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Published on Web 04/12/2002

Duplex Oligomers Defined via Covalent Casting of a One-Dimensional Hydrogen-Bonding Motif

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Received December 14, 2001

Abstract: Hydrogen-bonded tapes comprised of monomeric molecular precursors are used to define structural parameters for the design of related oligomers encoded with predetermined modes of assembly. Application of this "covalent casting" strategy vis-à-vis the one-dimensional H-bonding motif expressed by 2-amino-4,6-dichlorotriazine has enabled the design of high-affinity duplex molecular strands. Dimeric, trimeric, and tetrameric duplex oligomers are prepared through an iterative synthetic protocol involving sequential homologation of the oligo(aminotriazine). The mode of assembly and interstrand affinity of homologous oligomers are established in solution by ^{1}H NMR dilution experiments, isothermal titration calorimetry (ITC), vapor pressure osmometry (VPO), cross-hybridization experiments involving the analysis of dye-labeled strands via thin-layer chromatography (TLC), and in the solid state by X-ray crystallographic analysis. Binding free energy per unimer ($-\Delta G°/n$) increases significantly upon extension from monomer to dimer to trimer, signifying a strong positive cooperative effect. Nanomolar binding affinity ($K_d = 1.44 \pm 0.50$ nM) was determined for the duplex trimer by ITC in 1,2-dichloroethane at 20 °C. In-register duplex formation is not observed for the tetramer, which appears to adopt an alternative binding mode. These data give insight into the structural and interactional features of the oligomers required for high-affinity, high-specificity binding and define a platform for the design of second-generation systems and related duplex strands for use in nanoscale assembly.

Introduction

The capability of defining structure carries with it the potential to engineer functionality. As demonstrated by naturally occurring macromolecules, the precise control of structure confers exceptional mechanical properties (e.g., arachnid silk fibers),[1,2] remarkable catalytic functions (e.g., cytochrome-p450),[3] and high-density information storage capabilities (e.g., CD-ROM technology $\sim 10^8$ bits/cm^2 versus DNA $\sim 10^{21}$ bits/cm^3).[4] As insight into the relationship between biomacromolecular structure and function broadens, so does the capacity of humankind to address the design of conformationally distinct, functional synthetic oligomers endowed with properties that may complement or even exceed their natural counterparts. Progress toward these goals is underscored by the design of unnatural oligomers possessing therapeutically relevant biological activities.[5]

The development of increasingly sophisticated functional synthetic oligomers and polymers will require reliable methods for the control of their secondary and tertiary structure. However, few rational approaches to the directed organization of synthetic oligomers and polymers have been forthcoming.[6] To date, the vast majority of assembly strategies exploit global aspects of structure, for example, the formation of phase-separated and liquid-crystalline domains via solvophobically and sterically driven assembly of block copolymers,[7,8] dendronized polymers,[9,10] and dendritic macromolecules.[11,12] In comparison to solvophobic forces, hydrogen bond interactions possess greater

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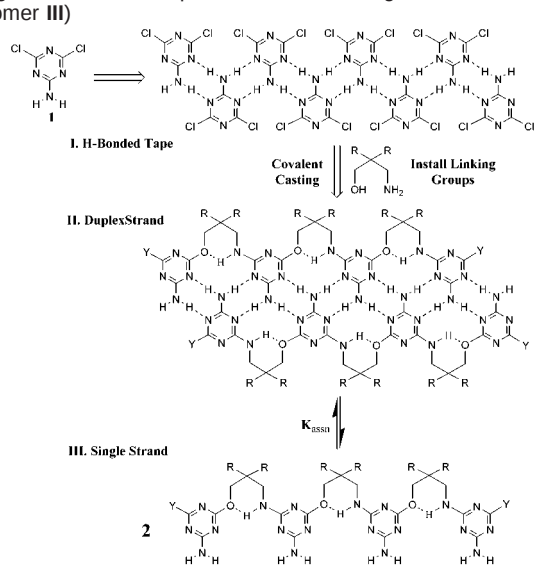
strength and directionality.[6c,13] Consequently, hydrogen bonds may be utilized to enforce more localized order. Moreover, the recurrent structure of oligomers and polymers makes such systems well suited to the periodic presentation of hydrogen bond donor/acceptor sites.

To address the assembly of molecular strands, we have introduced a molecular casting strategy whereby the supramolecular connectivities of monomeric molecular components are used to define structural parameters for the design of related oligomers encoded with predefined modes of assembly.[14,15] This strategy has been successfully applied to the design of high-affinity dimeric duplex oligomers based on the 2-amino-4,6-dichlorotriazine hydrogen-bonding motif.[6c,14−17] Here, a homologous series of oligomers is investigated via ^{1}H NMR spectroscopy, vapor pressure osmometry (VPO), isothermal titration calorimetry (ITC), and cross-hybridization experiments involving the analysis of dye-labeled strands via thin-layer chromatography (TLC). Whereas the programmable self-association characteristics of DNA have led to its successful application as a template for the spontaneous organization of nanostructured organic−inorganic hybrid material arrays,[18] the results reported herein are aimed at defining *synthetic* oligomers for use in nanoscale assembly and patterning (Scheme 1).

Scheme 1. Covalent Casting of the One-Dimensional H-Bonding Motif **I** Obtained upon Self-Assembly of Monomer **1** through the Introduction of Linking Groups (Resulting Duplex Strand **II** Is Designed To Exist in Equilibrium with the Single-Stranded Oligomer **III**)



Design

For hydrogen bond interactions, individual binding free energies are generally smaller than the energies required for discrimination between different assembly manifolds. Consequently, to bias the formation of a given ensemble under equilibrium conditions, it is essential to incorporate structural features that confer an energetic advantage to the target construct. Preorganization facilitates binding through the reduction of entropic terms. We have found that an effective method for achieving high levels of preorganization involves the superposition of conformationally constrained covalent frameworks upon the molecular precursors defining a noncovalent ensemble *prior* to assembly such that the distances and geometries of the covalent and noncovalent architectures are commensurate. Such casting of noncovalent ensembles is distinguished from "covalent capture" schemes, which involve the covalent fixing of discrete[19] or polymeric[20,21] noncovalent objects *after* their formation, representing a template-directed synthesis.[22]

To apply this design toward the synthesis of a duplex oligomer required selection of a parent one-dimensional hydrogen-bonding motif. 2-Aminopyrimidine is a well-established molecular precursor for the expression of a one-dimensional H-bonding motif.[23] An identical presentation of H-bond donor/acceptor sites is found in 2-amino-4,6-dichlorotriazine **1**, which readily participates in stepwise chloro-substitution reactions with heteroatom nucleophiles. Crystals of 4,6-dichlorotriazine **1** were grown from carbon tetrachloride, revealing the anticipated mode of assembly. From the crystal structure of **1**, ideal parameters were obtained for the design of an architecturally feasible covalent linkage. Specifically, as introduction of the covalent framework was envisioned to involve double chloro-substitution by a bifunctional heteroatom nucleophile, it was critical to preserve the preferred interchlorine distance of 3.28 Å between adjacent triazines. This distance is roughly commensurate with the interoxygen distances of 2.7 and 3.4 Å observed for 1,3-diols upon adoption of syn-periplanar and "staggered-periplanar" conformations, respectively. Appreciating the prescribed periplanar conformation could be induced via the Thorpe−Ingold effect; neopentyl glycols were selected as "first-generation" covalent linking moieties. The simplest neopentyl glycol-linked oligomer **2** was prepared, and its mode of assembly was determined in the solid state by X-ray crystallographic analysis. Notably, the supramolecular connectivities evident in the parent motif persist upon introduction of covalent scaffolding, validating the selection of 1,3-diols as linking groups. An identical motif is observed in the solid-state structure of **3** (Figure 1).[15,16]

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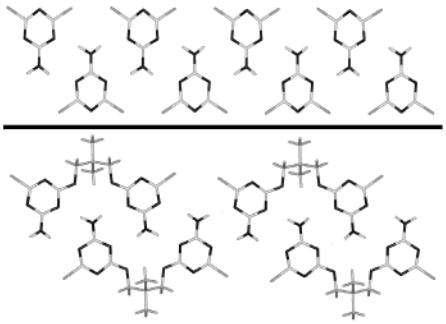
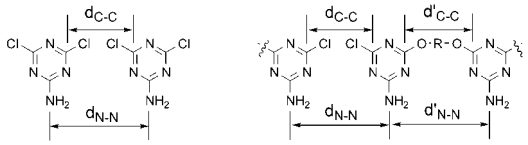


Figure 1. Top: X-ray crystal structure of **1**. Bottom: X-ray crystal structure of **2**, revealing persistence of the supramolecular connectivities upon introduction of covalent scaffolding.

Table 1. Interatomic Distances Taken from Crystallographic Data[a]



1 **2 and 3**

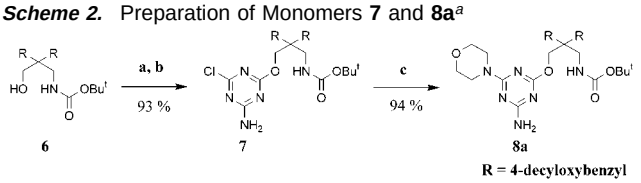
cmpd	$d_{N-H\cdots N}$ (Å)	d_{N-N} (d'_{N-N}) (Å)	d_{C-C} (d'_{C-C}) (Å)	d_{Cl-Cl} (Å)
1	3.22	8.459	6.273	3.283
2	3.083 ± 0.145	7.905± 0.001 (8.066 ± 0.003)	6.259± 0.001 (5.320 ± 0.002)	3.450 ± 0.003
3	3.062 ± 0.111	8.018 ± 0.014 (7.913 ± 0.019)	6.276 ± 0.104 (5.285 ± 0.024)	3.416 ± 0.173

[a] For **2** and **3**, R = neopentyl glycol linkage.

The goodness-of-fit of the covalent linkage may be approximated by comparing the geometries and interatomic distances found in the crystal structures of **2** and **3** with those of the parent motif expressed by **1**. For **2** and **3**, there are three unique molecules in the unit cell, each differing slightly in conformation, resulting in multiple unique NH···N hydrogen bonds. The average NH···N hydrogen bond lengths in the solid-state structures of **2** and **3**, 3.08 and 3.06 Å, respectively, are significantly shorter than the NH···N hydrogen bond length found in the parent motif, 3.22 Å, suggesting a slightly noncommensurate relationship between the covalent and noncovalent frameworks. Indeed, for both **2** and **3** the distance d'_{C-C} between triazine carbon atoms bearing oxygen averages 5.3 Å, while the carbon atoms bearing chlorine are further apart, d_{C-C} = 6.3 Å, a value nearly identical to the uniform intertriazine spacing of **1**, d_{C-C} = 6.273 Å. These data suggest that 1,3-diol linkages enforce an intertriazine distance approximately 1 Å shorter than that intrinsically preferred. Consequently, accumulated strain may contribute to significant backbone curvature and unfavorable geometries for duplex binding in higher oligomers. This analysis does not account for the contribution of long-range crystal packing forces (Table 1).

The identification of neopentyl glycols as viable intertriazine linkages enabled the design of refined second-generation covalent scaffolding. Neopentyl amino alcohol-based linking groups doubly stabilize the effective binding conformation via the Thorpe−Ingold effect and the presence of an intramolecular NH···O hydrogen bond. Owing to increased preorganization of the backbone, oligomers incorporating neopentyl amino alcohol linkages were anticipated to display enhanced duplex binding affinities. Indeed, the neopentyl amino alcohol-linked aminotriazine dimer **5b** exhibits an association constant 3 orders of magnitude greater than its neopentyl glycol-linked counterpart **4** (vide supra).[16]

Scheme 2. Preparation of Monomers **7** and **8a**[a]



6 **7** **8a**

R = 4-decyloxybenzyl

[a] Reagents: (a) cyanuric chloride, 2,6-lutidine, 80 °C; (b) NH_3, ^{i}PrOH-CH_2Cl_2, 25 °C; (c) morpholine, $CHCl_3$, reflux.

Synthesis

The results obtained for the neopentyl amino alcohol-linked dimer justified efforts toward the preparation of longer oligomers. An iterative method for the preparation of sequentially homologated oligo(aminotriazines) has been devised, whereby the condensation of three components, mono-aminotriazines **1**, **7**, and **8a**, yields dimeric, trimeric, and tetrameric oligo-aminotriazines **9b**, **9c**, and **9d**.

The oligomer building blocks **1**, **7**, and **8a** are all derived from cyanuric chloride. Amino-dichlorotriazine **1** is prepared via aminolysis of cyanuric chloride according to the literature procedure.[24] Intermediate **6** is prepared via dialkylation of ethyl cyanoacetate, followed by $LiAlH_4$ reduction to afford the amino alcohol and, finally, BOC-protection of the amine. Monomer **7** is prepared via triazinylation of the BOC-protected neopentyl amino alcohol **6** with cyanuric chloride, with subsequent aminolysis. Finally, chloro-substitution of **7** with morpholine yields **8a** (Scheme 2).

Monomeric aminotriazine **8a** contains a latent nucleophilic terminus in the form of the BOC-protected amine. Exposure of **8a** to trifluoroacetic acid unmasks the amine nucleophile, which is subject to capture by **7** to yield dimeric aminotriazine **8b**, which retains the latent nucleophilic terminus. Dimer **8b** may, in turn, be deprotected and condensed with **7** to afford the homologous trimer **8c**, which again retains the latent nucleophilic terminus. Finally, the monomeric, dimeric, and trimeric intermediates **8a**, **8b**, and **8c** may be "capped" by reaction of the N-terminus with amino-dichlorotriazine **1**. In this way, dimeric, trimeric, and tetrameric oligo-aminotriazines **9b**, **9c**, and **9d** were prepared in good yield (Scheme 3).

Dimeric aminotriazines **2**−**4** and monomeric aminotriazine **5a** were prepared in accord to our previously described protocol.[13−15] Monomeric aminotriazine **9a** was prepared via chloro-substitution of **5a** with morpholine. Dansyl-labeled monomer **10a** was prepared via *O*-triazinylation of *N*-dansyl 1,3-aminopropanol with cyanuric chloride followed by aminolysis of the resulting dichloroalkoxy triazine (Figure 2).

Dimeric and trimeric dye-labeled strands **10b** and **10c**, required for cross-hybridization experiments, were readily prepared through a variation of the aforementioned homologation protocol, whereby capping of the *N*-Boc-terminated intermediates **8a** and **8b** is performed with the dansyl-labeled monomer **10a**, rather than dichloroaminotriazine **1** (Scheme 4).

^{1}H NMR Dilution Studies. The association of monomeric aminotriazines **5a**, **9a**, dimeric aminotriazines **4**, **5b**, **9b**, trimeric aminotriazine **9c**, and tetrameric aminotriazine **9d** were inves-

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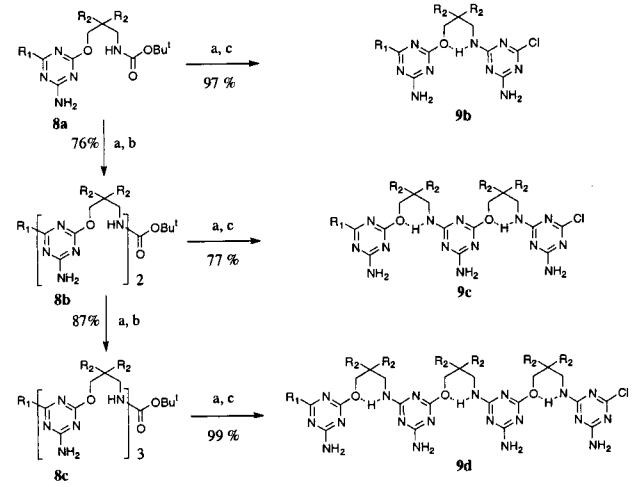
Scheme 3. Synthesis of Amino Alcohol-Linked Oligo(aminotriazines) **9b**, **9c**, and **9d** (R_1 = *N*-morpholine, R_2 = 4-decyloxybenzyl)[a]



[a] Reagents: (a) 10% TFA-CH_2Cl_2, 25 °C; (b) **7**, $^iPr_2NEt$, $CHCl_3$, reflux; (c) **1**, $^iPr_2NEt$, $CHCl_3$, reflux.

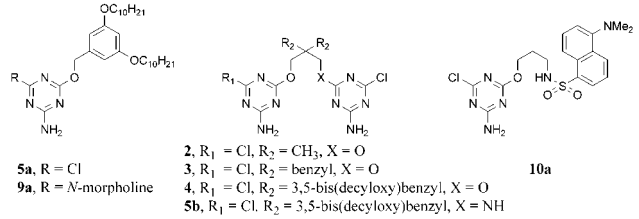
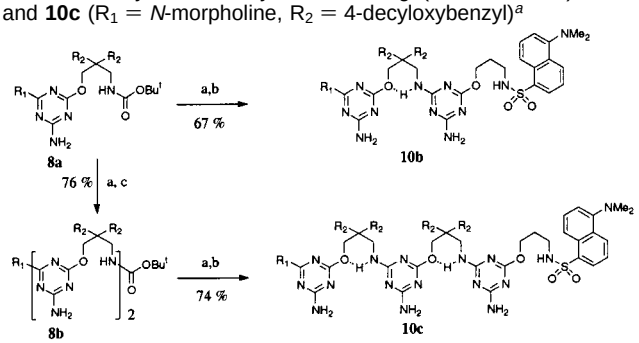


Figure 2. Related monomeric and dimeric aminotriazines.

Scheme 4. Synthesis of Dye-Labeled Oligo(aminotriazines) **10b** and **10c** (R_1 = *N*-morpholine, R_2 = 4-decyloxybenzyl)[a]



[a] Reagents: (a) 10% TFA-CH_2Cl_2, 25 °C; (b) **10a**, $^iPr_2NEt$, $CHCl_3$, reflux; (c) **7**, $^iPr_2NEt$, $CHCl_3$, reflux.

tigated by ^1H NMR dilution studies at 300 MHz.[25,26] Association constants were calculated by fitting the observed data to a 2-fold self-association model using an iterative minimization protocol. Analyses of monomeric aminotriazines **5a** and **9a** were performed in neat $CDCl_3$. Association constants of 2.9 M^{-1} (log $K = 0.46 \pm 0.026$) and 5.4 M^{-1} (log $K = 0.73 \pm 0.57$) were obtained, respectively. The difference in association constant for monomers **5a** and **9a** may arise from pK_a matching effects,[27] whereby amino-substitution in **9a** enhances the basicity of the endocyclic triazine nitrogens.

Whereas the diol-linked aminotriazine dimer **4** exhibits an association constant of 100 M^{-1} (log $K = 2.0 \pm 0.10$) in neat $CDCl_3$, no changes in chemical shift were observed for the analogous amino alcohol-linked dimer **5b** under identical conditions, suggesting persistence of the duplex at the limits of ^1H NMR detection. The addition of d_6-DMSO provides a more competitive medium for hydrogen bond formation, causing dissociation to occur in a higher concentration range.[28] ^1H NMR dilution experiments performed on **5b** in 5% d_6-DMSO:$CDCl_3$ yield a K_a of 28 000 M^{-1} (log $K = 4.5 \pm 0.57$). Notably, this value is ca. 3000 times greater than that of the diol-linked dimer **4** in the same medium ($K_a = 9.2$ M^{-1}, log $K = 0.96 \pm 0.065$). As previously described, the superior binding affinity displayed by **5b** is attributed to enhanced preorganization conferred by the neopentyl amino alcohol linkage. In 10% d_6-DMSO:$CDCl_3$, the morpholine-substituted dimer **9b** exhibits a K_a of 980 (log $K = 3.0 \pm 0.26$), which approximates that of its chloro-substituted counterpart **5b**. The proposed effects of pK_a matching, such as seen in the case of monomers **5a** and **9a**, were not apparent for the dimer series by NMR.

The dependence of K_a on DMSO concentration for the diol-linked versus amino alcohol-linked dimers **4** and **5b** provides further evidence for existence of the intramolecular hydrogen bond proposed for the amino alcohol-linked series. Increasing the proportion of d_6-DMSO from 5% to 10% reduces the strength of binding for amino alcohol-linked dimer **5b** considerably more than for the diol-linked analogue **4** (K_a changes from 28 000 to 1100 M^{-1} versus 9.2 to 2.0 M^{-1}, respectively). Competition for the intramolecular N−H···O bond by the exogenous H-bond acceptor DMSO diminishes its preorganizing effect. As such, changes in DMSO content influence binding of the amino alcohol-linked dimer more profoundly.

In comparison to the dimeric amino alcohol-linked aminotriazine **5b**, the ^1H NMR signals for longer oligomers were significantly broadened. Alkylaminotriazines exhibit rotational isomerism similar to amides (15 kcal mol^{-1} rotational barrier),[29] and, for an oligomer of *n* repeat units, $2^{(n-1)}$ rotamers is possible. ^1H NMR spectra of **9c** and **9d** recorded at 100 °C in d_8-toluene display appreciable sharpening of the spectral signals. At ambient temperature, the dilution data obtained for trimer **9c** in 10% d_6-DMSO were amenable to interpretation. However, dissociation of the duplex could not be observed until the d_6-DMSO content was increased to 50%, whereupon an association constant of 1500 M^{-1} (log $K = 3.2 \pm 0.19$) was measured. For tetramer **9d**, broadened spectral lines precluded analysis of dilution data taken at ambient temperature (Table 2).

Isothermal Titration Calorimetry (ITC). An assessment of the effects of cooperativity in the assembly process required that association constants be obtained for a series of oligomers in a common medium. ^1H NMR studies dictate a limited concentration range, precluding use of this technique for the evaluation of cooperative effects. Isothermal titration calorimetry (ITC) permits characterization of subnanomolar binding phenomena. Though typically applied toward heteromeric host−guest systems, a model for homomeric binding has been described.[30]

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Table 2. Association Constants (K_a, M^{-1}) Determined by ^1H NMR[a]

	percent d_6-DMSO in $CDCl_3$ (v:v)				
cmpd	0%	1%	5%	10%	50%
5a	2.9				
9a	5.4				
4	100	66	9.2	2.0	
5b	n.d.[b]		28 000	1100	
9b	n.d.[b]			980	
9c				n.d.[b]	1500

[a] Dimerization constants were obtained from ^1H NMR dilution data (300 MHz) using the computer program ChemEquili developed by Dr. Vitaly Solov'ev. For a detailed description, see: Solov'ev, V. P.; Baulin, V. E.; Strakhova, N. N.; Kazachenko, V. P.; Belsky, V. K.; Varnek, A. A.; Volkova, T. A.; Wipff, G. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1489. [b] No dissociation was observed at the limits of NMR detection (n.d. = no dissociation).

ITC experiments were performed in 1,2-dichloroethane rather than in chloroform to circumvent error incurred by evaporation. The dipole moment of $CDCl_3$ ($\mu = 1.1$ D) is lower than that of 1,2-DCE ($\mu = 1.8$ D). Consequently, hydrogen bond interactions are stronger in $CHCl_3$ than in 1,2-dichloroethane.[31] Concentrated analyte solutions were injected into a reservoir initially containing neat 1,2-dichloroethane, and enthalpy changes were monitored. A nonlinear least-squares minimization protocol was used to fit the experimental curve to a 2-fold self-association model. Experiments were repeated a minimum of three times to ensure reproducibility. The average values obtained for K_d and $\Delta H°$ were used to calculate binding free energy ($\Delta G°$) and enthalpy ($T\Delta S°$).

ITC analysis of monomeric aminotriazines **5a** and **9a** revealed association constants of 1.9 M^{-1} ($K_d = 530 \pm 415$ mM) and 4.7 M^{-1} ($K_d = 214 \pm 38.1$ mM), respectively. The relative binding affinities of **5a** and **9a** are consistent with those values obtained by ^1H NMR analysis and, as previously indicated, may arise from pK_a matching effects. Upon strand extension from monomer to dimer, an increase in binding affinity of over 3 orders of magnitude is observed. Dimeric oligotriazines **5b** and **9b** exhibit binding constants of 5.0×10^3 M^{-1} ($K_d = 199 \pm 87$ μM) and 2.3×10^4 M^{-1} ($K_d = 44.4 \pm 1.4$ μM), respectively. Again, the enhanced binding affinity of **9b** in relation to **5b** may be attributed to pK_a matching effects. *Strand extension from dimers **5b** and **9b** to trimer **9c** further increases binding affinity by 4- and 5-orders of magnitude.* For trimer **9c**, an association constant of 6.9×10^8 M^{-1} ($K_d = 1.44 \pm 0.50$ nM) is observed. Finally, tetramer **9d** exhibits a binding constant of 1.1×10^3 M^{-1}. This association constant is below that observed for trimer **9c** and resembles values observed for duplex dimer formation. These data suggest **9d** folds upon itself rather than adopting an in-register mode of duplex binding. Modeling of the possible folded states suggests association of the terminal subunits, leaving the two interior aminotriazine residues available for intermolecular complexation. This interpretation is consistent with the observance of binding energies comparable to duplex dimer formation (Table 3).

Vapor Pressure Osmometry (VPO). To corroborate the intended mode of assembly, the binding stoichiometry of dimeric, trimeric, and tetrameric oligo(aminotriazines) **5b**, **9c**, and **9d** was investigated by vapor pressure osmometry (VPO) in $CHCl_3$. The ratio of observed molar mass (M_{obs}) to molecular weight (MW) was calculated. As VPO measurements can vary considerably in response to the choice of calibration standard,[32] two standards were employed: sucrose octaacetate (SO; MW 678.6) and low-polydispersity polystyrene (PS; $M_n = 4288$, PD = 1.04). In the former case, M_{obs}/MW values consistent with the intended mode of aggregation were observed for trimer **9c** and tetramer **9d**; that is, M_{obs}/MW equaled approximately two, suggesting formation of a 1:1 complex in solution. However, for dimer **5b**, M_{obs}/MW was somewhat low. Recalibration using low-polydispersity polystyrene gave results consistent with 1:1 binding, in the case of **5b** alone (Table 4).

For dimer **5b** and trimer **9c**, the correlation coefficient R^2 (from the linear regression used to analyze VPO data) is high, but in the case of the tetramer **9d**, $R^2 = 0.704$ due to curvature rather than scatter. This deviation from linearity suggests that the tetramer's aggregation state varies over the concentration range studied.

Cross-Hybridization Experiments. The use of fluorescent labels in conjunction with thin-layer chromatographic (TLC) analysis provides a qualitative test for duplex formation. Fluorophore-tagged dimeric and trimeric oligo(aminotriazines) **10b** and **10c** were analyzed by TLC (SiO_2 stationary phase) in the presence and absence of analogous nonlabeled strands **9b** and **9c**. The TLC experiment shown on the left corresponds to the analysis of triazine dimers **9b** and **10b**. The TLC experiment shown on the right corresponds to the analysis of triazine trimers **9c** and **10c**. In each experiment, the left track was spotted with unlabeled oligomer, the center track was cospotted with both dye-labeled and unlabeled oligomers, and the right track was spotted with dye-labeled oligomer. Upon elution of the TLC plates, comigration of the trimeric strands is observed, whereas dimeric strands do not comigrate. Comigration corroborates cross-hybridization of labeled and unlabeled triazine trimers, underscoring the high interstrand affinity of the oligotriazine trimers. Streaking observed upon elution of the dimers and dansyl labeled trimer can be explained upon consideration of the effect of duplex formation on the polarity of the oligomeric components. In the bound state, polar binding residues are masked in the core of the duplex, minimizing interaction with the polar chromatographic support. Therefore, oligomers migrate faster in the bound state, which is favored at the center of the applied sample spot where concentration is highest. Unlabeled trimer **9c** does not streak, suggesting that the duplex form dominates. The fluorescent tag is highly polar, causing **10b** and **10c** to interact strongly with the polar silica support. Though tagged trimer **10c** likely exists predominantly in the duplex form, its polarity is too great to permit migration when **9c** is not present for cross-hybridization (Figure 3).

Discussion

For each single-stranded oligotriazine, three isomeric binding modes are possible, each bound by an equivalent number of hydrogen bonds: a head-to-head binding mode and two frame-shifted head-to-tail binding modes. The observance of a single apparent association constant for each oligomer suggests the isomeric binding modes are roughly equienergetic (Figure 4).

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Table 3. Thermodynamic Parameters of Duplex Binding As Determined by ITC in 1,2-Dichloroethane at 20 °C[a]

cmpd	*n*	HB	K_d	K_a (M^{-1})	$\Delta G°$	$\Delta H°$	$T\Delta S°$	$\Delta G°/n$	$\Delta G°$/HB
5a	1	2	530 ± 415 mM	1.9	−0.376	−7.80 ± 4.48	−7.42	−0.376	−0.19
9a	1	2	214 ± 38.1 mM	4.7	−0.912	−2.50 ± 0.227	−1.59	−0.912	−0.46
5b	2	6	199 ± 87 μM	5.0×10^3	−5.05	−14.4 ± 3.14	−9.35	−2.53	−0.84
9b	2	6	44.4 ± 1.4 μM	2.3×10^4	−5.93	−13.6 ± 0.41	−7.67	−2.97	−0.99
9c	3	10	1.44 ± 0.50 nM	6.9×10^8	−12.1	−95.0 ± 11.3	−82.9	−4.03	−1.21
9d	4		925 ± 52 μM	1.1×10^3	−4.14	−15.0 ± 1.78	−10.9	−1.04	

[a] n = oligomer length; HB = number of H-bonds per duplex; K_d = dissociation constant; $K_a = 1/K_d$; $\Delta G/n$ = binding free energy per aminotriazine; ΔG/HB = binding free energy per H-bond. Units of $\Delta G°$, $\Delta H°$, and $T\Delta S°$ are in kcal mol^{-1}.

Table 4. Vapor Pressure Osmometry: Results Based on Calibration with Sucrose Octaacetate (SO) and Polystyrene (PS)[a]

	concentration			calibrated with SO		calibrated with PS	
cmpd	range (mM)	MW	R^2	M_{obs}	M_{obs}/MW	M_{obs}	M_{obs}/MW
5b	3.2−17	1137.4	0.973	1711	1.50	2223	1.95
9c	1.5−21	1535.1	0.999	3006	1.96	3906	2.54
9d	6.2−28	2195.45	0.704	4106	1.87	5535	2.52

[a] VPO analysis was conducted at 40 °C in anhydrous, ethanol-free $CHCl_3$.

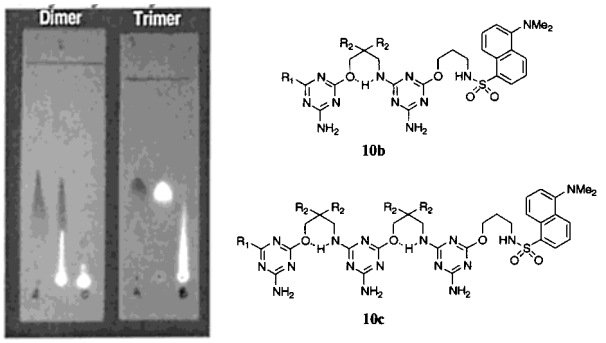

Figure 3. Cross-hybridization experiment involving the analysis of dye-labeled strands via thin-layer chromatography (TLC). R_1 = *N*-morpholine, R_2 = 4-decyloxybenzyl. Approximately equimolar amounts of analyte were employed in TLC binding experiments. Eluant: 25% acetone-hexanes. Stationary phase: silica gel 60 F_{254} TLC plates. Visualization: short-wave (254 nm) and long-wave (365 nm) handheld UV lamps.

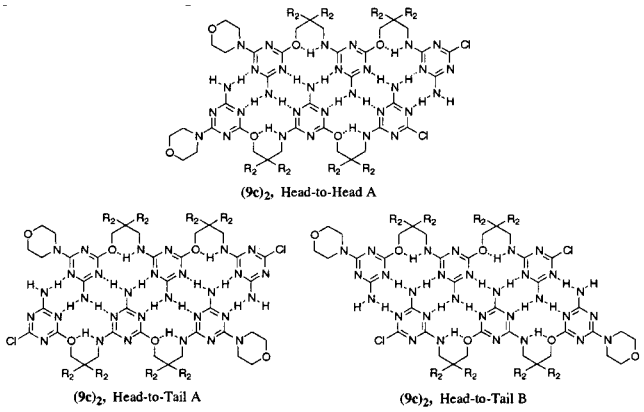

Figure 4. Isomeric duplex binding modes as illustrated for trimer **9c**.

Unsatisfied hydrogen bond donor/acceptor sites that reside at the termini of each isomeric duplex give rise to the possibility of higher-order aggregation as in $[(\mathbf{9c})_2]_2$. However, the low binding energy of ditopic aminotriazine association (K_a = 1.9−4.7 M^{-1}, as determined for **5a** and **9a**), coupled with the limited solubility of these high molecular weight oligomers, precluded analyses in a concentration range suitable for the observation of higher-order binding phenomena (Figure 5).

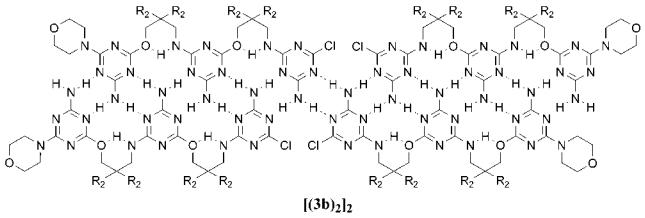

Figure 5. Higher-order aggregate $[(\mathbf{9c})_2]_2$.

The extranuclear chloro- and *N*-morpholinyl substituents modulate the basicity of the endocyclic triazine nitrogens; for example, 2-chloro-4,6-diamino[1,3,5]triazines (pK_a = 1.00−1.85) are substantially poorer bases than their electron-rich 2-methoxy counterparts (pK_a = 4.0−4.5).[33] Significant pK_a matching effects for the chloro- versus morpholine-terminated monomers and dimers are revealed by ITC analysis and are corroborated, in part, by ^{1}H NMR analysis.[25] The relative binding energies of chloro-terminated monomer **5a** (K_a = 2.9 M^{-1}) and morpholine-terminated monomer **9a** (K_a = 5.4 M^{-1}), as determined by ^{1}H NMR, are consistent with those determined by ITC for **5a** (K_a = 1.9 M^{-1}) and **9a** (K_a = 4.7 M^{-1}). ITC reveals an analogous trend for dimers **5b** and **9b**. The chloro-terminated dimer **5b** exhibits a lower binding constant ($K_a = 5.0 \times 10^3$ M^{-1}) than does the morpholine-terminated dimer **9b** ($K_a = 2.3 \times 10^4$ M^{-1}). The K_a values determined for dimers **5b** and **9b** by ^{1}H NMR appear to contradict the apparent pK_a matching trends. However, in the case of dimers **5b** and **9b**, the relative margin of error for the K_a values obtained by ^{1}H NMR is substantially greater than that of those obtained by ITC.

Duplex binding is enthalpically driven. The binding free energy per unimer ($-\Delta G°/n$) increases significantly upon extension from monomer to dimer to trimer, indicating a strong positive cooperative effect. On the basis of the analysis of the crystallographic data for monomer **1** and dimers **2** and **3**, this result is surprising as the amino alcohol linkage is estimated to enforce an intertriazine distance approximately 1 Å shorter than that required. Presumably, the flexibility of the oligomer backbone compensates for the noncommensurate relationship between the covalent and noncovalent connectivities. However, beyond the stage of the trimer, it is likely such noncommensurate geometries, along with the flexibility inherent to the oligomer backbone, promote intramolecular folding of tetrameric oligo(aminotriazine) **9d** in favor of in-register duplex formation. Further rigidification of the linking moiety should overcome this limitation.

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Conclusion

The covalent casting of noncovalent ensembles has been introduced as a rational strategy for the preparation of oligomeric constructs encoded with *predefined* modes of aggregation. Through covalent casting, the intrinsic predisposition of small molecular precursors to adopt targeted modes of assembly is amplified through their attachment to rigid covalent scaffolding in their effective binding conformation. In this fashion, the self-assembly characteristics of small molecules are parlayed into a high-affinity high-specificity interactional algorithm for oligomer assembly. The casting of alternative one-dimensional hydrogen-bonding motifs should enable the preparation of diverse duplex oligomers that embody orthogonal modes of association. Ultimately, conjugation of orthogonal strand segments will permit the creation of information-rich oligomers capable of sequence specific hybridization for use in nanoscale patterning schemes, and the design of polymer-based architectures en route to functional supramolecular materials.[34]

Experimental Section

General. Reagents were purchased from Aldrich and used as received unless otherwise indicated. All reactions were carried out under an atmosphere of dry N_2 unless otherwise indicated. Anhydrous THF was prepared by distillation from sodium/benzophenone. Anhydrous $CHCl_3$ was obtained by distillation from P_2O_5. All other solvents were of technical grade unless noted. Silica gel (SiO_2, 60 Å 32−63μm) for column chromatography was oven-dried prior to use. Thin-layer chromatography (TLC) was performed on 200 μm layer silica gel 60 F_{254} aluminum-backed plates. NMR spectra were recorded on either a Varian Unity Plus or a Bruker AMX-500 spectrometer. Chemical shifts are reported in parts per million (ppm) relative to solvent residual signal. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., and used as received. IR spectra were recorded on a Nicolet Impact 410 spectrometer. Melting points were obtained on a Thomas−Hoover UniMelt apparatus and are uncorrected.

Vapor Pressure Osmometry (VPO). Sucrose octaacetate used for VPO calibration was obtained from Jupiter Instrument Co., Inc. Polystyrene used for VPO calibration was obtained from Polysciences, Inc. (cat. no. 08280). Analyses were performed on a Jupiter 833 Vapor Pressure Osmometer thermostated to 40 °C. Chloroform was freshly distilled from P_2O_5 prior to use. Polystyrene was characterized by analytical GPC prior to use as a molecular weight standard. VPO data were analyzed by linear regression using *Osmomat* software. Reported results represent single experimental runs.

Isothermal Titration Calorimetry (ITC). Analyses were performed on a MicroCal VP-ITC instrument thermostated to 20 °C. Reported results represent the average of three or more runs. 1,2-Dichloroethane (EM Science AR Grade) was prepared by distillation from P_2O_5, storage over molecular sieves, and filtration through a 0.45 μM nylon membrane. The solvent was degassed by sonication in vacuo prior to each run. Following is a summary of the mathematical model used for data analysis.

$$f_{\text{monomer}} + f_{\text{dimer}} = 1$$

$$f_{\text{dimer}} = 1 - K_d[(1 + 8A_0/K_d)^{1/2} - 1]/4A_0 \quad (1)$$

where f_{dimer} is the mole fraction in the associated state, K_d is the dissociation constant (mol/L), and A_0 is the analyte concentration

$$A_0(i-1) = A_0(i) - (\text{syr} \times V_{\text{inj}})/(V_{\text{inj}} + V_o) \quad (2)$$

$$q_{\text{obs}}(i) = {}^1/_2\Delta H^\circ[n(i)f_{\text{dimer}}(i) - n(i-1)f_{\text{dimer}}(i-1) - n(\text{inj})f_{\text{dimer}}(\text{inj})] \quad (3)$$

where ΔH° is the molar enthalpy of binding, $q_{\text{obs}}(i)$ is the integrated heat observed at injection i, $n(i)$ is the moles of analyte after injection i, $n(i-1)$ is the moles of analyte prior to injection i, n(inj) is the moles of analyte in V_{inj}, syr is the concentration of analyte in syringe, V_{inj} is the injection volume, and V_o is the sample cell volume.

Substitution of eqs 1 and 2 into eq 3 yields an expression from which K_d and ΔH_o were computed from raw ITC data by nonlinear least squares curve fitting in the *Origin* software package.

NMR Dilution Experiments. Dilution studies were carried out by incrementally diluting concentrated analyte samples while obtaining ^{1}H NMR spectra. For each experiment, if significant concentration-dependent shifting of spectral signals was observed, the data were analyzed in terms of a 2-fold self-association model to obtain a value for log(K). For **5a**, data from NH and benzyl protons were processed simultaneously. For **9a**, NH, benzyl, and CH_2 (α to oxygen), signals were processed simultaneously. For **4**, NH and CH_2 (α to oxygen) signals were processed simultaneously. For **5b** and **9b**, the CH_2 (α to oxygen) signal was processed. For **9c**, aryl and CH_2 (α to nitrogen) signals were processed simultaneously.

General Method A. Boc-protected oligomer **8a**, **8b**, or **8c** (1 mmol) is dissolved in a 10% (v:v) solution of trifluoroacetic acid (14 mL, 18 mmol) in CH_2Cl_2 at ambient temperature, and stirred under an atmosphere of Ar until consumption of starting material is complete (2−6 h), as judged by TLC analysis (10% ^{i}PrOH−$CHCl_3$, ninhydrin stain). The reaction mixture is then diluted with CH_2Cl_2 (15 mL) and carefully neutralized by washing with saturated aqueous $NaHCO_3$ (100 mL). The resulting organic phase is separated, dried over $MgSO_4$, filtered, and evaporated to dryness in vacuo at 40 °C. The product, a white waxy solid, is used immediately.

General Method B. Boc-protected monomer **8a** or dimer **8b** (1 mmol) is deprotected according to general method A. The resulting material is taken up in $CHCl_3$ (20 mL), then charged with **7** (1 mmol) and ^{i}Pr$_2$NEt (3 mmol). After refluxing the mixture for 6 h, it is diluted with $CHCl_3$ (20 mL), washed with aqueous citric acid (15% w:v, 50 mL), dried over $MgSO_4$, and evaporated to dryness. Purification by column chromatography (SiO_2, 100 cm^3/g of crude product, 10% acetone-hexanes) affords the $n + 1$ homologue of the starting material (dimer **8b** or trimer **8c**).

General Method C. Boc-terminated monomer **8a**, dimer **8b**, or trimer **8c** (1 mmol) is deprotected according to general method A. The resulting material is taken up in $CHCl_3$ (20 mL), then charged with **1** (1.1 mmol) and ^{i}Pr$_2$NEt (3 mmol). After refluxing the mixture for 1 h, it is diluted with $CHCl_3$ (20 mL), and washed with aqueous citric acid (15% w:v, 50 mL), then dried over $MgSO_4$, and evaporated to dryness. Purification by column chromatography (SiO_2, 100 cm^3/g of crude product, 10% acetone-hexanes) affords the chlorotriazine-capped strand (dimer **9b**, trimer **9c**, or tetramer **9d**).

General Method D. Boc-terminated monomer **8a** or dimer **8b** (1 mmol) is deprotected according to general method A. The resulting material is taken up in $CHCl_3$ (20 mL), then charged with **10a** (1 mmol) and ^{i}Pr$_2$NEt (3 mmol). After refluxing the mixture for 16 h under N_2, it is diluted with $CHCl_3$ (20 mL), washed with aqueous citric acid (15% w:v, 40 mL), dried over $MgSO_4$, filtered, and evaporated to dryness in vacuo. Purification by column chromatography (SiO_2, 100 cm^3/g of crude product) affords dansyl-tagged dimer **10b** or trimer **10c**.

4-(3,5-Bis-decyloxy-benzyloxy)-6-chloro-[1,3,5]triazin-2-yl-amine (5a). (3,5-Bis-decyloxy-phenyl)-methanol[35] (1.00 g, 2.38 mmol), 2,6-lutidine (0.28 mL, 2.38 mmol), and cyanuric chloride (0.400 g,

(34) For selected reviews on supramolecular materials, see: (a) Kazmaier, P.; Chopra, N. *MRS Bull.* **2000**, *25*, 30. (b) Mio, M. J.; Moore, J. S. *MRS Bull.* **2000**, *25*, 36. (c) Stupp, S. I.; Pralle, M. U.; Tew, G. N.; Li, L.; Zubarev, E. R. *MRS Bull.* **2000**, *25*, 42. (d) Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W. *MRS Bull.* **2000**, *25*, 49. (e) Hawker, C. J.; Hedrick, J. L.; Miller, R. D.; Volksen, W. *MRS Bull.* **2000**, *25*, 54. (f) Kato, T. *Struct. Bonding* **2000**, *96*, 95.

(35) Prepared in analogy to a published procedure: Johansson, G.; Percec, V.; Ungar, G.; Abramic, D. *J. Chem. Soc., Perkin Trans. 1* **1994**, 447.

2.16 mmol) were dissolved in CH_2Cl_2 (20 mL). The red-orange mixture was refluxed under N_2 for 1 h, then cooled to ambient temperature. After addition of anhydrous NH_3 (0.5 M in 1,4-dioxane, 10 mL, 5.0 mmol), stirring was continued for an additional 10 h. The resulting cloudy mixture was washed with aqueous citric acid (15% w:v, 20 mL), dried over $MgSO_4$, filtered, and evaporated to dryness in vacuo. Purification by column chromatography (SiO_2, 110 cm^3, 10% → 20% acetone in hexanes) afforded **5a** as a white solid (0.276 g, 23%). R_f = 0.2 (10% acetone-hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.51 (m, 2H), 6.38 (m, 1H), 5.79 (br s, 1H), 5.59 (br s, 2H), 5.30 (s, 2H), 3.90 (t, J = 6.6, 4H), 1.73 (quintet, J = 6.6, 4H), 1.25−1.43 (m, 28H), 0.86 (t, J = 6.6, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 170.7, 168.2, 160.4, 137.1, 106.2, 101.2, 69.7, 68.0, 31.8, 29.6, 29.5, 29.3, 29.2, 29.1, 25.9, 22.6, 14.1. MS (CI+, CH_4) *m*/*z* (relative intensity): 577 (12), 552 (10), 551 (30), 550 (23), 549 (M + 1, 100), 548 (15), 547 (15), 513 (13), 421 (8), 287 (22). HRMS calcd for $C_{30}H_{50}ClN_4O_3$: 549.3571. Found: 549.3561. IR (neat): 3506, 3324, 3188, 2922, 2844, 1662, 1604, 1565, 1533, 1468, 1422, 1344, 1305, 1247, 1156, 1059, 1000, 935, 812, 728, 676 cm^{-1}. mp (capillary) 71−74 °C.

Cyano-bis-(4-decyloxy-benzyl)-acetic Acid Ethyl Ester. A solution of 1-chloromethyl-4-decyloxybenzene[36] (58.7 g, 207 mmol) and ethyl cyanoacetate (10.0 mL, 94.3 mmol) in anhydrous DMF (200 mL) was prepared. 1,8-Diazabicyclo[5.4.0]undec-7-ene (31.0 mL, 207 mmol) was added with stirring, causing a moderate exotherm. After the exotherm subsided, the mixture was heated to 80 °C under an atmosphere of Ar for 1 h. The reaction mixture was then poured into a mixture of H_2O (1000 mL) and brine (150 mL), and the resulting suspension was extracted with Et_2O (300 mL). The ethereal layer was washed with H_2O (1000 mL) and brine (2 × 100 mL), then dried over $MgSO_4$, filtered, and concentrated to dryness in vacuo, giving the title compound as a beige solid (52.5 g, 92%). R_f = 0.5 (10% ethyl acetate in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, 4H, J = 8.7 Hz), 6.81 (d, 4H, J = 8.7 Hz), 4.01 (q, 2H, J = 7.2 Hz), 3.91 (t, 4H, J = 6.7 Hz), 3.22 (part A of AB system, 2H, J = 13.6 Hz), 3.00 (part B of AB system, 2H, J = 13.8 Hz), 1.75 (quintet, 4H, J = 6.7 Hz), 1.42−1.25 (m, 28H), 1.01 (t, 3H, J = 7.2 Hz), 0.86 (t, 6H, J = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 158.8, 131.0, 125.9, 118.8, 114.4, 67.9, 62.5, 53.8, 42.4, 31.9, 29.5, 29.4, 29.3, 29.2, 26.0, 22.6, 14.1, 13.8. MS (CI+, CH_4) *m*/*z* (relative intensity): 609 (13), 608 (44), 607 (M + 1, 100), 606 (15), 605 (15), 360 (19), 248 (10), 247 (45). IR (neat): 2925, 2854, 1738, 1612, 1512, 1468, 1301, 1248, 1178, 1117, 1050, 831 cm^{-1}. mp (capillary) 53−55 °C.

3-Amino-2,2-bis-(4-decyloxy-benzyl)-propan-1-ol. A suspension of $LiAlH_4$ (4.54 g, 119 mmol) in THF (100 mL) was cooled in an external wet ice bath and stirred, while a solution of cyano-bis-(4-decyloxy-benzyl)-acetic acid ethyl ester (51.8 g, 85.5 mmol) in THF (200 mL) was delivered in by cannulation under N_2 atmosphere. After addition was completed, the vessel was equipped with a water-jacketed condenser and refluxed for 14 h under N_2, then quenched by cautious addition of H_2O (10 mL) while cooling in a wet ice bath. The gray-white solids thereby formed were removed by filtration through a medium porosity glass frit under suction. The filtrand was washed with Et_2O (3 × 100 mL), and the combined filtrate was concentrated in vacuo, yielding the title compound as a colorless oil which solidified to a white wax (97.3 g, 97%) upon further vacuum-drying. R_f = 0.2−0.5 (10% ^{i}PrOH in hexanes). ^{1}H NMR ($CDCl_3$): δ 7.06 (d, 4H, J = 8.7 Hz), 6.78 (d, 4H, J = 8.5 Hz), 3.91 (t, 4H, J = 6.7 Hz), 3.54 (s, 2H), 2.77 (s, 2H), 2.71 (part A of AB system, 2H, J = 13.8 Hz), 2.43 (part B of AB system, 2H, J = 13.6 Hz), 1.75 (quintet, 4H, J = 6.7 Hz), 1.45−1.25 (m, 28H), 0.86 (t, 6H, J = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6, 131.4, 129.4, 113.9, 68.5, 67.9, 49.2, 41.8, 39.4, 31.9, 29.6, 29.5, 29.4, 29.3, 26.0, 22.6, 14.1. MS (CI+, CH_4) *m*/*z* (relative intensity): 598 (6), 597 (13), 571 (7), 570 (28), 569 (M + 1, 100), 568 (22), 567 (28), 553 (6). IR (neat): 3025, 2917, 2856, 1600, 1494, 1452, 1062, 1030, 752, 702 cm^{-1}. mp (capillary) 109−113 °C.

[2,2-Bis-(4-decyloxy-benzyl)-3-hydroxy-proply]-carbamic Acid *tert*-Butyl Ester (6). A solution of 3-amino-2,2-bis-(4-decyloxy-benzyl)-propan-1-ol (46.7 g, 82.3 mmol) in CH_2Cl_2 was added portionwise to di-*tert*-butyl pyrocarbonate (20.8 mL, 90.5 mmol) with stirring at ambient temperature. After gas evolution subsided, the vessel was maintained under an atmosphere of N_2 for 16 h. The solvent was removed in vacuo, and the residue thus obtained was purified by column chromatography (SiO_2, 1200 cm^3, 5% → 10% ethyl acetate in hexanes), yielding **6** as a colorless oil (50.1 g, 91%). R_f = 0.35 (10% ethyl acetate in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (d, 4H, J = 8.7 Hz), 6.81 (d, 4H, J = 8.7 Hz), 4.36 (t, 1H, J = 6.9 Hz), 3.91 (t, 4H, J = 6.7 Hz), 3.34 (s, 2H), 3.03 (d, 2H, J = 6.7 Hz), 2.62 (A part of AB system, 2H, J = 13.8 Hz), 2.40 (B part of AB system, 2H, J = 13.8 Hz), 1.76 (quintet, 4H, J = 6.7 Hz), 1.43−1.26 (m, 28H), 1.37 (s, 9H), 0.87 (t, 6H, J = 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7, 157.5, 131.3, 129.6, 114.3, 79.7, 67.9, 64.1, 45.1, 44.0, 38.9, 31.9, 31.6, 29.6, 29.5, 29.4, 29.3, 28.2, 26.1, 22.7, 14.1. MS (CI+, CH_4) *m*/*z* (relative intensity): 671 (7), 670 (32), 669 (M + 1, 88), 668 (35), 667 (16), 641 (16), 614 (34), 613 (100), 612 (15), 610 (25), 597 (19), 594 (17), 570 (16), 569 (41). IR (neat): 2925, 2854, 1692, 1611, 1510, 1468, 1391, 1366, 1297, 1246, 1175, 1035, 836 cm^{-1}. mp (capillary) 64−66 °C.

[3-(4-Amino-6-chloro-[1,3,5]triazin-2-yloxy)-2,2-bis-(4-decyloxy-benzyl)-propyl]-carbamic Acid *tert*-Butyl Ester (7). To a solution of **6** (26.5 g, 39.7 mmol) in toluene (200 mL) was added 2,6-lutidine (10.2 mL, 87.2 mmol) and cyanuric chloride (14.6 g, 79.3 mmol). The resulting orange mixture was heated to 80 °C under N_2 for 16 h, then diluted with toluene (200 mL) and washed sequentially with H_2O (2 × 600 mL), aqueous citric acid (15% w:v, 120 mL), and brine (50 mL). The organic phase was separated, then treated simultaneously with activated carbon and $MgSO_4$. After filtration, the solution was concentrated to an amber oil in vacuo (41.9 g). This material was redissolved in CH_2Cl_2 (250 mL), and a solution of anhydrous NH_3 (2 M in ^{i}PrOH, 90 mL, 180 mmol) was added. After 3 h, the reaction mixture was washed with H_2O (2 × 750 mL), causing emulsification, which was remedied upon suction filtration through a pad of Celite. The filtrate was washed with H_2O (750 mL), the organic phase was separated, dried over Na_2SO_4, and concentrated in vacuo to a viscous tawny oil (36.5 g). Purification by column chromatography (SiO_2, 1200 cm^3, 20% acetone in hexanes) yielded **7** as a yellow wax (29.6 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05 (d, 4H, J = 7.2), 6.81 (d, 4H, J = 7.2), 6.47 (br s, 1H), 6.32 (br s, 1H), 4.68 (s, 1H), 4.03 (s, 2H), 3.93 (t, J = 6.2, 4H), 3.13 (s, 2H), 2.74 (AB system, 4H, $\Delta\nu$ 4 Hz, J = 14.6), 1.93 (s, 1H), 1.78 (m, 4H), 1.29 (s, 9H), 1.45 (s, 28H), 0.90 (t, 6H, J = 7.1). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 170.7, 168.1, 157.8, 155.9, 131.3, 128.2, 114.3, 79.5, 67.9, 42.1, 38.9, 31.8, 31.5, 29.5, 29.4, 29.3, 28.3, 26.0, 22.6, 14.1. MS (CI, CH_4) *m*/*z* (relative intensity): 797 (M + 1, 100), 769 (5), 741 (16), 669 (57), 613 (15), 595 (12), 391 (18), 247 (22), 167 (25), 165 (37). HRMS calcd for $C_{45}H_{71}ClN_5O_5$: 796.5144. Found: 796.5137. IR (neat): 3326, 3206, 2924, 2854, 1699, 1650, 1611, 1564, 1511, 1468, 1420, 1363, 1301, 1246, 1175, 1015, 892, 810, 673 cm^{-1}. mp (capillary) 69−75 °C.

[3-(4-Amino)-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy)-2,2-bis-(4-decyloxy-benzyl)-propyl]-carbamic Acid *tert*-Butyl Ester (8a). Morpholine (1.41 mL, 16.1 mmol) was added to a solution of **7** (6.27 g, 7.87 mmol) in $CHCl_3$ (50 mL), and the mixture was refluxed under N_2 for 1 h, then washed with aqueous citric acid (15% w:v, 100 mL), H_2O (2 × 150 mL), dried over Na_2SO_4, and filtered. Concentration of the filtrate to dryness in vacuo yielded **8a** as a glassy foam (6.29 g, 94%). R_f = 0.3 (33% ethyl acetate in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (d, 4H, J = 8.5 Hz), 6.76 (d, 4H, J = 8.5 Hz), 5.42 (br s, 2H), 4.81 (s, 1H), 3.96 (s, 2H), 3.88 (t, 4H, J = 6.4 Hz), 3.69 (s, 4H), 3.66 (s, 4H), 3.08 (d, 2H, J = 4.6 Hz), 2.69−2.75 (m, 4H), 1.73 (m, 4H), 1.41 (s, 9H), 1.24 (s, 28H), 0.85 (t, 6H, J = 6.5 Hz). ^{13}C

(36) Leu, Yi-Fun; Lai, Chung K. *J. Chin. Chem. Soc.* **1997**, *44(2)*, 89−91.

NMR (75 MHz, $CDCl_3$): δ 170.8, 168.2, 166.0, 157.7, 155.9, 131.5, 128.6, 114.1, 67.9, 66.6, 43.6, 41.9, 38.9, 31.8, 29.6, 29.5, 29.4, 29.3, 28.3, 26.0, 22.6, 14.1. HRMS calcd for $C_{49}H_{79}N_6O_6$: 847.6061. Found: 847.6070. IR (neat): 2924, 2854, 1714, 1537, 1510, 1442, 1410, 1365, 1302, 1246, 1175, 1117, 1069, 1013, 886, 836, 813, 738 cm^{-1}. mp (capillary) 47−50 °C.

Boc-Protected Dimer (8b). This was prepared from **8a** according to general method B. Yield 76%. $R_f = 0.5$ (25% acetone-hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 7.04 (d, 4H, $J = 8.5$ Hz), 6.96 (d, 4H, $J = 8.5$ Hz), 6.78 (d, 4H, $J = 8.2$ Hz), 6.70 (d, 4H, $J = 8.5$ Hz), 5.94 (s, 1H), 4.96 (s, 1H), 4.11 (s, 2H), 3.98 (s, 2H), 3.83 (m, 8H), 3.70 (m, 8H), 3.49 (s, 2H), 3.23 (s, 2H), 2.57−2.80 (m, 8H), 1.70 (s, 8H), 1.48 (s, 9H), 1.24 (m, 56H), 0.854 (t, 12H, $J = 6.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4, 166.8, 157.8, 156.2, 131.5, 128.6, 128.2, 114.2, 114.0, 79.7, 67.9, 66.7, 43.7, 41.3, 40.5, 39.4, 32.2, 31.8, 29.6, 29.4, 29.3, 28.5, 26.1, 26.0, 22.6, 14.1. MS (CI+, CH_4) *m*/*z* (relative intensity): 1507 (M+, 45), 1466 (8), 1464 (10), 1422 (10), 1392 (7), 1364 (23), 1336 (56), 1322 (12), 1292 (14), 1263 (31), 1236 (100), 1222 (5), 1206 (5), 1162 (6), 1002 (9). IR (neat): 3434, 3154, 2925, 2854, 1690, 1650, 1573, 1510, 1471, 1428, 1409, 1357, 1302, 1246, 1176, 1117, 1069, 1015, 887, 835, 813, 738 cm^{-1}. mp (capillary) 119−121 °C.

Boc Trimer (8c). This was prepared from **8b** according to general method B. Yield 87%. ^1H NMR (300 MHz, 34 mM in $CDCl_3$): δ 9.54 (br s, 1H), 9.31 (br m, 2H), 6.98−7.07 (m, 12H), 6.71−6.81 (m, 12H), 6.07 (br s, 1.5H), 4.99 (br s, 0.7H), 4.13 (br s, 4H), 3.99 (s, 2H), 3.70−3.85 (m, 20H), 3.53 (br s, 2H), 3.48 (br s, 2H), 3.24 (br s, 2H), 2.57−2.76 (m, 12H), 1.70 (m, 12H), 1.23−1.54 (m, 99H), 0.85 (t, $J = 6.9$ Hz, 18H). ^{13}C NMR (75 MHz, 34 mM in $CDCl_3$): δ 157.8, 131.5, 114.0, 67.9, 31.8, 29.6, 29.4, 29.3, 28.5, 26.0, 22.6, 14.1. HRMS calcd for $C_{129}H_{201}N_{16}O_{12}$: 2166.5650. Found: 2166.5610. MS (FAB, NBA) *m*/*z* (relative intensity): 2167 (M+, 2.7), 1516 (1.4), 1310 (3.5), 1179 (1.9), 857 (5), 717 (5), 694 (9), 660 (100), 605 (10), 551 (15), 533 (17), 520 (27). IR (neat): 3429, 3120, 2924, 2854, 1691, 1649, 1570, 1510, 1470, 1423, 1356, 1301, 1246, 1175, 1118, 1080, 1014, 993, 811, 711, 539 cm^{-1}. mp (capillary) 173−179 °C.

4-(3,5-Bis-decyloxy-benzyloxy)-6-morpholin-4-yl-[1,3,5]triazin-2-ylamine (9a). To a solution of **5a** (0.100 g, 0.182 mmol) in $CHCl_3$ (3 mL, 60mM) was added morpholine (0.050 mL, 0.573 mmol), and the mixture was refluxed under air for 45 min. The reaction mixture was then washed with aqueous citric acid (15% w:v, 5 mL), and the organic layer which separated was dried over Na_2SO_4, filtered through cotton, and evaporated to dryness in vacuo. Purification by column chromatography (SG60, 15 cm^3, 2:3:5 ethyl acetate-$CHCl_3$-hexanes) yielded **9a** (0.080 g, 73%) as a white solid. $R_f = 0.3$ (33% ethyl acetate in hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 6.52 (m, 2H), 6.35 (m, 1H), 5.23 (s, 2H), 5.02 (s, 2H), 3.89 (t, 4H, $J = 6.5$ Hz), 3.77 (m, 4H), 3.67 (m, 4H), 1.73 (quintet, 4H, $J = 6.8$ Hz), 1.40−1.24 (m, 28H), 0.86 (t, 6H, $J = 6.4$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 168.1, 166.2, 160.3, 138.6, 106.2, 100.8, 68.3, 68.0, 66.7, 43.8, 31.9, 29.6, 29.4, 29.3, 29.2, 26.0, 22.7, 14.1. MS (ESI+) *m*/*z* (relative intensity): 602.4 (8), 601.5 (30), 600.5 (M+, 100), 403.7 (7). HRMS calcd for $C_{34}H_{58}N_5O_4$: 600.4489. Found: 600.4494. IR (neat): 2954, 2923, 2853, 1649, 1600, 1573, 1541, 1479, 1437, 1412, 1351, 1303, 1281, 1266, 1177, 1120, 1069, 1015, 811 cm^{-1}. mp (capillary) 119−122 °C.

***N*-[3-(4-Amino-6-morpholin-4-yl-[1,3,5]triazin-2-yloxy)-2,2-bis-(4-decyloxy-benzyl)-propyl]-6-chloro-[1,3,5]triazine-2,4-diamine (9b).** This was prepared from **8a** according to general method C. Yield 97%. $R_f = 0.4$ (25% acetone in hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 6.97 (d, 4H, $J = 8.5$ Hz), 6.75 (d, 4H, $J = 8.5$ Hz), 6.08 (t, 1H, $J = 5.9$ Hz), 4.13 (s, 2H), 3.89 (t, 4H, $J = 6.2$ Hz), 3.71 (s, 8H), 3.54 (d, 2H, $J = 5.4$ Hz), 2.77 (part A of AB system, 2H, $J = 14.1$ Hz), 2.60 (part B of AB system, 2H, $J = 13.6$ Hz), 1.74 (quintet, 4H, $J = 7.2$, 6.4 Hz), 1.42−1.24 (m, 28H), 0.85 (t, 6H, $J = 6.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 169.4, 168.0, 166.4, 165.6, 165.4, 157.9, 131.6, 128.0, 114.1, 73.0, 67.9, 66.6, 43.7, 40.3, 39.8, 31.8, 29.6, 29.5, 29.4, 29.3, 26.0, 22.6, 14.1. HRMS calcd for $C_{47}H_{72}N_{10}O_4Cl$: 875.5423. Found: 875.5439. IR (neat): 3425, 3156, 2924, 2854, 1687, 1637, 1574, 1510, 1408, 1362, 1294, 1247, 1176, 1118, 1013, 989, 810 cm^{-1}. mp (capillary) 89−93 °C.

Trimer (9c). This was prepared from **8b** according to general method C. Yield 77%. $R_f = 0.5$ (25% acetone-hexanes). ^1H NMR (500 MHz, 16 mM in d_8-toluene, 100 °C): δ 9.80 (br s, 3H), 7.08 (d, $J = 8.6$ Hz, 4H), 7.03 (d, $J = 8.6$ Hz, 4H), 6.82 (d, $J = 8.6$ Hz, 4H), 6.78 (d, $J = 8.6$ Hz, 4H), 6.30 (br s, 1H), 6.10 (br s, 1H), 4.28 (s, 2H), 4.21 (s, 2H), 3.78 (m, 8H), 3.61 (m, 8H), 3.48 (m, 4H), 2.85−2.71 (m, 8H), 1.66 (m, 8H), 1.37 (br m, 8H), 1.26 (br m, 48H), 0.87 (m, 12H). ^{13}C NMR (125 MHz, 16 mM in d_8-toluene, 100 °C): δ 171.17, 171.09, 169.58, 169.36, 168.04, 167.01, 166.93, 159.16, 132.29, 132.22, 115.34, 115.38, 68.84, 68.81, 66.88, 44.68, 41.59, 40.84, 40.31, 32.46, 30.16, 30.14, 30.04, 29.85, 26.75, 23.13, 14.18. HRMS calcd for $C_{87}H_{133}N_{15}O_7Cl$: 1535.0200. Found: 1535.0222. IR (neat): 3500, 3424, 3117, 2924, 2854, 1691, 1639, 1567, 1511, 1471, 1440, 1408, 1356, 1297, 1247, 1176, 1117, 1086, 1015, 989, 921, 885, 810, 704, 594 cm^{-1}. mp (capillary) 171−175 °C.

Tetramer (9d). This was prepared from **8c** according to general method C. Yield 99%. $R_f = 0.6$ (25% acetone-hexanes). ^1H NMR (500 MHz, 11 mM in d_8-toluene, 100 °C): δ 9.85 (br s, 4H), 7.18 (d, $J = 8.4$ Hz, 4H), 7.10 (d, $J = 8.4$ Hz, 4H), 6.84 (m, 8H), 6.80 (d, $J = 8.6$ Hz, 4H), 6.45 (br s, 2H), 6.18 (br s, 1H), 4.34 (s, 2H), 4.32 (s, 2H), 4.23 (s, 2H), 3.80 (m, 12H), 3.64 (m, 8H), 3.48 (m, 4H), 2.87−2.78 (m, 12H), 1.68 (m, 12H), 1.38 (br m, 12H), 1.27 (br s, 78H), 0.87 (m, 18H), 0.45 (s, 2H). ^{13}C NMR (125 MHz, 11 mM in d_8-toluene, 100 °C): δ 171.29, 171.24, 169.73, 168.17, 159.27, 132.48, 132.45, 132.39, 129.78, 129.61, 129.57, 115.45, 115.40, 69.02, 68.99, 68.94, 67.04, 44.79, 42.04, 41.73, 40.91, 40.42, 40.27, 32.59, 30.31, 30.25, 30.20, 29.99, 26.90, 23.26, 14.33. MS (ESI) *m*/*z* (relative intensity): 2211 (5), 2195 (M+, 20), 2194 (95), 2193 (100), 2192 (85), 2164 (25), 2037 (4), 1997 (5), 1534 (5), 1517 (12), 1516 (20), 1099 (25), 1085 (8). IR (neat): 3424, 3119, 2924, 2854, 1691, 1638, 1566, 1511, 1470, 1426, 1408, 1355, 1298, 1247, 1176, 1144, 1117, 1081, 1015, 991, 968, 922, 810, 707 cm^{-1}. mp (capillary) 220−224 °C.

5-Dimethylamino-naphthalene-1-sulfonic Acid (3-Hydroxy-propyl)-amide. A solution of 5-(dimethylamino)-naphthalene-1-sulfonyl chloride (1.50 g, 5.56 mmol) in CH_2Cl_2 (50 mL) was combined with a solution of 3-aminopropan-1-ol (0.64 mL, 8.34 mmol) in 2 M aqueous Na_2CO_3 (30 mL), and the resulting biphasic, yellow mixture was vigorously stirred for 1 h. The reaction mixture was acidified cautiously with 100 mL of 15% aqueous citric acid and shaken. The organic phase was separated, dried over Na_2SO_4, decanted, and evaporated to dryness in vacuo, yielding the title compound as a pale yellow solid (1.58 g, 92%). $R_f = 0.4$ (66% ethyl acetate-hexanes). ^1H NMR (300 MHz, d_6-DMSO): δ 8.44 (d, 1H, $J = 8.7$ Hz), 8.29 (d, 1H, $J = 8.7$ Hz), 8.09 (dd, 1H, $J = 1.1$, 7.4 Hz), 7.80 (br s, 1H), 7.59 (m, 2H), 7.24 (d, 1H, $J = 7.4$ Hz), 4.37 (s, 1H), 3.29 (s, 2H), 2.84−2.79 (m, 8H), 1.47 (quintet, 2H, $J = 7.0$ Hz). ^{13}C NMR (75 MHz, d_6-DMSO): δ 151.3, 136.0, 129.3, 129.1, 129.0, 128.3, 127.8, 123.6, 119.1, 115.1, 58.0, 45.1, 39.9, 32.5. MS (CI+, CH_4) *m*/*z* (relative intensity): 349 (3), 337 (14), 311 (7), 310 (16), 309 (M + 1, 100), 308 (7). IR (neat): 3503, 3297, 2944, 2873, 2833, 1587, 1574, 1477, 1312, 1142, 1073, 944, 790, 625 cm^{-1}. mp (capillary) 117−119 °C.

5-Dimethylamino-naphthalene-1-sulfonic Acid [3-(4,6-Dichloro-[1,3,5]triazin-2-yloxy)-propyl]-amide. 5-Dimethylamino-naphthalene-1-sulfonic acid (3-hydroxy-propyl)-amide (1.58 g, 5.12 mmol) was dissolved in $CHCl_3$ (50 mL), followed by 2,6-lutidine (1.31 mL, 11.3 mmol) and cyanuric chloride (1.88 g, 10.2 mmol). The resulting pale orange solution was refluxed for 6 h, and allowed to cool. After washing the reaction mixture with 15% aqueous citric acid (100 mL), the organic layer was separated dried over Na_2SO_4, decanted, and evaporated to dryness in vacuo. Purification was achieved by column chromatography (SiO_2, 60 cm^3/g crude product), eluting with 1:1:2 $CHCl_3$:ethyl acetate:hexanes, followed by 2:1:1 $CHCl_3$:ethyl acetate:hexanes, affording the

title compound as a yellow solid (1.68 g, 72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50 (d, 1H, J = 8.5 Hz), 8.24 (m, 2H), 7.51 (q, 2H, J = 8.5, 7.2 Hz), 7.12 (d, 1H, J = 7.8 Hz), 4.94 (t, 1H, J = 6.4 Hz), 4.36 (t, 2H, J = 5.8 Hz), 3.07 (q, 2H, J = 6.4 Hz), 2.86 (s, 6H), 1.90 (quintet, 2H, J = 6.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 170.6, 152.1, 134.0, 130.7, 130.1, 129.8, 129.4, 128.5, 123.1, 118.3, 115.1, 67.1, 45.3, 39.5, 28.4. HRMS calcd for $C_{18}H_{20}Cl_2N_5O_3S$: 456.0664. Found: 456.0668. IR (neat): 1541, 1508, 1442, 1304, 1252, 1162, 1146, 1054, 1040, 789 cm^{-1}. mp (capillary) 166−169 °C.

5-Dimethylamino-naphthalene-1-sulfonic Acid [3-(4-Amino-6-chloro-[1,3,5]triazin-2-yloxy)-propyl]-amide (10a). Anhydrous NH_3 (0.5 M in dioxane, 16.0 mL, 8.00 mmol) was added to a solution of 5-(dimethylamino)-naphthalene-1-sulfonic acid [3-(4,6-dichloro-[1,3,5]-triazin-2-yloxy)-propyl]-amide (1.61 g, 3.52 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred at ambient temperature for 18 h, during which time a precipitate developed. The precipitate was collected by suction filtration and dried in vacuo, affording **10a** as a yellow solid (1.42 g, 92%). ^{1}H NMR (300 MHz, d_6-DMSO): δ 8.42 (d, 1H, J = 8.5 Hz), 8.27 (d, 1H, J = 8.7 Hz), 8.08 (d, 1H, J = 7.4 Hz), 8.03 (t, 1H, J = 5.7 Hz), 7.93 (d, 2H, J = 20 Hz), 7.56 (m, 3H), 7.40 (s, 1H), 7.20 (m, 1H), 4.12 (t, 2H, J = 6.1 Hz), 2.88 (q, 2H, J = 6.1, 6.4 Hz), 1.71 (quintet, 2H, J = 6.4, 6.1 Hz). ^{13}C NMR (75 MHz, d_6-DMSO): δ 170.1, 169.7, 167.9, 151.3, 135.7, 129.4, 129.0, 128.4, 127.8, 123.5, 119.0, 115.1, 64.6, 45.1, 28.3. MS (CI+, CH_4) m/z (relative intensity): 465 (10), 440 (8), 439 (36), 438 (21), 437 (M + 1, 100), 436 (15), 329 (7), 327 (18), 291 (10). HRMS calcd for $C_{18}H_{22}ClN_6O_3S$: 437.1163. Found: 437.116. IR (neat): 3362, 3134, 1667, 1574, 1529, 1417, 1313, 1297, 1136, 1067, 783 cm^{-1}. mp (capillary) 198−202 °C.

Dansyl Dimer (10b). This was prepared from **8a** (0.193 g, 0.228 mmol) according to general method D. The crude material was purified by column chromatography (SiO_2, 5% → 10% ^{i}PrOH in $CHCl_3$). The combined pure fractions yielded **10b** as a pale yellow solid (0.177 g, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.47 (d, 1H, J = 8.2 Hz), 8.24 (m, 2H), 7.47 (m, 2H), 7.09 (d, 1H, J = 7.2 Hz), 6.97 (d, 4H, J = 8.2 Hz), 6.71 (d, 4H, J = 8.2 Hz), 5.97 (s, 1H), 4.22 (m, 2H), 4.11 (s, 2H), 3.85 (t, 4H, J = 6.7 Hz), 3.67 (s, 8H), 3.51 (d, 2H, J = 4 Hz), 2.99 (m, 2H), 2.80 (s, 6H), 2.74 (s, 1H), 2.59 (d, 2H, J = 13.3 Hz), 1.84 (m, 2H), 1.69 (m, 10H), 1.40−1.24 (m, 32H), 0.85 (t, 6H, J = 6.5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 169.9, 168.5, 167.7, 166.8, 165.8, 157.8, 151.8, 134.8, 131.6, 130.3, 129.8, 129.6, 128.3, 123.1, 118.8, 115.2, 114.0, 67.9, 66.6, 63.9, 45.3, 43.8, 40.6, 31.9, 29.6, 29.4, 29.3, 26.1, 22.7, 14.1. HRMS calcd for $C_{62}H_{91}N_{12}O_7S$: 1147.6854. Found: 1147.6899. IR (neat): 2923, 2854, 1577, 1509, 1432, 1414, 1334, 1247, 1140, 1115, 1071, 1020, 809, 788 cm^{-1}. mp (capillary) 165−169 °C.

Dansyl Trimer (10c). This was prepared from **8b** (0.326 g, 0.216 mmol) according to general method D. The crude product was purified by column chromatography (SiO_2, 5% MeOH in $CHCl_3$), affording **10c** as a pale yellow solid (0.288 g, 74%). ^{1}H NMR (500 MHz, d_8-toluene, 100 °C): δ 8.70 (br s, 1H), 8.39 (d, 1H, J = 8.5 Hz), 8.29 (d, 1H, J = 6.9 Hz), 7.43 (t, 1H, J = 8.1 Hz), 7.22−7.12 (m, 9H), 6.93 (d, 1H, J = 7.6 Hz), 6.82 (d, 4H, J = 7.3 Hz), 6.76 (m, 4H), 4.40 (br s, 2H), 4.33 (br s, 2H), 4.17 (br s, 2H), 3.79−3.75 (m, 12H), 3.62 (s, 4H), 3.50 (s, 4H), 3.00 (d, 2H, J = 5.6 Hz), 2.89−2.73 (m, 8H), 2.59 (s, 6H), 1.68−1.62 (m, 10H), 1.38 (t, 8H, J = 6.6 Hz), 1.28 (s, 48H), 0.87 (m, 12H). ^{13}C NMR (125 MHz, d_8-toluene, 100 °C): δ 171.7, 171.2, 169.6, 168.0, 159.0, 137.8, 132.5, 132.4, 131.1, 131.0, 123.5, 115.9, 115.2, 115.1, 68.9, 68.8, 66.9, 45.4, 44.9, 41.9, 32.5, 30.2, 30.1, 29.9, 26.8, 23.2, 14.2. MS (FAB) m/z (relative intensity): 1809 (3), 1808 (M + 1, 5), 1807 (4), 951 (15), 674 (8), 661 (100). HRMS calcd for $C_{102}H_{152}N_{17}O_{10}S$: 1807.1629. Found: 1807.1596. IR (neat): 3429, 3128, 2923, 2854, 1684, 1583, 1510, 1426, 1353, 1246, 1176, 1141, 1115, 1072, 810 cm^{-1}. mp (capillary) 211−215 °C.

Acknowledgment. Acknowledgment is made to the Robert A. Welch Foundation (F-1466), the NSF-CAREER program, the NIH, donors of the Petroleum Research Fund administered by the ACS, the Herman Frasch Foundation, and the Advanced Research Program of the Texas Higher Education Coordinating Board for partial support of this research. Dr. Vitaly Solov'ev is thanked for use of the program ChemEquili. Dr. Russell Wolz of Commonwealth Biotechnology, Inc., is recognized for assistance in developing the dimerization model used for analysis of ITC data.

Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA012696H