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The supramolecular chemistry of monodisperse 1,3,5-triazine oligomers

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Organic compounds based on 1,3,5-triazine scaffolds are utilised in practical applications in agriculture, as well as in the pharmaceutical and plastic industries. In fundamental research, 1,3,5-triazines are used as building blocks for the construction of oligomers that are relevant to the areas of supramolecular chemistry, chemical biology and polymer science. Here, we review the molecular recognition and self-assembly properties of monodisperse linear and branched oligomers, macrocycles, and dendrimers of 1,3,5-triazine. We focus mainly on experimental studies conducted in solution, describing the key interactions and structural features of these systems.

1. Introduction

1,3,5-Triazine-based compounds are extensively used in fundamental research and practical applications, owing to their facile preparation from 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride).^{1–3} In general, the synthesis of these compounds involves sequential nucleophilic aromatic substitution (S_NAr) reactions with identical or different nucleophiles (e.g. alcohols,

amines, thiols, and Grignard reagents) (Fig. 1a).^{2–4} With amine nucleophiles, the substitution pattern can be controlled by the reaction temperature, since the substitution of chlorine by nitrogen reduces the reactivity at the other sites. Specifically, the monosubstitution reaction of cyanuric chloride with an amine takes place below 0 °C, whereas the second substitution occurs around room temperature, and the third substitution reaction requires heating above 60 °C. Thus, by controlling the temperature of each reaction step, the preparation of triply functionalised 1,3,5-triazine derivatives can be performed in one-pot.

Fig. 1b illustrates practical applications of some 1,3,5-triazine-based compounds. The 1,3,5-triazine scaffold is essential for the formulation of a number of herbicides (e.g. atrazine and

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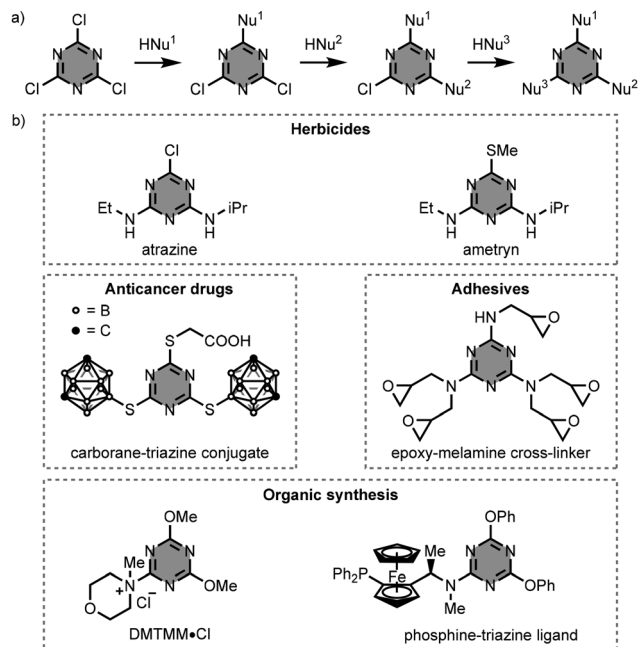


Fig. 1 (a) General synthesis of 1,3,5-triazine-based compounds starting from cyanuric chloride, and (b) structures of compounds used in practical applications. HNu = nucleophile.^{5–10}

ametryn),⁵ anticancer drugs (e.g. carborane-triazine conjugates),^{6,7} and adhesives (e.g. epoxy-melamine cross-linkers).⁸ In organic synthesis, 1,3,5-triazine derivatives are used as activating reagents for carboxylic acids (e.g. 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, DMTMM-Cl),⁹ and as ligands in catalysis (e.g. phosphine-triazine ligands).¹⁰

The 1,3,5-triazine scaffold has also been widely used as building block in supramolecular chemistry and polymer science for the construction of discrete monodisperse oligomers featuring distinct structural topologies: linear, branched, macrocyclic, and dendrimeric.^{2,3} These synthetic oligomers have interesting molecular recognition and self-assembly characteristics, often derived from hydrogen-bonding interactions involving 2,4,6-triamine-1,3,5-triazine (melamine) groups.¹¹ Melamine units have also been used as the backbone in recognition-encoded melamine oligomers (REMO) that form sequence-selective duplexes in a similar manner to nucleic acids.¹²

In this review, we focus on monodisperse 1,3,5-triazine-based oligomers. We illustrate selected synthetic approaches used for the preparation of linear oligomers (section 2), macrocycles (section 3), branched oligomers (section 4), and dendrimers (section 5). In each section, we discuss the molecular recognition and self-assembly properties of these oligomers based on experimental studies conducted in solution, and we only refer to solid-state structures when necessary to clarify structural features.

2. Linear oligomers

1,3,5-Triazine-based linear oligomers have triazine residues incorporated either into the backbone as structural com-

ponents or as side-chain recognition units appended to the backbone. In some cases, the triazine components of the backbone can also function as recognition units. In solution, the linear oligomers interact with identical or different compounds leading to the self-assembly of hydrogen-bonded complexes (e.g. homo- and heteroduplexes).

Krische and co-workers proposed a synthetic approach, termed “covalent casting”, to prepare linear oligomers that can form homoduplexes.^{13,14} Specifically, the synthesis of the 2-mer oligomer **1** involves the connection of two molecules of cyanuric chloride with a 1,3-diol linker, followed by the treatment with ammonia (Fig. 2a).^{15,16} The 2-aminotriazine units in **1** can act as both hydrogen-bonding donor and acceptor groups. Thus, in chloroform solution, the oligomer **1** gives a homoduplex through the formation of 6 hydrogen-bonds (Fig. 2b). The relatively low self-association constant, $K_a = 10^2 \text{ M}^{-1}$, suggests a geometry that is not optimal for self-assembly into the dimer **1**₂, probably, due to the steric and/or electronic clashes between the two oxygen atoms of the 1,3-diol linker.

To solve this issue, the authors replaced the 1,3-diol linker by a 1,3-amino alcohol in oligomer **2**.^{16,17} The 1,3-amino alcohol linker establishes an intramolecular hydrogen-bond between the amino group and the oxygen atom that helps pre-organise the structure of **2** for the formation of the homoduplex. The synthesis of the oligomer **2** involves the substitution of cyanuric chloride with the Boc-protected 1,3-amino alcohol linker and ammonia to give the intermediate **3**, followed by cleavage of the Boc-protecting group and coupling with 2-amino-4,6-dichlorotriazine to obtain **2** (Fig. 3a). In chloroform solution, **2** self-assembles into the homoduplex **2**₂, with a self-association constant greater than 10^4 M^{-1} (Fig. 3b). In 95 : 5 chloroform/dimethyl sulfoxide, the self-association constant for formation of **2**₂ is three orders of magnitude larger than that of **1**₂ ($K_a = 2.8 \times 10^4 \text{ M}^{-1}$ versus 9.2 M^{-1}). These results confirm that preorganisation of the linear oligomer has a significant impact on the thermodynamic stability of the duplex. Binding studies were carried out on a series of linear

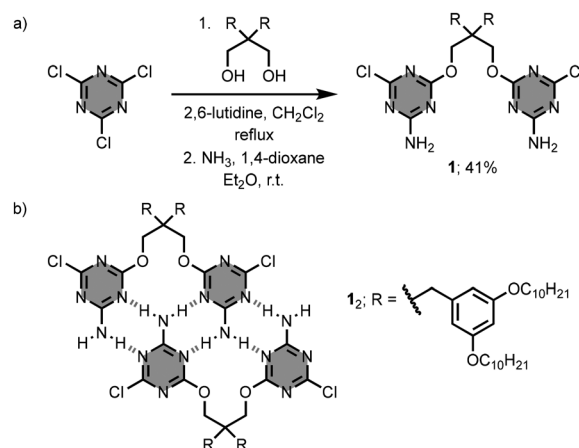


Fig. 2 (a) Synthesis of 1,3,5-triazine-based linear oligomer **1**, and (b) structure of the homoduplex **1**₂.^{15,16}

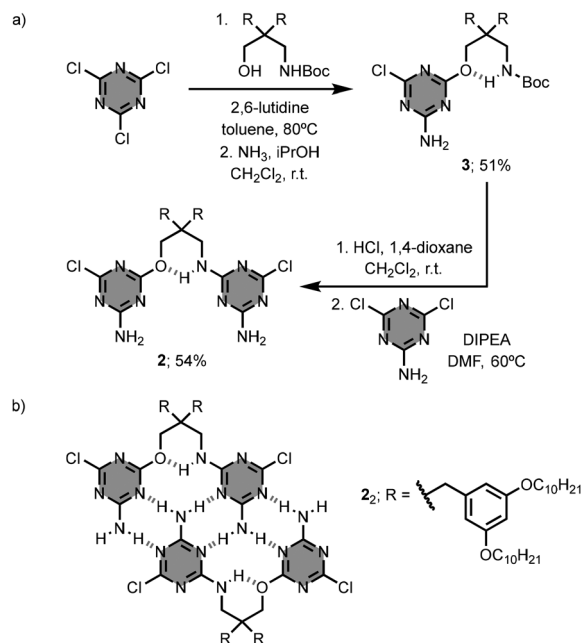


Fig. 3 (a) Synthesis of 1,3,5-triazine-based linear oligomer **2**, and (b) structure of the homoduplex **2₂**.^{16,17}

oligomers, and the stability of the homoduplex increases as the number of monomer units from one to three, indicating that the self-assembly process for duplex formation displays positive cooperativity. On the contrary, the binding free energy decreases for the homoduplex assembled from the 4-mer, which could be due to competitive binding processes, such as intramolecular folding.

The research group of Timmerman and Reinhoudt described the 3-mer oligomer **4** having 2-aminotriazine units and *m*-xylenediamine linkers in the backbone.^{18,19} In this case, the amino groups of the linkers can engage in intermolecular hydrogen-bonding interactions. The authors investigated the binding properties of the oligomer **4** with the bis-barbituric acid derivative **5**. Interestingly, mixing equimolar amounts of **4** and **5** in chloroform solution leads to the self-assembly of a 2 : 2 complex, **5₂·4₂**, stabilised by 24 hydrogen-bonds (Fig. 4). The formation of other species, such as the 1 : 1 complex, **5·4**, or polymeric assemblies, (**5·4**)_{*n*}, was not detected in the course of the titration experiment.

Chan, Zimmerman and co-workers prepared the 4-mer oligomer **6** from the azide and alkyne linear precursors **7** and **8**, using the copper(i)-catalysed azide–alkyne cycloaddition (CuAAC) reaction (Fig. 5).²⁰ The oligomer **6** contains four melamine and two bis-amidinium units, connected by alkyl and triazole linkers, in the backbone. The authors showed that **6** interacts with nucleic acids and inhibits the formation of nucleic acid–protein complexes.

Linear oligomers formed by a triazine backbone with information encoded as a sequence of different side-chains have also been described. For example, Grate and co-workers used solid-phase synthesis to prepare the 6-mer oligomer **9**, which

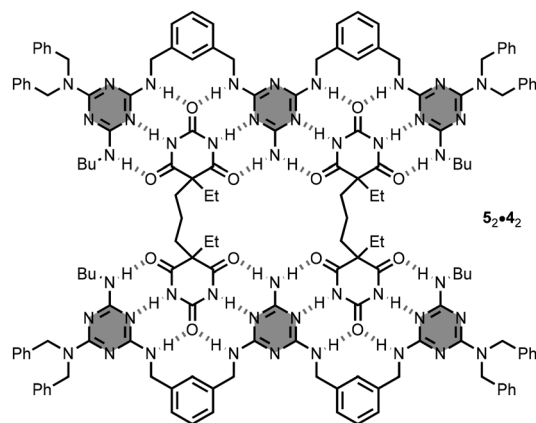


Fig. 4 Structure of the 2 : 2 complex, **5₂·4₂**.¹⁸

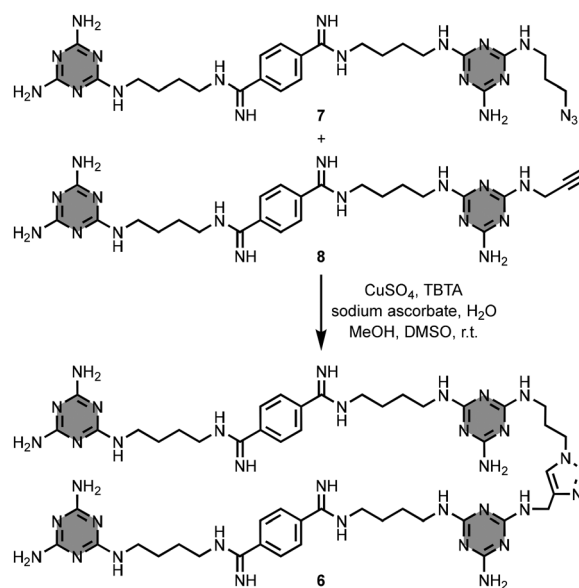


Fig. 5 Synthesis of 1,3,5-triazine-based linear oligomer **6**.²⁰

is decorated with a number of different side-chains (Fig. 6a and b).²¹ Starting from a resin with terminal amino groups, the synthetic approach consists of iterative *S_NAr* reactions between functionalised dichlorotriazine units and 1,2-ethylenediamine linkers. These linkers in the backbone provide conformational flexibility and sites for hydrogen-bonding interactions, but the supramolecular assembly properties of these systems were not characterised experimentally.^{22,23} Related oligomers were explored to assess their potential as therapeutic agents.²⁴

Hunter *et al.* have developed a series of linear oligomers featuring a triazine–piperazine backbone equipped with phenol and phosphine oxide side-chains (REMO).²⁵ In this case, the nitrogen atoms of the triazine units in the backbone are sterically blocked by the piperazine linkers, so they cannot act as hydrogen-bonding acceptor groups. The side-chains appended to the backbone are the recognition units that



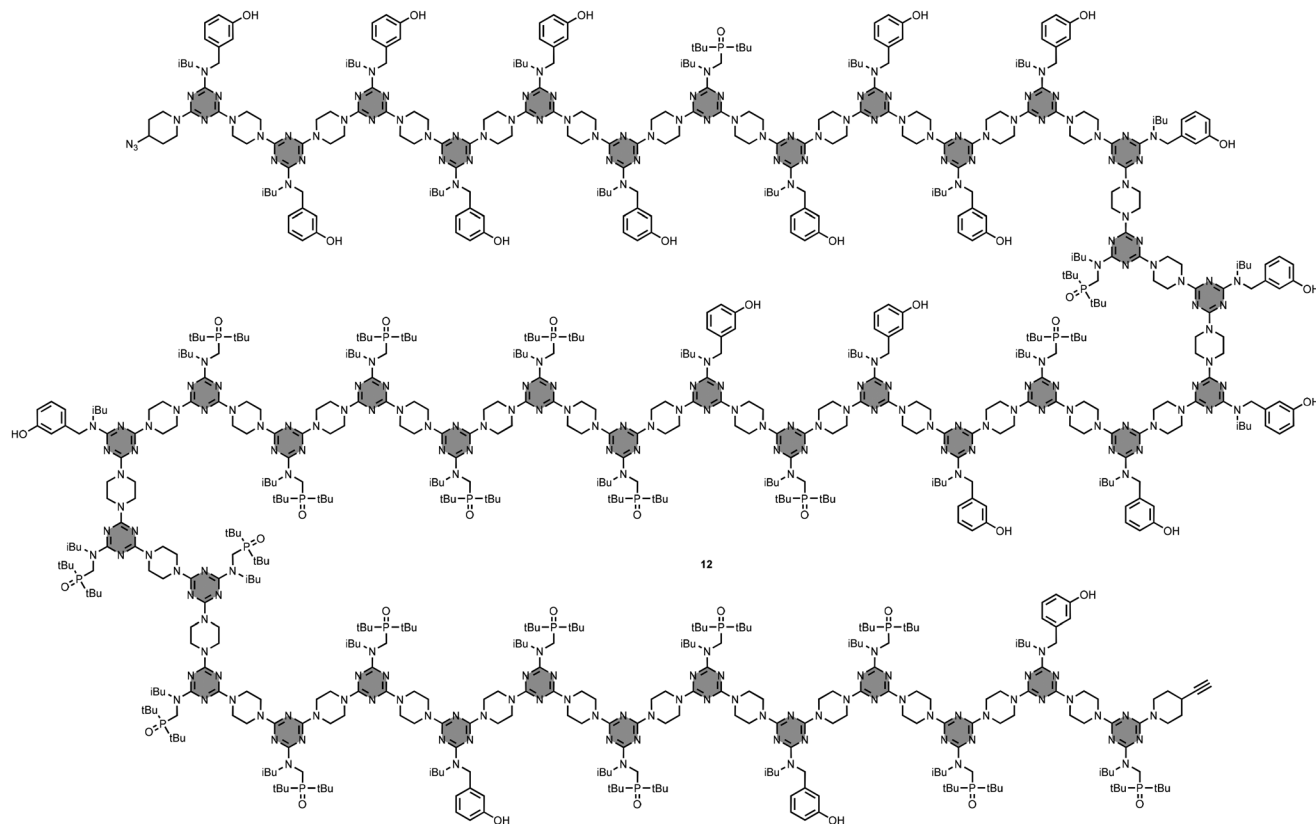


Fig. 8 Structure of REMO 12 prepared by automated solid-phase synthesis.²⁶

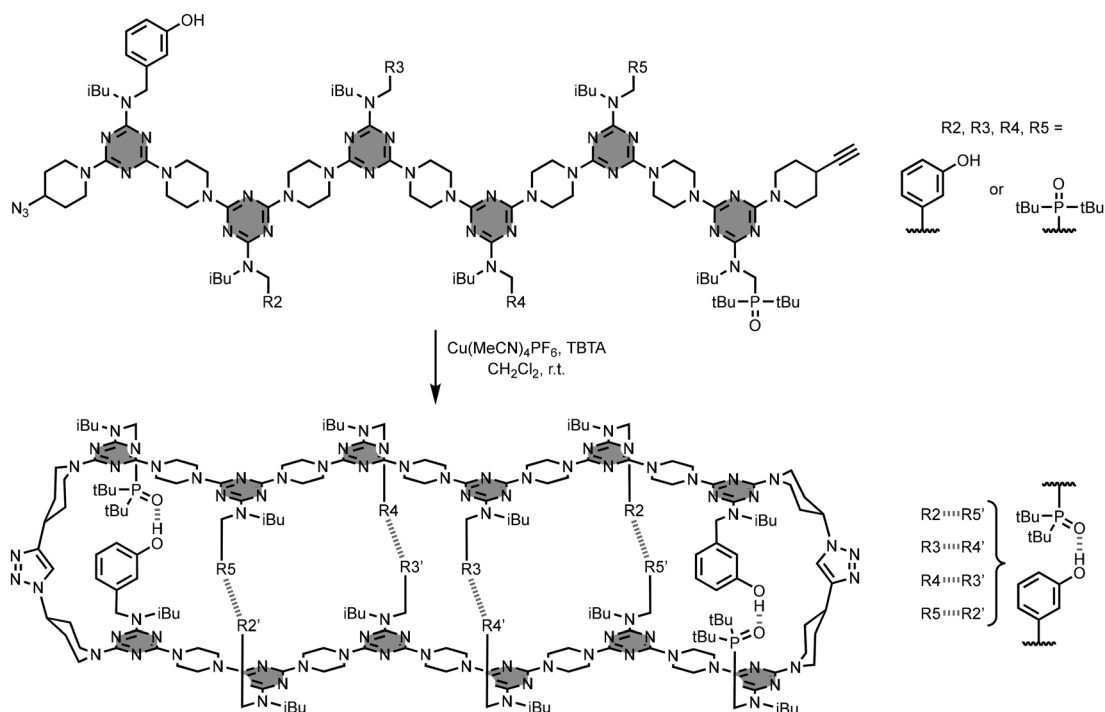


Fig. 9 Trapping of REMO duplexes in a library of mixed sequence 6-mers. All possible combinations of the two recognition side-chains are present at positions R2–R5 on the oligomers.²⁷



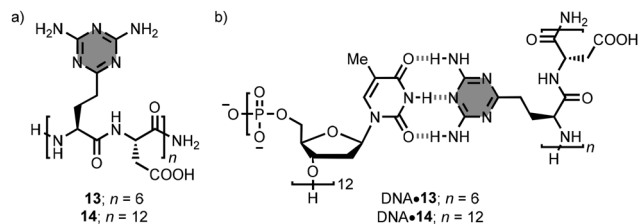


Fig. 10 Structures of (a) 1,3,5-triazine-based linear oligomers **13**–**14**, and (b) heteroduplexes DNA-**13**/**14**.²⁸

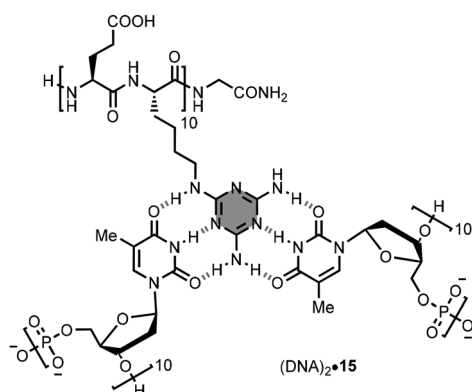


Fig. 11 Structure of the 2 : 1 complex formed by **15** with DNA.²⁹

ation and carbamation reactions.³³ The oligomer **16** formed an heteroduplex with the 3-mer oligomer **17**, comprised of thymine nucleobases (Fig. 12). There are 9 intermolecular hydrogen-bonding interactions in the heteroduplex **16**•**17**, and the association constant is $7.9 \times 10^4 \text{ M}^{-1}$ in chloroform solution. Binding studies with a series of linear oligomers indicate positive cooperativity in the self-assembly process.

3. Macrocycles

1,3,5-Triazine-based macrocycles consist of triazine units linked together by either diamines or diols in a cyclic fashion.

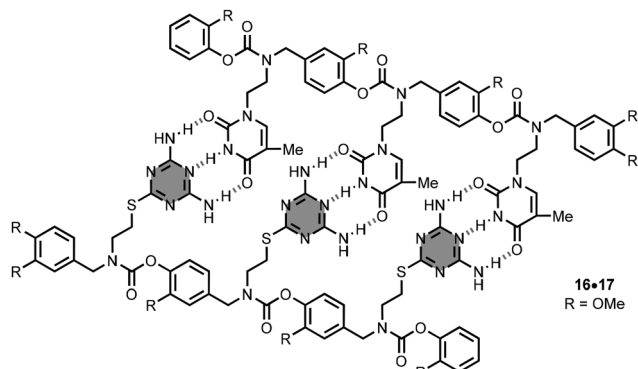


Fig. 12 Structure of the heteroduplex **16**•**17**.³³

The macrocycles bearing hydrogen-bonding donor and acceptor groups can recognise complementary substrates, such as cyanuric acid, barbituric acid derivatives, and monosaccharides. The macrocycles can also bind mono- and polyatomic anions by establishing anion- π interactions with the triazine units.

Typically, the synthesis of 1,3,5-triazine-based macrocycles requires the preparation of the linear precursor, followed by an intramolecular macrocyclisation reaction. Lowe and co-workers reported a series of macrocycles (*i.e.* 3-, 4-, 5-, and 6-mers) having piperazine linkers. Preparation of the macrocycles **18** from the linear precursors **19** involved removal of the Boc-protecting group of the terminal piperazine unit in **19**, macrocyclisation, and substitution of the remaining chlorine atom with a primary amine (Fig. 13).^{34,35} Although these macrocycles have a bowl-shaped cavity, the molecular recognition properties were not investigated. It is worth mentioning that the preorganisation of the terminal reacting groups by intramolecular hydrogen-bonds in the linear precursor can lead to excellent yields in the macrocyclisation reaction.^{36–38}

The research group of Lowe prepared macrocycle **20** using *m*-xylenediamine linkers.³⁵ The structure of **20** has an array of hydrogen-bond donors and acceptors inwardly-directed into the central cavity. Excellent complementarity with cyanuric acid **21** was found with possibility for 9 intermolecular hydrogen-bonds (Fig. 14). Addition of **21** to **20** leads to the formation of a 1 : 1 complex, **21**•**20**, with an association constant of $2.5 \times 10^4 \text{ M}^{-1}$ in chloroform solution. Macrocycle **20** is also capable

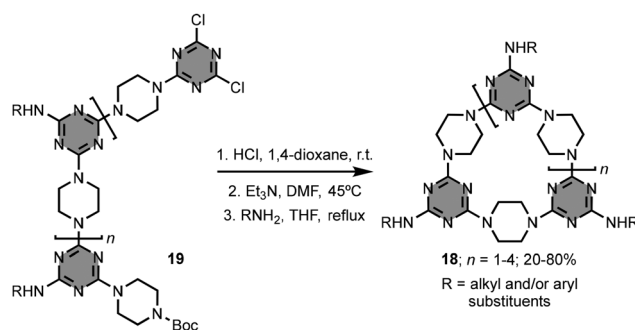


Fig. 13 Synthesis of 1,3,5-triazine-based macrocycles **18**.^{34,35}

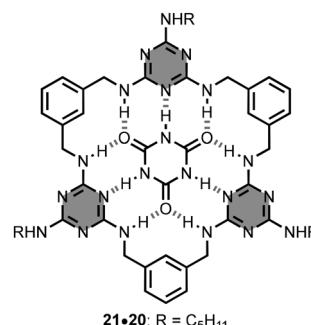


Fig. 14 Structure of the **21**•**20** complex.³⁵

of binding octyl glycosides in the same solvent.³⁵ These complexes have a 1 : 1 stoichiometry and association constants in the range 10^3 – 10^4 M⁻¹. Replacing the *m*-xylylenediamine linkers by *m*-phenylenediamine counterparts in the macrocycle prevented the binding with the same substrates.³⁹

Kondo and co-workers employed a similar macrocycle with *m*-xylylenediamine linkers to study complexation of barbitol.⁴⁰ In this case, 1 : 1 and 2 : 1 complexes were observed in chloroform solution. The association constants, $K_{1:1} = 4.2 \times 10^4$ M⁻¹ and $K_{2:1} = 2.4 \times 10^2$ M⁻¹, indicate negative cooperativity for the binding of the second guest molecule. An X-ray crystal structure of the 2 : 1 complex showed that one barbitol molecule binds to two of the melamine units through 6 hydrogen-bonding interactions, and the other barbitol molecule forms 3 hydrogen-bonds with the remaining melamine unit.

Wang *et al.* developed a series of oxygen-bridged calix[2]arene[2]triazine macrocycles.^{41–46} These macrocycles are fixed in a 1,3-alternate conformation and possess a cleft-like cavity. For example, the macrocycle **22** contains two opposing monochlorotriazine units connected by 1,3-benzenediol linkers (Fig. 15a).⁴⁷ In acetonitrile solution, the macrocycle **22** forms 1 : 1 complexes with anions, such as chloride, nitrate and hexafluorophosphate, with association constants between 10^2 and 10^4 M⁻¹.^{48,49} In these complexes, the substrates make anion- π interactions with the receptor. The attachment of an aza-crown ether moiety at the R² positions gave ion-pair receptors.⁵⁰ Functionalisation of the R³ positions with hydroxyl groups in **23** enabled the binding of neutral substrates, such as 2,2'-bipyridine **24**, 4,4'-bipyridine **25** and 1,10-phenanthroline **26**, *via* hydrogen-bonding interactions (Fig. 15a and b).⁵¹ The association constants for formation of 1 : 1 complexes are between 10 and 10^2 M⁻¹ in chloroform solution. Structurally related macrocycles were used as receptors in enantioselective molecular recognition and were incorporated into lipid membranes to act as ion-pair carriers.^{52–56}

Calix[2]arene[2]triazine macrocycles with nitrogen bridges were also reported.⁵⁷ Moiteiro, Félix and co-workers decorated the macrocycles **27** and **28** with amide or urea groups at the R² positions (Fig. 16a).^{58,59} Macrocycle **27** bound aromatic carboxylate anions in dimethyl sulfoxide solution. The association constants of the 1 : 1 anionic complexes formed with benzoate **29** and isophthalate **30** are between 10 and 10^3 M⁻¹ (Fig. 16b).

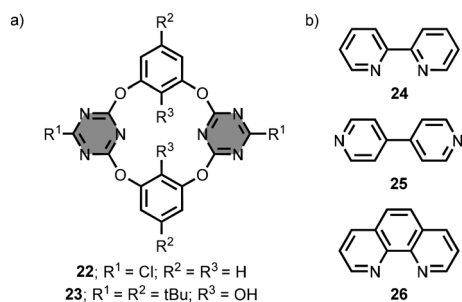


Fig. 15 Structures of (a) 1,3,5-triazine-based macrocycles **22**–**23**, and (b) substrates **24**–**26**.^{47–49,51}

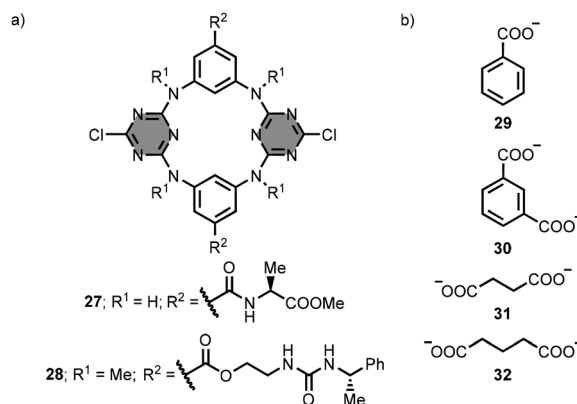


Fig. 16 Structures of (a) 1,3,5-triazine-based macrocycles **27**–**28**, and (b) substrates **29**–**32** (used as tetrabutylammonium salts).^{58,59}

Macrocycle **28** formed ion-pair complexes with the tetraalkylammonium salts of aliphatic carboxylate anions in chloroform solution. The association constants of the complexes formed with tetrabutylammonium succinate **31** and glutarate **32** are between 10^2 and 10^3 M⁻¹ (Fig. 16b). In addition, the authors described a calix[2]arene[2]triazine macrocycle with carboxylate groups at R¹ for the coordination of Cu(II) ions.⁶⁰

Kusano, Hayashida and co-workers reported macrocycle **33**, which has an aromatic cavity defined by two diphenylmethane and two triazine units (Fig. 17).⁶¹ The macrocycle **33** also bears six carboxylate groups to ensure water solubility. In buffer solution at pH 7.4, addition of the diammonium anthracene derivative **34** (Fig. 17) gave a 1 : 1 complex with the anthracene moiety included within the hydrophobic aromatic cavity of **33**, leading to an association constant between 10^3 and 10^4 M⁻¹.

Triazine macrocycles with larger cavities have been described.^{62–66} Wang *et al.* prepared the bis-calix[2]arene[2]triazine macrocycle **35** (Fig. 18).⁶⁷ Binding studies in chloroform solution showed low affinity interactions (association constants less than 10 M⁻¹) with tetrabutylammonium salts of carboxylate anions, such as 2-carboxyacetate **36** (Fig. 18).

Macrobicycle **37** is based on two 1,3,5-triazine-based aromatic panels bridged by three diphenylmethanes (Fig. 19a).⁶⁸ This architecture provides an aromatic cavity suitable for the inclusion of planar aromatic substrates, such as **38** (Fig. 19a). Association constants were measured in a range of different solvents with values as high as 10^5 M⁻¹ in dimethyl sulfoxide solution.

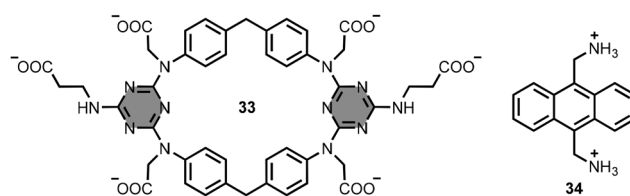


Fig. 17 Structures of 1,3,5-triazine-based macrocycle **33** and substrate **34** (used as sodium and chloride salts, respectively).⁶¹



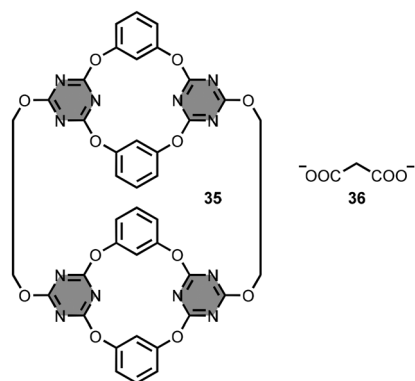


Fig. 18 Structures of 1,3,5-triazine-based macrocycle **35** and substrate **36** (used as tetrabutylammonium salt).⁶⁷

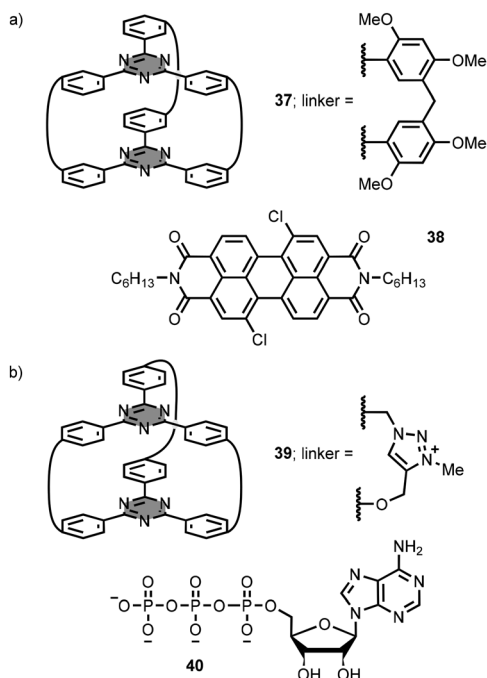


Fig. 19 Structures of (a) macrocycle **37** and substrate **38**, and (b) macrocycle **39** and substrate **40** (used as chloride and sodium salts, respectively).^{68,69}

Natarajan *et al.* synthesised a similar macrobicyclic **39** using a CuAAC reaction followed by methylation of the triazoles (Fig. 19b).⁶⁹ The water-soluble tricationic receptor exhibits binding selectivity for adenosine-5'-triphosphate **40** (Fig. 19b) with an association constant of 10^4 M^{-1} in aqueous buffer at pH 7.4.

4. Branched oligomers

1,3,5-Triazine-based branched oligomers have been prepared with a central hub and spokes containing melamine residues as recognition units. In solution, these branched oligomers form hydrogen-bonded assemblies, called rosettes, with either isocyanuric or barbituric acid derivatives.

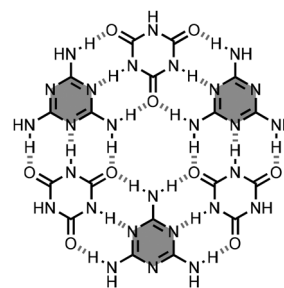


Fig. 20 Structure of melamine-cyanuric acid rosette.^{3,70}

Previous studies showed that the combination of melamine with isocyanuric acid in a 1 : 1 ratio produces a 2D hydrogen-bonded network.³ This 2D network contains the hydrogen-bonded rosette motif shown in Fig. 20.^{70–72} To control the formation of these rosettes in solution, one approach is preorganisation of the three melamine units using branched oligomers.

Whitesides and co-workers reported a series of branched melamine oligomers, and studied their self-assembly properties with isocyanuric acid derivatives.⁷³ The synthesis of the branched oligomers involved reaction of 1,3,5-benzenetricarbonyl trichloride (*i.e.* central hub) with 3 equivalents of a linear 1,3,5-triazine-based oligomer functionalised with a primary amine (*i.e.* spoke). For example, the branched oligomer **41** has aromatic amide linkers that connect the three terminal melamine units to the central hub (Fig. 21a).^{74–77} Addition of *neo*-hexyl isocyanurate **42** to **41** leads to the 3 : 1

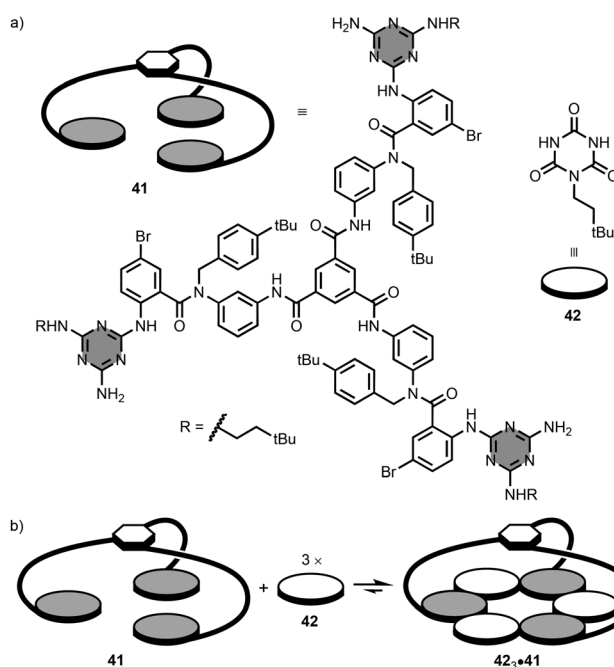


Fig. 21 (a) Structures of 1,3,5-triazine-based branched oligomer **41** and isocyanuric acid derivative **42**, and (b) self-assembly of the 3 : 1 complex, **42**₃·**41**.^{74,75}



complex, **42**₃·**41**, in chloroform solution (Fig. 21b). The complex contains one rosette stabilised by 18 hydrogen-bonding interactions between the three melamine units of **41** and the three molecules of **42**. It is worth mentioning that intermediate complexes (*i.e.* 1:1 and 2:1) were not detected in the titration, indicating that the self-assembly process displays positive cooperativity.

Bong *et al.* designed a similar branched oligomer with three terminal melamine units attached to a phospholipid central hub through alkyl amide linkers.^{78,79} This oligomer was incorporated into the lipid membranes of vesicles, and an analogue bearing three terminal isocyanurate units was incorporated into separate vesicles. In phosphate buffer at pH 6.7–7.4, the formation of a rosette involving the complementary branched oligomers promoted the interaction between the two types of vesicles. A similar approach was used for the binding of peptides to lipid membranes and the establishment of protein–protein assemblies.^{80,81}

The research group of Whitesides also increased the number of melamine units incorporated into the branched oligomers. Branched oligomer **43** has six melamine units: three are located at internal positions and the other three at terminal positions, separated by *m*-xylyl linkers (Fig. 22a).⁸² In the

presence of **42**, a 6:1 complex is formed with positive cooperativity in chloroform solution (Fig. 22b). The **42**₆·**43** complex has two stacked rosettes with a total of 36 hydrogen-bonding interactions. The combination of bis-isocyanurate derivatives with either **41** or **43** also yielded assemblies featuring two stacked rosettes.^{82–84} Similarly, branched oligomer **44**, which

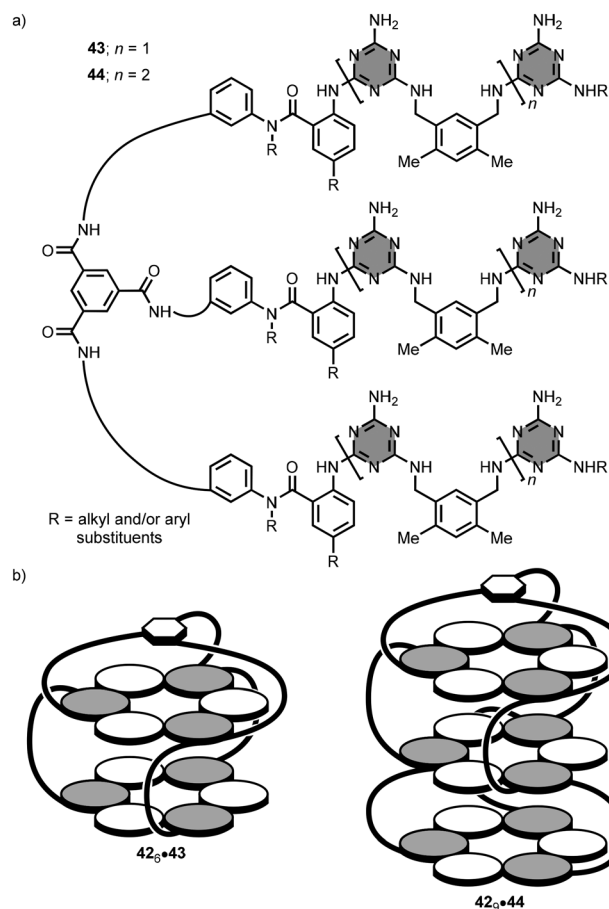


Fig. 22 Structures of (a) 1,3,5-triazine-based branched oligomers **43**–**44**, and (b) **42**₆·**43** and **42**₉·**44** complexes.^{82,85}

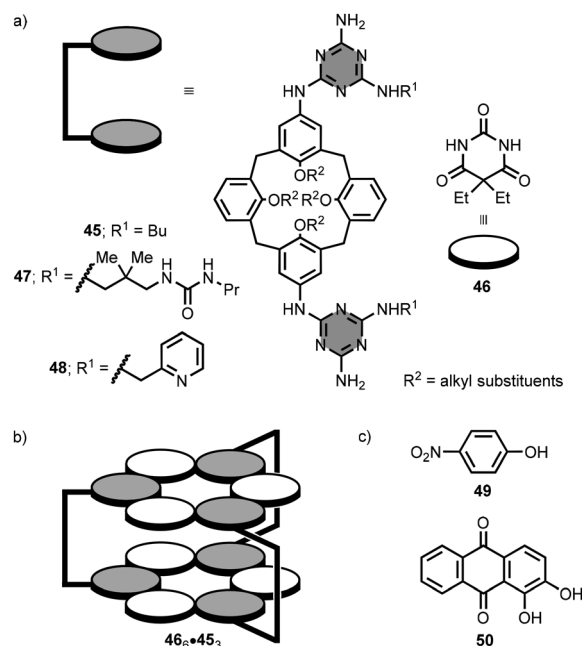


Fig. 23 Structures of (a) 1,3,5-triazine-based calix[4]arene macrocycles **45**, **47** and **48** and barbituric acid derivative **46**, (b) **46**₆·**45**₃ complex, and (c) substrates **49** and **50**.^{90–92}

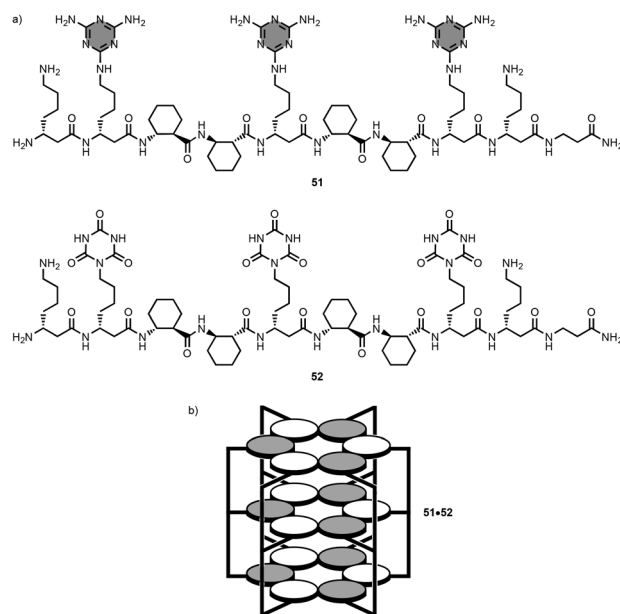


Fig. 24 Structures of (a) 1,3,5-triazine-based linear oligomers **51**–**52**, and (b) **51**·**52** complex.⁹³



has nine melamine units, formed three stacked rosettes with nine molecules of **42** (Fig. 22a and b).⁸⁵ The resulting **42**₉·**44** complex is held together by a total of 54 hydrogen-bonding interactions.

A number of other research groups have used either macrocycles or linear oligomers to preorganise melamine units for the self-assembly of stacked rosettes. Reinhoudt and co-workers employed a series of calix[4]arene macrocycles with melamine

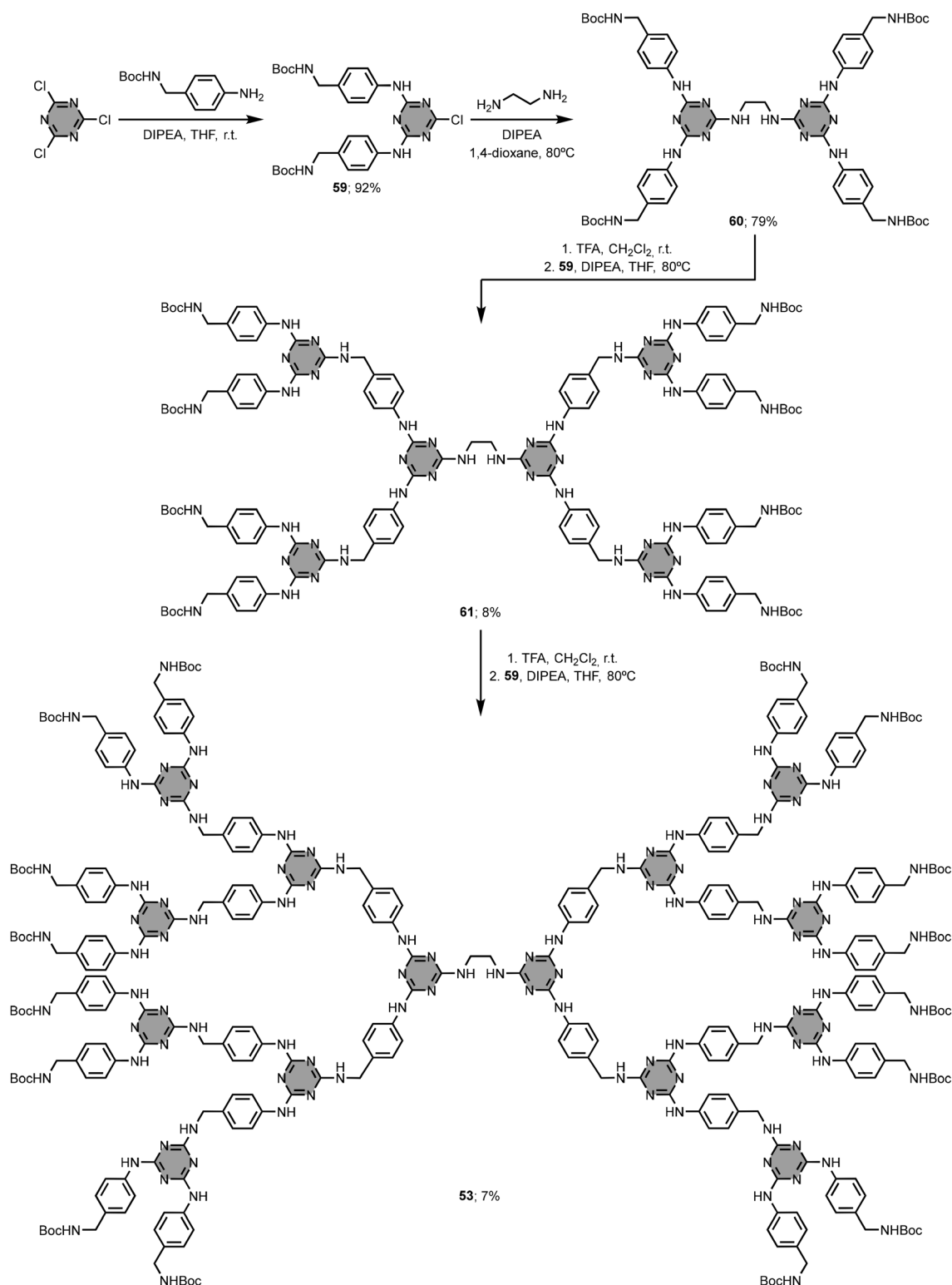


Fig. 25 Divergent synthesis of 1,3,5-triazine-based dendrimer **53**.¹⁰²



units at the upper rim in combination with barbituric acid derivatives.^{86–89} For example, the calix[4]arene macrocycle **45** features two opposing melamine units decorated with *n*-butyl groups (Fig. 23a).⁹⁰ The addition of 5,5-diethylbarbituric acid **46** to a chloroform solution of **45** gave the 6 : 3 complex, **46**·**45**₃, containing two stacked rosettes (Fig. 23b). Replacing the *n*-butyl groups on the melamine units by urea or pyridyl groups in **47** and **48**, respectively (Fig. 23a), endows the two stacked rosettes with additional molecular recognition properties.^{91,92} Both **46**·**47**₃ and **46**·**48**₃ can interact with polar aromatic substrates in chloroform solution. While six molecules of 4-nitrophenol **49** bind at the periphery of **46**·**47**₃, three molecules of alizarin **50** (Fig. 23c) are encapsulated within **46**·**48**₃ via hydrogen-bonding and aromatic stacking interactions.

Diederichsen *et al.* prepared the 10-mer linear oligomers **51** and **52** featuring three melamine and three isocyanurate side-chains, respectively, using an automated solid-phase peptide synthesiser (Fig. 24a).⁹³ In acetate buffer at pH 7.4, the peptide backbone of **51** and **52** adopt a right-handed helical conformation that arranges the complementary recognition units for self-assembly of three stacked rosettes (Fig. 24b).

5. Dendrimers

1,3,5-Triazine-based dendrimers are comprised of melamine branching units linked to a central core.^{94,95} The branching units possess terminal functional groups exposed at the surface of the dendrimer. The number of branching points defines the dendrimer generation (*i.e.* *G_n*, where *n* is the generation number), which determines the overall size and the number of terminal groups. In aqueous solution, 1,3,5-triazine-based dendrimers adopt globular three-dimensional structures, and have been found to bind hydrophobic compounds.

In general, the construction of 1,3,5-triazine-based dendrimers follows either a divergent or a convergent synthetic approach.^{96–101} While the divergent approach consists of synthesising the dendrimer from the central core to the periphery, the convergent approach involves the preparation of the branching units (dendrons) that are then attached to the central core. Simanek and co-workers compared the two synthetic approaches for the preparation of the third generation (*G*₃) dendrimer **53**.¹⁰² This compound has a 1,2-ethylenedia-

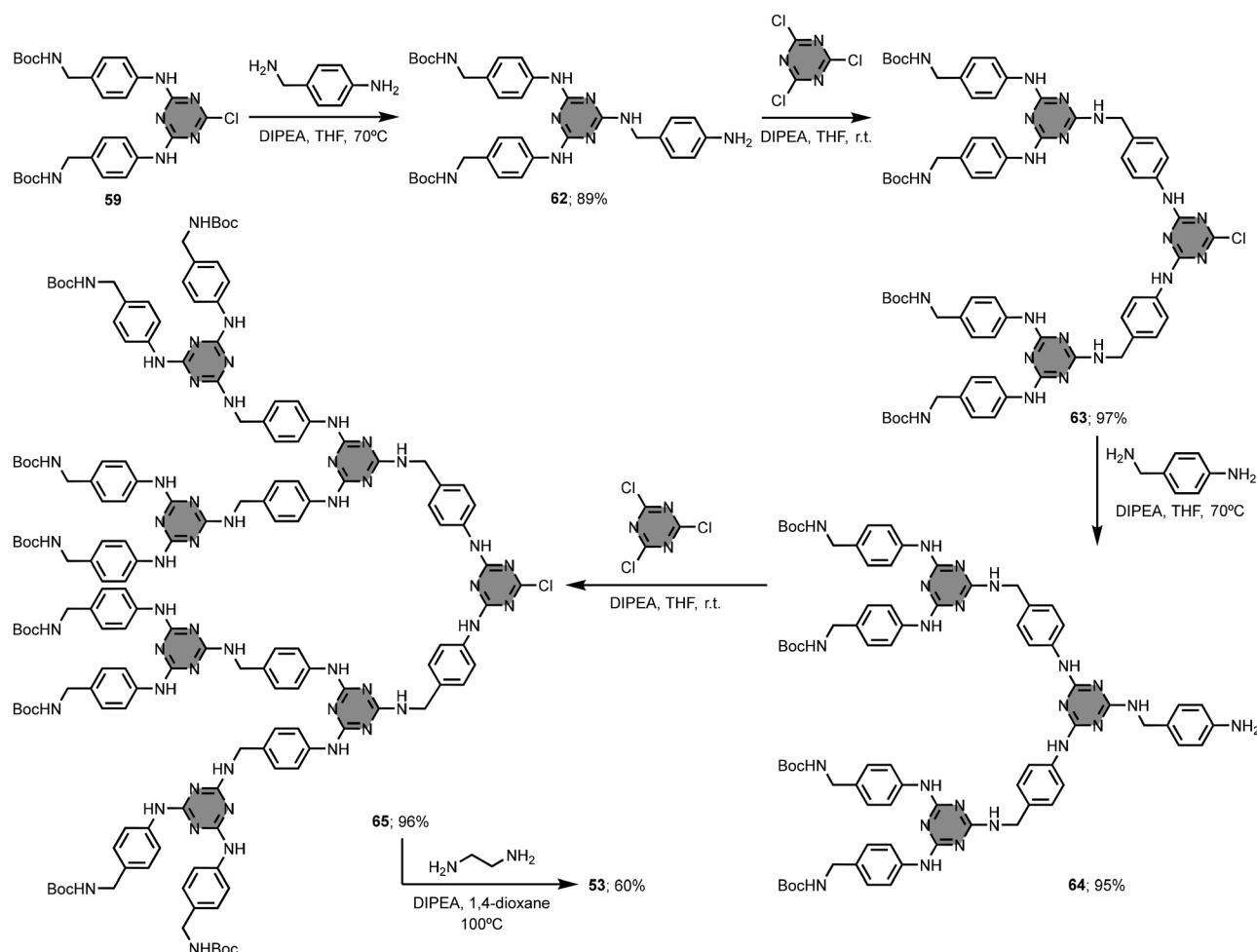
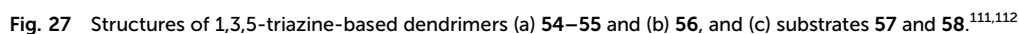


Fig. 26 Convergent synthesis of 1,3,5-triazine-based dendrimer **53**.¹⁰²



lated overall yield of **53** was less than 1%. The convergent approach gave the G3 dendrimer **53** in good yield (47%) and excellent purity (Fig. 26). Although the divergent approach was used to synthesise larger analogues (*e.g.* the G13 dendrimer),^{103,104} it becomes increasingly difficult to identify



defects and separate side-products after each coupling cycle when n is greater than 3, and the overall yields are very low. These issues can be alleviated to some extent using more elaborate monomers (macromonomers).¹⁰⁵ In addition to the high yields, an attractive feature of the convergent approach is that protecting groups are not required on the diamine linkers, provided the two amino groups exhibit sufficiently different reactivities.^{106,107} However, the convergent approach is limited to the synthesis of dendrimers up to G3, since the yield of the final reaction step involving the central core is limited by steric clashes between the large dendrons.

Simanek *et al.* described methods for functionalisation of the peripheral groups on the dendrimers.^{108,109} Incorporation of 48 ionisable groups (*e.g.* amine, guanidine or carboxylate) on the ends of the arms of G3 dendrimers resulted in good solubilities in water.¹¹⁰ It was also possible to selectively functionalise G3 dendrimers with either one or two polyethylene glycol chains bearing Boc-protected amino groups (compounds **54** and **55** in Fig. 27a).¹¹¹ These dendrimers have *n*-butyl groups at the remaining terminal positions.

The research group of Simanek applied dendrimers to the solubilisation of hydrophobic substrates in aqueous solution. Specifically, the G3 dendrimer **56**, equipped with 24 polyethylene glycol chains and terminal amino groups, is capable of binding and increasing the solubilities of pyrene **57** and 10-hydroxycamptothecin **58** in phosphate buffer at pH 7.5 (Fig. 27b and c).¹¹² Using a series of odd generation dendrimers having polyethylene glycol and piperazine linkers, the authors showed that the number of bound hydrophobic substrates increases with the dendrimer generation until G7, but decreases at G9.¹¹³ Based on these findings, preliminary studies were conducted to evaluate the use of 1,3,5-triazine-based dendrimers as drug carriers.¹¹⁴

6. Conclusion and perspectives

In summary, a variety of different types of monodisperse 1,3,5-triazine-based oligomers have been explored featuring distinct structural topologies. Linear oligomers have been prepared by iterative S_NAr reactions in solution or using solid-phase synthesis. The incorporation of recognition units either into the backbone or into the side-chains encodes the formation of hydrogen-bonded duplexes, which resemble the duplex structures of nucleic acids. Intramolecular S_NAr reactions of linear oligomers has been used to obtain the corresponding macrocycles. These cyclic oligomers are capable of binding complementary substrates. Branched oligomers have been synthesised by the attachment of linear oligomers to a central core. In the presence of complementary isocyanuric or barbituric acid derivatives, branched melamine oligomers self-assemble into hydrogen-bonded rosettes. Finally, the dendrimers with branching units linked to a central core have been prepared by either divergent or convergent synthetic approaches involving S_NAr reactions. The dendrimers adopt globular three-dimensional structures in aqueous solution and can

encapsulate hydrophobic substrates in their interior. The synthetic accessibility of monodisperse 1,3,5-triazine-based oligomers makes them an attractive target for applications in different areas of research, such as in supramolecular chemistry, polymer science, materials science, and chemical biology, and the advent of automated synthesis opens the way for rapid development of these platforms.

Author contributions

Conceptualisation, L. E. and C. A. H.; funding acquisition, C. A. H.; writing – original draft, L. E.; writing – review and editing, L. E. and C. A. H.

Data availability

This is a review article that does not report original data.

Conflicts of interest

There are no conflicts to declare.

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References

- G. Giacomelli, A. Porcheddu and L. De Luca, *Curr. Org. Chem.*, 2004, **8**, 1497–1519.
- G. Blotny, *Tetrahedron*, 2006, **62**, 9507–9522.
- P. Gamez and J. Reedijk, *Eur. J. Inorg. Chem.*, 2006, 29–42.
- T. J. Mooibroek and P. Gamez, *Inorg. Chim. Acta*, 2007, **360**, 381–404.
- J. M. Oliva, M. E. D. G. Azenha, H. D. Burrows, R. Coimbra, J. S. Seixas de Melo, M. L. Canle, M. I. Fernández, J. A. Santaballa and L. Serrano-Andrés, *ChemPhysChem*, 2005, **6**, 306–314.
- S. Ronchi, D. Prosperi, F. Compostella and L. Panza, *Synlett*, 2004, 1007–1010.
- M. Kellert, D. J. Worm, P. Hoppenz, M. B. Sárosi, P. Lönnecke, B. Riedl, J. Koeberling, A. G. Beck-Sickinger and E. Hey-Hawkins, *Dalton Trans.*, 2019, **48**, 10834–10844.
- J. Luo, J. Luo, Y. Bai, Q. Gao and J. Li, *RSC Adv.*, 2016, **6**, 67669–67676.
- M. Kunishima, C. Kawachi, J. Monta, K. Terao, F. Iwasaki and S. Tani, *Tetrahedron*, 1999, **55**, 13159–13170.
- X.-P. Hu, H.-L. Chen and Z. Zheng, *Adv. Synth. Catal.*, 2005, **347**, 541–548.
- B. Roy, P. Baire and A. K. Nandi, *RSC Adv.*, 2014, **4**, 1708–1734.
- J. D. Watson and F. H. C. Crick, *Nature*, 1953, **171**, 737–738.



- 13 E. A. Archer, A. E. Sochia and M. J. Krische, *Chem. – Eur. J.*, 2001, **7**, 2059–2065.
- 14 E. A. Archer, H. Gong and M. J. Krische, *Tetrahedron*, 2001, **57**, 1139–1159.
- 15 E. A. Archer, N. T. Goldberg, V. Lynch and M. J. Krische, *J. Am. Chem. Soc.*, 2000, **122**, 5006–5007.
- 16 E. A. Archer, D. F. Cauble, V. Lynch and M. J. Krische, *Tetrahedron*, 2002, **58**, 721–725.
- 17 E. A. Archer and M. J. Krische, *J. Am. Chem. Soc.*, 2002, **124**, 5074–5083.
- 18 P. Lipkowski, A. Bielejewska, P. Timmerman, D. N. Reinhoudt, H. Kooijman and A. L. Spek, *Chem. Commun.*, 1999, 1311–1312.
- 19 M. Arduini, M. Crego-Calama, P. Timmerman and D. N. Reinhoudt, *J. Org. Chem.*, 2003, **68**, 1097–1106.
- 20 L. M. Luu, L. Nguyen, S. Peng, J. Lee, H. Y. Lee, C.-H. Wong, P. J. Hergenrother, H. Y. E. Chan and S. C. Zimmerman, *ChemMedChem*, 2016, **11**, 1428–1435.
- 21 J. W. Grate, K.-F. Mo and M. D. Daily, *Angew. Chem., Int. Ed.*, 2016, **55**, 3925–3930.
- 22 S.-H. Ahn, J. W. Grate and E. F. Darve, *J. Chem. Phys.*, 2018, **149**, 072330.
- 23 S.-H. Ahn and J. W. Grate, *J. Phys. Chem. B*, 2019, **123**, 9364–9377.
- 24 P. Gunasekaran, M. Fan, E. Y. Kim, J. H. Shin, J. E. Lee, E. J. Son, J. Kim, E. Hwang, M. S. Yim, E.-H. Kim, Y.-J. Choi, Y.-H. Lee, Y.-H. Chung, H. N. Kim, E. K. Ryu, S. Y. Shin, E.-K. Kim and J. K. Bang, *Sci. Rep.*, 2019, **9**, 15161.
- 25 P. Troselj, P. Bolgar, P. Ballester and C. A. Hunter, *J. Am. Chem. Soc.*, 2021, **143**, 8669–8678.
- 26 M. Dhiman, R. Cabot and C. A. Hunter, *Chem. Sci.*, 2024, **15**, 5957–5963.
- 27 M. Dhiman, R. Cons, O. N. Evans, J. T. Smith, C. J. Anderson, R. Cabot, D. O. Soloviev and C. A. Hunter, *J. Am. Chem. Soc.*, 2024, **146**, 9326–9334.
- 28 G. K. Mittapalli, K. R. Reddy, H. Xiong, O. Munoz, B. Han, F. De Riccardis, R. Krishnamurthy and A. Eschenmoser, *Angew. Chem., Int. Ed.*, 2007, **46**, 2470–2477.
- 29 Y. Zeng, Y. Pratumyot, X. Piao and D. Bong, *J. Am. Chem. Soc.*, 2012, **134**, 832–835.
- 30 X. Xia, X. Piao and D. Bong, *J. Am. Chem. Soc.*, 2014, **136**, 7265–7268.
- 31 X. Xia, X. Piao, K. Fredrick and D. Bong, *ChemBioChem*, 2014, **15**, 31–36.
- 32 J. Mao and D. Bong, *Synlett*, 2015, 1581–1585.
- 33 R. K. Weigel and C. A. Alabi, *Chem. Sci.*, 2024, **15**, 9138–9146.
- 34 D. W. P. M. Löwik and C. R. Lowe, *Tetrahedron Lett.*, 2000, **41**, 1837–1840.
- 35 D. W. P. M. Löwik and C. R. Lowe, *Eur. J. Org. Chem.*, 2001, 2825–2839.
- 36 J. A. Zerkowski, L. M. Hensley and D. Abramowitz, *Synlett*, 2002, 557–560.
- 37 V. R. Sharma, A. Mehmood, B. G. Janesko and E. E. Simanek, *RSC Adv.*, 2020, **10**, 3217–3220.
- 38 A. J. Menke, N. C. Henderson, L. C. Kouretas, A. N. Estenson, B. G. Janesko and E. E. Simanek, *Molecules*, 2023, **28**, 1144.
- 39 X. Yang and C. R. Lowe, *Tetrahedron Lett.*, 2003, **44**, 1359–1362.
- 40 S.-I. Kondo, T. Hayashi, Y. Sakuno, Y. Takezawa, T. Yokoyama, M. Unno and Y. Yano, *Org. Biomol. Chem.*, 2007, **5**, 907–916.
- 41 S. Li, D.-X. Wang and M.-X. Wang, *Tetrahedron Lett.*, 2012, **53**, 6226–6229.
- 42 D.-X. Wang, S.-X. Fa, Y. Liu, B.-Y. Hou and M.-X. Wang, *Chem. Commun.*, 2012, **48**, 11458–11460.
- 43 W. Liu, Q.-Q. Wang, Z.-T. Huang and D.-X. Wang, *Tetrahedron Lett.*, 2014, **55**, 3172–3175.
- 44 W. Liu, Q.-Q. Wang, Y. Wang, Z.-T. Huang and D.-X. Wang, *RSC Adv.*, 2014, **4**, 9339–9342.
- 45 R.-B. Xu, Q.-Q. Wang, Y.-F. Ao and D.-X. Wang, *Supramol. Chem.*, 2018, **30**, 568–574.
- 46 X.-C. Li, Y. Cheng, X.-D. Wang, S. Tong and M.-X. Wang, *Chem. Sci.*, 2024, **15**, 3610–3615.
- 47 M.-X. Wang and H.-B. Yang, *J. Am. Chem. Soc.*, 2004, **126**, 15412–15422.
- 48 D.-X. Wang, Q.-Y. Zheng, Q.-Q. Wang and M.-X. Wang, *Angew. Chem., Int. Ed.*, 2008, **47**, 7485–7488.
- 49 D.-X. Wang and M.-X. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 892–897.
- 50 Y. Chen, D.-X. Wang, Z.-T. Huang and M.-X. Wang, *Chem. Commun.*, 2011, **47**, 8112–8114.
- 51 Q.-Q. Wang, D.-X. Wang, H.-B. Yang, Z.-T. Huang and M.-X. Wang, *Chem. – Eur. J.*, 2010, **16**, 7265–7275.
- 52 Q. He, Y. Han, Y. Wang, Z.-T. Huang and D.-X. Wang, *Chem. – Eur. J.*, 2014, **20**, 7486–7491.
- 53 Q. He, Z.-T. Huang and D.-X. Wang, *Chem. Commun.*, 2014, **50**, 12985–12988.
- 54 X.-D. Wang, S. Li, Y.-F. Ao, Q.-Q. Wang, Z.-T. Huang and D.-X. Wang, *Org. Biomol. Chem.*, 2016, **14**, 330–334.
- 55 S. Bozkurt and M. B. Türkmen, *Tetrahedron: Asymmetry*, 2016, **27**, 443–447.
- 56 H. N. Genc, *J. Inclusion Phenom. Macrocyclic Chem.*, 2019, **94**, 75–83.
- 57 Q.-Q. Wang, D.-X. Wang, H.-W. Ma and M.-X. Wang, *Org. Lett.*, 2006, **8**, 5967–5970.
- 58 A. I. Vicente, J. M. Caio, J. Sardinha, C. Moiteiro, R. Delgado and V. Félix, *Tetrahedron*, 2012, **68**, 670–680.
- 59 M. M. Santos, I. Marques, S. Carvalho, C. Moiteiro and V. Félix, *Org. Biomol. Chem.*, 2015, **13**, 3070–3085.
- 60 J. M. Caio, T. Esteves, S. Carvalho, C. Moiteiro and V. Félix, *Org. Biomol. Chem.*, 2014, **12**, 589–599.
- 61 S. Kusano, S. Konishi, R. Ishikawa, N. Sato, S. Kawata, F. Nagatsugi and O. Hayashida, *Eur. J. Org. Chem.*, 2017, 1618–1623.
- 62 M. Xue and C.-F. Chen, *Org. Lett.*, 2009, **11**, 5294–5297.
- 63 M. M. Naseer, D.-X. Wang, L. Zhao, Z.-T. Huang and M.-X. Wang, *J. Org. Chem.*, 2011, **76**, 1804–1813.
- 64 T. Jiao, G. Wu, L. Chen, C.-Y. Wang and H. Li, *J. Org. Chem.*, 2018, **83**, 12404–12410.



- 65 J. Luo, J. Zhu, D.-H. Tuo, Q. Yuan, L. Wang, X.-B. Wang, Y.-F. Ao, Q.-Q. Wang and D.-X. Wang, *Chem. – Eur. J.*, 2019, **25**, 13275–13279.
- 66 S. Fang, Z. Bao, Z. Liu, Z. Wu, J.-P. Tan, X. Wei, B. Li and T. Wang, *Angew. Chem., Int. Ed.*, 2024, **63**, e202411889.
- 67 J. Luo, Y.-F. Ao, Q.-Q. Wang and D.-X. Wang, *Angew. Chem., Int. Ed.*, 2018, **57**, 15827–15831.
- 68 X. Zhao, H. Cui, L. Guo, B. Li, J. Li, X. Jia and C. Li, *Angew. Chem., Int. Ed.*, 2024, **63**, e202411613.
- 69 S. Maji, J. Samanta and R. Natarajan, *Chem. – Eur. J.*, 2024, **30**, e202303596.
- 70 J. A. Zerkowski, C. T. Seto and G. M. Whitesides, *J. Am. Chem. Soc.*, 1992, **114**, 5473–5475.
- 71 J. P. Mathias, E. E. Simanek and G. M. Whitesides, *J. Am. Chem. Soc.*, 1994, **116**, 4326–4340.
- 72 J. P. Mathias, E. E. Simanek, J. A. Zerkowski, C. T. Seto and G. M. Whitesides, *J. Am. Chem. Soc.*, 1994, **116**, 4316–4325.
- 73 G. M. Whitesides, J. P. Mathias and C. T. Seto, *Science*, 1991, **254**, 1312–1319.
- 74 C. T. Seto and G. M. Whitesides, *J. Am. Chem. Soc.*, 1990, **112**, 6409–6411.
- 75 C. T. Seto and G. M. Whitesides, *J. Am. Chem. Soc.*, 1993, **115**, 905–916.
- 76 E. E. Simanek, M. I. M. Wazeer, J. P. Mathias and G. M. Whitesides, *J. Org. Chem.*, 1994, **59**, 4904–4909.
- 77 D. N. Chin, D. M. Gordon and G. M. Whitesides, *J. Am. Chem. Soc.*, 1994, **116**, 12033–12044.
- 78 M. Ma, Y. Gong and D. Bong, *J. Am. Chem. Soc.*, 2009, **131**, 16919–16926.
- 79 M. Ma and D. Bong, *Langmuir*, 2011, **27**, 8841–8853.
- 80 M. Ma and D. Bong, *Langmuir*, 2011, **27**, 1480–1486.
- 81 M. Ma and D. Bong, *Org. Biomol. Chem.*, 2011, **9**, 7296–7299.
- 82 J. P. Mathias, C. T. Seto, E. E. Simanek and G. M. Whitesides, *J. Am. Chem. Soc.*, 1994, **116**, 1725–1736.
- 83 C. T. Seto and G. M. Whitesides, *J. Am. Chem. Soc.*, 1991, **113**, 712–713.
- 84 C. T. Seto, J. P. Mathias and G. M. Whitesides, *J. Am. Chem. Soc.*, 1993, **115**, 1321–1329.
- 85 J. P. Mathias, E. E. Simanek, C. T. Seto and G. M. Whitesides, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1766–1769.
- 86 P. Timmerman, R. H. Vreekamp, R. Hulst, W. Verboom, D. N. Reinhoudt, K. Rissanen, K. A. Udachin and J. Ripmeester, *Chem. – Eur. J.*, 1997, **3**, 1823–1832.
- 87 L. J. Prins, J. Huskens, F. de Jong, P. Timmerman and D. N. Reinhoudt, *Nature*, 1999, **398**, 498–502.
- 88 P. Timmerman, K. A. Jolliffe, M. Crego Calama, J.-L. Weidmann, L. J. Prins, F. Cardullo, B. H. M. Snellink-Ruël, R. H. Fokkens, N. M. M. Nibbering, S. Shinkai and D. N. Reinhoudt, *Chem. – Eur. J.*, 2000, **6**, 4104–4115.
- 89 M. G. J. ten Cate, M. Omerović, G. V. Oshovsky, M. Crego-Calama and D. N. Reinhoudt, *Org. Biomol. Chem.*, 2005, **3**, 3727–3733.
- 90 R. H. Vreekamp, J. P. M. van Duynhoven, M. Hubert, W. Verboom and D. N. Reinhoudt, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1215–1218.
- 91 J. M. C. A. Kerckhoffs, T. Ishi-i, V. Paraschiv, P. Timmerman, M. Crego-Calama, S. Shinkai and D. N. Reinhoudt, *Org. Biomol. Chem.*, 2003, **1**, 2596–2603.
- 92 M. A. Mateos-Timoneda, J. M. C. A. Kerckhoffs, M. Crego-Calama and D. N. Reinhoudt, *Angew. Chem., Int. Ed.*, 2005, **44**, 3248–3253.
- 93 S. Kabatas Glowacki, K. Koszinowski, D. Hübner, H. Frauendorf, P. Vana and U. Diederichsen, *Chem. – Eur. J.*, 2020, **26**, 12145–12149.
- 94 M. B. Steffensen, E. Hollink, F. Kuschel, M. Bauer and E. E. Simanek, *J. Polym. Sci., Part A: Polym. Chem.*, 2006, **44**, 3411–3433.
- 95 E. E. Simanek, *Molecules*, 2021, **26**, 4774.
- 96 K. Takagi, T. Hattori, H. Kunisada and Y. Yuki, *J. Polym. Sci., Part A: Polym. Chem.*, 2000, **38**, 4385–4395.
- 97 W. Zhang and E. E. Simanek, *Tetrahedron Lett.*, 2001, **42**, 5355–5357.
- 98 W. Zhang, S. O. Gonzalez and E. E. Simanek, *Macromolecules*, 2002, **35**, 9015–9021.
- 99 L.-L. Lai, L.-Y. Wang, C.-H. Lee, Y.-C. Lin and K.-L. Cheng, *Org. Lett.*, 2006, **8**, 1541–1544.
- 100 M. A. Mintzer, L. M. Perez and E. E. Simanek, *Tetrahedron Lett.*, 2010, **51**, 1631–1634.
- 101 A. E. Enciso, Z. M. Abid and E. E. Simanek, *Polym. Chem.*, 2014, **5**, 4635–4640.
- 102 W. Zhang and E. E. Simanek, *Org. Lett.*, 2000, **2**, 843–845.
- 103 H. Crampton, E. Hollink, L. M. Perez and E. E. Simanek, *New J. Chem.*, 2007, **31**, 1283–1290.
- 104 J. Lim, M. Kostianinen, J. Maly, V. C. P. da Costa, O. Annunziata, G. M. Pavan and E. E. Simanek, *J. Am. Chem. Soc.*, 2013, **135**, 4660–4663.
- 105 J. Lim, M. A. Mintzer, L. M. Perez and E. E. Simanek, *Org. Lett.*, 2010, **12**, 1148–1151.
- 106 M. B. Steffensen and E. E. Simanek, *Org. Lett.*, 2003, **5**, 2359–2361.
- 107 K. X. Moreno and E. E. Simanek, *Tetrahedron Lett.*, 2008, **49**, 1152–1154.
- 108 M. B. Steffensen and E. E. Simanek, *Angew. Chem., Int. Ed.*, 2004, **43**, 5178–5180.
- 109 E. Hollink and E. E. Simanek, *Org. Lett.*, 2006, **8**, 2293–2295.
- 110 H.-T. Chen, M. F. Neerman, A. R. Parrish and E. E. Simanek, *J. Am. Chem. Soc.*, 2004, **126**, 10044–10048.
- 111 W. Zhang, D. T. Nowlan, L. M. Thomson, W. M. Lackowski and E. E. Simanek, *J. Am. Chem. Soc.*, 2001, **123**, 8914–8922.
- 112 W. Zhang, J. Jiang, C. Qin, L. M. Pérez, A. R. Parrish, S. H. Safe and E. E. Simanek, *Supramol. Chem.*, 2003, **15**, 607–616.
- 113 J. Lim, G. M. Pavan, O. Annunziata and E. E. Simanek, *J. Am. Chem. Soc.*, 2012, **134**, 1942–1945.
- 114 J. Lim and E. E. Simanek, *Adv. Drug Delivery Rev.*, 2012, **64**, 826–835.

