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Structural and conformational study of substituted triazines by ^{15}N NMR and x-ray analysis

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ABSTRACT: Since the discovery of the multi-drug resistance (MDR) phenotype, reversant agents of various origins and structures have been extensively studied. In the present work, two series of related 2,4,6-tris(amino)-*s*-triazines with different MDR potential[1] were studied by ^{15}N NMR spectroscopy. The ^{15}N nucleus allows an easy identification of two protonation sites and an estimation of the electronic effects. ^{15}N was further found to be well suited to demonstrate the occurrence at room temperature of restricted rotation around the Ar—N bonds between the amino substituents and the *s*-triazine ring and to measure the rotational barriers. Crystal structures were determined by x-ray analysis of the compounds at various stages of protonation. The effects of the protonation at the sterically less hindered nitrogen of the triazine, detected by the NMR study, were confirmed in the solid-state structures. In the crystals, the orientation of the N—H and N—C bonds of the NHallyl substituent with respect to the triazine ring does not depend on the protonation state and corresponds to one of the conformations postulated in solution. © 1998 John Wiley & Sons Ltd.

KEYWORDS: NMR; ^{15}N NMR; MDR; ^{15}N, ^{1}H coupling constants; 2,4,6-triamino-*s*-triazines; protonation; variable temperature; rotamers; x-ray analysis

INTRODUCTION

Failure of many anticancer treatments involving chemotherapy often result from the development of the multidrug resistance (MDR) phenotype in which a glycoprotein P-gp is involved. Two related 2,4,6-tris(amino)-*s*-triazines present different activities as reversants of this phenotype:[1] **3** is less effective than **1**. In order to gain information on the structure–activity relationship, comparative structural and conformational studies were attempted using ^{15}N NMR spectroscopy.

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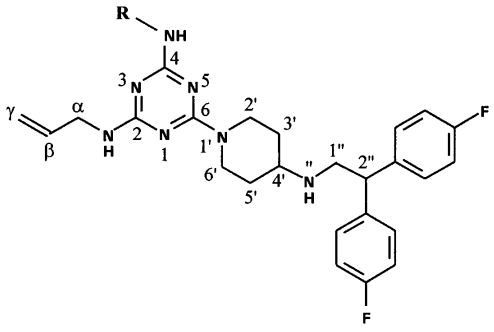
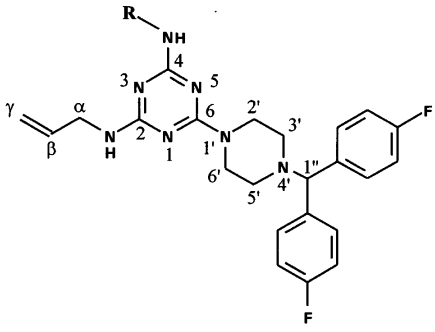
The structures of the compounds studied are shown in Scheme 1 with the numbering adopted for the atoms.

Very different types of nitrogen atoms are present in these compounds, the endocyclic *s*-triazine N atoms (AzN), the aniline-like N atoms (Ar-N) linked to the triazine, one of them being included in a piperazine or a piperidine ring, and an aliphatic tertiary amino-nitrogen in the piperazine ring or a secondary one in the aliphatic link.

Mono- and bis-salts were isolated by treatment of the bases with methanesulfonic acid. If in such compounds the Ar-N might be excluded from the potential protonation sites,[2] two problems remain: which one is the first protonation site and, among the three triazinic nitrogen atoms, which is the most basic. The ^{15}N nucleus appears also to be a good probe to determine



1 (S9788) **R** = allyl
2 (ED007) **R** = propyl



3 (S2620) **R** = allyl
4 (S3024) **R** = H

Scheme 1

 CCC 0749-1581/98/080587–10 $17.50

the protonation sites by NMR spectroscopy.

Restricted rotations around the Ar—N bonds have been evidenced in the case of 4,6-bis- or 2,4,6-tris(*N*,*N*-dialkylamino)-*s*-triazines by Katritzky *et al.*[3] by dynamic ^{1}H and ^{13}C NMR studies at ambient temperature. The steric hindrance appears less stringent for the compounds under study. One substituent only is an *N*,*N*′-dialkylamino group (N-1′ included in a cyclic structure), the second is an NHallyl group and the last one is either an NH_2 or NHR group (R is an allyl or alkyl substituent). At room temperature, the ^{1}H and ^{13}C NMR spectra did not show any decoalescence or even significant broadening of the various signals. The ^{15}N nucleus was expected to be a more sensitive probe to approach the conformational analysis of the side-chains. Both the Ar-N and the AzN atoms might be affected by restricted rotation around the Ar—N bonds. We present an approach to the dynamic phenomenon by natural abundance ^{15}N NMR spectroscopy using the INEPT technique.[4] The values of the rotational barriers around the Ar—N bonds were evaluated.

Crystals suitable for x-ray analysis were obtained from **3** base, **3** monomethanesulfonate and **1** bismethanesulfonate. Some aspects of the ^{15}N NMR results and of the conformational behavior of the molecules in solution will be discussed in the light of the structural features of the solid state.

RESULTS

Signal assignments

Owing to conformational problems, the ^{15}N NMR spectra, first recorded for the bases at room temperature, exhibit very complex patterns except in the region of the aliphatic amino nitrogen, where a single signal occurs. Spectra recorded at higher temperature, 350 K, contain well resolved signals and assignments can be based on known expected shieldings for the various types of nitrogens and on symmetry considerations. For example, the spectra recorded for compound **1** base are shown in Fig. 1.

The AzN atoms give signals around −205 ppm.[5] The shifts are scarcely dependent on the nature of the proximate amino groups. The resonances of the Ar-N nuclei are located in a narrow range, less than 10 ppm, around −285 ppm.[5,6] With respect to the NHallyl resonance, the NH_2 signal is shielded and that of the NHpropyl is deshielded. It is noteworthy that, even at 350 K, a well resolved triplet (Ar-NH_2) and doublets (Ar-NH) were observed for the aromatic amino nitrogens with ^{1}J(N, H) coupling constants of *ca.* 92 Hz. Finally, the aliphatic amino nitrogens are the most shielded. The ^{1}J(N, H) coupling was not observed for the secondary aliphatic nitrogen N″. The results are given in Table 1.

Protonation study

The s-character of the hybrid orbital involved in the N—H bond may be deduced from the coupling constant according to the relation $\%s = 0.43[^{1}J(N, H)]—6$.[7] For the Ar-$NH_2$ and Ar-NHR nitrogens, the value of the coupling constant, 92 Hz, yields $\%s = 33$. Clearly, for all the cases under study, the conjugation of the lone pair of electrons on the exocyclic nitrogen with the very electron-deficient triazine ring results in high double-bond character of the Ar—N bonds. Although no direct information is accessible in the case of the Ar-N atom included in the piperidine or piperazine ring, a similar result is expected. Thus protonation is not likely to occur at these sites.[2]

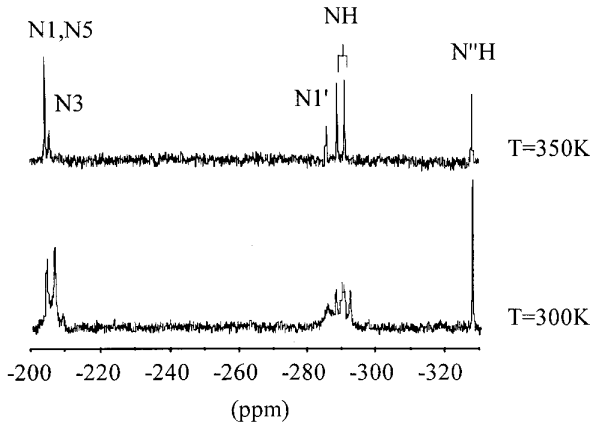


Figure 1. ^{15}N NMR spectra (40.56 MHz) of **1** base recorded without proton decoupling at 300 and 350 K.

Since all the compounds bear an aliphatic amino nitrogen, protonation might be expected to occur first at this site and to result in limited signal deshielding.[8]

Protonation at a nitrogen atom of an *s*-triazine usually occurs only in very acidic media and is expected to result in strong shielding of the ^{15}N signal.[2,9,10]

The effect of the protonation was studied in two ways. The solid salts previously isolated were directly dissolved in DMSO-d_6 or a titration was realized by adding successive amounts of methanesulfonic acid to a solution of the base in DMSO-d_6. The ^{15}N spectra were recorded without decoupling of the protons at 300 K. The relevant ^{15}N NMR data are given in Table 1.

For **1** and **2**, the protonation occurs first, as expected, at the secondary amine. Nevertheless, the lack of multiplicity for this nitrogen signal in the monomethanesulfonate shows that the exchange of the protons remains fast at ambient temperature. A triplet with a coupling constant of 75 Hz (26% s-character of the hybrid orbitals) is observed only after further addition of methanesulfonic acid. The limited difference in the values of the two pK_a values determined by UV spectrophotometry, 7.3 ± 0.1 and 4.8 ± 0.1, might contribute to this phenomenon. The second protonation results in several changes of the spectrum. Two signals are strongly displaced. A resolved triplet at *ca.* −270 ppm is assigned to N-3 in the triazine, the ^{3}J interaction (4 Hz) occurring with the NH proton of each side-chain (the two other AzN, N-1, N-5, give a doublet with the same coupling constant). The other signal at *ca.* − 260 ppm which remains broad is then assigned to the piperi-

Table 1. ^{15}N chemical shift data in DMSO-d_6 solution (δ in ppm with respect to $MeNO_2$) at 300 and (values in square brackets) 350 K[a]

	1			2		3			4		
Site	b	ms	bs	b	bs	b	ms	bs	b	ms	bs
N-1	−204.3	−204.4	−212.1	−204.7		−204.1		−212.5	—		
	−206.5	−206.8	−212.9	−206.9	−213.8	−206.5	−212.3	−211.6	[−203.4]	−212.1	−212.0
	[−204.4]	[−205.1]		[−204.4]		[−203.8]		[−211.4]			
N-3	−204.3	−206.8		−204.7		−204.1		—			
	−206.5	−208.6	−269.1	−206.9	−270.1	−206.5	∼−272	−279.2	[−204.8]	∼−260	−280.9
	−208.3	[∼−209]		−209.1		−208.6		[−279.2]			
	−205.7]			[−205.7]		[−204.9]					
N-5	−204.3	−204.4	−212.1	−204.7		−204.1		−212.5	—		
	−206.5	−206.8	−212.9	−206.9	−213.8	−206.5	−212.3	−211.6	—	−212.1	−212.0
	[−204.4]	[−205.1]		[−204.4]		[−203.8]		[−211.4]	[−204.8]		
NH	−289.4	−288.7		−289.6		−289.0					
	−291.2	−290.4	−285.9	−291.5	−283.3	−290.8	−286.2	−284.4	−290.4[b]	−285.7	−284.4
	[−290.4]	[−289.3]		[−290.9]		[−290.1]		[−283.4]	[−290.5]		
NH′				−286.3							
				−287.3	−286.7						
				[−287.7]							
NH_2									−293.6[b]		
									−295.4[b]	−290.4	−289.0
									[−296.7]		
N-1′						∼−290					
	∼−286	∼−286	−264.5	∼−286	−265.3	∼−291	∼−261	−263.7	—	−272.6	−262.3
	[−286.0]	[∼−287]		[−286.6]		[−290.3]		[?]	[−290.3]		
N-4′						−321.2	−321.6	−319.6	—	−321.9	−319.4
						[−321.8]		[−319.7]	[−321.9]		
N″	−327.9	−323.9	−324.7	−327.9	−325.2						
	[−328.5]	[−323.7]		[−328.6]							

[a] b, Base; ms, monomethanesulfonate; bs, bismethanesulfonate.
[b] Owing to the low solubility of **4** base at 300 K the data at this temperature were only collected with the INEPT sequence.

dine nitrogen N-1′. The spectrum recorded for **1** bismethanesulfonate is shown in Fig. 2.

The very strong shielding of N-3 clearly demonstrates that the second protonation has occurred at this site of the triazine even if it does not result in a detectable ^1J(N, H) coupling interaction.[2] The significant deshielding observed for N-1′ in the piperidine results from the changes in electron delocalization through the conjugated system.

For **3** and **4**, surprisingly, the first protonation leads to modifications of the spectrum similar to those observed for the second protonation in the piperidine series. Hence the first protonation has not occurred at the tertiary aliphatic amino nitrogen but at the N-3 site of the triazine. The second protonation occurs at the non-conjugated nitrogen included in the piperazine ring, N-4′, which give a broad doublet [^1J(N, H) 75 Hz]. The main difficulty in this case concerns the assignment of the broad signals observed between −260 and −280 ppm. It was first achieved by following the shifts as a function of progressive addition of methanesulfonic acid to the base. The two signals were shown to cross each other, hence the most shielded of them must be assigned to N-3. After addition of 3 equiv. of methanesulfonic acid to the base, the signal becomes reasonably resolved. An INEPT experiment allowed the detection of N-3 coupled to the two NH protons of the side-chains and N-1, N-5 each coupled to one NH proton only (in both cases $^3J \approx 4$ Hz). The spectra recorded for **3** are shown in Fig. 3(a) and (b).

The signal of the protonated nitrogen N-3 evolves between −272 and −280 ppm when the [acid]/[base] molar ratio increases from 1 to 3. From the pK_a values of the basic sites, 4.8 ± 1 and 3.8 ± 1, it might be inferred that protonation is not completed at the N-3 site of the triazine after the first addition of monomethanesulfonic acid.

The shifts observed upon protonation are greater in the piperazine series than in the piperidine series, *ca.* 29 and 22 ppm, respectively, for N-1′ and *ca.* −74 and −64 ppm, respectively, for N-3. For the two series it was checked that further addition of several equivalents of methanesulfonic acid does not induce significant modifications of the spectra not showing any protonation at the N-1 and N-5 sites of the triazine. The significance of small supplementary signals in the spectra of the bismethanesulfonates will be discussed later.

Conformational study

Bases. A planar network involves the triazine ring and all the bonds originating from the Ar-N atoms. No effect of a rotation by 180° around the Ar—N bond

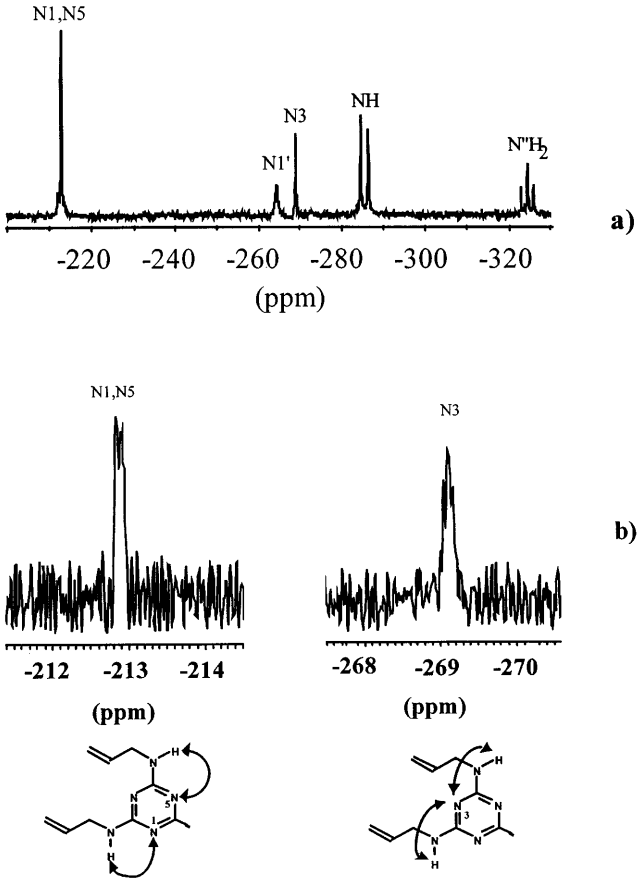


Figure 2. ^{15}N NMR spectrum (50.69 MHz) of **1** bismethanesulfonate recorded without proton decoupling at 300 K. (a) Full range; (b) expansion of the signals obtained for N-1/N-5 and N-3 after Gaussian transformation.

may be observed in the case of an NH_2 group and in the particular case of the N-1′ nitrogen included in the piperazine or in the piperidine ring no significant modification of the environment is expected. A significant barrier to rotation around the Ar—N bonds has been evidenced for the bases by the complexity of the ^{15}N spectra recorded at room temperature. The rotamers $\mathbf{R_I}$ and $\mathbf{R_{II}}$ are shown in Scheme 2.

For **4** base, which bears an NH_2 and an NHallyl substituent, the exchange phenomenon is related only to the slow interconversion between the rotamers $\mathbf{R_I}$ and $\mathbf{R_{II}}$. For this compound, which is scarcely soluble at room temperature, the ^{15}N observable signals are those originating from the NHallyl and NH_2 groups, which may be studied with the INEPT technique.[4] Whereas the NH gives only one signal, an antiphase doublet (intensities 1, −1 with $^1J \approx 92$ Hz), two signals (intensities 1, 0, −1) are obtained for the NH_2 group. The spectra recorded for **4** base using the INEPT technique without refocusing and with refocusing and decoupling are shown in Fig. 4.

The similarity of the ArCNH allyl chemical shifts and the significant differences in the NH_2 chemical shifts may be explained on the following basis (Scheme 3): the discriminating interactions appear to be one between the NH···H_α in the case of rotamer $\mathbf{R_I}$ (closest distance between hydrogens 3.8 Å) and one between the NH···HN in the case of rotamer $\mathbf{R_{II}}$ (closest distance between hydrogens 4.4 Å). The two resonances are of similar intensity.

For the symmetrically substituted compounds **1** and **3** bases, which are more soluble, complicated patterns are observed at room temperature, around −210 ppm in the AzN region and around −290 ppm in the Ar-N region. The spectrum recorded for **1** base is shown in Fig. 1.

The three possible overall conformations resulting from the combination of rotamers $\mathbf{R_I}$ and $\mathbf{R_{II}}$ are shown in Scheme 4.

The NH groups may be studied alone by use of the INEPT technique. In the light of the results obtained for the monosubstituted compound **4**, it might be inferred that the chemical shift of one particular nitrogen is determined by the rotamer existing at the second site. Two signals only are effectively observed with similar intensities. Since conformation B contributes equally to the intensities of the two signals, the conformations A and C must also be equally populated. For the equivalent nuclei N-1/N-5, two different environments are possible if only the orientation of the more proximate substituent is taken into account (Scheme 4), and thus two signals with similar intensities are also expected. The spectrum shows two signals which partially overlap the signals originating from N-3.

For the tertiary nitrogen N-1′ bonded to the triazine and for the N-3, three environments (A, B, C) are possible (Scheme 4). As shown in Fig. 5 for **1** base, the signal observed for N′-1 comprises three components. In the low-field region a deconvolution was attempted for the signals of N-1/N-5 and N-3. Assuming equal intensities for the two signals of N-1/N-5, this clearly shows the occurrence of three distinct signals for N-3. This region of the spectrum is shown in Fig. 6 for **3** base. The overall conformation B is probably favored but a precise evaluation of the population for each environment remains difficult.

Finally, when the substituents are different, NHpropyl and NHallyl groups in **2** base, the shift for the NH groups slightly depends on the nature of the side-chain. Despite the numerous combinations available for the rotamers, the INEPT experiment shows only four signals. Two signals are centered at the usual position of the NHallyl. The last two signals of unequal intensities are assigned to the NHpropyl group.

Taking advantage of the lack of any chemical exchange of the protons bonded to the sp^2-hybridized nitrogens, it was possible to use the INEPT technique in order to estimate the free enthalpies of activation at the coalescence temperature for the rotational barriers around the Ar—N bonds. Figure 7 shows the evolution of the INEPT signals recorded as a function of the temperature in the case of **3** base.

At room temperature, the signal contains only two antiphase doublets. In the spectrum recorded at 50.69 MHz the shift difference between the two signals, 92 Hz, is equal to the ^1J(N, H) coupling constant. Hence the high-frequency line of the shielded doublet and the low-

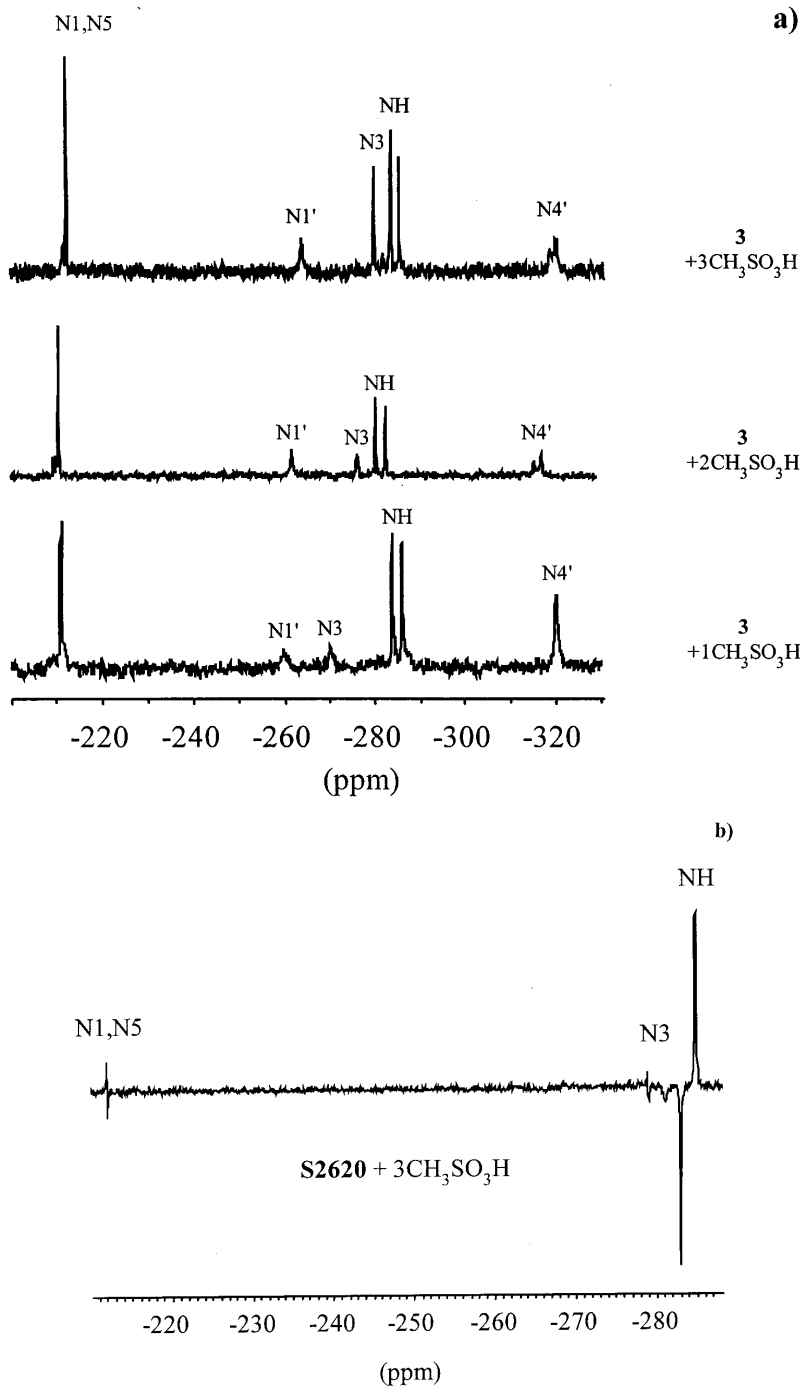
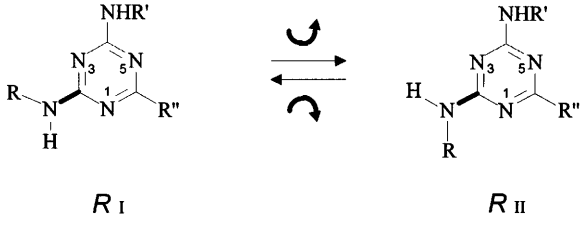


Figure 3. ^{15}N NMR spectra (50.69 MHz) recorded at 300 K without proton decoupling for **3** as a function of methanesulfonic acid equivalents added; (b) ^{15}N NMR spectrum (59.69 MHz) recorded at 300 K for **3** with 3 equiv. of methanesulfonic acid added using the INEPT sequence.



R I *R* II

R= allyl
R'= H, allyl or propyl
R"= piperidine or piperazine moiety

Scheme 2

frequency line of the second doublet cancel at their coincident position. As the temperature is raised, the separation between the two antiphase doublets decreases and the coalescence in one antiphase doublet occurs at 315 ± 2 K. The same results are obtained for **1** base with the same coalescence temperature. In the case of **2** base, where the two substituents are distinct, the coalescence temperatures are slightly different, 305 ± 2 K for the nitrogen which bears the propyl group and 315 ± 2 K for the nitrogen which bears the allyl group. In the case of the monosubstituted **4** base,

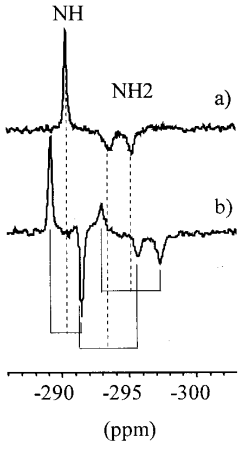


Figure 4. ^{15}N NMR spectra (40.56 MHz) recorded at 300 K for **4** base using the INEPT sequence, (a) with refocusing and decoupling and (b) without refocusing.

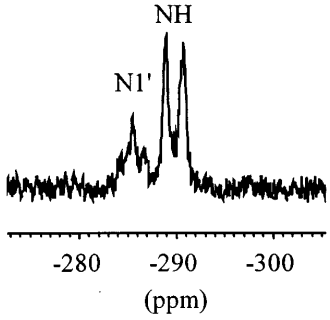


Figure 5. ^{15}N NMR partial spectrum (50.69 MHz) of **1** base recorded with proton decoupling at 300 K.

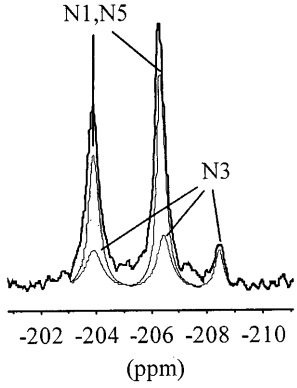


Figure 6. ^{15}N NMR partial spectrum (40.56 MHz) of **3** base recorded without proton decoupling at 300 K showing deconvolution of the Ar-N signals.

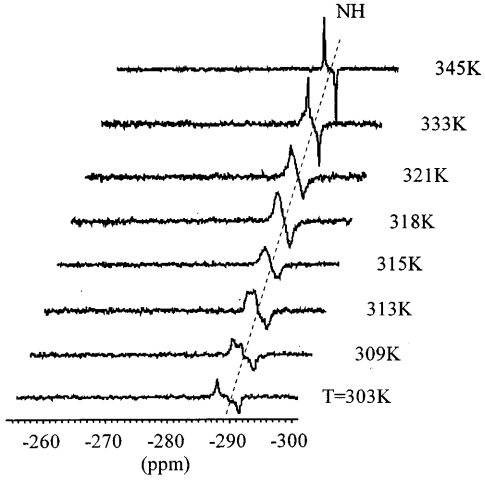
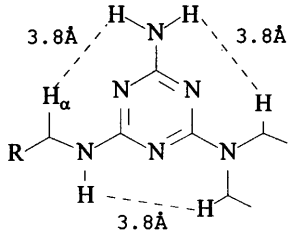
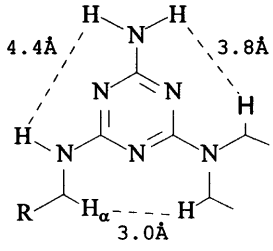


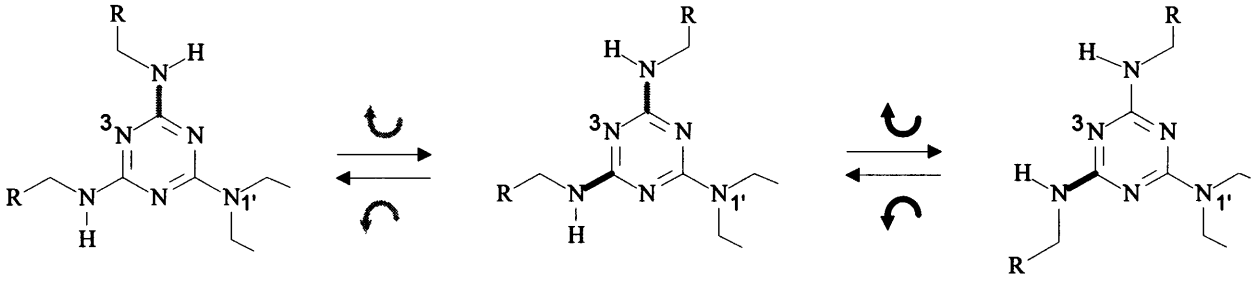
Figure 7. ^{15}N NMR spectra (50.69 MHz) of **3** base recorded as a function of temperature using the INEPT sequence.





*R*I *R*II

Scheme 3



A(*R*I,*R*I) B(*R*I,*R*II) C (*R*II,*R*II)

Scheme 4

the signals are very broad around the coalescence temperature, estimated to be 313 ± 3 K.

It is then possible to evaluate the free enthalpy of activation at the coalescence temperature T_c by use of the Eyring equation,[11] $\Delta G^* = 19.14\ T_c\ [9.97 + \log (T_c/\delta\nu)]$ where $\delta\nu$ is the frequency separation observed for the two signals of each nitrogen in the spectra recorded in the slow exchange limit. For the symmetrical bases of **1** and **3** the same value is obtained, 63.3 ± 0.5 kJ mol^{-1}. In the case of **2** base, a value of 64 ± 1 kJ mol^{-1} is estimated from the coalescence of the nitrogen in the NHpropyl group, taking into account the effect of unequal populations, and a value of 63.4 ± 0.5 kJ mol^{-1} from the coalescence of the nitrogen in the NHallyl group. In the monosubstituted base of **4** the value deduced from the coalescence of the signals of the NH_2 might be estimated to be 63.0 ± 1.5 kJ mol^{-1}. These values do not significantly differ as a function of the nature of the central ring, piperidine or piperazine, or as a function of the nature of the nitrogen side-chain substituent.

For the 4,6-bis- and 2,4,6-tris(*N*,*N*-dialkylamino)-*s*-triazine, similar values between 62.2 and 65.2 kJ mol^{-1} have been reported depending on the nature of the chain, isopropyl or butyl (the coalescence of the observed ^{13}C signals occurred in the same temperature range).[12] Furthermore, these values compare well with those determined for the rotational barriers in amides[13] and enamines.[14,15]

Mono- and bismethanesulfonates. The study of the protonation sites has shown that as soon as protonation has occurred on the N-3 triazinic site, the spectra recorded at room temperature comprise essentially one signal for each type of nitrogen taking into account the symmetry of the molecule. Nevertheless, small signals are detected beside the main signals, in particular for the two non-protonated nitrogens of the triazine and for the Ar-NH atoms. They are shown in Fig. 8 for N-1/N-5 in **1** bismethanesulfonate.

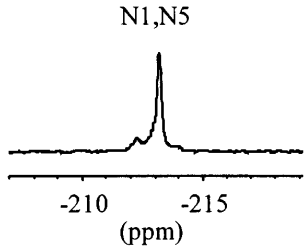


Figure 8. ^{15}N NMR partial spectrum (40.56 MHz) of **1** bismethanesulfonate recorded without proton decoupling at 300 K showing the signals of the Ar-N (N-1/N-5) in two conformers.

A possible explanation is that a stable ion pair is formed with the voluminous counter ion in close proximity to N-3. Thus the rotamer $\mathbf{R}_{II}$ is most likely favored for both side-chains leading to the overall conformation C (Scheme 4). Nevertheless, another minor conformer exists at room temperature. At 320 K coalescence has occurred and one broad signal only is observed.

The occurrence of similar ion pair association was postulated when 2,4-diaminopyrimidine was dissolved in H_3PO_4 buffer. Stabilization results from the formation of hydrogen bonds involving the hydrogen at the protonation site and one of the hydrogens in the adjacent NH_2 group with two oxygen atoms in the counter ion.[10]

Crystal structures

Structures were determined by single-crystal x-ray crystallography for the base and the monomethanesulfonate of **3** in the piperazine series (Fig. 9) and for the bismethanesulfonate of **1** in the piperidine series (Fig. 10). The bond distances and angles are available as supplementary material.

3 Base. The sp^2 hybridization state of the three amino nitrogens bound to the triazine is well reflected in the low value of the ArC—N bond length (1.36 Å). Furthermore, the sum of the angles around the Ar-N atoms is very close to 360° (360, 356 and 359°). It is noteworthy that the orientations of the N—H and N—C_α bonds in each NHallyl group correspond to the rotamer II, leading globally to the conformer C previously considered in solution. Both NHallyl substituents are located on the same side of the triazine ring. As found previously for some substituted amino-*s*-triazines,[12] the triazine ring is nearly planar but deviates from a regular hexagon (Table 2) with an alternation of more acute internal angles at the nitrogen atoms (*ca.* 113°) and more obtuse internal angles at the carbon atoms (*ca.* 127°).

The orientation of the allylic chains seems almost perpendicular to the planar network involving the triazine ring and all the bonds originating from the Ar-N. The disposition of the chains facing each other minimizes interactions between the two of them and also between each of them and the piperazine ring.

The piperazine ring is significantly flattened, as shown by the low values of the internal torsional angles reported in Scheme 5. The substituent of the piperazine at N-4′ is in equatorial position.

Table 2. Internal angles (°) in the triazine ring of 3 base and 3 monomethanesulfonate (from crystal structures)

Summit of angle	N-1	C-2	N-3	C-4	N-5	C-6
3 Base	113.3	127.3	112.0	127.2	113.1	127.0
3 Monomethanesulfonate	113.9	122.5	118.0	124.5	111.9	129.1

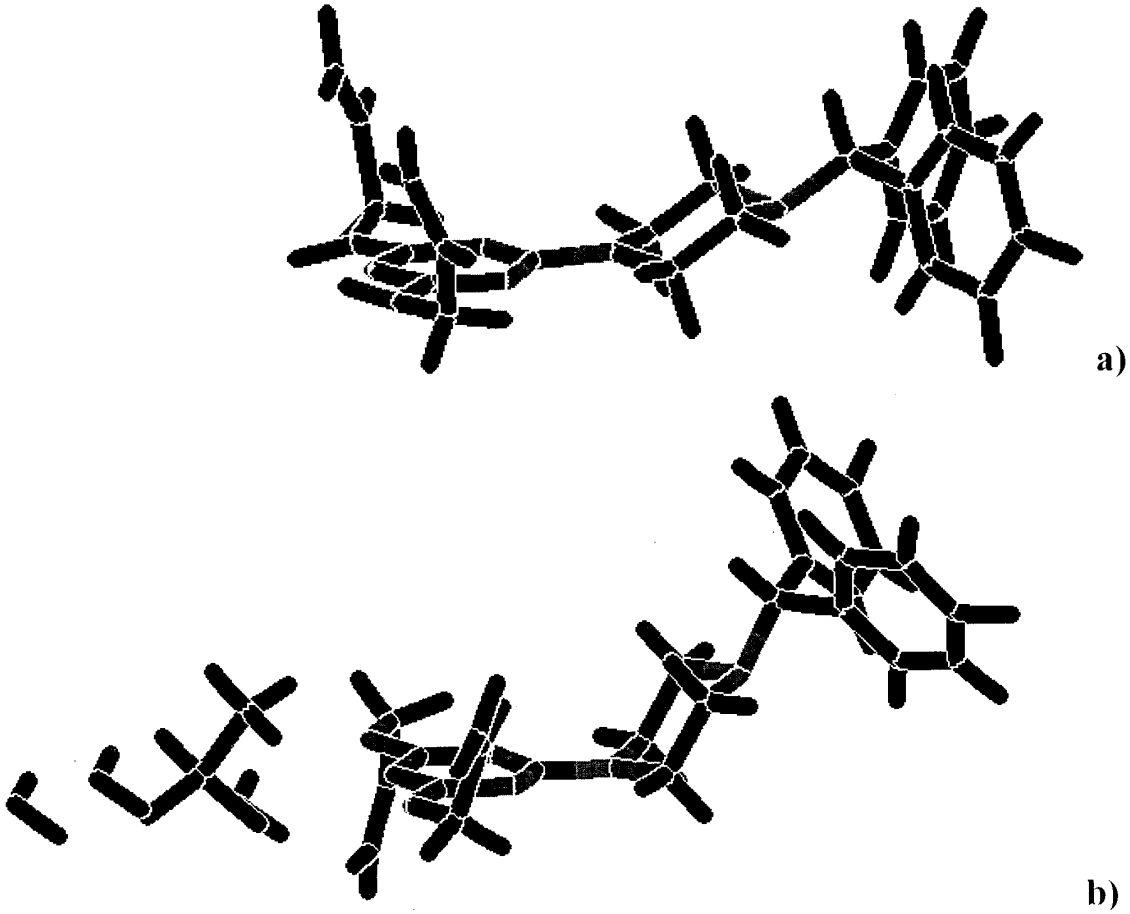


Figure 9. View of the crystalline structure of (a) **3** base and (b) **3** monomethanesulfonate.

3 Monomethanesulfonate. The planar network involving the triazine ring and all the bonds originating from the Ar-N atoms is preserved. The orientation of the bonds around the Ar-N nitrogens corresponds to rotamer $\mathbf{R}_{II}$ (overall conformation C as in the base). Nevertheless, significant modifications have occurred. The molecule is no longer symmetric. The counter ion is situated in front of the molecule near N-3 but the two sites, with equal occupancies, are shifted on each side of the plane bisecting the triazine and the piperazine rings. The conformation within the allylic chains has been modified in such a way that they adopt opposite orien-

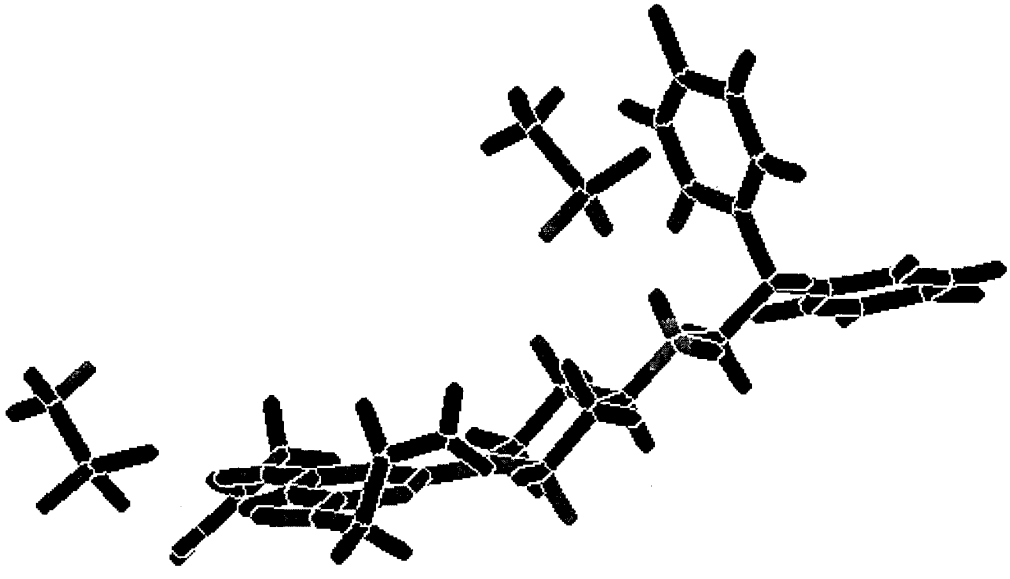
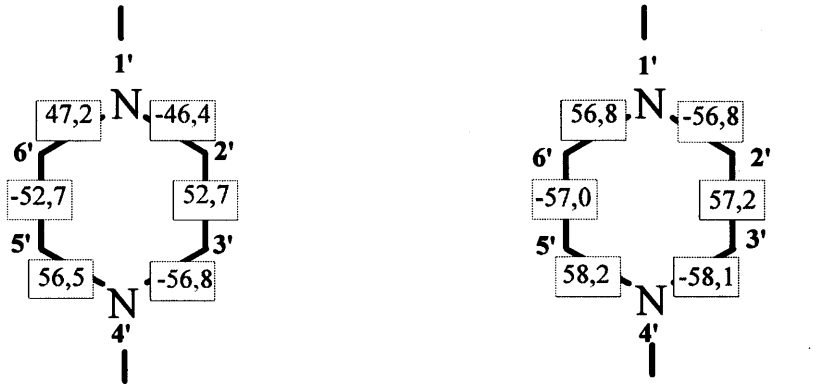


Figure 10. View of the crystalline structure of **1** bismethanesulfonate.



3 base **3** monomethanesulfonate

Scheme 5

tations with respect to the plane of the triazine ring. For the chain which is more remote from the counter ion, a rotation has occurred around the N—C_α bond (the value of the C-4—N—C_α—C_β torsional angle is 96.3° instead of −106.7°). For the chain which is the more proximate of the counter ion a rotation has occurred within the allylic group around the C_α—C_β bond (the value of the N—C_α—C_β—C_γ torsion angle is 133.4° instead of −6.8°). Other modifications are important. In the triazine ring, the internal angles have been significantly modified as shown in Table 2. These results suggest that the protonation has occurred at N-3 of the triazine ring. Increased puckering of the piperazine ring is noticeable with all the intracyclic dihedral angles which are significantly greater than in the base, particularly around the bonds involving the N-1′ atom (Scheme 5).

1 Bismethanesulfonate. The counter ions appear localized near the secondary amino nitrogen and in front of the triazine ring. The last one is disordered with approximately equal site occupancies. The protonation sites are fully confirmed. A hydrogen bonded to the N-3 atom is well localized in addition to the two hydrogens bonded to N″. The characteristic features of the bismethanesulfonate of **1** compare well with those of the monomethanesulfonate of **3** previously described, in particular the orientations of the ArN—H bonds corresponding to conformer C, the disposition of the NHallyl chains on both sides of the triazine plane, the conformation of each chain and finally similar values of the internal angles in the triazine, in particular at N-3 and C-6.

The proton N-3H and one of the NHallyl are involved in hydrogen bonds with the oxygen atoms of the counter ion. The second NHallyl is bonded to a water molecule. The N···O distances, between 2.78 and 2.94 Å, are all greater than the O···O or N···N distances found for very strong (< 2.50) or strong hydrogen bonds (2.50–2.65). The results observed in the present case confirm the hypothesis that homonuclear (NH···N or OH···O) and heteronuclear (NH···O) hydrogen bonds have different properties.[16] It has been reported that, in the NH···O bond system, the NH bond can be only slightly stretched (from 1.01 to 1.06) and thus the covalent contribution is hindered in spite of the strong electronegativities of the donor and acceptor atoms.

Finally, it should be noted that the most important characteristics of the structures in the solid state are well reflected in the spectral NMR data of the various compounds in solution.

The sp^2 hybridization state of the Ar-N amino-nitrogens is well reflected in the lack of any exchange phenomenon for the NH protons even at 350 K. The significant distortion of the triazine ring when protonation has occurred at N-3 may be correlated with the strong shifts of N-3 and N-1′ in the ^{15}N NMR spectra corresponding to a dramatic change in electron charge delocalization to give a *p*-quinonoid form. Hydrogen bonds similar to those observed in the solid state might stabilize conformer C in solution when protonation at N-3 has occurred. Very stable hydrogen-bonded networks involving *N*,*N*′-bis(4-*tert*-butylphenyl)melamine and 5,5-diethylbarbituric acid were observed both in organic solvents and in the solid-state structure.[17]

CONCLUSION

The chemical shifts of the ^{15}N resonances in the compounds under study follow the known behaviour of 2,4,6-tris(amino)-*s*-triazine (melamine). In the two series, the occurrence of two rotamers around the Ar—N bonds, with nearly equal probabilities, was clearly established in solution at room temperature for monosubstituted *N*-amino groups linked to the *s*-triazine. A barrier to rotation around the Ar—N bonds similar to the barrier around the N—C=O bond in amides, *ca.* 63 kJ mol^{-1}, was measured by a dynamic ^{15}N study using the INEPT technique. When protonation occurs at N-3 in the triazine, one of the conformations is highly favored. Stabilized by a network of hydrogen bonds in solution, this conformation is observed in the solid state both for the salts and for the base. Nevertheless, the protonation at N-3 in the triazine results in significant differences for the two series. In the ^{15}N spectra, the resonances of N-1′ and N-3 are more shifted in the piperazine series

than in the piperidine series. From the crystalline structures, it appears that the piperazine ring is puckered in a quasi-theoretical chair conformation while the piperidine ring remains more flattened in the region of the nitrogen linked to the triazine. Despite the fact that the bonds around N-1′ are almost coplanar in both cases, the electronic effects appear more important when a piperazine is bonded to the triazine.

EXPERIMENTAL

^{15}N NMR chemical shifts are reported in parts per million from the reference $MeNO_2$ at 0.0 ppm. The spectra being recorded in DMSO-d_6, [^{15}N]formamide in DMSO was used as a secondary external reference, −265.4 ppm with respect to $MeNO_2$. The accuracy of chemical shifts data is ±0.1 ppm except for very broad signals, ±1 ppm. The spectra were recorded on Bruker AM400 and AM500 spectrometers operating at 40.56 and 50.69 MHz for ^{15}N. All the experiments were performed with 32K data points and a digital resolution of *ca.* 0.7 Hz for a concentration of *ca.* 0.5 M. For the 1D spectra, a 90° flip angle (17 and 24 μs for the AM400 and AM500, respectively) was used with a relaxation delay of 10 s or a 45° flip angle with a relaxation delay of 3 s. For the INEPT sequence, the ^{1}H 90° pulse was 22 or 34 μs (on the AM400 or AM500) and the delay used for polarization transfer was 2.7 ms via ^1J coupling (92 Hz) and 7.0 ms via ^3J coupling (4 Hz). In the latter case a value smaller than the theoretical value 1/4J(N, H), 62 ms, must be used to avoid excessive effects of transverse relaxation. For spectra of reasonable signal-to-noise ratio, the number of scans which were acquired vary from *ca.* 1000 to 2500 for variable temperature study (INEPT experiments) and from 10 000 to 25 000 as a function of temperature and signal broadening (1D spectra).

Crystallographic data

A CAD4 diffractometer and Cu Kα radiation were used

3 base. The crystal system is monoclinic, space group $P2_1/n$. The cell dimensions are $a = 13.735(8)$, $b = 12.746(2)$ and $c = 14.766(9)$ Å and $\beta = 99.81(2)°$. $Z = 4$. Reflections collected, 4747; reflections used [$I > 3\sigma(I)$], 2298. The structure was resolved with the direct method[18] and refined by the least-squares method.[19] $R = 8.7\%$. All non-hydrogen atoms were anisotropically refined. Hydrogen atoms were included in calculated positions. H atoms bonded to the exocyclic nitrogens were located on difference Fourier maps.

3 Monomethanesulfonate. Owing to its instability, the crystal (0.3 × 0.2 × 0.1 mm^3) was sealed in a capillary. The crystal system is monoclinic, space group $P2_1/n$. The cell dimensions are $a = 13.815(8)$, $b = 12.718(6)$, $c = 18.896(12)$ Å and $\beta = 105.02(5)°$. $Z = 4$. V = 3207 Å^3. Data collected, θ range 3–67° (±h, +k, +l). Reflections measured, 6142; reflections used [$I > 3\sigma(I)$], 1869. The structure was resolved with the direct method[18] and refined by the least-squares method.[19] $R = 9.3\%$. All non-hydrogen atoms were anisotropically refined. Hydrogen atoms were included in calculated positions. H atoms were not located on difference Fourier maps.

1 Bismethanesulfonate. The crystal system is triclinic space group P^{-1}. The cell dimensions are $a = 12.006(1)$, $b = 12.549(2)$, $c = 13.401(3)$ Å, $\alpha = 113.79(1)$, $\beta = 90.22(1)$, $\gamma = 101.41(1)°$. $Z = 2$. $V = 1803.1$ Å^3. Data collected, θ range 3.62–68.59° (±h, ±k, +l). Reflections collected, 6921; reflections used [$I > 2\sigma(I)$], 5026. Final R indices: $R1 = 7.26\%$, $wR2 = 0.2032$. The structure was resolved with the direct method[18] and refined by the least-squares method.[20] All non-hydrogen atoms were anisotropically refined. Hydrogen atoms non-bonded to nitrogen atoms were included in calculated positions. H atoms bonded to nitrogen atoms, not previously introduced, were located on difference Fourier maps.

SUPPLEMENTARY MATERIAL

For the three structures, tables of atomic coordinates, bond lengths and angles, thermal parameters and calculated and observed structure factors have been deposited at the Cambridge Crystallographic Data Centre.

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