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Synthesis and Modulation of Bis(triazine) Hydrogen-Bonding Receptors

Pamela V. Mason,[a] Neil R. Champness,*[a] Simon R. Collinson,[a] Matthew G. Fisher,[a] and Gudrun Goretzki[a]

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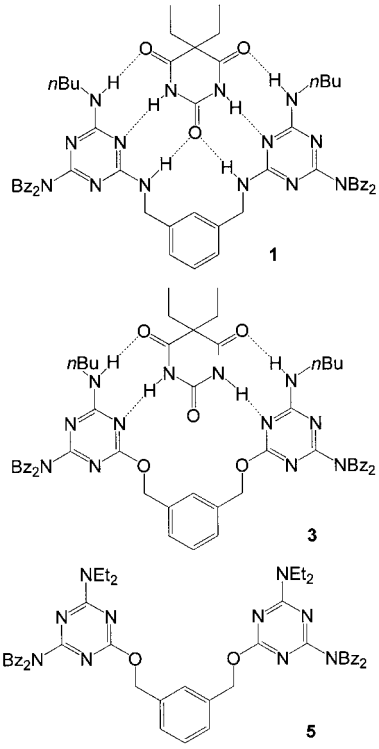
The synthesis of bis(triazine) molecules capable of acting as synthetic receptors for barbiturate guest molecules is described. The binding properties are also reported illustrating the modulation of the binding properties of these species by the modification of the hydrogen-bonding patterns of the receptor molecule, namely 1,3-*N*,*N*′-bis[4-(dibenzylamino)-6-(butylamino)-1,3,5-triazin-2-yl]xylylenediamine (**1**). Thus 1,3-*O*,*O*′-bis[4-(dibenzylamino)-6-(butylamino)-1,3,5-triazin-2-yl]benzenedimethanol (**3**) and 1,3-*O*,*O*′-bis[4-(dibenzylamino)-6-(diethylamino)-1,3,5-triazin-2-yl]benzenedimethanol (**5**) have been prepared, and their binding constants compared to those observed for **1**. In the case of compounds **3** and **5** the hydrogen-bonding secondary amines at the apex of the receptor **1** are substituted by non-hydrogen-bonding ether links. The hydrogen-bonding ability is further modified in the case of **5** by the removal of all hydrogen-bond donors from the receptor site, replacing secondary amines by tertiary amines. NMR binding studies illustrate how these simple modifications of the hydrogen-bonding patterns of these receptors influences the overall strength of binding demonstrating a simple mechanism for controlling host-guest complex formation.

Introduction

The design and synthesis of receptor molecules that act as hosts for barbiturate molecules is perhaps one of the most widely studied areas of supramolecular chemistry and builds on the wider research field studying the interactions between melamine and cyanuric acid and their derivatives.[1–4] Indeed, the concerted hydrogen bonding observed between diaminopyridine and diimide moieties has been widely used in a range of applications from synthetic receptors[3,5] to surface self-assembly and templating.[6]

Key studies have developed barbiturate receptors using either diamidopyridines[7–9] or amino-substituted triazine molecules.[10–12] Both systems offer the pre-organised sequence of hydrogen-bond acceptors and donors in the form of N–H moieties, either as amines or as amides, coupled with aromatic nitrogen hydrogen-bond acceptors in a donor–acceptor–donor sequence. The designed coupling of two such moieties provides a highly pre-organised receptor for a guest barbiturate group that show strong binding constants of up to 10^6 M^{-1}.[7] More advanced systems show the development of this area towards sensing systems[13] and the use of the strong interactions between barbiturates and the host molecules for the construction of self-assembled arrays.[3,4,14]

In this study, we have developed methods for the synthesis of a number of symmetric receptor molecules capable of



Scheme 1. Illustration of the target bis(triazine) receptor–barbital interactions, appropriate substitution of the triazine allows modulation of the number of hydrogen-bonding acceptor and donor sites allowing a degree of control over the strength of the host–guest interaction.

[a] School of Chemistry, The University of Nottingham, University Park,
Nottingham NG7 2RD, UK
Fax: +44-115-9513563
E-mail: Neil.Champness@nottingham.ac.uk
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forming multiple hydrogen bonds to guest molecules such as barbital, a generic barbiturate. The pocket systems are composed of two identical triazine derivatives linked by one of two linker groups, either *m*-xylylenediamine or 1,3-benzenedimethanol (Scheme 1). Through the variation of not only the linking unit but also the triazine substituents we show that the pattern of hydrogen-bonding donors and acceptors can be readily modified allowing controlled variation in the binding ability of the receptor species. This in turn shows that such receptors can be modulated allowing tuning of this host–guest interaction, indicating their potential application in self-assembled devices where such modulation is required.

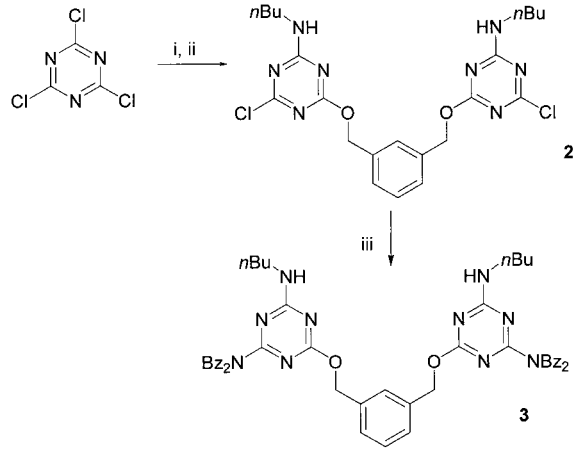
Results and Discussion

A range of hydrogen-bonding systems has been prepared, based on the Reinhoudt systems,[10,11] by the use of cyanuric chloride as the basis for the subsequent preparation. This approach is extremely attractive as it allows a high degree of variation in the substituents added to the triazine appendages of the hydrogen-bonding receptor molecule. By simple adaptations the ability of a hydrogen-bonding pocket to effectively bind to the barbiturate guest can be significantly altered. This has been achieved by preparing receptors with simple ether analogues or tertiary amines replacing secondary amine N–H hydrogen-bond donors. By this simple approach, changing the nature of the hydrogen-bonding sites within the receptor, the binding of barbiturates has been modulated.

In the first instance, the hydrogen-bonding receptor bis(melamine) species 1,3-*N*,*N*′-bis[4-(dibenzylamino)-6-(butylamino)-1,3,5-triazin-2-yl]xylylenediamine (**1**) (Scheme 1) was prepared following an adaptation of the route described by Reinhoudt et al.[10] This species was prepared to act as a standard for comparison of barbiturate binding ability.

The hydrogen-bonding ability, and thus the barbiturate binding ability, was then modulated by replacing the diamine bridge between the triazine substituents by a simple diether linkage. Thus, in the case of **1** the triazine molecules are bridged by the introduction of 1,3-xylylenediamine, so simple replacement of this species by 1,3-benzenedimethanol in the preparation of **3**, 1,3-*O*,*O*′-bis[4-(dibenzylamino)-6-(butylamino)-1,3,5-triazin-2-yl]benzenedimethanol (Scheme 1) resulted in a hydrogen-bonding receptor with only two hydrogen-bond donors (N–H groups) and with two hydrogen-bond acceptors (triazine N sites). Although the ether linkages can in principal act as hydrogen-bonding acceptor sites, they are relatively poor in doing so, and the arrangement of donors and acceptors around the pocket are less compatible with those presented by the barbiturate guest species.

The synthesis of compound **3** follows the procedure outlined in Scheme 2. Firstly it is important to note that when adding an alcohol rather than an amine to cyanuric chloride, slightly stronger conditions are required, stronger base and higher reaction temperatures, and that the alcoholic substituent needs to be added first.[15] In our experience, mono-substitution of cyanuric chloride with an amine results in the deactivation of the triazine ring with respect to further substitution, and thus harsher conditions are required to add additional substituents. Thus, it was found that attempts to add alkoxy substituents to mono- or diamino-substituted chlorotriazines were unsuccessful. But the reverse approach of adding amines to alkoxy-substituted triazines was successful.[15] Compound **2** was obtained as a brown sticky oil, which was used without further purification, as attempts at separation were unsuccessful, but reaction of **2** with dibenzylamine afforded **3** as a colourless solid in 32% yield following purification by column chromatography (2% MeOH/CH_2Cl_2 on silica).

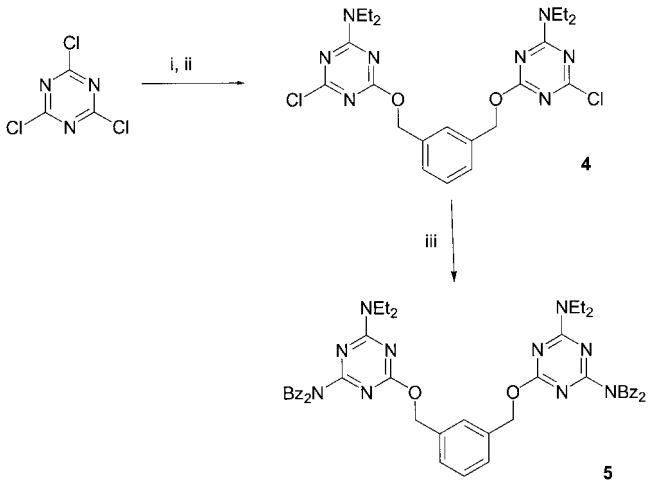


Scheme 2. i. 1,3-Benzenedimethanol, 2,6-lutidine, room temp. CH_2Cl_2; ii. butylamine, 2,6-lutidine, room temp. CH_2Cl_2; iii. $(PhCH_2)_2NH$, refluxing THF.

The hydrogen-bonding ability of the receptor can be further modulated by additional adaptation of the hydrogen-bonding potential presented by the pocket, by replacement of the remaining hydrogen-bond donors with comparatively hydrogen-bond inactive groups (in this context) such as tertiary amines, for example in compound **5** (Scheme 1).

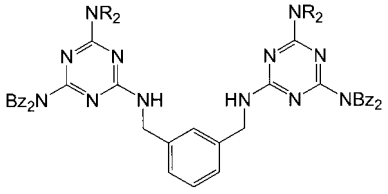
Compound **5**, 1,3-*O*,*O*′-bis[4-(dibenzylamino)-6-(diethylamino)-1,3,5-triazin-2-yl]benzenedimethanol, was prepared according to the procedure outlined in Scheme 3. The first step was the preparation of 1,3-*O*,*O*′-bis[4-chloro-6-(diethylamino)-1,3,5-triazin-2-yl]benzenedimethanol (**4**), which was prepared as a sticky brown oil that was used without further purification, as in the case of compound **2**. Reaction of **4** with dibenzylamine gave the bis(triazine) **5** in 22% yield as a colourless solid following purification by column chromatography (CH_2Cl_2 on silica).

A variety of attempts were made to prepare the hydrogen-bonding receptor bis(melamine) compounds in which both triazines were substituted exclusively by tertiary amine moieties (Scheme 4). Thus, each triazine appendage would be substituted by 1,3-xylylenediamine and dibenzylamine and one further amine moiety, either dibenzylamino, dibutylamino or diethylamino. This final series of compounds



Scheme 3. i. 1,3-Benzenedimethanol, 2,6-lutidine, room temp. CH_2Cl_2; ii. diethylamine, 2,6-lutidine, room temp. CH_2Cl_2; iii. $(PhCH_2)_2NH$, DIPEA, refluxing THF.

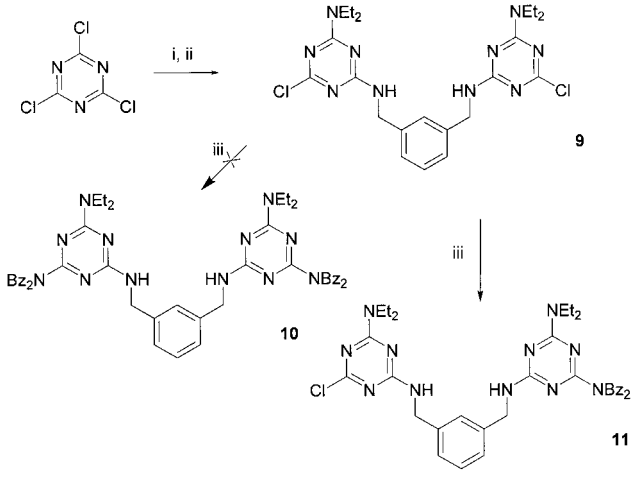
would have yielded host molecules with each triazine appendage offering two hydrogen-bond donors to the guest.



Scheme 4. Targeted-amine-substituted bis(triazine) receptor molecules, R = Bz, Bu, Et.

In all three cases (R = NBz_2, NBu_2, NEt_2) 1,3-xylylenediamine was treated with an excess of the appropriate triazine [R = NBz_2, 2-chloro-4,6-bis(dibenzylamino)-1,3,5-triazine (**6**); R = NBu_2, 2-chloro-4-(dibenzylamino)-6-(dibutylamino)-1,3,5-triazine (**7**); R = NEt_2; 2-chloro-4-(dibenzylamino)-6-(diethylamino)-1,3,5-triazine (**8**)]. However, in each case the reaction was found to produce only monosubstituted 1,3-xylylenediamine even following prolonged reflux and none of the desired product was identified.

An alternative strategy was then employed in an attempt to prepare 1,3-*N*,*N*′-bis[4-(dibenzylamino)-6-(diethylamino)-1,3,5-triazin-2-yl]xylylenediamine (**10**) proceeding via 1,3-*N*,*N*′-bis[4-chloro-6-(diethylamino)-1,3,5-triazin-2-yl]-xylylenediamine (**9**) (Scheme 5). Compound **9** was prepared by addition of *m*-xylylenediamine to a solution of cyanuric chloride in THF at 0 °C, followed by addition of diethylamine at room temperature. The product was purified by column chromatography (2% MeOH/CH_2Cl_2 silica) and isolated as a colourless solid. Attempts were made to prepare compound **10** by heating compound **9** with an excess of dibenzylamine in THF at reflux for 6 days. The resulting mixture of products was separated by column chromatography (*n*-hexane/ethyl acetate, 3:1, silica) and the major product purified and identified as 1-*N*-[4-(dibenzylamino)-6-(diethylamino)-1,3,5-triazin-2-yl]-3-*N*′-[4-chloro-6-(diethylamino)-1,3,5-triazin-2-yl]xylylenediamine (**11**), by ^1H NMR and mass spectrometry analysis. Further attempts to fully substitute the triazine under conditions using stronger bases such as 2,6-lutidine and solvents with higher reflux temperatures such as toluene were also unsuccessful.



Scheme 5. i. 1,3-Xylylenediamine, DIPEA, THF, 0 °C; ii. diethylamine, DIPEA, THF, room temp.; iii. $(PhCH_2)_2NH$, DIPEA, refluxing THF.

Binding Studies

The ability of compounds **1**, **3** and **5** to bind barbital through hydrogen-bonding interactions has been studied by NMR titrations in dry [D]chloroform at 25 °C using the method of continuous variation.[16] Where possible binding modes were established from Job plots of the NMR spectroscopic data and the binding energies of complex formation between the receptors and barbital have been calculated.

In order to standardise the results observed, the interaction between **1** and barbital was assessed. The Job plot of the NMR results confirmed the formation of a 1:1 **1**/barbital complex with a binding energy of $(1.8 \pm 1) \cdot 10^5$ M^{-1} or 30 kJ mol^{-1}. This results is consistent with those previously reported[10] for systems that adopt six cooperative hydrogen bonds between the receptor (**1** in the current case) and the guest barbital. Attempts to measure the binding energy of this system, and those below, by UV/Vis spectroscopy were hampered by the absence of appropriate reporter groups in compounds **1**, **3**, **5**.

Receptor **3** is capable of adopting four hydrogen-bonding interactions with barbital (Scheme 1). The replacement of the bridging 1,3-xylenediamine bridge by a non-hydrogen-bonding diether link in this case was anticipated to significantly alter the mode and strength of binding with barbital. The overall shape of the Job plot is indicative of a 1:1 complex; small variations in the overall shape observed are a result of experimental error (Figure 1). Clearly the less distinct maximum in this case supports the smaller binding constant as has been noted previously.[17] The possibility that the small variations in the Job plot were due to the formation of a variety of dynamic structures, which are ini-

tially formed as kinetic products,[3] was precluded by heating samples to 40 °C in $CDCl_3$ (over periods of 30 min, 1 h or 5 h) prior to cooling to room temperature and collection of ^1H NMR spectra.

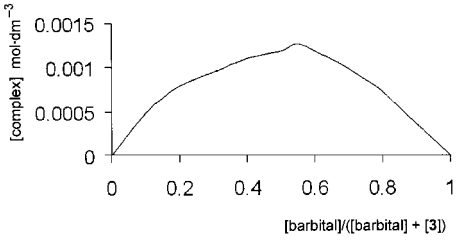


Figure 1. Job plot of [Complex] vs. [Host]/([Host] + [Guest]) for barbital and **3**.

The association constant for this system was calculated using EQNMR,[18] on the basis of a 1:1 complex being the only species present, giving 140 ± 3 M^{-1}, significantly lower than that of **1**/barbital. This confirms that the interaction between the xylylenediamine NH of **1** and barbital is particularly significant in the binding of barbiturates by pockets of this design. The smoothing of the Job plot curve is a reflection of the weaker binding of this pocket in comparison to that observed for **1**, caused by both reduced numbers of hydrogen-bonding interactions and by repulsive electrostatic interactions between the ether linkers and one of the barbiturate oxygen atoms in the case of **3**.

The receptor **5** is capable of adopting two hydrogen-bonding interactions with barbital (Scheme 1) and, thus, is expected to exhibit weak host–guest interactions. As in the case of **3**, this system suffers the absence of the well-defined hydrogen-bonding position between barbital and the xylylenediamine NH seen in **1**. The ^1H NMR titration experiments indicate a small shift in the baribital NH shift, potentially indicating an interaction between barbital and **5**. However, because of the much smaller chemical shifts involved in this system it was decided to investigate further the nature of the interaction in which the barbital is taking part. It was established that the ^1H NMR shifts observed for the barbital NH were also found in the absence of compound **5**, and therefore it can be concluded that the shifts observed in the ^1H NMR spectrum are due to barbital self-association (a binding constant of 14 ± 4 mol dm^{-3} was found for this species; which compares well with a previously reported values[11]). This is perhaps to be expected considering that barbital self-association will take place via the formation of double N–H···O hydrogen bonds; which are likely to be stronger than any hypothetical hydrogen-bonding interactions between barbital and **5**.

Conclusions

A range of hydrogen-bonding receptor systems has been prepared and the synthetic routes thoroughly investigated. It has been shown that the number of hydrogen-bonding sites available to interact with a guest such as a barbiturate can be modulated. Two distinct routes to the receptors have been demonstrated, depending on the nature of the linker group between the two triazine rings. Whereas when the linker used is *m*-xylylenediamine, the di-substituted triazine can be prepared before the linking step, when the linker used is 1,3-benzenedimethanol, the two triazines must be linked in the first step by the diether bridge prior to subsequent substitutions of the triazine rings.

By examining the hydrogen-bonding interaction between hydrogen-bonding pocket systems and barbital it has been shown that the number of hydrogen-bonding sites capable of binding a guest such as barbital has a significant effect on the overall strength of binding. This study illustrates the capability to modulate the hydrogen-bonding strength of such receptors indicating that the host–guest interaction of such receptors with barbiturate may be tuned potentially for subsequent use in devices where a reversible self-assembly process may be required.

Experimental Section

General: ^1H and ^{13}C NMR spectra were measured with a Bruker 300 MHz spectrometer. Infra-red spectra were measured as KBr disks with a Nicolet Avatar 380 FT-IR spectrometer over the range 400–4000 cm^{-1}. Microanalyses were performed by the University of Nottingham Chemistry Department microanalytical service with a Perkin–Elmer 240B analyser. All chemicals were purchased from Aldrich Chemicals, Lancaster Chemicals or Acros Chemicals and used without further purification. Compound **1** was prepared according to the procedures described by Reinhoudt et al.,[10] except that instead of refluxing 2-chloro-4-(dibenzylamino)-6-(butylamino)-1,3,5-triazine in neat *m*-xylylenediamine, THF solvent was used with an excess of the triazine starting material.

1,3-*O*,*O*′-Bis[6-(butylamino)-4-chloro-1,3,5-triazin-2-yl]benzenedimethanol (2): To a solution of cyanuric chloride (3.68 g, 20 mmol) and 2,6-lutidine (5 mL) in CH_2Cl_2 (50 mL) was added a solution of 1,3-benzenedimethanol (1.38 g, 10 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for ca. 20 h resulting in a dark red mixture. Butylamine (1.46 g, 20 mmol) in CH_2Cl_2 (5 mL) was added and the mixture stirred at room temperature for a further 20 h. The mixture was washed with 1 M HCl (50 mL), water (50 mL) and brine (50 mL) and the organic layers dried with $MgSO_4$. The solvent was evaporated under reduced pressure to give a brown sticky foam, which was used without further purification. ES-MS: m/z = 507 [M^+ + H].

1,3-*O*,*O*′-Bis[6-(butylamino)-4-(dibenzylamino)-1,3,5-triazin-2-yl]-benzenedimethanol (3): A solution of 1,3-*O*,*O*′-bis[6-(butylamino)-4-chloro-1,3,5-triazin-2-yl]benzenedimethanol (**2**) (ca. 2 g, 4 mmol), dibenzylamine (2.0 g, 10 mmol), and DIPEA (5 mL) in THF (100 mL) was heated at reflux for 3 days. The solvent was evaporated under reduced pressure and the residue dissolved in dichloromethane (100 mL), washed with 1 M HCl (50 mL), water (50 mL) and brine (50 mL). The solvent was evaporated under reduced pressure to give the crude product as a brown sticky foam. The filtrate was purified by column chromatography (CH_2Cl_2 on silica) to give the product as a white foamy solid (1.04 g, 32%). ^1H NMR ($CDCl_3$): δ = 7.40–7.19 (m, 24 H), 5.25 (s, 4 H), 4.75 (s, 8 H), 3.35 (m, 4 H), 1.49 (m, 4 H), 1.30 (m, 4 H), 0.86 (t, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.6, 167.6, 167.2, 166.7, 138.1, 137.9, 137.0, 128.5, 127.9, 127.1, 67.8, 48.5, 40.6, 31.8, 20.0, 13.8 ppm. ES-MS: m/z = 829 [M + H]. $C_{50}H_{56}N_{10}O_2$ (829.05): calcd. C 72.44, H 6.81, N 16.89; found C 72.04, H 6.83, N 16.76.

1,3-*O*,*O*′-Bis[4-chloro-6-(diethylamino)-1,3,5-triazin-2-yl]benzenedimethanol (4): To a solution of cyanuric chloride (3.68 g, 20 mmol) and 2,6-lutidine (5 mL) in CH_2Cl_2 (50 mL) was added a solution of 1,3-benzenedimethanol (1.38 g, 10 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for ca. 20 h resulting in a dark red mixture. Diethylamine (1.46 g, 20 mmol) in CH_2Cl_2 (5 mL) was added and the mixture stirred at room temperature for a further 20 h. The mixture was washed with 1 M HCl (50 mL), water (50 mL) and brine (50 mL) and the organic layers dried with $MgSO_4$. The solvent was evaporated under reduced pressure to give a brown sticky foam which was used without further purification. ES-MS: *m*/*z* = 507, 509 [M^+ + H].

1,3-*O*,*O*′-Bis[4-(dibenzylamino)-6-(diethylamino)-1,3,5-triazin-2-yl]-benzenedimethanol (5): A solution of 1,3-*O*,*O*′-bis[4-chloro-6-(diethylamino)-1,3,5-triazin-2-yl]benzenedimethanol (ca. 5 g, 10 mmol), dibenzylamine (3.94 g, 20 mmol), and 2,6-lutidine (5 mL) in THF (100 mL) was heated at reflux for 3 days. The solvent was evaporated under reduced pressure and the residue dissolved in dichloromethane (100 mL), washed with 1 M HCl (50 mL), water (50 mL) and brine (50 mL). The solvent was evaporated under reduced pressure to give a brown sticky residue which was purified by column chromatography (2% MeOH in CH_2Cl_2 on silica) to give the product as a white foam (1.8 g, 22%). ^{1}H NMR [$CDCl_3$]: δ = 7.34–7.20 (m, 24 H), 5.31 (s, 4 H), 4.80 (s, 4 H), 4.75 (s, 4 H), 3.59 (q, 4 H), 3.51 (q, 4 H), 1.18 (t, 6 H), 1.06 (t, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170.7, 167.0, 165.7, 138.5, 138.2, 137.4, 128.4, 127.9, 127.7, 127.5, 127.0, 67.9, 48.5, 41.5, 41.3, 13.4, 13.0 ppm. ES-MS: *m*/*z* = 829 [M + H]. $C_{50}H_{58}N_{10}O_3$ (**5**·0.5H_2O, 847.06): calcd. C 71.66, H 6.86, N 16.71; found C 71.67, H 6.66, N 16.52.

2-Chloro-4,6-bis(dibenzylamino)-1,3,5-triazine (6): To a solution of cyanuric chloride (1.84 g, 10 mmol) and DIPEA (5 mL) in THF (50 mL) was added dibenzylamine (3.94 g, 20 mmol) in THF (20 mL) dropwise. The reaction mixture was stirred at room temperature for ca. 20 h during which time a white precipitate formed. The solvent was evaporated under reduced pressure and the residue dissolved in CH_2Cl_2. The solution was washed with 1 M HCl (50 mL) and brine (50 mL), the organic layer dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was recrystallised from diethyl ether to give 2-chloro-4,6-bis(dibenzylamino)-1,3,5-triazine as a white solid (3.36 g, 66%). ^{1}H NMR $CDCl_3$]; δ = 7.38–7.10 (m, 20 H), 4.83 (s, 4 H), 4.68 (s, 4 H). ^{13}C NMR ($CDCl_3$). δ = 169.93, 165.82, 137.24, 137.08, 128.58, 128.52, 128.18, 127.64, 127.46, 127.25, 48.76, 48.60 ppm. ES-MS: *m*/*z* = 506 [M + H^+]. $C_{31}H_{28}ClN_5$ (506.03): calcd: C 73.58, H 5.58, N 13.84; Found C 73.10, H 5.60, N 13.70.

2-Chloro-6-(dibenzylamino)-4-(dibutylamino)-1,3,5-triazine (7): To a solution of cyanuric chloride (1.84 g, 10 mmol) and DIPEA (5 mL) in THF (50 mL) at 0 °C, was added dibutylamine (1.29 g, 10 mmol) in THF (10 mL) dropwise. The resulting slurry was stirred at 0 °C for 2 h. The reaction mixture was warmed to room temperature; and dibenzylamine (1.98 g, 10 mmol) in THF (10 mL) was added dropwise. The reaction was stirred at room temperature for ca. 20 h. The solvent was evaporated under reduced pressure and the residue dissolved in dichloromethane (100 mL), washed with water (50 mL), 1 M HCl (2 × 50 mL) and brine (50 mL) and the organic layer dried with $MgSO_4$. The solvent was evaporated under reduced pressure and the residue recrystallised from hot ethanol to give compound **7** as a white solid (2.45 g, 56%). ^{1}H NMR ($CDCl_3$): δ = 7.36–7.18 (m, 10 H), 4.79 (s, 2 H), 4.70 (s, 2 H), 3.51 (t, 2 H), 3.38 (t, 2 H), 1.57 (m, 2 H), 1.43 (m, 2 H), 1.35 (m, 2 H), 1.14 (m, 2 H), 0.95 (t, 3 H), 0.75 (t, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 170, 167, 165.5, 137.9, 128.9, 128.5, 127.8, 127.5, 49.4, 49.2, 48.0, 47.5, 30.5, 31.5, 20.6, 20.5, 14.4, 14.2 ppm. ES-MS: *m*/*z* = 438 [M^+]. $C_{25}H_{32}ClN_5$ (438.01): calcd. C 68.55, H 7.36, N 15.99; found C 68.49, H 7.34, N 15.76.

2-Chloro-4-(dibenzylamino)-6-(diethylamino)-1,3,5-triazine (8): To a solution of cyanuric chloride (1.84 g, 10 mmol) and DIPEA (4 mL) in THF (50 mL) at 0 °C, was added dibenzylamine (1.97 g, 10 mmol) in THF (10 mL) dropwise. The resulting slurry was stirred at 0 °C for 2 h. The reaction mixture was warmed to room temperature and diethylamine (0.73 g, 10 mmol) in THF (10 mL) was added dropwise. The reaction was stirred at room temperature for ca. 20 h. The solvent was evaporated under reduced pressure and the residue dissolved in dichloromethane (150 mL) which was washed with water (50 mL), 1 M HCl (2 × 50 mL) and brine (50 mL). The organic layers were combined and dried with $MgSO_4$ and the solvent evaporated under reduced pressure to give the crude product as a sticky yellow solid. Recrystallisation from hot ethanol gave 2-chloro-4-(dibenzylamino)-6-(diethylamino)-1,3,5-triazine (**5**) as a colourless solid (2.9 g, 76%). ^{1}H NMR ($CDCl_3$): δ = 7.35–7.21 (m, 10 H), 4.79 (s, 2 H), 4.71 (s, 2 H), 3.59 (q, 2 H), 3.47 (q, 2 H), 1.19 (t, 3 H), 1.04 (t, 3 H) ppm. ^{13}C NMR [$CDCl_3$]; δ = 169.4, 165.6, 164.2, 137.6, 137.5, 128.9, 128.5, 128.1, 127.5, 127.3, 127.2, 48.7, 48.6, 41.6, 41.5, 13.3, 12.6 ppm. $C_{21}H_{25}ClN_5$ (382.91): calcd. C 66.04, H 6.33, N 18.34; found C 65.60, H 6.32, N 18.00. ES-MS: *m*/*z* = 382 [M + H].

1,3-*N*,*N*′-Bis[4-chloro-6-(diethylamino)-1,3,5-triazin-2-yl]xylylenediamine (9): To a solution of cyanuric chloride (1.84 g, 10 mmol) and DIPEA (8 mL) in THF (50 mL) at 0 °C was slowly added a solution of *m*-xylylene diamine (0.68 g, 5 mmol) in THF (5 mL). The resulting slurry was stirred at 0 °C for ca. 4 h. The mixture was warmed to room temperature and a solution of diethylamine (0.73 g, 10 mmol) in THF (5 mL) was slowly added. The resulting mixture was stirred at room temperature for ca. 20 h. The solvent was evaporated under reduced pressure and the residue dissolved in dichloromethane (150 mL) which was washed with water (50 mL), 1 M HCl (2 × 50 mL) and brine (50 mL). The organic layers were combined and dried with $MgSO_4$ and the solvent evaporated under reduced pressure to give the crude product as a yellow oil. Column chromatography (2% MeOH in CH_2Cl_2) yielded compound **6** as a colourless solid (2.4 g, 47%). ^{1}H NMR ($CDCl_3$): δ = 7.29–7.17 (m, 4 H), 4.58 (s, 2 H), 4.56 (s, 2 H), 3.56 (q, 4 H), 3.48 (q, 4 H), 1.17 (t, 6 H), 1.05 (t, 6 H) ppm. ES-MS: *m*/*z* = 506 [M^+]. $C_{22}H_{30}Cl_2N_{10}$ (505.46): calcd. C 52.28, H 5.98, N 27.72; Found C 52.70, H 6.04, N 27.33.

3-*N*′-[4-Chloro-6-(diethylamino)-1,3,5-triazin-2-yl]-1-*N*-[4-(dibenzylamino)-6-(diethylamino)-1,3,5-triazin-2-yl]xylylenediamine, (11): To a solution of 1,3-*N*,*N*′-bis[4-chloro-6-(diethylamino)-1,3,5-triazin-2-yl]xylylenediamine (**6**, 2.0 g, 4 mmol) in THF (50 mL) was added dibenzylamine (1.58 g, 8 mmol) in THF (5 mL) and the mixture heated at reflux for 6 days. The solvent was evaporated under reduced pressure and the residue dissolved in dichloromethane (150 mL) which was washed with water (50 mL), 1 M HCl (2 × 50 mL) and brine (50 mL). The organic layers were combined and dried with $MgSO_4$ and the solvent evaporated under reduced pressure to give the crude product as a brown sticky foam. Column chromatography (*n*-hexane/ethyl acetate, 3:1 on silica) yielded the product **7** as a white solid (1.7 g, 64%). ^{1}H NMR ($CDCl_3$): δ = 7.34–7.18 (m, 24 H), 6.29 (s, 2 H, NH), 4.78 (s, 4 H), 4.60 (s, 2 H), 4.58 (s, 2 H), 3.59 (m, 8 H), 1.15 (m, 12 H) ppm. ES-MS: *m*/*z* = 666 [M^+].

4-(Butylamino)-2-chloro-6-(dibenzylamino)-1,3,5-triazine: To a solution of cyanuric chloride (9.2 g, 50 mmol) and DIPEA (12 mL) in

THF (150 mL) at 0 °C, was added butylamine (3.65 g, 50 mmol) in THF (10 mL) dropwise. The resulting slurry was stirred at 0 °C for 2 h. The reaction mixture was warmed to room temperature and dibenzylamine (9.86 g, 50 mmol) in THF (10 mL) was added dropwise. The reaction was stirred at room temperature for ca. 20 h. The solvent was evaporated under reduced pressure and the residue dissolved in dichloromethane (150 mL). The solution was washed with water (50 mL), 1 M HCl (2×50 mL) and brine (50 mL) and the organic layer dried with $MgSO_4$. The solvent was removed and the residue recrystallised from hot ethanol to give **1** as a white solid (14.0 g, 73%). ^{1}H NMR ($CDCl_3$): δ = 7.35–7.18 (m, 10 H), 5.95 (t, 1 H, NH), 4.79 (s, 2 H), 4.75 (s, 2 H), 3.34 (m, 2 H), 1.51 (m, 2 H), 1.30 (m, 2 H), 0.85 (t, 3 H) ppm. ^{13}C NMR [$CDCl_3$]; δ = 168.9, 165.8, 165.6, 137.2, 137.1, 128.5, 128.1, 127.7, 127.5, 127.4, 127.3, 48.7, 48.5, 40.7, 31.4, 19.9, 13.7 ppm. ES-MS: *m*/*z* = 382 [M + H$^+$]. $C_{21}H_{24}ClN_5$ (381.90): calcd. C 66.04, H 6.33, N 18.34; found C 65.78, H 6.37, N 18.51.

NMR Titrations: All titrants were thoroughly dried under vacuum. Deuterated chloroform was dried with molecular sieves and run through alumina prior to use. A series of NMR samples were prepared with varying pocket/barbital ratios such that the total concentration of pocket and barbital remained constant.[16] ^{1}H NMR experiments were carried out at 298 K and the barbital NH peaks followed. Eleven sample solutions of the titrant samples were prepared maintaining constant concentration of 5.0 mmol dm^{-3} but varying the respective concentrations of host and guest by 0.5 mmol dm^{-3} from sample to sample. EQNMR[18] was used to calculate binding constants and binding energies. In the case of **3**–barbital small variations in the overall shape of the Job plot were observed. Multiple measurements were made for this compound to assess the shape of the Job plot, but consistent results were found and attributed to small experimental errors. The Job plot was generated from ^{1}H NMR shifts averaged from experimental measurements on three different samples for each point.

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