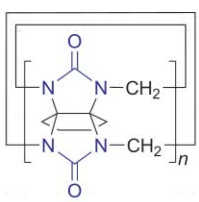

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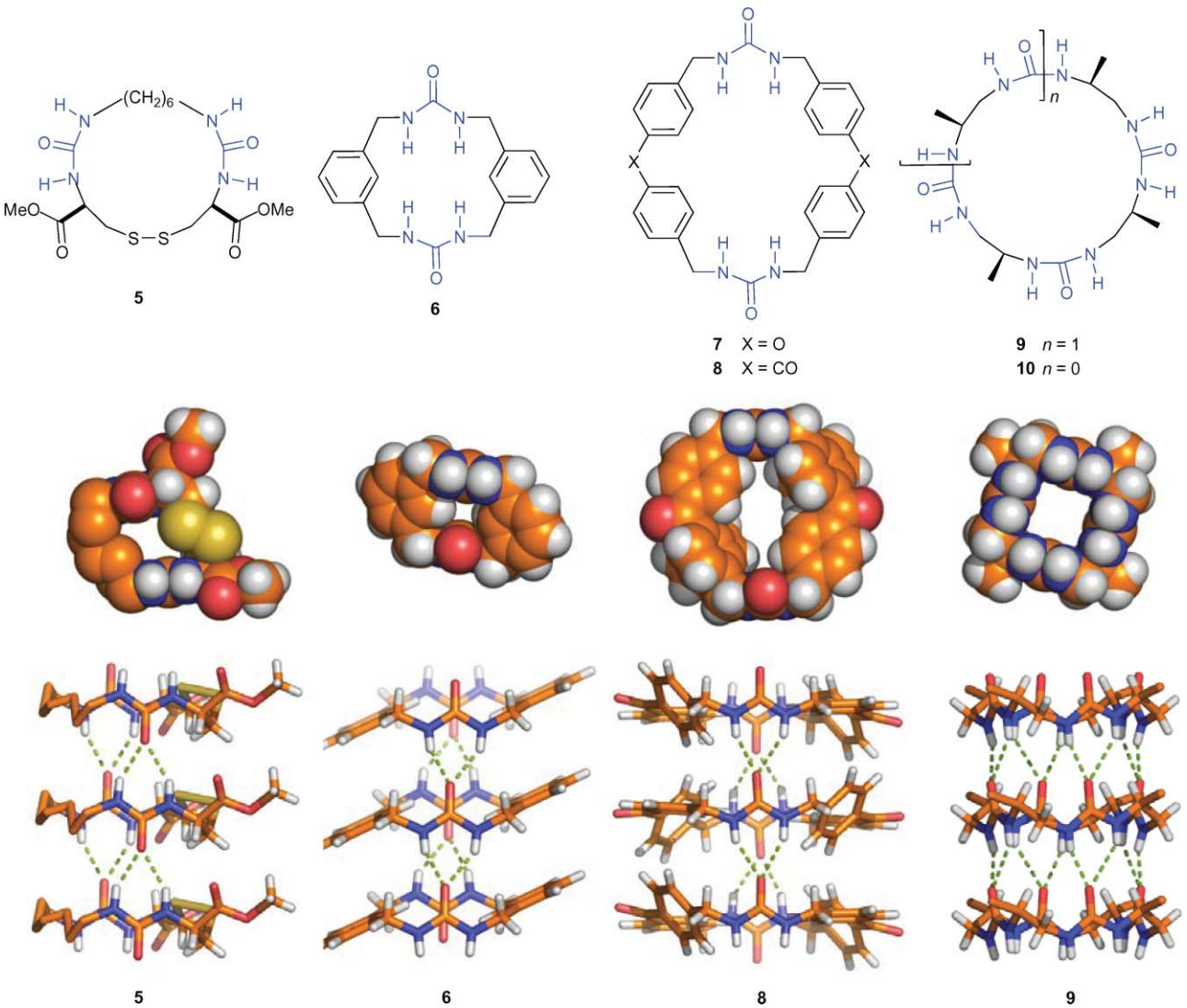

Fig. 1 Structure at atomic resolution of macrocyclic oligoureas forming H-bonded columnar and tubular self-assemblies.

rich chemistry, structures and applications of all these systems. They have been the focus of a number of comprehensive and authoritative reviews (*vide supra*) to which interested readers are referred.

2. H-bonded columnar and nanotubular assemblies of *N*,*N*′-linked *cyclo*-oligoureas

Synthetic peptides represent versatile elements for the construction of bio-inspired H-bonded nanostructures, owing to their diversity in size, conformations and appended functionalities.[15,20] Hollow tubular ensembles with adjustable internal diameter and outer surfaces have been created by the sheet-like assembly of flat macrocyclic peptide units.[13] Reported applications for these interesting materials include transport of ions[62] and small molecules, antibacterial[63] and antiviral activities, as well as sensing and electron transfer reactions.[64] Likewise, macrocyclic *N*,*N*′-linked oligoureas display a strong propensity to form various types of H-bonded columnar and tubular stacks: this potential has been recognized by several groups (Fig. 1).[65–67] In the solid state, non-symmetrical macrocyclic bisureas consisting of one cystine unit and one hexamethylenediamine unit bridged together (*e.g.* **5**) self-assemble into tube-like structures stabilized by three-centered intermolecular H-bonds.[65] Diurea **5**, as well as related cystine-based cyclic triureas and tetraureas, display interesting anion binding properties.[65,68] More examples of neutral receptors for anions (oxoanions, chloride) based on oligo(thio)urea or hybrid amide–urea macrocycles have since been reported.[69–74] Macrocyclic bisureas **6–8** connected by aromatic spacers self-assemble into H-bonded tubular stacks.[66,75,76] In the crystal structures of bisurea macrocycles **5–8**, the urea units are parallel, but point in opposite directions: possibly in order to minimize the overall dipole moment. Alternatively, robust hydrogen-bonded polar nanotubes in which all urea groups point in the same direction have been generated from enantiopure macrocyclic *N*,*N*′-linked oligoureas (*e.g.* **9**).[67] N···O distances of three-centered H-bonds in **4–9** range from 2.80–3.28 Å, creating a spacing between urea groups of 4.61–4.72 Å. The dimensions of the cavity in these systems can be controlled by variation of either the size and the

shape of the spacer (*e.g.* *meta*-xylene *versus* diphenyl ether units in **6** and **7**, respectively[66,75]) or the number of repeat units in the ring (tetraurea **9** *versus* triurea **10**, G. Guichard, unpublished work).

It is significant that the size of the pores formed by bisurea **7** (4.8 × 3.8 Å), bisurea **8** (3.7 × 2.7 Å) and tetraurea **9** (3.5 × 3.5 Å) are actually large enough to accommodate guest molecules. Like zeolites, bisureas **7** and **8** form porous crystals that have been shown to reversibly bind solvent molecules such as DMSO, EtOAc, THF, AcOH.[75,77,78] More importantly, *Shimizu* and coworkers have shown that the empty cavity in bisureas can be used as a confined environment to promote various photochemical reactions.[79,80] For example, crystalline bisurea **7** was shown to induce the [2 + 2] photocycloaddition of α,β-unsaturated ketones (*e.g.* 2-cyclohexenone) with high selectivity to yield head-to-tail photodimers. In contrast, **8**, which contains a benzophenone linker, was found to promote the rapid photoisomerization of *trans*-β-methylstyrene to the less stable *cis*-β-methylstyrene, a reaction that is not mediated by **7** (Fig. 2).

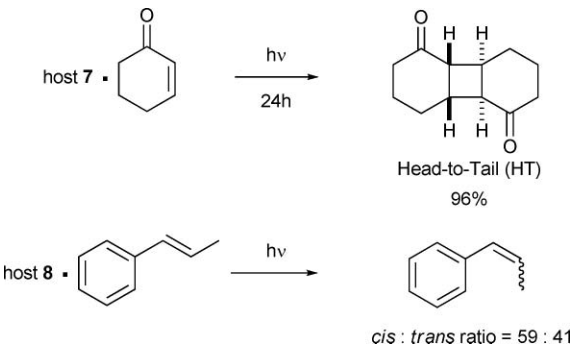

Fig. 2 Host–guest chemistry with macrocyclic oligoureas. [2 + 2]-cycloaddition of 2-cyclohexenone (top) and photoisomerization of *trans*-β-methylstyrene (bottom) in the presence of hosts **7** and **8**, respectively.

Self-assembling properties of hybrid urea–amide macrocycles generated by cyclooligomerization of chiral dipeptide-derived building blocks have also been investigated. High levels of hierarchical and directional control have been achieved in these systems.[81] For example, 14-membered C_2 symmetric macrocycles **11** and **12** with partially *N*-alkylated backbones form columnar arrangements with either parallel or antiparallel growing modes depending on the level of backbone pre-organization (Fig. 3a).

In the solid state, partially *N*-methylated macrocycles such as **11** form antiparallel H-bonded dimers that further stack into columns. Substituting proline for the *N*-methyl amino acids (*e.g.* **12**) modifies the ring geometry and promotes another mode of column formation. Although no backbone–backbone H-bonding is involved, the rings are linked in a parallel orientation *via* bridging water molecules. In the case of **12**, hierarchical assembly into tubular nanostructures has been observed using TEM imaging (Fig. 3b). Recent studies have shown that macrocyclic urea–amide hybrids are functional, anion-selective membrane transporters in lipid bilayer membranes. Of note are "antiparallel" macrocycles that self-assemble into "antiparallel" nanotubes without macrodipole (*e.g.* **11**), exhibiting Hofmeister selectivity. In contrast, parallel macrocycles that self-assemble into parallel nanotubes (*e.g.* **12**) with strong macrodipoles are capable of overcoming the dehydration penalty of the Hofmeister bias.[82]

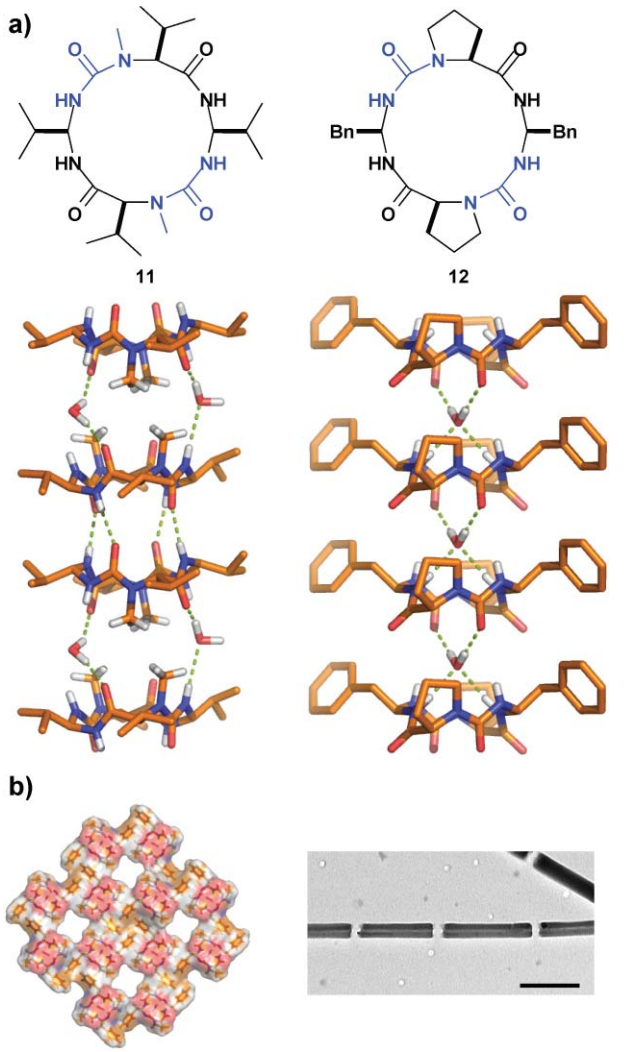

Fig. 3 Columnar self-assembly of heterogeneous amide–urea macrocycles **11** and **12**. (a) Antiparallel stacks (**11**, left) *versus* parallel stacks (**12**, right); (b) channels formed by lateral packing of columns in **12** viewed along the channel axis (left) and TEM image of tubular nanostructures of **12** (right, scale bar = 500 nm).

3. Controlling folding over self-assembly: local H-bonded interactions in aromatic *N*,*N*′-linked oligoureas

Local conformational control through H-bonding provides robust and predictable means to enforce folding of π-conjugated oligomers over self-assembly. Arylamide foldamers are by far the most heavily investigated and several comprehensive reviews have recently been published.[3,83,84] Multiple H-bonding patterns for restricting rotation around Ar–NHCO and Ar–CONH have been employed, leading to a wealth of conformations and shapes depending on the relative orientation of bridged units: *e.g.* helices, crescents, linear and zig-zag ribbons, as well as macrocycles. Similar principles also apply to the design of aromatic oligourea foldamers. For example, conformational control over the Ar–NHCONH bond has been achieved by introducing a H-bond acceptor (*e.g.* endocyclic nitrogen or exocyclic carbonyl oxygen) *ortho* to the urea group as shown in Fig. 4.

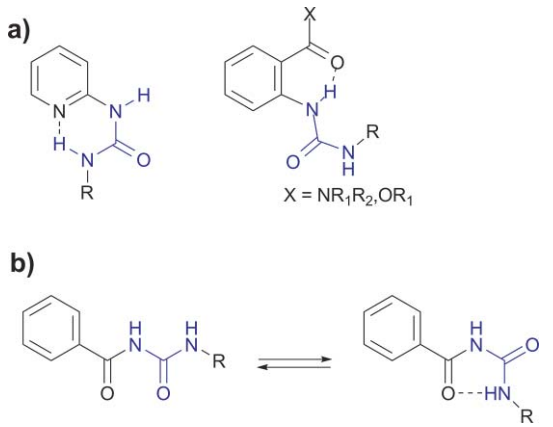

Fig. 4 Local conformational control around aryl urea bonds by introduction of a H-bond acceptor in the vicinity of the urea group. (a) An endocyclic nitrogen (left), an exocyclic carbonyl oxygen (right), (b) a carbonyl oxygen in benzoyl urea.

Concurrent with the work of *Meijer et al.* on (bis)ureidopyrimidone-based compounds (*e.g.* **2**),[42,85–87] *Zimmerman* and coworkers have studied mono- and diureas of 2,7-diamino-1,8-naphthyridine as model systems towards the development of switchable oligomers. Simple pyridinylureas and cognate naphthyridinylureas exist as folded, intramolecularly H-bonded (*E*,*Z*) conformations (*e.g.* **13a**) but can undergo concentration-dependent unfolding to form linear H-bonded complexes (Fig. 5).[88,89] Of note is that when two complementary strands (*e.g.* **13b** and **14** with DDAADD and AADDAA H-bonding modules, A = H-bond acceptor and D = H-bond donor) are mixed, mutual unfolding results in the formation of a linear heterodimer (K_{assoc} 5×10^5 M^{-1} for **13b**·**14**). Further extension of **13** by one naphthyridine unit (with appended solubilizing R groups) gives a self-complementary strand (DDAADDAA H-bonding array) that forms a very stable duplex with eight H-bonds.[90] Whether longer oligomers maintain this capacity to form H-bonded linear dimers or start to fold into intramolecular H-bonded helical structures, is an issue that still needs to be addressed.

Extending the work on aromatic oligoamides that adopt helical structures, the *Meijer* and *Gong* groups independently reported the design of urea-based aromatic helices (Fig. 6). Chiral Poly(ureidophthalimides) **15** ranging from 2 to 30 residues were synthesized in a single condensation step between diisocyanato and diamino monomers (Fig. 6a).[91,92] Helical folding in these oligomers was inferred from the observation of a Cotton effect in THF (but not $CHCl_3$) for $n > 7$. The turn enforced by the combination of *para*-connectivity between urea groups and H-bonded 6-membered rings between urea protons and imide carbonyls is slightly larger than 120°. This is consistent with 6–8 heterocyclic units per helix turn and an inner part of approximately 14 Å diameter. The helical fold is further stabilized by π–π interactions once a turn is completed. Additional evidence for backbone organization and helix nucleation came from STM analysis of short-chain fractions (2–8 repeat units) of oligomers decorated with chiral oligo(*p*-phenylenevinylene) chromophores (**15b** in Fig. 6a).[92] A water-soluble version of poly(ureidophthalimides) was obtained by appending hydrophilic chiral side chains (**15c**).[93] Temperature-dependent CD studies in water revealed stable helical

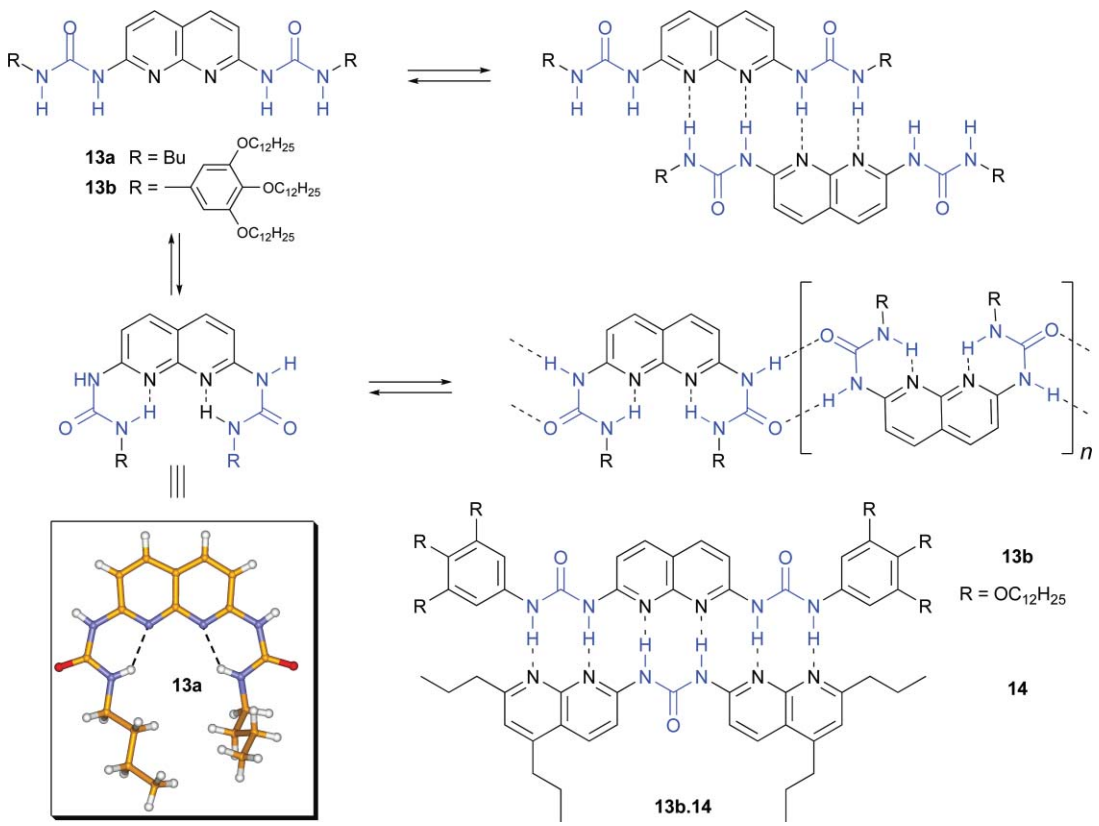

Fig. 5 Folding and aggregation behaviour of short oligomers of naphthyridinylureas.

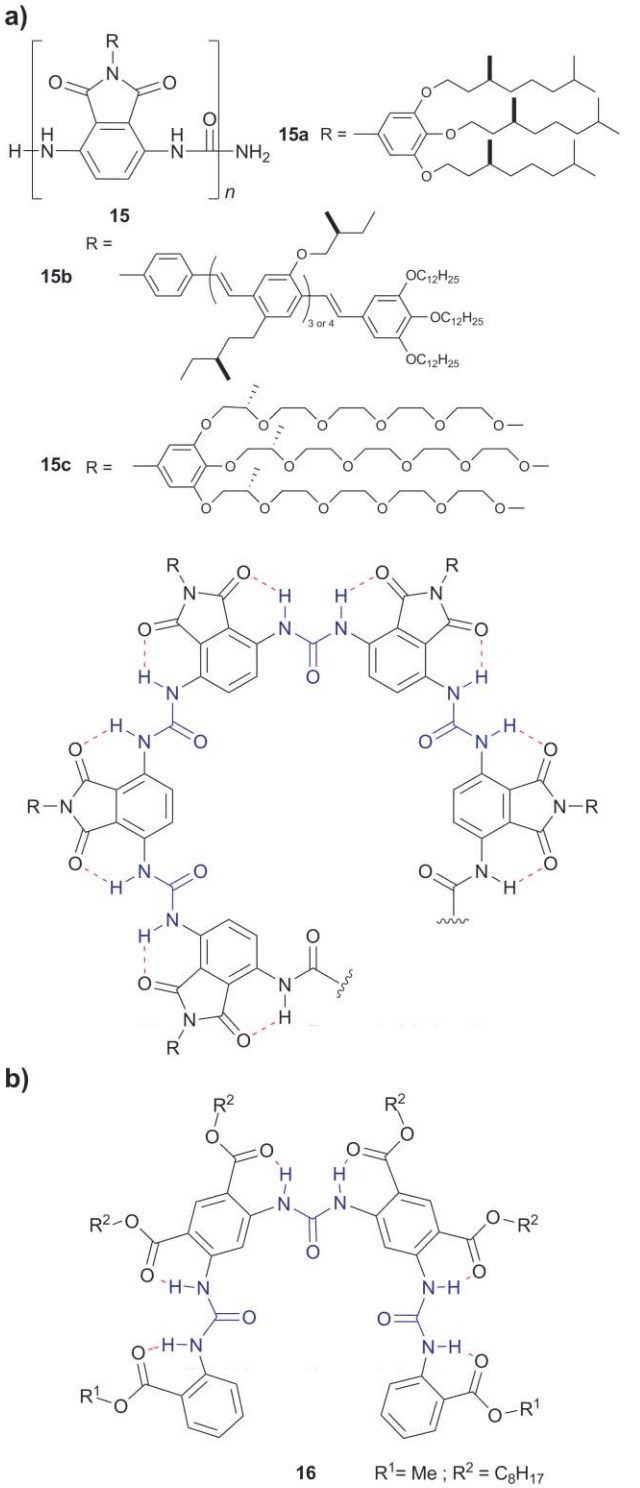

Fig. 6 Urea-based aromatic helices reported by *Meijer* (**15**) and *Gong* (**16**).

folding. Surprisingly, the Cotton effect measured in water was of opposite sign compared to THF, indicating inversion of helical handedness. Moreover, CD experiments in THF–water mixtures were consistent with a dominant effect of water in determining handedness of the helical architecture.

Alternatively, the pitch can be adjusted to 4 heterocyclic units per helix turn by simply turning the connectivity between urea groups from *para* to *meta* (*e.g.* **16**, Fig. 6b).[94] The size of the resulting hydrophilic cavity is then reduced to ~4 Å.

Local backbone pre-organization through H-bonding is also a very effective way to drive the condensation reactions towards macrocyclic end products, without the need for high-dilution or templating (Fig. 7). For example, cyclotrimers were formed predominantly by condensation of 2,6-diaminopyridine (*e.g.* **17**) and 2,7-diamino-1,8-naphthyridine with 1,1′-carbonyldiimidazole.[95] The presence of a singlet at ~12 ppm as well as characteritic NOE cross-peaks were consistent with the proposed thermodynamically favoured H-bonded conformation. In contrast, the same reaction with isosteric 1,3-phenylenediamine yielded exclusively linear urea oligomers. Other interesting examples of one-pot folding-assisted macrocylization include the formation of tetraurea **18** in 49% yield by reaction of *N*-substituted 3,6-diaminopyridazines with tolylene-2,6-diisocyanate[95] and the [2 + 2] macrocyclization of **19** to give tetramer **20** (65% yield).[94] The folded nature of pyridazyl urea-linked oligomers was confirmed by X-ray crystal structure determination of **18** and by studies of open-chain oligomers in solution and in the crystal state.[96]

Conformational control through H-bonding (Fig. 4b) has also been used to generate extended linear strands. One interesting example is provided by benzoylurea oligomers, a new class of α-helix mimetics (see also section 7) reported by *Hamilton*. In these oligomers (*e.g.* **21**, **22**, Fig. 8), the conformation of the acylurea is stabilized by intramolecular H-bonds between the urea amide NH group and the acyl carbonyl group. Intramolecular H-bonding was confirmed by NMR variable temperature experiments ($\Delta\delta/\Delta T = -2.9$ ppb K^{-1} in a model mono benzoylurea), by the presence of sharp singlets for NH groups around 11.4 ppm and by X-ray diffraction. Benzoylurea **22** extends a distance of ~21.7 Å, which is fairly close to the length of 15-residue long α-helix (22.3 Å).

4. Folding based on solvophobic effects: pseudo helical stacked conformations of *N*,*N*′-dimethyl-*N*,*N*′-diaryl urea oligomers

The *cis*-amide preference of *N*-acyl-*N*-methylarylamine (Fig. 9a), *i.e.* the *N*-methyl amide effect, is a general structural feature that has been explored successfully for the construction of various types of foldamers with amide,[97,98] imide,[99] guanidine,[100,101] and urea backbones. Whereas *N*,*N*′-diaryl ureas essentially adopt *transoid* conformations (*trans*,*trans*, Fig. 9b),[102] *N*,*N*′-dimethyl-*N*,*N*′-diaryl ureas exhibit intrinsic preference for *cisoid* geometry (*cis*,*cis* or *E*,*E*) with aromatic groups located in a face to face arrangement (Fig. 9c).[103,104]

Taking advantage of this conformational bias, *Shudo* and coworkers have designed aromatic oligoureas of *N*,*N*′-dimethyl-*p*-phenylenediamine (**23**),[97] *N*,*N*′-dimethyl-*m*-phenylenediamine (**24**),[100] and *N*,*N*′-dimethyl-1,5-naphthalenediamine (**27**)[97] that all fold in the crystal state into ladder-type or pseudo-helical structures with almost perfect overlap of central aromatic rings (Fig. 10a–c).

Investigation by NMR spectroscopy provided some evidence that π-stacked structures persists in solution. These studies also revealed the dynamic character of *N*,*N*′-dimethyl-*N*,*N*′-diaryl oligoureas. For example, rotation around the Ar–N bond in diureas of *N*,*N*′-dimethyl-*m*-phenylenediamine (*e.g.* **25**, **26**) and

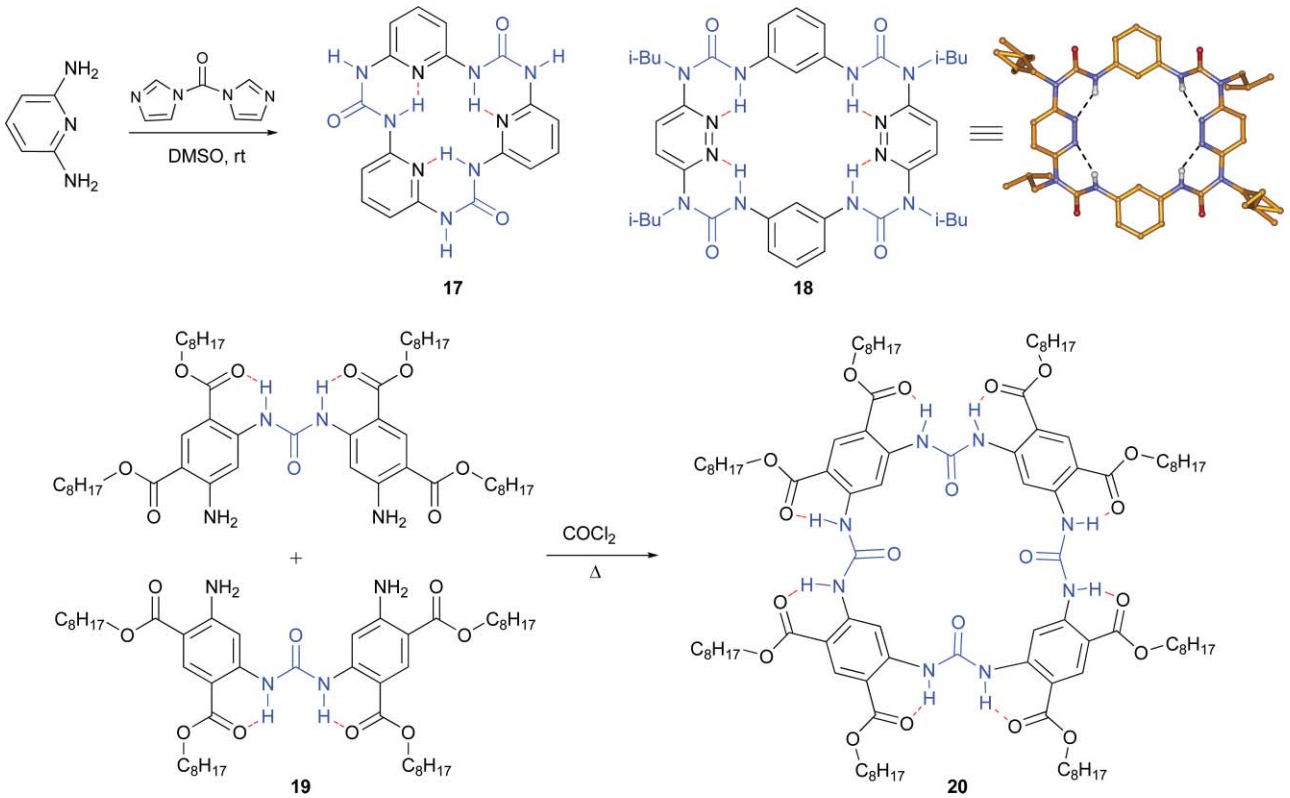

Fig. 7 Macrocyclization reactions directed by intramolecular H-bonding.

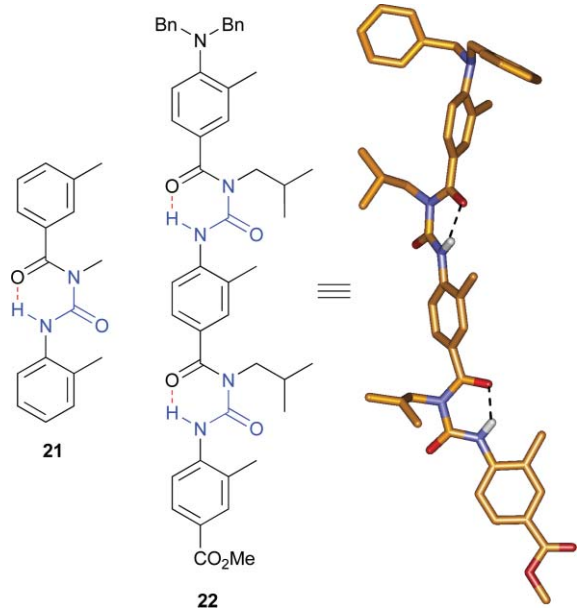

Fig. 8 Benzoylurea oligomers.

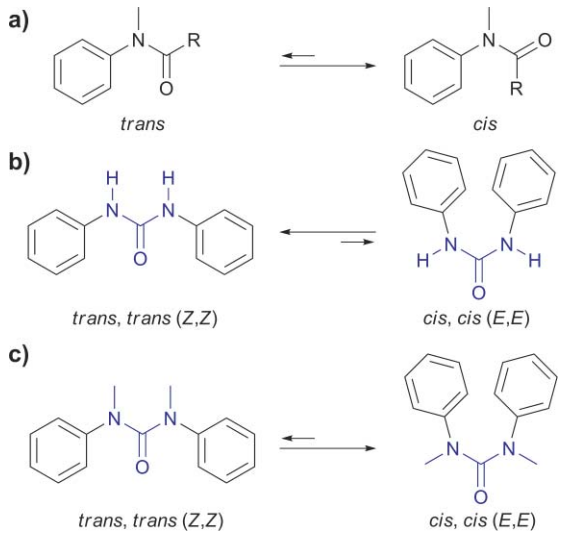

Fig. 9 *Cis-trans* isomerism and conformational preferences in (a) *N*-acyl-*N*-methylanilines; (b) *N*,*N*′-diaryl ureas and (c) *N*,*N*′-dimethyl-*N*,*N*′-diaryl ureas.

N,*N*′-dimethyl-1,5-naphthalenediamine (*e.g.* **27**, **28**) generates mixtures of three closely related *cis*,*cis* (*E*,*E*) conformers (namely *syn*,*syn*; *anti*,*anti* and *syn*,*anti*) in equilibrium, that only differ by the relative orientations of the aromatic rings (Fig. 10d and 10e). Both *syn*,*syn* and *anti*,*anti* conformers have been observed in the asymmetric unit of crystals of **28** (Fig. 10f).[105] The effects of substituting terminal benzyl rings (*meta* and *ortho* substituents) on the conformation and dynamics of oligomers of *N*,*N*′-dimethyl-*m*-phenylenediamine have been investigated by *Clayden* and coworkers.[106] In the crystal state, diureas with *ortho* (*e.g.* **25**) and *meta* (*e.g.* **26**) substituents adopt *syn*,*syn* and *anti*,*anti* conformations, respectively (Fig. 10g). In solution, the three conformers of *meta*-substituted diureas interconvert too fast to be distinguishable by NMR even at low temperature. In contrast, the NMR spectra of *ortho*-substituted diureas revealed

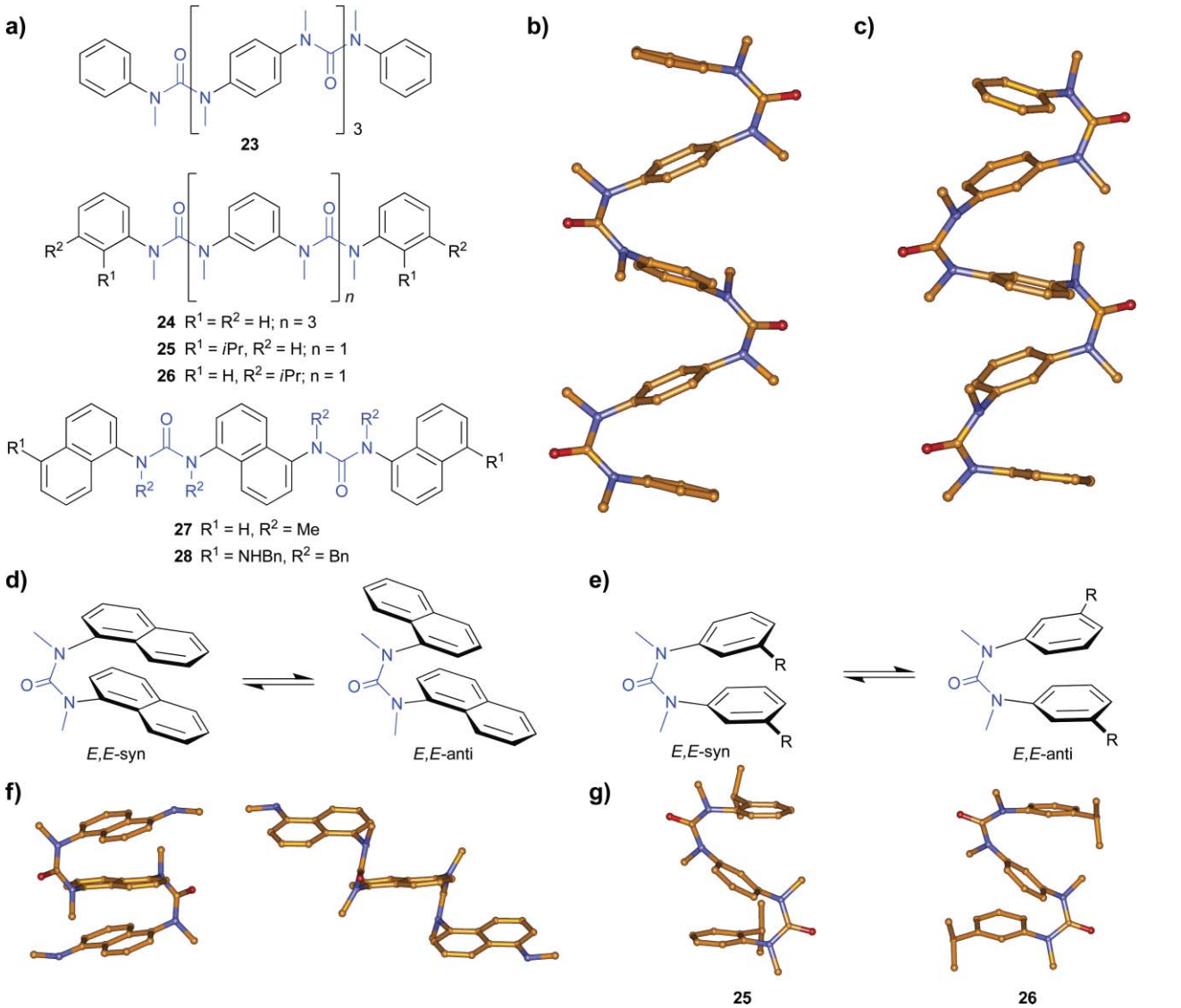

Fig. 10 *N*,*N*′-Dimethyl-*N*,*N*′-diaryl urea oligomers. (a) Structures of oligoureas of *N*,*N*′-dimethyl-*p*-phenylenediamine (**23**), *N*,*N*′-dimethyl-*m*-phenylenediamine (**24**–**26**), and *N*,*N*′-dimethyl-1,5-naphthalenediamine (**27**,**28**); (b) crystal structure of **23**; (c) crystal structure of **24**; (d) equilibrium between *cis*,*cis* conformers in ureas of (d) *N*,*N*′-dimethyl-1,5-naphthalenediamine and (e) *N*,*N*′-dimethyl-*m*-phenylenediamine; (f) crystal structures of *syn*,*syn* and *anti*,*anti* conformers in diurea **28**, aromatic rings of benzyl groups and hydrogens have been omitted for clarity; and (g) *N*,*N*′-dimethyl-*m*-phenylenediamine **25** and **26**.

two sets of peaks below −30 °C in $CDCl_3$, which coalesce at higher temperature. A barrier for interconversion of rotamers ($\Delta G^{\ddagger}$) of 59.6 ± 2.5 kJ mol^{-1} was thus estimated for **25**. Interestingly, the orientation of the Ar–N bond in model dimethyl-*N*,*N*′-diaryl ureas can been controlled with selectivities up to >95 : 5 by introducing an adjacent stereogenic center (sulfoxide or oxazolines) or through stereochemical relay,[107] by interposing a tertiary aromatic amide between the stereogenic center and the diarylurea.[108] Examination of longer *N*,*N*′-dimethyl-*N*,*N*′-diaryl urea oligomers bearing a chiral sulfinyl group at one terminus and a diastereotopic probe at the other terminus was used to study helix persistence in solution.[109] These studies suggested that the increase in chain-length gradually causes loss of helicity and that the helix breaks down beyond a critical size of 4 urea linkages. Similar conclusions were drawn from experiments aimed at inducing remote stereoselective control of nucleophilic attack on oligomers terminated by a reactive carbonyl substituent.[110]

Alternatively, by analogy to polyamides[98] and oligoimides,[99] helicity of *N*,*N*′-diaryl urea foldamers may eventually be controlled by substituting chiral side chains for methyl groups at urea nitrogen atoms. In a recent report, *Kudo et al.* introduced chiral substituents at the nitrogen atoms of the central benzene rigs of a *N*-alkylated tetra(*m*-phenylurea) structure to induce handedness in the helical structure.[111] Experimental and calculated CD and VCD spectra were used to assign the absolute configuration of the structures.

The generality of the (*E*,*E*) preference makes the *N*,*N*′-dimethyl-*N*,*N*′-diaryl urea a useful element of design for application in molecular recognition. For example, *Shudo* and coworkers have reported triureas with a central *N*′-dimethyl-*N*,*N*′-diaryl urea

and two flanking *N*,*N*′-disubstituted ureas that formed tight 1 : 1 complexes ($K_a > 5 \times 10^6$ M^{-1}) with dinucleotide analogues (*e.g.* bis(cytosyl) derivatives).[112]

5. Peptidomimetic helical foldamers based on remote H-bond interactions

The periodic connection of sequentially remote H-bond donors and acceptors is another highly effective way to promote helical folding of open-chain oligomers.[113] Aliphatic oligoamides built from enantiopure *β*- or *γ*-amino acid residues, namely *β*- and *γ*-peptides, are the quintessential helical foldamers stabilized by remote interactions.[1,4,5,12,114–116] The pattern of intrastrand H-bond interactions in helix-forming oligoamide foldamers can be further manipulated through insertion of heteroatoms in the backbone to generate non-amide linkages (*e.g.*, *N*-oxyamide,[117] hydrazide,[118] urea,[119,120]). This is an interesting opportunity for the design of new oligomers with folding propensity. Enantiopure *N*,*N*′-linked oligoureas of general formula –[NH–CH(R)–CH_2–NH–CO–]$_n$– are peptide backbone mimetics belonging to the *γ*-peptide lineage (Fig. 11). A general synthetic approach to such urea-based oligomers was described by *Burgess* and coworkers in 1995.[121] Stepwise elongation was performed on solid support using 1-substituted-2-phthalimidoethyl isocyanate **29** as building blocks. Several related and complementary approaches based on alternative monomers (*e.g.* **30–32**) have since been described by others.[122–125]

N,*N*′-Linked oligoureas are formally obtained by the substitution of NH for the $^{\alpha}CH_2$ of the amino acid constituents of *γ*-peptides. We envisioned the urea modification to be compatible with the *γ*-peptide 14-helical fold.[119,120] *γ*-Amino acid residues within the 14-helix are characterized by large *ψ* values ~140° (or –140°).[126–128] The additional nitrogen was believed to act as a rigidifying element by fixing the pseudo *ψ* angle to a value close to 170–180°. Detailed NMR studies provided compelling evidence that enantiopure *N*,*N*′-linked oligoureas adopt a well-defined and stable 2.5-helical fold, akin to the γ^4-peptide 14-helix.[119,129] The helix is right-handed with a pitch of *ca.* 5.1 Å and held by H-bonds closing both 12- and 14-membered rings (12,14-helix) (Fig. 12). The structural analogy between oligourea

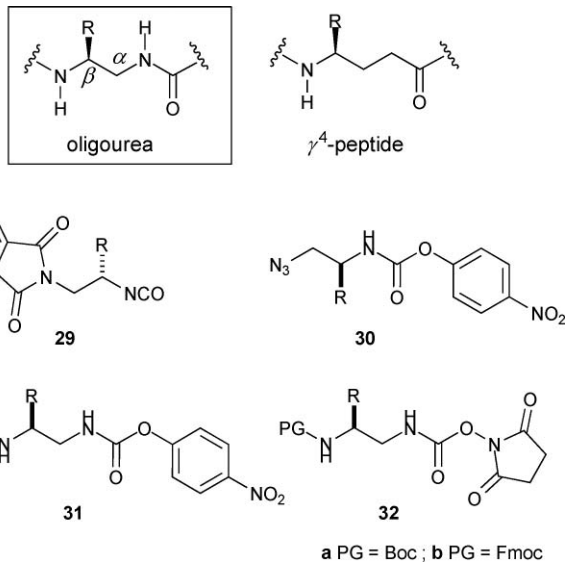

Fig. 11 Aliphatic *N*,*N*′-linked oligoureas and structures of activated building blocks **29–32**.

and the *γ*-peptide helical backbone is striking when comparing main backbone torsion angles (Fig. 13).

Furthermore, NMR at ^{13}C natural abundance was utilized recently to further improve the quality of the structure calculations.[130] Conformation-dependent vicinal couplings $^3J_{HH}$ from diastereotopic proton resonances are generally difficult if not impossible to obtain with standard NMR experiments. A CH_2-TROESY derived sequence was introduced to precisely measure the missing $^3J_{HH}$ couplings. Applied to a nonameric oligourea, this pulse scheme provided nineteen previously unobserved scalar coupling measurements. Incorporation of these couplings in the simulation annealing protocol was accompanied by a *ca.* 30% decrease of the root mean square deviation (RMSD) obtained over an ensemble of 20 structures. This approach developed for *N*,*N*′-linked oligoureas is likely to be of practical value to increase the quality of NMR-based structures when applied to other classes of peptidomimetic folding oligomers bearing backbone methylene groups (*e.g.* *β*-, *γ*- and *δ*-peptides, peptides as well as *β*- and *γ*-aminoxy acids).

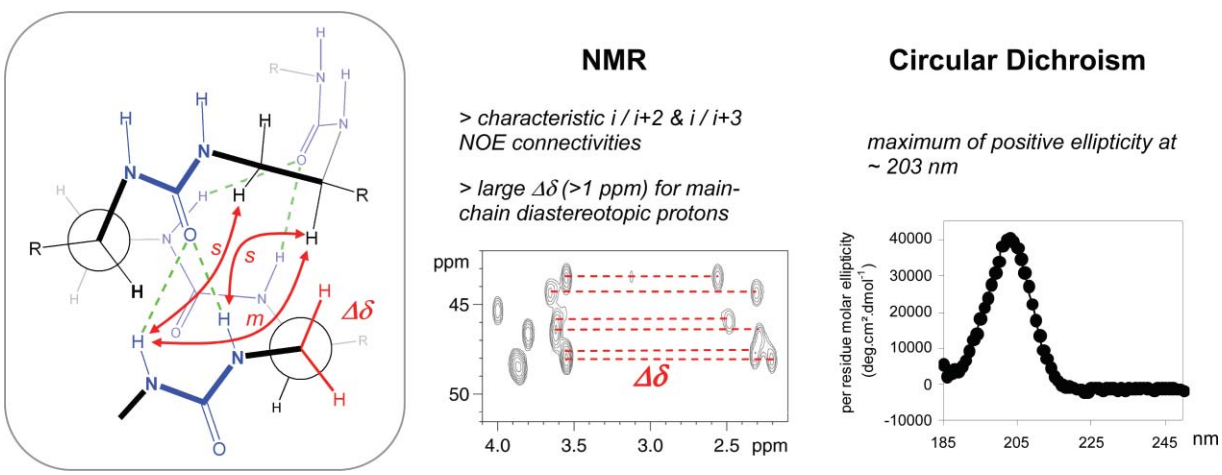

Fig. 12 Characteristic features of helical *N*,*N*′-linked oligoureas revealed by NMR spectroscopy and circular dichroism.

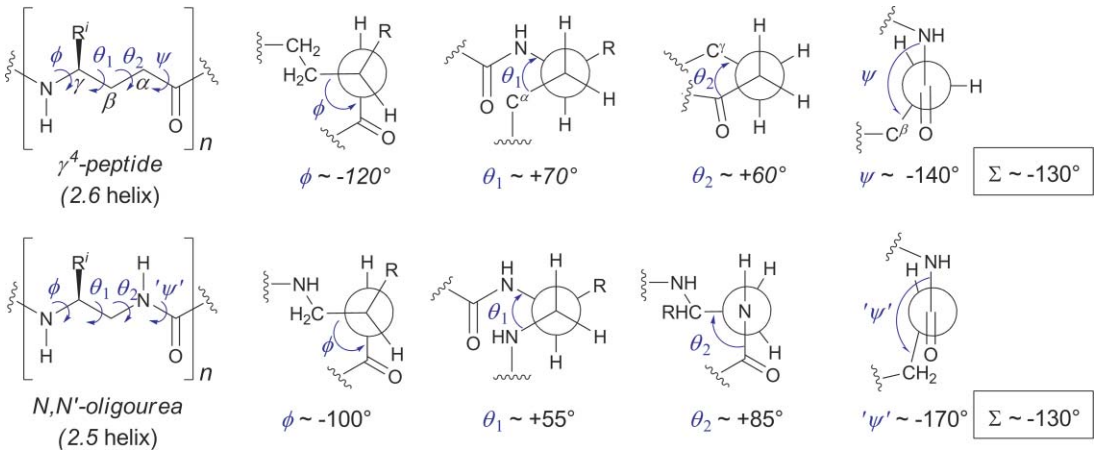

Fig. 13 Comparison of main chain dihedral angles between helical *N*,*N*′-linked oligourea and γ^4-peptide backbones.

The chemical shift difference between backbone diastereotopic CH_2 protons ($\Delta\delta_{HH}$) is a reliable and easily accessible descriptor of the conformational homogeneity of helical *N*,*N*′-linked oligoureas (Fig. 12). In some cases, $\Delta\delta_{HH}$ values as high as 1.5 ppm have been measured for central residues in helical oligoureas. Thus, $\Delta\delta_{HH}$ values have been used to compare oligoureas differing in chain length, sequence, and capping mode, as well as to assess the influence of the surrounding environment.[129] Of note is that extraction of $\Delta\delta_{HH}$ values has been achieved directly during chain elongation of oligoureas on DEUSS, a perdeuterated poly(oxyethylene)-based solid support using high-resolution magic-angle-spinning (HRMAS) NMR spectroscopy.[131] One advantage of the method is that only minute amounts of material are needed (*i.e.* typically 1–2.5 μmol of immobilized oligomer).

Circular dichroism (CD) has also proven useful to study *N*,*N*′-linked oligoureas experimentally (Fig. 12). CD spectra recorded in MeOH and trifluoroethanol display a characteristic signature with a maximum of positive ellipticity near 203 nm, whose intensity per residue increases dramatically with the chain-length.[129] Tentative assignment of this CD signal to the 2.5-helical structure was strengthened by detailed NMR experiments in MeOH. Although electronic transitions of simple ureas have been characterized in a few experimental UV spectroscopy studies,[132,133] the precise relationship between the structure and excited states of *N*,*N*′-linked oligoureas remain poorly understood. With the aim of reproducing experimental spectra, several calculations on the excited states of simple ureas using high-level quantum chemical calculations have been performed.[133–135] Recently, the exciton matrix method was applied to the calculation of the circular dichroism spectrum of an oligourea containing eight urea groups.[136] The finding that the experimental spectrum could not be reproduced without the inclusion of electronic excitations involving the side chains tends to suggest, however, that additional studies are still needed to increase our understanding of the electronic structure of oligoureas.

Overall, several trends on the conformational propensities of oligoureas can be drawn from NMR and CD studies: (1) in low polarity solvents, four to five urea units are sufficient to initiate folding of *N*,*N*′-linked oligoureas; smaller oligomers tend to favour intermolecular H-bonding and to form sheet-like arrangements. (2) By analogy to the α-helix, 2.5-helix stability can be enhanced by suppressing repulsive electrostatic interactions between the terminal charges and the helix dipole, using appropriate capping groups for the amino group of the ultimate residue. (3) Helical folding is high in both protic and polar aprotic media (MeCN > MeOH > DMSO) and maximized in a low polarity environment like pyridine. CD investigations of water soluble *N*-capped oligoureas in hepes buffer saline (HBS) pH 7.4 (see also section 7) have shown that the CD signature is retained, thus suggesting that the 2.5-helical structure, although weaker, remains significantly populated in aqueous solution.[137] Helix formation in aqueous environment is particularly relevant in the context of possible applications of oligoureas in biology (section 7).

Recently, the structures of several oligoureas ranging in size from tetramer to octamer have been characterized at atomic resolution (Fig. 14).[138] The similarity between these crystal

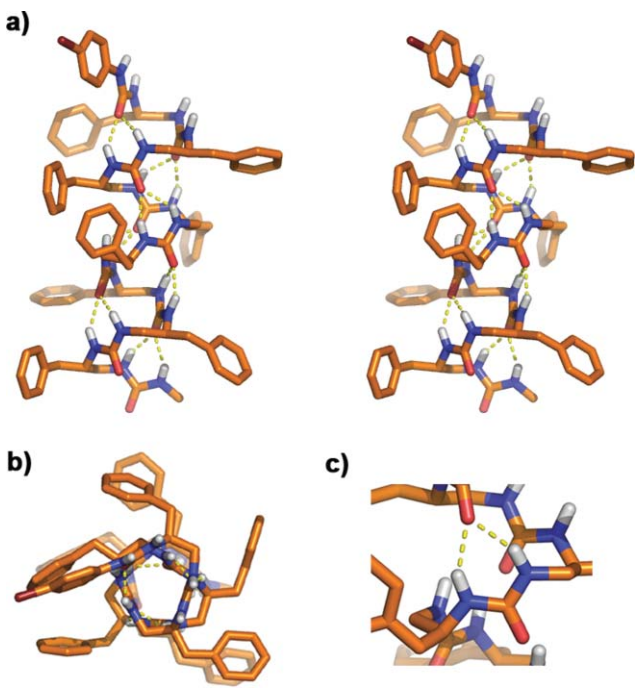

Fig. 14 Crystal structure of helical *N*,*N*′-linked oligoureas. (a) Stereoview of a nonaurea; (b) view along the helical axis; (c) detail of the three-centered H-bonding.

structures and those deduced earlier from NMR studies in solution underlines the complementarities of the two techniques to analyze urea-based foldamers.[119,120,129,130,139,140] Four acyclic residues were found to be sufficient to drive complete helix formation in the solid state with all complementary H-bonding sites being satisfied. Oligourea helices possess four free donor and two acceptor groups capable of hydrogen bonding at both ends of the molecule. Different modes of helix aggregation mediated by head-to-tail H-bonding (columns, wavy lines, supramolecular helices) have been observed in the solid state.[138] Controlling the formation of these different topologies may prove useful for the design of bioinspired helix-based fibrous materials akin to peptide-based fibres.[17,141,142]

6. Molecular scaffolds for mimicking protein β-turns and sheets

This area of research was pioneered by *Nowick* and coworkers in the early 1990s.[143] These authors introduced acyclic diureas and higher oligoureas **33** derived from 1,2-ethanediamine and from 1,3-propanediamine as molecular scaffolds to induce artificial parallel β-sheet formation in attached α-peptide strands (Fig. 15a). Spectroscopic investigation in nonpolar solvents and X-ray diffraction analysis have shown that these scaffolds adopt well-defined hydrogen-bonded conformations in which the urea groups formed 9- and 10-membered rings depending on the length of the spacer (for $n = 2$ and 3, respectively). Comparison of 1,2-diaminoethane and 1,3-diaminopropane diureas revealed that two-carbon spacers were more effective than three-carbon spacers in stabilizing H-bonded ring structures. In these systems, conformational control is provided in part by the phenyl group localized at the bottom of the scaffold. Similar to the oligoureas of *N*,*N*-dimethyl-*m*-phenylenediamines discussed in section 4, the orientation of the phenyl group in *N*-phenyl-*N*-alkyl ureas is preferentially *trans* to the carbonyl group. This conformational bias preorganizes the 'lower' carbonyl group for intramolecular H-bonding with the upper urea nitrogen. Capping and further stabilization of the scaffold is provided by substituting the top backbone urea nitrogen with a cyanoethyl group. ^{1}H NMR analysis of diurea **34** with two dipeptide strands appended (Fig. 15b), confirmed that β-sheetlike structure is indeed populated in chloroform, albeit in fast equilibrium with some other conformers (*e.g.* unfolded, turns). By varying the sequences of peptide appendages in a library format, it has been possible to determine the propensities of amino acids to form parallel β-sheets: Leu, Val > Ala > Gly.

Further rigidification of artificial β-sheets was achieved by substituting a β-strand mimic of appropriate length and H-bonding functionalities for the upper peptide strands (Fig. 15c). In chloroform solution, compound **35**, a 1,2-diaminoethane diurea turn unit holding a 5-amino-2-methoxybenzamide β-strand mimic is tightly folded. Folding is partially retained in competitive

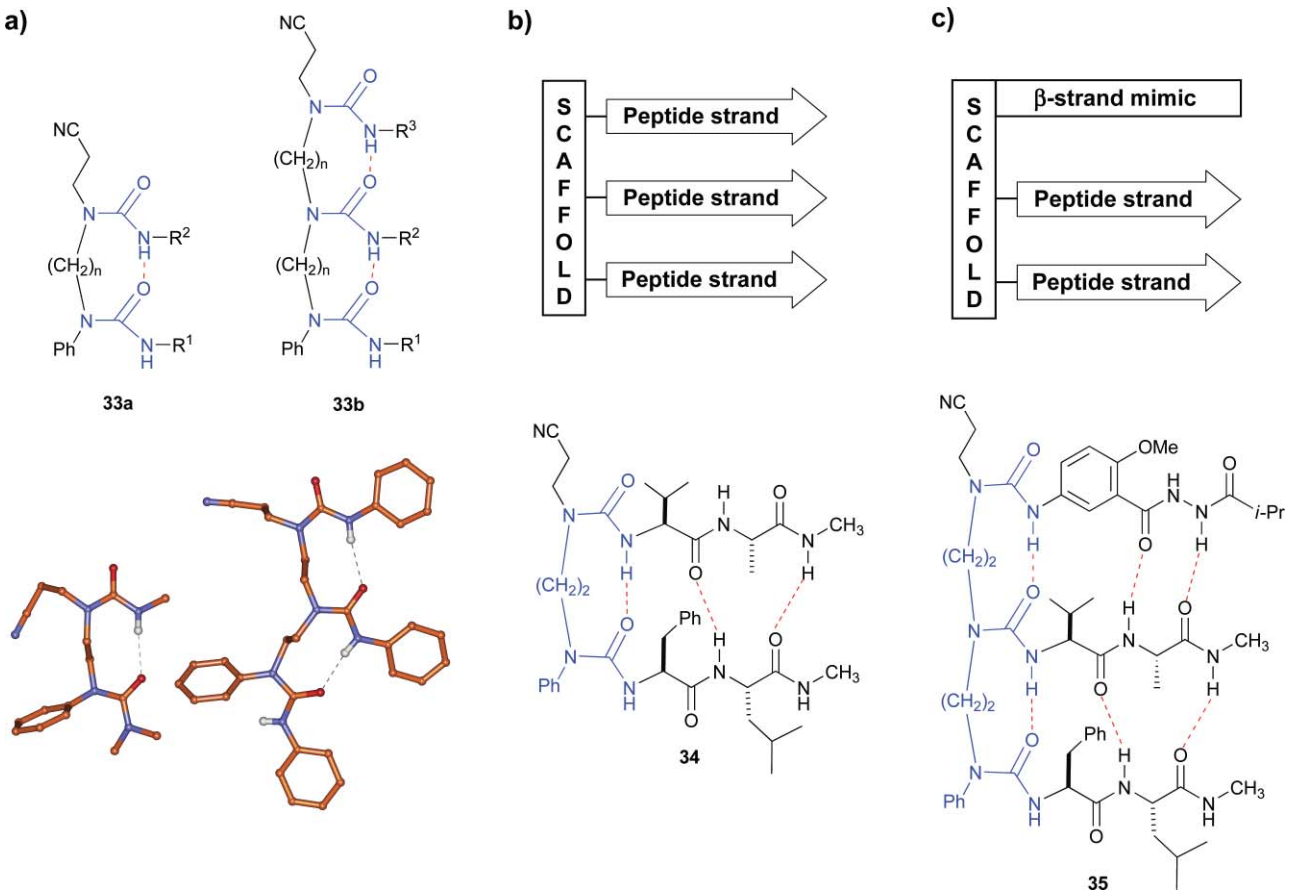

Fig. 15 *N*,*N*-Linked oligoureas as templates for the formation of parallel β-sheets. (a) Crystal structures of diurea and triurea-based templates **33**; (b) parallel β-sheets by attachment of peptide strands to oligourea templates; (c) additional rigidification of the template by introduction of a 5-amino-2-methoxybenzamide β-strand mimic.

solvents such as methanol and 50% aqueous methanol but is abolished in dimethyl sulfoxide. This concept combining an oligourea scaffold and a β-strand mimic was further improved to prepare larger artificial β-sheets containing more and longer peptide strands.

In a related approach, the propensity of 1,2-diaminoethane diureas to form the H-bonded folded structure was exploited to create peptidomimetic hairpin turns (Fig. 16). The peptide/oligourea/azapeptide hybrid **36** was shown to populate the hairpin conformation to a large extent in chloroform solution.[144] More recently, new turn scaffolds whereby two (thio)urea strands are connected to an appropriate rigid diamine linker (*i.e.* D-Pro-*cis*(1*S*,2*R*)-cH*x*DA in **37** and a combination between a β-amino alcohol and an aromatic amine in **38**) have been reported.[145,146] NMR and X-ray diffraction studies confirmed that **37** and **38** adopt a *β*-turn type conformation stabilized by intramolecular H-bonding in both nonpolar solvent and crystalline form.

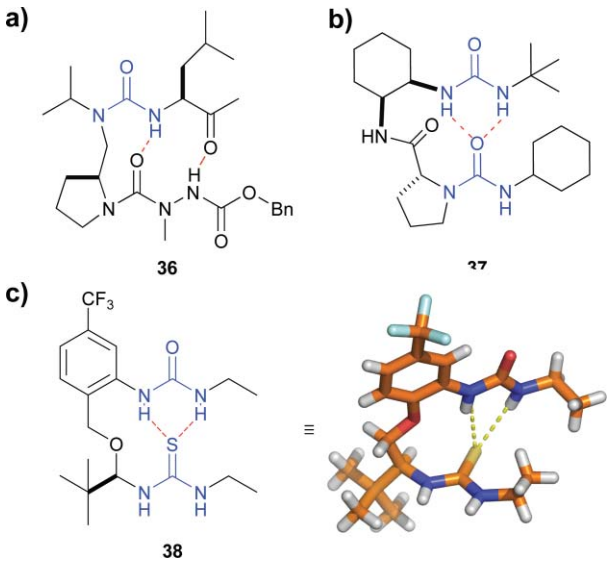

Fig. 16 (Thio)urea-based *β*-turn mimics **36–38**.

7. Towards folded oligoureas with function

7.1. Application in catalysis

The possibility to use double H-bonding with disubstituted (thio)ureas as an activation mechanism in catalysis was first recognized by *Curran* and *Kuo* in 1994.[147] This early work was inspired in part by a report by *Etter* showing that disubsituted ureas with electron-withdrawing groups readily formed co-crystals with a variety of proton acceptors including carbonyl groups.[31,32] A major contribution to the field was made a few years later by the group of Jacobsen who found that highly enantioselective reactions could be promoted by chiral (thio)urea derivatives.[148] Since then, the general utility of monofunctional and bifunctional ureas and thioureas as acid catalysts has been intensively explored and a number of excellent reviews have been published.[36,39–41,149-151]

Recently, *Smith* and coworkers have proposed an interesting extension of the concept by integrating positive cooperativity through folding to enhance catalyst efficiency.[146] Preorganizing the catalyst through H-bonding is believed to minimize the entropic cost of transition state (TS) binding. It is well known from the early work of *Miller* and others that folded peptides can serve as efficient catalysts for a range of synthetic reactions.[152,153] By using an original turn mimetic structure that populates a well defined hairpin conformation (*e.g.* **38**, *vide supra*), Smith's group generated conformationally defined but still flexible thiourea catalysts (*e.g.* **39**) for asymmetric synthesis (Fig. 17). Although some bis-thiourea catalysts have been disclosed earlier,[154–156] they did not involve intramolecular cooperative H-bonding. The hairpin type bis(thio)urea **39b** at a loading of 1 mol% catalyzed the *Mannich* reaction between *N*-Boc benzaldimines and silyl ketene acetal with high yield (74–96%) and excellent enantioselectivity (94 to >99%). Although asymmetric induction was not considerably improved over **40b** (a control catalyst lacking the intramolecular H-bond donor group), competition experiments at 1 mol% loading suggested dramatic rate enhancement for **39b**. Evidence for cooperative ligand binding was further supported by anion binding experiments which showed increased chloride anion binding capacity for **39a** over **40a** by two orders of magnitude.

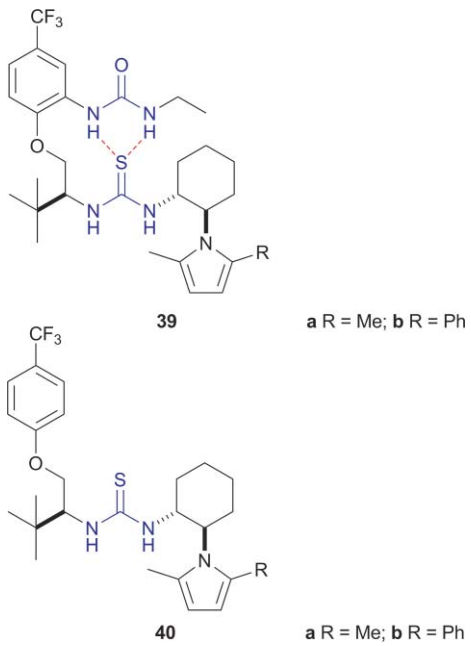

Fig. 17 Conformationally defined thiourea catalysts based on turn mimic **38**.

7.2. Biological and biomedical applications

The possibility to mimic bioactive peptides with unnatural oligomers containing a urea backbone has been addressed by several research groups. Oligoureas have been evaluated as inhibitors of protein–protein[157] interactions, protein–RNA interaction, as analogues of neuropeptides and for their capacity to disrupt bacterial membranes. Although most investigations were concerned with aliphatic *N*,*N*′-linked oligoureas described in section 5, aromatic oligourea backbones have also recently been investigated (*vide infra*). Because conformational preferences of enantiopure aliphatic oligoureas were virtually unknown before 2002 (see section 5), early studies mainly focused on systematic substitutions of amide bonds by urea fragments in

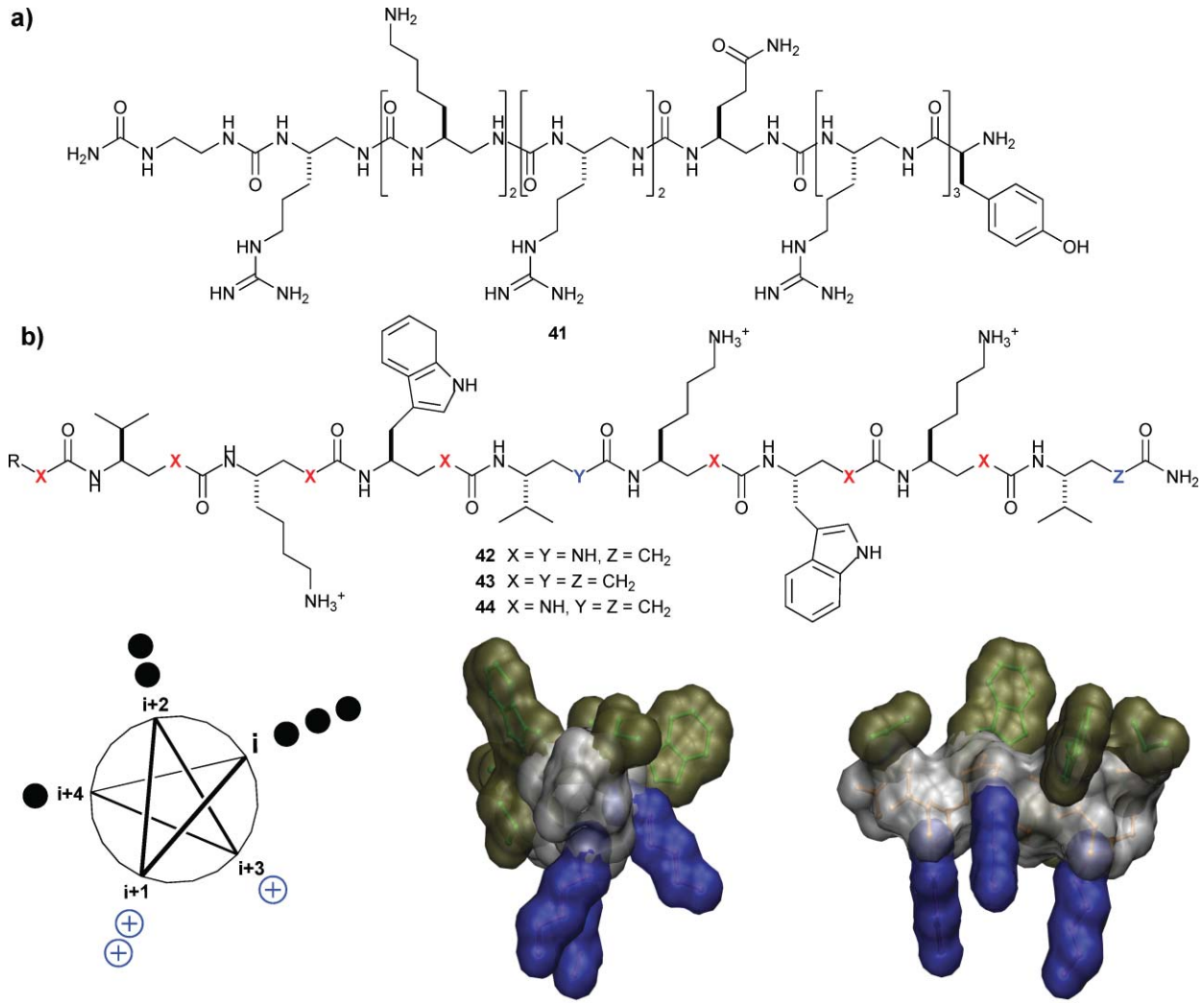

Fig. 18 Bioactive *N*,*N*′-linked aliphatic oligoureas. (a) Oligourea analogue of the RNA binding domain of the human immunodeficiency virus type 1 (HIV-1) trans-activator of transcription (Tat) protein; (b) sequences of oligourea, γ-peptide and oligo(urea–amide) hybrid mimicking host defense peptides (top). Helical wheel and molecular model of the antimicrobial oligourea **42** showing the amphipathic character of the 2.5 helix. Cationic side chains ("+") are segregated on two-fifths of the helix circumference. Remaining residues have hydrophobic aliphatic and aromatic side chains (black circles).

biologically relevant peptide sequences (*e.g.* Leu-enkephalin,[157,158] neurotensin[159]). In the first report, a 160-member library of Leu-enkephalin (Tyr-Gly-Gly-Phe-Leu) analogue containing one to five urea linkages was screened for recognition by a monoclonal antibody selective for the enkephalin sequence.[157] The backbone of urea-containing oligomers is elongated compared to peptides and, not surprisingly, the antibody displayed affinity only for a limited subset of oligo(amide–urea) hybrids bearing one or two urea bonds. Interesting results were obtained by *Rana* and colleagues with a 10-mer oligourea (**41**) designed to mimic a short arginine-rich peptide H-Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-OH encompassing the RNA binding domain (residues 48–57) of the human immunodeficiency virus type 1 (HIV-1) trans-activator of transcription (Tat) protein (Fig. 18a).[160] The interaction between Tat and the transactivation responsive (TAR) RNA promotes efficient transcription of the full-length HIV genome.[161,162] This RNA–protein complex was proposed as a potential target for therapeutic intervention.[163,164] Oligourea **41** was found to bind TAR RNA with a 7-fold higher affinity than the Tat peptide. Moreover, it was reported to be resistant to protease degradation (proteinase K) *in vitro* and to inhibit transcriptional activation by Tat protein in human cells with an IC_{50} of 0.5 μM.[165]

The finding that enantiopure *N*,*N*′-linked oligoureas adopt a stable and regular 2.5-helical fold (see section 5) suggested to us that they could serve to mimic the structure and function of α-helices. We have been investigating membrane disruption properties and the antimicrobial activity of oligoureas designed to mimic globally amphiphilic cationic α-helical host–defense peptides. Compared to conventional antibiotics, they possess a low potential for the induction of bacterial resistance, which makes them attractive candidates for the development of antimicrobial agents.[166–168] Antimicrobial peptides that adopt cationic amphipathic structures (*e.g.* helices) are believed to cause cell death by a two-step mechanism involving interaction with the lipid component of the membrane followed by membrane permeabilization.[169] In the case of helical structures, the lytic

activity and membrane selectivity are strikingly dependent on parameters such as helix stability, amphiphilicity (hydrophobic moment), hydrophobicity, relative width of the hydrophilic and hydrophobic faces of the helix, as well as net charge.[170,171] However, structure–activity relationship studies remain challenging because sequence modifications of α-peptides generally affect several parameters at the same time. Over the last decade, a number of facially amphiphilic foldamers (mainly oligoamides) have been reported to be able to mimic the structure and function of such antimicrobial peptides.[172–178] We found that designed amphiphilic oligoureas as short as 8 residues (exemplified by **42**, Fig. 18b) were as active as mellitin (a cytotoxic and antibacterial peptide from bee venom) against gram-negative and gram-positive bacteria (including methicillin-resistant *Staphylococcus aureus* (MRSA)), and yet displayed selectivity for prokaryotic *versus* mammalian red blood cell membrane.[137] Oligomer **42** was shown to display minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) values in the same value range, and to be equally potent on methicillin-sensitive and methicillin-resistant *S. aureus* strains.[179] These results suggest that antibacterial oligoureas may be acting by a mechanism involving membrane permeation. Circular dichroism studies in hepes buffer saline (HBS) and in the presence of negatively charged phospholipid vesicles as model membranes are consistent with increased helix population in a lipid environment. Overall, the strong helix folding propensity, together with the diversity of available side chain appendages and resistance to protease degradation,[137] makes the oligourea backbone a promising candidate for biomedical applications.

As detailed in section 5, oligourea and γ^4-peptide backbones are quasi-isostructural. How the two systems compare in biomolecular recognition events is a question that we recently attempted to address.[179] The γ^4-peptide **43** analogue of oligourea **42** was prepared and evaluated for antimicrobial activity. The results showed a large difference between the two backbones in their antibacterial profile, with the γ-peptide being poorly active (MIC > 256 μg mL^{-1}) against all bacterial strains tested. To question whether the functional difference between oligourea and oligoamide backbones results from differential membrane disruption activities, we have undertaken detailed physicochemical investigations using negatively charged phospholipid large unilamellar vesicles (LUV). Our results show that oligourea **42** has a higher affinity for the model membrane and is more potent in inducing efflux of carboxyfluorescein from LUV than cognate γ-peptide **43**.

Interestingly, combining the two sets of monomers can be used to create heterogeneous amide–urea backbones with new properties. The potential of mixing multiple types of building block to create backbone heterogeneity and structural diversity is enormous. The concept has been successfully applied by several research groups to oligoamide foldamers (*e.g.* α/β peptides and β/γ peptides).[12] Preliminary investigation of mixed oligourea–γ^4-peptides analogues of **42** suggests that γ^4-amino acid residues have a tendency to destabilize the 2.5-helical structure of oligoureas and can be used to selectively modulate the conformational flexibility of the backbone. The incorporation of a limited number of γ^4-amino acid residues in the 2.5 helical backbone is tolerated. This strategy yielded hybrid urea–amide foldamers (*e.g.* **44**) with improved selectivity towards mammalian cells at no cost for antibacterial activity.[179]

Non-natural oligomers designed to mimic the structure and function of α-helices need not necessarily be helical. An alternative strategy developed by *Hamilton* and others is to use rigid scaffolds whose appended side chains can mimic peripheral functionalities on the helical surface.[180,181] For example, by adopting a staggered conformation, tris-*ortho*-substituted terphenyl and related terpyridine derivatives can mimic the *i*, *i* + 4, and *i* + 7 residues of the α-helix. To alleviate the synthetic requirements and increase the solubility of such helix mimetics, Hamilton recently introduced benzoyl urea oligomers (see also section 3) as analogues of oligophenylene structures for disrupting α-helix-protein interactions.[182] The striking similarity between the two backbones is shown in Fig. 19 (compounds **45** and **46**). Benzoylurea **45** was designed to mimic the α-helical BH3 domain of Bak, a proapoptotic Bcl-2 family member that binds Bcl-x_L: an antiapoptotic family member. Activation of the Bcl-2-regulated apoptosis pathway by BH3 mimetics represents a promising approach for induction of apoptosis in tumor cells.[183] Structures of α-helical BH3 peptides in complex with Bcl-x_L showed that several conserved hydrophobic residues along one edge of the α-helix at position *i*, *i*+4, *i*+7 make extensive contacts with the hydrophobic cleft on the surface of Bcl-x_L.[184] Alkyl and aryl substituents at the three *ortho*-positions of **45** were intended to mimic these key hydrophobic substituents. Carboxylic acid moieties on both ends

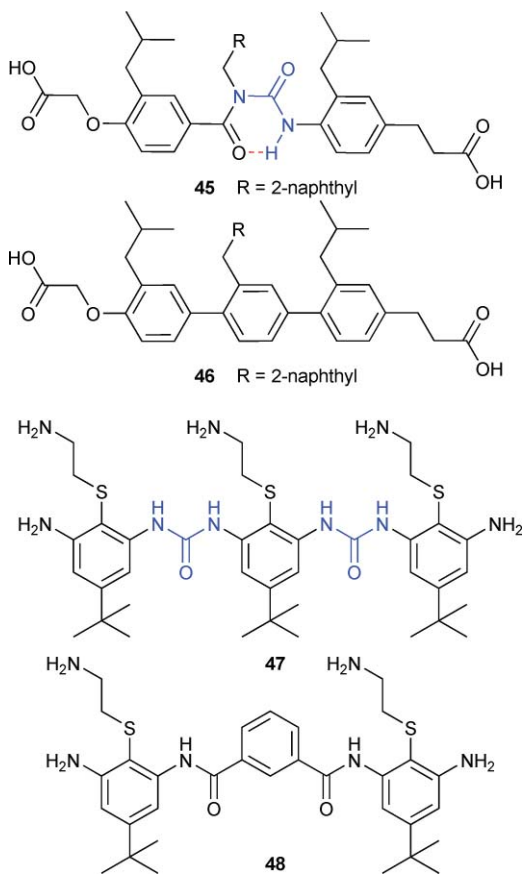

Fig. 19 Bioactive aromatic oligoureas (a) Mimic the α-helical BH3 domain of Bak. Benzoylureas such as **45** (see also section 3) were designed as simplified analogues oligophenylene compounds; (b) antimicrobial urea-linked aryl oligomers. Facially amphiphilic oligoureas exemplified by **47** are direct analogues of antimicrobial arylamides (*e.g.* **48**).

of **45** were introduced to mimic the Bak aspartate side chain at position 83 which ion pairs with a lysine residue of Bcl-x_L. In a fluorescence polarization competition assay, benzoylurea **45** was found to displace a fluorescently labelled Bak BH3 peptide from Bcl-xL with an inhibitory constant (K_i) of 2.4 μM. It is, however, less potent than the corresponding terphenyl derivative **46** which displayed a K_i of 114 nM.[185]

In another interesting example, *Tew* and collaborators reported facially amphiphilic urea-linked aryl oligomers (*e.g.* **47**) with potent antibacterial activities (Fig. 19).[186] Weak hydrogen bonding of thioether groups to urea protons allows conformational control; amine and *tert*-butyl groups being sequestrated on opposite sides of the backbone. Although urea oligomers were found to compare favourably in term of MICs with related antimicrobial amphiphilic arylamides (*e.g.* **48**),[174] they exhibit significant haemolytic activity with HC_{50} near their MIC.

8: Outlook and future directions

Aromatic and aliphatic urea-based oligomers with the propensity for folding and/or self-assembly have emerged in the literature over the last few years. Strategies developed to impose conformational restriction and to promote folding for oligoamides largely apply to oligoureas—*i.e.*: local conformational control, solvophobic interactions or long range H-bond interactions. A variety of *secondary structural motifs* formed by urea strands, such as duplexes, helices, sheets and turn segments, have been described at high resolution. Of note is that oligomers with heterogeneous amide–urea backbones are also emerging as important structural motifs, which is allowing further expansion of accessible conformational space. One can speculate that more complex architectures (*i.e.* supersecondary, tertiary and quaternary structural elements) and nanostructures generated through multiple combination of monomeric units and through the preparation of longer chain oligomers are now within reach in the oligourea family. Concurrently, macrocyclic versions of homo- or hetero-oligomers have been investigated in detail. They display a high propensity to form H-bonded columnar and tubular aggregates reminiscent of nanotubes formed by cyclo-L,D-peptides. Importantly, structural knowledge is providing a basis for *function*. Current applications range from anion recognition and transport, to host–guest chemistry, to interactions with biomacromolecules, and to organocatalysis. Though significant advances have already been made towards the design of folded and/or self-assembled oligourea-based systems with functional properties, more exiting developments and applications are yet to come.

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