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Molecule-Responsive Block Copolymer Micelles

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Abstract: Ring-opening metathesis polymerization was used to generate an ABC triblock copolymer, containing complementary diamidopyridine (DAP) and thymine (THY) outer blocks, which assembles into spherical aggregates held together by DAP–THY noncovalent interactions. Addition of THY-containing small guest molecules results in complete opening and deaggregation of the block copolymer micelle. This molecular recognition and macroscopic response shows high selectivity to the guest structure, and tolerates only a small amount of conformational mobility in the THY guest. On the other hand, addition of a small DAP-containing guest does not break the aggregates, but instead, results in new micelles which show a different selectivity profile from the parent morphology. We have examined the effect of a number of structural features in the block copolymers, on both the *extent* and *selectivity* of their macroscopic response to guests (that is, opening of the micelle). This study has resulted in a set of structural guidelines, which help in the design of effective molecule-responsive micelles for applications in selective drug delivery, sensing, and surface patterning.

Keywords: block copolymers · host-guest systems · micelles · molecular recognition · self-assembly

Introduction

The self-assembly of block copolymers into nanostructured aggregates has recently witnessed a dramatic increase in research activity.[1–7] Numerous potential applications of these materials are anticipated in drug delivery,[2] nanomaterials synthesis,[3] nanolithography,[4] catalysis,[5] separation,[6] and dispersant technologies.[7] In contrast to small-molecule amphiphilic micelles, block copolymer assemblies display significant stability,[8] increased ability to encapsulate guests without premature release,[9] and facile, highly tunable functionalization.[8,10] Of particular interest are environmentally responsive block copolymer micelles, in which morphological changes can be deliberately induced with the use of an external stimulus.[11–13] These materials are attractive for applications in targeted drug delivery[12b] as well as tissue repair.[11c] Stimuli that have been used to modify the self-assembly of block copolymers are pH and ionic strength,[11] temperature,[11c,12] light irradiation,[11c,13a] and oxidation.[13b] In contrast, the use of a specific molecule to trigger the opening and deaggregation of a block copolymer micelle has not been explored. This can give access to selective drug delivery micelles, which open and release their cargo in a biological environment in which a specific molecule is overexpressed. In addition, these architectures can potentially serve as small-molecule sensors, the morphology of which changes upon interaction with a specific molecule; this can be visually detected (for example, by large changes in light scattering). Finally, orthogonal patterning of surfaces with specific molecules can be achieved using these block copolymer micelles.[18l]

Polymeric materials containing molecular recognition units have recently been extensively investigated.[14–18] Molecularly imprinted polymer networks capable of selective recognition,[14] biomolecule sensitive hydrogels,[15] and supramolecular polymers constructed by the molecular recognition of smaller units have been studied.[16] In addition, we[17] and others[18] have reported the synthesis of polymers containing molecular recognition units in their side chains. These have been explored for their ability to noncovalently bind to a number of other moieties (for example, nanoparti-

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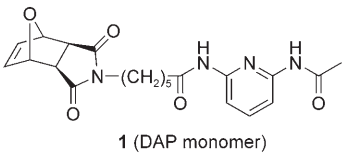
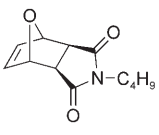
cles,[18d] dendritic molecules,[18a] and other polymers[18e]). In particular, we have previously reported[17] the synthesis of polymers and block copolymers containing a regular arrangement of DNA bases and analogues by living ring-opening metathesis polymerization (ROMP).[19] Control over the block sequence of the DNA base analogues along the copolymer backbone was readily achieved. This sequence, as well as the molecular recognition properties, were found to directly influence the self-assembly of these block copolymers into nanostructured morphologies.[17]

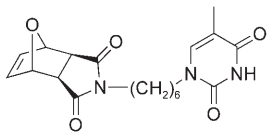
We herein report the rational design and synthesis of the first small molecule-responsive block copolymer micelles. ROMP[19] is used to generate diblock and triblock copolymers, containing complementary molecular recognition blocks. By tuning the nature of the molecular recognition units and the length of the different blocks, we show the creation of morphologies which deaggregate and open when a specific guest is added. In addition, we find that these micellar structures show exquisite selectivity in the structural requirements of the molecules which can trigger this morphological change.

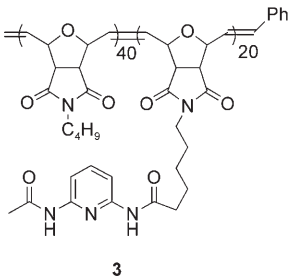
Results and Discussion

Self-assembly of diblock copolymer 3: We have previously described the synthesis of monomer **1**, containing a diamidopyridine (DAP) moiety, and its ready incorporation into homopolymers and block copolymers by living ROMP.[17c] Diblock copolymer **3** was generated by the sequential polymerization of DAP monomer **1**, and hydrophobic monomer **2**.









Solutions of diblock copolymer **3** in $CHCl_3$ are highly turbid, consistent with aggregation. Transmission electron microscopy (TEM) shows the formation of large spherical aggregates (Figure 1), of average diameter 190 nm and a broad size distribution, consistent with the formation of large compound micelles (LCMs).[1] Dynamic light scattering (DLS) measurements of $CHCl_3$ solutions of **3** at different angles also reveals the formation of spherical aggregates with an approximate size of 280 nm. These micelles are equally polydisperse when formed at lower (0.1 mg mL^{-1}) or higher (10 mg mL^{-1}) polymer concentration. The aggregation behavior of block copolymer **3** is possibly the result of

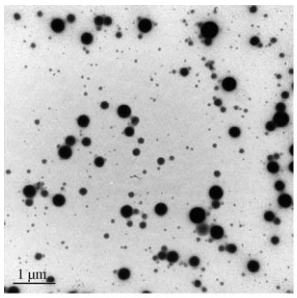


Figure 1. a) TEM image of diblock copolymer **3** in $CHCl_3$ (1 mg mL^{-1} solution) and b) DAP–DAP hydrogen bonding in **3**.

the hydrogen-bonding association of the DAP units, which are weakly self-complementary ($K_{DAP-DAP} < 10\,M^{-1}$),[20] and the subsequent creation of noncovalently crosslinked DAP–DAP regions (Figure 1b, Scheme 1).

We reasoned that if the formation of spherical aggregates in **3** is the result of weak DAP–DAP interactions, then the addition of a small molecule guest which binds more strongly to these units may cause the opening of these aggregates (Scheme 1). We added maleimide (1 equiv per DAP unit) to the $CHCl_3$ solution of copolymer **3** at room temperature, as the association constant of this thymine (THY) analogue with DAP is high ($K_{assoc} \approx 500$–$1000\,M^{-1}$).[20] The turbid sample instantly became clear, and aggregation could no longer be detected by DLS or TEM (Scheme 1). Thus, this small molecule was able to open the aggregates of copolymer **3**. To ascertain the selectivity of this interaction, we added *N*-methylmaleimide to a solution of copolymer **3** (Table 1, entry 3). This molecule possesses similar structural features to maleimide, but cannot associate with DAP by molecular recognition. The solution remained turbid, even after boiling in $CHCl_3$, and both DLS and TEM showed that the aggregate size, shape, and size distributions were unchanged. Thus, the deaggregation of copolymer **3** morphologies by maleimide most likely occurs through a molecular recognition mechanism, in which the small maleimide molecules associate with the DAP units on the polymer and displace the crosslinked DAP chains (Scheme 1).

Having established that small molecules can indeed break aggregation in copolymer **3**, we proceeded to further test the selectivity of this association (Table 1, row 1). Not surprisingly, succinimide, which possesses very similar structural and molecular recognition features to maleimide, was able to open these morphologies (entry 1). We were interested in testing the tolerance of this system to steric and entropic costs, and thus added *N*-butylthymine as well as *N*-hexylthy-

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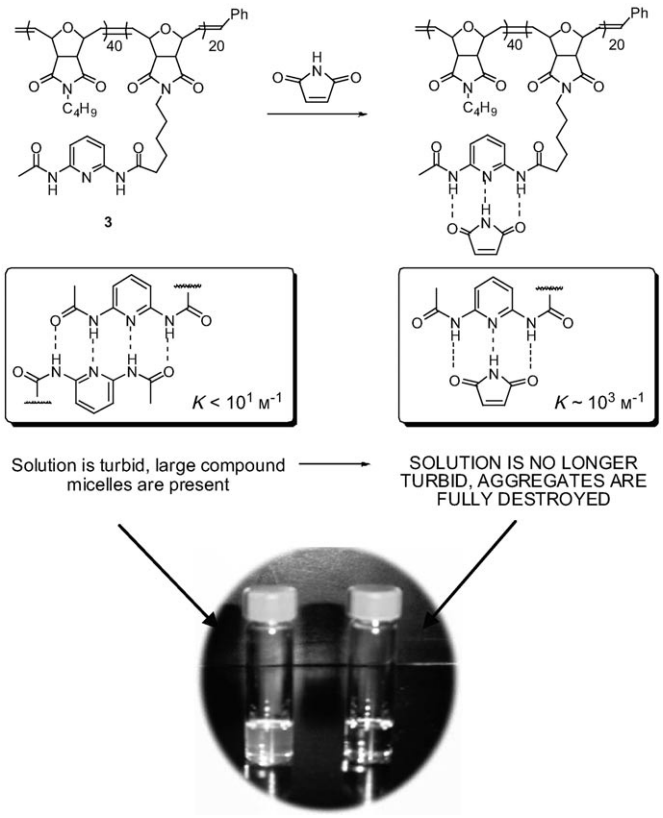

Scheme 1. Addition of a small-molecule guest, maleimide, to diblock copolymer **3**, resulting in aggregate destruction and loss of solution turbidity.

mine (entries 4 and 5). These guest molecules contain THY units with similar molecular recognition ability to maleimide, but also possess conformationally mobile alkyl chains attached to the THY units. Thus, association of many of these molecules with the DAP units on the backbone of the polymer would present additional entropic costs. Despite these constraints, addition of either of these molecules (even at 1 equiv per DAP unit) to solutions of copolymer **3** resulted in loss of turbidity and aggregation (DLS and TEM).

To further increase the steric costs of association, we added monomer **4** (Table 1, entry 6), which contains a thymine moiety, a long (C_6) alkyl chain, as well as a bulky oxanorbornene unit. This compound resulted in deaggregation of copolymer **3** morphologies as well, even at one equivalent of guest per DAP unit of copolymer. Thus, the enthalpic gain from the DAP–THY association for all these guest molecules was enough to offset any steric or entropic costs. We then tested the response of copolymer **3** micelles to guest molecules with DAP units, which are expected to associate only weakly with the DAP units of the copolymer ($K_{DAP-DAP} < 10\,M^{-1}$).[20] Addition of a small amount of 2,6-bis(acetylamino)pyridine (entry 7) (<5 equiv per DAP unit of copolymer) did not disrupt these aggregates; however, a large excess of this guest (>20 equiv per DAP unit of copolymer) opened these aggregates, as evidenced visually, and confirmed by TEM and DLS. In contrast, bulkier DAP-containing guest molecules, such as 2,6-bis(benzoylamino)pyridine and monomer **1** (entries 8 and 9) did not affect these aggregates even upon any excess addition. This is consistent with the fact that disrupting block copolymer **3** micelles would involve the replacement of the DAP–DAP interactions which hold these micelles together, with similar or less energetically favorable interactions. We finally tested the selectivity of this system by adding *p*-cresol to copolymer **3** aggregates (entry 10). This small molecule can only present a single hydrogen bond with the DAP unit to offset the DAP–DAP interactions which hold the aggregates together. Small amounts of *p*-cresol (<5 equiv per DAP unit of copolymer) indeed did not affect the aggregates; however, addition of larger quantities (>20 equiv per DAP unit) of this molecule did open and destroy the aggregates, as evidenced visually and by DLS and TEM. Thus, block copolymer **3** micelles are opened by small molecules containing thymine or thymine analogues, which are complementary to its diamidopyridine units, regardless of their size and steric bulk. In addition, these micelles are also somewhat responsive to small hydrogen-bonding molecules which are not complementary to DAP units.

Synthesis and self-assembly of triblock copolymer 6: The low selectivity in the response of copolymer **3** aggregates to guests is likely due to the fact that these aggregates are held together by weak interactions between DAP units, and thus a large spectrum of molecules can disrupt these interactions. We reasoned that the creation of block copolymers that are held together by stronger interactions may improve selectivity. We thus designed triblock copolymer **6**, containing a DAP block, a hydrophobic spacer block, and a THY block (Scheme 2). The DAP and THY units in **6** are complementary through a strong three-point hydrogen-bonding interaction ($K_{DAP-THY} \approx 500$–$1000\,M^{-1}$).[20,21] The two outer complementary blocks are expected to associate in $CHCl_3$, creating a similar crosslinked region to diblock **3**, which would, however, be held together by stronger interactions (DAP–THY versus DAP–DAP). We have previously reported the synthesis of DAP monomer **1** and its ROMP reaction; however, we needed to access monomer **4** containing THY and establish its polymerization by ROMP.

The synthesis of monomer **4** was achieved by reaction of *exo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide with 1,6-dibromohexane and K_2CO_3, followed by a reaction with thymine and K_2CO_3. The ROMP reaction of monomer **4** was first performed in CH_2Cl_2 at room temperature by using the ruthenium catalyst **5** (Scheme 2).[19d] However, this standard polymerization solvent resulted in precipitation of the polymer. ^{1}H NMR showed that the ROMP reaction did occur with quantitative conversion; however, the polydispersity index (PDI) of the obtained polymer was high (PDI = 1.50), indicating reduced living character of the reaction. We were able to construct more uniform polymers containing **4** by performing the ROMP reaction in a 1:4 CH_3OH/CH_2Cl_2 mixed solvent system, which most likely prevented undesired hydrogen-bond self-association of these

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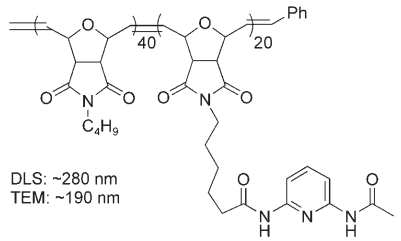
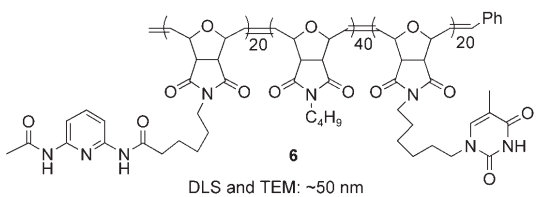
Table 1. Addition of small-molecule guests (entries 1–10) to block copolymer hosts **3**, **6**, and **7**.

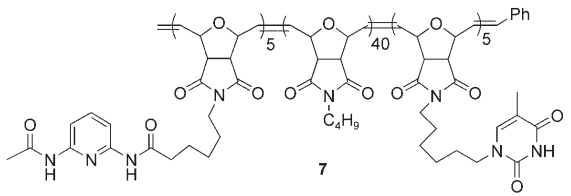


3



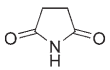
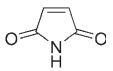
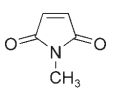
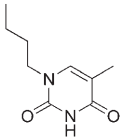
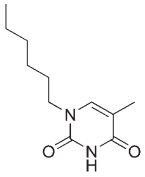
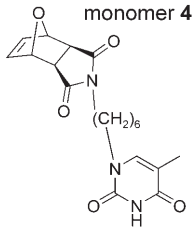
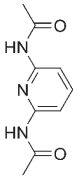
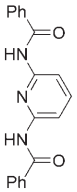
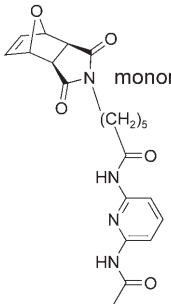
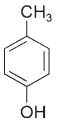
6

DLS and TEM: ~50 nm



7

DLS: ~200 nm, TEM: ~140 nm

Entry	1	2	3	4	5	6	7	8	9	10
						 monomer **4**			 monomer **1**	
3	AGGREGATES DESTROYED	AGGREGATES DESTROYED	aggregates unmodified	AGGREGATES DESTROYED	AGGREGATES DESTROYED	AGGREGATES DESTROYED	unmodified at low guest concn (<5 equiv) DESTROYED at high guest concn (>20 equiv)	aggregates unmodified	aggregates unmodified	unmodified at low guest concn (<5 equiv) DESTROYED at high guest concn (>20 equiv)
6	aggregates unmodified	aggregates unmodified	aggregates unmodified	aggregates unmodified	aggregates unmodified	aggregates unmodified	aggregates unmodified	aggregates unmodified	aggregates unmodified	aggregates unmodified
7	AGGREGATES DESTROYED	AGGREGATES DESTROYED	aggregates unmodified	AGGREGATES DESTROYED	unmodified at low guest concn (<5 equiv) DESTROYED at high guest concn (>20 equiv)	aggregates unmodified	aggregates modified: DLS: −160 nm TEM: −120 nm	aggregates unmodified	aggregates unmodified	aggregates unmodified

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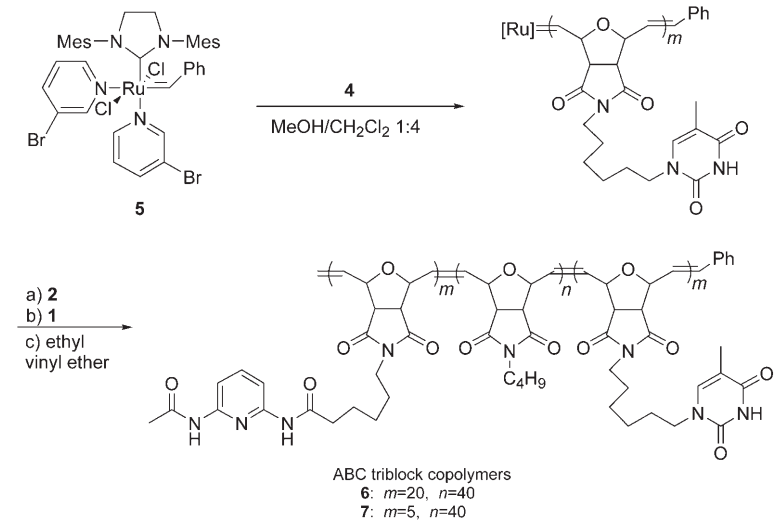

Scheme 2. Synthesis of block copolymers **6** and **7**.

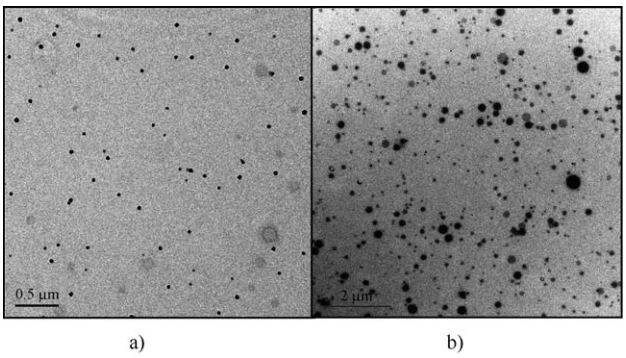

Figure 2. TEM image of a 1 mg mL^{-1} $CHCl_3$ solution of a) triblock copolymer **6** and b) triblock copolymer **7**.

polymers. These conditions resulted in quantitative conversion in minutes (monitored by ^{1}H NMR spectroscopy) without any precipitation of polymer. Very narrow molecular weight distributions for all polymers and block copolymers were obtained,[23] and the degrees of polymerization were consistent with the initial monomer-to-initiator ratios used. ABC triblock copolymer **6** was thus constructed by sequential polymerization of THY-containing monomer **4**, hydrophobic monomer **2**, and then DAP-containing monomer **1** (Scheme 2), all of which were performed in 1:4 CH_3OH/CH_2Cl_2. This triblock copolymer possesses two complementary blocks, containing an average of 20 units of THY and 20 units of DAP.

The self-assembly behavior of **6** in $CHCl_3$ was examined by TEM and DLS. Both methods showed the presence of small spherical aggregates ($\approx$50 nm in diameter, shown by TEM, Figure 2a, and DLS), and a narrow size distribution, consistent with the formation of star micelles from this polymer.[24] Unlike the LCMs from copolymer **3**, star micelles have a more defined architecture and their size is directly related to the length of the polymer chains, thus they are expected to be more monodisperse.[1] The aggregation in **6** is likely due to the strong hydrogen bond complementarity of the two outer blocks of this copolymer, and may be possibly perturbed with the addition of small molecules. However, the addition of maleimide or succinimide did not affect these aggregates, even with extensive heating or sonication of the copolymer with a large excess of these guest molecules. The addition of any of the previously used small-molecule guests to the copolymer solution at boiling or at room temperature did not break the aggregates either (Table 1, row 2). Both DLS and TEM showed that the presence of the aggregates, their size, spherical nature, and size distributions were undisturbed by the addition of any guest. Thus, the interchain interactions in triblock copolymer **6** aggregates are likely too strong to show any dynamic behavior or any ability to be affected by small molecules present at the exterior of the micelles.

Self-assembly of triblock copolymer 7: To create block copolymer micelles which are molecule-responsive with a high degree of selectivity, we needed to design a copolymer with 1) chain–chain interactions strong enough to show a high level of discrimination in the guest molecules which can break their aggregates, but 2) not excessively strong as to render the aggregates incapable of opening. We used the same ROMP method (Scheme 2) to synthesize ABC triblock copolymer **7**, containing five units each of DAP and THY in its two outer blocks, and a relatively large hydrophobic spacer block (40 units). This copolymer is still expected to associate by using DAP–THY recognition; however, the overall chain–chain interactions between the short complementary blocks are predicted to be far less strong than in copolymer **6**, and can possibly be disrupted when guests are added (Table 1, row 3). Copolymer **7** forms large compound micelles (of average size $\approx$140 nm by TEM, Figure 2b, and $\approx$200 nm by DLS), with a slightly narrower size distribution than diblock **3** in $CHCl_3$. As expected, these LCMs are not as monodisperse as the star micelles from **6**. As in **3**, the size distribution does not change when these morphologies are formed from $CHCl_3$ solutions of lower (0.1 mg mL^{-1}) or higher (10 mg mL^{-1}) concentration.

Addition of succinimide or maleimide did result in opening the micelles of triblock copolymer **7**, as evidenced by the absence of aggregates by DLS and TEM (Table 1, entries 1 and 2). This is most likely due to hydrogen-bond-mediated binding of these thymine analogues to the DAP units of **7**, and concomitant breaking of the chain–chain

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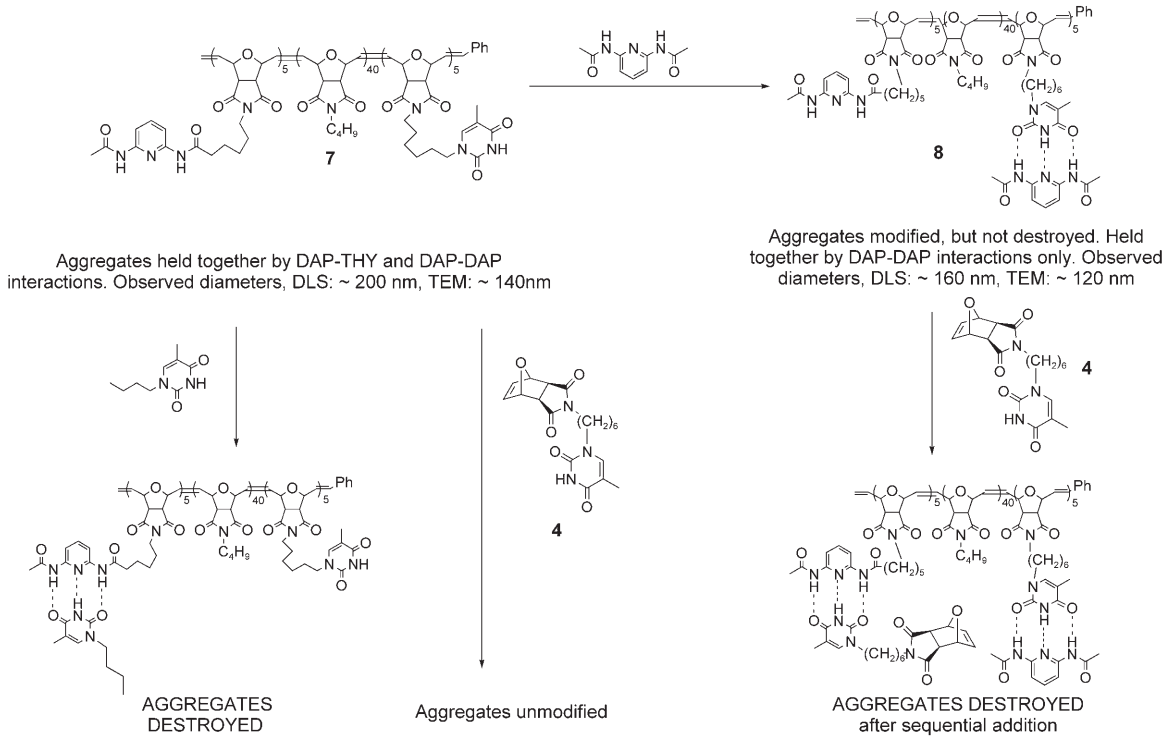

Scheme 3. Addition of small-molecule guests to triblock copolymer **7** micelles.

crosslinking between the DAP and THY blocks (Scheme 3). In contrast, *N*-methylmaleimide did not affect these morphologies, even after prolonged heating (entry 3). Thus, the interaction between the DAP and THY outer blocks of copolymer **7** is dynamic enough to be selectively affected with the addition of complementary guests. To compare the selectivity of this copolymer with diblock copolymer **3**, we added *p*-cresol to the aggregates of **7** (entry 10). No change in morphology was detected, even with heating or addition of a large excess of this guest molecule. Thus, these aggregates show superior selectivity to copolymer **3** micelles. To further test this selectivity, we treated copolymer **7** aggregates with thymine-containing guests of increasing conformational mobility and steric demand. Addition of *N*-butylthymine caused destruction of the aggregates even when used in small amounts (1 equiv per DAP unit of **7**, entry 4). *N*-Hexylthymine, on the other hand, was only able to open these aggregates when added in larger amounts (>20 equiv per DAP unit), and did not affect their morphology when added in smaller amounts (<5 equiv per DAP unit, even with heating; entry 5). Thus, the *N*-hexylthymine guest appears to present enough of an entropic cost to render the two states—closed, self-associated micelle and open polymer associated with this guest—approximately isoenergetic. This molecule is likely the upper limit of conformational mobility that can be tolerated by the host polymer.[22] Monomer **4**, which possesses a sterically demanding oxanorbornene unit in addition to the structural features of *N*-hexylthymine, did not affect copolymer **7** morphologies even at large excess (>20 equiv, entry 6).

In addition to using analogues of THY as guest molecules for copolymer **7** micelles, analogues of DAP are equally viable, as they can associate with the THY units of copolymer **7** and break the chain–chain DAP–THY interactions (Scheme 3). The addition of larger DAP-containing molecules (Table 1, entries 8 and 9) did not affect the morphologies of copolymer **7**, consistent with the high steric and entropic cost of their association with the polymer. In contrast, the addition of 2,6-bis(acetylamino)pyridine to copolymer **7** aggregates affected the morphologies noticeably, resulting in smaller aggregates ($\approx$120 nm by TEM, $\approx$160 nm by DLS, entry 7). The fact that the morphologies did not disappear entirely is consistent with the self-complementary nature of the DAP units in copolymer **7**. Guest molecules with DAP moieties are expected to associate with the THY units of copolymer **7**, thus "freeing up" the DAP units of the polymer strands (Scheme 3). As was shown earlier with diblock **3**, weak DAP–DAP interactions can cause aggregate formation, and this explains the formation of the new observed micellar aggregates from complex **8** (Scheme 3). Because these new aggregates would only be held together by DAP–DAP interactions, they should respond to the same guests which break the aggregation of copolymer **3**. Indeed, addition of the sterically demanding, THY-containing monomer **4** to aggregates of copolymer **7**, which had been pretreated with 2,6-bis(acetylamino)pyridine (complex **8**, Scheme 3), resulted in destroying these aggregates. This is in contrast with the behavior of micelles of copolymer **7**, which are unresponsive to this large THY guest without this prior complexation (Scheme 3). Thus, block copolymer **7** micelles ex-

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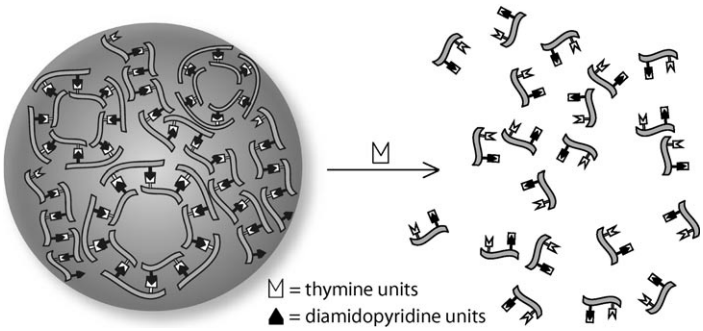
hibit two-stage complexation: first, DAP-containing guests result in new morphologies, which in turn can be opened with THY-containing guests.

Copolymer **7** thus shows exquisite selectivity in the structural requirements of the molecules which can open and deaggregate its morphology. Not only is the presence of a specific molecular recognition group required, but in addition, the conformational mobility of the guest cannot be very large (for example, succinimide and *N*-butylthymine can open the aggregates, but *N*-hexylthymine cannot unless a large excess is added), so that the unfavorable entropic cost of associating these guest molecules with the polymer backbone is not excessive. In addition, its response to THY guests is noticeably different from its interaction with DAP guests. Complete deaggregation is the result of addition of THY guests, whereas a change in morphology of the aggregate occurs with DAP guests. This can be exploited to achieve a two-stage response of the same morphologies to two guests, which can reside on spatially segregated portions of this copolymer.

Copolymer morphology and environmental response: We have shown that the nature and number of molecular recognition units in copolymers **3**, **6**, and **7** can result in different *selectivities* to guest molecules, exhibited by the aggregates of these copolymers. In addition, we believe that the morphologies adopted by the copolymer aggregates play an active role in determining the *extent* of their interaction with guest molecules. Copolymer **6**, containing relatively long and complementary molecular recognition blocks, forms small, uniform spherical aggregates with an approximate diameter of 50 nm, consistent with a star micelle morphology.[24] ^{1}H NMR spectroscopic studies of these aggregates in $CDCl_3$ show a nearly complete disappearance of the THY and DAP peaks of copolymer **6**, while the peaks corresponding to the middle, hydrophobic block are visible.[23] This is consistent with the presence of the THY and DAP units of this copolymer in the unsolvated core of these star micelles. This is, however, in contrast to the spectrum of the unaggregated copolymer **6** in [D_6]DMSO, in which the peaks of all three blocks are visible with the correct integral area ratios.[23] Whether this core is the result of intra- or intermolecular association of the self-complementary outer blocks of **6** is unclear at present.[24] However, the lack of response of these morphologies to any added guest molecule can be readily explained by the inaccessibility of the molecular recognition units in the desolvated core of these aggregates. This morphology is in turn a direct result of the nature, length, and architecture of the molecular recognition blocks in copolymer **6**.

On the other hand, copolymers **3** and **7**, with more loosely associated molecular recognition regions, form larger spherical aggregates, the size and polydispersity of which are more consistent with large compound micelles.[1a] Unlike copolymer **6**, ^{1}H NMR spectroscopic studies of the aggregates of copolymer **3** or **7** in $CDCl_3$ clearly show the peaks corresponding to their molecular recognition units (DAP for copolymer **3**; DAP and THY for copolymer **7**) with expected integral area ratios.[23] Thus, in each of these two copolymers, these molecular recognition units are readily accessible to solvent, as well as to guest molecules. For copolymer **7** in $CDCl_3$, the ^{1}H NMR spectrum shows significant downfield shifts of both NH protons of the DAP and THY units, compared to polymers containing exclusively DAP or exclusively THY, clearly indicating DAP–THY interactions for this copolymer.[23] Monitoring the addition of a guest molecule, such as succinimide to copolymer **7** by ^{1}H NMR spectroscopy also shows a downfield shift of the NH proton of this THY-analogue guest, indicating its hydrogen-bonded association with the DAP portion of the copolymer.[23]

These studies are consistent with the ready accessibility of the molecular recognition units in the large compound micelles obtained from copolymers **3** and **7**. Large compound micelles have been previously observed[1a,12h] for a number of amphiphilic di- and triblock copolymers and, in many systems, they have been postulated to occur as a result of weak segregation between the different blocks of a copolymer.[25] Copolymers **3** and **7** can indeed display two weakly segregated regions, namely noncovalently crosslinked DAP–DAP or DAP–THY domains, and an aliphatic, $CDCl_3$ soluble region (the C4 middle block). Thus, these large compound micelles may consist of a continuous aliphatic and soluble phase, with solvent and guest accessible DAP–DAP and DAP–THY regions (Scheme 4).



Scheme 4. Possible arrangement of the DAP–THY domains within a soluble phase (grey) in copolymer **7** large compound micelles, and opening of these micelles upon addition of a THY guest.

The structural difference between the morphologies of copolymer **6** and copolymers **3** and **7** accounts for the difference in the *extent* of response of the polymers to guest molecules. It should be emphasized that the *selectivity* of these copolymer micelles to guest molecules is largely the result of the nature of the molecular recognition units, as well as their degree of polymerization, rather than their morphology.

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Conclusion

We have reported the first example of a block copolymer micellar aggregate, which is capable of selective recognition of small-molecule guests, with concomitant opening of the aggregate. Spherical micelles from ABC triblock copolymer **7**, containing two complementary thymine and diamidopyridine outer blocks, can be selectively and completely opened with small molecules containing thymine analogues. This molecular recognition and macroscopic response is highly sensitive to the guest structure, and tolerates only a small amount of conformational mobility; larger thymine-containing guests do not affect these micellar aggregates. In addition, copolymer **7** aggregates also respond to small, diamidopyridine-containing guests, but rather than deaggregating completely, this molecular recognition results in new, smaller micellar aggregates. In turn, these new aggregates, which are held together by weaker interactions, show a different molecular recognition response from the original aggregates, and can now be opened with large, thymine-containing guests.

The field of small-molecule host-guest chemistry is well-established, and more recently, a number of studies have examined the use of polymer matrices as viable host systems.[18] From this fundamental perspective, the present contribution is the first example of a detailed study on the use of block copolymer micelles as hosts for small molecules. Through rational variation of various components of the copolymers, this study has resulted in a set of useful guidelines, and a possible design for molecule-responsive block copolymer morphologies: 1) the copolymer contains complementary molecular recognition blocks, which cause the formation of noncovalently crosslinked domains, and which can be disrupted by the addition of guests; 2) the binding of the guest molecule with the polymer results in an unassociated polymer in the solvent system (achieved by using a long soluble middle block); 3) the interaction between these blocks is strong enough to render the polymer selective towards guest molecules (for example, a DAP–THY interaction works better than a weaker DAP–DAP interaction); and 4) this interaction is not excessively strong, so as to allow the polymer morphology to be dynamic and environmentally responsive (achieved by using shorter complementary blocks). In addition, this study has illustrated the importance of the morphology of the copolymer aggregates, requiring the molecular recognition regions of the copolymer to be in a solvated and accessible domain of the micelles. This insures a high extent of interaction of these units with guest molecules on the exterior of the micelles. Many applications of the resulting molecule-responsive morphologies can be anticipated, including selective drug delivery agents and biomolecule sensing systems, and are currently being explored in our laboratory.

Experimental Section

General considerations: All polymerization reactions were carried out under a dry nitrogen atmosphere, using standard Schlenk techniques. ^{1}H NMR spectra were recorded on a Varian M400 spectrometer operated at 400.140 MHz, ^{13}C NMR on a Varian M300 spectrometer operated at 75.459 MHz. Chemical shifts are reported in ppm relative to tetramethylsilane. IR spectra were collected as potassium bromide (KBr) pellets, on a Perkin–Elmer model MB100 Fourier Transform infrared (FTIR) spectrometer at 1 cm^{-1} resolution. UV/Vis spectra were recorded on a Varian Cary 300 spectrophotometer. Gel permeation chromatography (GPC) measurements were performed with an Agilent Technologies 1100 series HPLC system equipped with a differential refractive index (RI) detector and a multiangle light scattering (LS) detector (Optilab-DSP and Dawn-Eos, Wyatt Technology). Tosoh Biosep-18340 and Tosoh Biosep-18344 TSK gel columns at 40 °C eluted with DMF (flow rate: 0.5 mL min^{-1}) were used to determine the molecular weights. RI and LS signals were transferred to the computer to calculate the weight-average (M_w) and number-average (M_n) molecular weight according to the instruction manual (Wyatt Technology) for Dawn-DSP. Dynamic light scattering (DLS) experiments were performed on a Brookhaven Instruments Corporation system equipped with a BI-200SM goniometer, a BI-9000AT digital correlator and a Compass 315–150 CW laser light source from Coherent operating at 532 nm (150 mW). All DLS samples were prepared by using copolymers dissolved in spectrophotometric grade $CHCl_3$ (1% w/v), small-molecule guests were added when applicable, and the solution was then filtered with 4.5 μm PTFE syringe filters (Chromatographic Specialties). The block copolymers generated the same morphologies whether they were dissolved in $CHCl_3$ at room temperature or in refluxing $CHCl_3$.

Transmission electron microscopy: Samples were prepared by placing a drop of the corresponding DLS sample onto transmission electron microscopy copper grids (400 mesh, carbon coated, purchased from Electron Microscopy Sciences). The grids were air-dried for 12 h. The aggregates were then examined using a JEOL 2000FX electron microscope operated at 80 kV.

Materials: Reagents were purchased from Aldrich and used as received. The ruthenium alkylidene Grubbs second-generation catalyst was purchased from Strem Chemicals, and was used to synthesize Grubbs third-generation catalyst **5** by using reported procedures.[19d] Monomers **1**[17c] and **2**,[26] *exo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide,[26] *N*-butylthymine,[28] 2,6-bis(acetylamino)pyridine,[21] and 2,6-bis(benzoylaminopyridine)[21] were synthesized according to literature procedures. *N*-Hexylthymine was prepared by using the same procedure as *N*-butylthymine.[28b] CH_2Cl_2 was distilled over calcium hydride, and CH_3OH was distilled over magnesium. Deuterated solvents were purchased from Cambridge Isotope Laboratories and used without further purification.

Synthesis of polymers poly(1)$_{20}$ and 3: Grubbs third-generation catalyst **5** (15 mg, 0.017 mmol, 1.0 equiv) was dissolved in a 1:4 CH_3OH/CH_2Cl_2 solution (1.0 mL) and was sonicated for 10 min. It was then added dropwise to a 4.0 mL solution of monomer **1** (140.0 mg, 0.339 mmol, 20 equiv, same solvent system as above) and the resulting solution was stirred at room temperature. After 30 min, ^{1}H NMR spectroscopy showed a quantitative conversion of monomer **1**, and hence the solution was split into two halves. The first half was quenched with ethyl vinyl ether (0.3 mL, 400 equiv), stirred for 15 min and DAP homopolymer poly(**1**)$_{20}$ (91% yield) was collected by precipitating this solution slowly into stirring hexanes and by drying in vacuo. A solution of monomer **2** (75.0 mg, 0.339 mmol, 40 equiv) in 1:4 CH_3OH/CH_2Cl_2 (2.0 mL) was added to the other half, and the solution was stirred. ^{1}H NMR spectroscopy showed complete conversion after 15 min, after which ethyl vinyl ether (0.3 mL, 400 equiv) was added and the stirring was continued for 15 min. The quenched solution was precipitated in stirring hexanes and dried in vacuo to give copolymer **3**, a light beige solid (94% yield).

*DAP homopolymer poly(**1**)$_{20}$*: GPC: $M_n = 7.4 \times 10^3$; PDI = 1.02; ^{1}H NMR ([D$_6$]DMSO; 50% *trans*): $\delta = 9.97$ (brs, 40H), 7.67 (brs, 60H), 5.92 (brs, 20H; *trans*), 5.71 (brs, 20H; *cis*), 4.85 (brs, 20H; *cis*), 4.37 (brs, 20H; *trans*), 3.34 (brs, 80H), 2.35 (brs, 40H), 2.07 (brs, 60H), 1.54 (brs, 80H),

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1.23 ppm (brs, 40H); ^{13}C NMR ([D$_6$]DMSO): δ = 176.10, 172.58, 169.84, 150.94, 140.49, 132.10, 109.60, 80.50, 53.35, 38.79, 36.67, 27.73, 26.63, 25.33, 24.84 ppm; FTIR (KBr): 3315 (br, w), 2934 (w), 2858 (w), 1777 (w), 1701 (s), 1586 (w), 1508 (w), 1449 (m), 1400 (m), 1369 (w), 1295 (w), 1242 (w), 1150 (w), 1038 (w), 1007 (w), 981 (w), 853 (w), 802 (w), 734 (w), 642 (w), 548 cm^{-1} (w); UV-Vis: λ_{max} (CHCl$_3$) = 249.3, 293.3 nm.

Diblock copolymer ***3***: GPC: $M_n = 17.7 \times 10^3$; PDI = 1.03; ^{1}H NMR ([D$_6$]DMSO); 50% *trans*: δ = 9.96 (brs, 40H), 7.67 (s, 60H), 5.94 (brs, 60H; *trans*), 5.72 (brs, 60H; *cis*), 4.84 (brs, 60H; *cis*), 4.36 (brs, 60H; *trans*), 3.38 (brs, 240H), 2.34 (brs, 40H), 2.06 (s, 60H), 1.53 (brs, 80H), 1.44 (brs, 80H), 1.22 (brs, 120H), 0.85 ppm (brs, 120H); ^{13}C NMR ([D$_6$]DMSO): δ = 175.70, 171.76, 169.05, 150.11, 144.47, 139.68, 131.58, 131.24, 108.83, 108.69, 80.22, 79.98, 53.11, 52.10, 37.83, 35.91, 29.17, 26.92, 25.84, 24.53, 24.03, 19.49, 13.56 ppm; FTIR (KBr): 3461 (w), 3334 (br, w), 2958 (w), 2937 (w), 2872 (w), 1777 (w), 1701 (s), 1604 (w), 1586 (w), 1505 (w), 1450 (m), 1399 (m), 1369 (w), 1344 (w), 1294 (w), 1243 (w), 1191 (w), 1138 (w), 1040 (w), 1008 (w), 970 (w), 921 (w), 802 cm^{-1} (w); UV/Vis: λ_{max} (CHCl$_3$) = 248.9, 293.1 nm.

Synthesis of *exo-N*-(6-bromohexyl)-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide:[29] K_2CO_3 (10.73 g, 77.62 mmol, 5.1 equiv), 1,6-dibromohexane (14.66 g, 60.09 mmol, 4.0 equiv), and dry DMF (20 mL) were placed in a flame-dried round-bottomed flask and the setup was purged with N_2. *exo*-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide (2.50 g, 15.1 mmol, 1.0 equiv) was dissolved in dry DMF (30 mL), purged with N_2 and was transferred dropwise to the reaction flask. The resulting mixture was then stirred at a constant temperature of 55 °C for 2 h, followed by stirring at room temperature for an additional 16 h. The solvent was removed in vacuo, after which water and ethyl acetate (EtOAc) were added to the reaction flask. The organic layer was separated and the aqueous layer was extracted with EtOAc. All the organic fractions were collected, dried over magnesium sulfate ($MgSO_4$) and evaporated in vacuo. Column chromatography (silica gel, 2:3 EtOAc/hexanes) yielded a pure white solid (3.73 g, 11.38 mmol, 75%). ^{1}H NMR ($CDCl_3$): δ = 6.51 (s, 2H), 5.26 (s, 2H), 3.47 (t, J = 7 Hz, 2H), 3.38 (t, J = 7 Hz, 2H), 2.83 (s, 2H), 1.86 (quin., J = 7 Hz, 2H), 1.58 (quin., J = 7 Hz, 2H), 1.45 (quin., J = 7 Hz, 2H), 1.30 ppm (quin., J = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 176.29, 136.6, 81.04, 47.61, 39.02, 34.00, 32.79, 27.88, 27.63, 26.02 ppm.

Synthesis of monomer 4: Thymine (7.40 g, 58.7 mmol, 5.8 equiv) and K_2CO_3 (7.50 g, 54.3 mmol, 5.3 equiv) were mixed in dry DMF (40 mL) in a flame-dried round-bottomed flask and the setup was purged with N_2. A solution of *exo-N*-(6-bromohexyl)-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide (3.38 g, 10.2 mmol, 1.0 equiv) in dry DMF (10 mL) was then added dropwise under N_2 and the resulting mixture was stirred at a constant temperature of 55 °C for 7 h, followed by stirring at room temperature overnight. The solvent was removed in vacuo, and water and EtOAc were added to the reaction flask. The organic layer was separated and the aqueous layer was extracted with EtOAc. All the organic fractions were collected, dried over $MgSO_4$, and evaporated in vacuo to afford ≈3 g of crude product. Column chromatography (silica gel, 5% CH_3OH/CH_2Cl_2) yielded a pure white solid (1.45 g, 3.88 mmol, 38%). ^{1}H NMR ([D$_6$]DMSO): δ = 11.14 (s, 1H), 7.47 (s, 1H), 6.52 (s, 2H), 5.10 (s, 2H), 3.56 (t, J = 7 Hz, 2H), 3.31 (t, J = 7 Hz, 2H), 2.89 (s, 2H), 1.73 (s, 3H), 1.50 (m, 2H), 1.40 (m, 2H), 1.20 ppm (m, 4H); ^{13}C NMR ([D$_6$]DMSO): δ = 177.07, 164.86, 151.45, 142.01, 137.09, 109.07, 81.07, 47.88, 47.79, 38.57, 29.11, 27.75, 26.37, 26.12, 12.77 ppm; FTIR (KBr): 3446 (br, w), 3152 (w), 3098 (w), 3086 (w), 3012 (w), 2941 (w), 2865 (w), 2827 (w), 1768 (w), 1703 (s), 1668 (s), 1478, 1469, 1435, 1401 (m), 1367 (m), 1357 (m), 1333 (w), 1259 (w), 1227 (w), 1220 (w), 1200 (w), 1195 (w), 1152 (w), 1145 (w), 1102 (w), 1035 (w), 1012 (w), 969 (w), 956 (w), 917 (w), 897 (w), 876 (m), 854 (w), 828 (w), 810 (w), 801 (w), 792 (w), 759 (w), 727 (w), 706 (w), 650 (w), 592 (w), 570 cm^{-1} (w); UV/Vis: λ_{max} (CHCl$_3$) = 272.1 nm; EIMS: (monomer **4** lost furan, C_4H_4O, in a *retro*-Diels–Alder pathway when it was injected at 200 °C): 305.1.

Synthesis of polymers poly(4)$_{20}$, poly(4)$_{20}$-*block*-poly(2)$_{40}$, 6, and 7: Catalyst **5** (40 mg, 0.045 mmol, 1.0 equiv) was dissolved in a 1:4 CH_3OH/CH_2Cl_2 solution (2.0 mL) and was sonicated for 10 min. It was then transferred to a 4.0 mL solution of monomer **4** (337.7 mg, 0.905 mmol, 20 equiv, same solvent system as catalyst) and the resulting solution was stirred at room temperature. ^{1}H NMR spectroscopy showed the complete conversion of monomer **4** after 15 min, and hence the solution was split into two halves. The first half was quenched with ethyl vinyl ether (0.8 mL, 400 equiv), stirred for 15 min and THY homopolymer poly(**4**)$_{20}$ (88% yield) was collected by precipitating the solution into stirring hexanes, and drying in vacuo. To the other half, a solution of monomer **2** (200.1 mg, 0.905 mmol, 40 equiv) in 1:4 CH_3OH/CH_2Cl_2 (2.0 mL) was added and the solution was stirred. ^{1}H NMR spectroscopy showed quantitative conversion after 15 min. Again, the solution was split into two equal portions and diblock copolymer poly(**4**)$_{20}$-*block*-poly(**2**)$_{40}$ (89% yield) was collected in the same way as polymer poly(**4**)$_{20}$. Finally, a 1:4 CH_3OH/CH_2Cl_2 solution (3.0 mL) of monomer **1** (93.1 mg, 0.226 mmol, 20 equiv) was added to the polymerization solution. After stirring for 30 min, ^{1}H NMR spectroscopy showed that the monomer was fully consumed. The reaction mixture was quenched with ethyl vinyl ether (0.4 mL, 400 equiv), stirred for 15 minutes, and triblock **6** (95% yield), a light yellowish solid, was collected by precipitating the solution in stirring hexanes and drying in vacuo. Triblock copolymer **7** was synthesized similarly by using different equivalents of the monomers to generate the 5:40:5 triblock copolymer (monomer **4**: 84.4 mg, 0.226 mmol, 5 equiv; monomer **2**: 200.1 mg, 0.905 mmol, 40 equiv; monomer **1**: 23.3 mg, 0.056 mmol, 5 equiv).

*THY homopolymer poly(****4****)$_{20}$*: GPC: $M_n = 8.3 \times 10^3$; PDI = 1.04; ^{1}H NMR ([D$_6$]DMSO; 48% *trans*): δ = 11.13 (s, 20H), 7.46 (s, 20H), 5.94 (brs, 20H; *trans*), 5.72 (brs, 20H; *cis*), 4.84 (brs, 20H; *cis*), 4.37 (brs, 20H; *trans*), 3.57 (brs, 40H), 3.38 (brs, 80H), 1.72 (brs, 60H), 1.47 (brs, 80H), 1.22 ppm (brs, 80H); ^{13}C NMR ([D$_6$]DMSO): δ = 176.43, 164.85, 151.44, 141.99, 132.02, 109.07, 80.45, 53.82, 52.83, 47.76, 38.45, 29.13, 27.74, 26.58, 26.21, 12.79 ppm; FTIR (KBr): 3463 (br, w), 3214 (br, w), 3062 (br, w), 2939 (w), 2861, 1776, 1701 (s), 1468 (w), 1439 (w), 1400 (w), 1354 (w), 1255 (w), 1218 (w), 1169 (w), 1152 (w), 1139 (w), 1043 (w), 976 (w), 915 (w), 768 cm^{-1} (w); UV/Vis: λ_{max}(CHCl$_3$) = 271.8 nm.

*Diblock copolymer poly(****4****)$_{20}$*-block-*poly(****2****)$_{40}$*: GPC: $M_n = 15.6 \times 10^3$; PDI = 1.05; ^{1}H NMR ([D$_6$]DMSO; 49% *trans*): δ = 11.12 (s, 20H), 7.46 (s, 20H), 5.94 (brs, 60H; *trans*), 5.71 (brs, 60H; *cis*), 4.84 (brs, 60H; *cis*), 4.37 (brs, 60H; *trans*), 3.57 (brs, 40H), 3.34 (brs, 240H), 1.72 (brs, 60H), 1.45 (brs, 160H), 1.22 (brs, 160H), 0.88 ppm (brs, 120H); ^{13}C NMR ([D$_6$]DMSO): δ = 176.47, 164.87, 151.45, 150.91, 142.01, 140.76, 132.35, 132.11, 109.95, 109.56, 109.10, 81.01, 78.05, 53.75, 52.84, 47.79, 38.62, 35.80, 29.96, 29.16, 27.79, 26.23, 25.32, 20.28, 14.35, 12.79 ppm; FTIR (KBr): 3459 (br, w), 2956 (w), 2933 (w), 2868 (w), 1776 (w), 1702 (s), 1467 (w), 1439 (w), 1399 (w), 1357 (w), 1260 (w), 1192 (w), 1137 (w), 1043 (w), 968 (w), 921 cm^{-1} (w); UV/Vis: λ_{max} (CHCl$_3$) = 271.2 nm.

Triblock copolymers ***6*** *and* ***7***: GPC: $M_n = 59.9 \times 10^3$; PDI = 1.05 (copolymer **6**); $M_n = 33.6 \times 10^3$; PDI = 1.09 (copolymer **7**); ^{1}H NMR ([D$_6$]DMSO; 49% *trans*): δ = 11.11 (brs, 20H), 9.91 (brs, 40H), 7.63 (brs, 60H), 7.45 (brs, 20H), 5.90 (brs, 80H; *trans*), 5.70 (brs, 80H; *cis*), 4.81 (brs, 80H; *cis*), 4.35 (brs, 80H; *trans*), 3.54 (brs, 40H), 3.32 (brs, 320H), 2.32 (brs, 40H), 2.04 (brs, 60H), 1.70 (brs, 60H), 1.44 (brs, 240H), 1.20 (brs, 200H), 0.85 ppm (brs, 120H) (copolymer **6**); ^{1}H NMR ([D$_6$]DMSO; 49% *trans*): 11.15 (brs, 5H), 9.96 (brs, 10H), 7.67 (brs, 15H), 7.48 (brs, 5H), 5.93 (brs, 50H; *trans*), 5.72 (brs, 200H), 4.84 (brs, 50H; *cis*), 4.38 (brs, 50H; *trans*), 3.58 (brs, 10H), 3.38 (brs, 200H), 2.37 (brs, 10H), 2.08 (brs, 15H), 1.72 (brs, 15H), 1.45 (brs, 120H), 1.20 (brs, 110H), 0.87 ppm (brs, 120H) (copolymer **7**); ^{13}C NMR ([D$_6$]DMSO): δ = 176.47, 172.54, 169.83, 164.87, 151.45, 150.91, 142.01, 140.76, 132.35, 132.11, 109.95, 109.56, 109.10, 81.01, 78.05, 53.75, 52.84, 47.79, 38.62, 36.70, 35.80, 29.96, 29.16, 27.79, 26.62, 26.23, 25.32, 24.28, 20.28, 14.35, 12.79 ppm (both **6** and **7**); FTIR (KBr): 3463 (br, w), 3059 (w), 2936 (w), 2863 (w), 1777 (w), 1701 (s), 1585 (w), 1539 (w), 1450 (m), 1400 (m), 1368 (w), 1290 (w), 1243 (w), 1192 (w), 1139 (w), 1041 (w), 971 (w), 920 (w), 804 cm^{-1} (w) (copolymer **6**); 3461 (br, w), 2958 (w), 2936 (w), 2872 (w), 1777 (w), 1701 (s), 1585 (w), 1449 (m), 1399 (m), 1367 (w), 1344 (w), 1290 (w), 1244 (w), 1192 (w), 1137 (w), 1042 (w), 1010 (w), 970 (w), 921 (w), 879 (w), 805 cm^{-1} (w) (copolymer **7**); UV/Vis: λ_{max} (CHCl$_3$) = 279.7 nm (both **6** and **7**).

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[1] a) N. S. Cameron, M. K. Corbierre, A. Eisenberg, *Can. J. Chem.* **1999**, *77*, 1311–1326; for reviews see: b) G. Riess, *Prog. Polym. Sci.* **2003**, *28*, 1107–1170; c) J.-F. Gohy, *Adv. Polym. Sci.* **2005**, *190*, 65–136.

[2] For reviews see: a) C. Allen, D. Maysinger, A. Eisenberg, *Colloids Surf. B* **1999**, *16*, 3–27; b) G. S. Kwon, T. Okano, *Pharm. Res.* **1999**, *16*, 597–600; c) V. P. Torchilin, *Expert Opin. Ther. Pat.* **2005**, *15*, 63–75; d) N. Nishiyama, K. Kataoka, *Adv. Polym. Sci.* **2006**, *193*, 67–101.

[3] For reviews see: a) I. W. Hamley, *Nanotechnology* **2003**, *14*, R39–54; b) G. ten Brinke, O. Ikkala, *Chem. Rec.* **2004**, *4*, 219–230; c) M. Lazzari, M. A. Lopez-Quintela, *Adv. Mater.* **2003**, *15*, 1583–1594; d) S. Förster, M. Antonietti, *Adv. Mater.* **1998**, *10*, 195–217.

[4] For reviews see: a) M. Trawick, D. Angelescu, P. Chaikin, R. Register, in *Nanolithography and Patterning Techniques in Microelectronics* (Ed.: D. G. Bucknall), CRC Press/Taylor & Francis, Boca Raton, FL, **2005**, pp. 1–38; b) M. A. Hillmyer, *Adv. Polym. Sci.* **2005**, *190*, 137–181; c) M. Li, C. A. Coenjarts, C. K. Ober, *Adv. Polym. Sci.* **2005**, *190*, 183–226.

[5] a) B. M. Rossbach, K. Leopold, R. Weberskirch, *Angew. Chem.* **2006**, *118*, 1331–1335; *Angew. Chem. Int. Ed.* **2006**, *45*, 1309–1312; b) D. A. Durkee, H. B. Eitouni, E. D. Gomez, M. W. Ellsworth, A. T. Bell, N. P. Balsara, *Adv. Mater.* **2005**, *17*, 2003–2006; c) C. Hinderling, Y. Keles, T. Stoeckli, H. F. Knapp, T. De Los Arcos, P. Oelhafen, I. Korczagin, M. A. Hempenius, G. J. Vancso, R. Pugin, H. Heinzelmann, *Adv. Mater.* **2004**, *16*, 876–879.

[6] A. Choucair, A. Eisenberg, *J. Am. Chem. Soc.* **2003**, *125*, 11993–12000.

[7] a) G. Liu, H. Yang, J. Zhou, S. -J. Law, Q. Jiang, G. Yang, *Biomacromolecules* **2005**, *6*, 1280–1288; b) H. -i. Shin, B. G. Min, W. Jeong, C. Park, *Macromol. Rapid Commun.* **2005**, *26*, 1451–1457; c) G. Moad, K. Dean, L. Edmond, N. Kukaleva, G. Li, R. T. A. Mayadunne, R. Pfaendner, A. Schneider, G. Simon, H. Wermter, *Macromol. Symp.* **2006**, *233*, 170–179; d) S. Jain, F. S. Bates, *Science* **2003**, *300*, 460–464.

[8] A. Shen, A. Eisenberg, *Angew. Chem.* **2000**, *112*, 3448–3450; *Angew. Chem. Int. Ed.* **2000**, *39*, 3310–3312.

[9] S. A. Jenehke, X. L. Chen, *Science* **1998**, *279*, 1903–1907.

[10] a) A. Choucair, A. Eisenberg, *Eur. Phys. J. E* **2003**, *10*, 37–44; b) O. Terreau, L. Luo, A. Eisenberg, *Langmuir* **2003**, *19*, 5601–5607.

[11] a) Y. Chang, E. S. Powell, H. R. Allcock, *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 2912–2920; b) G. Koutalas, S. Pispas, N. Hadjichristidis, *Eur. Phys. J. E* **2004**, *15*, 457–464; c) B. Jeong, A. Gutowska, *Trends Biotechnol.* **2002**, *20*, 305–311; d) H. Shen, L. Zhang, A. Eisenberg, *J. Am. Chem. Soc.* **1999**, *121*, 2728–2740; e) J. J. L. M. Cornelissen, M. Fischer, N. A. J. M. Sommerdijk, R. J. M. Nolte, *Science* **1998**, *280*, 1427–1430; f) A. S. Lee, V. Bütün, M. Vamvakaki, S. P. Armes, J. A. Pople, A. P. Gast, *Macromolecules* **2002**, *35*, 8540–8541; g) T. J. Martin, K. Procházka, P. Munk, S. E. Webber, *Macromolecules* **1996**, *29*, 6071–6073.

[12] a) J. Raez, J. P. Tomba, I. Manners, M. A. Winnik, *J. Am. Chem. Soc.* **2003**, *125*, 9546–9547; b) B. Liu, S. Perrier, *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 3643–3654; c) Y. Cai, Y. Tang, S. P. Armes, *Macromolecules* **2004**, *37*, 9728–9737; d) A. J. Convertine, B. S. Lokitz, Y. Vasileva, L. J. Myrick, C. W. Scales, A. B. Lowe, C. L. McCormick, *Macromolecules* **2006**, *39*, 1724–1730; e) J. E. Chung, M. Yokoyama, M. Yamato, T. Aoyagi, Y. Sakurai, T. Okano, *J. Controlled Release* **1999**, *62*, 115–127; f) B. S. Sumerlin, A. B. Lowe, D. B. Thomas, C. L. McCormick, *Macromolecules* **2003**, *36*, 5982–5987; g) M. Arotcarena, B. Heise, S. Ishaya, A. Laschewsky, *J. Am. Chem. Soc.* **2002**, *124*, 3787–3793; h) X. Chen, X. Ding, Z. Zheng, Y. Peng, *Macromol. Biosci.* **2005**, *5*, 157–163.

[13] a) J. Jiang, X. Tong, Y. Zhao, *J. Am. Chem. Soc.* **2005**, *127*, 8290–8291; b) A. Napoli, M. J. Boerakker, N. Tirelli, R. J. M. Nolte, N. A. J. M. Sommerdijk, J. A. Hubbell, *Langmuir* **2004**, *20*, 3487–3491.

[14] a) U. G. Spizzirri, N. A. Peppas, *Chem. Mater.* **2005**, *17*, 6719–6727; b) C. C. Huval, M. J. Bailey, W. H. Braunlin, S. R. Holmes-Farley, W. H. Mandeville, J. S. Petersen, S. C. Polomoscanik, R. J. Sacchiro, X. Chen, P. K. Dhal, *Macromolecules* **2001**, *34*, 1548–1550; for a review see: c) J. Steinke, D. C. Sherrington, I. R. Dunkin, *Adv. Polym. Sci.* **1995**, *123*, 81–125.

[15] For a review see: a) T. Miyata, T. Uragami, K. Nakamae, *Adv. Drug Delivery Rev.* **2002**, *54*, 79–98; b) X. Y. Wu, Q. Zhang, R. Arshady, in *The PBM Series Vol. 1: Introduction to Polymeric Biomaterials, Vol.1* (Ed.: R. Arshady), Citus Books, UK, **2003**, pp. 157–194.

[16] a) J. -M. Lehn, in *Supramolecular Polymers* (Ed.: A. Ciferri), 2nd ed., CRC Press/Taylor & Francis, FL, **2005**, pp. 3–27; b) A. W. Bosman, R. P. Sijbesma, in *Supramolecular Polymers* (Ed.: A. Ciferri), 2nd ed., CRC Press/Taylor & Francis, Boca Raton, FL, **2005**, pp. 555–570; for reviews see: c) G. Armstrong, M. Buggy, *J. Mater. Sci.* **2005**, *40*, 547–559; d) A. W. Bosman, L. Brunsveld, B. J. B. Folmer, R. P. Sijbesma, E. W. Meijer, *Macromol. Symp.* **2003**, *201*, 143–154; e) L. Brunsveld, B. J. B. Folmer, E. W. Meijer, R. P. Sijbesma, *Chem. Rev.* **2001**, *101*, 4071–4097; f) R. F. M. Lange, E. W. Meijer in *Bioorganic Chemistry*, 1st ed. (Eds: U. Diederichsen, T. K. Lindhorst, B. Westermann, L. A. Wessjohann), Wiley-VCH, **1999**, pp. 72–77.

[17] a) J. Dalphond, H. S. Bazzi, K. Kahrim, H. F. Sleiman, *Macromol. Chem. Phys.* **2002**, *203*, 1988–1994; b) H. S. Bazzi, H. F. Sleiman, *Macromolecules* **2002**, *35*, 9617–9620; c) H. S. Bazzi, J. Bouffard, H. F. Sleiman, *Macromolecules* **2003**, *36*, 7899–7902.

[18] Examples in the literature include: a) R. Shenhar, H. Xu, B. L. Frankamp, T. E. Mates, A. Sanyal, O. Uzun, V. M. Rotello, *J. Am. Chem. Soc.* **2005**, *127*, 16318–16324; b) H. Nakade, M. F. Ilker, B. J. Jordan, O. Uzun, N. L. LaPointe, E. B. Coughlin, V. M. Rotello, *Chem. Commun.* **2005**, 3271–3273; c) F. Ilhan, M. Gray, V. M. Rotello, *Macromolecules* **2001**, *34*, 2597–2601; d) B. L. Frankamp, O. Uzun, F. Ilhan, A. K. Boal, V. M. Rotello, *J. Am. Chem. Soc.* **2002**, *124*, 892–893; e) O. Uzun, A. Sanyal, H. Nakade, R. J. Thibault, V. M. Rotello, *J. Am. Chem. Soc.* **2004**, *126*, 14773–14777; f) L. P. Stubbs, M. Weck, *Chem. Eur. J.* **2003**, *9*, 992–999; g) C. Burd, M. Weck, *Macromolecules* **2005**, *38*, 7225–7230; h) J. M. Pollino, L. P. Stubbs, M. Weck, *J. Am. Chem. Soc.* **2004**, *126*, 563–567; i) H. J. Spijker, A. J. Dirks, J. C. M. van Hest, *Polymer* **2005**, *46*, 8528–8535; j) W. H. Binder, C. Kluger, *Macromolecules* **2004**, *37*, 9321–9330; k) H. Hofmeier, R. Hoogenboom, M. E. L. Wouters, U. S. Schubert, *J. Am. Chem. Soc.* **2005**, *127*, 2913–2921; l) K. Yamauchi, J. R. Lizotte, T. E. Long, *Macromolecules* **2003**, *36*, 1083–1088; m) H. Xu, T. Lu, O. Uzun, V. M. Rotello, *J. Am. Chem. Soc.* **2006**, *128*, 3162–3163.

[19] a) S. T. Nguyen, L. K. Johnson, R. H. Grubbs, *J. Am. Chem. Soc.* **1992**, *114*, 3974–3975; b) Z. Wu, S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1995**, *117*, 5503–5511; c) P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100; d) J. A. Love, J. P. Morgan, T. M. Trnka, R. H. Grubbs, *Angew. Chem.* **2002**, *114*, 4207–4209; *Angew. Chem. Int. Ed.* **2002**, *41*, 4035–4037.

[20] F. H. Beijer, R. P. Sijbesma, J. A. J. M. Vekemans, E. W. Meijer, H. Kooijman, A. L. Spek, *J. Org. Chem.* **1996**, *61*, 6371–6380.

[21] L. Yu, H. -J. Schneider, *Eur. J. Org. Chem.* **1999**, 1619–1625.

[22] Although the effect of a few carbons can be reflected in binding constants (for example, 3-fold reduction in binding constant to thymine is observed for 2,6-(butyrylamino)pyridine versus 2,6-bis(acetylamino)pyridine[21]), large changes in binding affinity of *N*-butyl versus *N*-hexylthymine to DAP are not expected. However, any small differences in individual binding constants (and especially in the entropic cost of binding) may be amplified by cooperative effects within the multivalent polymer, which contains many DAP binding sites in close proximity. Another important factor is the pos-

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sible reduction in diffusion constant of *N*-hexyl versus the more compact *N*-butylthymine into the polymer micelle, which possesses domains of entangled polymer chains. This may reduce the number of *N*-hexylthymines that come into contact with the DAP-THY units within this micelle. These factors may all contribute to the different response of polymer **7** micelles to *N*-butyl versus *N*-hexylthymine.

[23] See the Supporting Information.

[24] The spherical micelle size was estimated by using Amber Force Field calculations (HyperChem 7). The main chain length of each monomer unit is 6 Å and triblock **6** has an average of 80 units. If the THY and DAP units intramolecularly assemble within each polymer chain, the polymer may fold in two: each polymer strand would thus have a length of $80\times6/2=240$ Å $=24$ nm. Self-assembly of these folded chains into star micelles with the middle C4 block on the corona and the DAP and THY units in the core would result in a diameter of 48 nm, similar to the 50 nm experimental diameter.

[25] R. Wang, P. Tang, F. Qiu, Y. Yang, *J. Phys. Chem. B* **2005**, *109*, 17120–17127.

[26] R. C. Clevenger, K. D. Turnbull, *Synth. Commun.* **2000**, *30*, 1379–1388.

[27] H. Kwart, I. Burchuk, *J. Am. Chem. Soc.* **1952**, *74*, 3094–3097.

[28] Synthesis of *N*-butylthymine was reported in: a) A. D. Hamilton, D. Van Engen, *J. Am. Chem. Soc.* **1987**, *109*, 5035–5036; b) D. T. Browne, in *Synthetic Procedures in Nucleic Acid Chemistry*, (Eds.: W. W. Zorbach, R. S. Tipson) Wiley Interscience, New York, **1968**, pp. 98.

[29] Synthesis of the *endo* form of this compound was reported in the Supporting Information of reference [18b].

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