Tetrahedron 64 (2008) 8558–8570

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Bis-ureidodeazapterin (Bis-DeAP) as a general route to supramolecular star polymers☆

Eric M. Todd, Steven C. Zimmerman *

Department of Chemistry, University of Illinois at Urbana-Champaign, 600 S. Mathews Avenue, Urbana, IL 61801, United States

ARTICLE INFO

Article history:
Received 11 March 2008
Received in revised form 13 May 2008
Accepted 16 May 2008
Available online 21 May 2008

ABSTRACT

Supramolecular recognition unit Bis-DeAP, **1**, containing two high affinity hydrogen-bonding acceptor–acceptor–donor–donor (AADD) arrays was designed to self-assemble into cyclic assemblies. It was prepared through a highly scalable synthesis and was further functionalized with 2-bromo-2-methylpropanoyl bromide and used to initiate the polymerization of methylmethacrylate (MMA). Bis-DeAP–PMMA polymers quantitatively self-assembled into star polymers in toluene. In DMF Bis-DeAP–PMMA forms a mixture of star polymers and unassembled polymers. Bis-DeAP was also functionalized with polyethylene glycol (PEG) polymers. The Bis-DeAP–PEG polymers formed star polymers in DMF; however, higher molecular weight polymeric assembles that varied with concentration were observed in water. Mixing studies in toluene indicated that the self-assembled star polymers are kinetically stable and resist mixing even at elevated temperatures. In DMF, kinetically controlled structures are initially observed, however, mixing occurs at a faster rate and assembled star polymers show a decrease in polydispersity index (PDI) over time. In addition, Bis-DeAP functionalized PS and PMMA were mixed in DMF to generate a star copolymer through self-assembly.

1. Introduction

Significant effort has gone into the development of recognition units for use in supramolecular polymers. Partly this is a result of the unique properties noncovalent interactions can bestow upon polymeric materials.[1] These properties include stimuli responsive and self-healing abilities, as well as, dramatic decreases in melt viscosity, permitting facile processing. The directionality of hydrogen bonds and the ability to prepare modules containing hydrogen-bonding arrays, thereby controlling the strength and specificity of their interactions, has lead to hydrogen bonding occupying a privileged place among the noncovalent forces utilized in supramolecular polymer chemistry.[2] Although numerous recognition units that use hydrogen bonding are available, and several have been used in applications, the ureidopyrimidinone (UPy) hydrogen-bonding module developed by Meijer and co-workers[3] has seen the most widespread use and has maturated to the point of commercialization.[4] More recent advances involve newly developed hydrogen-bonding modules that form heterocomplexes with high fidelity.[5]

The majority of hydrogen-bonding supramolecular polymers previously investigated have been based on individual recognition units connected by flexible linkers (either discrete or polymeric). Flexible linkers allow for a large amount of entropic freedom and typically lead to main-chain random-coil polymers when ditopic modules are used and network polymers when tritopic, or higher, modules are employed (Fig. 1a). An alternative approach is to fix the hydrogen-bonding arrays at a specific angle to each other, either through constraining the faces in a common heterocyclic scaffold or connecting the modules through a conformationally biased linker. As a result of the fixed angle, constrained ditopic modules tend to form discrete, cyclic structures that often show cooperative behavior leading to assemblies with unique stability and responses to stimuli.[6–8] In addition, the angle between the recognition units provides an additional level of molecular information storage by determining the type of cyclic structure that is formed (Fig. 1b).

Using ditopic hydrogen-bonding modules that assembled dendrimers,[7b] we investigated the supramolecular assembly of star polymers.[9] Herein, we describe the synthesis and characterization of a general-purpose ditopic hydrogen-bonding module based on the bis-ureidodeazapterin (Bis-DeAP) motif (Fig. 2).[10] This general-purpose module, **1**, is an analog of a previously reported ditopic module.[7b] It contains two di-*tert*-butyl benzyl groups providing solubility in nonpolar organic solvents and an alcohol group as an attachment point for polymerization initiators or direct functionalization with telechelic polymers. Furthermore, we describe the incorporation of **1** into conventional polymers and report the self-assembly behavior of these materials.

☆ Taken in part from the Ph.D. thesis of Eric M. Todd, University of Illinois, 2007.

* Corresponding author.

E-mail address: sczimmer@uiuc.edu (S.C. Zimmerman).

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doi:10.1016/j.tet.2008.05.076

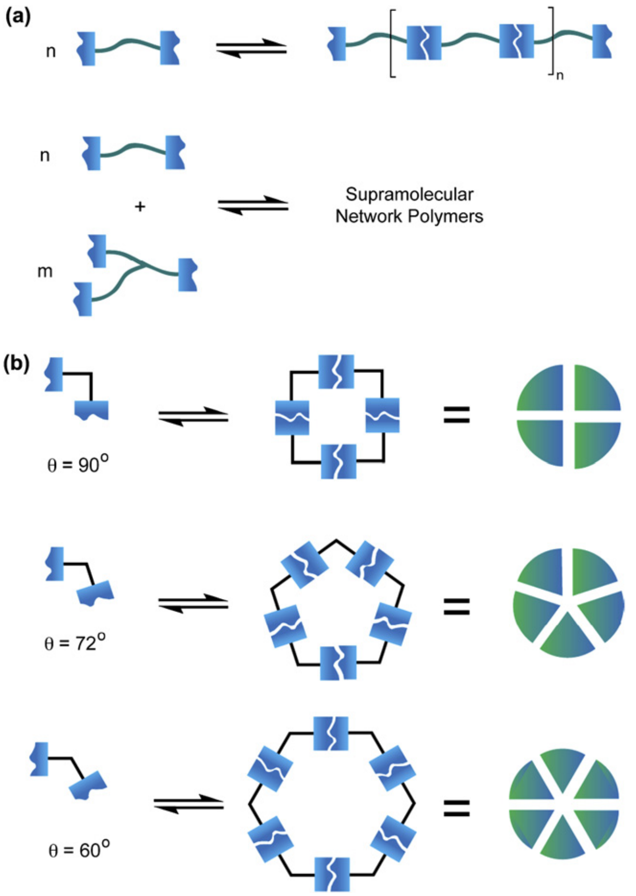


Figure 1. Schematic representations of ditopic hydrogen-bonding modules. (a) Flexible linkers lead to main-chain supramolecular polymers. (b) Modules connected by a conformationally constrained linker favor discrete, cyclic structures. The size of the cyclic assemblies is determined by the angle between the hydrogen-bonding modules.

2. Synthesis and characterization

2.1. Preparation of aryl-ether solubilizing group

The synthesis of the aryl-ether solubilizing group (Scheme 1) began with methyl gallate, **2**, which can be regioselectively alkylated at the 4-postion. Alkylation of **2** proceeded in poor yield, most likely a result of the oxidative instability of **4**; however, this yield was serviceable as the THP protected bromohydrin, **3**, is easily and cheaply prepared from 1,4-butanediol and methyl gallate is an inexpensive, commercially available starting material. Alkylation of **4** with di-*tert*-butyl benzyl bromide, **5**, proceeded in good yield affording **6**, which showed no sign of instability. Ester **6** was easily reduced to benzyl alcohol **7** with DIBAL-H.

2.2. Preparation of ditopic hydrogen-bonding module

An improved preparation of **1** was developed that avoided the Curtius rearrangement.[7b] Thus, Meijer and co-workers reported the synthesis of ureidopyrimidinones by reacting amines with 1,1′-carbonyldiimidazole (CDI) activated isocytosines.[11] This approach was adapted to the synthesis of **1** as outlined in Scheme 2. Beginning with dinitrophenol **8**, the aryl-ether solubilizing group, **7**, was attached using a Mitsunobu reaction to yield **9**. Quantitative reduction of the nitro-groups yielded the bis-amine **10** that was coupled with the CDI activated deazapterin **13**. Compound **13** was difficult to characterize as a result of its low solubility. Because the presence of unreacted starting material could not be ruled out, 6–8 equiv of **13** was used in coupling with bis-amine **10**. Subsequent removal of the THP group in acidic THF yielded the general-purpose ditopic hydrogen-bonding module **1**.

The synthetic approach in Scheme 2 offers multiple advantages over the previously published route.[7b] The reactions generally afford products in higher yields and require shorter reaction times with less purification. Indeed, only one silica gel column was required for the conversion of **8** to **1** (Scheme 2). As a result, the synthesis was quite scalable and multiple grams of **1** could be prepared within 2 weeks.

2.3. Characterization of ditopic hydrogen-bonding modules

The MALDI spectrum and a representative SEC trace (toluene eluent) for **11** are shown in Figure 3. The sodium, potassium, and proton adducts of **11** are all clearly present, as is the proton adduct of **1**, which may result from the acid wash used in the workup of **11** or be formed during the MALDI ionization process. Using polystyrene (PS) standards the number average molecular weight (M_n) determined for the aggregates by SEC is 6.6 kDa, which is close to

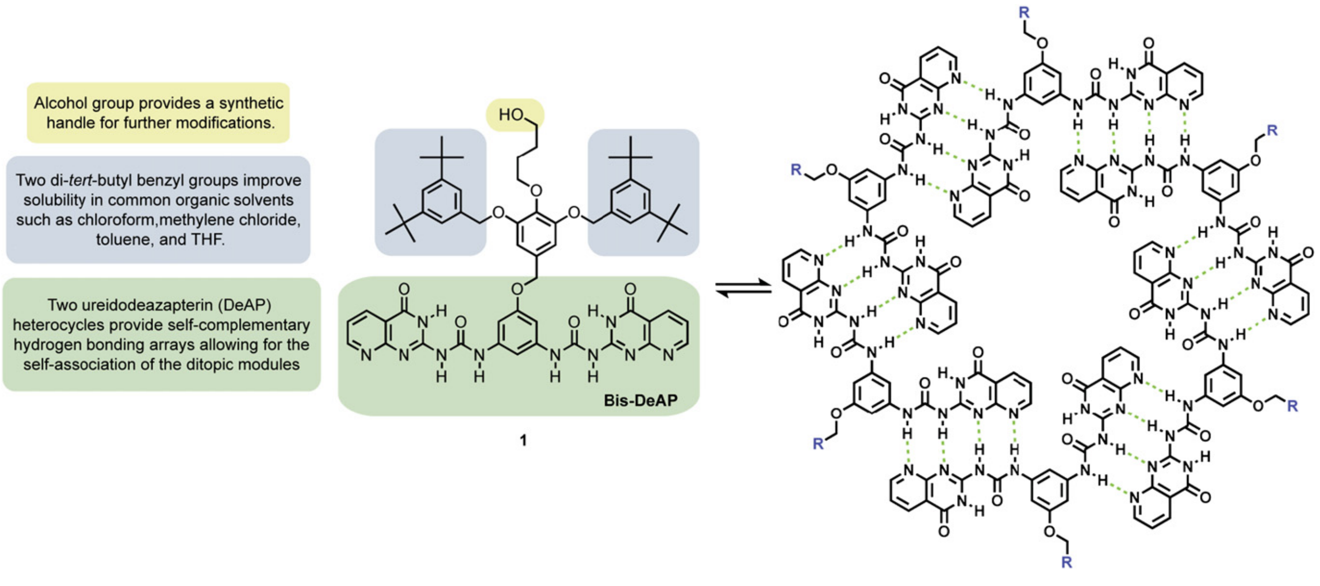
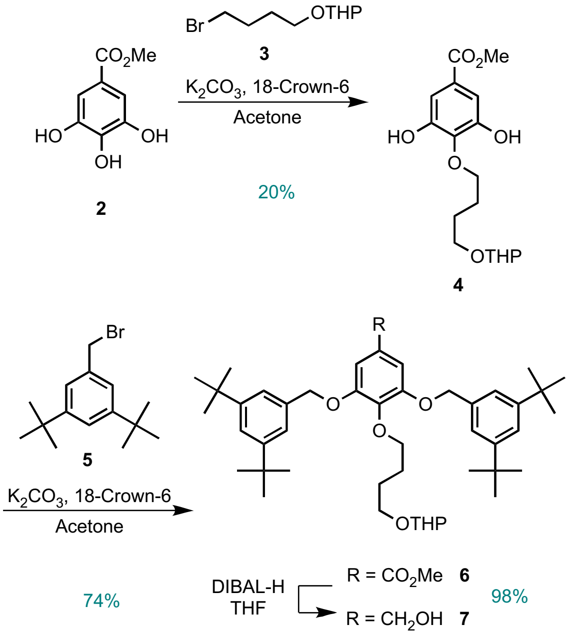
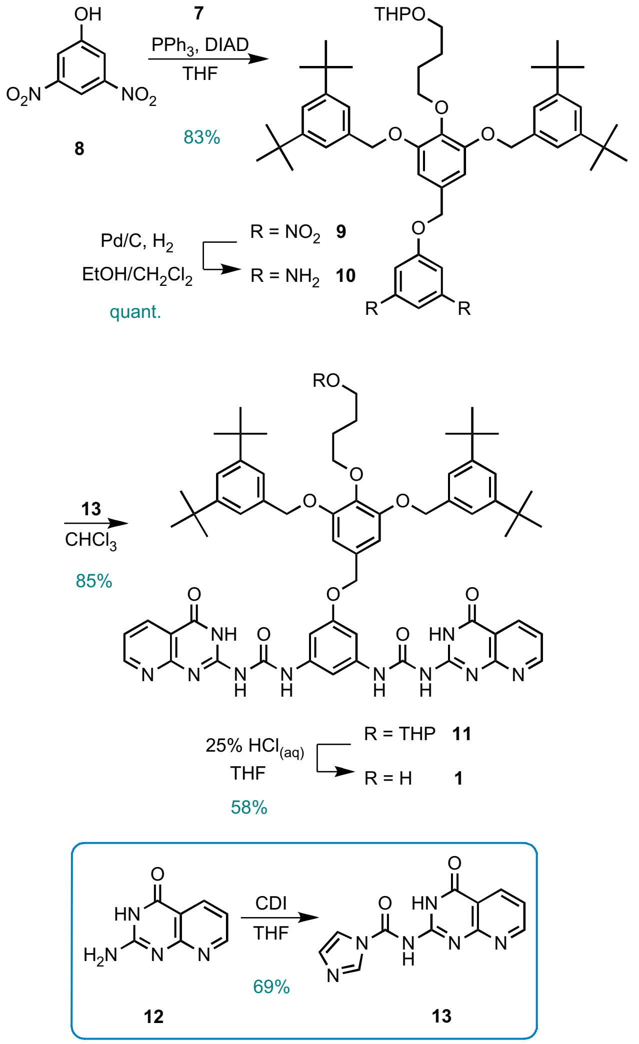


Figure 2. Design and self-assembly of general-purpose bis-ureidodeazapterin (Bis-DeAP) module.



Scheme 1.



Scheme 2.

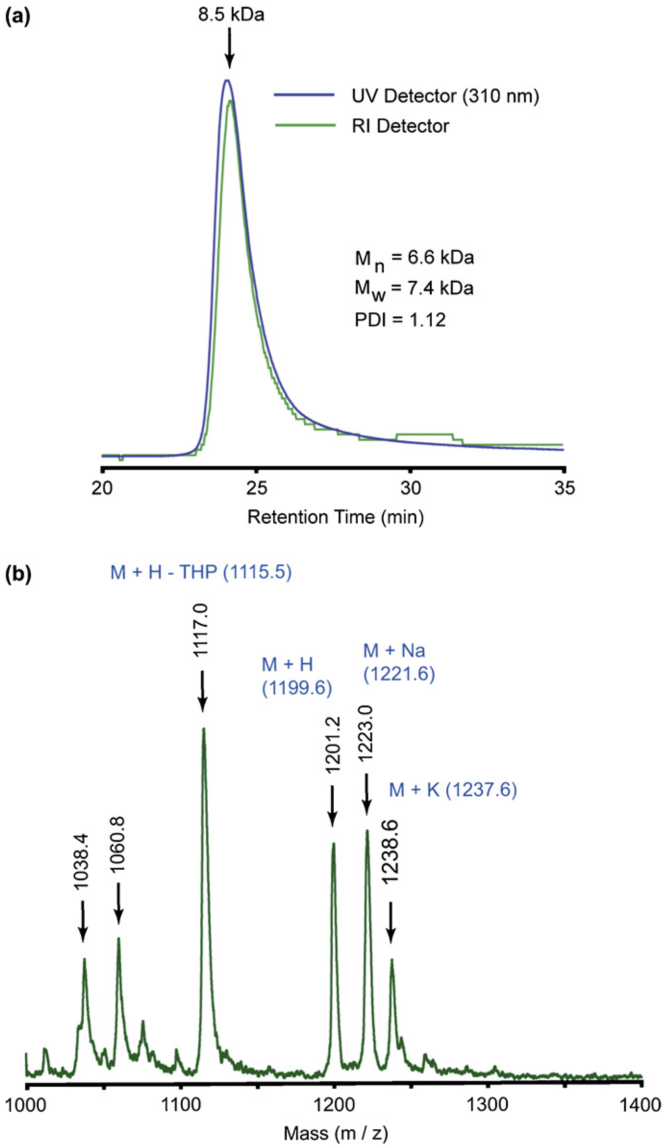


Figure 3. (a) Toluene SEC of Bis-DeAP–OTHP, **11**; molecular weights determined from RI signal using conventional calibration with polystyrene standards. (a) MALDI mass spectrum of **11**, using IAA as matrix.

the calculated molecular of a hexamer (7.2 kDa). The narrow polydispersity index (PDI) suggests that there is only one species present and the calculated molecular weight of the peak does not change significantly over a 10-fold change in concentration, suggesting the formation of a discrete aggregate. The UV detector detects the presence of the heterocyclic portion of the Bis-DeAP module at a wavelength of 310 nm, where the modified dendron is mostly transparent.

Proton NMR analysis of **11** is complicated by broadening of the signals (Fig. 4). This broadening can be attributed to the formation of polymeric aggregates, either main-chain supramolecular polymers or polymeric stacks of the assembled, cyclic **11**. However, there was no evidence for large polymeric structures that could lead to the observed broadening. Alternatively, the broadness of the proton NMR spectrum may be the result of a large number of stereoisomers. The ureidodeazapterin (DeAP) heterocycle exists in several protomeric forms,[12] which would also exist in **11** (Fig. 5). These stereoisomers can be combined in thousands of ways[13] leading to the observed broadness in the NMR spectrum.

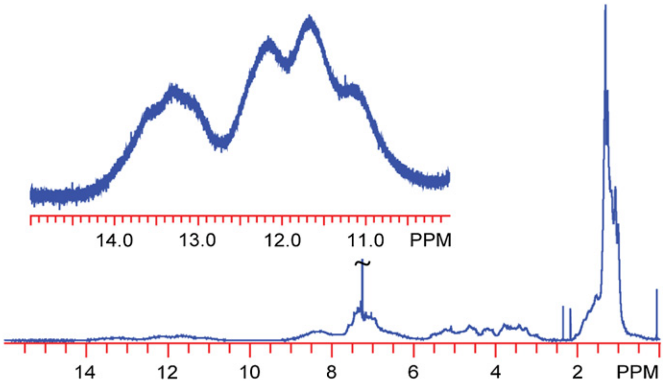


Figure 4. Proton NMR of Bis-DeAP–OTHP **11** in $CDCl_3$ with an expansion of the hydrogen-bonding region.

Although compound **1** is only sparingly soluble in toluene, the UV signal from the SEC indicates the formation of a discrete assembly with a molecular weight close to what would be predicted for a hexamer. Unfortunately, compound **1** is not soluble enough to get a reliable RI signal, which is needed to apply the PS standard calibration curve (PS is not observable in toluene by UV). The MALDI mass spectrum of **1** is shown in Figure 6, along with a representative SEC trace (THF eluent). Compound **1** has better solubility in THF and forms assemblies whose relative amounts vary with concentration.

2.4. Molecular modeling and hexagonal close-packed approximation

A computational investigation was undertaken to gain further insight into the structure of the Bis-DeAP assemblies. Although there are always difficulties in unequivocally determining the structure of supramolecular assemblies, the above data is consistent with a discrete hexamer, which agrees with previous work involving the Bis-DeAP modules self-assembly of dendrimers.[7b] Figure 7a shows the semi-empirical PM3 equilibrium geometry of a hexameric Bis-DeAP core, substituting methyl groups where the aryl-ether solubilizing groups would be attached. Viewed from above, the assembly appears to be circular with a diameter of approximately 33 Å and an approximately 12 Å void in the center. When the assembly is viewed from the side it appears to have a significant curvature. This curvature is most likely a result of the heterocycles' inability to form a planar dimer due to steric interaction between the aryl C–H and the substituent attached to the urea (Fig. 7b). Although similar tilting has been observed in the crystal structures of related recognition units, a reported crystal structure of the DeAP dimer indicates that the modules are nearly planar. This discrepancy may be due to the PM3 method overestimating steric interactions or to crystal packing effects forcing planar arrangements in the solid state. Regardless of these ambiguities, the structure in Figure 7 is still a useful first approximation of the size and shape of the Bis-DeAP assembly.

To understand better the self-assembly behavior of **1**, it is useful to know the amount of space available to each substituent attached to a Bis-DeAP unit before it begins to interact sterically with its neighbors. To obtain an estimate of this parameter, the Bis-DeAP module was assumed to form a perfect, circular hexamer with its substituents arranged on a hexagonal close-packed lattice (Fig. 8). Addition of the aryl-ether solubilizing groups to the Bis-DeAP core increases the size of the assembly to a point were semi-empirical calculations are no longer feasible, therefore, molecular mechanics was employed to minimize the structure and obtain an estimate of 55 Å for its diameter. In the approximation of hexagonal close-packed spheres this implies that a substituent larger then 55 Å will be in physical contact with its nearest neighbors.

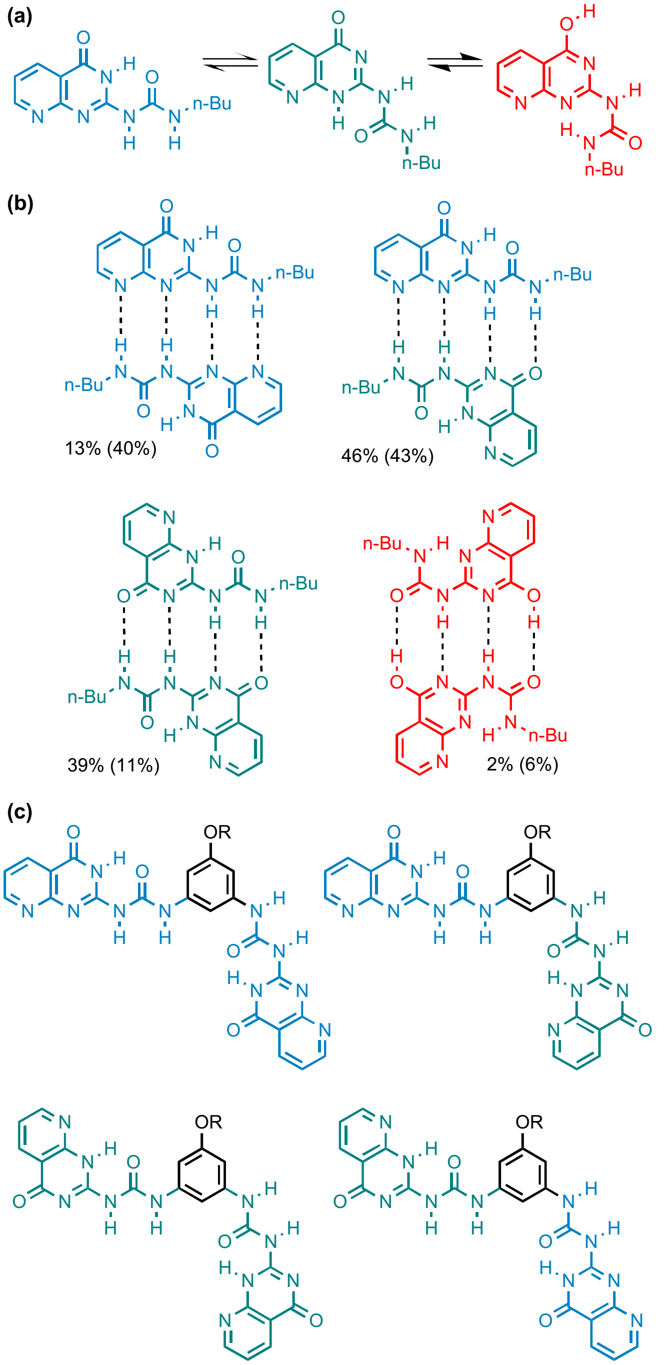


Figure 5. Self-association of ureidodeazapterin (DeAP) regardless of tautomerism. (a) Self-complementary protomeric forms of DeAP. Two non-complementary protomeric forms omitted. (b) Dimers of DeAP with percentage of each dimer in toluene-d_6 ($CDCl_3$) as measured by ^1H NMR.[12] (c) Four likely stereoisomers of Bis-DeAP after considering the multiple tautomeric forms of DeAP.

3. Atom transfer radical polymerization (ATRP) of methylmethacrylate (MMA)

Controlled polymerization methods have recently received an impressive amount of attention because their living character produces polymers of low polydispersity, wide monomer scope, and ability to generate a range of polymer architectures.[14] With this

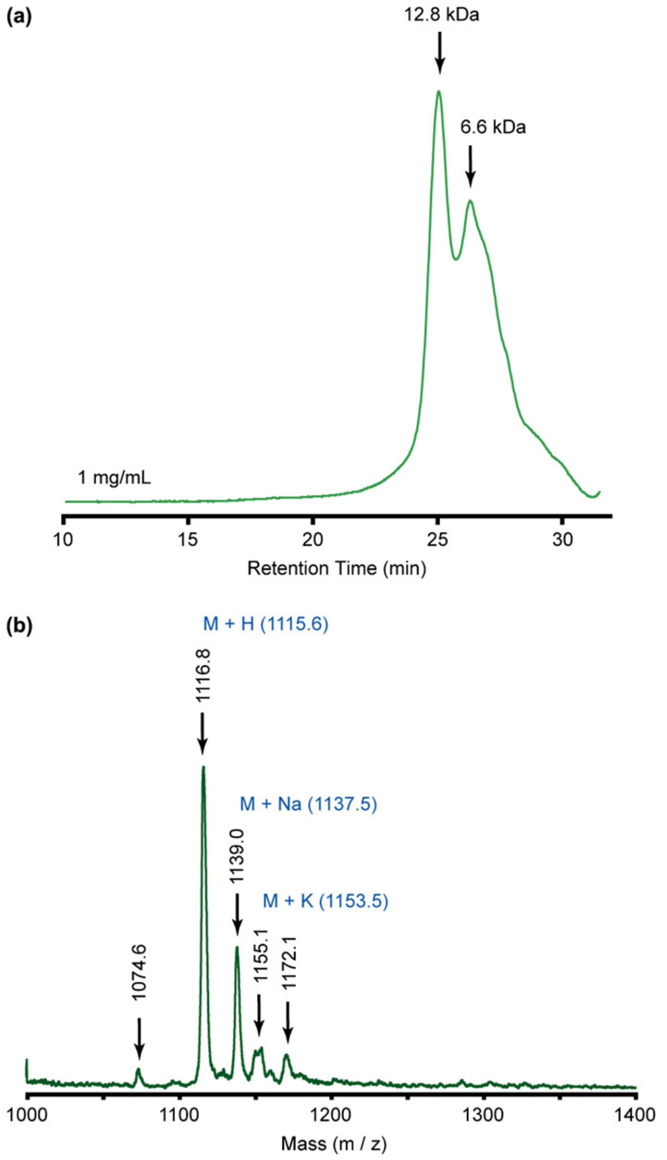


Figure 6. (a) THF SEC of Bis-DeAP–OH, **1**, using an RI detector. Molecular weights determined using conventional calibration with polystyrene standards. (b) MALDI mass spectrum of **1** using IAA as matrix.

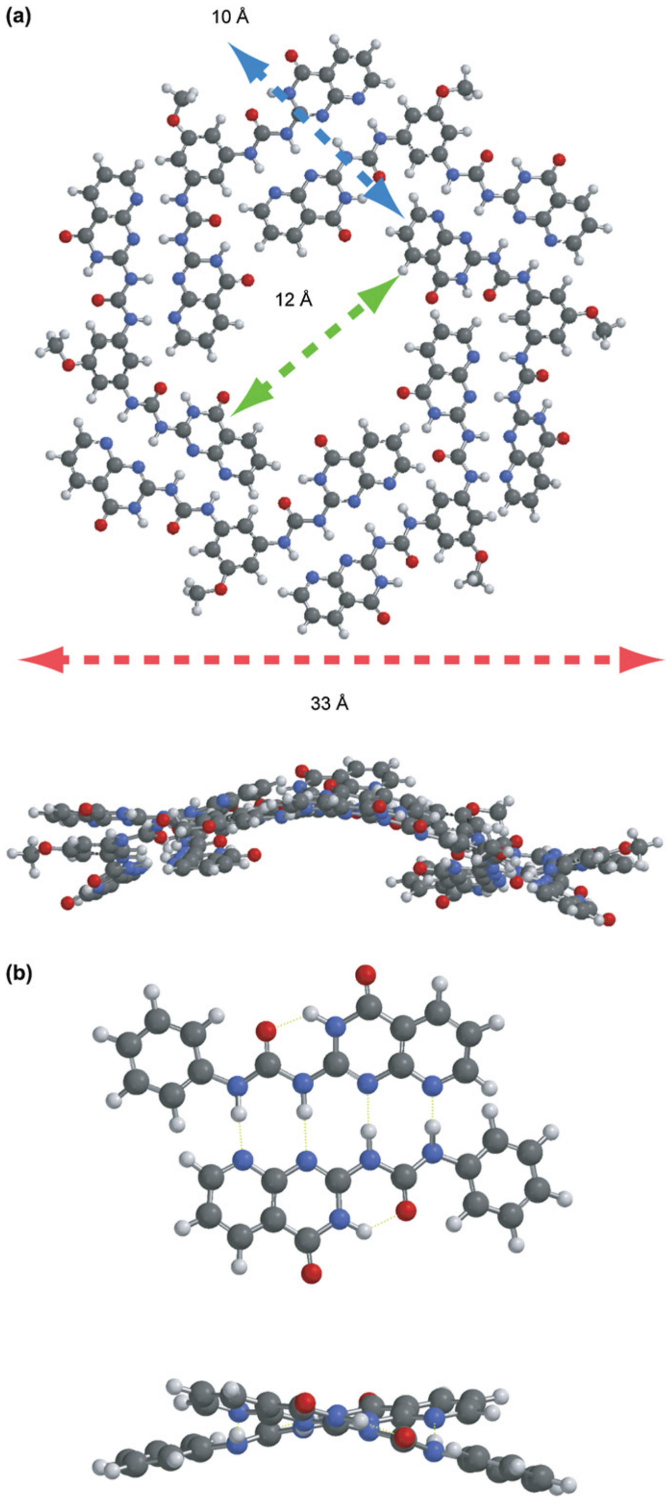


Figure 7. Semi-empirical/PM3 energy minimizations. (a) Bis-DeAP core with the aryl-ether solubilizing groups replaced by methyl groups. (b) Single DeAP dimer illustrating its inability to form a planar complex through PM3 minimization.

utility in mind, **1** was reacted with 2-bromo-2-methylpropanoyl bromide to yield the atom transfer radical polymerization (ATRP) initiator **14** (Scheme 3). We have previously reported the preparation of polystyrene star polymers using **14** as the initiator.[9] To further expand the utility of the Bis-DeAP module, **14** was used to initiate the polymerization of methylmethacrylate at 70 °C in anisole with [**14**]=[CuBr]=[PMDETA]=11 mM and [MMA]=3.1 M (Fig. 9). Model initiator **16** was also subjected to identical polymerization conditions to estimate the molecular weight of the polymer in the absence of self-assembly. Analysis of the polymer by SEC (DMF with 50 mM LiBr eluent, 50 °C) results in two peaks that do not significantly shift over a 10-fold concentration range indicating the formation of discrete aggregates. The larger molecular weight peak is assigned as assembled star polymer and the lower molecular weight peak, which is very similar to the PMMA generated from model initiator **16**, is assigned as unassembled polymer. The lower molecular weight Bis-DeAP–PMMA could also be analyzed by SEC with toluene eluent resulting in a single, high molecular weight peak, indicating that all the polymers contained the Bis-DeAP module. In addition, reinvestigation of the Bis-DeAP–PS star polymers by DMF SEC gave similar results with a high and a low molecular weight peak.

Closer examination of the data in Figure 9 shows that the best-fit lines for the assembled star polymer and unassembled PMMA polymers have a lower R^2 value then in the previously reported bulk PS polymerization.[9] This is a result of the PMMA polymerization

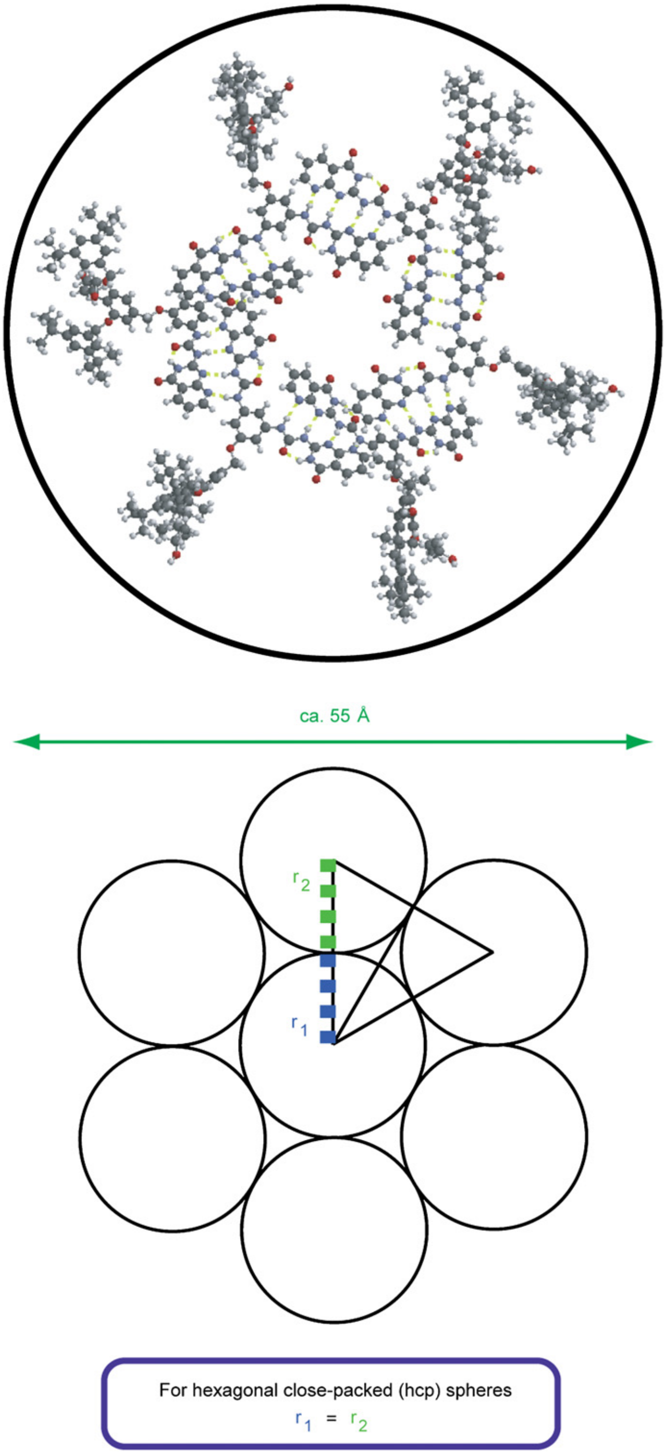
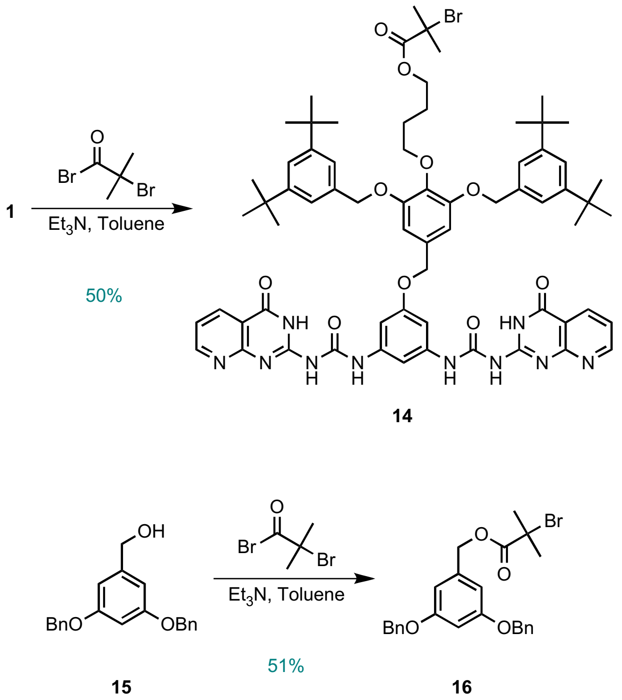


Figure 8. Estimating the amount of space available to substituents attached to a hexameric assembly of **1** using a hexagonal close-packed approximation. Compound **1** was minimized using molecular mechanics employing the MMFF force field.



Scheme 3.

occurring in solution and the concentration of the monomer decreasing as the polymerization proceeds. This causes the rate of polymerization to slow with conversion and the relationship between molecular weight and time is no longer linear. To provide a valid comparison using a linear approximation, the polymerization was only carried out to approximately 10% conversion, resulting in a minimal change in the monomer concentration. Comparison of the slopes indicates that the unassembled material's best-fit line has a slope 1/9 that of the assembled material and considering each time point separately, the assembled material is on average 8 times the molecular weight of the unassembled material. Comparison of the assembled material with the PMMA generated from the model initiator **16** gave similar results. That the SEC molecular weight is independent of concentration indicates the presence of cyclic aggregates. A hexamer model is favored by analogy to the previously examined systems and the uncertainty in these measurements. However, the presence of other similar sized aggregates (pentamers, heptamers) cannot be ruled out with the data reported here.

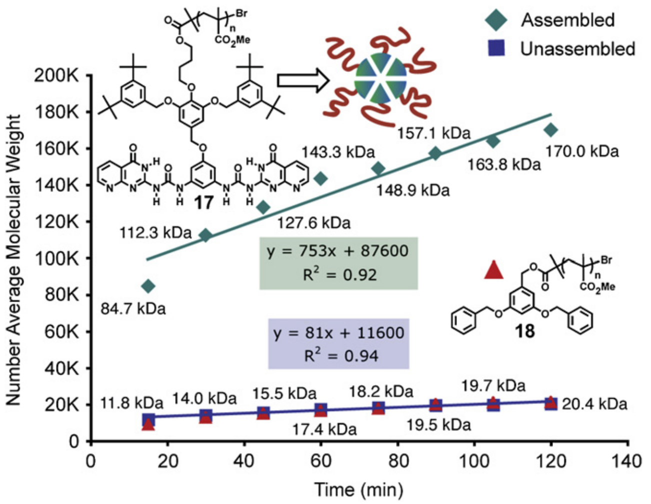


Figure 9. M_n of PMMA generated by ATRP of **14** and of model initiator **16** versus time. Molecular weights determined from DMF SEC (50 mM LiBr, 50 °C) using RI detection and conventional calibration with polystyrene standards. Labels indicate the MW of assembled and unassembled **17**. Polymerization conditions: [Initiator]=[CuBr]=[PMDETA]=11 mM, [MMA]=3.1 mM in anisole, 70 °C.

4. Size exclusion chromatography (SEC) studies of star polymer mixing

Investigation of the mixing of different sized star polymers in toluene by SEC indicated that they were very slow to mix, suggesting that the star polymers are kinetically stable. Thermodynamically, mixing should occur both for entropic reasons and also to minimize steric interactions.[7c] Figure 10 shows the toluene SEC chromatograms of a solution containing Bis-DeAP–PMMA **17** and Bis-DeAP–PS **19** that was stirred at room temperature. The experiment was set up so that there was significantly less of the smaller polymeric component in hopes that this would decrease the time needed for mixing to occur. However, even after 4 months, the polymers do not appear to be completely mixed as indicated by the discrepancy between the RI and UV signals. Both detector signals should be identical when the polymers have mixed to a homogenous composition. Similar results were obtained when the larger and smaller polymers were identical (PMMA or PS).

To determine if annealing could facilitate mixing, a solution was prepared containing Bis-DeAP–PMMA **17** and unfunctionalized Bis-DeAP, **20** (Fig. 11). Compound **20** was prepared using the literature method and is proposed to assemble into a dodecameric structure in toluene.[7b] A solution was prepared with equal amounts by mass of **17** and **20**. After 5 days of stirring at 80 °C, there is clear evidence for mixing, including a decrease in the RI signal for **20**, and an increase in the UV signal for the polymeric material. The molecular weight of the star polymer peak also decreases as it incorporates **20**. Mixing is still very slow in toluene, even at 80 °C and unfortunately further heating led to decomposition, observed as lower molecular weight peaks in the chromatogram.

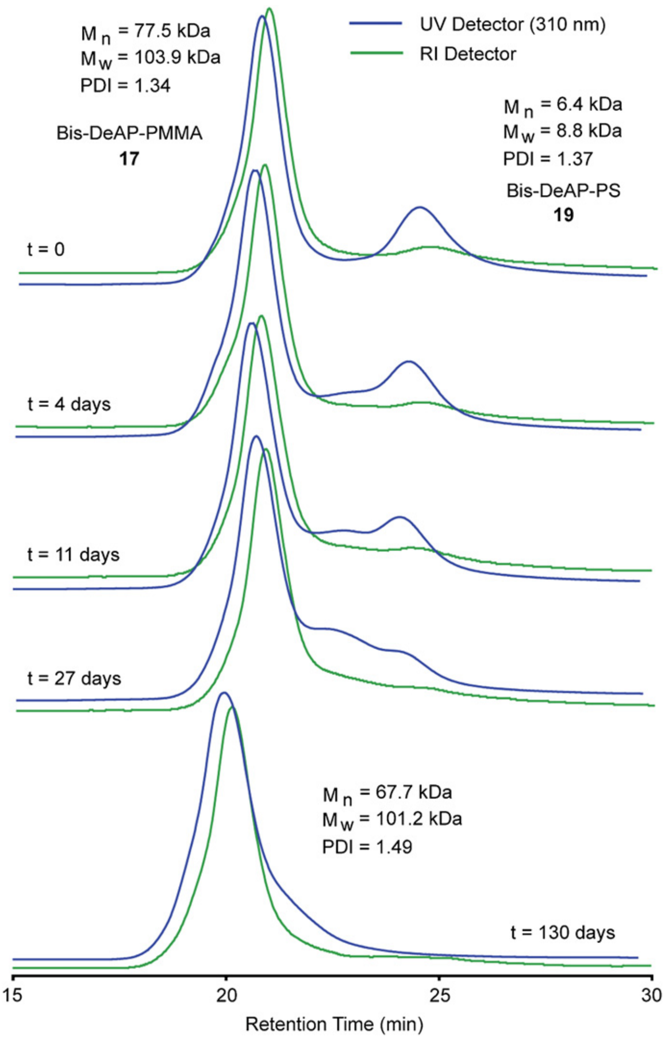


Figure 10. Bis-DeAP–PMMA, **17**, and Bis-DeAP–PS, **19**, mixed in toluene at room temperature. Aliquots analyzed by toluene SEC. Molecular weights determined from RI signal using conventional calibration with polystyrene standards.

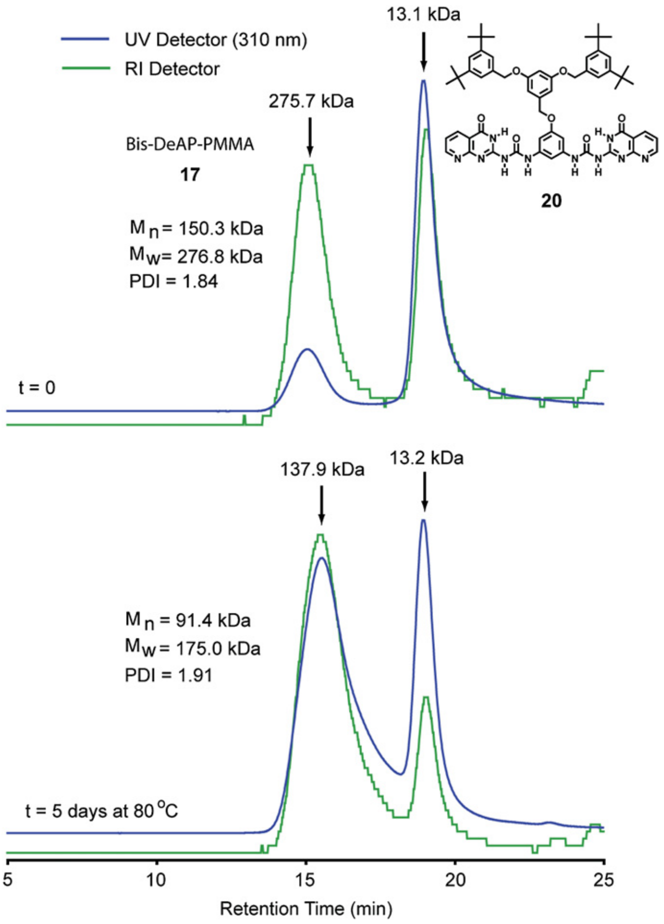


Figure 11. Bis-DeAP–PMMA, **17**, and Bis-DeAP, **20**, mixed in toluene at 80 °C. Aliquots analyzed by toluene SEC at room temperature. Molecular weights determined from RI signal using conventional calibration with polystyrene standards.

The mixing of different sized star polymers occurs much faster in DMF. Figure 12 illustrates the mixing of equal amounts by mass of Bis-DeAP–PS **19** and Bis-DeAP–PMMA **17** in DMF at room temperature. A significant amount of mixing is evident immediately after the solution was prepared and the polymers appear to be mostly mixed after 24 h. This mixing process represents an alternative synthesis of star copolymers where instead of utilizing covalent chemistry the PMMA/PS copolymer is generated through self-assembly.

5. Decreased polydispersity with increased molecular weight

Previously published results demonstrated how Bis-DeAP recognition units assemble low molecular weight polymers into high molecular weight materials accompanied by a decrease in the molecular weight distribution as measured by the PDI.[9] Application of quantitative statistical models to the assembly of the star polymers indicated that even more dramatic decreases in the molecular weight distribution should be achievable.[15] Two possible explanations for this larger than statistical molecular weight distribution

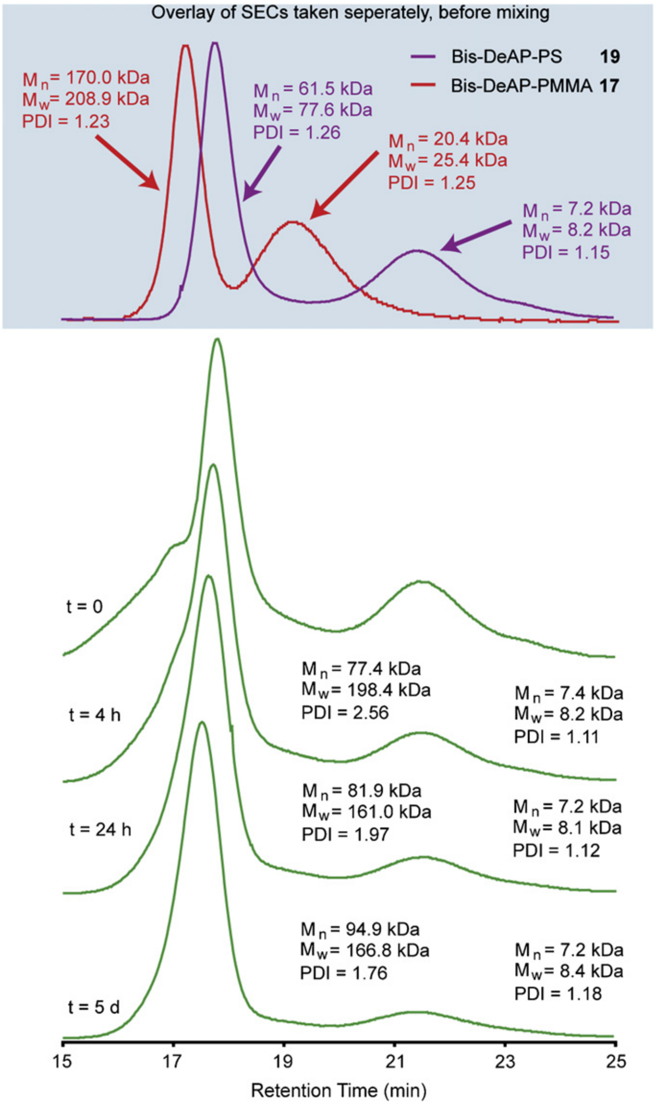


Figure 12. Relatively fast mixing of Bis-DeAP–PMMA **17** and Bis-DeAP–PS **19** in DMF at room temperature to generate a star copolymer through self-assembly. Molecular weights determined from DMF SEC (50 mM LiBr, 50 °C) using RI detection and conventional calibration with polystyrene standards.

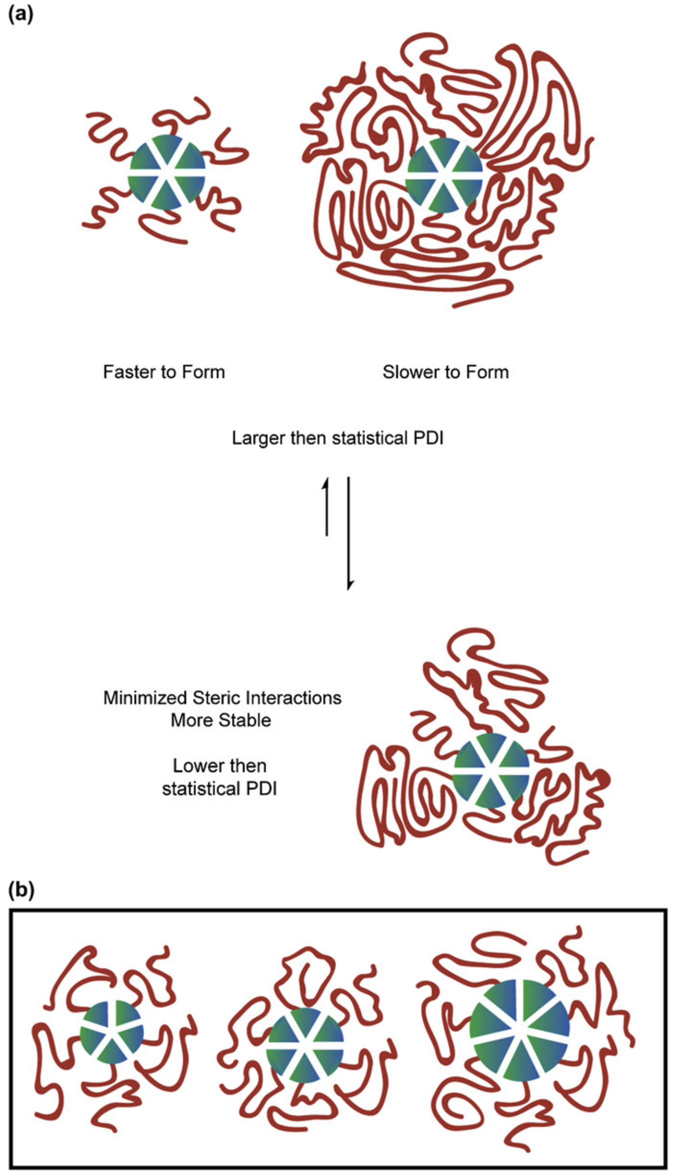


Figure 13. Schematic representation of possible explanations for larger then statistical PDI. (a) Initially the smaller polymeric material assembles first followed by the larger material leading to a kinetically controlled molecular weight distribution. Sterically the polymer coils should want to alternate between large and small leading to a thermodynamically controlled molecular weight distribution. (b) The original star polymer distribution contains multiple discrete aggregates.

seem likely and are illustrated schematically in Figure 13. The assembly of the polymers in toluene could be under kinetic control, where small polymers assemble together before larger polymers. Alternatively, there could be more then one discrete structure present. It is also conceivable that both mechanisms are active.

The mixing studies reported above indicated that the assemblies were more dynamic in DMF, although a kinetically controlled structure is still initially observed. When monitored over time the PDI of the assembled material slowly decreases and approaches a presumably thermodynamic state as illustrated in Figure 14. In Figure 14a the number (M_n), weight (M_w), and peak (M_p) molecular weights of an assembled Bis-DeAP–PS star polymer are plotted. There is little variation in M_n and M_p over time; however, M_w decreases dramatically from 287.7 kDa to almost 200 kDa in 24 h and continues to decrease slightly over time. This drop in M_w corresponds to a similar drop in PDI of the assembled material from 1.69 to 1.28, which further drops to a minimum value of 1.20 (Fig. 14b). Both the molecular weight parameters and PDI appear to increase near the end of the experiment, which is attributed to experimental error. The molecular weight parameters and PDI of the unassembled material do not significantly change over the course of the experiment (Fig. 14c). Furthermore the fraction of assembled polymer increases over time, as would be predicted for a state closer to a thermodynamic minimum. Although it seems clear that the initial assembly of the polymers is governed by kinetics, this kinetic state could consist of both large and small discrete star polymers that mix to form an alternating structure or a mixture of different sized aggregates that eventually coalesce into a smaller number of more stable aggregates.

6. Polyethylene glycol functionalized Bis-DeAP for assembly in water

The assembly of hydrogen-bonding modules in water has received considerable interest over the past several years.[16,17] As a result of the general-purpose design of **1**, it is easy to functionalize

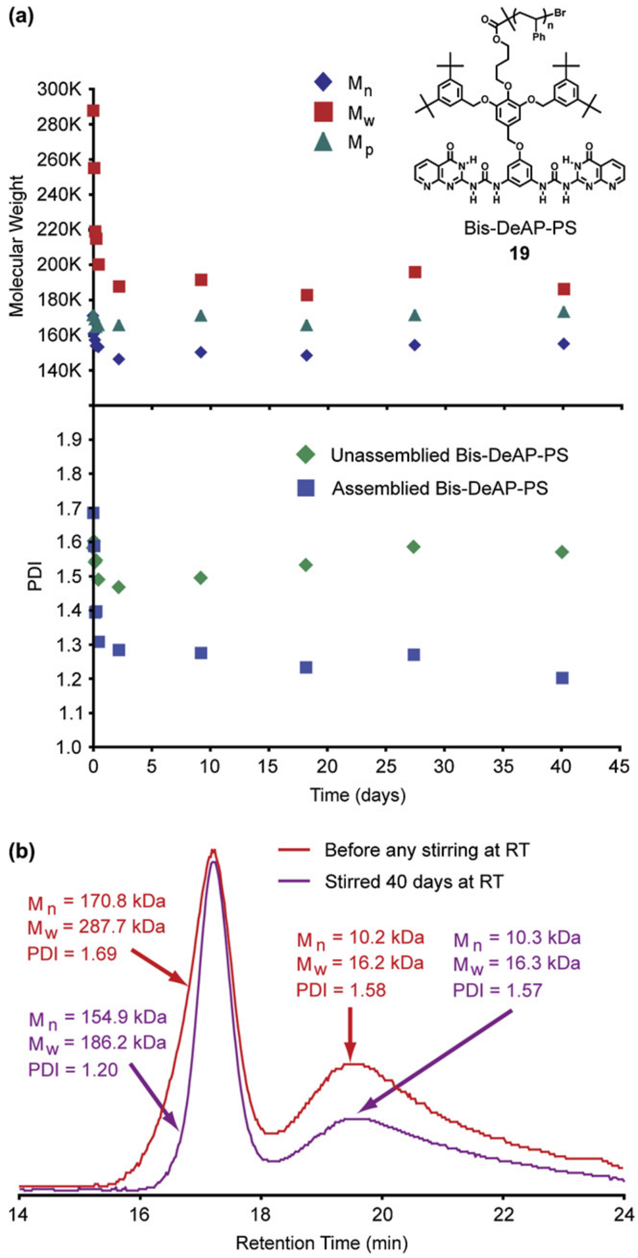
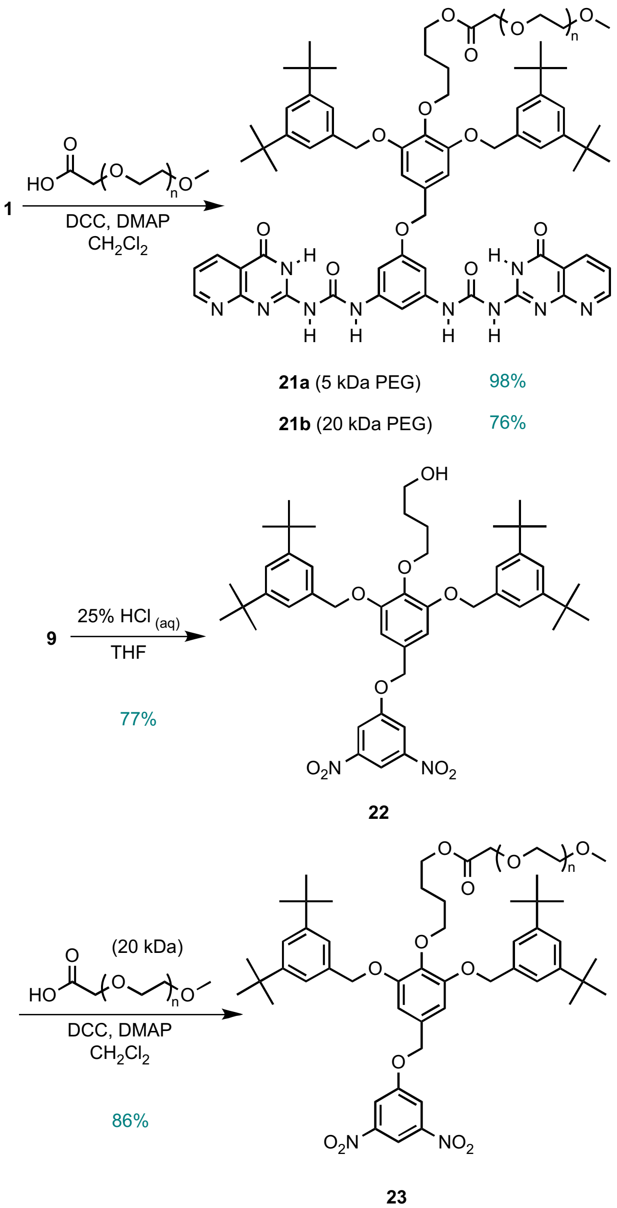


Figure 14. Kinetic investigation of Bis-DeAP–PS **19** in DMF at room temperature. (a) Molecular weight parameters of assembled material in DMF over time. The molecular weight of the unassembled material did not change appreciably over the course of the experiment. (b) PDI of assembled and unassembled material over time. (c) Representative chromatographs at beginning of experiment and after 40 days.



Scheme 4.

it with polyethylene glycol (PEG) polymers and investigate its assembly in water. Initially, **1** was functionalized with a 5 kDa PEG with a single acid end group (MPEG–5K-acid) through a DCC/DMAP esterification. Unfortunately, the Bis-DeAP–5K-PEG **21a** was not soluble in water, although it did appear to form hexameric structures in DMF along with unassembled material. Bis-DeAP–OH **1** was then reacted under the same conditions with MPEG–20K-acid. End group analysis by proton NMR indicated approximately 80% functionalization and this material was water-soluble. In addition compound **23** was prepared as a control compound, maintaining the majority of the design of **1** but lacking the DeAP heterocycles capable of forming hydrogen-bonded assemblies (Scheme 4).

Bis-DeAP–20K-PEG, **21b**, appears to form hexameric assemblies in DMF as evidenced by a value of 6.2 for the ratio of the peak molecular weights (M_p) of the assembled to unassembled material in the SEC chromatogram (Fig. 15a). The absolute molecular weights determined by DMF SEC appear to be significantly overestimated. In particular, the 20 kDa unassembled material is calculated as 62 kDa from the chromatogram. This is a result of the molecular weight being derived from a polystyrene calibration curve and analysis of the MPEG–20K-acid starting material yields a molecular weight of approximately 60 kDa in DMF.

Analysis by water SEC using conventional calibration with PEG standards provides a more accurate estimation of the molecular weight. First looking at the control compound **23**, peaks at 18 and 28 kDa are observed. The 18 kDa peak is assigned as the aryl-ether functionalized PEG, which assumes a collapsed confirmation in water to bury the hydrophobic aryl groups and therefore appears to be a smaller molecular weight than the starting MPEG–acid.[18] The peak at 28 kDa is most likely unreacted MPEG–acid. There is also a small, higher molecular weight shoulder that could arise from either hydrophobic association of **23** or larger polymers generated from impurities in the PEG starting material. The water SEC chromatogram of Bis-DeAP–20K-PEG **21b** contains lower molecular

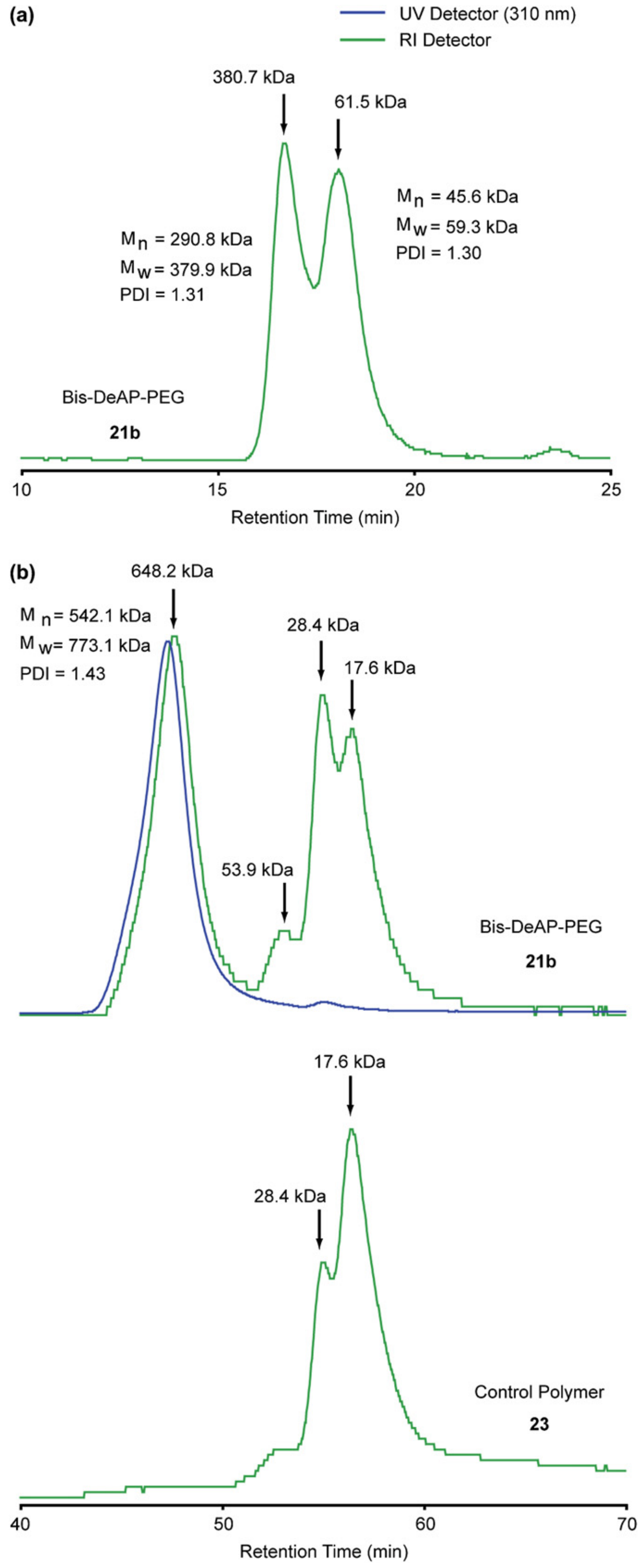


Figure 15. (a) SEC analysis of Bis-DeAP–20K-PEG **21b** in DMF. (b) SEC analysis of Bis-DeAP–20K-PEG **21b** and control polymer **23** in water. SEC samples prepared at approximately 7 mg/mL.

weight peaks that are very similar to the chromatogram obtained for the control polymer, in addition to, a high molecular weight peak with a strong absorbance at 310 nm. The molecular weight of this peak is much larger then the presumably unassembled material (approximately 35 times larger in the chromatogram shown) and shifts as the concentration is varied. The higher molecular weight peak is assigned as either a random-chain supramolecular polymer or an assembly of stacked, cyclic structures. The lack of high molecular weight components in the chromatogram of the control polymer suggests that the hydrogen-bonding modules are necessary for the assembly process in water. Interestingly, if these assignments are correct, these data suggest that the Bis-DeAP core absorbs at 310 nm only when engaged in hydrogen bonding.

7. Conclusion

We presented the synthesis and characterization of a general-purpose ditopic hydrogen-bonding module, **1**, which is programed to self-assemble into cyclic aggregates stabilized by hydrogen bonding. This module can be prepared on a gram scale in 2 weeks, a significant improvement over previous synthetic routes to analogous compounds. Bis-DeAP–OH **1** was functionalized with 2-bromo-2-methylpropanoyl bromide to yield atom transfer radical polymerization (ATRP) initiator **14**, which was used to polymerize methylmethacrylate. The resultant polymers self-assembled into higher molecular weight structures with narrowed molecular weight distributions. Although large and small Bis-DeAP star polymers are very slow to mix in toluene, much faster mixing kinetics are observed in DMF and mixing of a larger Bis-DeAP–PMMA **17** and a smaller Bis-DeAP–PS **19** in DMF yielded a PMMA/PS star copolymer through self-assembly. The general-purpose nature of **1** was further demonstrated by its facile functionalization with MPEG acids to generate water-soluble self-assembled structures that appear to depend both on hydrogen-bonding and hydrophobic interactions. The general-purpose nature of this module and its unique self-assembly behavior in both aqueous and organic solvents makes Bis-DeAP–OH, **1**, a valuable addition to the rapidly developing ‘supramolecular toolbox’ available to chemists and material scientists for the generation of ordered nanoscale materials.

8. Experimental

8.1. General methods

All reactions were carried out under a dry nitrogen atmosphere and reported reaction temperatures are the temperatures of the heating medium. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl prior to use. Toluene, chloroform ($CHCl_3$), methylene chloride (CH_2Cl_2), DMF, and DMSO were dried over 4 Å molecular sieves and stored under nitrogen. Monomers where purified by passage through a basic alumina plug to remove inhibitors and then oxygen was displaced by bubbling $N_{2(g)}$ through the liquids for 1 h. All other solvents and reagents were of reagent grade quality and used without further purification.

Analytical thin-layer chromatography (TLC) was performed on 0.25 mm silica gel coated glass plates (Merck) with F_{254} indicator. Flash chromatography was performed on Merck 40–63 μm silica gel and ratios of solvents for flash chromatography are reported as volume percentages. Preparative size exclusion chromatography (SEC) was performed on polystyrene Bio-Beads® S-X (Bio-Rad: 400–14,000) in toluene. Melting points were determined on a Thomas–Hoover melting point apparatus without calibration. Brine refers to a saturated aqueous solution of NaCl. Light petroleum ether is abbreviated as PE and ethyl acetate as EtOAc.

All NMR spectra were acquired in the VOICE NMR laboratory at the University of Illinois at Urbana-Champaign. ^1H and ^{13}C spectra were acquired on a Varian Unity 500 MHz spectrometer (^{13}C, 125 MHz) in $CDCl_3$ unless otherwise noted. ^1H coupling constants are given in hertz. ^{1}H NMR chemical shifts were referenced to the residual protio solvent peak at 7.26 ppm in $CDCl_3$. ^{13}C NMR chemical shifts were referenced to the solvent peak at 77.0 ppm in $CDCl_3$. Mass spectra (MS) were obtained on a Micromass ZAB-SE (FAB) mass spectrometer, a Micromass Q-Tof Ultima (ESI) spectrometer or a PerSeptive Biosystems Voyager-DE-STR (MALDI-TOF) at the University of Illinois Mass Spectrometry Laboratory. Elemental analyses were preformed at the University of Illinois School of Chemical Sciences Microanalysis Laboratory.

8.2. General polymerization methods

8.2.1. Preparation of polymethylmethacrylate (PMMA)

The polymerization was conducted with [Initiator]=[CuBr]=[PMDETA]=11 mM, [MMA]=3.1 mM in anisole at 70 °C. A typical procedure follows: an oven dried schlenk tube was charged with 100 mg (0.08 mmol) of **14** and 11.5 mg (0.08 mmol) of CuBr. The schlenk tube was placed under vacuum for 45 min, occasionally venting to $N_{2(g)}$. The tube was then placed under a high positive pressure of $N_{2(g)}$ and 5 mL of anisole and 2.5 mL of methylmethacrylate were added by a $N_{2(g)}$ flushed syringe. After adding 16.7 μL (13.9 mg, 0.08 mmol) of PMDETA, the tube was sealed and heated at 70 °C.

8.2.2. Preparation of polystyrene (PS)

The polymerization was conducted with [Initiator]=[CuBr]=[PMDETA]=21 mM in styrene at 90 °C. A typical procedure follows: an oven dried schlenk tube was charged with 40 mg (0.032 mmol) of **14** and 4.6 mg (0.032 mmol) of CuBr. The schlenk tube was place under vacuum for 45 min, occasionally venting to $N_{2(g)}$. The tube was then placed under a high positive pressure of $N_{2(g)}$ and 1.5 mL of styrene was added by a $N_{2(g)}$ flushed syringe. After adding 6.6 μL (5.5 mg, 0.032 mmol) of PMDETA, the tube was sealed and heated at 90 °C.

8.2.3. Purification of polymers

Both PS and PMMA were purified by diluting in $CHCl_3$ (30 mL) and washing with an aqueous Na_2EDTA solution (30 mM in 5% $NaHCO_3$, 15 mL). The organic layer was then reduced to approximately 2–5 mL and precipitated into cold MeOH (PS) or cold heptane (PMMA).

8.3. Analytical methods

8.3.1. Size exclusion chromatography (SEC)

Analytical SEC molecular weights were determined using conventional calibration with polystyrene (THF, DMF, and toluene eluents) or PEG/PEO (water eluent) standards. THF SEC was performed using Waters Styragel columns (2×HR3, 1×HR4E) with a flow rate of 1.0 mL/min at ambient temperature. Detection of peaks was achieved using a Viscotek TDA 300 refractive index detector. Toluene SEC was performed using Waters Styragel columns (1×HR3, 1×HR4E, 1×HR5E) with a flow rate of 1.0 mL/min at ambient temperature. Detection of peaks was achieved using a Viscotek VE3580 refractive index detector and a Hitachi L-4000H UV detector. Water (100 mM of $NaNO_3$) SEC was performed using Waters Ultrahydrogel columns (1×250, 1×120) and Polymer Laboratories columns (2×PL-aquagel-OH Mixed 8 μM) in series with a flow rate of 0.5 mL/min at ambient temperature. Detection of peaks was achieved using a Viscotek VE3580 refractive index detector and a Hitachi L-4000H UV detector. DMF (50 mM of LiBr) SEC was performed using Viscotek columns (2×I-MBLMW-3078, 1×MBHMW-3078) with a flow rate of 1 mL/min at 50 °C. Detection of peaks was achieved using a Viscotek TDA 300 refractive index detector.

8.3.2. Polymerization kinetic measurements

Aliquots were removed from the polymerizations by opening the sealed tube to a high positive pressure of $N_{2(g)}$ and then withdrawing a portion of the reaction mixture (typically 0.3–0.7 mL) with a $N_{2(g)}$ flushed syringe. The aliquot was then purified as described above.

8.4. Synthetic methods

Compounds **3**,[19] **8**,[20] and **12**[21] were prepared using methods that have already been published in the literature.

8.4.1. N-(4-Oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-1H-imidazole-1-carboxamide (13)

A heterogeneous solution of 4.14 g (25.5 mmol, 1 equiv) of **12**, 5.35 g (33 mmol, 1.3 equiv) of CDI, and 135 mL of THF was heated for 14 h at 60 °C. The solution was then allowed to cool to room temperature and 4.53 g (69.4%) of the desired product was collected by vacuum filtration, rinsing with dry acetone, as a white powder. Characterization was complicated by the insolubility of product. It was assumed to be pure for the yield calculation and it was used in excess in next reaction.

8.4.2. 3,5-Dihydroxy-4-[4-(tetrahydro-pyran-2-yloxy)-butoxy]-benzoic acid methyl ester (4)

A mixture of 10.13 g (55 mmol, 1.3 equiv) of methyl 3,4,5-trihydroxybenzoate, 2.05 g (7.8 mmol, 0.2 equiv) of 18-crown-6, 550 mL of acetone (dried over 4 Å sieves), and 5.83 g (42.2 mmol, 1 equiv) of K_2CO_3 was cooled in an ice bath. A solution of 10 g (42.2 mmol, 1 equiv) of **3** in 200 mL of acetone was then added dropwise. The reaction mixture was refluxed for 19 h. The mixture was concentrated under reduced pressure and the residue was partitioned between 300 mL of CH_2Cl_2 and 300 mL of H_2O. The organic phase was separated and the aqueous phase was extracted twice with 300 mL of CH_2Cl_2. The combined organic phases were washed with 600 mL of brine, dried with Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (9:1 $CHCl_3$–acetone, R_f=0.26) to give 2.92 g (20%) of the desired product as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.20 (s, 2H), 6.58 (s, 2H), 4.61 (t, J=2.9), 4.17 (t, J=6.3), 3.90–3.83 (m, 2H), 3.86 (s, 3H), 3.52 (m, 2H), 1.91–1.68 (m, 6H), 1.64–1.48 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 167.2, 149.3, 138.1, 125.6, 109.8, 99.4, 73.4, 67.6, 62.8, 52.4, 30.7, 27.5, 26.1, 25.4, 19.7. HRMS (ESI): Calcd for $C_{17}H_{25}O_7$ (MH^+): 341.1600. Found: 341.1594. Calcd for $C_{17}H_{24}O_7Na$: 363.1420. Found: 363.1412.

8.4.3. 3,5-Bis-(3,5-di-tert-butylbenzyloxy)-4-[4-(tetrahydro-pyran-2-yloxy)-butoxy]-benzoic acid methyl ester (6)

A mixture of 1.84 g (5.4 mmol, 1 equiv) of **4**, 70 mL of acetone (dried over 4 Å sieves), 291 mg (1.1 mmol, 0.2 equiv) of 18-crown-6, and 2.24 g (16.2 mmol, 3 equiv) of K_2CO_3 was cooled in an ice bath. A solution of 3.36 g (11.88 mmol, 2.2 equiv) of **5** in 50 mL acetone was then added. The reaction mixture was refluxed for 7 h. The mixture was concentrated under reduced pressure and the residue was partitioned between 50 mL of CH_2Cl_2 and 50 mL of H_2O. The organic phase was separated and the aqueous phase was extracted twice with 50 mL of CH_2Cl_2. The combined organic phases were washed with 150 mL of brine, dried with Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (9:1 to 1:1 PE–Et_2O, R_f=0.07, 0.58) to give 3.02 g (74.0%) of the desired product as a white solid: mp 113–114 °C. ^{1}H NMR ($CDCl_3$) δ 7.42 (s, 2H), 7.39 (t, J=1.9, 2H), 7.32 (d, J=2.1, 4H), 5.13 (s, 4H), 4.51 (br t, J=3.5, 1H), 4.15 (t, J=6.5, 2H), 3.90 (s, 3H), 3.79(m, 1H), 3.66 (m, 1H), 3.43 (m, 1H), 3.30 (m, 1H), 1.90–1.43 (m, 10H), 1.34 (s, 36H); ^{13}C NMR ($CDCl_3$) δ 166.9, 152.8, 151.1, 143.0, 136.0, 124.9, 122.1, 122.0, 109.3, 98.7, 73.4, 72.0, 67.2, 62.1, 52.3, 35.0, 31.6, 30.8, 27.4, 26.3, 25.6, 19.6. HRMS (ESI): Calcd for $C_{47}H_{68}O_7Na$: 767.4863. Found: 767.4886. Anal. Calcd for $C_{47}H_{68}O_7$: C, 75.77; H, 9.20. Found: C, 75.88; H, 9.28.

*8.4.4. 3,5-Bis-(3,5-di-tert-butylbenzyloxy)-4-[4-(tetrahydro-pyran-2-yloxy)-butoxy]-benzyl alcohol (**7**)*

A solution of 3.59 g (4.8 mmol, 1 equiv) of **6** and 30 mL of THF was cooled in an ice bath before adding 16.8 mL (16.8 mmol, 3.5 equiv) of 1 M DIBAL-H in hexanes with a syringe pump (0.5 mL/min). The solution stirred at room temperature for 16 h and then was cooled in an ice bath before adding 2 mL of H_2O dropwise. The gray solid that formed was removed by vacuum filtration and washed with EtOAc. The filtrate was concentrated under reduced pressure to yield 3.40 g (97.9%) of the desired product as a colorless viscous oil that solidified to a white oily solid. ^1H NMR ($CDCl_3$) δ 7.42 (t, *J*=1.7, 2H), 7.42 (d, *J*=1.6, 4H), 6.74 (s, 2H), 5.12 (s, 4H), 4.62 (s, 2H), 4.55 (br t, *J*=3.5, 1H), 4.12 (t, *J*=6.5, 2H), 3.83 (m, 1H), 3.71 (m, 1H), 3.46 (m, 1H), 3.34 (m, 1H), 2.16 (br s, 1H), 1.95–1.46 (m, 10H), 1.38 (s, 36H); ^{13}C NMR ($CDCl_3$) δ 153.2, 150.9, 138.0, 136.5, 136.3, 121.9, 121.8, 106.5, 98.6, 73.3, 71.9, 67.2, 65.4, 62.0, 34.9, 31.6, 30.7, 27.3, 26.3, 25.5, 19.5. HRMS (ESI): Calcd for $C_{46}H_{68}O_6Na$: 739.4914. Found: 739.4905. Anal. Calcd for $C_{46}H_{68}O_6$: C, 77.05; H, 9.56. Found: C, 77.18; H, 9.54.

*8.4.5. 2-(4-(2,6-Bis(3,5-di-tert-butylbenzyloxy)-4-((3,5-dinitrophenoxy)methyl)phenoxy) butoxy) tetrahydro-2H-pyran (**9**)*

A solution of 4.52 g (6.3 mmol, 1 equiv) of **7**, 1.28 g (7.0 mmol, 1.1 equiv) of **8**, 2.49 g (9.5 mmol, 1.5 equiv) of PPh_3, and 150 mL of THF was cooled in an ice bath. A separate solution of 1.87 mL (9.5 mmol, 1.5 equiv) of DIAD and 150 mL of THF was added to the first dropwise with an addition funnel. The combined solutions were stirred for 18 h while they slowly warmed to room temperature and then solvent was removed under reduced pressure. The residual was partitioned between 150 mL each of H_2O and Et_2O and the aqueous layer was extracted twice with 150 mL of Et_2O. The combined organic fractions were washed twice with 400 mL of 5% $KOH_{(aq)}$, once with 400 mL of H_2O, once with 400 mL of brine, dried with Na_2SO_4, and solvent was reduced under reduced pressure to yield a yellow heterogeneous mixture. The crude material was purified by column chromatography using silica gel (7:3 PE/Et_2O, R_f=0.37) to yield 4.63 g (82.5%) of desired product as a yellow powder. ^1H NMR ($CDCl_3$) δ 8.66 (t, *J*=2.0, 1H), 8.14 (d, *J*=2.0, 2H), 7.39 (t, *J*=1.8, 2H), 7.30 (d, *J*=1.8, 4H), 6.78 (s, 2H), 5.13 (s, 2H), 5.10 (s, 4H), 4.50 (m, 1H), 4.10 (t, *J*=6.6, 2H), 3.78 (m, 1H), 3.66 (m, 1H), 3.43 (m, 1H), 3.29 (m, 1H), 1.90–1.42 (m, 10H), 1.33 (s, 36H); ^{13}C NMR ($CDCl_3$) δ 159.9, 153.6, 151.1, 149.3, 139.3, 136.0, 129.5, 122.1, 121.9, 115.7, 111.2, 107.7, 98.7, 73.4, 72.2, 72.0, 67.2, 62.2, 35.0, 31.6, 30.8, 27.4, 26.3, 25.6, 19.6. HRMS (ESI): Calcd for $C_{52}H_{70}N_2O_{10}Na$: 905.4928. Found: 905.4919. Anal. Calcd for $C_{52}H_{70}N_2O_{10}$: C, 70.72; H, 7.99; N, 3.17. Found: C, 70.63; H, 7.98; N, 3.29.

*8.4.6. 5-(3,5-Bis(3,5-di-tert-butylbenzyloxy)-4-(4-(tetrahydro-2H-pyran-2-yloxy)butoxy) benzyloxy) benzene-1,3-diamine (**10**)*

Pd/C (143 mg, 10%) was added to a solution of 2.0 g (2.26 mmol, 1 equiv) of **9**, 45 mL of CH_2CH_2, and 45 mL of EtOH. $H_{2(g)}$ was bubbled through the solution for 1 h using a balloon and needle after which the solution was stirred for 4 h at room temperature under a static $H_{2(g)}$ atmosphere (balloon). The solution was then filtered through a pad of Celite to remove Pd/C and solvent was removed from the filtrate under reduced pressure to yield 1.85 g (quant) of desired product as a brown glass. ^1H NMR ($CDCl_3$) δ 7.38 (t, *J*=1.8, 2H), 7.30 (d, *J*=1.8, 4H), 6.76 (s, 2H), 5.79 (d, *J*=1.8, 2H), 5.69 (t, *J*=1.9, 1H), 5.08 (s, 4H), 4.87 (s, 2H), 4.50 (m, 1H), 4.08 (t, *J*=6.7, 2H), 3.79 (m, 1H), 3.65 (m, 1H), 3.58 (br s, 4H), 3.43 (m, 1H), 3.29 (m, 1H), 1.89–1.45 (m, 10H), 1.33 (s, 36H); ^{13}C NMR ($CDCl_3$) δ 161.2, 153.3, 151.0, 148.6, 138.5, 136.4, 132.6, 121.9, 107.4, 98.7, 95.4, 93.1, 73.4, 72.1, 70.2, 67.3, 62.1, 35.0, 31.64, 31.61, 30.8, 27.4, 26.4, 25.6, 19.6.

*8.4.7. 1,1′-(5-(3,5-Bis(3,5-di-tert-butylbenzyloxy)-4-(4-(tetrahydro-2H-pyran-2-loxy)butoxy) benzyloxy)-1,3-phenylene)bis(3-(4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)urea). Bis-DeAP–OTHP (**11**)*

A solution of 1.85 g (2.23 mmol, 1 equiv) of **10**, 4.53 g (17.7 mmol, 8 equiv) of **13**, and 83 mL of $CHCL_3$ was sealed in a round bottom flash with a septum and heated in an oil bath at 60 °C for 12 h. The solution was then filtered through Celite to remove excess heterocycle and diluted with 50 mL $CHCl_3$. The organic layer was then washed with 50 mL of 10% $HCl_{(aq)}$, 50 mL of satd $NaHCO_{3(aq)}$, 100 mL of brine, and solvent was removed under reduced pressure. The crude material was dissolved in a minimal amount of toluene, precipitated into cold MeOH, and 2.28 g (84.5%) of the desired product was collected by vacuum filtration as a brown powder. Further purification could be achieved by preparative SEC (toluene eluent), although was not typically necessary. ^1H NMR ($CDCl_3$) δ 14.40–10.20 (br m, 3H), 9.40–6.00 (br m, 17H), 5.70–5.75 (br m, 11H), 2.10–0.80 (br m, 40H). MALDI-MS (IAA) *m*/*z* (rel int.) 1238.6 (30, MK^+), 1223.0 (70, MNa^+), 1199.6 (70, MH^+), 1115.5 (100, MH^+−THP), 1060.8 (30), 1038.4 (30). Anal. Calcd for $C_{68}H_{82}N_{10}O_{10}$: C, 68.09; H, 6.89; N, 11.68. Found: C, 67.82; H, 7.03; N, 11.72.

*8.4.8. 1,1′-(5-(3,5-Bis(3,5-di-tert-butylbenzyloxy)-4-(4-hydroxybutoxy)benzyloxy)-1,3-phenylene)bis(3-(4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)urea). Bis-DeAP–OH (**1**)*

A homogenous solution of 286.1 mg (0.24 mmol, 1 equiv) of **11**, 25 mL of THF, and 4 mL of 25% $HCl_{(aq)}$ was heated in an oil bath at 45C for 12 h. The solution was added to 40 mL of H_2O and the precipitate that formed was collected by vacuum filtration, rinsing with a large amount of H_2O. The dry crude material was then dissolved in THF, precipitated into cold MeOH, and 153.5 mg (58.3%) of desired product was collected by vacuum filtration as a brown powder. ^1H NMR ($CDCl_3$) δ 14.20–10.10 (br m, 3H), 9.00–6.10 (br m, 14H), 5.5–3.0 (br m, 10H), 2.10–0.70 (br m, 40H). HRMS (ESI): Calcd for $C_{63}H_{75}N_{10}O_9$ (MH^+): 1115.5718. Found: 1115.5662. MALDI-MS (IAA) *m*/*z* (rel int.) 1172.1 (10) 1155.1 (10, MK^+), 1139.0 (45, MNa^+), 1115.6 (100, MH^+), 1074.6 (10). Anal. Calcd for $C_{63}H_{74}N_{10}O_9$: C, 67.84; H, 6.69; N, 12.56. Found: C, 67.43; H, 6.45; N, 11.67.

*8.4.9. 4-(4-((3,5-Bis(3-(4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)ureido)phenoxy) methyl)-2,6-bis(3,5-di-tert-butylbenzyloxy)phenoxy)butyl-2-bromo-2-methylpropanoate. Bis-DeAP–ATRP (**14**)*

A heterogeneous solution of 400 mg (0.36 mmol, 1 equiv) of **1**, 6.5 mL of toluene, 0.09 mL of Et_3N, and 0.09 mL of (0.72 mmol, 2 equiv) 2-bromo-2-methylpropanoyl bromide was stirred at room temperature overnight. The solution was added to 30 mL of $CHCl_3$ and washed with 15 mL of 10% $HCl_{(aq)}$, 15 mL of saturated $NaHCO_{3(aq)}$, 30 mL of brine, dried with Na_2SO_4, and solvent was removed under reduced pressure. The crude material was dissolved in a minimal amount of toluene and precipitated into cold MeOH and 233.4 mg (50.0%) of the desired product was isolated by vacuum filtration. Further purification could be achieved by preparative SEC (toluene eluent), although was not typically necessary. ^1H NMR ($CDCl_3$) δ 14.20–10.10 (br m, 3H,), 9.00–6.10 (br m, 14H), 5.7–3.2 (br m, 10H), 2.10–0.70 (br m, 46H). MALDI-MS (IAA) *m*/*z* (rel int.) 1317.1 (30) 1301.3 (100, MK^+), 1284.4 (40, MNa^+), 1262.3 (60, MH^+).

*8.4.10. 3,5-Bis(benzyloxy)benzyl 2-bromo-2-methylpropanoate (**16**)*

A solution of 5.0 g (15.6 mmol, 1 equiv) of **15**, 100 mL of CH_2Cl_2, and 2.6 mL of Et_3N was cooled in an ice bath before adding a separate solution of 2.3 mL (18.7 mmol, 1.2 equiv) of 2-bromo-2-methylpropanoyl bromide in 5 mL of CH_2Cl_2. Combined solution was left stirring in ice bath to slowly warm to room temperature over 18 h and then washed with 100 mL of H_2O, 100 mL of brine, dried with Na_2SO_4, and solvent was removed under reduced pressure. The crude material was purified by column chromatography on silica gel (8:2 PE/Et_2O, R_f=0.41) to yield 4.19 g (57.1%) of desired product as a white powder. ^{1}H NMR ($CDCl_3$) δ 7.43–7.37 (m, 8H, H-2), 7.33 (t, J=7.0, 2H), 6.62 (d, J=2.1, 2H), 6.59 (t, J=1.8, 1H), 5.14 (s, 2H), 5.04 (s, 4H), 1.94 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.5, 160.2, 137.9, 136.8, 128.7, 128.2, 127.6, 106.7, 102.0, 70.2, 67.4, 55.9, 30.9. HRMS (ESI): Calcd for $C_{25}H_{26}O_4Br$ (MH^+): 469.1014. Found: 469.1016. Anal. Calcd for $C_{25}H_{25}O_4Br$: C, 63.97; H, 5.37. Found: C, 63.95; H, 5.35.

8.4.11. *Bis-DeAP–PEG (**21b**)*

A solution of 11.2 mg (0.01 mmol, 1 equiv) of **1**, 200 mg (0.01 mmol, 1 equiv) of MPEG–20K-acid, 6.1 mg (0.05 mmol, 5 equiv) of DMAP, 2.5 mL of CH_2Cl_2, and 31.0 mg (0.15 mmol, 15 equiv) of DCC was stirred at room temperature. After 12 h, 6.1 mg (0.05 mmol, 5 equiv) of DMAP and 31.0 mg (0.15 mmol, 15 equiv) of DCC were again added and the solution was stirred for an additional 12 h. The solution was filtered to remove DHU, solvent was reduced, and 151 mg (76%) of polymer was isolated as a white solid after precipitation into cold Et_2O.

8.4.12. *Bis-DeAP–PEG (**21a**)*

Prepared in analogous manner to **27b**.

8.4.13. *4-(2,6-Bis(3,5-di-tert-butylbenzyloxy)-4-((3,5-dinitrophenoxy)methyl)phenoxy) butan-1-ol (**22**)*

A homogenous solution of 150 mg (0.17 mmol, 1 equiv) of **9**, 18 mL of THF, and 3 mL of 25% $HCl_{(aq)}$ was heated in an oil bath at 45 °C for 5 h. The solution was diluted with 50 mL of $CHCl_3$ and washed twice with 40 mL of saturated $NaHCO_{3(aq)}$, once with 40 mL of brine, dried with Na_2SO_4 and solvent was removed under reduced pressure. The crude material was purified by column chromatography on silica gel (1:1 PE/Et_2O, R_f=0.31) to yield 102.6 mg (76.5%) of desired product as a light yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.66 (t, J=2.0, 1H, H-1), 8.14 (d, J=2.0, 2H, H-2), 7.40 (t, J=1.8, 2H, H-7), 7.30 (d, J=1.8, 4H, H-6), 6.79 (s, 2H, H-4), 5.14 (s, 2H, H-3), 5.09 (s, 2H, H-5), 4.09 (t, J=6.1, 2H, H-9), 3.50 (q, J=6.2, 2H, H-12), 1.79 (m, 2H, H-10), 1.65 (m, 2H, H-11), 1.33 (s, 36H, H-8); ^{13}C NMR ($CDCl_3$) δ 159.8, 153.6, 151.2, 149.4, 139.1, 135.9, 129.7, 122.2, 122.0, 115.7, 111.2, 107.5, 73.4, 72.2, 72.1, 62.7, 35.0, 31.6, 29.7, 27.0. HRMS (ESI): Calcd for $C_{47}H_{63}N_2O_9$ (MH^+): 799.4534. Found: 799.4534. Anal. Calcd for $C_{47}H_{62}N_2O_9$: C, 70.65; H, 7.82; N, 3.51. Found: C, 70.78; H, 7.95; N, 3.61.

8.4.14. *Control polymer for Bis-DeAP–PEG (**23**)*

A solution of 5.8 mg (0.007 mmol, 1.2 equiv) of **22**, 125 mg (0.006 mmol, 1 equiv) of MPEG–20K-acid, 3.7 mg (0.03 mmol, 5 equiv) of DMAP, 2 mL of CH_2Cl_2, and 18.6 mg (0.09 mmol, 15 equiv) of DCC was stirred at room temperature. After 12 h, 3.7 mg (0.03 mmol, 5 equiv) of DMAP and 18.6 mg (0.09 mmol, 15 equiv) of DCC were again added and the solution was stirred for an additional 12 h. The solution was filtered to remove DHU, solvent was reduced, and 103.6 mg (86%) of polymer was isolated after precipitation into cold Et_2O.

Acknowledgements

Funding of this work by the NSF (CHE-0212772) and by ICI National Starch and Chemical Company (SRF 2209 R2AB3287) is gratefully acknowledged.

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