Synthesis and Evaluation of Thioether-Based Tris-Melamines as Components of Self-Assembled Aggregates Based on the CA·M Lattice

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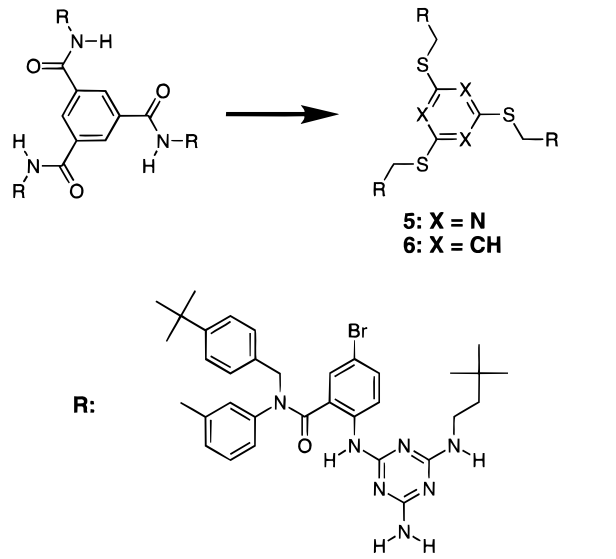
Two new tris-melamine derivatives, triazine-thio-M_3 (**5**) (C_3N_3-2,4,6-[$SCH_2C_6H_4$-3-$N(CH_2C_6H_4$-4-$C(CH_3)_3)COC_6N_3$-2-$NHC_3N_3(NH_2)(NHCH_2CH_2C(CH_3)_3)$-5-Br]$_3$) and benzene-thio-$M_3$ (**6**) (C_6H_3-1,3,5-[$SCH_2C_6H_4$-3-$N(CH_2C_6H_4$-4-$C(CH_3)_3)COC_6H_3$-2-$NHC_3N_3(NH_2)(NHCH_2CH_2C(CH_3)_3)$-5-Br]$_3$), were synthesized by reactions of 2,4,6-trithiocyanuric acid and 1,3,5-trimercaptobenzene with a bromobenzyl melamine derivative **19** ($BrCH_2C_6H_4$-3-$N(CH_2C_6H_4$-4-$C(CH_3)_3)COC_6H_3$-2-$NHC_3N_3(NH_2)(NHCH_2$-$CH_2C(CH_3)_3)$-5-Br). These two compounds formed stable and structurally well-defined 1 + 3 supramolecular aggregates with neohexyl isocyanurate (R′CA) (**9**) as shown by NMR spectroscopy and gel permeation chromatography. ^{1}H NMR competition experiments indicated that the stability of triazine-thio-M_3·(R′CA)$_3$ (**1**) was similar to that of benzene-thio-M_3·(R′CA)$_3$ (**2**). The order of stabilities of tris-melamine-based 1 + 3 complexes was hubM_3·(R′CA)$_3$ (**3**) > triazine-thio-M_3·(R′CA)$_3$ (**1**) ∼ benzene-thio-M_3·(R′CA)$_3$ (**2**) > flexM_3·(R′CA)$_3$ (**4**). Computational simulations were also carried out on triazine-thio-M_3·(R′CA)$_3$ and hubM_3·(R′CA)$_3$ fully solvated in $CHCl_3$. Values of DP (the deviation from planarity of the cyanuric acid and melamine rosette) obtained from these simulations correlated correctly with the observed stabilities and suggested a structural reason why triazine-thio-M_3·(R′CA)$_3$ was less stable than hubM_3·(R′CA)$_3$.

Introduction

This paper describes the synthesis and evaluation of two new tris-melamines, triazine-thio-M_3 and benzene-thio-M_3, for use in hydrogen-bonded aggregates based on the CA·M lattice.[1] In these compounds, the central "hub" and the attached "spokes" are connected by thioether rather than amide bonds (Scheme 1). These modifications were intended to increase the solubilities of the aggregates (by decreasing the potential for interaggregate and component hydrogen bonding) and to eliminate ambiguities about the role of these amides in intra-aggregate hydrogen bonding. The assembly of the six molecules (three CA with three M) in the rosette structure of the CA·M lattice is entropically unfavorable.[2] We therefore link the three melamine units to a central "hub" to minimize the loss in entropy that occurs on assembly. We have previously described the synthesis of hubM_3, hub$(MM)_3$, and hub$(MMM)_3$, molecules designed to form aggregates that minimize the loss in entropy upon assembly.[3−5] These polymelamines form stable 1 + 3, 1 + 6, and 1 + 9 hydrogen-bonded aggregates, respectively, with monosubstituted cyanuric acid (typically neohexyl cyanuric acid, R′CA). This series of polymelamines incorporated a primary amide bond between the central hub and the spokes. Large polymelamines [hub$(MM)_3$ or hub$(MMM)_3$] based on this linkage are, however, not very soluble in chloroform. We have therefore sought an alternative linkage that would increase the solubility, while maintaining the stability of the complex in chloroform. The thioether bond has been used to prepare a variety of macrocycles and cage compounds because it is easily formed.[6] For example, 1,3,5-trimercaptobenzene was successfully used in the synthesis of thioether-based C_3-symmetric receptors that bind peptides,[7] and in hosts that sequester small nonpolar molecules.[8] Polymelamines

Scheme 1. Formal Replacement of the Amide Bond Linkages of HubM_3 (7) with Thioether Bonds To Give Triazine-thio-M_3 (5) and Benzene-thio-M_3 (6)



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(4) For a 1 + 6 aggregate, see: Mathias, J. P.; Seto, C. T.; Simanek, E. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1994**, *116*, 1725.

(5) For a 1 + 9 aggregate, see: Mathias, J. P.; Simanek, E. E.; Seto, C. T.; Whitesides, G. M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1766.

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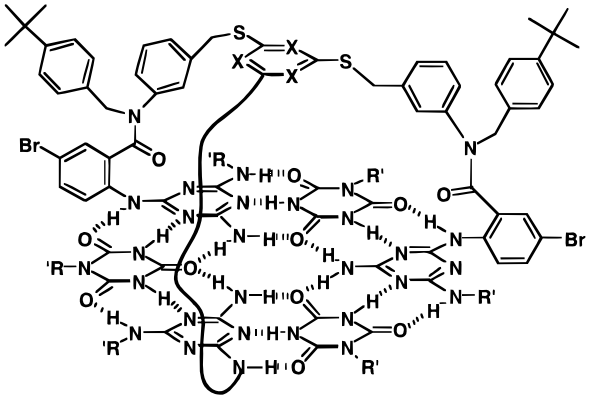
Scheme 2.[a] Triazine-thio-M_3·(R′CA)$_3$ (1) and Benzene-thio-M_3·(R′CA)$_3$ (2)



1: X = N, 2: X = CH

[a] The third spoke is shown as a black line for clarity.

that have thioether linkages are more soluble (as we will show) than those with amide linkages. The structure of the thioether spoke is similar to that in hubM_3, except that the amide bond linkage is replaced by thioether bonds. In this paper, we establish that the two thioether based tris-melamines form stable 1 + 3 hydrogen-bonded aggregates with R′CA. To characterize the new aggregates triazine-thio-M_3·(R′CA)$_3$ and benzene-thio-M_3·(R′CA)$_3$ (Scheme 2), we used ^{1}H NMR spectroscopy and gel permeation chromatography (GPC). ^{1}H NMR competition experiments were used to determine the order of stabilities among aggregates based on tris-melamines with thioether linkages and those based on tris-melamines with amide and ester linkages (Scheme 3).[9] Examination of the shapes of peaks in GPC traces and computer simulations confirmed this order of relative stabilities and suggested possible structural origins for it.

Our objectives in this work are to (i) develop a general and efficient synthetic approach for thioether-based polymelamines; (ii) explore new connections between the central "hub" and the "spokes"; (iii) use experiments and computations to determine the relative stabilities of these aggregates; (iv) study the interplay between enthalpy and entropy of self-assembly for these aggregates; (v) develop aggregates based on thioether-linked tris-melamines as a basis for larger aggregates.

Results and Discussion

Synthesis of Triazine-thio-M_3 (5) and Benzene-thio-M_3 (6). We coupled 2,4,6-trithiocyanuric acid and 1,3,5-trimercaptobenzene with a benzylic bromide melamine derivative **19** to prepare triazine-thio-M_3 and benzene-thio-M_3 (Scheme 4). The 2,4,6-trithiocyanuric acid component was commercially available, and 1,3,5-trimercaptobenzene was easily made from 1,3,5-trichlorobenzene and 2-propanethiol using a known procedure.[10]

Synthesis of the Benzylic Bromide Compound 19. The commercially available 3-aminobenzyl alcohol (**10**) was chosen as the starting material (Scheme 5). The deprotection of the benzyl hydroxyl group on compound **17** was achieved in 84% yield by the mild hydrolysis with HOAc−H_2O−THF (3:1:1) (the commonly used *n*-Bu_4NF caused decomposition of the starting material **17**).[11,12] The final conversion of the benzylic alcohol **18** to the bromide **19** was not straightforward: all the mild reagents, such as CBr_4−PPh_3,[13] NBS−PPh_3,[14] $BrCl_2CCCl_2Br$−PPh_3,[15] and CBr_4−(*n*-octyl)$_3$P,[16] either did not react with the benzylic alcohol compound or reacted extremely slowly. Bromination with PBr_3 was found to be the best, and we initially observed a broad range of yields (10−92%). THF was a much better solvent than CH_2Cl_2 or Et_2O for the reaction, and the slow addition of PBr_3 to the benzylic alcohol solution under anhydrous conditions was established as essential in achieving a good yield for this reaction. High yields (>90%) of the desired benzylic bromide compound **19** were obtained in THF under the optimized conditions.

Preparation of the Supramolecular Aggregates. Triazine-thio-M_3 (**5**) and benzene-thio-M_3 (**6**) were both very soluble in chloroform. The 1 + 3 aggregates were made by adding 3 equiv of R′CA to a $CHCl_3$ solution of the tris-melamines. The white insoluble suspension of R′CA originally present in the solution became soluble after either sonication or gentle heating.

Characterization of the 1 + 3 Aggregates: Triazine-thio-M_3·(R′CA)$_3$ (1) and Benzene-thio-M_3·(R′CA)$_3$ (2). Visual Inspection of the Formation and Stoichiometry of the Aggregates. Neohexyl cyanuric acid itself is not soluble in chloroform, and 1 equiv of tris-melamine can dissolve only 3 equiv of R′CA. If more is present, the excess does not dissolve. This observation suggests a 1:3 stoichiometry for the aggregates.

^{1}H NMR Spectroscopy. Figure 1a,b shows the ^{1}H NMR spectra of triazine-thio-M_3·(R′CA)$_3$ and benzene-thio-M_3·(R′CA)$_3$. The sharp peaks suggest that the 1 + 3 aggregates have well-defined geometry and structure on the NMR time scale. We titrated both tris-melamines with R′CA in chloroform. If less than 3 equiv of R′CA were used, background peaks from the free tris-melamines were observed in addition to the sharp peaks attributed to the 1 + 3 aggregates. The hydrogen-bonded imide protons on R′CA for benzene-thio-M_3·(R′CA)$_3$ appear as a doublet centered at 14.9 ppm ($\Delta\delta$ = 9.8 Hz). The ^{1}H NMR signal for the hydrogen-bonded imide protons of triazine-thio-M_3·(R′CA)$_3$ gives a sharp singlet at 15.1 ppm in $CDCl_3$: the signals for the two different protons are inseparable. The inset in Figure 1b shows that the NMR signals for the two different cyanurate N*H*CO protons were resolved when *o*-dichlorobenzene-d_4 was used as the solvent; they appear as a doublet with equal intensities at 15.25 and 15.31 ppm.[17]

Low-Temperature ^{1}H NMR Spectroscopy. Variable temperature NMR spectroscopy is useful in characterizing hydrogen-bonded aggregates: different conformational isomers can often be resolved at low temper-

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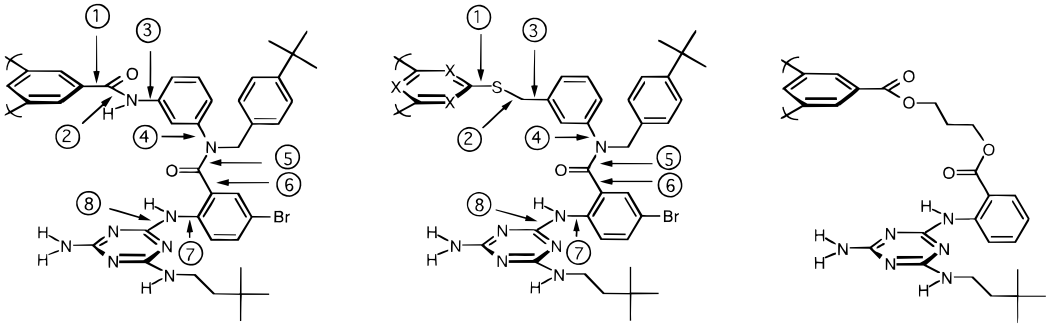
(17) The ^{1}H NMR signals for the two different imide protons on neohexyl cyanuric acid are usually more separated in *o*-dichlorobenzene than in chloroform. This phenomenon has also been observed for other hydrogen-bonded aggregates based on the CA·M lattice. Li, X.; Whitesides, G. M. Unpublished results.

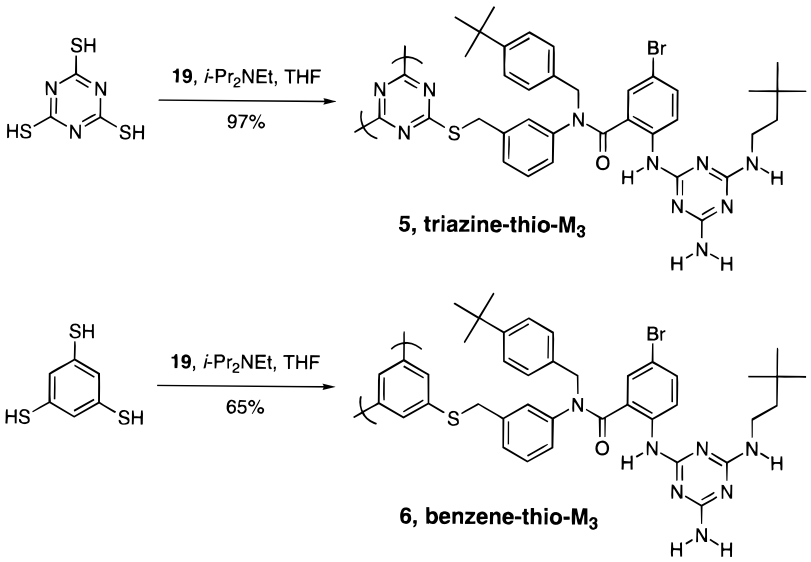
Scheme 3. Structures of Tris-melamines: Triazine-thio-M_3 (5), Benzene-thio-M_3 (6), $HubM_3$ (7), and $FlexM_3$ (8)[a]



7, $hubM_3$ 5, triazine-thio-M_3 (X = N) 6, benzene-thio-M_3 (X = CH) 8, $flexM_3$

[a] The circled numbers on the spokes represent labels for the families of torsional angles. Each family contains the three structurally symmetric torsional angles of the tris-melamine spokes.

Scheme 4. Synthesis of Triazine-thio-M_3 (5) and Benzene-thio-M_3 (6)



ature.[18] We carried out low temperature ^1H NMR studies for triazine-thio-M_3·(R′CA)$_3$. Figure 1, parts b and c, show that the single peak in the imide region represents the major isomer at all temperatures (217−297 K). At low temperatures a minor isomer was observed that appeared as a doublet (although the two lines are superimposed at temperatures around 247 K). Similar behavior was observed for $hubM_3$·(R′CA)$_3$ in previous studies.[18] Both the major and the minor isomers appear to have C_3 symmetry; we will characterize their structures in a future report.

Gel Permeation Chromatography. GPC provides information about the size, molecular weight distribution, and the stability of a complex.[3−5] Peaks for triazine-thio-M_3 and benzene-thio-M_3 alone were broad. We obtained well-defined traces of the GPC for triazine-thio-M_3·(R′CA)$_3$ and benzene-thio-M_3·(R′CA)$_3$ in $CHCl_3$ and CH_2Cl_2. CH_2Cl_2 proved to be a better solvent than $CHCl_3$ for use with GPC because the aggregates are more soluble and stable in CH_2Cl_2. Figure 2 shows GPC traces for triazine-thio-M_3·(R′CA)$_3$, benzene-thio-M_3·(R′CA)$_3$, and $hubM_3$·(R′CA)$_3$ eluted with CH_2Cl_2; the trace of $hubM_3$·(R′CA)$_3$ is provided for comparison. The slanting front edge and the tailing of the traces from the two thioether-based aggregates suggested that the aggregates dissociate partially during passage through the column. When we injected more solution of triazine-thio-M_3·(R′CA)$_3$ onto the column, we observed a trace with a very sharp edge at short retention time that represents the stable aggregate (Figure 2a).[19] The dissociated products were clearly observed.[20] The elution times at which peaks first appear (the shortest retention time in each chromatogram) for triazine-thio-M_3·(R′CA)$_3$,[21] benzene-thio-M_3·(R′CA)$_3$, and $hubM_3$·(R′CA)$_3$ are all about the same (8.6 to 8.8 min). These results suggest that the sizes of triazine-thio-M_3·(R′CA)$_3$ and benzene-thio-M_3·(R′CA)$_3$ are similar to that of $hubM_3$·(R′CA)$_3$.

The sharp straight front edge and small tailing of the trace for $hubM_3$·(R′CA)$_3$ suggests that this aggregate is

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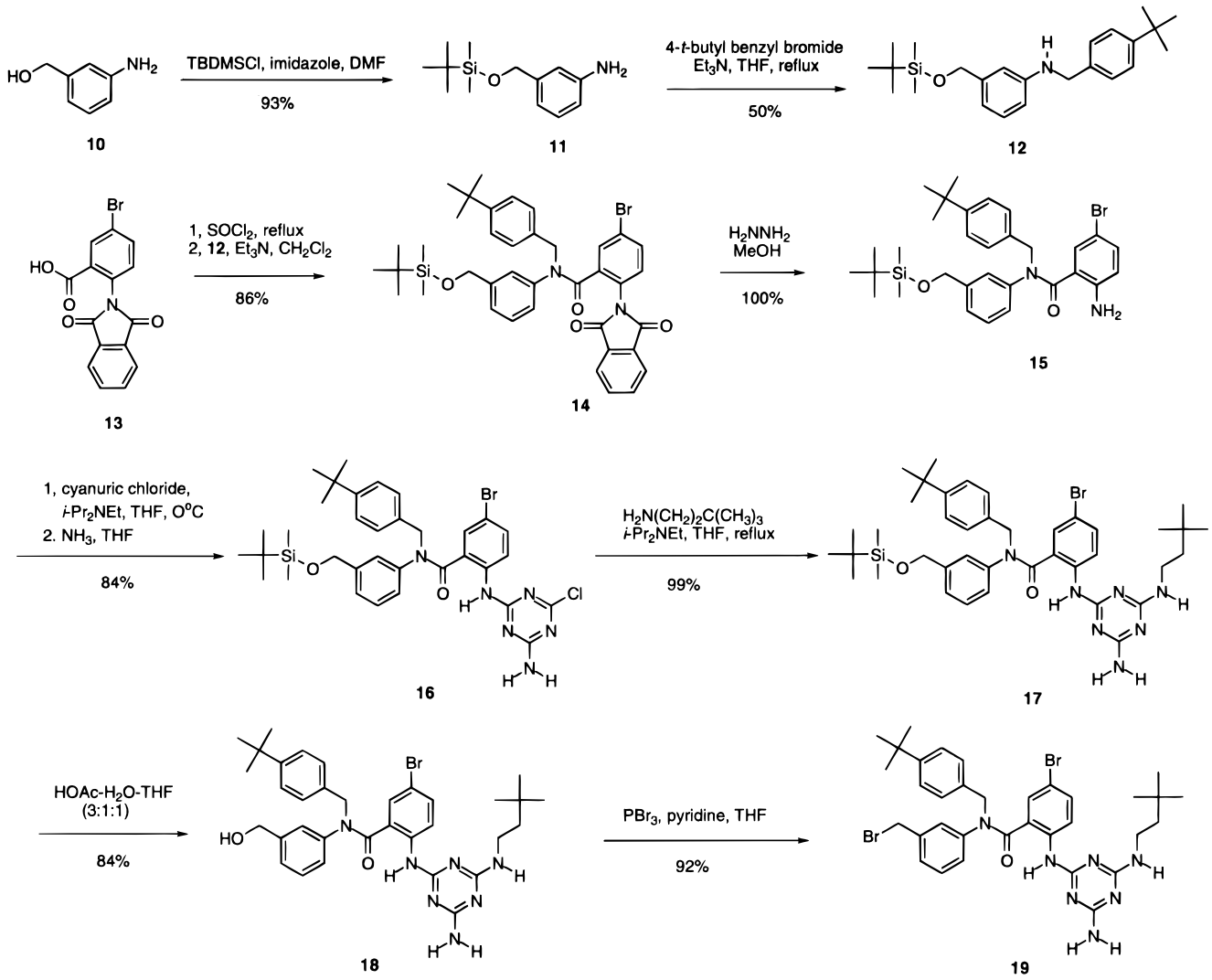
(19) Similar behavior was also observed for $hubM_3$·(R′CA)$_3$ and $flexM_3$·(R′CA)$_3$. The minimum amount of the aggregate required varies for different aggregates in order to observe the sharp peak (with shorter retention time) which might represent the real aggregate. This minimum amount is much larger for $flexM_3$·(R′CA)$_3$ than that for $hubM_3$·(R′CA)$_3$. Li, X.; Whitesides, G. M. Unpublished results.

(20) We suspect that the broad peak with longer retention time in the GPC trace is attributed to free triazine-thio-M_3 that results from the complete dissociation of triazine-thio-M_3·(R′CA)$_3$. But we cannot exclude the possibility that this peak is from a mixture of triazine-thio-M_3 and half-dissociated aggregates, such as triazine-thio-M_3·(R′CA)$_2$ or triazine-thio-M_3·R′CA.

(21) We believe that the short retention time represents the retention time of the real 1 + 3 aggregates.

Scheme 5. Synthesis of the Benzylic Bromide Compound 19



significantly more stable than triazine-thio-M_3·(R′CA)$_3$ and benzene-thio-M_3·(R′CA)$_3$. The line shapes of the GPC for both triazine-thio-M_3·(R′CA)$_3$ and benzene-thio-M_3·(R′CA)$_3$ are similar; this observation may suggest that the stabilities of the two aggregates are similar.

Comparison of the Relative Stabilities of Triazine-thio-M_3·(R′CA)$_3$, Benzene-thio-M_3·(R′CA)$_3$, Hub-M_3·(R′CA)$_3$, and FlexM_3·(R′CA)$_3$ by Competition Experiments in $CDCl_3$ Monitored by ^{1}H NMR Spectroscopy. We compared the relative stabilities of aggregates formed from thioether-based triazine-thio-M_3 and benzene-thio-M_3 with hubM_3·(R′CA)$_3$ and flexM_3·(R′CA)$_3$ using ^{1}H NMR spectroscopy.[9] The preformed 1 + 3 aggregates were titrated with the free tris-melamines and monitored by ^{1}H NMR spectroscopy. Peaks due to the different aggregates are clearly separated in the imide region (δ: 14−16 ppm) of the ^{1}H NMR spectra (Figure 3). These competition experiments indicate that the stabilities of triazine-thio-M_3·(R′CA)$_3$ and benzene-thio-M_3·(R′CA)$_3$ are very similar, but that both are less stable than hubM_3·(R′CA)$_3$. We did not observe any triazine-thio-M_3·(R′CA)$_3$ or benzene-thio-M_3·(R′CA)$_3$ when up to a 10-fold excess of triazine-thio-M_3 or benzene-thio-M_3 was added to a $CDCl_3$ solution of preformed hubM_3·(R′CA)$_3$. This result suggests that hubM_3·(R′CA)$_3$ is more stable than triazine-thio-M_3·(R′CA)$_3$ and benzene-thio-M_3·(R′CA)$_3$ by $\Delta G \geq 1.4$ kcal/mol. From a similar experiment, we found that triazine-thio-M_3·(R′CA)$_3$ and benzene-thio-M_3·(R′CA)$_3$ were more stable than flexM_3·(R′CA)$_3$ by $\Delta G \geq 1.4$ kcal/mol. These results are in qualitative agreement with those obtained from the shape analysis of the GPC chromatograms.

Computational Simulations

The Values of the Deviations from Planarity (DP) of the CA·M Correlate with the Observed Relative Stabilities of Triazine-thio-M_3·(R′CA)$_3$ and HubM_3·(R′CA)$_3$. We have previously introduced DP as a measure of the relative stabilities of aggregates based on CA·M that could be easily obtained by computations.[9] These values of DP measure the extent that the CA·M groups are out of the mean plane of the CA·M rosette. We hypothesized that the stabilities of the aggregates would correlate inversely with the DP: the larger the value of DP, the less stable the complex. The values of DP were 0.65 ± 0.04 Å and 0.55 ± 0.03 Å for triazine-thio-M_3·(R′CA)$_3$ and hubM_3·(R′CA)$_3$, respectively. The computations correlated correctly with the experimentally observed stabilities: that is, that triazine-thio-M_3·(R′CA)$_3$ was less stable than hubM_3·(R′CA)$_3$.

Conformational Analysis. To describe the conformations spanned by the molecules of tris-melamine when complexed with R′CA, we analyzed the torsional angles of each spoke in triazine-thio-M_3 and hubM_3 from 120 ps simulations (Figure 4). These torsional angles were sampled every 0.2 ps from these simulations. Each group of three structurally equivalent torsions within a tris-

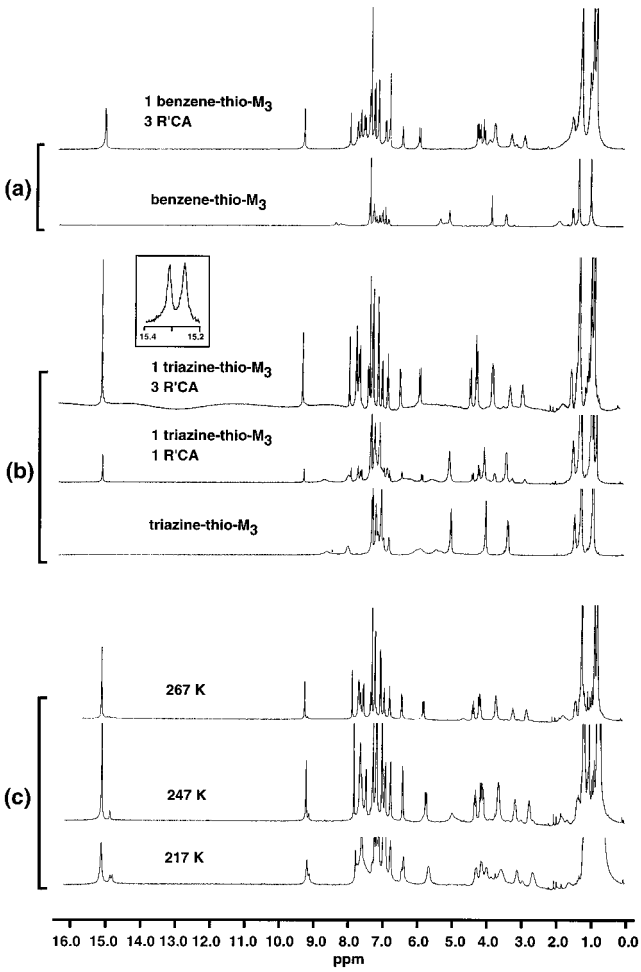


Figure 1. ^{1}H NMR (400 MHz, $CDCl_3$) spectra of complexed and free triazine-thio-M_3 and benzene-thio-M_3. (a) Spectra of benzene-thio-M_3 and benzene-thio-M_3·(R′CA)$_3$. (b) Spectra of the titration of triazine-thio-M_3 with R′CA. The figure in the small box shows the imide region of the spectrum of triazine-thio-M_3·(R′CA)$_3$ in *o*-dichlorobenzene-d_4. (c) Spectra of triazine-thio-M_3·(R′CA)$_3$ at low temperatures.

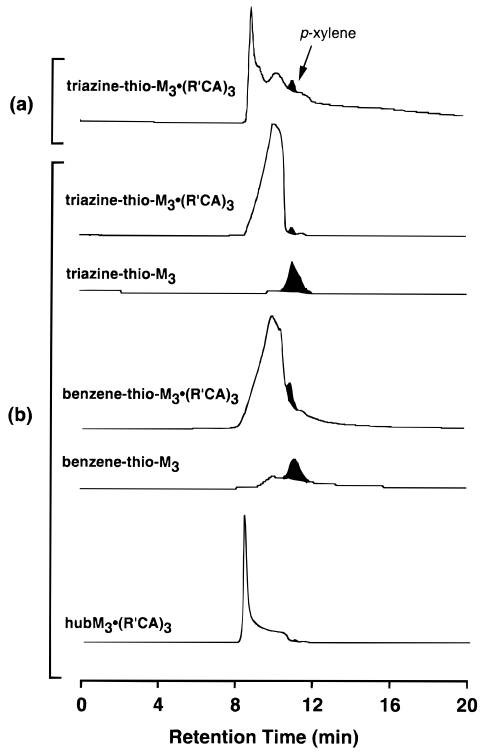


Figure 2. The gel permeation chromatograms of triazine-thio-M_3, benzene-thio-M_3, triazine-thio-M_3·(R′CA)$_3$, benzene-thio-M_3·(R′CA)$_3$, and hubM_3·(R′CA)$_3$. CH_2Cl_2 was used as eluent, and *p*-xylene was used as an internal standard. For the chromatograms shown in part b, the concentrations for all samples were 1.0 mM, and the injection volume was 20 μL. The top chromatogram (a) shows triazine-thio-M_3·(R′CA)$_3$ when the injection volume was 40 μL and the concentration was 1.0 mM.

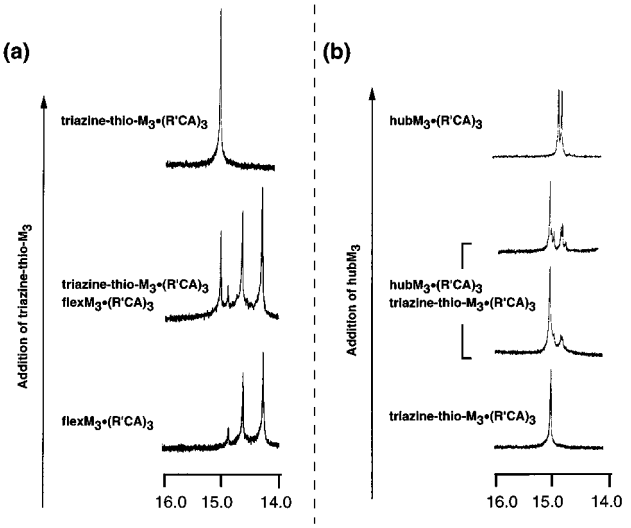


Figure 3. Selected portions of ^{1}H NMR spectra (500 MHz, $CDCl_3$) obtained from competition experiments: (a) Adding up to 1 equiv of triazine-thio-M_3 to the preformed flexM_3·(R′CA)$_3$ gave a mixture of triazine-thio-M_3·(R′CA)$_3$ and flexM_3. The spectrum in the middle shows the mixture of flexM_3·(R′CA)$_3$ and triazine-thio-M_3·(R′CA)$_3$ during addition of triazine-thio-M_3 to flexM_3·(R′CA)$_3$. (b) Adding up to 1 equiv of hubM_3 to the preformed triazine-thio-M_3·(R′CA)$_3$ gave a mixture of hubM_3·(R′CA)$_3$ and triazine-thio-M_3. The two spectra in the middle show the mixture of triazine-thio-M_3·(R′CA)$_3$ and hubM_3·(R′CA)$_3$ during addition of hubM_3 to triazine-thio-M_3·(R′CA)$_3$.

melamine is referred to as a torsional family, and is grouped as such along the *x*-axis in Figure 4. Each dash (−) corresponds to a torsional value (*y*-axis). The order of the three sets of torsional values in each family is the same for each family: *i.e.*, the first set of values in each family belong to one spoke, the second set of values belong to a second spoke, *etc.* Figure 4 emphasizes the range spanned by each torsion and the preferred conformations of the tris-melamines. These data show that a major portion of the spokes, defined by torsional families 4 through 8 (see Scheme 3), is similar for both tris-melamies. Triazine-thio-M_3 adopts a different range of torsional values about its central hub than does hubM_3 (as defined by torsional families 1 through 3). The central benzene hub in hubM_3 is coplanar with its adjacent amide groups, while the central triazine hub in triazine-thio-M_3 projects down into the center of its complex with R′CA (Figure 5). These simulations suggest that the higher values of DP for triazine-thio-M_3·(R′CA)$_3$ relative to hubM_3·(R′CA)$_3$, and therefore a lower relative stability, might be due to competing interactions between the cyanuric acid and melamine groups with the proximate central triazine-thio group.

We suggested previously that a molecule of $CHCl_3$ occupied the central cavity of hubM_3·(R′CA)$_3$ and that this role of solvent might be important to the stability of this complex and other related tris-melamines having amide linkages. These simulations also suggested that without a molecule of $CHCl_3$ in the center of hubM_3·

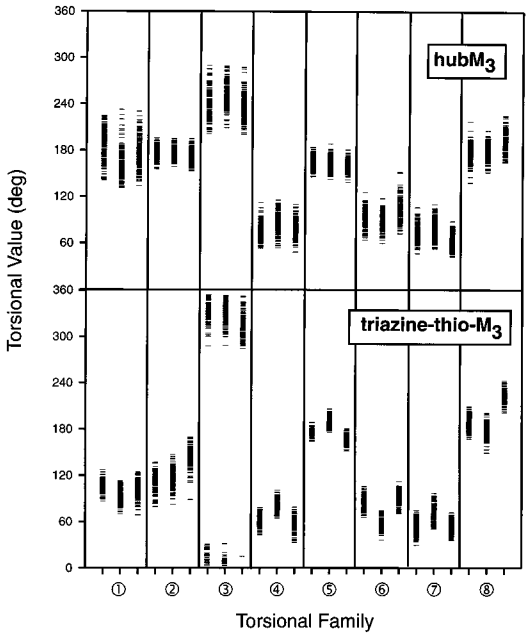


Figure 4. The torsional values from the simulations, grouped into structurally equivalent torsional families, are shown for hubM_3·(R′CA)$_3$ and triazine-thio-M_3·(R′CA)$_3$.

(R′CA)$_3$, the complex would be unstable. In this work, the simulations suggest that the conformation of the central triazine-hub of triazine-thio-M_3 is such that it fills the central cavity of triazine-thio-M_3·(R′CA)$_3$ (Figure 5) and contributes to its stability.

Conclusions

We have developed an efficient synthetic approach for tris-melamines based on thioether bonds. These tris-melamines are easy to synthesize and form stable 1 + 3 hydrogen-bonded aggregates with neohexyl cyanuric acid. The new aggregates [triazine-thio-M_3·(R′CA)$_3$ (**1**) and benzene-thio-M_3·(R′CA)$_3$ (**2**)] are somewhat less stable than hubM_3·(R′CA)$_3$, but much more soluble. Computations suggest that the central thioether hub projects down into the center of the complex and contributes to its stability. The modification from amide bond to thioether bond indeed increases the solubilities of both the tris-melamines and the aggregates dramatically, while maintaining most of the stability of the aggregates in chloroform. We therefore believe that thioether-based polymelamines will be a useful framework on which to build larger polymelamine-based aggregates.

Experimental Section

General Methods. THF was distilled from sodium benzophenone ketyl. Methylene chloride and triethylamine were distilled from calcium hydride. Dimethylformide was dried and stored over 4-Å molecular sieves. Elemental analyses were performed by Robertson Microlit Laboratory, Inc. (Madison, NJ). The compounds that have a triazine unit in their chemical structures show doubling of several resonances in their ^{1}H and ^{13}C NMR spectra due to slow exchange of conformers around the NHR triazine bonds.

3-Aminobenzyl (1,1-Dimethylethyl)silyl Ether (11). A 250-mL round-bottomed flask was charged with 4.00 g (32.48 mmol) of 3-aminobenzyl alcohol, 5.00 g (33.17 mmol) of *tert*-butyldimethylsilyl chloride, 2.62 g (38.48 mmol) of imidazole, and 80 mL of DMF. The solution was stirred at room temperature for 10 h under N_2. The reaction mixture was concd *in vacuo*, and the residue was taken up in 150 mL of ethyl acetate and 100 mL of water. The organic layer was separated, washed with water (2 × 100 mL) and brine (100 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was purified by flash column chromatography (eluted with 50:50 ethyl acetate/hexanes) to give 7.20 g (30.33 mmol, 93%) of the product as a light yellow liquid: R_f 0.55 (50:50 ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (t, J = 7.8 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.59 (s, 1H), 6.58 (d, J = 7.7 Hz, 1H), 4.68 (s, 2H), 3.73 (s, 2H), 0.96 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.11, 142.77, 129.13, 116.46, 113.83, 112.92, 64.91, 26.01, 18.47, −5.22; HRMS-EI (M^+) calcd for $C_{13}H_{23}NOSi$ 237.1549, found 237.1544.

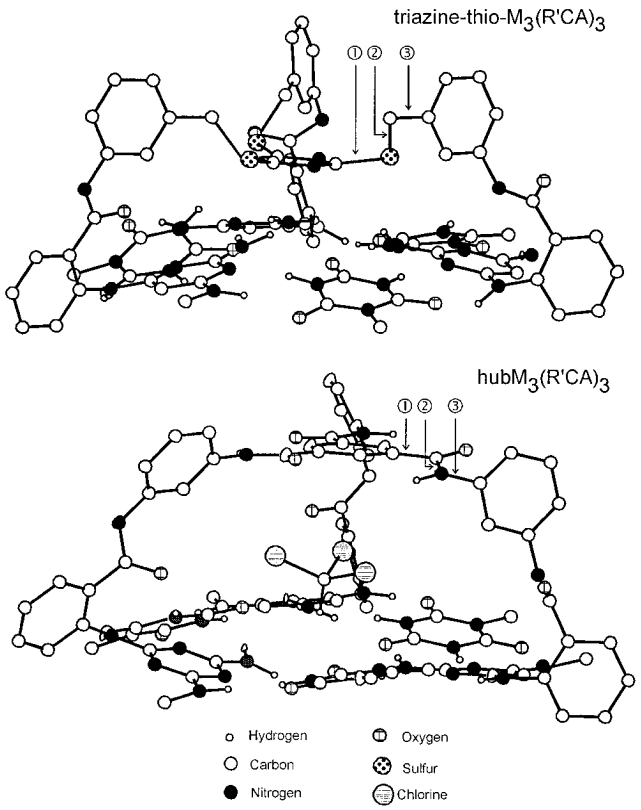


Figure 5. Ball and stick figures of the average structures of hubM_3·(R′CA)$_3$ and triazine-thio-M_3·(R′CA)$_3$ from the simulations. The suggested location of a molecule of $CHCl_3$ in the center of hubM_3·(R′CA)$_3$ is shown. Some atoms are omitted for clarity.

3-[[4-(1,1-Dimethylethyl)benzyl]amino]benzyl (1,1-Dimethylethyl)dimethylsilyl Ether (12). A 250-mL round-bottomed flask was charged with 4.75 g (20.00 mmol) of compound **11**, 6.36 g (28.00 mmol) of 4-*tert*-butylbenzyl bromide, 4.05 g (5.58 mL, 40.00 mmol) of triethylamine, and 100 mL of dry THF. The solution was heated at reflux under a nitrogen atmosphere for 4 h. The reaction mixture was cooled to room temperature and concd *in vacuo*. The residue was mixed with 150 mL of ethyl acetate and 100 mL of water. The organic layer was separated, washed twice with 100-mL portions of water and once with 100 mL of brine, and dried over $MgSO_4$. The solvent was removed by rotary evaporation at aspirator pressure. The residue was purified by flash column chromatography (eluted with 5:95 ethyl acetate/hexanes), giving 3.80 g (9.90 mmol, 50%) of the product as a colorless oil: R_f 0.60 (25:75 ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.37 (m, 4H), 7.19 (t, J = 7.9 Hz, 1H), 6.73 (m, 2H), 6.60 (d, J = 7.9 Hz, 1H), 4.75 (s, 2H), 4.35 (s, 2H), 1.40 (s, 9H), 1.02 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.28, 148.16, 143.73, 136.32, 129.11, 127.50, 125.59, 115.49, 111, 71, 110.67, 65.12, 48.26, 34.55, 31.45, 26.06, 18.49, −5.18; HRMS-EI (M^+) calcd for $C_{24}H_{37}NOSi$ 383.2644, found 383.2640. Anal. Calcd for $C_{24}H_{37}NOSi$: C, 75.14; H, 9.72; N, 3.65. Found: C, 75.33; H, 9.61; N, 3.59.

5-Bromo-2-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-*N*-[3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]phenyl]-

***N*-[[4-(1,1-dimethylethyl)phenyl]methyl]benzamide (14).** A 250-mL round-bottomed flask was charged with 6.00 g (17.34 mmol) of compound **13**[3] and 40 mL of thionyl chloride. The mixture was heated at reflux with stirring under a nitrogen atmosphere for 2 h. The reaction mixture was cooled to room temperature and diluted with 100 mL of toluene, and the solvent and the excess thionyl chloride were removed *in vacuo*. The residue was again dissolved in 100 mL of toluene, concd, and dried *in vacuo*. The resulting acid chloride was dissolved in 50 mL of methylene chloride and 100 mL of toluene. The solution was cooled in an ice bath, and 7.05 g (9.72 mL, 69.60 mmol) of triethylamine was added, followed by 6.66 g (17.36 mmol) of **12**. The mixture was allowed to warm to room temperature, stirred for 2 h, and diluted with 150 mL of toluene. This solution was washed with 150 mL of water, twice with 150-mL portions of saturated aqueous sodium carbonate, 200 mL of water, and 150 mL of brine. The solution was dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The residue was purified by column chromatography (eluted with 33:66 ethyl acetate/hexanes) to give 10.63 g (14.93 mmol, 86%) of the product as a white foam: R_f 0.48 (33:66 ethyl acetate/hexanes); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.03−7.93 (m, 4H), 7.68 (d, J = 7.1 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.31 (s, 2H), 7.27 (d, J = 7.9 Hz, 1H), 7.21−7.17 (m, 3H), 7.10 (d, J = 7.5 Hz, 1H), 7.05 (d, J = 7.9 Hz, 2H), 4.92 (s, 2H), 4.53 (s, 2H), 1.18 (s, 9H), 0.84 (s, 9H), −0.04 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.69, 164.82, 149.11, 142.39, 142.10, 134.97, 133.79, 132.39, 131.99, 131.54, 130.00, 128.72, 126.81, 125.79, 124.89, 124.50, 123.67, 120.66, 63.73, 52.19, 34.04, 31.06, 25.77, 17.90, −5.35; HRMS-FAB (M + Na^+) calcd for $C_{39}H_{43}BrN_2O_4SiNa$ 733.2073, found 733.2052.

2-Amino-5-bromo-*N*-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]phenyl]-*N*-[[4-(1,1-dimethylethyl)phenyl]methyl]benzamide (15). A 250-mL round-bottomed flask was charged with 2.80 g (3.93 mmol) of compound **14**, 0.20 g (0.2 mL, 6.30 mmol) of hydrazine, and 100 mL of methanol. The solution was stirred and heated at reflux for 6 h under a nitrogen atmosphere. The solution was then cooled and concd *in vacuo*. The residue was mixed with 200 mL of ethyl acetate and 200 mL of toluene and stirred for 15 h at room temperature. The precipitated residue was filtered off, mixed again with 100 mL of 1:1 ethyl acetate/toluene, and stirred for 4 h at room temperature. After filtration the combined filtrates were washed twice with 200-mL portions of water and once with 200 mL of brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation, and 2.28 g (3.92 mmol, 100%) of the product was obtained as a white foam: R_f 0.25 (25:75 ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.23 (m, 4H), 7.13−6.98 (m, 4H), 6.88 (m, 2H), 6.54 (d, J = 8.4 Hz, 1H), 5.06 (s, 2H), 4.59 (s, 2H), 1.30 (s, 9H), 0.92 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.29, 150.26, 145.09, 143.40, 143.02, 134.27, 133.18, 132.11, 128.93, 127.77, 125.55, 125.50, 124.55, 124.33, 121.84, 118.42, 108.69, 64.30, 53.39, 34.52, 31.39, 25.98, 18.39, −5.22; HRMS-FAB (M + Na^+) calcd for $C_{31}H_{41}BrN_2O_2SiNa$ 603.2018, found 603.1989. Anal. Calcd for $C_{31}H_{41}BrN_2O_2Si$: C, 64.01; H, 7.10; N, 4.82. Found: C, 64.30; H, 7.22; N, 4.78.

2-[(4-Amino-6-chloro-1,3,5-triazin-2-yl)amino]-5-bromo-*N*-[3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-phenyl]-*N*-[[4-(1,1-dimethylethyl)phenyl]methyl]benzamide (16). A solution of amine **15** (2.00 g, 3.44 mmol), cyanuric chloride (1.00 g, 5.42 mmol), and diisopropylethylamine (1.33 g, 10.3 mmol) in THF (100 mL) was stirred under N_2 at 0 °C for 1.5 h, and then gaseous ammonia was passed through the solution for an additional 1.5 h. The solution was then warmed to room temperature, and the solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate/toluene (1:1) (400 mL) and water (100 mL). The organic extract was washed with H_2O (2 × 100 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concd *in vacuo*. The mixture was purified by column chromatography (eluted with 33:66 EtOAc/hexanes) to give 2.05 g (2.89 mmol, 84%) of the product as a white solid: R_f 0.28 (33:66 EtOAc/hexanes); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.38 (s, 1H), 7.62 (s, 1H), 7.60 (s, 1H), 7.45−7.41 (m, 2H), 7.28−7.26 (m, 3H), 7.16−7.14 (m, 2H), 7.11−7.07 (m, 3H), 7.00 (s, 1H), 5.00 (s, 2H), 4.47 (s, 2H), 1.23 (s, 9H), 0.80 (s, 9H), −0.08 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.58, 166.79, 166.67, 164.29, 149.26, 142.05, 141.92, 135.04, 134.03, 132.25, 128.44, 127.07, 125.68, 125.00, 124.49, 124.24, 63.44, 52.33, 34.05, 31.04, 25.65, 17.76, −5.48; HRMS-FAB (M + Na^+) calcd for $C_{34}H_{42}BrClN_6O_2SiNa$ 731.1909, found 731.1916.

2-[(4-Amino-6-[(3,3-dimethylbutyl)amino]-1,3,5-triazin-2-yl)amino]-5-bromo-*N*-[3-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]phenyl]-*N*-[[4-(1,1-dimethylethyl)-phenyl]methyl]benzamide (17). A solution of compound **16** (1.79 g, 2.52 mmol), neohexylamine (1.10 g, 10.87 mmol), and diisopropylethylamine (0.87 g, 6.73 mmol) in THF (150 mL) was heated at reflux for 10 h under an atmosphere of N_2. The reaction mixture was then cooled and concd *in vacuo*. The residue was mixed with EtOAc (150 mL), washed with H_2O (2 × 150 mL) and brine (150 mL), dried over $MgSO_4$, filtered, and concd *in vacuo*. The mixture was purified by column chromatography (eluted with 50:50 EtOAc/hexanes) to give 1.94 g (2.50 mmol, 99%) of the product as a white-foam solid: R_f 0.20 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.44−8.35 (m, 2H), 7.28 (d, J = 6.2 Hz, 2H), 7.23−7.16 (m, 4H), 7.11−7.01 (m, 3H), 6.87 (s, 2H), 6.52 (s, 1H), 6.40 (s, 1H), 5.04 (s, 2H), 4.47 (s, 2H), 3.26 (bs, 2H), 1.43 (bs, 2H), 1.22 (s, 9H), 0.90 (s, 9H), 0.78−0.77 (two conformers, s, 9H), −0.11, −0.12 (two conformers, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.87, 165.87, 149.37, 142.31, 137.99, 133.85, 132.10, 130.90, 128.73, 127.20, 125.09, 124.32, 111.59, 63.24, 52.42, 43.07, 42.71, 36.44, 34.06, 31.01, 29.28, 25.60, 17.70, −5.54; HRMS-FAB (M + Na^+) calcd for $C_{40}H_{56}BrN_7O_2SiNa$ 796.3346, found 796.3370.

2-[(4-Amino-6-[(3,3-dimethylbutyl)amino]-1,3,5-triazin-2-yl)amino]-5-bromo-*N*-[[4-(1,1-dimethylethyl)phenyl]-methyl]-*N*-[3-(hydroxymethyl)phenyl]benzamide (18). A solution of HOAc (45 mL) and H_2O (15 mL) was added dropwise to a solution of compound **17** (0.80 g, 1.03 mmol) in THF (15 mL) at 0 °C under an atmosphere of N_2. The reaction mixture was warmed to room temperature and stirred for 3 days. This solution was concd *in vacuo*, and the residue was partitioned between toluene (200 mL) and H_2O (100 mL). The organic extract was washed with H_2O (2 × 150 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concd *in vacuo*. The residue was purified by column chromatography (eluted with EtOAc) to give 0.57 g (0.86 mmol, 84%) of the product as a white solid: R_f 0.28 (EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47−8.38 (two conformers, bs, 1H), 8.27 (m, 1H), 7.32−7.30 (m, 3H), 7.20−7.10 (m, 6H), 7.01−6.85 (m, 2H), 6.66−6.57 (two conformers, bs, 2H), 5.20 (s, 1H), 5.05 (s, 2H), 4.34 (s, 2H), 3.26 (bs, 2H), 1.46−1.35 (m, 2H), 1.24 (s, 9H), 0.92, 0.90 (two conformers, s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.69, 165.03, 149.41, 143.73, 142.06, 141.85, 133.94, 132.20, 131.71, 130.98, 128.56, 127.17, 125.44, 125.10, 124.72, 124.50, 62.14, 52.49, 42.96, 42.63, 36.61, 34.09, 31.06, 29.32; HRMS-FAB (M + Na^+) calcd for $C_{34}H_{42}BrN_7O_2Na$ 682.2481, found 682.2490. Anal. Calcd for $C_{34}H_{42}BrN_7O_2$: C, 61.81; H, 6.41; N,14.84. Found: C, 61.90; H, 6.64; N, 14.61.

2-[(4-Amino-6-[(3,3-dimethylbutyl)amino]-1,3,5-triazin-2-yl)amino]-5-bromo-*N*-[3-(bromomethyl)phenyl]-*N*-[[4-(1,1-dimethylethyl)phenyl]methyl]benzamide (19). A solution of PBr_3 (0.162 g, 56.8 μL, 0.60 mmol) and pyridine (0.10 mL, 0.098 g, 1.24 mmol) in THF (1 mL) was added slowly to a solution of compound **18** (0.60 g, 0.91 mmol) and pyridine (0.1 mL, 0.098 g, 1.24 mmol) in THF (80 mL) at 0 °C under an atmosphere of N_2 *via* syringe. The addition was complete in 30 min. After an additional 1 h, the reaction mixture was warmed to room temperature and concd *in vacuo*. The residue was partitioned between EtOAc (100 mL) and saturated $NaHCO_3$ solution (30 mL). The organic extract was washed with H_2O (100 mL), brine (100 mL) and dried over $MgSO_4$, filtered, and concd *in vacuo*. The residue was purified by column chromatography (eluted with 50:50 EtOAc/hexanes) to give 0.61 g (0.84 mmol, 92%) of the product as a white solid: R_f 0.24 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (bs, 1H), 8.17, 8.04 (two conformers, bs, 1H), 7.33−7.20 (m, 4H), 7.13−7.05 (m, 4H), 6.89 (s, 1H), 6.82 (d, J = 6.5 Hz, 2H), 5.24, 5.13 (two conformers, bs, 2H), 5.05 (s, 2H), 4.24 (s, 2H), 3.39 (m, 2H), 1.46 (m, 2H), 1.30 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.52, 165.39, 164.47, 150.67, 142.92, 139.12, 136.87, 133.76, 132.66, 131.43, 129.53,

128.26, 128.12, 127.72, 127.23, 125.66, 124.47, 114.21, 53.30, 43.64, 37.57, 34.56, 32.14, 31.39, 30.72, 29.96, 29.56; HRMS-FAB (M + H^+) calcd for $C_{34}H_{42}Br_2N_7O$ 722.1818, found 722.1808.

***N,N′,N″*-[1,3,5-triazine-2,4,6-triyltris(thiomethylene-3,1-phenylene)]tris[2-[[4-amino-6-[(3,3-dimethylbutyl)-amino]-1,3,5-triazin-2-yl]amino]-5-bromo-*N*-[[4-(1,1-dimethylethyl)phenyl]methyl]benzamide (5).** A solution of trithiocyanuric acid (5.2 mg, 0.0293 mmol), compound **19** (80.0 mg, 0.111 mmol), and diisopropylethylamine (0.5 mL, 0.37 g, 2.87 mmol) in THF (20 mL) was stirred for 6 h at room temperature and then heated at reflux for 10 h under N_2. The resulting mixture was cooled and concd *in vacuo*. The residue was mixed with EtOAc (70 mL), washed with H_2O (3 × 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concd *in vacuo*. The residue was purified by column chromatography (eluted with EtOAc) to give 60.0 mg (0.0285 mmol, 97%) of the product as a white solid: R_f 0.25 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (bs, 3H), 7.99 (bs, 3H), 7.29−7.26 (m, 9H), 7.18−7.15 (m, 6H), 7.12 (bs, 3H), 7.02 (s, 9H), 6.96 (s, 3H), 6.80 (s, 3H), 5.92, 5.42 (two conformers, bs, 6H), 5.01 (s, 6H), 4.02 (s, 6H), 3.39 (m, 6H), 1.46 (m, 6H), 1.27 (s, 27H), 0.94 (s, 27H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.43, 163.89, 150.58, 142.92, 138.04, 133.80, 133.18, 132.58, 131.73, 131.56, 129.36, 128.60, 127.97, 127.92, 126.13, 125.65, 124.60, 53.45, 43.41, 37.67, 34.56, 34.10, 31.41, 29.95, 29.55; LRMS-FAB (M + H^+) calcd for $C_{105}H_{124}Br_3N_{24}O_3S_3$ 2101, found 2101; MS ion profile calcd (M + H^+) *m*/*z* (relative intensity) 2101 (17), 2102 (22), 2103 (66), 2104 (73), 2105 (100), 2106 (90), 2107 (74), 2108 (50), 2109 (28), found 2101 (23), 2102 (32), 2103 (72), 2104 (79), 2105 (100), 2106 (83), 2107 (67), 2108 (47), 2109 (26).

***N,N′,N″*-[1,3,5-benzenetriyltris(thiomethylene-3,1-phenylene)]tris[2-[[4-amino-6-[(3,3-dimethylbutyl)amino]-1,3,5-triazin-2-yl]amino]-5-bromo-*N*-[[4-(1,1-dimethylethyl)phenyl]methyl]benzamide (6).** A solution of 1,3,5-trimercaptobenzene (5.8 mg, 0.033 mmol), compound **19** (80.0 mg, 0.111 mmol), and diisopropylethylamine (1.0 mL, 0.74 g, 5.73 mmol) in THF (30 mL) was stirred at room temperature for 2 h and then heated at reflux for an additional 12 h under N_2. The reaction mixture was cooled and concd *in vacuo*. The residue was mixed with EtOAc (80 mL), washed with H_2O (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concd *in vacuo*. The residue was purified by column chromatography (eluted with 80:20 EtOAc/hexanes) to give 44.9 mg (21.4 mmol, 65%) of the product as a white solid: R_f 0.13 (80:20 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (bs, 3H), 8.13, 8.03 (two conformers, bs, 3H), 7.30−7.20 (m, 9H), 7.16 (m, 9H), 7.09 (s, 3H), 7.00 (s, 3H), 6.93−6.91 (m, 6H), 6.83 (s, 3H), 6.74 (d, J = 7.24 Hz, 3H), 5.25 (bs, 6H), 4.99 (s, 6H), 3.77 (s, 6H), 3.38−3.33 (m, 6H), 1.44−1.42 (m, 6H), 1.27 (s, 27H), 0.93 (s, 27H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.56, 164.59, 164.40, 150.53, 142.98, 138.11, 133.84, 132.64, 131.41, 128.52, 127.24, 127.16, 126.10, 124.40, 114.06, 53.47, 43.62, 37.96, 37.50, 34.55, 31.40, 29.94, 29.75, 29.57; LRMS-FAB (M + H^+) calcd for $C_{108}H_{127}Br_3N_{21}O_3S_3$ 2098, found 2098; MS ion profile calcd (M + H^+) *m*/*z* (relative intensity) 2098 (17), 2099 (22), 2100 (65), 2101 (73), 2102 (100), 2103 (91), 2104 (75), 2105 (51), 2106 (29), 2107 (13), found 2098 (24), 2099 (36), 2100 (84), 2101 (85), 2102 (100), 2103 (94), 2104 (80), 2105 (49), 2106 (35), 2107 (18).

Titration of Triazine-thio-M_3 or Benzene-thio-M_3 with R′CA Monitored by ^{1}H NMR Spectroscopy. For a typical experiment, an NMR tube was charged with triazine-thio-M_3 (10.0 mg, 0.0048 mmol) and $CDCl_3$ (0.7 mL). Small portions of R′CA (1.01 mg, 0.0048 mmol) were added to the NMR tube, and the tube was shaken or sonicated until all the solid had dissolved. The ^{1}H NMR spectrum was recorded after each addition. When 3 equiv of R′CA had been added, there was no further change in the spectrum, and the additional R′CA remained as a solid.

Gel Permeation Chromatography. Gel permeation chromatography was performed using a Waters 600E HPLC with a Waters 484 UV detector and Waters analytical gel permeation column (Ultra-styragel, 1000 Å pore size). Elutions were performed at room temperature using HPLC grade chloroform and methylene chloride as the solvent at a flow rate of 1.0 mL/min.

Competition Experiments Monitored by ^{1}H NMR Spectroscopy. For a typical comparison between hubM_3·(R′CA)$_3$ and triazine-thio-M_3·(R′CA)$_3$, the following two experiments were performed:

A. An NMR tube was charged with triazine-thio-M_3·(R′CA)$_3$ (0.0024 mmol) and $CDCl_3$ (0.7 mL). HubM_3 was added to the NMR tube in small portions (∼1.0 mg, 0.00048 mmol), and the tube was shaken or sonicated until all the solid had dissolved. The ^{1}H NMR spectrum was recorded after each addition. HubM_3·(R′CA)$_3$ was observed immediately after the addition of the first portion of hubM_3. When 1 equiv of hubM_3 had been added, all the peaks corresponding to triazine-thio-M_3·(R′CA)$_3$ disappeared, and ^{1}H NMR signals from hubM_3·(R′CA)$_3$ and triazine-thio-M_3 were observed.

B. HubM_3·(R′CA)$_3$ (0.0024 mmol) in $CDCl_3$ (0.5 mL) was loaded in an NMR tube. A solution of triazine-thio-M_3 (48 mM) in $CDCl_3$ was added to the NMR tube in small portions (0.05−0.1 mL) *via* a syringe. The ^{1}H NMR spectrum was recorded after each addition. No triazine-thio-M_3·(R′CA)$_3$ was observed even when a ten-fold excess of triazine-thio-M_3 was added. We observed only hubM_3·(R′CA)$_3$ and triazine-thio-M_3 in the solution. We did not try to add more triazine-thio-M_3 to the NMR tube.

Computational Methods. All simulations were carried out using the CHARMm 22 molecular mechanics program,[22] with the QUANTA 4.0 parameter set.[23] The parameters for $CHCl_3$ were from Jorgenson.[24] We used the Berendson constant pressure and temperature (CPT) molecular dynamics algorithm to carry out all simulations.[25] SHAKE was used to constrain all covalent bonds,[26] and a time step of 2 ps was used in the simulations. The complexes were built and assembled in QUANTA.[27] We adjusted the conformations of hubM_3 and triazene-thio-M_3, in their complexes with R′CA, to be consistent with the C_3 symmetry of hubM_3·(R′CA)$_3$ inferred from ^{1}H NMR spectroscopy.[9] Unfavorable steric interactions in the complexes were removed by minimizing the energy using the conjugate-gradient method for 1000 steps.[22] These complexes were overlaid with a pre-equilibrated box of 342 molecules of $CHCl_3$ with dimensions of 35.53 Å. The density of the solvent used in the simulation was 1.473 g/mL, which was consistent with that from experiment (1.480 g/mL at 298 K).[24] Molecules of $CHCl_3$ that were within 2.9 Å of the complexes were deleted. The conformation of the complexes was fixed and a short simulation carried out to equilibrate the solvent around the complexes: the constraint on the complexes was removed and the entire system equilibrated for 20 ps at 298 K. After equilibration, the simulation was carried out for 120 ps and analyzed.

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