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Synthesis, structural determination and dynamic behavior of 2-chloro-4,6-bis(pyrazolylamino)-1,3,5-triazines †

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A series of 2-chloro-4,6-bis(pyrazolylamino)-1,3,5-triazines with applications in crystal engineering have been prepared. At low temperature, the presence of two or three isomers has been detected and these assigned to 4,6-diamino-1,3,5-triazine structures on the basis of comparison with model compounds. 2D-Exchange spectroscopy studies in various solvents and at different temperatures have been used to determine the equilibrium constants and the activation free energies of the restricted rotation about the amino–triazine bond. A plot of the activation free energy *versus* temperature showed a good linear correlation and confirmed that the same process is present in all of the compounds under investigation. Comparison with model compounds also confirmed both the occurrence of the restricted rotation and the 4,6-diamino-1,3,5-triazine tautomerism for triazines **1**–**4** in solution. The structure of compound **1** has been determined in the solid state by X-ray crystallography and consists of a 4,6-diamino-1,3,5-triazine structure stabilized by intra and intermolecular hydrogen bonds.

Introduction

Control of structures using supramolecular interactions is an area of great interest in chemistry and biochemistry as well as in crystal engineering.[1,2] Heterocyclic derivatives of 1,3,5-triazine, particularly tris-pyridyltriazines, are polydentate compounds useful for the preparation of complexes and have often been used as C_3-symmetry ligands[3,4] and for molecular encapsulation.[5] However, analogs derived from azolyltriazines have been much less studied probably because their synthesis is less straightforward. Tris-azolyl-1,3,5-triazines can be prepared by cyclotrimerization of aromatic nitriles under acidic or basic conditions,[6] for instance, we have recently described the synthesis of tris-pyrazolyltriazines from nitriles in the absence of solvent.[7]

The triazines here described and other related aminotriazines can be used for the preparation organometallic complexes, these studies being still in course. A second option involves the formation of supramolecular structures using hydrogen bonds.[8–11] The importance of these secondary interactions has also been thoroughly studied.[12] For instance, the interaction between cyanuric acid and melamine[13] is well documented and its stability has been used to obtain polymers in the solid state. Modification of the system formed by cyanuric acid and/or melamine has allowed the synthesis of linear polymers,[14] the non-covalent synthesis of nanostructures,[15] as well as diastereoselective and enantioselective non-covalent synthesis.[16]

Crystal engineering and supramolecular synthetic methodology requires the knowledge of the strength and directional characteristics of the intermolecular forces. The objective in this field should be that, given the molecular structure of a particular substance, it should be possible to predict the crystal structure of the material.[2] Therefore, it is of great importance to determine the molecular structure of these compounds both in solution and in the solid state.

We planned the synthesis of several melamine and cyanuric acid analogs, modified by attachment to azoles, in order to change the nature of the intermolecular bonds and to allow interactions with other substrates. It is well known that reaction of amines with cyanuric chloride leads to the corresponding substitution products. In this paper we describe the synthesis of 2-chloro-4,6-bis(pyrazol-1-ylphenylamino)-1,3,5-triazines **1**–**3** and 2-chloro-4,6-bis(phenylpyrazol-4-ylamino)-1,3,5-triazine **4** by reaction of cyanuric chloride with the corresponding amines (Scheme 1). The structures of these compounds were determined in solution by variable-temperature NMR in various solvents. In the case of 2-chloro-4,6-bis(2-pyrazol-1-ylphenylamino)-1,3,5-triazine (**1**), the structure was compared with the mono- and trisubstituted compounds 2,4-dichloro-6-(2-pyrazol-1-ylphenylamino)-1,3,5-triazine (**6**) and 2,4,6-tris(2-pyrazol-1-ylphenylamino)-1,3,5-triazine (**5**) (Scheme 1) as well as with its structure in the solid state.

Results and discussion

Synthesis of 1–4

Disubstituted derivatives **1**–**4** were prepared by reaction of cyanuric chloride with the corresponding amine in THF using diisopropylethylamine as the base. Preparation of trisubstituted derivatives usually required stronger reaction conditions, *i.e.* higher temperatures for long reaction times, specially with sterically hindered amines. However using microwave irradiation in solvent-free conditions a mixture of compounds **5** and **6** was obtained in only 10 min. Selective preparation of **5** was achieved in higher yield with a longer irradiation time.

† Electronic supplementary information (ESI) available: Tables S-1 to S-4 containing the NMR data of compounds **1**–**8**. See http://www.rsc.org/suppdata/ob/b3/b310693d/

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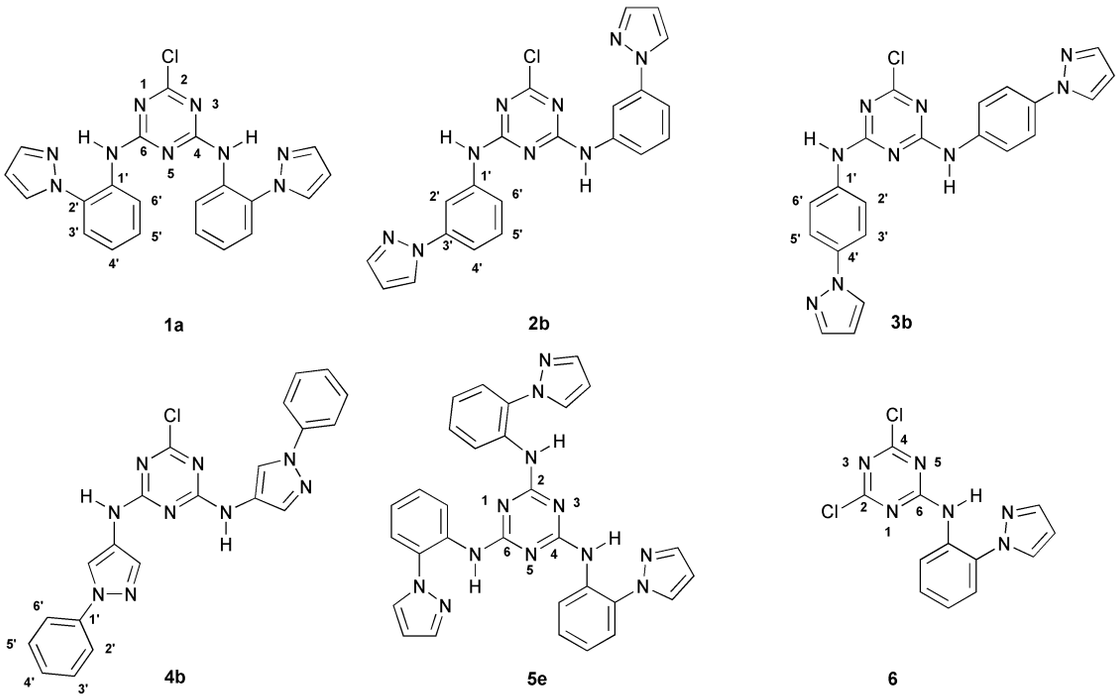


Scheme 1 Structure of the most abundant isomer (^{1}H-NMR) of compounds **1**–**6**.

Reactions were performed in a focused microwave reactor with full control of the incident power and reaction temperature.

Structure determination

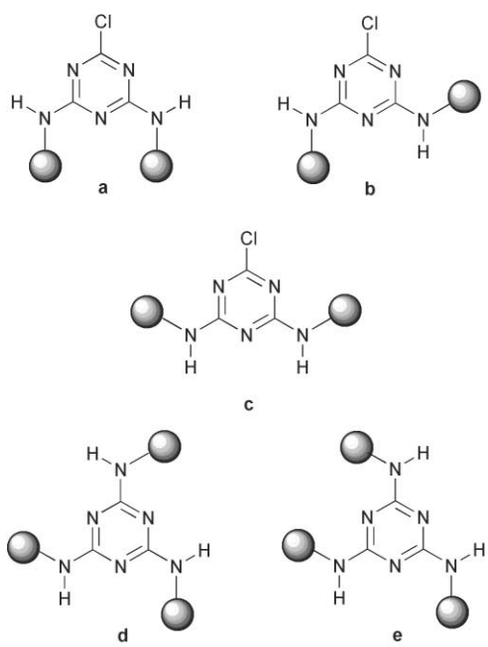
Compounds **1**–**4** may exist in amino and imino forms and these may exhibit three dynamic processes: i) tautomerism between amino and imino triazines and, besides, ii) the imino tautomers, stabilized by conjugation with the aromatic substituents, could undergo *E*–*Z* isomerism and iii) the amino tautomers could present conformational isomerism due to restricted rotation about the amino triazine bond. This situation means that up to nineteen possible isomers can be expected as a combination of these three processes. Moreover, a restricted rotation about the amino phenyl and amino pyrazole ring could also be considered.

An *a priori* exclusion of some tautomers is not evident. Simple considerations based on the aromaticity of the triamino derivatives (which is lost in the imino tautomers) are counterbalanced by the empirical knowledge that when several functional groups are present on the same heterocyclic ring, at least, one of them is often in the oxo-, thioxo- or imino-form.[17] Moreover, molecular mechanics calculations did not confirm conclusively the preference of the amino- or imino-form.

However, studies involving NMR structure determination and comparison with model compounds indicated that the compounds under study existed preferentially in an all-amino tautomeric form. The definitive proof was the X-ray structural determination of compound **1**. Compounds **1**–**4** can exist in three different conformations, **a**–**c**, while compound **5**, due to its higher symmetry, presents only two conformations, **d** and **e** (Scheme 2). Assignment of the NMR signals to the isomers was performed with the help of molecular mechanics calculations. Finally, the free energy of activation of the restricted rotation was determined by 2D EXSY NMR studies.

NMR Structure determination

The NMR spectra of **1** at 293 K showed the presence of a unique compound, although broad signals were observed for the NH, H-5′ and H-6′ protons (Fig. 1 and Tables S-1 and S-2†). The NMR spectra were recorded in $CDCl_3$, DMSO-d_6 and DMF-d_6 solutions, as some of the proposed kinetic processes



Scheme 2 Possible rotamers of the all-amino structures of compounds **1**–**5**.

and tautomeric equilibria are very dependent on the polarity of the solvent. At 213 K the signals were split and, in particular, four signals were observed for the NH and H-6′ protons (Fig. 1 and Tables S-3 and S-4†). One signal of high intensity, two similar signals of medium intensity and one signal of low intensity were observed. This pattern could be assigned to three isomeric compounds, two symmetrical isomers, denoted as **a** and **c** (the major and the minor isomers), and one asymmetrical isomer, denoted as isomer **b** (Fig. 1 and Tables S-3 and S-4). A similar behavior was observed in the ^{13}C-NMR spectra.

Here evidence is presented that the three isomers present are aminotriazine rotamers exhibiting restricted C–N rotation (Scheme 2). The symmetry of the phenyl ^{13}C-NMR spectra of **1** and **3** suggested that rotation of the amino phenyl bond is fast even at 213 K.

The NMR spectra of **2** at 293 K in DMSO and DMF

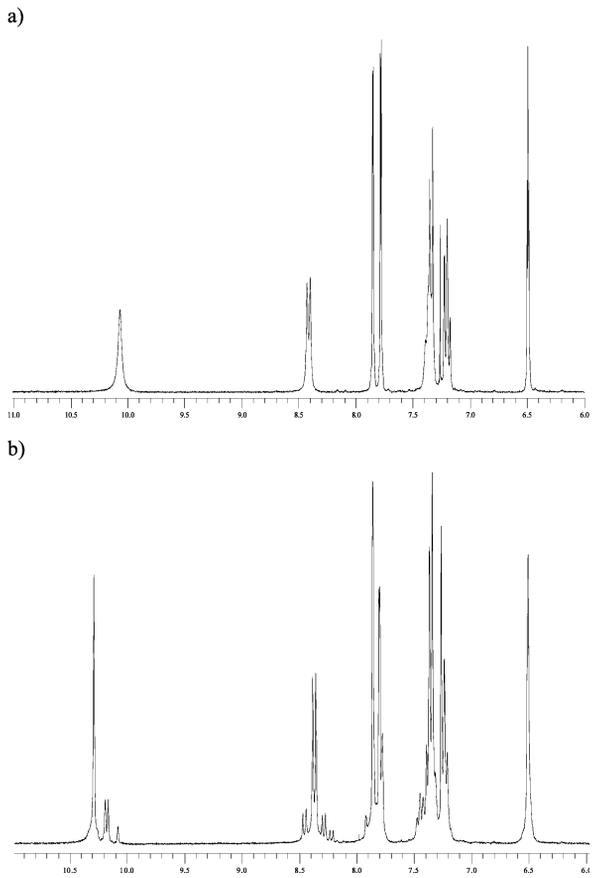


Fig. 1 NMR spectra of compound **1** in $CDCl_3$ solution. a) 293 K. b) 213 K.

Table 1 Ratio of isomers determined by ^{1}H-NMR spectroscopy

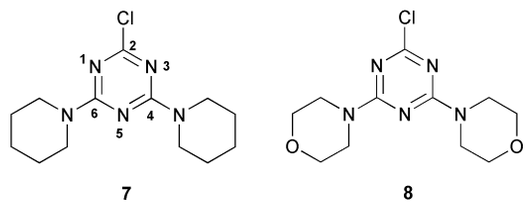
Comp.	Solvent	Temp. (K)	Isomer **a**	Isomer **b**	Isomer **c**
1	DMF	213	59.5	33.6	6.9
1	$CDCl_3$	213	72.6	22.6	4.8
2	DMF	213	36.0	55.7	8.3
3	DMF	213	45.5	54.5	0
4	DMSO	298	47.1	62.9	0
4	DMF	298	35.7	64.3	0
			Isomer **d**	Isomer **e**	
5	DMF	213	40.7	59.3	
5	$CDCl_3$	203	46.4	53.4	

solutions showed broad signals that coalesce to give signals for a single compound at 333 K in DMSO and at 363 K in DMF (Tables S-1 and S-2). Similarly, at 223 K (DMF) three isomeric compounds could be detected, two symmetrical isomers (assigned to isomers **a** and **c**) and one asymmetrical isomer (assigned to isomer **b**) (Table S-4).

The NMR spectrum of **3** at 293 K in DMSO showed a single compound, whereas in DMF broad signals were observed. However, at 333 K a single compound was found in DMF (Tables S-1 and S-2). At 213 K in DMF solution two isomeric compounds were detected—a symmetrical isomer (assigned to isomer **a**) and an asymmetrical one (assigned to isomer **b**) (Tables S-3 and S-4).

Finally, the NMR spectra of **4** at 298 K in DMSO and DMF solutions again showed the presence of two isomeric compounds—one symmetrical (assigned to isomer **a**) and the other asymmetrical (assigned to isomer **b**) (Tables S-3 and S-4). On heating the sample to 403 K the signals coalesced to show the presence of one single isomer in DMSO and DMF (Tables S-1 and S-2). Table 1 shows the ratio of isomers determined by ^{1}H-NMR spectroscopy.

Assignment of the NMR spectra to the all-amino structures was performed by considering in addition to the NMR spectra of **1**–**4** those of compounds **5**, **6**, **7** and **8** as model systems (Scheme 3).



Scheme 3 Structure of compounds **7** and **8**.

Compounds **5** and **6** can also exist as a mixture of different tautomers and isomers. In compound **5** up to twenty-one isomers are possible, while for compound **6** up to four isomers are possible. Again, if one excludes amino/imino tautomerism, the problem is greatly simplified. The NMR spectra of compound **5** at 293 K in $CDCl_3$, DMSO and DMF solutions contained broad signals for the NH and H-6′ protons in a similar way to compound **1** (Tables S-1 and S-2). At 213 K in DMF and 203 K in $CDCl_3$ the signals split (Table S-4), with three NH and H-4 pyrazole protons clearly observed. These were assigned to two isomers a symmetrical one (**5d**) and an asymmetrical one (**5e**) (Scheme 2).

The NMR spectrum of compound **6** at 293 K in $CDCl_3$ showed the presence of a single compound with sharp signals and chemical shifts that are very similar to those found for **1** and **5** (Tables S-1 and S-2). This spectrum did not change when the temperature was decreased to 213 K. This result was again in agreement with an amino structure.

The main differences between the amino and imino structures concern the N–H groups at C-4 and C-6. Compounds **1**–**4** showed only one NH group for the symmetrical isomers **a** and **c**, this result is in favor of the amino structures as two different NH groups are expected for the all-imino structures, although a rapid tautomerism could make them equivalents. These amino and imino structures are still very close and in both cases the N–H group participates in hydrogen bonding since the triazine C-4 and C-6 sites are guanidinium-like carbons. Compounds **7** and **8** with tertiary amino groups, can exist only in the amino forms, tautomerism being not possible. The ^{13}C- and ^{1}H-NMR spectra of these compounds are collected in Tables S-1 and S-2 and significant differences are not observed. In compounds **1**–**4** the triazine carbons resonate at δ_{C-Cl} = 168.05–171.05 and $\delta_{C=N}$ = 163.44–165.16, whereas in **7** and **8** the values are δ_{C-Cl} = 169.45–169.67 and $\delta_{C=N}$ = 164.10–164.45. These results are again in favor of the all-amino structure and of a restricted rotation of the amine triazine bond.

Assignment of the NMR signals of **1**–**4** to isomers **a**, **b** and **c** was not straightforward due to the similarity of these isomers. It was made by considering: i) the symmetry of isomers **a** and **c**, ii) the intensity of signals in the NMR spectra, iii) the relation of this intensity with the stability deduced by molecular mechanics calculations using the MMX force field[18] and iv) the recently described steric hindrance to rotation, and the relation with the stability, described for related compounds.[19] NOE experiments did not give any conclusive result especially in symmetric isomers. Isomers **a** and **c** are symmetric and should give a single signal for each substituent and for the NH group, while isomer **b** is asymmetric and should give two signals of equal intensity for each substituent and for the NH group. In this way isomer **b** was easily assigned in all cases. The same approximation was used for the assignment of the NMR spectra of **5d** and **5e**; isomer **5d** is symmetric and should give a single signal while **5e** is asymmetric and should give two signals in a 2 : 1 ratio. The symmetric isomers were differentiated on the basis of the intensity of the signals and their relation to the theoretical stability determined by molecular mechanics calculations. Isomer **a** is always more stable than isomer **c** and

the resonances of the former compound were assigned to the higher intensity signals. Fig. 2 shows the optimized structure of isomer **4a** where a π–π interaction between the aromatic rings of the substituents must stabilize the structure.[20]

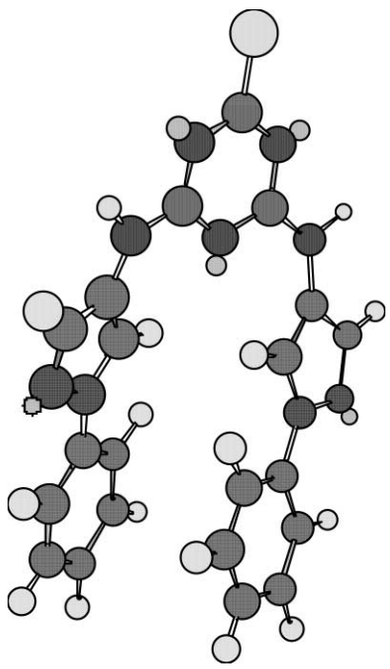


Fig. 2 Chem3D representation of the optimised structure of isomer **4a**.

X-Ray structure determination of compound 1

The definitive assignment of the structures of compounds **1**–**5** to all-amino tautomers was performed by X-ray structure determination of compound **1**. In the solid state compound **1** corresponds to the diaminotriazine tautomer **1a** and in this state it does not possess internal symmetry, as illustrated in Fig. 3. Phenyl substituent **A** is more coplanar with the triazine ring than phenyl **B** and both rings present a *cis* conformation with respect to the triazine N3 atom. The molecular structure shows that the three connected atoms to N18A and N18B are

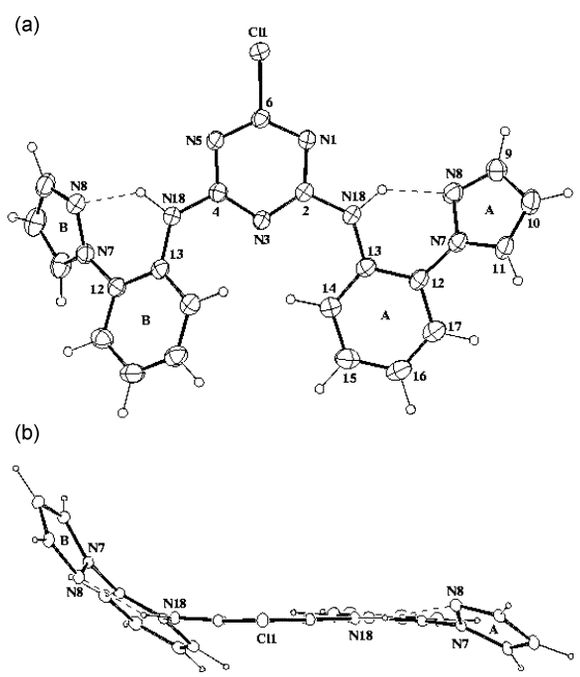


Fig. 3 Molecular structure of compound **1** showing the numbering system, the intramolecular hydrogen interactions and the conformation of the molecule.

planar (Fig. 3), as confirmed by the unambiguous location of the atoms H18A,B and by the pattern of bond distances and angles around them, which are similar to those found in seventeen substituted 1,3,5-triazine 2-*ortho*-, *meta*- or *para*-R-phenylamino compounds (26 fragments) retrieved from the Cambridge Crystallographic Database[21] (April 2002 release). The average values along with the standard deviation of the sample are: N–C(triazine) = 1.353(14), N–C(phenyl) = 1.419(11) Å, CNC = 127.9(36)°. The large dispersion of the CNC angle is due to the correlation ($\rho = -0.869$) between this angle and the twist of the phenyl ring—the greater the torsion angle the smaller the bond angle [Fig. 4, $\tau = -0.869$, CNC-(calc.) = 131.8(6)–0.123(14) τ where τ = minimum (|C2–N18–C13–C12|, |C2–N18–C13–C14|) torsion angles according to the numbering scheme in Fig. 3]. Both amino N18–H groups act as hydrogen-bond donors to the pyrazole N8 atoms and that to the **A** group presents the shorter intramolecular interaction in terms of the N ··· N distance (Table 2). The supramolecular structure consists of ribbons formed by molecules linked by C_{phenyl}–H ··· Cl–C interactions which could be considered strong when compared with the recently tabulated values for Ow–H ··· Cl–C interaction.[22]

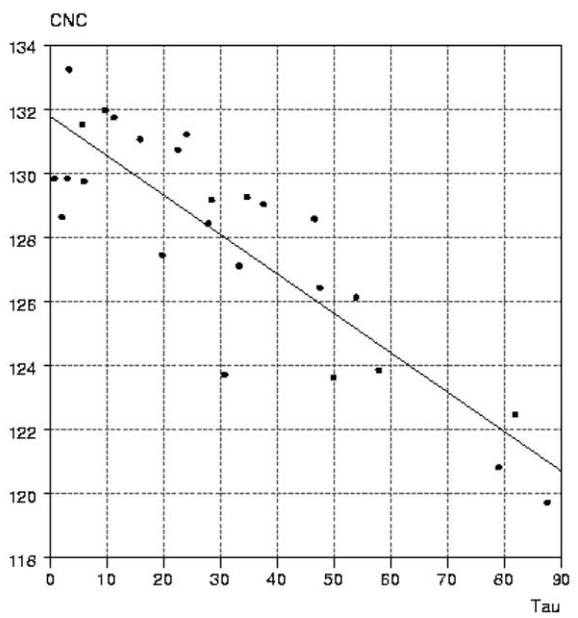


Fig. 4 Scatterplot of C2–N18–C13 angle *versus* τ, where τ = minimum (|C2–N18–C13–C12|, |C2–N18–C13–C14|) torsion angle for the seventeen substituted 1,3,5-triazine 2-*ortho*-, *meta*- or *para*-R-phenylamino compounds (26 fragments) retrieved from the Cambridge Crystallographic Database. CNC = 131.8(6)–0.123(14) τ.

Dynamic NMR studies of compounds 1–6

Using dynamic NMR spectroscopy (DNMR) we studied the restricted rotation of these triazines (Scheme 1). The most commonly used techniques for the evaluation of reaction rates are line-shape analysis and magnetization transfer.[23] However, the application of both methods becomes increasingly difficult when the number of possible lines increases or the chemical shift separation decreases.[24]

Multisite systems that are not amenable to study by conventional methods can be studied by 2D exchange spectroscopy (2D EXSY). Another recent method consists in the application of diffusion ordered spectroscopy (DOSY).[25] 2D exchange spectroscopy involves separating each single process in the 2D map, meaning that interferences between processes are avoided.[26] 2D EXSY has been applied to the resolution of numerous complex kinetic processes in areas including organometallic chemistry, metallotropy, fluxional behavior and conformational studies.[27] A special feature of 2D EXSY is that

Table 2 Selected intra and intermolecular parameters (distances in Å, angles in °) from the X-ray diffraction data

C2–N18A	1.367(3)	C4–N18B	1.351(3)
N18A–C13A	1.399(3)	N18B–C13B	1.404(3)
C2–N18A–C13A	131.2(2)	C4–N18B–C13B	129.5(2)
N3–C2–N18A–C13A	−0.2(5)	N3–C4–N18B–C13B	4.2(4)
C2–N18A–C13A–C14A	4.5(5)	C4–N18B–C13B–C14B	33.0(4)
N18A–C13A–C12A–N7A	1.0(4)	N18B–C13B–C12B–N7B	5.4(4)
C13A–C12A–N7A–N8A	−29.9(4)	C13B–C12B–N7B–N8B	−37.9(4)

Hydrogen interactions	D–H	H ⋯ A	D ⋯ A	D–H ⋯ A
N18A–H18A ⋯ N8A	1.02	1.87	2.710(3)	136
N18B–H18B ⋯ N8B	1.02	1.97	2.729(3)	128
C14A–H14A ⋯ N3	1.06	2.19	2.891(4)	121
C14B–H14B ⋯ N3	1.06	2.43	2.948(3)	109
C17B–H17B ⋯ Cl1(−1/2 + x,3/2 − y,−1/2 + z)	1.07	2.78	3.570(3)	131

Table 3 Activation free energies for compounds **1**–**5** determined from 2D EXSY spectra

			$\Delta G^{\ddagger}$ (kJ mol^{-1})				
Comp	Solvent	Temp. (K)	Process **a** ⇌ **b**	Process **b** ⇌ **c**	Process **a** ⇌ **c**	Process **b** ⇌ **b**	Mean value
1[a]	$CDCl_3$	213	58.76	57.73	57.57	55.73	57.79
2	DMF	223	60.11	57.13	63.11	61.11	59.49
3	DMF	253	62.30			70.30	64.96
4	DMSO	298	76.14			75.19	75.82
4	DMF	298	75.24			74.16	74.88
			Process **d** ⇌ **e**			Process **d** ⇌ **e**	
5[b]	$CDCl_3$	203	49.07			51.96	50.03

[a] Mean value. [b] Experiments in DMF at 213 K did not give reproducible results.

the kinetic constant for each independent process rather than the activation free energy is deduced from the data in the NMR spectra. More recently, 1D EXSY techniques have also been introduced.[28]

The essential feature of a quantitative 2D EXSY experiment is the relationship between the intensity of a cross-peak and the rate constants for chemical exchange. Cross-peaks in the spectrum correspond to nuclei that exchange from one site to another. The intensities of those cross-peaks do not correspond directly to the exchange matrix but to its exponential form.[25]

We performed 2D EXSY experiments on compounds **1**–**5**. In all cases a 1 s mixing time was found to be optimum. A second experiment with a 0.02 s mixing time was performed in order to obtain the pure diagonal peaks without exchange cross-peaks. Experiments were performed at the temperature of the slow process, as indicated in Table S-4. Experiments at low temperature were performed in DMF and $CDCl_3$ and at 298 K in DMF and DMSO for compound **4**. Rate constants can be deduced from the spectra according to the following equation:

$$R = -\ln A/\tau_m = -X(\ln \Lambda)X^{-1}/\tau_m$$

where $A_{ij} = I_{ij}/M_j$, τ_m is the mixing time. $I_{ij}(\tau_m)/M_j$ and X are the square matrix of eigenvectors of A_i such that $X^{-1}AX = \Lambda = \text{diag}(\lambda_i)$, with λ_i the i^{th} eigenvalue of A. I_{ij} can be deduced by measuring the volume of each peak intensity directly from the spectrum. M_j is the volume of the diagonal peak of the spectrum registered with a mixing time close to 0 and without any chemical exchange.

An essential feature of the process is that

$$k_{ij}p_i = k_{ji}p_j$$

where k_{ij} and k_{ji} are the rate constants of processes $i \longrightarrow j$ and $j \longrightarrow i$, respectively, and p_i is the relative population of the i^{th} site.

Activation free energies for compounds **1**–**5** were calculated (Table 3) from the rate constants according to Sandström.[23]

Although the calculated activation free energies were in a wide range (50–76 kJ mol^{-1}), they were determined in a wide range of temperatures (203–298 K) and representation of $\Delta G^{\ddagger}$ *versus* temperature showed a linear plot with a good correlation constant, $R^2 = 0.96$ (Fig. 5).

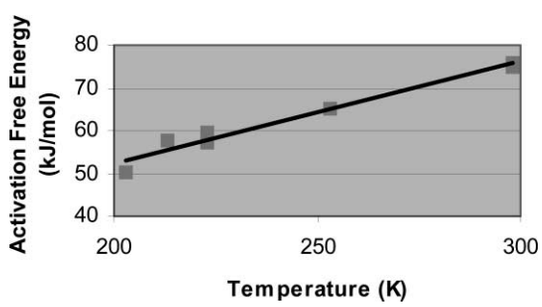


Fig. 5 Linear plot of the calculated activation free energy (mean value) *vs.* temperature for compounds **1**–**5** as indicated in Table 3.

This linear plot permitted the calculation of $\Delta H^{\ddagger} = 5.3519$ kJ mol^{-1} and $\Delta S^{\ddagger} = -0.2358$ kJ mol^{-1} K^{-1}. The $\Delta G^{\ddagger}$ value was similar to those measured for *N*-arylguanidines.[29]

Conclusions

The structures of 2-chloro-4,6-bis(pyrazolylamino)-1,3,5-triazines were determined in solution by NMR spectroscopy and confirmed in the solid state by X-ray diffraction. In solution an "all-amino" structure was deduced from the NMR spectra. In the solid state also an "all-amino" structure was found for compound **1**.

Isomers resulting from the restricted rotation about the amino triazine bond were detected and identified in solution and at low temperatures. Comparison with diamino triazines **7** and **8** confirmed the "all-amino" structures in solution. The more crowded isomer **a** was predominant over the less crowded isomer **c**, which was only detected in compounds **1** and **2**. This effect was confirmed by molecular mechanics calculations and it was attributed, in related compounds, to steric hindrance to solvation.[19] The restricted rotation was studied by 2D EXSY spectroscopy. A plot of the calculated activation free energies

versus temperature showed a good correlation coefficient, indicating that a unique and similar process occurred in all the present triazines. An excellent correlation with previously reported values was observed, specially in polar solvents (DMF),[19] however the dependence of the calculated free energy of activation with the polarity of the solvent was less pronounced in our triazines.

The "all-amino" structure was confirmed by an X-ray diffraction study of compound **1**. Isomer **1a** was observed, its structure was stabilized by a C_{phenyl}–H ⋯ Cl–C strong hydrogen bond in the solid state.[22]

The present study shows the importance of determining the molecular structure in solution and in the solid state in order to predict the crystal structure of a system and, hence, to gain an insight into possible supramolecular interactions.

Experimental

X-Ray analysis

Crystals of **1** were grown from a solution in hexane/ethyl acetate (1 : 1). For the crystal structure determination, data collection was carried out on a Seifert XRD3000-S diffractometer (Cu-Kα radiation, λ = 1.5418 Å) at room temperature. Crystal data: C_{21} H_{16} Cl_1 N_9, M = 429.88, a = 8.0587(8), b = 11.2534(11), c = 22.104(3) Å, β = 98.529(13)°, V = 1982.4(4) Å^3, $P2_1/n$, Z = 4, μ = 1.956 mm^{-1} (psi-scan absorption correction), 3374 reflections were recorded up to θ = 67.5°, of which 3002 were independent (R_{int} = 0.053). The structure was solved by direct methods (SIR97)[30] and the hydrogen atoms were located in difference Fourier maps and kept fixed[31] during the last cycles of refinement. Full-matrix least-squares methods on F converged to R/R_w = 0.043/0.055 for 2480 observed reflections [$I > 2\sigma(I)$]. ‡

NMR Studies

NMR spectra were recorded on a VARIAN UNITY 300 spectrometer operating at 299.980 MHz for proton spectra. Spectra were recorded at the temperature indicated (±0.1 K) with a probe calibrated with methanol. The standard VARIAN pulse sequence was used (VNMR 6.1B software). Samples were prepared by dissolving the triazine (0.25 mmol) in DMF-d_6, DMSO-d_6 and $CDCl_3$ (0.6 mL) under an argon atmosphere.

The 2D exchange spectra (EXSY) were acquired in the phase-sensitive mode using the States–Haberkorn method.[32] Typically, a 3.1 kHz spectral width, 16 transients of 2048 data points were collected for each 256 t_1 increments. A 1 s relaxation delay, a 21.5 s (90°) pulse width and a 0.165 s acquisition time were used. The free induction decays were processed with square cosine-bell filters in both dimensions and zero filling was applied prior to double Fourier transition.

Determination of the kinetic parameters required two experiments with mixing times of 1 s (optimized) for the exchange experiment and 0.02 s for the non-exchange spectra, respectively. The cross peak/diagonal ratio was determined by integrating the volume under the peaks.

Preparation of triazines

Microwave irradiations were performed in a modified PROLABO Maxidigest MX350 microwave reactor. The temperature was measured with an IR pyrometer and controlled using a computer with PACAM MPX-2 software. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. The IR spectra were obtained with an FT-IR Nicolet-550 spectrophotometer. The mass spectra were recorded on a VG AutoSpec apparatus using electronic impact at 70 eV. Flash column chromatography was performed on silica gel 60 (Merck, 230–400 mesh).

Compounds **7** and **8** were prepared by the general procedure and have been previously described.[33]

General procedure for the synthesis of 2-chloro-4,6-bisamino-1,3,5-triazines[34]

A solution of cyanuric chloride (1.1 g, 5.9 mmol) in THF (10 mL) was stirred under argon at 0 °C. The appropriate amine (12.3 mmol) was added portionwise and then *N*,*N*-diisopropylethylamine (2 mL) was added to the solution. The mixture was stirred at 0 °C for 2 h and at room temperature for 24 h. The solution was filtered and the solvent removed *in vacuo*. Triazines were purified as described below.

2-Chloro-4,6-bis(3-pyrazol-1-ylphenylamino)-1,3,5-triazine (2). From 1-(3-aminophenyl)pyrazole (1.95 g, 12.3 mmol) following the general procedure. The solid was dissolved in CH_2Cl_2 (20 mL) and the solution was washed with 0.1 M hydrochloric acid (3 × 7 mL). The organic solution was neutralized with sodium carbonate and dried with anhydrous magnesium sulfate. The solution was filtered and purified by column chromatography using hexane/ethyl acetate (7 : 3) as the eluent. Yield 1.2 g (47%), mp 138–141 °C. Anal. Calcd. for $C_{21}H_{16}ClN_9$: C, 58.7 H, 3.8 Cl, 8.3 N, 29.3. Found: C, 58.8 H, 4.1 N, 29.5. IR (KBr) ν_{max} 3268, 1579, 1499 cm^{-1}. MS (EI) *m*/*z* 429.3 (M^+).

2-Chloro-4,6-bis(4-pyrazol-1-ylphenylamino)-1,3,5-triazine (3). From 1-(4-aminophenyl)pyrazole (1.95 g, 12.3 mmol) following the general procedure. The crude product was filtered and purified by column chromatography using hexane/ethyl acetate (7 : 3) gradient ethyl acetate as eluent. Yield 2.04 g (79%), mp 223–226 °C. Anal. Calcd. for $C_{21}H_{16}ClN_9$: C, 58.7 H, 3.8 Cl, 8.3 N, 29.3. Found: C, 58.9 H, 3.9 N, 29.6. IR (KBr) ν_{max} 3248, 1579, 1518 cm^{-1}. MS (EI) *m*/*z* 429.1 (M^+).

2-Chloro-4,6-bis(1-phenylpyrazol-4-ylamino)-1,3,5-triazine (4). From 4-amino-1-phenylpyrazole (0.93 g, 5.8 mmol) following the general procedure. The crude product was washed with dichloromethane (3 × 5 mL) and the solid was filtered off to give the pure product. Yield 0.735 g (62%), mp 236–237 °C. Anal. Calcd. for $C_{21}H_{16}ClN_9$: C, 58.7 H, 3.8 Cl, 8.3 N, 29.3. Found: C, 58.6 H, 3.8 N, 29.3. IR (KBr) ν_{max} 3276, 1559, 1523, 1499 cm^{-1}. MS (EI) *m*/*z* 429.2 (M^+).

2-Chloro-4,6-bis(2-pyrazol-1-ylphenylamino)-1,3,5-triazine (1). A solution of cyanuric chloride (1.1 g, 5.9 mmol) and THF (10 mL) under argon was stirred at 0 °C. 1-(2-Aminophenyl)-pyrazole (1.6 g, 10.5 mmol) was added portionwise and *N*,*N*-diisopropylethylamine (2 mL) was then added to the solution. The mixture was stirred at 0 °C for 2 h and then at 65 °C for 24 h. The solution was filtered and the solvent was evaporated. The crude product was purified by column chromatography using hexane/ethyl acetate (9 : 1) gradient hexane/ethyl acetate (1 : 1) as the eluent. Yield 1.08 g (50%), mp 147–148 °C. Anal. Calcd. for $C_{21}H_{16}ClN_9$: C, 58.7 H, 3.8 Cl, 8.3 N, 29.3. Found: C, 58.7 H, 3.8 N, 29.4. IR (KBr) ν_{max} 3253, 1569, 1522, 1507 cm^{-1}. MS (EI) *m*/*z* 429.0 (M^+).

Synthesis of 2,4,6-tris(2-pyrazol-1-ylphenylamino)-1,3,5-triazine (5) and 2,4-dichloro-6-(2-pyrazol-1-ylphenylamino)-1,3,5-triazine (6). A mixture of cyanuric chloride (0.56 g, 3 mmol) and 1-(2-aminophenyl)pyrazole (1.41 g, 9 mmol) was exposed to microwave irradiation (90 W, temperature, 140 °C) for 10 min. The crude mixture was dissolved in dichloromethane and purified by column chromatography using hexane/ethyl acetate (6 : 4) as the eluent to give to give 2,4-

‡ CCDC reference number 197194. See http://www.rsc.org/suppdata/ob/b3/b310693d/ for crystallographic data in .cif or other electronic format.

dichloro-6-(2-pyrazol-1-ylphenylamino)-1,3,5-triazine (0.13 g, 14%) and 2,4,6-tris(2-pyrazol-1-ylphenylamino)-1,3,5-triazine (0.3 g, 18%).

2,4,6-Tris(2-pyrazol-1-ylphenylamino)-1,3,5-triazine (5). Mp 190–191 °C. Anal. Calcd. for $C_{30}H_{24}N_{12}$: C, 64.7 H, 4.4 N, 30.4. Found: C, 64.7 H, 4.4 N, 30.1. IR (KBr) ν_{max} 3386, 1597, 1450, 1416 cm^{-1}. MS (EI) *m/z* 552.3 (M^+).

2,4-Dichloro-6-(2-pyrazol-1-ylphenylamino)-1,3,5-triazine (6). Mp 170–171 °C. Anal. Calcd. for $C_{12}H_8Cl_2N_6$: C, 46.9 H, 2.6 Cl, 23.1 N, 27.36. Found: C, 47.0 H, 2.9 N, 27.0. IR (KBr) ν_{max} 3188, 1617, 1575, 1552 cm^{-1}. MS (EI) *m/z* 306.0 (M^+).

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