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Hydrogen bonding in noncovalent synthesis: selectivity and the directed organization of molecular strands

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1. Introduction

A major theme in the development of the chemical sciences resides in improving the capability to negotiate issues of selectivity in the organization of matter across length scales.[1] In this progression from condensed matter to nanostructured material, molecular self-assembly has emerged as a powerful technology for synthesis in the nanoscopic size regime.[2] In particular, H-bond directed organization of molecular precursors has garnered much success.[2a,3] Efforts toward nanostructured materials are, in part, fueled by the observation that the physical properties of both inorganic and organic materials may depend significantly upon the size and relative orientation of the constituents.[4] For example, quantum confinement effects displayed by nanoparticles allow band-gap to be tuned as a function of particle size.[5] Precise inter-arene register is required for optimum performance of organic conductors formed from TTF/TCNQ charge transfer stacks.[6] In nature, nanoscopic objects are typically assembled from macromolecular precursors. Biomacromolecules, such as proteins and DNA, not only exhibit high levels of structural homogeneity, they possess exceptional mechanical properties (e.g. arachnid silk fibers[7,8]), impressive catalytic functions (e.g. cytochrome-p450[9]), and information storage capabilities (e.g. DNA[10]). By developing technologies for the induction of predefined secondary structural motifs via self-assembly of oligomeric and polymeric precursors, the first steps are taken toward the definition of a platform for the de novo design of abiotic polymer-based devices of nanometric dimensions, which, upon sufficient development, may embody capabilities beyond those displayed by their natural counterparts.

Herein, we review the utilization of H-bond interactions toward the directed organization of abiotic oligomers. An introductory discussion on issues of selectivity in H-bond mediated synthesis also serves to provide general background on the use of H-bonds in self-assembly. This account is not exhaustive, but is intended to highlight some of the major advances in this area of research with special

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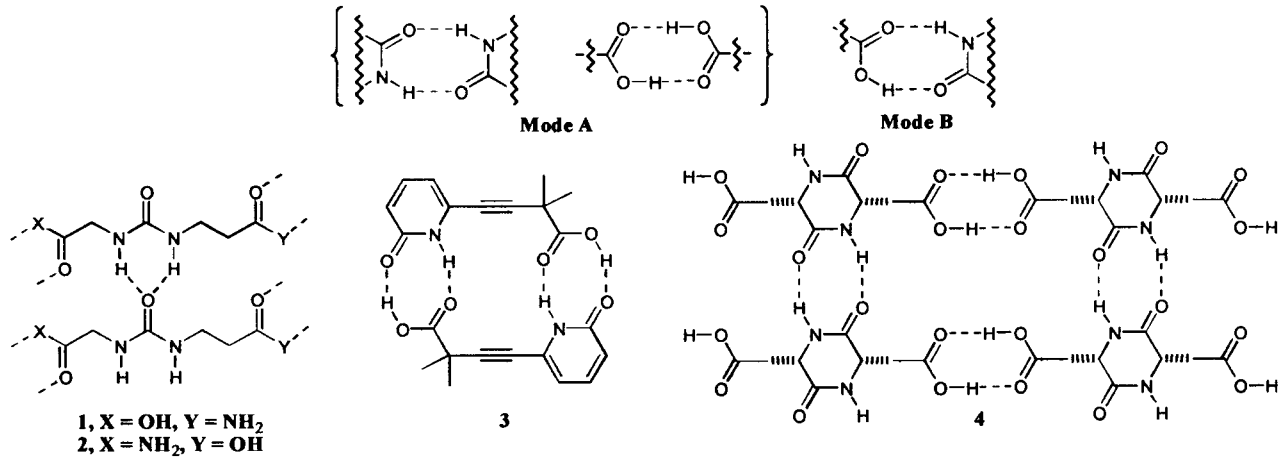


Figure 1. Chemoselectivity issues involving acid-amide association: homo- vs heteromeric aggregation.

attention given to representative design strategies. The growing body of literature pertaining to the organization of molecular strands through the utilization of metal-ligand coordination,[11] π-stacking/solvophobic interactions,[12,13] ionic interactions[14] and nonbonded interactions[15] will not be covered.

2. Selectivity in noncovalent synthesis using H-bonds

To extend synthetic technology to the nanoscopic size regime via self-assembly, chemists are challenged to define and address issues of selectivity in noncovalent synthesis. Covalent bond formations are characterized in terms of chemo-, regio-, stereo- and enantioselectivity.[16] A unified perspective on synthetic technology would classify the formation of H-bonds and covalent bonds in a mutually consistent manner. The importance of defining guiding principles for the de novo design and retrosynthesis of noncovalent ensembles stems from the increasingly significant role of such architectures in the design of supramolecular materials.[1c,4,17]

Perhaps the most significant difference between covalent and noncovalent interactions lies in bond strength. The impact of low binding energies upon selectivity in H-bonded systems is significant. Generally, under ambient conditions H-bonded ensembles are kinetically labile. Reversibility precludes selectivities associated with kinetic control, unless the noncovalent interaction is coupled to an irreversible event (e.g. a kinetic template effect[18]). Under thermodynamic control, the energy hypersurface representing all possible assembly manifolds may be sampled over the course of time and specific modes of assembly favored on the basis of their relative thermodynamic stabilities. A corollary to the absence of kinetic control is spontaneous error correction and self-healing processes. These phenomena arise from the capacity of kinetically labile systems to reestablish equilibrium once perturbed. The challenge of directing the selectivity of noncovalent synthetic operations thus resides in the engineering of an energetic bias of sufficient magnitude that discrimination between alternate modes of assembly may be achieved (ca. 4 kcal/mol for >99.9% homogeneity). That the energy differences required for selection between competitive assembly manifolds is generally on the same order of magnitude as the very strength of the binding interactions in play makes this a nontrivial task. Issues of selectivity as applied to noncovalent systems are illustrated below.

2.1. Chemoselectivity

The ability to act upon a given functional group in the presence of like or unlike functionality defines chemoselectivity. For H-bond mediated synthesis, chemoselectivity refers to the specificity of functional group aggregation. For example, both carboxylic acids and amides embody self-complementary recognition groups defined by H-bond donor–acceptor pairs. In molecules that incorporate these two functional groups, homomeric (mode A) and heteromeric (mode B) modes of assembly are possible (Fig. 1). Selection of homomeric vs heteromeric assembly modes is nontrivial as the strength of the H-bond interactions[19] are themselves on the same order of magnitude as the energy differences required for discrimination between alternate modes of assembly. Furthermore, analysis in the solid state is complicated by crystal packing forces, which are comparable in energy to H-bonds.[20] Consequently, modes of aggregation in the solid state may not correspond to those observed in solution. For acid–amide complexation, some studies suggest the heteromeric mode of assembly is energetically more favorable.[21] However, the balance is delicate. For example, the nearly identical monoacid monoamides **1** and **2** exhibit heteromeric and homomeric modes of assembly, respectively.[22] While **3** aggregates heteromerically,[23] the diketopiperazine **4** adopts a homomeric mode of assembly.[24] The structural assignments of complexes **1**–**4** have been established via X-ray diffraction of single crystals (Fig. 1).

Given that H-bonds may be viewed as arrested intermediates in deprotonation events, there is a significant acid-base component to their behavior.[3i,25] It is believed that optimum H-bond strength is achieved when the pK_a of the H-bond donor and the conjugate acid of the acceptor are matched.[26] With this being the case, one strategy for directing the chemoselectivity of aggregation involves modulation of the acid-base characteristics of the H-bond

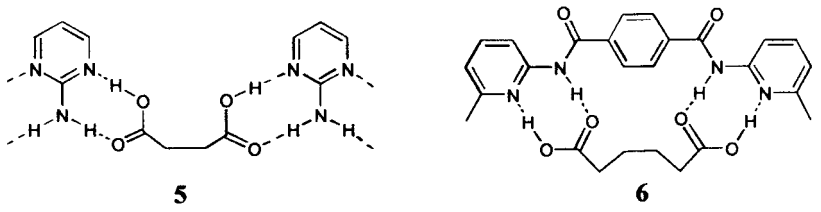
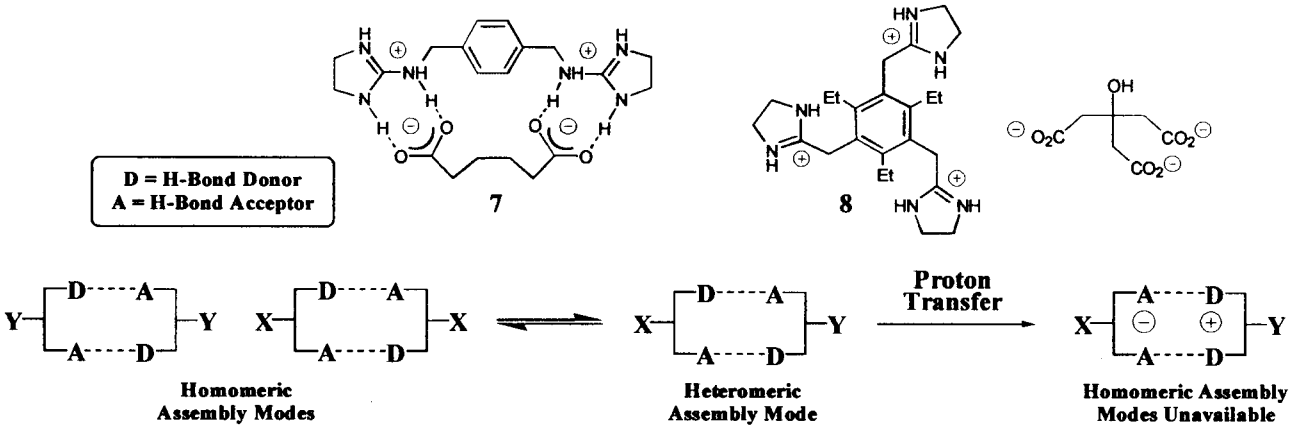


Figure 2. Chemoselective formation of heteromeric aggregates directed by pK_a matching.



Scheme 1. The impact of proton transfer upon chemoselectivity.

donor–acceptor pairs. The pK_a of the conjugate acid of 2-aminopyrimidine is ca. 3.5, which nearly matches that of a carboxylic acid, pK_a=4.5. As evidenced by the formation of the crystalline complex **5** and related cocrystals, association of 2-aminopyrimidines and carboxylic acids is highly chemoselective for heteromeric assembly.[27] Similarly, 2-aminopyridines exhibit a strong preference for heteromeric association with carboxylic acids, as revealed in the solid-state structure of **6** and related cocrystals (Fig. 2).[28] The successful design of molecular receptors[29] and self-assembled capsules[30] has been predicated on the chemoselectivity of carboxylic acid–aminopyrimidine and carboxylic acid–aminopyridine association.

Complete proton transfer doubly impacts chemoselectivity by introducing charge–pairing interactions[31,32] and inverting the arrangement of one H-bond donor–acceptor pair. Upon proton transfer, complementarity amongst H-bond donors and acceptors can only be achieved upon heteromeric aggregation. Binding is robust for systems integrating such ionic H-bonds. Dissociation of the

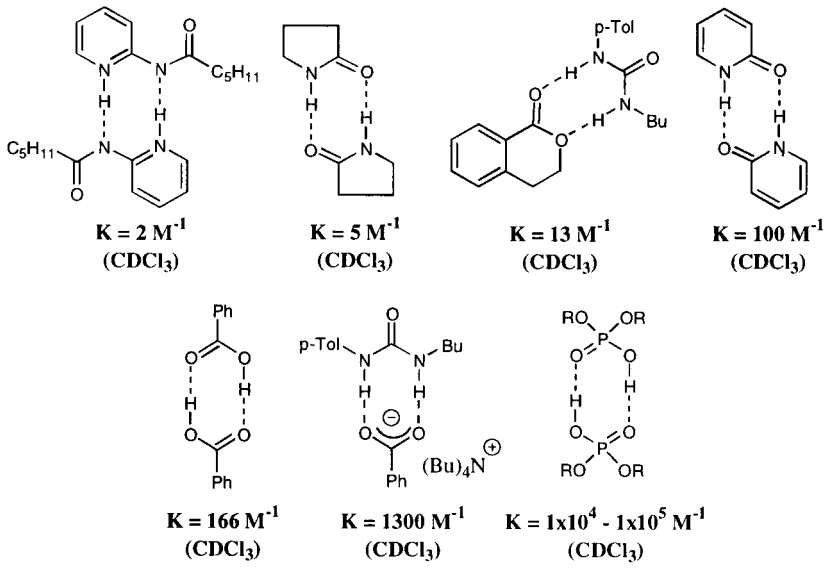
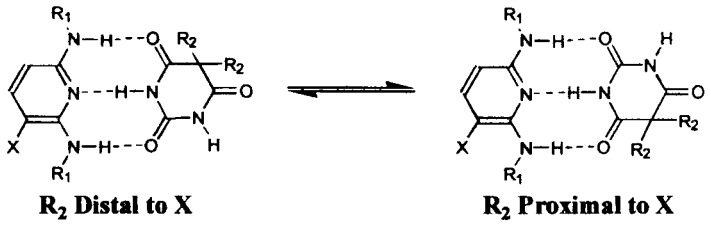


Figure 3. Association constants for homo- and heteromeric complexes arising from ditopic H-bond interactions.



Scheme 2. Regioisomeric association of unsymmetrical DAD–ADA H-bond arrays.

guanidinium–carboxylate receptor–substrate complex **7** cannot be observed by ^{1}H NMR upon dilution in neat DMSO.[33] Binding through the cooperative action of three amidinium residues, as in citrate receptor **8**, is sufficiently high to permit complexation in aqueous media.[34] The structural assignment of aggregates **7** and **8** has been established by X-ray diffraction of single crystals (Scheme 1).

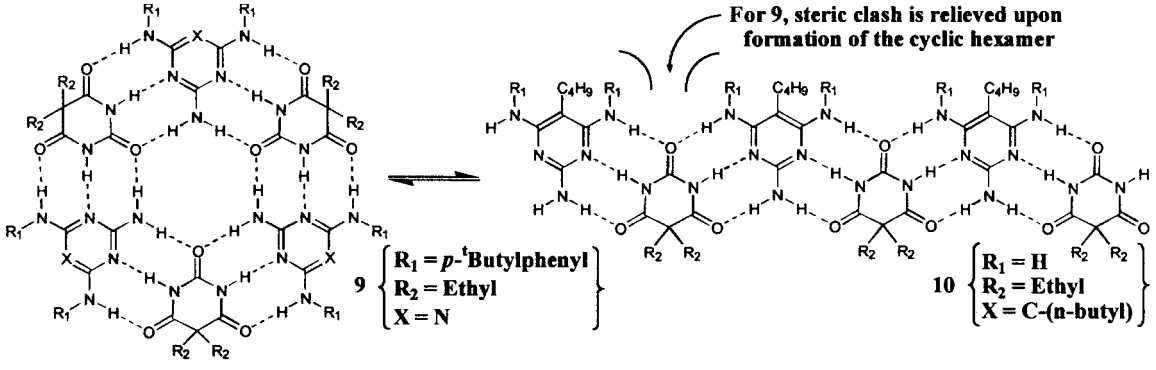
Association constants of some representative ditopic H-bonded complexes are indicated below (Fig. 3).[35] The considerable range of values (ca. 10^1–10^5 M^{-1}) is noteworthy and may be attributed primarily to pK_a matching effects and secondary electrostatic interactions (vide supra).

2.2. Regioselectivity

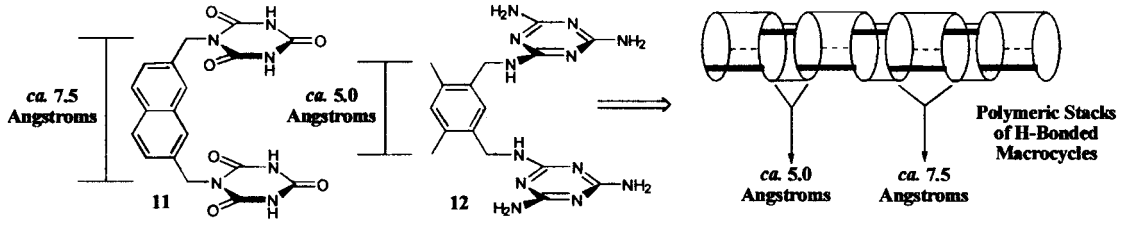
The ability to control the relative orientation of two or more reacting partners defines regioselectivity. For noncovalent binding events, the regioselective association of molecular components can result in the formation of alternative superstructures. For example, unsymmetrical molecules manifesting DAD–ADA H-bond donor–acceptor arrays may, in principle, yield two regioisomeric ensembles (Scheme 2).

Regioselectivity can be induced under thermodynamic control via steric direction or preorganization of the molecular components using covalent scaffolds. This amounts to the incorporation of structural features that become sterically repulsive upon formation of objects derived from undesired regioisomeric assembly manifolds. For the association of an *N*-substituted melamine (or triaminopyrimidine) with barbituric acid (or cyanuric acid), two limiting arrangements are possible: the linear motif **10**[36] or the cyclic motif **9**.[37] An intermediate 'crinkled' tape motif has also been observed.[37a,38] To assist in directing the regiochemical outcome of assembly, the steric demand of substituent R_1 may be modulated. If R_1 is large, nonbonded interactions evident in the linear ensemble are relieved upon formation of the cyclic array (Scheme 3).

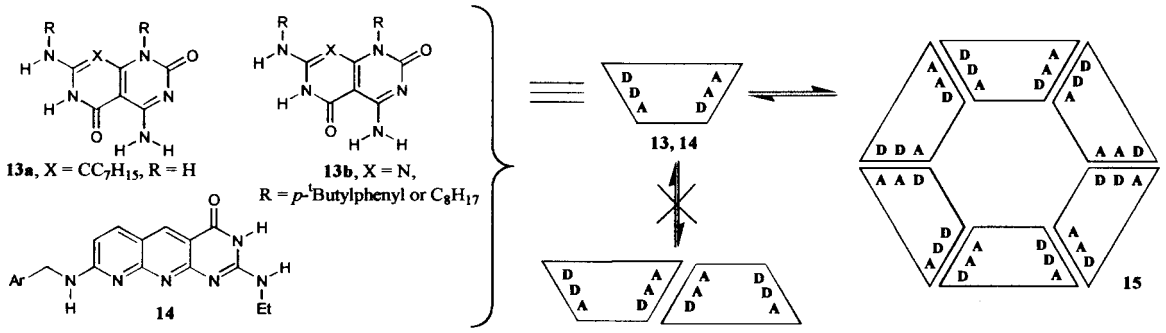
The assembly of related singly,[39] doubly,[40] triply,[41] quadruply[42] and polymerically[43] stacked H-bonded macrocycles based on ADA–DAD H-bond recognition motifs has been achieved similarly through steric direction and preorganization of the molecular components upon covalent scaffolds. In the case of molecular components **11** and **12**,[43b] the chemoselectivity (interactions discriminating between closed dimer vs polymeric aggregate) and regioselectivity (interactions discriminating between macrocyclic vs linear motifs) of aggregation for **11** and **12** is directed by the non-commensurate nature of the scaffolds separating H-bonding recognition groups (7.5 vs. 5.0 Å, respectively).



Scheme 3. Regioselective association directs the formation of discrete vs 1-dimensional motifs.



Scheme 4. The formation of noncovalent rods exploits the use of covalent scaffolds to direct the chemo- and regioselectivity of aggregation.



Scheme 5. 'Fully instructed' molecular components unambiguously define the regiochemistry of aggregation.

The self-assembled rods were observed via transmission electron microscopy (Scheme 4).

For the systems described above, the array of H-bond donor–acceptor sites displayed by the molecular components is such that, barring steric or geometric constraints, alternative modes of assembly may be adopted in which all H-bond donors and acceptors may be satisfied. In this way, the information embodied by the molecular components is ambiguous and, hence, regiochemistry is undefined. Such regiochemical issues may be rendered moot through judicious arrangement of H-bond donor–acceptor sites as in **13a**,[44] **13b**[45] and **14**.[46] These self-complementary molecular precursors each display DDA–AAD H-bond arrays. A 60° angle between the H-bonding faces of these heterocycles directs the formation of the cyclic hexamer **15**, the only arrangement for which all H-bond donors and acceptors may be satisfied in an intra-ensemble sense (Scheme 5).

2.3. Stereoselectivity

Control of the relative orientation of two or more stereocenters in a given molecule defines stereoselectivity. Diastereoselectivity more specifically refers to stereoselective bond formations in which two stereogenic centers result. In a diastereoselective transformation, there exist two limiting cases: (a) the stereogenic centers may form in concert, or (b) a preexisting stereogenic center may induce the relative stereochemistry of an incipient stereocenter. For noncovalent systems, the association of two chiral molecular precursors may result in the formation of a diastereomeric aggregate. Additionally, since noncovalent bond formations may be stereogenic (see Scheme 6), chiral–achiral or achiral–achiral molecular associations may also exhibit diastereoselectivity.

Owing to extensive studies in the area molecular recognition and host–guest chemistry,[47,59] particularly in the area of amino acid/peptide receptors,[48] numerous chiral molecular receptors that act through the formation of H-bonds to bind racemic guests have been described. Although referred to as 'enantioselective binding', strictly speaking, such substrate–receptor interactions result in the formation of diastereomeric complexes and thus involve the control of relative stereochemistry. Therefore, these binding events are best described as stereoselective. To effectively discriminate among diastereomeric modes of binding, synergy among the collective noncovalent forces is required in the form of multiple points of contact. L-Tryptophan receptor–substrate complex **16**[49] binds through three points of attachment: a ditopic guanidinium–carboxylate interaction, a tritopic ammonium ion–crown ether interaction and aromatic π-stacking/solvophobic interactions. Upon exposure to aqueous solutions of racemic tryptophan or phenylalanine, phase transfer of the aromatic amino acids into dichloromethane occurs with quantitative stereoselectivity. For receptor–substrate complex **17**, the affinity of the (*S*,*S*)-receptor for the indicated (*S*)-lactic acid carbamate is approximately an order of magnitude higher than for the corresponding (*R*,*R*)-receptor–substrate complex.[50] Similarly, the affinity of binaphthalene based receptor **18** for *N*-Cbz-(L)-Asp is roughly one order of magnitude higher than for *N*-Cbz-(D)-Asp, with an energy difference of 6.9 kJ/mol between the diastereomeric complexes (Fig. 4).[51]

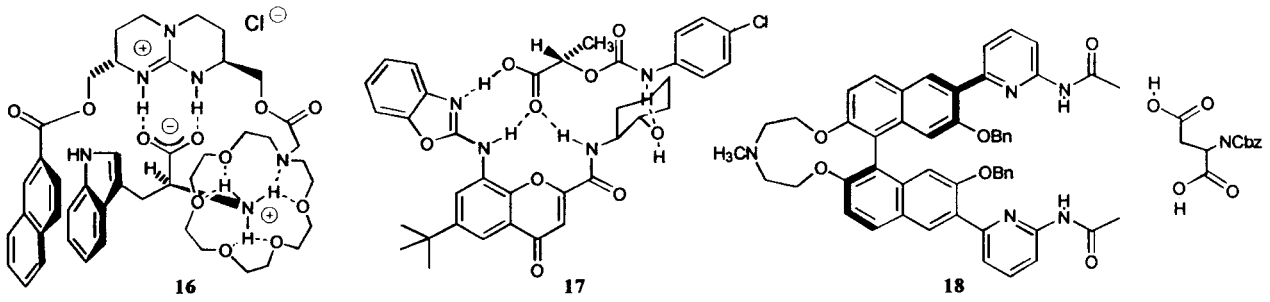
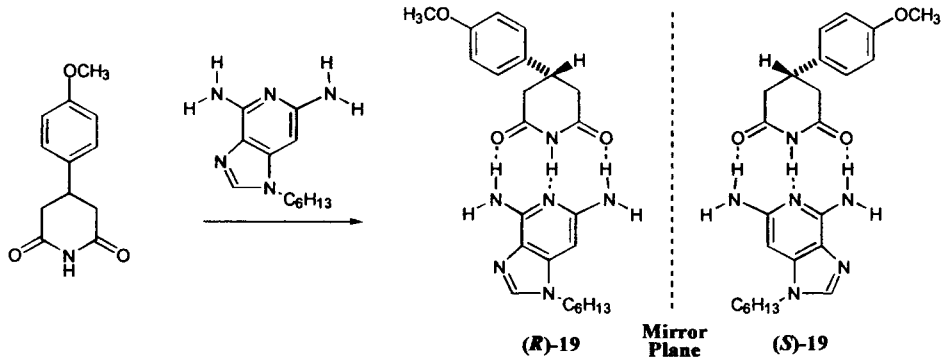


Figure 4. Stereoselective binding of racemic guests.



Scheme 6. A stereogenic noncovalent bond formation.

2.4. Enantioselectivity

Enantioselectivity relates to the control of absolute stereochemistry. Sustained induction of enantiomeric excess in a stereogenic transformation requires the chiral product to be kinetically inert. Reversibility in the formation of a chiral product would preclude any enduring optical enrichment as mirror image isomers are equi-energetic (this is not exactly true due to parity violations involving the weak force[52]) and form in equimolar amounts under equilibrium conditions. Stereogenic associations occurring through the action of H-bonds, as in the formation of **19**, are known. However, the kinetic lability of the derived ensembles makes their synthesis in non-racemic form nontrivial (Scheme 6).[53]

A successful yet capricious method for symmetry breaking in the stereogenic formation of noncovalent ensembles involves spontaneous resolution upon crystallization. This topic has been extensively reviewed.[52,54] Resolution of chiral superstructures arising from H-bond associations is viable provided the following conditions are met: (1) the formation of crystal nuclei are infrequent and slow, (2) crystal growth is rapid once initiated, and (3) the interconversion of enantiomeric forms in solution is fast. Spontaneous resolution in the stereogenic formation of H-bonded aggregates has been observed for both achiral and 'chiral non-resolvable' precursors in the solid state. In the former case, urea self-assembles with the aid of an *n*-alkane template to form helical channels.[55] In the latter case, chiral gauche conformations of hydrogen peroxide or ethylenediamine sulfate are resolved upon crystallization.[54d]

2.5. Preorganization, cooperativity and allostery

In addition to their reversible formation, low energy binding interactions are typically associated with shallow potential energy wells. As such, single H-bonds are manifested by 'soft' directionality, being amenable to considerable distortion accompanied by minimal loss of binding energy.[56] The overall strength and directionality of the binding interaction can be enhanced through the use of H-bond donor–acceptor arrays. Such composite binding sites may be thought of as 'recognition groups' as they encode for selective association with a complementary array. Representative tritopic H-bond recognition groups are schematically depicted below along with a corresponding range of K_{assn} values (Fig. 5).[3d] For the three tritopic motifs, the strength of binding increases with decreasing number of repulsive secondary electrostatic interactions.[57] A linear correlation for the prediction of H-bond associations in chloroform a priori has been proposed in which each H-bond contributes 1.9 ± 0.69 kcal/mol for each attractive or repulsive secondary interaction.[19] While useful for qualitative predictions, this method does not account for the considerable range of values observed for the tritopic (Fig. 5) or ditopic motifs (Fig. 3). The great disparity in K_a values are a consequence of factors beyond the nature and number of primary and secondary H-bond interactions. Preorganization, cooperativity, binding site solvation and pK_a matching effects all strongly influence binding (Fig. 5).

Barring significant entropy/enthalpy compensation,[58] preorganization of binding residues in an arrangement suitable for complexation reduces the entropic cost of association, thereby enhancing the stability of the noncovalent ensemble. Enhanced association via preorganization of binding residues has been evidenced in the complexation of metal ions[59] and π-molecular guests.[60] In the latter case, it was estimated that the removal of a free bond rotation contributed ca. 1 kcal/mol to the free energy of

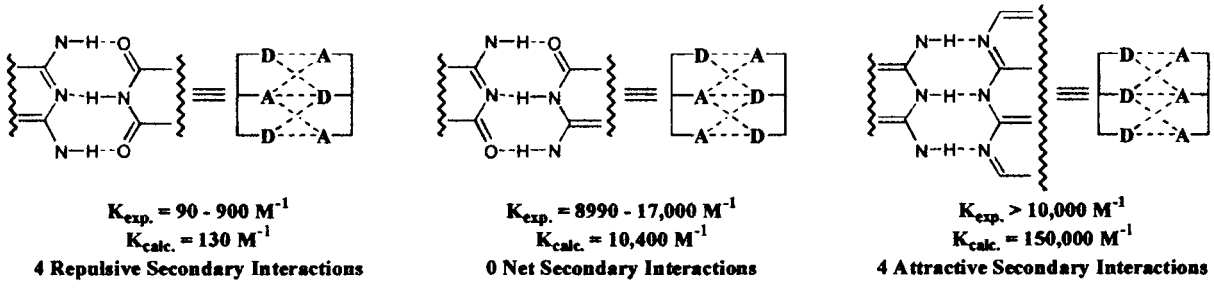


Figure 5. Triptopic H-bond recognition groups and related K_{assn} value ranges.

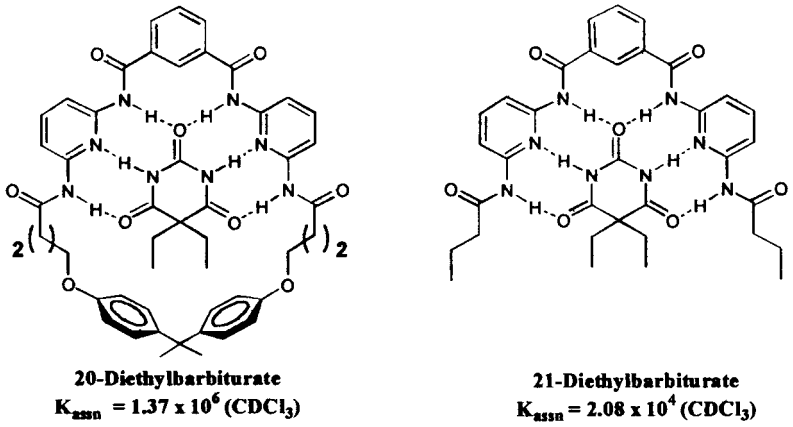


Figure 6. Preorganization of residues comprising a binding site can enhance association.

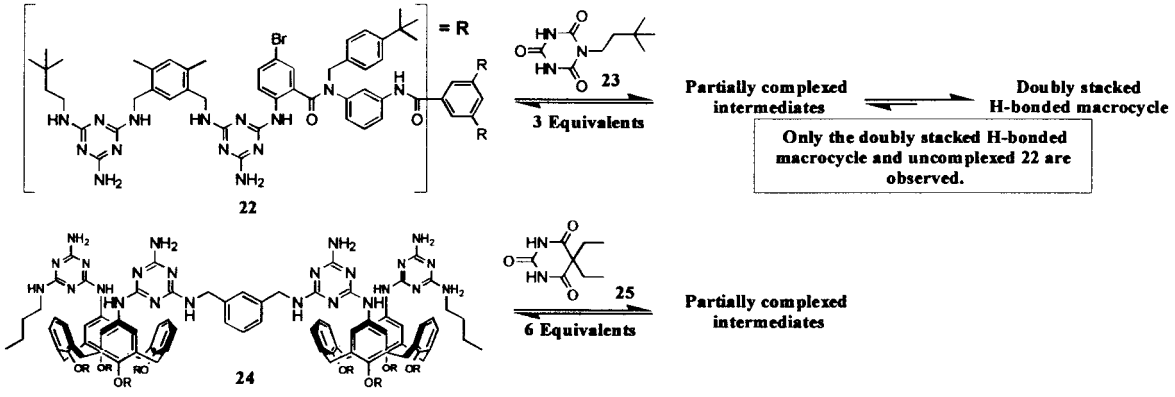
binding. Preorganization also plays a key role in H-bonded systems. For example, the binding of diethyl barbiturate to the macrocyclic *iso*-phthalamide-based receptor **20** is nearly two orders of magnitude greater than for the related conformationally unrestricted receptor **21** (Fig. 6).[61]

That an initial complexation event may influence the energetics of subsequent complexation events is the basis of cooperative and allosteric effects. Cooperativity is a common characteristic in biological systems[62] and results from the coupling of tandem associations such that the energies of successive interactions are related in non-linear increments. In synthetic H-bonded systems, both positive and negative cooperativity have been noted in the self-assembly of doubly and quadruply stacked H-bonded macrocycles, respectively. In the case of molecular precursor **22**,[40c] equilibration in the presence of three equivalents of cyanurate **23** yields a mixture containing only doubly stacked H-bonded macrocycles (analogous to **9**) and uncomplexed **22**. The preferential complexation of six molecules of **23** in the form of the doubly stacked H-bonded macrocycle, rather than a distribution of partially complexed intermediates, suggests a strong positive cooperative effect. In contrast, when molecular precursor **24**[40d] is treated with barbiturate **25**, a mixture of assemblies is obtained. The authors suggest that steric interactions between stacked H-bonded macrocycles provoke a negative cooperative effect (Scheme 7).

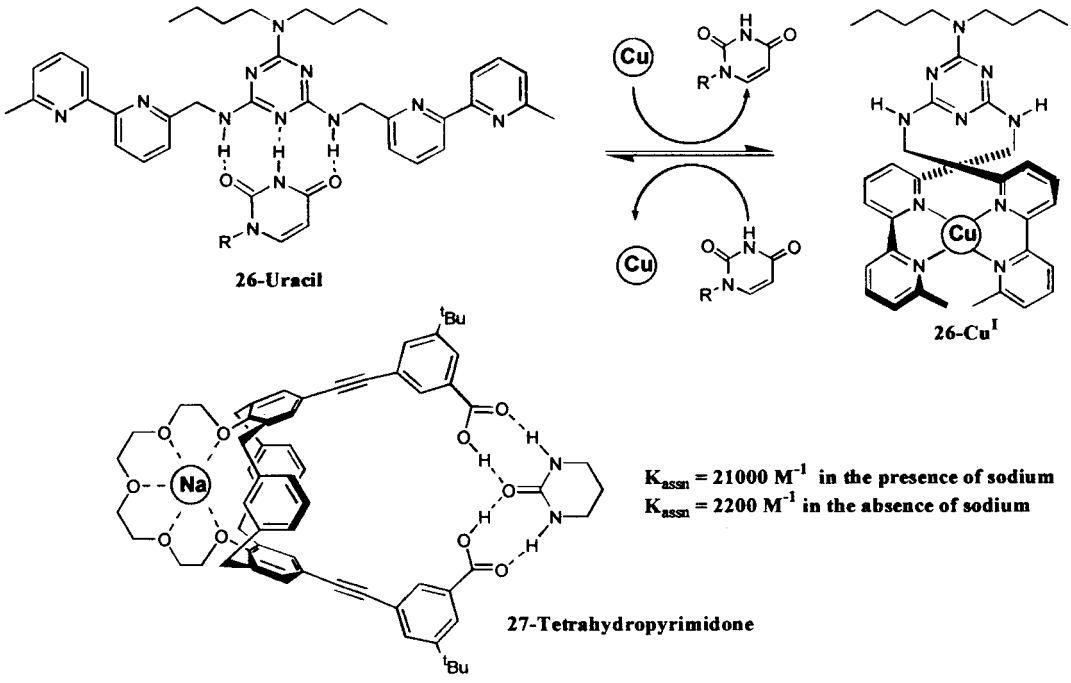
Whereas cooperativity broadly applies to tandem self-organization events, allostery more specifically refers to systems incorporating multiple receptor–substrate binding sites and the transfer of information between binding subunits. Allosteric effects are prevalent in naturally occurring systems and play a key role in the regulation of enzymatic processes.[63] Recently, synthetic systems displaying allostery have been reported.[64,65] In the specific case of H-bonded systems, metal ion complexation of a remote binding site has been exploited for the induction of positive and negative allosteric effects. The binding of uracil by receptor **26** is effectively turned off upon addition of Cu(I) salts.[66] The addition of sodium to oligo-ethylene glycol-strapped receptor **27** enhances binding of tetrahydropyrimidinone by roughly one order of magnitude (Scheme 8).[67]

3. H-Bond directed organization of molecular strands

Recent 'cross-pollination' between the fields of macromolecular and supramolecular chemistry has prompted investigations into the self-assembly of dendritic macromolecules,[68,69] block copolymers,[75a,70,71] polymers incorporating side chain H-bonding residues[72] and noncovalent main chains[73] and the polymerization of organized assemblies.[74,75] In general, these studies have focused on more global aspects of polymer structure, in particular microphase separated domains and liquid crystallinity. More recently, to direct the generation of more localized order, the H-bond mediated organization of 'instructed'



Scheme 7. Cooperativity in the assembly of stacked H-bonded macrocycles.



Scheme 8. Examples of negative and positive allostery in H-bonded systems.

molecular strands, also termed foldamers,[76a] has been the focus of intensive investigation.[12,76] In order to design a polyvalent molecular strand that assembles to yield a single conformer with high fidelity, complex issues of selectivity must be taken into account. In this section, we review examples of instructed molecular strands that adopt well-defined conformations through the action of H-bonds and outline key selectivity issues addressed in their design.

Strategies for the H-bond directed organization of abiotic molecular strands may be categorized as follows: (a) strands which undergo self-induced organization and (b) those which assemble in response to intermolecular complexation events.

3.1. Self-induced organization of molecular strands

3.1.1. Aliphatic oligoamides. In peptidic biomacromolecules, amide H-bonds are used to contribute to the stabilization of diverse secondary structural features. Therefore, it is natural that the H-bonding capabilities of amides have found extensive use in the directed organization of abiotic molecular strands. Secondary structures derived from abiotic oligoamides often have enhanced stability with respect to their naturally occurring counterparts. For

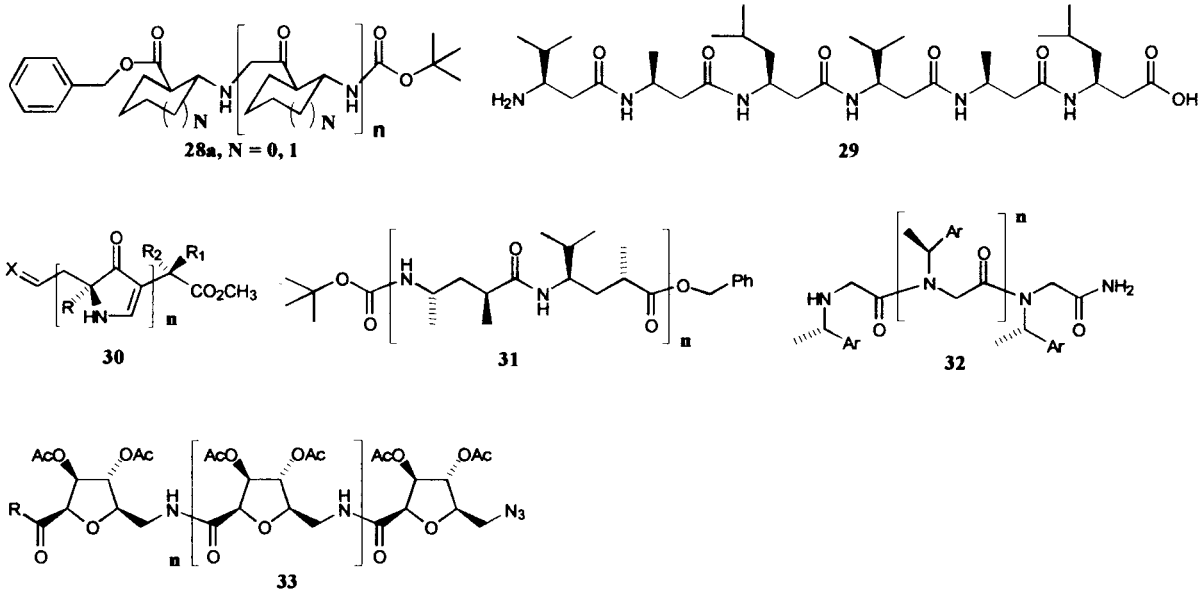


Figure 7. Self-organizing abiotic oligoamides that express well-defined secondary structural motifs.

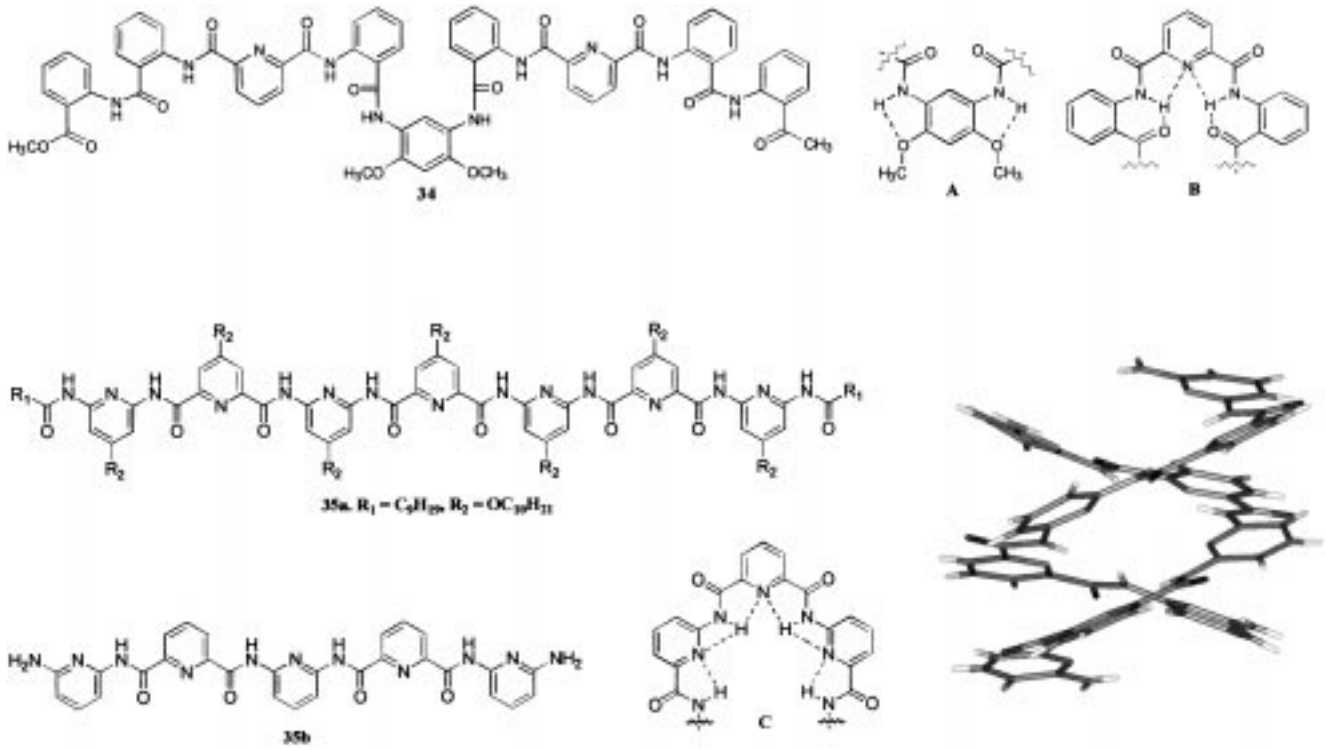


Figure 8. Self-organizing aromatic oligoamides that adopt helical secondary structures.

example, whereas natural peptides only adopt distinct secondary structures upon reaching a length of 15–20 amino acid residues, β-amino acid derived peptides **28**[77] and **29**,[78] γ-amino acid derived peptides **31**,[79] peptoids **32**[80] and furanose carbopeptoids **33**[81] all form stable helical motifs in solution and in the solid state with as few as 3–6 residues. β-Peptides that express turn, hairpin and sheet motifs have also been described.[82] Polypyrrolinones **30** adopt conformations analogous to peptide β-strands, β-turns and helices[83] (Fig. 7). ω-Amino acid containing peptides[84] and other abiotic oligoamides[85] and polyamides[86] possessing non-aromatic backbones also adopt well-defined superstructures. Abiotic oligoamides of undetermined superstructure have also been prepared.[87,88]

For these self-organizing strands, the kinetic and entropic advantages of intramolecular association direct the chemoselectivity of aggregation, i.e. intra-strand H-bonding is favored over intermolecular aggregation. In synergy with the information embodied by the H-bond donor/acceptor sites, the periodic placement of homochiral stereogenic centers over the length of the strands further assists in directing the formation of helical folded structures and defines the enantioselectivity of helix formation.

3.1.2. Aromatic oligoamides. Aromatic oligoamides are less conformationally mobile than their aliphatic counterparts and their assembly is more easily directed. Indeed, strategic juxtaposition of H-bond donor/acceptor sites upon the arene backbone allows complete control of amide rotamer equilibria and, as a result, all backbone dihedral angles of the oligomer may be defined. Ordered superstructures have thus been designed de novo. Oligo-*ortho*-aminobenzoic acid amide **34**[89] and related oligoanthranilamides[90] assume extended helical secondary structures. Internal H-bonding, in the form of motifs **A** and **B** (Fig. 8), induces curvature into the oligomer backbone. Similarly, pyridine 2,6-dicarboxamide derivatives **35**[91] assemble through the action of H-bonds according to motif **C**. Oligomer **35a** was found to dimerize in solution, undergoing dynamic exchange between single and double helical states. In the solid state, molecular strand **35b** resides

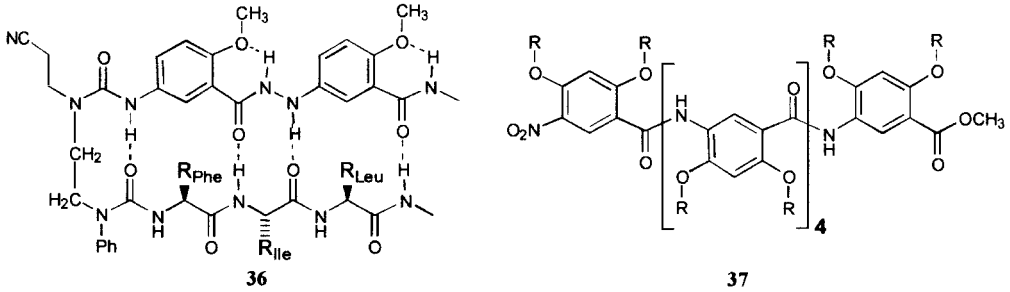
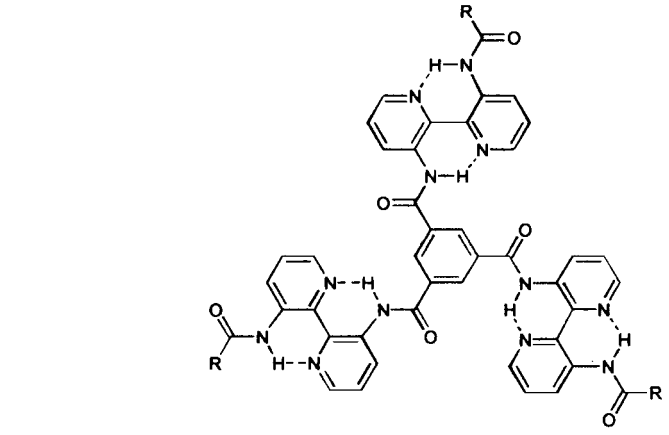


Figure 9. Self-organization of alkoxy-substituted oligoamides.



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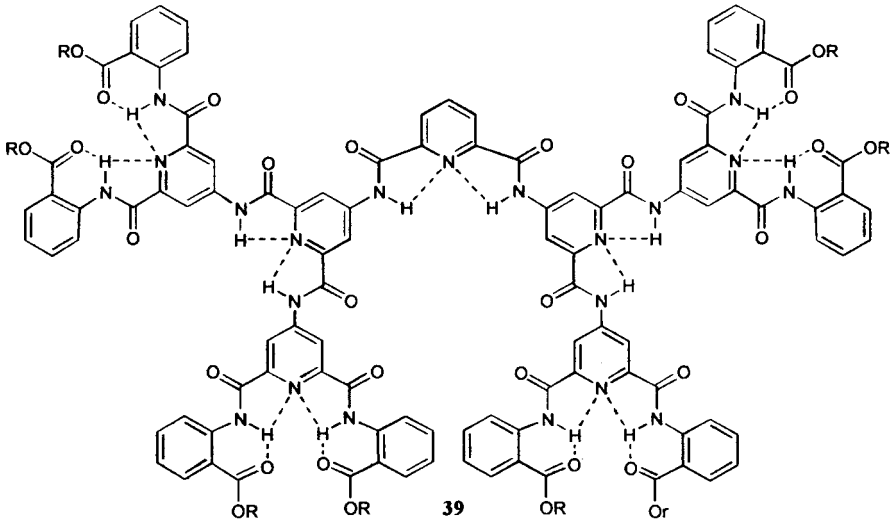

39

Figure 10. Conformationally defined branched aromatic oligoamides.

in the indicated double helical form $(\mathbf{35b})_2$, as observed by X-ray crystallographic analysis.

The strong conformational predisposition of aromatic oligoamides has been used to direct the secondary structure of appended 'conformationally promiscuous' strands. Specifically, conjugation of alkoxy-substituted aromatic oligoamides with small peptides comprised of natural amino acids yields hybrids of well-defined conformation. Oligomer **36** adopts a β-sheet type structure.[92] Related alkoxy-substituted aromatic oligoamides, such as **37**, have been found to take on a crescent shape in solution. Intramolecular H-bonding similar to motif **A** directs the folding process (Fig. 9).[93]

The persistence and fidelity of aromatic oligoamide superstructures has resulted in the modular utilization of aromatic oligoamides toward the design of branched systems. Rigid oligoamide side chains appended to a high symmetry core, as in compound **38**, permits the design of discotic liquid crystalline materials. The disk-like morphology of **38** promotes a solvophobically driven second-order self-assembly process: the formation of stacks resulting in a columnar mesophase.[94] The topography of increasingly complex dendritic systems has been controlled through the modular implementation of predefined oligoamide superstructures. Third-generation dendrimer **39** is expected to adopt a propeller-type conformation, as exhibited in the solid-state for the corresponding second-generation species (Fig. 10).[95]

To utilize self-organizing oligomers in biological applications, it would be desirable to define strand motifs that persist in aqueous media. Oligoamide **40**[96] has been found to adopt a stable turn conformation in DMSO, a

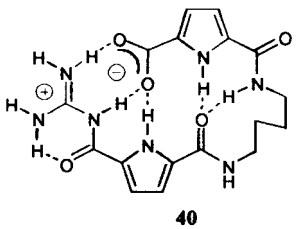

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Figure 11. A self-organizing oligoamide that assembles in competitive media.

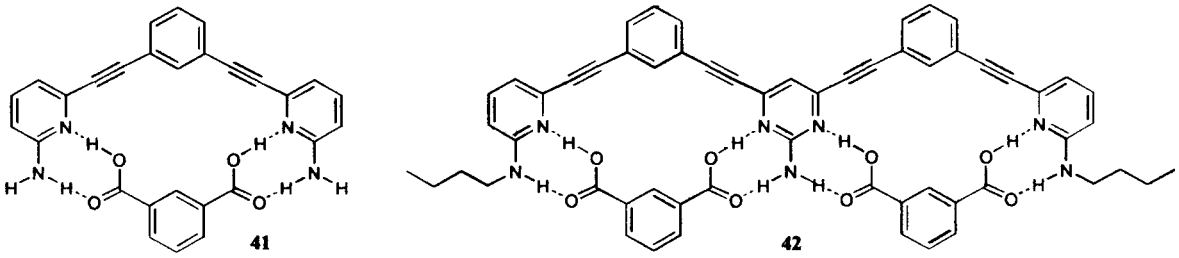
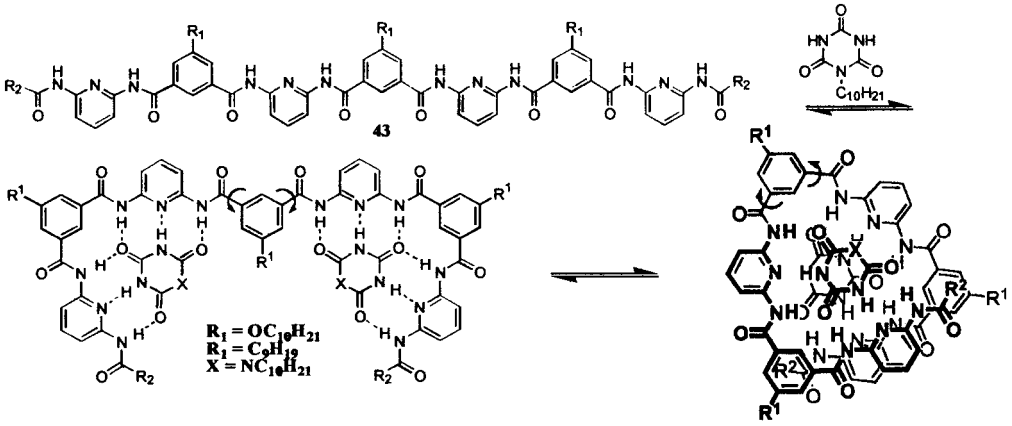


Figure 12. Oligomeric *iso*-phthalic acid receptor **42** adopts a linear arrangement upon binding.



Scheme 9. Template-induced helix formation of an oligomeric molecular receptor.

highly competitive medium, owing to robust carboxylate–guanidinium H-bond interactions (Fig. 11).

3.2. Template-induced organization of molecular strands

3.2.1. Molecular templates. While the self-induced organization of molecular strands benefits from the facility of intramolecular association, in the case of strands that assemble in response to an external template, competitive internal H-bonding must be overcome. This chemoselectivity issue is mitigated through the modular utilization of molecular receptors with established intermolecular binding properties as monomers for the synthesis of related *oligomeric* molecular receptors. For example, the dimeric receptor **42** may be viewed as a homologue of *iso*-phthalic acid receptor **41**.[97] For **42**, the binding of *iso*-phthalic acid reduces conformational space in the form of the linear 2:1 complex indicated below, as evidenced by X-ray crystallographic analysis. The chemoselectivity of aggregation is driven by pK_a matching effects and the rigidity of **42**, which precludes intramolecular associations (Fig. 12).

Oligo-*iso*-phthalamide **43**[98] may be viewed as a homologue of receptor **21** (Fig. 6). Whereas **21** binds a single substrate, oligomer **43** accommodates two substrate molecules, in this case decyl cyanurate. Upon binding, helical disk-like objects possessing radially disposed alkyl chains result. Solvophobic interactions direct a second-order assembly event: the stacking of the helical disks to yield fibers, as evidenced by electron microscopy (Scheme 9). The melamine containing molecular strands **22** and **24** also self-assemble upon exposure to cyanurate or barbiturate templates, respectively (Scheme 7).

Expanded porphyrins may be engineered to possess efficient anion binding properties.[99] Non-macrocyclic analogues, i.e. linear oligopyrroles, are also well-suited to this task. The dihydrochloride salt of hexapyrrole **44** adopts an 'S-shaped' conformation induced by the binding of two chloride anions.[100] The indicated S-shaped conformation was detected in solution and in the solid state (Fig. 13).

3.2.2. Oligomeric templates. In addition to templating by small molecules, synthetic oligomers may also assemble by virtue of homo- or heteromeric association with other molecular strands to yield oligomeric duplex or triplex ensembles. Studies on the chemical etiology of nucleic

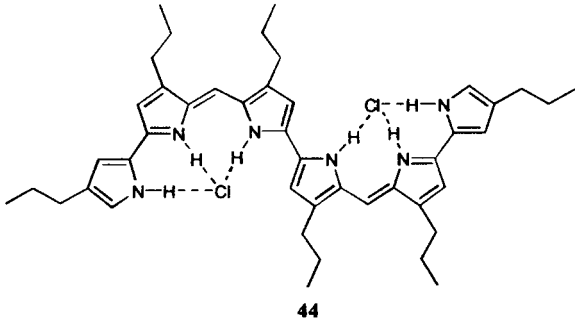


Figure 13. Oligo-pyrrole dihydrochloride **44** adopts an 'S-shaped' conformation upon binding chloride ion.

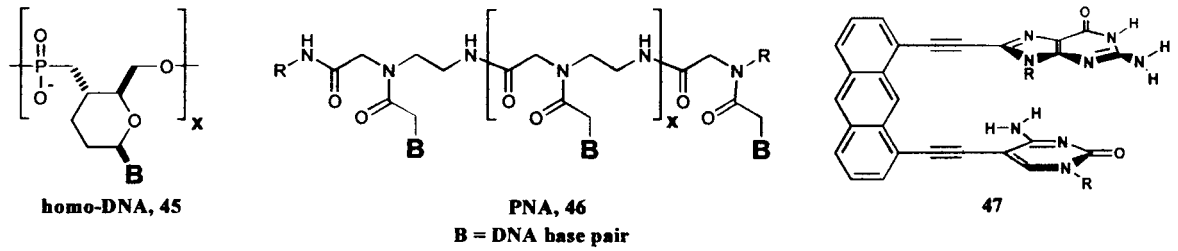


Figure 14. Duplex forming molecular strands incorporating DNA base pairs.

acid structure have brought forth a spectacular panorama of self-associating molecular strands structurally related to DNA, represented here by 'homo-DNA' **45**.[101] The modular nature of DNA recognition via base pairing has inspired the design of abiotic molecular strands decorated with DNA base pairs including 'polyamide nucleic acids'[102] (PNA) such as **46**.[103] Base pair functionalized oligomers further removed from those found in Nature may also be envisioned. Compound **47**,[104] which incorporates a fused aromatic backbone, self-assembles to form a duplex dimer (Fig. 14).

So-called 'molecular zippers', represented by complex **48**, were the first family of molecular strands devoid of DNA base pairing motifs reported to form duplex materials.[105] For homologous zipper strands, increasingly high association constants were obtained along with marked cooperativity effects. The association constant for complex **48** in 95:5 $CDCl_3$:CD_3OD (v:v) is $5.5\times10^4\ M^{-1}$. The remarkably robust association in a methanolic medium may, in part, be attributed to the absence of destabilizing secondary electrostatic interactions. Similarly, heteromeric complex **49**[106] is devoid of secondary interactions. Preorganization of the composite strands in the linear arrangement for duplex formation is achieved through the action of intramolecular H-bonds. The authors report an association constant of $1.3\times10^9\ M^{-1}$ in chloroform as determined by isothermal titration calorimetry (Fig. 15).

For complexes **48** and **49**, it is important to note that the composite strands bind in register. In principle, H-bonding could occur in a frame-shifted sense, resulting in the formation of polymeric aggregates. Although the H-bond donor acceptor sites of the composite strands are not in direct juxtaposition, they nevertheless act in concert as a composite H-bonding recognition group. This behavior is entropically driven, i.e. the formation of numerous discrete duplexes is favored relative to the formation of fewer polymeric complexes. The high preference for in register binding augurs well for the controlled assembly of higher oligomers.

Single strands that reside in well-defined conformations may adopt alternative forms upon complexation with a complementary strand. It was found that in dilute chloroform solution, compounds **50** and **51** exist as the folded conformers **50b** and **51b**, respectively.[107] However, when combined, **50** and **51** mutually unfold and dimerize yielding

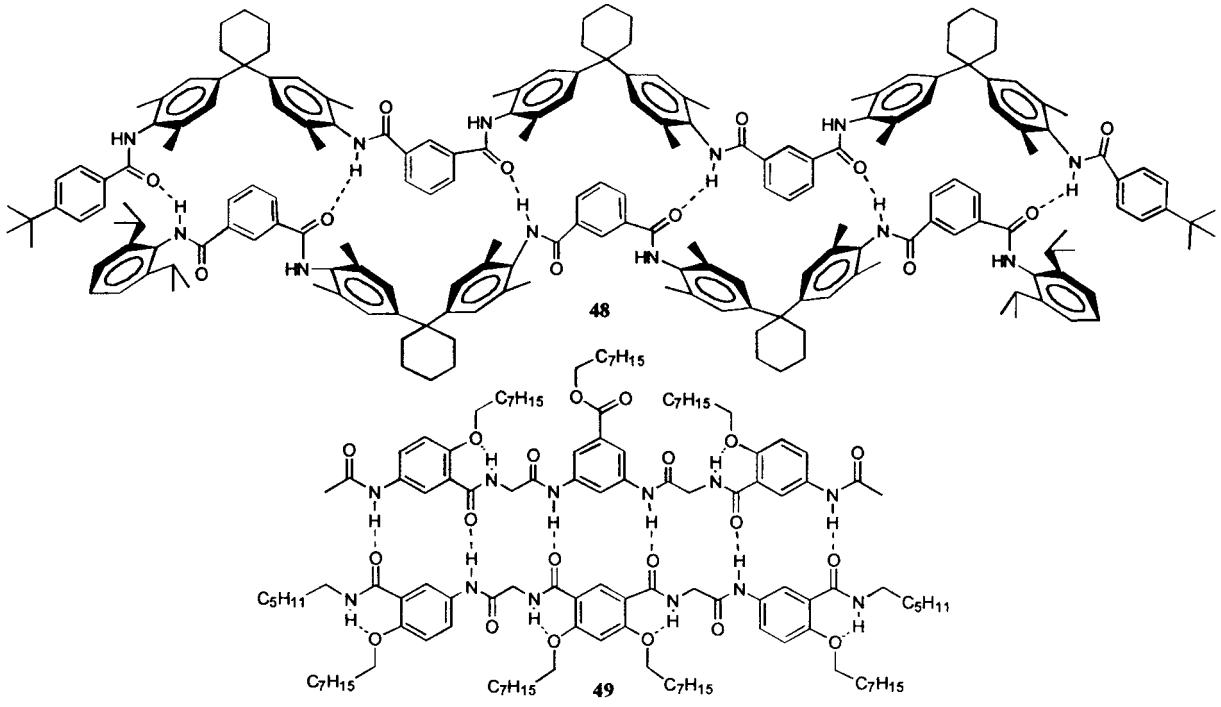
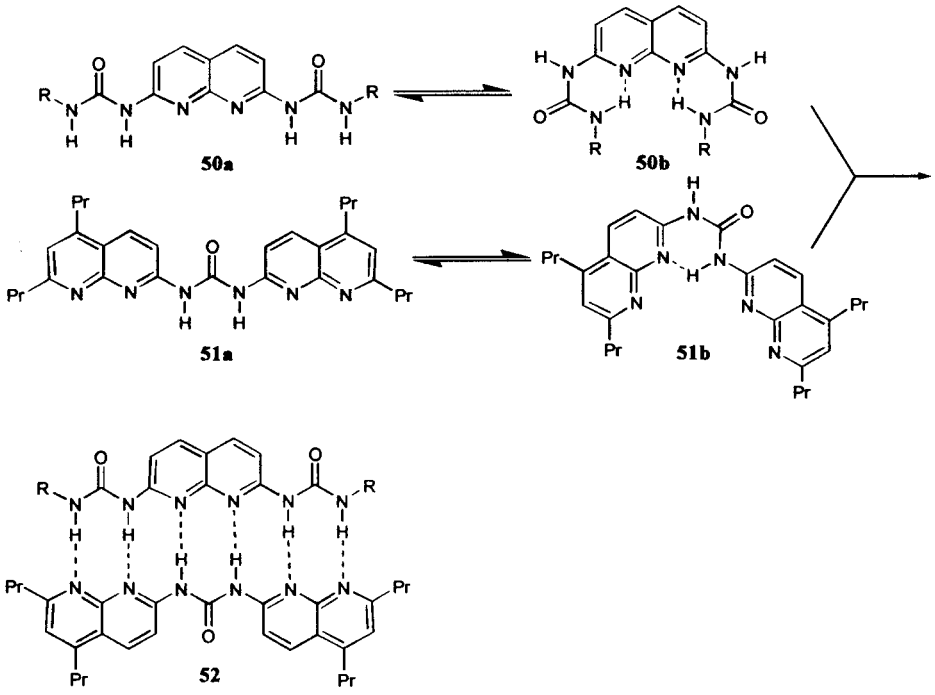


Figure 15. Formation of heteromeric duplexes through the association of complementary oligoamides.



Scheme 10. Adaptive oligomers undergo conformational reorganization upon complexation.

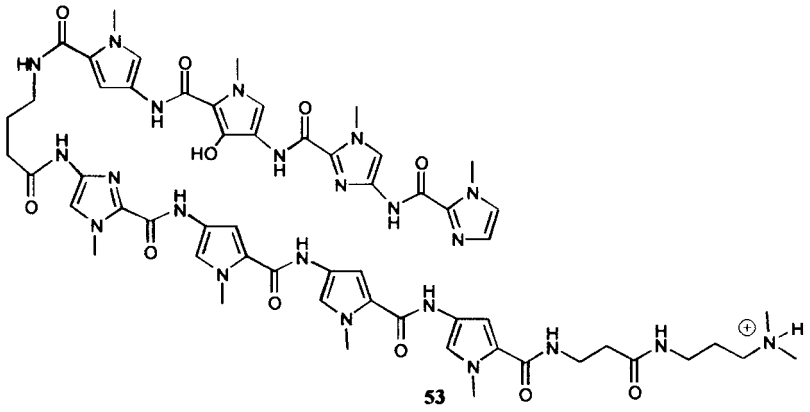
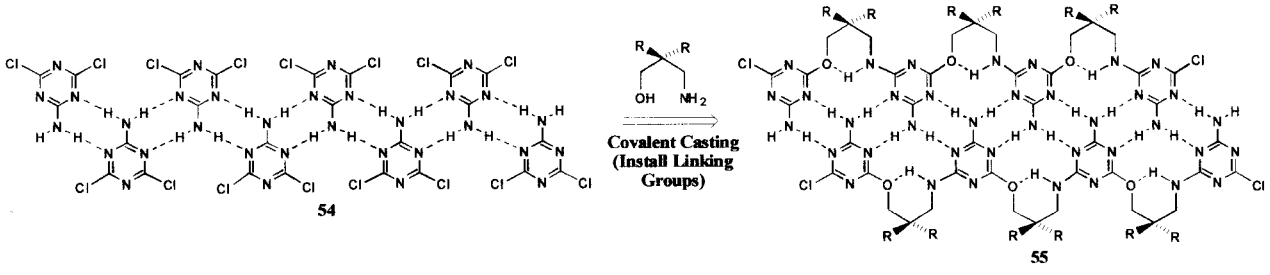


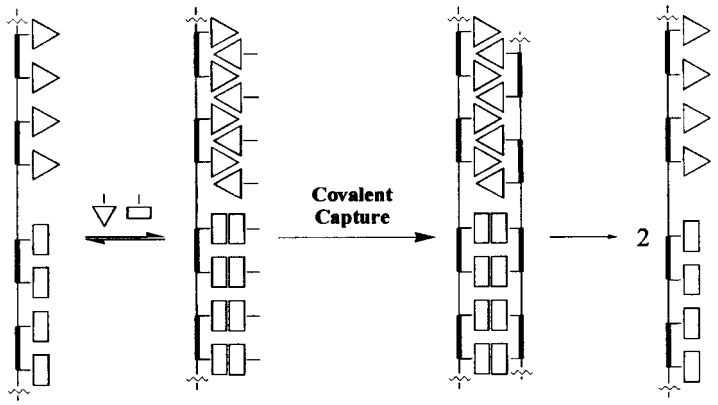
Figure 16. A molecular strand that site-specifically assembles upon a DNA template.

the heteromeric duplex **52**. An association constant of $5\times10^5\ M^{-1}$ was observed. These systems are likely to find use as modules for the development of higher oligomers with adaptive properties (Scheme 10).

The significance of instructed molecular strands toward the design of functional materials is underscored by the synthesis of oligomers, represented by **53**, capable of recognizing duplex DNA in a site-specific manner via triple helix formation.[108] Beyond the potential to mediate biological events in vivo (e.g. gene expression), the ability to devise oligomers capable of 'reading' information manifest in a polymer



Scheme 11. Covalent casting of a 1-dimensional H-bonding motif to yield an abiotic duplex oligomer.



Scheme 12. Self-replication of a block oligomer strand prepared via covalent casting.

sequence raises numerous possibilities regarding information storage (Fig. 16).

A general strategy for the development of molecular strands of predetermined superstructure involves the 'covalent casting' of 1-dimensional H-bonding motifs.[109] Through covalent casting, covalent frameworks are designed to embrace noncovalent ensembles, effecting preorganization of the composite binding sites and, in turn, augmenting the overall strength of the supramolecular framework. This differs from covalent capture,[110] which amounts to a template-directed synthesis. For a 1-dimensional superstructure, such as the H-bonded tape **54**, covalent casting is accomplished by substituting pairs of chloro-substituents on adjacent triazines with aminoalcohol-based linking groups.[107] The preparation of duplex polymers, and iterative approaches to monodisperse duplex oligomers, such as the tetramers comprising duplex **55**, have been developed (Scheme 11).[111]

It is significant that a 'cast' strand is equivalent to an oligomeric molecular receptor. In principle, such an oligomer could serve as a template for the covalent capture of complementary monomers in a process resembling an abiotic version of the polymerase chain reaction, as schematically depicted below for the case of a block copolymer system. In this way, self-replicating polymers may be devised, which retain information manifest in their sequence akin to DNA (Scheme 12).

4. Perspectives

Through the development of technologies for the induction of predefined secondary structural motifs via inter- and intramolecular assembly events, a platform for the de novo design of functional polymers and devices of nanometric dimensions is defined. To meet these goals, covalent objects are valued not only for their structural features, but are appreciated for their ability to embody, retrieve, transfer and process information. As such, synthetic chemistry takes on the characteristics of an information science, with covalent and noncovalent synthetic technologies as its foundation. The significance of self-assembly with respect to the preparation of functional materials resides in the potential to access nano-architectures in a spontaneous yet controlled fashion, bypassing the need to resort to demanding fabrication protocols. Owing to the dynamic nature of self-assembly, it is anticipated that materials obtained through self-assembly processes would exhibit unique adaptive and responsive characteristics. It is hoped that the examples presented in this account should assist in galvanizing the concepts underlying this burgeoning field of research and stimulate still deeper analyses.

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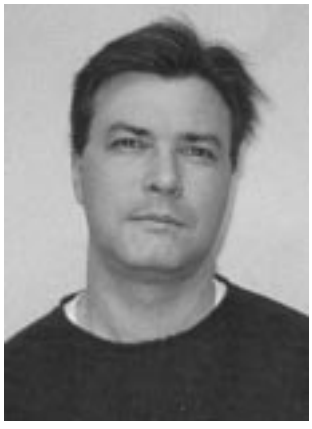

Michael J. Krische received a BS in Chemistry at the University of California at Berkeley, under the tutelage of Professor Henry Rapoport as a Presidents Undergraduate Fellow. Upon graduation, he was awarded a Fulbright Fellowship and a Sigma Xi grant to pursue research at the University of Helsinki, Finland and the University of Surrey, England. In 1996, Dr Krische obtained a PhD in chemistry from Stanford University for work conducted with Professor Barry M. Trost as a Peter Veatch Fellow, whereupon he pursued post-doctoral studies as an NIH fellow in the laboratories of Professor Jean-Marie Lehn at Université Louis Pasteur in Strasbourg, France. In January 1999, he was appointed Maître de Conference-College de France. Presently, Dr Krische is an assistant Professor of Chemistry at the University of Texas at Austin. His research interests relate to the control of selectivity in covalent and noncovalent bond formations.