Synthesis and Crystal Structure of Propane-1,2,3-triamine Trihydrochloride Monohydrate. Reactions of Propane-1,2,3-triamine with Hydrogen Ion. Thermodynamic Functions and Molecular Mechanics Calculations†

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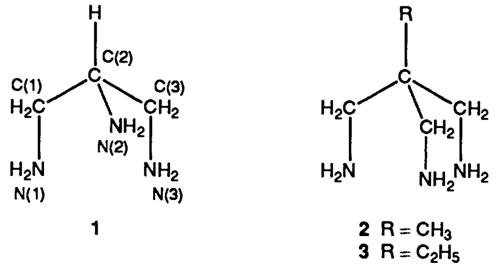
The crystal and molecular structure of propane-1,2,3-triamine trihydrochloride monohydrate (**1**$\cdot$3HCl$\cdot H_2O$) is reported. **1**$\cdot$3HCl$\cdot H_2O$ crystallizes in the triclinic system, space group $P\bar{1}$ (no. 2), a = 11.078(1), b = 11.935(2), c = 7.862(1) Å, α = 102.88(2), β = 100.79(1), γ = 81.07(1)°, Z = 4. The structure refinement converged to R = 0.036 and R_w = 0.038. Two **1**$\cdot H_3^{3+}$ cations, six Cl^- anions and two water molecules are contained in the asymmetric unit. The two triammonium ions have almost the same conformation. The four C–C bond lengths average 1.521(4) Å while the six C–N bond lengths average 1.485(4) Å. A network of strong hydrogen-bond interactions involve all of the chloride ions, the triprotonated nitrogen atoms as well as the water molecules. These forces are responsible for the non-equivalence in the two C–C–N(terminal) bond angles for the two **1**$\cdot H_3^{3+}$ cations.

The protonation equilibria of propane-1,2,3-triamine (**1**) in aqueous solution (0.15 mol dm^{-3} NaCl, 298 K) have been studied with potentiometric and calorimetric techniques. The logarithms of the protonation constants are 9.642 ± 0.002, 7.981 ± 0.001 and 3.715 ± 0.002 for **1**, **1**$\cdot H^+$ and **1**$\cdot H_2^{2+}$, respectively. A comparison with the log K values previously determined for similar triamines containing three equivalent $-CH_2NH_2$ groups, such as 2-methyl-2-aminomethylpropane-1,3-diamine (**2**) and 2-ethyl-2-aminomethylpropane-1,3-diamine (**3**), shows that **1** is the least basic ligand. The decrease in the basicity is particularly evident for the third step. The enthalpy changes for **1** are -10.97 ± 0.04, -11.07 ± 0.07 and -8.52 ± 0.08 kcal mol^{-1}‡ in the first, second and third protonation step, respectively.

A molecular-mechanics analysis was carried out on the **1**$\cdot H_3^{3+}$ cation to obtain a proper force field for this kind of triamine. Atomic charges for all the atoms were calculated by means of the semiempirical MNDO method. The energy-minimized conformation for the folded **1**$\cdot H_3^{3+}$ cation is in good agreement with the molecular structure found in the solid state for **1**$\cdot$3HCl$\cdot H_2O$. However, the two calculated C–C–N(terminal) bond angles are equal to each other showing that intermolecular interactions are responsible for the distortion found in the solid-state structure. In the most stable conformation of the **1**$\cdot H_2^{2+}$ species, the protonated amino groups are the terminal ones. The cation shows an elongated chain similar to that previously found for the protonated linear polyamine spermine when co-crystallized with nucleic acid molecules.

Aliphatic polyamines are widely distributed in a great variety of living organisms.[1] They play important biological roles in cellular growth, proteic synthesis and in the activity of many enzymes.[1–3] Some polyamines show pH-dependent antibacterial activity, which can be related to their polycationic nature under physiological conditions; the action is found to be proportional to the number of positively charged centres in the amine molecule.[1] Furthermore, it has been found that the antimicrobial activity of synthetic triamines depends on the number of primary amino groups present in the polyamine molecule.[3] Polyamines also interact with nucleic acids through the protonated nitrogen atoms.[4,5] They stabilize DNA against thermal denaturation, enzymatic degradation and radiation damage.[1,2]

It is well known that polyamines are able to bind both protons and metal ions under physiological conditions and the competitive equilibria in aqueous solution have been extensively studied.[6] Polyamine–metal complexes have shown high efficiency in inducing the formation of Z-DNA.[7]



Scheme 1

Propane-1,2,3-triamine (**1**) is the smallest aliphatic triamine (Scheme 1). However, its protonation and complex formation equilibria in solution have received little attention, the only reported investigation being that by Prue and Schwarzenbach.[8] Other primary triamines of similar structure have been more extensively studied. In particular, the solution equilibria involving tripod-like 1,1,1-tris(aminomethyl)alkanes have been investigated.[9–11] These amines (Scheme 1) contain three equivalent peripheral $-NH_2$ groups, being different from **1** in that one more $-CH_2-$ group is present in the side chain. Comparison of the thermodynamic functions for the protonation

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† The X-ray data collection and analysis were carried out at ISSEC-CNR, Firenze.

‡ 1 cal = 4.184 J.

of these ligands permits the evaluation of the effect of such structural change.

In this work we report the crystal and molecular structure of **1**·3HCl·H_2O as well as a detailed potentiometric and calorimetric investigation on the protonation of **1** in aqueous solution (0.15 mol dm^{-3} NaCl and 298 K). Molecular-mechanics computations (on isolated molecules) have been performed in order to explain differences in the C–C–N(terminal) [N(terminal) = N(1), N(3), N(4), N(6)] bond angles found in the solid-state structure, to obtain information about the conformation of the species in the three different protonation steps, and to obtain a proper force field for this kind of molecules.

Experimental

Materials.—High purity reagent-grade NaCl (Merck, Suprapur) was used without further purification.

The triamine **1** was prepared using the method previously described.[12] The crude product, obtained as a colourless oil, was distilled under vacuum. The middle fraction, collected at 73 °C and 2 mmHg, was used to prepare the hydrochloride. **1**·3HCl was prepared by the addition of an excess of hydrochloric acid to a cooled and continuously stirred ethanolic solution of the amine. The obtained product was recrystallized twice from ethanol–water and then dried to constant weight at 50 °C *in vacuo*, m.p. 255–257 °C (Found: C, 17.7; H, 7.6; N, 20.4; Cl, 53.8. $C_3H_{14}Cl_3N_3$ requires C, 18.1; H, 7.1; Cl, 53.6; N, 21.2%). The pure propane-1,2,3-triamine trihydrochloride product contains one cocrystallized water molecule per ligand molecule (see below; X-ray analysis) when stored at room temperature in an air atmosphere. Efflorescence of the solvent occurs on heating (50 °C) under vacuum.

A 0.1 mol dm^{-3} stock solution of **1**·3HCl was prepared by dissolving the crystalline powder in 0.15 mol dm^{-3} NaCl. The actual content of **1** in the solution was measured by alkalimetric titration. The titration data were analysed for the end-point determination with a purposely written Fortran IV program. The concentration was then refined as described below. Solutions of HCl and NaOH were prepared by diluting more concentrated solutions contained in Merck ampoules. Solid NaCl was added to adjust the ionic strength to 0.15 mol dm^{-3}. The diluted NaOH solutions were kept in polyethylene bottles under ultrapure nitrogen. The bottles were directly connected to the burette. The concentrations of the dilute solutions of NaOH were measured by titration against standard potassium hydrogen phthalate (Merck) according to the Gran[13] procedure for the weak acid–strong base case. The calibration of the potentiometric cell in terms of hydrogen-ion concentrations and the titre of HCl were obtained by titration of the HCl solutions with NaOH by following the Gran[13] procedure for the strong acid–strong base case. Twice-distilled and CO_2-free water was used for preparing all the solutions. The value of the ionic product of water was $K_w = 1.72 \times 10^{-14}$ mol^2 dm^{-6} ($pK_w = 13.764$) in 0.15 mol dm^{-3} NaCl solution at 25 °C.

Potentiometric Titrations.—The potentiometric titrations were automatically carried out at 25.0 ± 0.1 °C by using a Metrohm 665 Dosimat 10 cm^3 burette and a Metrohm 654 digital potentiometer equipped with a Metrohm glass electrode and a Metrohm saturated calomel reference electrode. The apparatus was connected to an Olivetti M24 personal computer and the titration experiments were performed under the control of a purposely written Basic program. All the solutions were maintained under an atmosphere of ultrapure nitrogen during the titrations. The basicity constants of the ligand were determined by titrating freshly prepared, CO_2-free, solutions containing known amounts of **1**·3HCl with 0.02 mol dm^{-3} NaOH. As the calculated junction potential values determined by using the Gran procedure[13] were less than 0.2 mV in the pH range investigated (2.75–10.80), no correction to the measured electromotive force (E) values was applied. The calculation of the protonation constants was performed by means of the least-squares computer program SUPERQUAD.[14] The sum of the weighted squared residuals between observed and calculated E values was mimimized. The weighting of the experimental observations takes into account the estimated errors of both electromotive force and titrant volume. We estimated these errors to be 0.2 mV and 0.002 cm^3, respectively, in our system. The concentration of **1** solutions was checked by refining the amounts of ligand and H^+ together with the basicity constants. A value of 3.0 for the H^+/**1** molar ratio was always obtained. This analysis led to a molecular weight of 199.9 (calculated for **1**·3HCl, 198.6).

Calorimetric Titrations.—An LKB Thermal Activity Monitor (model 2277) equipped with a perfusion/titration system and a Hamilton pump (model Microlab M) was used to perform stepwise titration experiments. Both the calorimetric system and the Hamilton pump were controlled by means of an IBM personal computer (PS/2 model 30) using the program AUTOTAM.[15] Chemical calibration of the whole apparatus was accomplished by measuring the heat of neutralization of hydrochloric acid with sodium hydroxide in 0.15 mol dm^{-3} NaCl. The value obtained, $\Delta H^\circ = -13.41 \pm 0.03$ kcal mol^{-1}, is in satisfactory agreement with previously reported values.[16] A typical calorimetric experiment consisted of 10 injections (6 mm^3 each) of 0.2 mol dm^{-3} aqueous NaOH into the reaction cell containing 2 cm^3 of a 2×10^{-3} mol dm^{-3} solution of **1**·3HCl in NaCl (0.15 mol dm^{-3}). The enthalpies of protonation have been calculated using the least-squares program KK90, an updated version of a program previously used by this group.[17]

X-Ray Crystallography.—A colourless prism of approximate dimensions 0.10 × 0.20 × 0.65 mm was used.

Crystal data. $C_3H_{16}Cl_3N_3O$, triclinic, space group $P\bar{1}$ (no. 2), $a = 11.078(1)$, $b = 11.935(2)$, $c = 7.862(1)$ Å, $\alpha = 102.88(2)$, $\beta = 100.79(1)$, $\gamma = 81.07(1)°$, $U = 988.4(2)$ Å^3 (by least-squares refinement on diffractometer angles for 25 automatically centred reflections, $\lambda = 0.710\,69$ Å), $Z = 4$, $D_c = 1.46$ g cm^{-3}, $F(000) = 228$, μ(Mo-Kα) = 8.83 cm^{-1}. The complete crystal data are reported in Table 1.

Data collection and processing. Enraf-Nonius CAD-4 graphite monchromated Mo-Kα radiation, intensity data $-12 \le h \le 12$, $-13 \le k \le 13$, $0 \le l \le 9$ recorded in $\omega/2\theta$ scan mode for $5 < 2\theta < 55$, scan width of 0.70 + 0.35 (tan θ) and a variable scan rate with a maximum scan time of 60 s per reflection; three standard reflections ($\bar{3}\,\bar{2}\,\bar{2}$, $\bar{3}\,\bar{4}\,2$, $1\,\bar{5}\,1$) measured every 120 min showed no variation; 4863 reflections measured at 22 °C, Lp corrections, 3093 unique reflections with $F_o \ge 3\sigma(F)$. Absorption corrections were introduced by applying the DIFABS[18] program.

Structure analysis and refinement. Direct methods, anisotropic full-matrix least-squares refinement on F for all non-H atoms; all the H atoms isotropic; final refinement of 309 parameters gave $R = 0.036$, $R_w = 0.038$, weighting scheme $= 1/[\sigma^2_{(F)} + 0.005F^2]$; no maxima in last $\Delta\rho$ map higher than 1 e Å^{-3} were found. Scattering factors for neutral atoms including f' and f'' were taken from the SHELX package.[19]

The final atomic co-ordinates are listed in Table 2. Hydrogen-atom co-ordinates and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre.*

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* For details of the CCDC deposition scheme, see 'Instructions for Authors (1991),' *J. Chem. Soc., Perkin Trans. 2*, 1991, issue 1.

Table 1 Crystal data for propane-1,2,3-triamine trihydrochloride monohydrate

Formula	$C_3H_{16}Cl_3N_3O$
M	216.54
Crystal dimension/mm	0.10 × 0.20 × 0.65
Crystal system	Triclinic
Space group	$P\bar{1}$ (No. 2)
a/Å	11.078(1)
b/Å	11.935(2)
c/Å	7.862(1)
α/°	102.88(2)
β/°	100.79(1)
γ/°	81.07(1)
U/Å^3	988.4(2)
Z	4
D_c/g cm^{-3}	1.46
μ(Mo-Kα)/cm^{-1}	8.83
Radiation	graphite monchromatized Mo-Kα, λ = 0.710 69 Å
Scan mode	$\omega/2\theta$
2θ range/deg	5–55
Scan width/deg	0.70 + 0.35 (tan θ)
Scan speed/deg min^{-1}	8.24
Total data	4863
Unique data, $F \geq 3\sigma(F)$	3093
No. of parameters	309
R	0.036
R_w	0.038
Abs. correction min., max	0.87–1.15

Table 2 Atomic co-ordinates (× 10^4) with esds in parentheses for propane-1,2,3-triamine trihydrochloride monohydrate

	x/a	y/b	z/c
Cl(1)	4169(1)	4238(1)	2826(1)
Cl(2)	1861(1)	2788(1)	−3274(1)
Cl(3)	561(1)	4089(1)	2043(1)
Cl(4)	4137(1)	9718(1)	−2808(1)
Cl(5)	786(1)	9050(1)	−2537(1)
Cl(6)	1590(1)	7529(1)	2314(1)
C(1)	2069(2)	5737(2)	−3945(3)
C(2)	2467(2)	6423(2)	−2097(3)
C(3)	3162(2)	5623(2)	−872(3)
C(4)	2384(2)	2118(2)	2603(3)
C(5)	2428(2)	1464(2)	2535(3)
C(6)	2513(2)	1591(2)	687(3)
N(1)	936(2)	6299(2)	−4904(3)
N(2)	3273(2)	7308(2)	−2137(3)
N(3)	2278(2)	5046(2)	−266(3)
N(4)	1907(2)	730(2)	4172(3)
N(5)	3506(2)	1939(2)	3774(3)
N(6)	1283(2)	1593(2)	−4375(3)
O(1)	4737(3)	7982(3)	1015(4)
O(2)	5596(4)	3007(3)	6125(5)

Table 3 Stretching and bending parameters used in the molecular-mechanics investigation on **1**

(a) Bond	K_b/kJ Å^{-2}	r_o/Å
C–NH$_2$	3700	1.438
C–NH$_3^+$	3700	1.480
C–C	3012	1.50
C–H	3012	0.97
N–H	3398	0.91

(b) Angle	K_θ/kJ rad^{-2}	θ_o/rad
C–C–N	271	1.911
C–C–C	271	1.911
C–C–H	217	1.909
C–N–H	217	1.909
N–C–H	217	1.909
H–C–H	192	1.902
H–N–H	199	1.902

Molecular Mechanics.—The strain energies of the ligand were computed as the sum of six energy contributions: $E_{tot} = E_b + E_\theta + E_\varphi + E_{nb} + E_e + E_{hb}$ where E_b and E_θ are the bond length and bond angle deformations, E_φ is the torsional angle deformation, E_{nb} is the non-bonding interaction, E_e is the electrostatic interaction and E_{hb} is the hydrogen-bond interaction. The force field used was MM2.[20] Modification of the force field was necessary in order to reach a good agreement between the calculated and observed (solid state, X-ray diffraction analysis) structure. The force-field parameters used in this study are reported in Table 3. They are in good agreement with those previously used in molecular-mechanics studies on polyamines.[21] The total energy E_{tot} was minimized with the block diagonal matrix Newton–Raphson method[22] until the root mean square value (RMS) of the first derivative vector was less than 0.002 kJ Å^{-1}. The calculations were carried out by using the MacroModel package version 2.5[23] implemented on a DEC MicroVax 2000 computer with the graphic output on an Evans and Sutherland PS390.

The atomic-charge calculations for the three different protonation steps were performed by using the semiempirical method MNDO[24] and the AMPAC package[25] implemented on a DEC MicroVax 2000 computer.

The starting structures for the calculations on the $1\cdot H_3^{3+}$ cations were those obtained from the solid-state X-ray study. A conformational analysis was carried out to explore the range 0–360° for N(1)–C(1)–C(2)–C(3) and N(2)–C(2)–C(3)–N(3) torsion angles with a rotation step of 30°. The absolute minimum of the analysis, performed on both the molecules found in the asymmetric unit of the crystal lattice, is coincident with that obtained by minimizing the conformation of each single molecule. This conformational analysis was also extended to the deprotonated, monoprotonated and biprotonated ligand. About 990 conformations were submitted to energy minimization.

Results and Discussion

X-Ray Structure.—Bond lengths and angles are reported in Table 4. The crystal lattice contains two molecules of $1\cdot H_3^{3+}$ in the asymmetric unit together with six chloride ions and two water molecules (Fig. 1). The cell content is reported in Fig. 2. $1\cdot H_3^{3+}$ cations adopt a folded conformation probably due to the electrostatic repulsion between the three ammonium centres (see below for the molecular-mechanics analysis in the gas phase).

It must be noted that corresponding metric parameters for the two $1\cdot H_3^{3+}$ cations of the asymmetric unit have the same values. This means that the data are of good quality and that the $P\bar{1}$ space group is a reasonable choice in agreement with the analysis of the intensity statistics for the normalized structure factors.

The four C–C bond distances average 1.521(4) Å and range from 1.516(4) to 1.528(3) Å. It should also be noted that the unweighted mean over 5777 C–C bonds which carry only C or H substituents is 1.530(15) Å as measured by X-ray and neutron-diffraction techniques.[26]

The six C–N bond lengths average 1.485(4) Å and range from 1.479(3) to 1.494(4) Å. The unweighted mean over 298 C–N bonds is 1.488(13) Å.[26] The C–C(–N) and C–N bond lengths previously found for the tetrakis(ammoniomethyl)methane

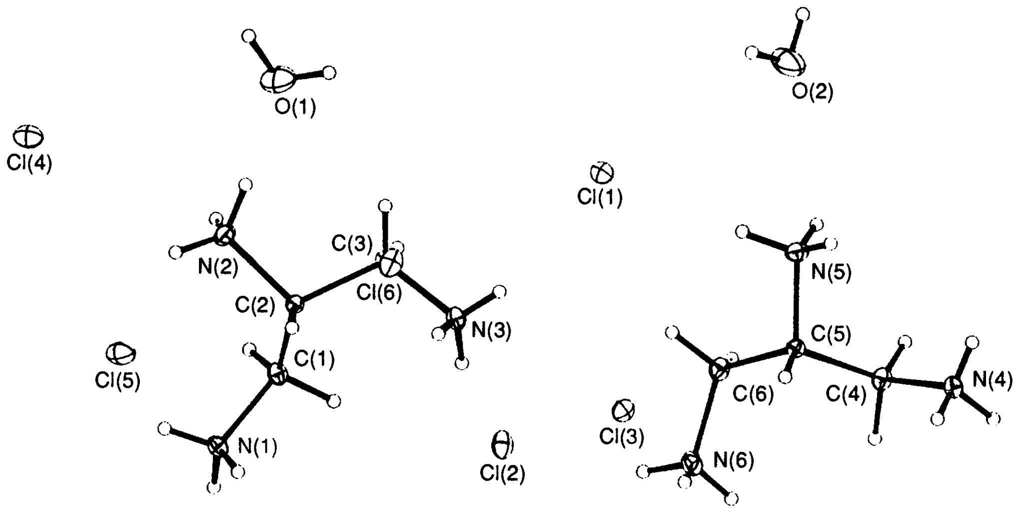


Fig. 1 ORTEP drawing of the asymmetric unit of **1**·3HCl·H_2O showing also the labelling scheme. The non H-atom ellipsoids enclose 30% probablity.

Table 4 Selected bond distances/Å, and bond and torsion angles/° for propane-1,2,3-triamine trihydrochloride monohydrate

C(1)–C(2)	1.522(3)	C(3)–N(3)	1.481(4)
C(2)–C(3)	1.528(3)	C(4)–N(4)	1.480(4)
C(4)–C(5)	1.516(4)	C(5)–N(5)	1.492(3)
C(5)–C(6)	1.516(4)	C(6)–N(6)	1.479(3)
C(1)–N(1)	1.484(3)	C–H[a]	0.96(4)
C(2)–N(2)	1.494(4)	N–H[a]	0.86(4)
C(1)–C(2)–C(3)	111.0(2)	C(2)–C(3)–N(3)	110.2(2)
C(4)–C(5)–C(6)	111.2(2)	C(5)–C(4)–N(4)	113.4(2)
C(2)–C(1)–N(1)	113.2(2)	C(4)–C(5)–N(5)	111.2(2)
C(1)–C(2)–N(2)	111.2(2)	C(6)–C(5)–N(5)	108.6(2)
C(3)–C(2)–N(2)	109.1(2)	C(5)–C(6)–N(6)	110.9(2)

C(1)–C(2)–C(3)–N(3)	−78.5(3)
C(4)–C(5)–C(6)–N(6)	80.2(3)
C(3)–C(2)–C(1)–N(1)	151.8(2)
C(6)–C(5)–C(4)–N(4)	−161.6(2)
N(1)–C(1)–C(2)–N(2)	−86.5(3)
N(4)–C(4)–C(5)–N(5)	77.2(3)
N(2)–C(2)–C(3)–N(3)	158.6(2)
N(5)–C(5)–C(6)–N(6)	−157.1(2)

[a] Mean values.

tetrachloride and putrescine dihydrochloride are 1.539(3) and 1.485(4) Å,[27] and 1.515(7) and 1.483(6) Å[28] respectively, in agreement with the values reported in this work.

The C–C–C bond angles for the two molecules are close to the canonical value for a sp^3 hybridization and average 111.1(2)°. In contrast, the C–C–N angles range from 108.6(2) to 113.2(2)°. The N(1)–C(1)–C(2) [113.2(2)°] and N(4)–C(4)–C(5) [113.4(2)°] bond angles deviate significantly from the values of the N(3)–C(3)–C(2) [110.2(2)°] and N(6)–C(6)–C(5) [110.9(2)°] angles. It should be pointed out that the two methylammonium residues linked to both C(2) and to C(5) atoms, respectively, are chemically equivalent for an isolated $\mathbf{1}\cdot H_3{}^{3+}$ cation. The differences reported above are probably due to the packing forces and, in particular, to strong hydrogen bonds involving the $\mathbf{1}\cdot H_3{}^{3+}$ cations, the chloride anions and the water molecules (Table 5). The molecular-mechanics energy-minimization carried out for the isolated molecule (see below) gave the same values for the two C–C–N(terminal) angles in both the molecules, confirming that intermolecular forces are responsible for the distortions.

Solution Studies.—The stepwise protonation constants of **1** are shown in Table 6. The agreement with the corresponding log K values reported in the literature (9.59, 7.95 and 3.72)[8] is excellent, taking into account the slightly different ionic strength and temperature conditions (0.10 mol dm^{-3} KCl and 293 K). In Table 6 the values of the protonation constants of the previously studied triamines **2** and **3** are also reported.[10] As expected, these ligands are more basic than **1** in all the protonation steps, owing to the presence of an extra $-CH_2-$ group in the aliphatic chain joining the amino groups, such a difference being particularly evident in the third step.

In Table 7 are reported the values of the stepwise standard enthalpy and entropy changes calculated for the three triamines. As already noted,[11] the $\Delta H°$ values for the protonation of **2** are very similar to those of **3** and they are nearly equal in the three steps. The values of the protonation enthalpies of **1** are nearly constant for the first two steps, being less than those of the other two triamines by *ca.* 0.7 kcal mol^{-1}. The third protonation step for **1** is appreciably less exothermic than that for **2** and **3**, the difference being more than 3 kcal mol^{-1}. The lower basicity of **1** with respect to **2** and **3** is due to these less favourable enthalpic contributions.

The $\Delta S°$ values for the protonation reactions of all these ligands are nearly the same in each step, even when they are corrected for the statistical term (see Table 7). This result can be simply explained by assuming that the solute–solvent interactions are approximately equal in each protonation stage of the three triamines. On the basis of these considerations it seemed interesting to perform molecular mechanics investigations on isolated molecules of **1** and its protonated forms. The force-field parameters obtained from this study may be useful in further investigations on the metal complexes of **1**.

Molecular Mechanics.—The structures of the most stable conformers (**I**–**III**) obtained by the conformational analysis on $\mathbf{1}\cdot H_3{}^{3+}$ are reported in Fig. 3. The geometrical parameters for **I** and **II** are reported in Table 8 and the energy contributions in Table 9. Structures **I** and **II** have a folded conformation whereas structure **III** has a stretched geometry. A comparison of bond distances and bond and torsion angles between structures **I** and **II** and the two molecules of the asymmetric unit, respectively, shows a good agreement between the energy-minimized and the X-ray structures. The C–C and C–N bond lengths average 1.540 and 1.504 Å in the calculated structures, respectively. The bond angles are well reproduced in the energy-minimized structures. The greatest differences are relevant to the C–C–N(terminal) bond angles. The two C–C–N(terminal) angles are 115.35 and 115.96° in the energy-minimized structure **I**. The same angles have very similar values in structure **II** (average 115.82°). These values confirm that the differences found for the

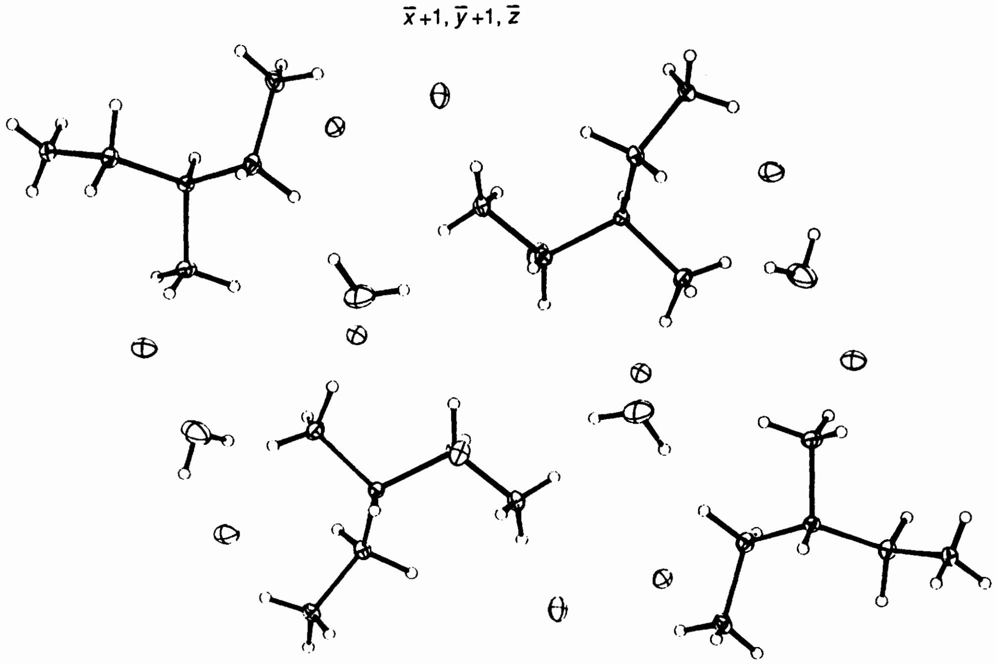


Fig. 2 A diagram showing four 1·3HCl·H_2O units

Table 5 Hydrogen bonds found in the crystal lattice of **1**·3HCl·3H_2O[a]

X Y		$d_{(x\cdots y)}$/Å	X–Ĥ···Y /°
N(1)···Cl(3)	$-x, -y+1, -z$	3.18	146.6
N(1)···Cl(6)	$x, y, z-1$	3.13	143.5
N(1)···Cl(3)	$x, y, z-1$	3.17	156.8
N(2)···Cl(1)	$-x+1, -y+1, -z$	3.20	143.6
N(2)···Cl(5)	x, y, z	3.19	140.8
N(2)···O(1)	x, y, z	2.73	166.6
N(3)···Cl(3)	$-x, -y+1, -z$	3.30	120.9
N(3)···Cl(6)	x, y, z	3.27	139.3
N(3)···Cl(2)	x, y, z	3.19	158.2
N(3)···Cl(1)	x, y, z	3.12	161.0
N(4)···Cl(6)	$x, y-1, z$	3.10	154.1
N(4)···Cl(5)	$-x, -y+1, -z$	3.14	139.6
N(4)···Cl(4)	$x, y-1, z+1$	3.14	156.0
N(5)···Cl(2)	$x, y, z+1$	3.11	148.6
N(5)···Cl(4)	$-x+1, -y+1, -z$	3.13	168.4
N(5)···Cl(1)	x, y, z	3.22	172.9
N(5)···O(2)	x, y, z	2.94	97.2
N(6)···Cl(2)	x, y, z	3.11	160.8
N(6)···Cl(5)	$x, y-1, z$	3.19	156.5
N(6)···Cl(3)	x, y, z	3.25	134.3
O(1)···O(2)	$-x+1, -y+1, -z+1$	2.87	164.7
O(2)···Cl(1)	x, y, z	3.29	109.2
O(2)···Cl(6)	$-x+1, -y+1, -z+1$	3.15	171.6
O(2)···Cl(1)	$-x+1, -y+1, -z+1$	3.25	161.3

[a] See ref. 30 for H-bond parameters.

Table 6 Logarithms of the stepwise protonation constants for **1** and related triamines at 298 K[a]

	1[b]	**2**[c]	**3**[c]
$L + H^+ = HL^+$	9.642(2)	10.157(1)	10.230(1)
$HL^+ + H^+ = H_2L^{2+}$	7.981(1)	8.253(2)	8.171(2)
$H_2L^{2+} + H^+ = H_3L^{3+}$	3.715(2)	5.853(3)	5.529(3)

[a] Values in parentheses are standard deviations on the last significant figure. [b] Ionic strength: 0.15 mol dm^{-3} NaCl. [c] Ionic strength: 0.5 mol dm^{-3} KNO_3.[10]

C–C–N(terminal) angles in the two molecules in the solid state are due to packing forces, reasonably hydrogen bonds. These intermolecular interactions are not considered in the present computations.

The lowest-energy minimim obtained for the **1**·$H_2{}^{2+}$ (**IV**) cations is reported in Fig. 4 and in Tables 8 and 9. The most stable structure for the biprotonated species is that in which the protons reside on the terminal nitrogen atoms. The driving force arises from the electrostatic term which stabilizes the cations protonated on N(1) and N(3) by *ca.* 20 kJ mol^{-1} with respect to the cations protonated on N(2) and N(terminal). It should be noted that the biprotonated cation is the prevailing species in aqueous solutions close to neutrality (see the protonation constants, Table 6). Moreover structure **IV** shows a significant elongation of the main chain due to the electrostatic repulsion between the terminal $-NH_3{}^+$ groups. This kind of conformation is that previously found for the spermine cation interacting with nucleic acid molecules.[5] Similar geometry was also found for **1**·$H_3{}^{3+}$ (Fig. 3, structure **III**) but with a relatively high strain energy in comparison with the folded conformations.

In the monoprotonated species, **1**·H^+, the N(terminal) protonated conformer **V** is found to be more stable than those protonated on N(2). The energy difference between the absolute minimum of the two forms is 24.86 kJ mol^{-1}, so that a significant percentage of the population of the N(2)-protonated species can be excluded. The stabilizing contribution comes from the electrostatic term (Table 9).

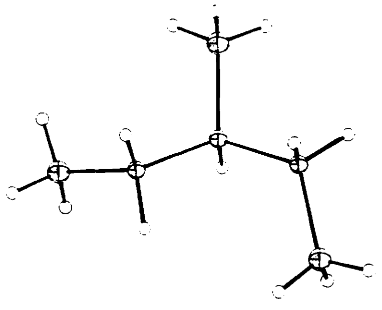
The metric parameters for the lowest-energy conformation obtained for the **1** (**VI**) are reported in Table 8. The C–C and C–N distances average 1.525 and 1.451 Å, respectively. The conformation shows an almost symmetrical structure around the C(2)–N(2) axis.

As can be seen from Table 9, the total strain energies diminish on decreasing the degree of protonation. In particular, it should be emphasized that the energy associated with the triprotonated cation is very high with respect to the energies of the other

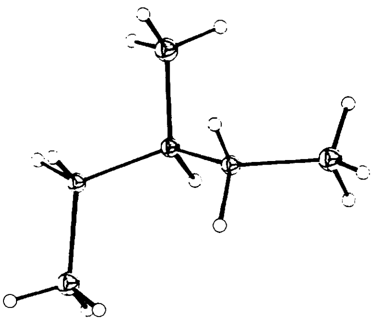
Table 7 Enthalpy/kcal mol^{-1} and entropy/cal K^{-1} mol^{-1} changes for the stepwise protonation of **1** and related triamines at 298 K[a]

	1[b]		**2**[c]		**3**[c]	
Step	$-\Delta H^\circ$	ΔS°	$-\Delta H^\circ$	ΔS°	$-\Delta H^\circ$	ΔS°
1	10.97(4)	7.3(2)	11.72(4)	7.2(1)	11.48(2)	8.3(1)
2	11.07(7)	−0.6(2)	11.65(3)	−1.3(1)	11.68(2)	−1.8(1)
3	8.52(8)	−11.6(3)	11.71(2)	−12.5(1)	11.94(1)	−14.7(1)
1		6.0(2)[d]		5.0(1)[d]		6.1(1)[d]
2		0.7(2)[d]		−1.3(1)[d]		−1.8(1)[d]
3		−11.6(3)[d]		−10.3(1)[d]		−12.5(1)[d]

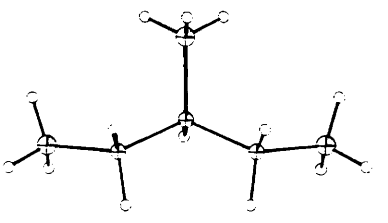
[a] Values in parentheses are standard deviations on the last significant figure. [b] Ionic strength: 0.15 mol dm^{-3} NaCl. [c] Ionic strength: 0.5 mol dm^{-3} KNO$_3$.[1] [d] Values corrected for the statistical term.



I E = 330.87 kJ mol^{-1}



II E = 332.01 kJ mol^{-1}

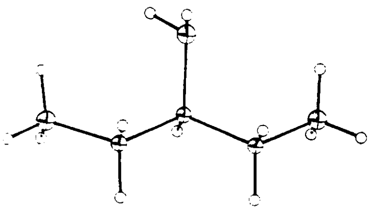


III E = 343.97 kJ mol^{-1}

Fig. 3 ORTEP drawing of the three most stable structures (I–III) obtained with the molecular-mechanics investigation on $1{\cdot}H_3{}^{3+}$. The strain energy of each conformation is reported.

species. Preliminary calculations performed on **3*** confirm the same trend in the total strain energies. In particular, the energy difference between $3{\cdot}H_3{}^{3+}$ and $3{\cdot}H_2{}^{2+}$ is found to be 206.0 kJ mol^{-1} while the corresponding value for **1** is 209.7 kJ mol^{-1}. The comparison of the above-reported values shows that, in the third protonation step, the strain-energy contribution is slightly more unfavourable for **1** with respect to **3**. This result is in good qualitative agreement with the observed lower exothermicity of the third protonation step of **1** with respect to **3**.

In conclusion, we propose that the low basicity of the third protonation site [probably the N(central) atom] and the



IV

Fig. 4 ORTEP drawing of the most stable energy-minimized structure of $1{\cdot}H_2{}^{2+}$ (IV) obtained from the molecular-mechanics investigation

Table 8 Bond lengths/Å, bond and torsion angles/° in the absolute minima of energy-minimized structures of **1** in the three different protonation steps. For a comparison with the solid-state structure see Table 4

	Energy-minimized structures				
	$1{\cdot}H_3{}^{3+}$		$1{\cdot}H_2{}^{2+}$	$1{\cdot}H^{+}$	**1**
	I	II	IV	V	VI
C(1)–C(2)	1.540	1.540	1.526	1.525	1.525
C(2)–C(3)	1.540	1.540	1.526	1.522	1.525
C(1)–N(1)	1.503	1.503	1.503	1.450	1.450
C(2)–N(2)	1.507	1.507	1.453	1.452	1.453
C(3)–N(3)	1.502	1.502	1.495	1.493	1.450
C–H[a]	0.979	0.979	0.978	0.977	0.976
N–H[a]	0.860	0.913	0.905	0.895	0.881
C(1)–C(2)–C(3)	112.3	112.3	112.3	111.8	111.2
C(2)–C(1)–N(1)	116.0	116.1	112.7	112.9	113.1
C(1)–C(2)–N(2)	112.5	112.6	111.5	111.5	110.9
C(3)–C(2)–N(2)	109.9	109.7	108.9	109.0	110.0
C(2)–C(3)–N(3)	115.3	115.4	111.2	110.8	112.6
C(1)–C(2)–C(3)–N(3)	69.7	−69.7	177.7	179.1	173.9
C(3)–C(2)–C(1)–N(1)	−162.6	161.1	−173.4	−173.5	−173.5
N(1)–C(1)–C(2)–N(2)	72.7	−74.3	64.1	64.2	63.7
N(2)–C(2)–C(3)–N(3)	−164.2	164.1	−58.3	−57.1	−62.7

[a] Mean values.

Table 9 Energy contributions and final strain energies/kJ mol^{-1} of the absolute minima for **1** in the three protonation steps. The energy contributions for structure II are also reported

	Structures				
	$1{\cdot}H_3{}^{33+}$		$1{\cdot}H_2{}^{2+}$	$1{\cdot}H^{+}$	**1**
	I	II	IV	V	VI
Bond-length deformation	8.25	8.30	3.56	2.89	3.06
Bond-angle deformation	10.36	10.51	3.84	2.91	2.98
Torsion-angle deformation	1.97	2.10	0.04	−4.29	−8.48
Non-bonded interaction	3.58	3.61	11.22	16.58	20.14
Electrostatic interaction	306.71	307.49	102.52	32.76	10.77
Total strain energy	330.87	332.01	121.18	50.85	28.47

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* The computations were carried out for isolated molecules following the procedure described for **1**. The starting structure was that observed in the solid state.[29]

stretched conformation for the most stable structure of $\mathbf{1}\cdot H_2^{2+}$ suggest that the triamine **1** may exhibit spermine-like behaviour towards nucleic acids at physiological pH. Experimental studies in this direction should prove worthwhile.

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