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Steric hindrance to the solvation of melamines and consequences for non-covalent synthesis†

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Steric hindrance to solvation disfavors structures like 1 *syn–anti* in which the melamine exposes to the solvent faces, such as *t*Bu–H, for whom binding to the ring nitrogen is hindered but not blocked; steric hindrance to solvation lowers the barriers to rotation in solvents which bind the triazine nitrogens, therefore these solvents display the fastest rates for assembling/disassembling processes.

The assembling of three melamine units and three cyanuric (or barbituric) acid units into a rosette has been used widely in non-covalent synthesis to connect two modules through 18 hydrogen bonds.[1] The pioneering work of Whitesides *et al.* identified peripheral crowding as one of the factors favoring the rosettes over the competing motifs, linear or crinkled tapes.[2] On the other hand, simulations of the assembly process, performed in Timmerman's group, showed that steric effects are much less important in determining the rosette concentration than other factors affecting the stability of the rosette.[3] We will show here that *steric hindrance to solvation* could destabilize the rosette in solvents like chloroform unless bulky substituents on melamine completely block the triazine nitrogen.

The stability of the melamine–imide complexes has been known to depend critically on the solvent; Whitesides *et al.* have even suggested that these complexes could be used as probes of solvent–solute interactions.[2] Reinhoudt's group reported that solvation affects the stability of the calix[4]arene double rosettes[4] and that it destabilizes specific isomers.[5] Wurthner *et al.* have shown that the constants for the association of melamines with imides depend on specific solvent–solute interactions, which are more important than the solvent polarity alone.[6]

Variable temperature proton spectra of three melamines (*N*,*N*-dimethylamino-bis(N-*tert*-butylamino)-*s*-triazine (**1**), tris(*N*-*tert*-butylamino)-*s*-triazine (**2**) and tris(*N*-methylamino)-*s*-triazine (**3**)) were recorded in four deuterated solvents (chloroform, methylene chloride, dimethylformamide and acetone). In all solvents, at low temperature melamine **1** displayed four non-equivalent sites corresponding to three conformers while melamines **2** and **3** displayed four non-equivalent sites corresponding to two conformers (Fig. 1). These conformers arise from the restricted rotation about the amino–triazine bond.[7] Deviation from the statistical distribution (which requires signals of equal intensity for the isochronous sites in all of these spectra) allowed the identification of the signals for the asymmetric and propeller conformers for melamines **2** and **3** and for the *syn–anti* conformer of melamine **1**. The assignment of the signals for the *syn–syn* and the *anti–anti* conformers of melamine **1** was based on the NOEs observed in the ROESY spectrum. To our surprise, in $CDCl_3$ at −60 °C, the conformational equilibrium was dominated by what intuitively would be the most sterically hindered conformers, namely the *anti–anti* conformer of **1** and the asymmetric conformer of **2**. The equilibrium constants given in Table 1 are corrected for symmetry, that is they would equal unity for a statistical distribution of isomers. The effect of self-association of melamines was eliminated by extrapolation of the equilibrium constants measured at concentrations 15–0.5 mM to concentration 0, as described in the ESI.†

One would expect negligible reaction entropies for the conformational exchange in the gas phase, thus negative entropies (and negative enthalpies) indicate that the product is more solvated than the starting material. In the range of temperature from −40 to 0 °C, the entropic cost of solvation is

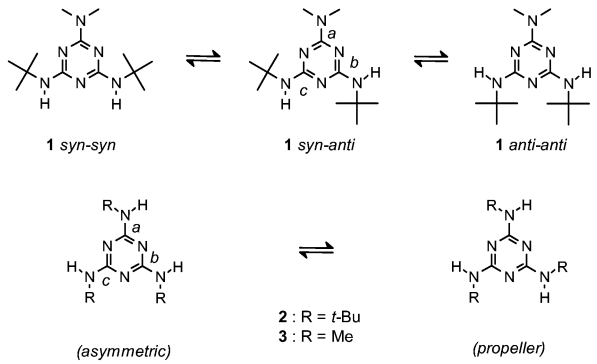

Fig. 1 Conformers of melamines **1**–**3**.

Table 1 Thermodynamic parameters for the conformational equilibria of melamines **1**–**3** as a function of the solvent

Reaction		Solvent			
		$CDCl_3$	CD_2Cl_2	Acetone-d_6	DMF-d_6
(*i*) **1** *syn–anti* ⇌ **1** *syn–syn*	ΔH^a	0.74	0.44	0.63	0.43
	ΔS^b	5.38	2.92	2.75	1.93
	K^c	2.99	1.74	1.04	1.10
(*ii*) **1** *syn–anti* ⇌ **1** *anti–anti*	ΔH	−0.84	−0.47	0.10	0.37
	ΔS	−1.62	−1.46	−0.13	1.04
	K	2.75	1.35	0.74	0.76
(*iii*) **2** asymmetric ⇌ **2** propeller	ΔH	2.51	1.44	−0.57	−0.40
	ΔS	6.94	4.93	-1.93	−1.37
	K	0.13	0.50	1.18	1.13
(*vi*) **3** asymmetric ⇌ **3** propeller	ΔH	−0.55	−0.38	−0.54	−0.52
	ΔS	−1.04	−0.62	−0.99	−0.96
	K	1.98	1.62	1.90	1.90

[a] Enthalpy of reaction in kcal mol^{-1}; standard errors are given the ESI,† a typical value being 0.05 kcal mol^{-1}. [b] Entropy of reaction in cal mol^{-1} K^{-1}, corrected for symmetry (does not include the entropy of symmetry); standard errors are given in the ESI, a typical value being 0.2 cal mol^{-1} K^{-1}. [c] Equilibrium constant measured at 232.1 K, corrected for symmetry, *i.e.* K = 2[*syn–syn*]/[*syn–anti*], K = 3[propeller]/[asymmetric].

† Electronic supplementary information (ESI) available: relevant properties of the solvents, preparation of melamines **1**–**3**, identification of the conformers, variable temperature proton spectra, measurement of the equilibrium constants and of the barriers to rotation. See http://www.rsc.org/suppdata/cc/b2/b206811g/

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comparable to the enthalpic gain, and their balance determines the position of the equilibrium with the more solvated conformers being favored at lower temperatures.

Data in Table 1 display a significant difference between the hydrogen bond donor solvents as $CDCl_3$ and CD_2Cl_2 and the hydrogen bond acceptor ones, such as acetone-d_6 and DMF-d_6, particularly in the case of melamine **2**. Relevant properties of the protonated solvents are given in Table 2S of ESI.†

The polarity of the solvent is not the dominant factor: the more polar *syn–syn* conformer of **1** is more favored in chloroform than in the more polar methylene chloride. Specific interactions of these solvents with melamines might include weak coordination between the ring nitrogen and the chlorine of the solvent, and/or hydrogen bonding. Carbon tetrachloride is known to interact with pyridine derivatives, and the difference in heat of transfer from hexane to CCL_4 between pyridine (-1.71 kcal mol^{-1}) and γ-collidine (-1.27 kcal mol^{-1}) represents the steric interaction with the solvent.[8] Of the three potential hydrogen bond acceptor sites in melamines: the ring nitrogen, the amine nitrogen and the π electron cloud, the former has the higher hydrogen bond basicity, as revealed by a comparison of the $\Sigma\beta^H_2$ values for pyrimidine (0.52), aniline (0.41) and benzene (0.14).[9] The conformational preferences of melamines in hydrogen bond donor solvents can be explained by *steric hindrance to solvation* imposed by the substituents on the same face with the ring nitrogen. The concept of steric hindrance of solvation reflects not an enthalpic process, but an ergonic one.[10] In some cases the process is entirely entropic (*e.g.* 2,6-di-*tert*-butylpyridine is a weaker base than the 2,4-isomer because hydration of the conjugated acid restricts the rotation of the *tert*-butyl groups[11]), in other cases the enthalpic term dominates.[12]

Writing the four reactions in Table 1 in terms of faces exposed to solvation,

(*i*) H–Me + *t*Bu–H → H–H + *t*Bu–Me
(*ii*) *t*Bu–Me + *t*Bu–H → Me–H + *t*Bu–*t*Bu
(*iii*) 2 *t*Bu–H → H–H + *t*Bu–*t*Bu
(*iv*) 2 Me–H → H–H + Me–Me

it becomes apparent that the disfavored sides of the reactions (reactants for *i–iii* and products for *iv*) all have a face for which solvation is hindered but not blocked, like *t*Bu–H or Me–Me. Restriction of the motion of the solvent upon binding to such a face makes the entropic price of solvation higher than the enthalpic gain.

In hydrogen bond acceptor solvents, the NH group of melamines acts as a hydrogen bond donor (for amides $\Sigma\alpha^H_2$ = 0.50[9]). In this case, hydrogen binding to the solvent is not significantly hampered by the substituents on melamine, the NH being on an 'outer' position. For melamine **1**, dipole–dipole interactions with acetone and DMF favor the *syn–syn* conformer (the most polar) and disfavor the *anti–anti* one.

Table 2 Barriers to rotation at 232.1 K ($\Delta G^{\neq}$ in kcal mol^{-1}) in melamines **1** and **2** as a function of the solvent

	Solvent			
Rotation about	$CDCl_3$	CD_2Cl_2	Acetone-d_6	DMF-d_6
Bond ***a*** in **1**[a]	12.66	13.17	13.63	14.15
Bond ***b*** in **1**	12.30	13.21	14.11	14.22
Bond ***c*** in **1**	13.87	14.27	14.97	14.91
Bond ***a*** in **2**	12.06	13.08	13.57	14.15
Bond ***b*** in **2**	—[b]	13.87	13.89	14.14
Bond ***c*** in **2**	13.76	15.38	14.90	15.89

[a] The bonds are identified in Fig. 1. [b] This barrier could not be reliably measured because in $CDCl_3$ the concentration of the propeller conformer was too small.

Barriers to rotation about the three non-equivalent bonds in the *syn–anti* conformer of **1** and the asymmetric conformer of **2** were determined by lineshape simulation in the temperature range of -50 to 0 °C, and are reported in Table 2. Barriers in chloroform are consistently lower than in any other solvents, indicative of a more favorable difference between the solvation of the transition state and the solvation of the ground state. As one of the alkylamino groups rotates out of plane in the transition state, the adjacent triazine nitrogens become more exposed to the hydrogen bond donor solvent. Of the three transition states corresponding to rotations about bonds ***a–c***, transition state ***a*** displays the lowest steric hindrance to solvation, while transition state ***c*** displays the highest, and indeed both melamines **1** and **2** present the lowest barrier for the rotation about bond ***a*** and the highest for rotation about bond ***c***. Lower barriers to rotation explain why a mixture of assemblies composed of three calix[4]arene dimelamines and six barbiturates/cyanurates equilibrates in seconds at -50 °C in $CDCl_3$ and in hours in toluene at 25 °C.[13]

In conclusion, we have demonstrated that steric hindrance to solvation disfavors structures in which melamines expose to the hydrogen bond donor solvent a face for which solvation is hindered but not blocked. Steric hindrance to solvation can explain why the stability of the rosettes decreases as the size of the substituents on the melamines and isocyanurates is reduced.[14]

Steric hindrance to solvation also lowers the barriers to rotation in hydrogen bond donor solvents, which therefore display the fastest rates for assembling/disassembling processes. Because these rates set a limit to the size of the regular networks that can be grown by non-covalent synthesis,[15] hydrogen bond donor solvents may be used instead of assembling catalysts when large regular networks, suitable for nanodevices, are desired.

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