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Crystal structures of the nitrate salt of 24-pyrimidinium crown 6 {5,12,19,26,33,40-hexaamino-3,10,17,24,31,38-hexamethyl[1.$_6$]-(1,5)pyrimidiniophane} and its degradation product in water–methanol mixtures

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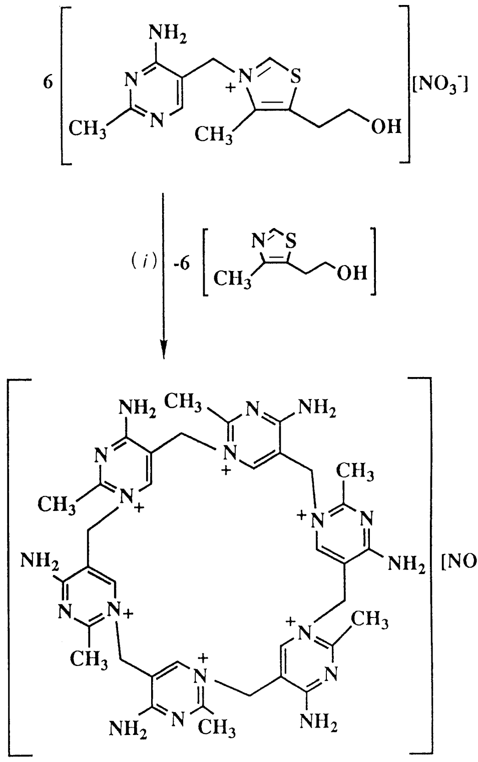
Reflux of thiamin [3-(4-amino-2-methylpyrimidin-5-ylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium] mononitrate in methanol for 2 h, followed by recrystallization from methanol, produced single crystals of $[L][NO_3]_6 \cdot 16H_2O$ {L = 5,12,19,26,33,40-hexaamino-3,10,17,24,31,38-hexamethyl[1.$_6$](1,5)pyrimidiniophane, or 24-pyrimidinium crown 6}. The compound crystallizes in the rhombohedral space group $R\bar{3}$, $a = b = c =$ 14.131(11) Å, $\alpha = \beta = \gamma = 115.26(5)°$, $Z = 1$, $R = 0.0469$, 1352 independent reflections with $F > 2.0\sigma(F)$. Reflux of $[L][NO_3]_6 \cdot 16H_2O$ in methanol–water (3:2) for 182 h produced single crystals of the nitric acid salt of 4-amino-5-methoxymethyl-2-methylpyrimidine. The compound crystallizes in the triclinic space group $P\bar{1}$, $a = 9.116(6)$, $b = 9.452(5)$, $c = 12.742(8)$ Å, $\alpha = 101.14(5)$, $\beta = 107.13(5)$, $\gamma = 93.27(5)°$, $Z = 4$, $R = 0.0644$, 2690 independent reflections with $F > 2.0\sigma(F)$. The nitric acid salt of 4-amino-2-methylpyrimidine-5-methanol has been isolated and identified by ^{1}H NMR spectroscopy from the thermal decomposition reaction of $[L][NO_3]_6 \cdot 16H_2O$ in water. The alcohol has also been observed by ^{1}H NMR spectroscopy in the decomposition of $[L]^{6+}$ in aqueous solutions at room temperature.

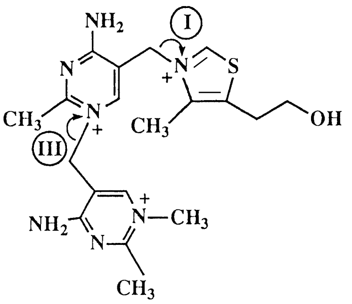
Thiamin [3-(4-amino-2-methylpyrimidin-5-ylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium] (vitamin B_1) was first shown to be rapidly destroyed by sulfite ion in aqueous solution by Williams,[1] fragmenting the molecule into the soluble thiazole portion and the insoluble pyrimidinesulfonate ion. Nearly forty years later, Shimahara *et al.*[2] reported a pyrimidinium oligomerization upon reflux in methanol resulting from what Zoltewicz *et al.*[3] later found to be a second-order thiazole displacement of one thiamin molecule by the pyrimidine nucleophile of a second thiamin. The compound was first inferred from chemical analysis and mass spectrometry to possess a pentameric structure. However, X-ray crystallographic studies[4] of a solid oligomer isolated and recrystallized by Evangelista[5] following the synthetic procedure of Shimahara *et al.* have since shown it to be the cyclic, hexameric 5,12,19,26,33,40-hexaamino-3,10,17,24,31,38-hexamethyl[1.$_6$](1,5)[pyrimidiniophane (24-pyrimidinium crown-6) salt, $[L][NO_3]_6$, shown in Scheme 1. Although crystal structures of the $[L]^{6+}$ cation have been reported in which the novel $[Hg_2I_7]^{3-}$,[6] $[Ba(NO_3)_6]^{4-}$, and $[Pb(NO_3)_6]^{4-}$ anions[7] occur, to date the crystal structure of the parent compound, the simple hexanitrate salt, has not been reported.

It can be concluded from the mechanistic studies of Zoltewicz *et al.*[3] that, by increasing the number of linked pyrimidinium groups, as in the $[L]^{6+}$ cation, the electrophilicity of the resultant molecule is increased, thus increasing its reactivity toward incoming nucleophiles. As shown in Scheme 2, it has been reported that the 1-(4-amino-1,2-dimethylpyrimidin-5-yl)thiaminium trication is 19 times more susceptible to loss of the thiazole group (I) than the 1-methylthiaminium dication (II), which contains just one less pyrimidinium group.[3] However, it was also found that cleavage of the bond between the methylene-carbon and the thiazole-nitrogen atom in this bis(pyrimidinium)-containing compound (I) was only twice as fast as breaking the bridging methylene/pyrimidinium-nitrogen bond (III). If thiazole cleavage becomes easier with increased pyrimidinium chain length, then so too may pyrimidinium cleavage. This has led to questions regarding the stability of the 24-pyrimidinium crown 6 cation in nucleophilic solvents. Indeed, even thiamin has been observed to yield hydrolytic decomposition products, one of which is 4-amino-2-methylpyrimidine-5-methanol.[8] Thus, since we have been studying the $[L]^{6+}$ cation in either pure or mixed aqueous media, it became apparent that it was necessary to investigatge the degradation of the cation in water and water–methanol mixtures.

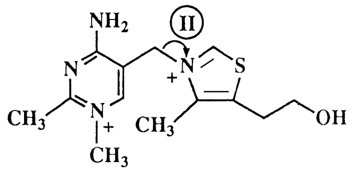


$[L][NO_3]_6$

Scheme 1 (*i*) Heat, MeOH



1-(4-amino-1,2-dimethylpyrimidin-5-yl)-thiaminium trication



1-methylthiaminium dication

Scheme 2

Experimental

Thiamin mononitrate was used as purchased (U.S. Biomedical Corp.) as were all reagent-grade solvents. A GE QE-300 FT spectrometer was employed to obtain ^1H NMR spectra with sodium 3-(trimethylsilyl)tetradeuteriopropionate as reference. Melting points were determined on a Fisher-Johns apparatus. A Corning Digital 109 pH meter was used to monitor solution pH. Mass spectra were recorded on a VG-70SE dual-focusing, high-resolution mass spectrometrer in electron-impact mode.

Syntheses

$[L][NO_3]_6\cdot16H_2O$. Crystals of $[L][NO_3]_6\cdot16H_2O$ were synthesized using a modification of the procedure reported by Shimahara *et al.*[2] Thiamin mononitrate (4.56 g, 0.014 mol) was refluxed in absolute methanol (150 cm^3) for 2 h, giving a white precipitate that was collected on a glass frit, washed with methanol (5 cm^3) and air dried. The crude product was dissolved in the minimum volume of deionized water and allowed to crystallize from the solution by slow evaporation of the solvent, yield 0.87 g (34%), decomp. 203 °C.

To 100 cm^3 of methanol was added 0.072 g of the recrystallized product. The methanol was heated to boiling, at which temperature most of the product had dissolved. The solution was quickly filtered to remove any undissolved compound, and the methanol was allowed slowly to evaporate, yielding colourless, nearly hexagonally shaped blocks. δ_H\{300 MHz, D_2O $[(CD_3)_2SO]$\} [9.45, 8.81] (12 H, s, s, 6 NH_2), 7.82 [7.83] (6 H, s, 6 CH), 5.25 [5.21] (12 H, s, 6 CH_2) and 2.66 [2.65] (18 H, s, 6 CH_3).

$[C_6H_9N_3OCH_3][NO_3]$. To absolute methanol (30 cm^3) was added deionized water (20 cm^3). To this solvent mixture was added $[L][NO_3]_6\cdot16H_2O$ (0.8832 g, 6.3×10^{-4} mol). The solution was heated to reflux with stirring for 182 h. After this time the solution had become slightly yellow. It was transferred to a crystallizing dish and the solvent allowed to evaporate, yielding transparent, colourless crystals suspended in a thick yellow oil. The crystals were isolated by dissolving the oil in absolute methanol and filtering through a glass frit; m.p. = 160–162 °C. δ_H\{300 MHz; D_2O $[(CD_3)_2SO]$\} [9.33, 8.54] (2 H, s, s, NH_2), 8.08 [8.09] (1 H, s, CH), [7.02] [1 H, t, *J*(NH) 52 Hz, NH], 4.48 [4.34] (2 H, s, CH_2), 3.42 [3.34] (3 H, s, OCH_3) and 2.57 [2.55] (3 H, s, CH_3). *m/z* 153.

$[C_6H_9N_3OH][NO_3]$. To deionized water (50 cm^3) was added $[L][NO_3]_6\cdot16H_2O$ (0.8684 g, 6.2×10^{-4} mol). The solution was heated to reflux with stirring for 7 d. It was transferred to a crystallizing dish and the solvent allowed to evaporate, depositing white crystals suspended in a thick yellow oil. The crystals were isolated by dissolving the oil in absolute methanol, decanting the solvent, and allowing the product to dry in air, yielding $[C_6H_9N_3OH][NO_3]$ (0.215 g, 28%), m.p. = 180–182 °C. δ_H\{300 MHz, D_2O $[(CD_3)_2SO]$\} [8.93] (2 H, s, NH_2), 7.99 [8.08] (1 H, s, CH), [7.21] [1 H, t, *J*(NH) 49 Hz, NH], 4.57 [4.36] (2 H, s, CH_2) and 2.56 [2.47] (3 H, s, CH_3).

Degradation studies

The long-term stability of $[L][NO_3]_6\cdot16H_2O$ in water at ambient temperatures was monitored by dissolving the compound in D_2O and observing its ^1H NMR spectrum over time. The pH of these solutions was adjusted by the addition of HNO_3. The short-term stability of $[L][NO_3]_6\cdot16H_2O$ in water and water–methanol mixtures at elevated temperatures was evaluated as described above for the synthesis of $[C_6H_9N_3OH][NO_3]$ and $[C_6H_9N_3OCH_3][NO_3]$, respectively.

Crystallography

Data were collected on a Nicolet R3mv diffractometer at 293(2) K with Mo-Kα radiation (λ 0.710 73 Å).

A crystal of $[L][NO_3]_6\cdot16H_2O$ was prepared as above and glued to a glass fibre, which was then fixed to the goniometer head. The unit cell was determined to be rhombohedral based on reflections with θ values between 7.5 and 15°. Three check reflections, which showed no decrease in intensity throughout data collection, were monitored after every 97th reflection. Table 1 summarizes the crystal data and parameters. A crystal of $[C_6H_9N_3OCH_3][NO_3]$ was sealed in a glass capillary tube which was then fixed to the goniometer head. The unit cell was determined to be triclinic. Other details as above.

Structure solution and refinement. $[L][NO_3]_6\cdot16H_2O$. The structure was solved using the direct methods package of SHELX 86.[9] The solution with the best combined figure of metit showed all of the atoms of one pyrimidinium unit and one nitrate ion. These atoms were refined *via* least squares using SHELXL 93[10] and a Fourier-difference map was calculated. Two water molecules were apparent and were included in the calculation. At this point the major features of the structure were clear, however a cluster of small peaks associated with the cavity of the cation remained unidentified. Two small peaks, one of which was located on the three-fold axis and the other in a general position, resembled a nitrate ion with a suitable N−O distance. However, since N(10) appeared to be fully occupied, charge balance did not require any nitrate ions to be associated with the cavity. Thus, inclusion of a nitrate ion on the three-fold axis, at the position reported here as N(20), resulted in too much nitrate ion in the structure. Therefore, the occupancy of the N(10) nitrate ion was refined using a group occupancy parameter to 0.940(3), giving a total occupancy of this nitrate position in the unit cell as 5.64. Since a total of six nitrate ions per unit cell are needed to balance the charge of the $[L]^{6+}$ cation, the N(20) position could account for the remaining 0.36 nitrate ions. Occupancy refinement of the N(20) position was performed yielding a value near the required amount, and so the occupancies of the N(10) and N(20) nitrates were constrained to a total value of 1.0 using a group occupancy parameter.

After inclusion of the N(20) and O(20) positions, several small peaks remained in the vicinity of the cavity. These were included as partially occupied water molecules, O(3), O(4), O(5) and O(6): O(3) is located on the centre of inversion at the centre of the cavity, O(4) on a general position near N(20), O(5) at a general position near O(2) and O(6) on a general position near O(20). The occupancies of these four atoms refined to 0.136(6), 0.19(3), 0.25(2) and 0.26(3), respectively. Since these positions are disordered and partially occupied it was necessary to apply some constraints.

Three constraints were used on the N(20) and O(20) positions in addition to the group occupancy constraint mentioned above. A FLAT instruction was used to make the nitrate anion more planar, a DFIX instruction to improve the N–O bond distances and a SIMU instruction to make the N(20) and O(20) thermal parameters similar. A SUMP instruction was applied to the occupancies of O(3) and O(4), which are located too close to each other to be present simultaneously, to restrain the sum of their occupancies in the unit cell to be 100%. Only after inclusion of all of these fractionally occupied atoms associated with the cavity of the cation it was possible to achieve a satisfactory refinement with sensible occupancy parameters and positive thermal parameters. The structure reported here with two partially occupied nitrate positions as well as several partially occupied waters is unusual and invites skepticism as to its accuracy. However, in the course of studying this system, we have obtained crystals of the compound on several occasions, and each of these is indistinguishable from that reported here in terms of nitrate and water occupancies. Partial nitrate ion occupancies are not uncommon, as they have been reported in the crystal structures of both the 16-pyrimidinium crown 4 cation, $[L']^{4+}$ [11] and the 9,12-dioxa-1,3,6,15,18,21-hexaazacyclotetracosane.[12]

Hydrogen atoms were included at calculated positions and allowed to 'ride' upon the atoms to which they are bonded. Hydrogen atoms on O(1) and O(2) were located in Fourier-difference maps and refined isotropically. A thermal parameter was refined for H(6) while group thermal parameters were refined for the methyl and methylene protons. In the final cycle of refinement all non-hydrogen atoms were refined anisotropically except for O(3), O(4), O(5) and O(6), the water molecules with the smallest occupancies. An absorption correction, which did not significantly improve *R*, was not included in the final model. Bond lengths and angles are listed in Tables 2 and 3.

$[L][Pb(NO_3)_6][NO_3]_2$. The arrangement of the nitrate ions with respect to the $[L]^{6+}$ cation in the above structure prompted us to re-examine the nitrate ions which were found to be associated with the cavity of the same cation in the structures of $[L][M(NO_3)_6][NO_3]_2$, where M = Pb or Ba.[7] In those isostructural compounds we had reported a nitrate ion located on the three-fold axis which we designated N(2). We reported two oxygen positions for this nitrate, O(21), which was 75% occupied, and O(22), which occupied the remaining 25%. The O(21) position formed a nitrate ion of good geometry, while that at O(22) gave a bond angle of 101° in the lead structure, a very unlikely value for a nitrate ion. This led us to question whether the O(22) position was actually that of a nitrate ion, or some other species. The program SHELXL 93 has many tools which allow one better to refine a disordered structure, and so we decided to apply it to the $[L][Pb(NO_3)_6][NO_3]_2$ data set.

Holding the occupancy of N(2) and O(21) fixed at full occupancy, we applied a FLAT constraint and refined these positions anisotropically. This lowered the *R* value by about 0.3%. In the resulting Fourier-difference map two peaks of about 0.45 e $Å^{-3}$ remained. One of these peaks was located on the inversion centre at the centre of the cavity (1/3, 2/3, 1/6), while the other was near the originally reported O(22) site. These two sites were separated by about 1.25 Å, which suggested that they represented a nitrate ion. They were included as N(30) and O(30) and their occupancies were refined. The occupancy of O(30) refined to about three times that of N(30), as would be expected for a nitrate ion, and so the occupancies of these two atoms were further refined using a group occupancy parameter, which refined to 2.7(5)%. Inclusion of these two positions lowered *R* by about 0.1%. Since the nitrate ion at N(30) is only 1.75 Å from that at N(2) they cannot be occupied at the same time. Therefore, the occupancy of the N(2) nitrate was refined, yielding a value of 0.275(6) in a position which has a maximum occupancy of 0.333. Refinement of this occupancy factor lowered *R* by a further 0.2%. The deficiency, $0.333 - 0.275 = 0.058$, is very close to twice the occupancy of the N(30) site, 0.027(5). This must be the case, since for each nitrate which occupies the N(30) site a nitrate must be lost from both of the N(2) locations, above and below the cavity.

Since the total charge of the cation is +6, and the $[Pb(NO_3)_6]^{4-}$ anion is fully occupied, there must be a total of two nitrate ions associated with the cavity. The amount accounted for in our model is $(0.027 \times 6) + (0.275 \times 6) = 1.81$. Therefore, 0.19 of a nitrate ion remains missing. It is reasonable that when the centre of the cavity is occupied by N(30) the nitrate ion at N(2) remains on the three-fold axis, but moves further away from the centre of the cavity. The occupancy of such a position would be $0.19/6 = 0.03$, a very small amount which would likely be difficult to find.

The 1.25(6) Å bond distance of the nitrate ion at N(30) is reasonable, while the bond angle is 108(4)°. While the error associated with both of these parameters is very high due to the low occupancy of this site, they are within 3σ of the expected values for a nitrate ion. Further, it may be that the nitrogen atom does not lie exactly on the inversion centre, so that confining it to that position may cause some distortion of the geometry of this nitrate ion. However, attempts to refine N(30) off the inversion centre were not successful, which is not surprising in view of its tiny occupancy.

The final *R* value for this model is 0.0273, which represents a significant improvement over the 0.0343 which we reported earlier.[7] The bond distances and angles within the $[Pb(NO_3)_6]^{4-}$ anion and the $[L]^{6+}$ cation are less than 1σ different from those previously reported, however due to the lower *R* value the standard deviations on those parameters are considerably lower. The metrical parameters for this improved structure are included in the supplementary material.

$[C_6H_9N_3OCH_3][NO_3]$. The structure was solved with great difficulty using the direct methods option of SHELXS 86.[9] The minimum *E* value was increased to 1.65 and a SUBS 8 instruction was used. This gave a solution with a combined figure of merit of 0.165 and an *R* value on *E* of 0.242. The *E* map revealed one pyrimidinium ring. Using these atoms as input, several additional cycles of direct methods and Fourier-difference maps eventually revealed the second pyrimidinium ring and all substituents on both rings. A Fourier-difference map generated by SHELXL 93 and based on these positions revealed a nitrate ion which was successfully included in the model. At this point we realized the structure was that of the nitric acid salt of the pyrimidine moiety. Another Fourier map revealed the second nitrate ion.

Hydrogen atoms were included at calculated positions and were refined 'riding' on the atom to which they were attached using isotropic thermal parameters. Examination of the Fourier-difference map showed disorder of the hydrogen atoms on methyl carbon C(21A), so two sets of half-occupied hydrogen atoms were included. All non-hydrogen atoms were refined using anisotropic thermal parameters. Bond lengths and angles are listed in Tables 2 and 3.

Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 186/453.

Results and Discussion

The crystal structures

$[L][NO_3]_6\cdot 16H_2O$. The asymmetric unit of $[L][NO_3]_6\cdot 16H_2O$ consists of a pyrimidine ring with its substituents, a 94.0(3)% occupied nitrate ion, one O atom and one N atom of the lesser

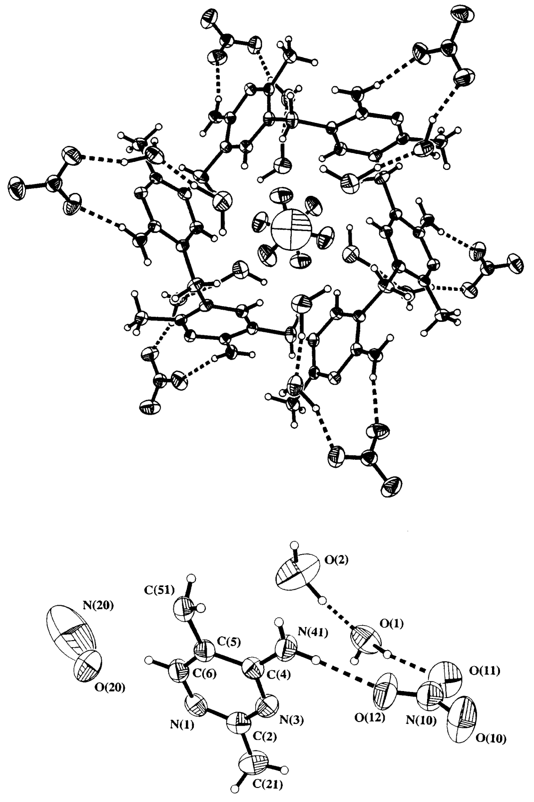


Fig. 1 Perspective view of the crystal structure of the asymmetric unit (inset, with 50% probability thermal parameters) and of the complete $[L][NO_3]_6$, with 25% probability thermal parameters. Atoms O(3), O(4), O(5) and O(6) have been removed for clarity

occupied nitrate ion, and one fully and five partially occupied water molecules. As seen in Fig. 1 the $R\bar{3}$ symmetry operations generate a unit cell containing one $[L]^{6+}$ cation, six nitrate ions with occupancies of 94.0(3)%, two nitrate ions with occupancies of 18.0(9)% each, and six fully and twentyfive partially occupied water sites. The partially occupied oxygen atoms O(3), O(4), O(5) and O(6) are not shown in Fig. 1 for clarity.

Although the bond lengths and angles of the cation, while more precise, are indistinguishable from those reported previously,[6,7] there is an important structural difference. This is illustrated by the dihedral angles between the pyrimidinium planes which have been reported as 105° for a structure in which $[HgI_4]^{2-}$ and $[HgI_3{\cdot}dmso]^-$ anions[6] were associated with the cavity and 94 and 92° for the $[M(NO_3)_6]^{4-}$ structures, where M = Pb and Ba, respectively.[7] In the structure reported here this interpyrimidinium dihedral angle is 90.3°. These structural differences are better understood by examining the dihedral angles formed between the pyrimidinium planes and the mean plane of the cyclic cation as defined by the six C(6) atoms. In the structure in which an iodide ligand of a $[HgI_4]^{2-}$ ion occupies the centre of the cavity,[6] the three dihedral angles of this type produced by the three crystallographically independent pyrimidinium rings are 66.2, 64.3 and 67.0°. In the $[L][M(NO_3)_6][NO_3]_2$, where M = Pb or Ba, the unique pyrimidinium plane forms an angle of 57.5°, while in the present structure this dihedral angle is 57.6°. In these latter three structures two nitrate ions are associated above and below the cavity in much the same way. Therefore, occupation of the centre of the cavity by a bulky iodide ligand causes this dihedral angle to increase, producing a larger, 4.35 Å cavity, as defined by the H(6) · · · H(6) distance of 6.75 Å minus a hydrogen van der Waals diameter of 2.4 Å. On the other hand, the cavity of the present structure is 3.45 Å, which is very similar to that found in the $[L][M(NO_3)_6][NO_3]_2$ structures.[7]

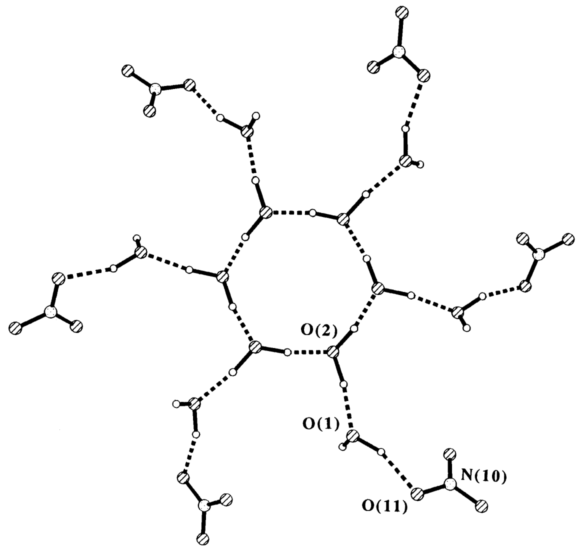


Fig. 2 Perspective view showing the hydrogen-bonding interactions between the major nitrate ions [centred at N(10)], the fully occupied waters [O(1)], and the 75%, partially occupied waters [O(2)] of $[L][NO_3]_6$

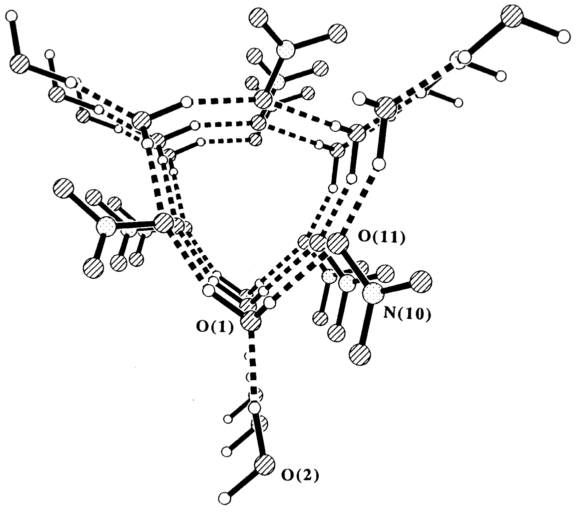


Fig. 3 Perspective view showing the N(10), O(1) hydrogen-bonding spiral in $[L][NO_3]_6$

The $[L]^{6+}$ cation is associated with an interesting cluster of 12 water molecules, six of which are fully occupied, the other six being 75(2)% occupied. Fig. 2 shows the hydrogen-bonding structure of these water molecules. The partially occupied O(2) waters are arranged in a similar manner to the puckered, six-membered rings that make up the structure of ordinary ice I, with O(2) · · · O(2) distances of 2.64 Å, O(2)–H(2a) distances of 1.02 Å, and H(2a) · · · O(2) distances of 1.66 Å (*cf.* bond distances of 2.75, 1.01 and 1.74 Å, respectively, for the ice I structure at 100 K).[13] The second hydrogen atom of the O(2) water molecule, H(2b), points towards the fully occupied O(1) atom. Again, strong hydrogen bonding is observed, with an O(1) · · · O(2) distance of 2.81 Å. Fig. 3 shows that, through interaction of both hydrogen atoms of the O(1) water molecule with two symmetry-equivalent O(11) atoms of the nitrate ions, an infinite spiral structure, which is positioned alongside the stacked $[L]^{6+}$ cations, is generated. The formation of two hydrogen bonds by each O(11) accounts for the elongated N(10)–O(11) bond of 1.255(4) Å, as compared with the N(10)–O(10) and N(10)–O(12) bonds, which are 1.225(4) and 1.224(4) Å, respectively. The positions occupied by the N(10) nitrate ions and the O(1)

Table 1 Crystal data and details of data collection and refinement procedures[a]

	$[L][NO_3]_6\cdot16H_2O$	$[C_6H_9N_3OCH_3][NO_3]$
Empirical formula	$C_{36}H_{72}N_{24}O_{34}$	$C_7H_{12}N_4O_4$
M	1385.18	216.21
Crystal structure	Rhombohedral	Triclinic
Space group	$R\bar{3}$	$P\bar{1}$
a/Å	14.131(11)	9.116(6)
b/Å	14.131(11)	9.452(5)
c/Å	14.131(11)	12.742(8)
α/°	115.26(5)	101.14(5)
β/°	115.26(5)	107.13(5)
γ/°	115.26(5)	93.27(5)
U/Å^3	1541(2)	1021.8(11)
Z	1	4
D_c/Mg m^{-3}	1.492	1.405
μ/mm^{-1}	0.132	0.116
F(000)	728	456
Crystal size/mm	0.55 × 0.41 × 0.22	0.60 × 0.50 × 0.11
Index ranges	$-14 < h, k, l < 15$	$-9 < h < 9$, $-10 < k < 10$, $0 < l < 13$
Reflections collected	4429	2951
Independent reflections (R_{int})	1352 (0.0228)	2690 (0.0246)
Data, restraints, parameters	1258, 12, 187	2544, 0, 282
Goodness of fit on F^2	1.088	1.029
Final $R1$, $wR2$ indices $[I > 2\sigma(I)]$[b]	0.0469, 0.1201	0.0644, 0.1769
(all data)	0.0696, 0.1359	0.0791, 0.1918
Largest difference peak and hole/e Å^{-3}	0.266, −0.232	0.334, −0.301
a, b	0.0696, 0.4399	0.1471, 0

[a] Details in common: θ range for data collection 1.71–22.55°; full-matrix least-squares refinement on F^2. [b] $w = 1/[\sigma^2(F_o^2) + aP^2 + bP]$, $P = (F_o^2 + 2F_c^2)/3$.

Table 2 Bond lengths (Å) for $[L][NO_3]_6\cdot16H_2O$ and $[C_6H_9N_3OCH_3][NO_3]$

		$[C_6H_9N_3OCH_3][NO_3]$	
	$[L][NO_3]_6\cdot16H_2O$	A	B
N(1)–C(2)	1.367(4)	1.333(4)	1.348(4)
N(1)–C(6)	1.369(4)	1.372(5)	1.358(4)
N(1)–C(51)	1.477(4)	—	—
C(2)–N(3)	1.310(4)	1.324(4)	1.324(4)
C(2)–C(21)	1.490(5)	1.509(5)	1.489(4)
N(3)–C(4)	1.366(4)	1.367(4)	1.349(4)
C(4)–N(41)	1.318(4)	1.320(4)	1.327(4)
C(4)–C(5)	1.424(4)	1.423(5)	1.442(5)
C(5)–C(6)	1.349(4)	1.344(5)	1.342(5)
C(5)–C(51^{I})	1.518(4)	1.515(5)	1.505(5)
C(51)–O(61)	—	1.405(4)	1.411(5)
O(61)–C(61)	—	1.435(5)	1.393(5)
N(10)–O(10)	1.225(4)	1.276(4)	1.240(4)
N(10)–O(11)	1.255(4)	1.226(4)	1.216(4)
N(10)–O(12)	1.224(4)	1.211(4)	1.235(4)
N(20)–O(20)	1.246(9)	—	—

Symmetry transformation used to generate equivalent atoms for $[L][NO_3]_6\cdot16H_2O$: I $-y + 1$, $-z + 1$, $-x + 1$.

Table 3 Bond angles (°) for $[L][NO_3]_6\cdot16H_2O$ and $[C_6H_9N_3OCH_3][NO_3]$

		$[C_6H_9N_3OCH_3][NO_3]$	
	$[L][NO_3]_6\cdot16H_2O$	A	B
C(2)–N(1)–C(6)	118.8(2)	120.5(3)	121.1(3)
C(2)–N(1)–C(51)	121.7(2)	—	—
C(6)–N(1)–C(51)	119.3(3)	—	—
N(3)–C(2)–N(1)	122.0(3)	123.0(3)	121.3(3)
N(3)–C(2)–C(21)	118.9(3)	119.4(3)	120.6(3)
N(1)–C(2)–C(21)	119.1(3)	117.6(3)	118.1(3)
C(2)–N(3)–C(4)	119.5(2)	117.5(3)	119.1(3)
N(41)–C(4)–N(3)	116.5(2)	116.1(3)	117.4(3)
N(41)–C(4)–C(5)	122.7(2)	122.2(3)	121.3(3)
N(3)–C(4)–C(5)	120.8(2)	121.7(3)	121.3(3)
C(6)–C(5)–C(4)	116.4(3)	116.9(3)	116.3(3)
C(6)–C(5)–C(51^{I})	122.1(3)	122.2(3)	122.6(3)
C(4)–C(5)–C(51^{I})	121.5(2)	120.9(3)	121.2(3)
C(5)–C(6)–N(1)	122.0(3)	120.4(3)	120.9(3)
O(61)–C(51)–C(5)	—	108.9(3)	108.1(3)
C(51)–O(61)–C(61)	—	112.4(3)	111.4(3)
N(1)–C(51)–C(5^{II})	112.0(2)	—	—
O(10)–N(10)–O(12)	120.3(4)	119.8(3)	116.7(3)
O(10)–N(10)–O(11)	118.8(3)	118.2(3)	123.0(3)
O(12)–N(10)–O(11)	120.9(3)	121.9(3)	120.1(3)
O(20)–N(20)–O(20^{III})	120.0(2)	—	—

Symmetry transformations used to generate equivalent atoms of $[L][NO_3]_6\cdot16H_2O$: I $-y + 1$, $-z + 1$, $-x + 1$; II $-z + 1$, $-x + 1$, $-y + 1$; III y, z, x.

and O(2) water molecules form a nearly planar sheet situated between two $[L]^{6+}$ cation rings, as seen in Fig. 4. The cation is hydrogen bonded through its six amino groups to this layer of water and nitrate ions, as seen in Fig. 4, which indicates the interaction of these amino groups with one of the oxygen atoms of the major nitrate ion, O(12), and with the oxygen atom of the fully occupied O(1) water molecule.

The nitrate ions in this structure are found to be distributed over two sites. The major site, represented by N(10), is 94.0(3)% occupied, and is hydrogen bonded through O(12) to the amino group on the pyrimidinium ring and through O(11) to the fully occupied water molecule. The nitrate position associated with the cavity, represented by N(20), is a minor site, and is occupied only 18.0(9)% of the time. The N(20) site is located on the three-fold axis, 2.48 Å from the centre of the cavity. The oxygen atoms of this nitrate, O(20), located 3.00 Å from C(51), apparently accept a hydrogen bond from the axially directed methylene hydrogen, with a C(51)–H(51a)–O(20) angle of 149.2°. The nitrate ions associated with the cavity of the cyclic 16-pyrimidinium crown 4 cation $[L']^{4+}$ {5,12,19,26-tetraamino-3,10,17,24-tetramethyl[$1._4$](1,5)pyrimidiniophane},[11] and of polyammonium macrocycles 1,13-dioxa-5,9,17,21-hexaazacyclotetracosane ($[24]aneN_6O_2\cdot4HNO_3$) and 1,10-dioxa-4,7,13,16-tetraazacyclooctadecane ($[18]aneN_4O_2\cdot4HNO_3$)[12] lie perpendicular to the plane of the cavity. In contrast, the plane of the N(20) nitrate group in the present structure is perfectly parallel to the average plane of the $[L]^{6+}$ cation, as defined by the six C(6) atoms. The relative rigidity and large diameter of the cation allows it to accommodate the parallel nitrate ion in

Table 4 Hydrogen-bond distances (Å) and angles (°) for $[L][NO_3]_6\cdot16H_2O$ and $[C_6H_9N_3OCH_3][NO_3]$

A–H–B	Equivalent position b	A–H	H···B	A···B	A–H–B
$[L][NO_3]_6\cdot16H_2O$					
O(1)–H(1a)–O(11)	x, y, z	1.047	1.900	2.892	156.7
O(1)–H(1b)–O(11)	$z, x + 1, y$	0.836	2.112	2.925	164.2
O(2)–H(2a)–O(2)	$-y, -z, -x$	1.023	1.655	2.643	160.9
O(2)–H(2b)–O(1)	x, y, z	1.025	1.795	2.808	169.0
N(41a)–H(41a)–O(12)	x, y, z	0.860	2.036	2.887	170.3
N(41a)–H(41b)–O(1)	$-y, -z, -x$	0.860	2.043	2.883	165.5
C(51)–H(51a)–O(20)	$1 - y, 1 - z, 1 - x$	0.970	2.114	2.998	149.2
$[C_6H_9N_3OCH_3][NO_3]$					
N(1a)–H(1a)–O(10b)	x, y, z	0.860	1.952	2.811	176.3
N(41a)–H(41a)–O(10a)	$1 - x, 1 - y, 2 - z$	0.860	2.088	2.948	178.0
N(41a)–H(41b)–O(11a)	x, y, z	0.860	2.180	2.983	155.3
N(1b)–H(1b)–O(10a)	$1 - x, 2 - y, 1 - z$	0.860	1.933	2.791	175.7
N(41b)–H(41c)–N(3b)	$-x - 1, 2 - y, -z$	0.860	2.198	3.058	178.3
N(41b)–H(41d)–O(11b)	x, y, z	0.860	2.167	2.942	149.7

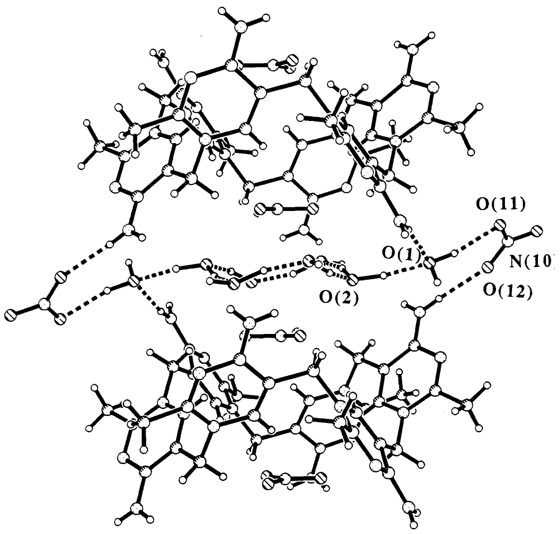


Fig. 4 Perspective view showing the plane of hydrogen-bonded waters and nitrates between two polypyrimidinium cations in $[L][NO_3]_6$. Four of the N(10) nitrates have been removed for clarity

contrast to the more flexible $[24]aneN_6O_2\cdot4HNO_3$[12] and the smaller $[L']^{4+}$[11] and $[18]aneN_4O_2\cdot4HNO_3$[13] macrocycles. Simiilarly, the nitrate ions in the $[L][M(NO_3)_6][NO_3]_2$ structures, where M = Ba or Pb,[7] are also positioned on the three-fold axis and are perfectly parallel to the plane of the $[L]^{6+}$ cation, with a distance of only 1.76 Å from the centre of the cavity. In the $[L][M(NO_3)_6][NO_3]_2$ structures the nitrate oxygen atoms, O(22), located 3.29 Å from C(6), accept hydrogen bonds from the equatorially directed aromatic hydrogen, with a C(6)–H(6a)–O(22) angle of 161.2°. The recent re-examination of the crystal structure of $[L][Pb(NO_3)_6][NO_3]_2$ structure led to the conclusion that a partially occupied nitrate ion, centred around N(30), was located at the exact centre of the cavity. The nitrate oxygen atoms, O(30), located 3.23 and 2.83 Å from two different, symmetry-equivalent C(6) atoms, accept hydrogen bonds from the aromatic hydrogen atoms, with O(30)–H(6)–C(6) bond angles of 137.2 and 89.6°, respectively.

There are eight locations for the nitrate ions in the present structure: six around the outside rim of the cation and two located within the mouth of the cavity. The six nitrate ions distribute themselves into all eight positions, with a total of 5.64 ions in the N(10) site and 0.36 ions in the N(20) site. Of course, distribution of the ions into the two positions is entropically favourable, but the energies of the two sites must also be very similar. The nitrate sites are stabilized by two interactions: electrostatic contact with the cation and hydrogen bonding. The N(10) site is less favourable for electrostatic interactions, since each ion is primarily in contact with only one of the six positively charged pyrimidinium rings. However, it is in a favourable hydrogen-bonding location where it strongly interacts with the N(41) amino group and various water molecules. The N(20) site is more favourable electrostatically, as it is located symmetrically with respect to all six positively charged pyrimidinium groups. However, it is in a less favourable hydrogen-bonding site, where it can only interact with the C(51) meythylene group. In general, hydrocarbons are not hydrogen-bond donors, yet in this case the C(51) group is both polarized by the adjacent N(1) atom as well as being part of a cation with a total +6 charge. Thus, some of this large positive charge finds its way onto the methylene hydrogens, and they do participate in hydrogen-bonding interactions.

The water molecule positioned at O(3) occupies the centre of the $[L]^{6+}$ cavity, and, after application of symmetry requirements, is 80(4)% occupied. The water molecule at O(4) has a complementary occupancy to that of O(3) due to their close proximity. Atoms O(4), O(5) and O(6) occupy positions that are too close to each other and to other atoms or groups of atoms to be present simultaneously. It is thus necessary and hence satisfying that their refined occupancies sum to less than one. None of the partially occupied water molecules indicated by atoms O(3) through O(6) is within hydrogen-bonding distance of any fully occupied atom. Owing to these fractional occupancies, statements regarding their hydrogen bonding to one another would not be informative or accurate. Hydrogen-bond distances and angles for $[L][NO_3]_6\cdot16H_2O$ are listed in Table 4.

$[C_6H_9N_3OCH_3][NO_3]$. The asymmetric unit of $[C_6H_9N_3OCH_3][NO_3]$ consists of two pyrimidinium rings with their substituents and two nitrate ions, shown in Fig. 5. Generation of the symmetry-equivalent positions gives a unit cell which contains four $[C_6H_9N_3OCH_3]^+$ cations and four nitrate anions.

Apart from the disorder in one of the methyl substituent groups, the pyrimidinium cations are nearly identical to one another. Both rings have a planar geometry which extends to the methoxymethyl side chain, with maximum deviations from the plane reaching only 0.28 Å. The interstices between pyrimidinium rings in the same plane are filled by nitrate ions, which are hydrogen bonded through two of the nitrate oxygen atoms to neighbouring pyrimidinium groups. Differences between the two pyrimidinium groups in the asymmetric unit arise from the hydrogen bonding of one of the amino groups. In pyrimidinium ring A the amino group is hydrogen bonded to two nitrate ions, while in pyrimidinium ring B the amino group is hydrogen bonded to one nitrate ion and the N(3) position of

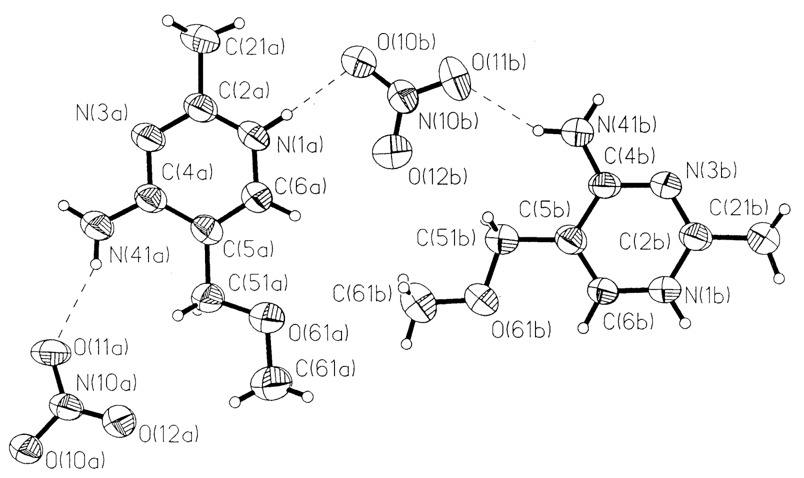
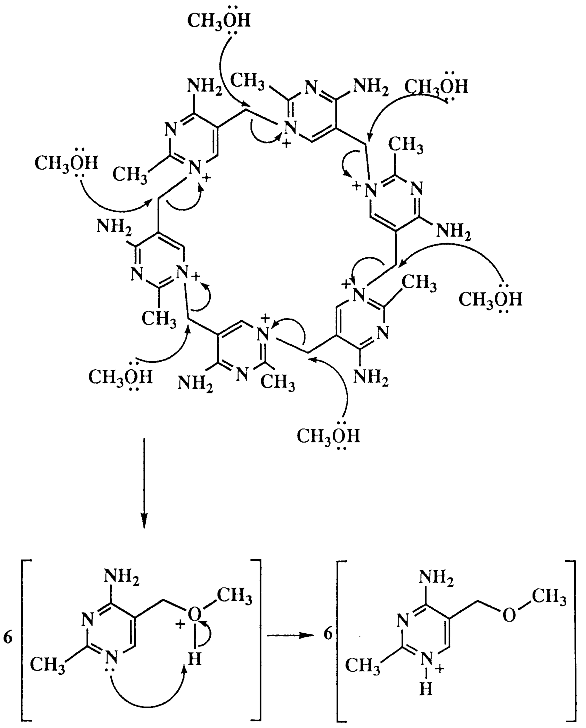


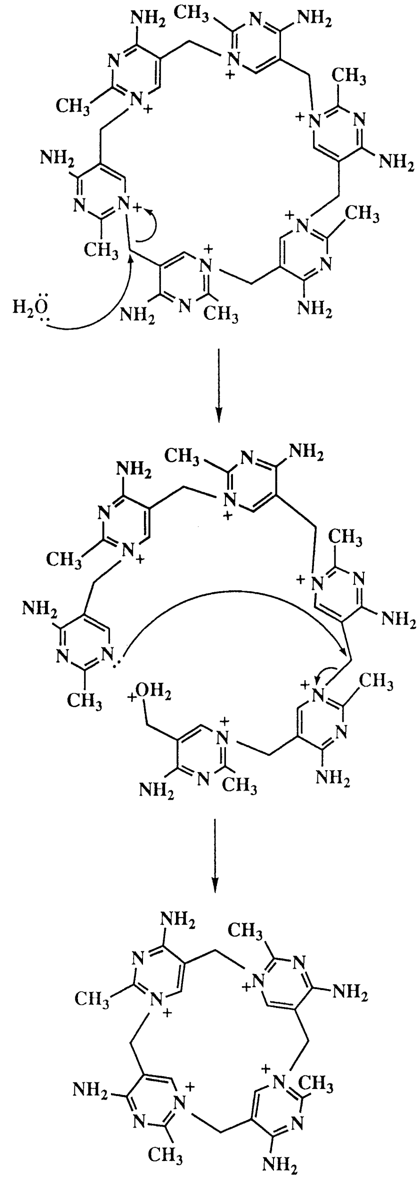
Fig. 5 Perspective view of the structure of the asymmetric unit of the nitric acid salt of 4-amino-5-methoxymethyl-2-methylpyrimidinium with 50% probability thermal parameters



Scheme 3

a symmetry-equivalent pyrimidinium ring. Hydrogen-bond distances and angles for [C$_6$H$_9$N$_3$OCH$_3$][NO$_3$] are listed in Table 4.

The protonation of the N(1) atom is evidenced by the slightly expanded C(2)–N(1)–C(6) bond angle, 120.5(3) and 121.1(3)°, as compared to that seen in the previously determined [L]$^{6+}$ structures.[6,7] Previously determined protonated thiamin structures[14] have shown this angle to range from 119.8(7) to 121.0(8)°. Also, protonation at the N(1) position results in shorter C(4)–N(41) bond lengths. This behaviour has been seen in all protonated[14,15a] and quaternized[16] thiamin analogues, and is due to a larger contribution of double-bond resonance structures[16] as compared to their similar non-protonated forms.[15b]



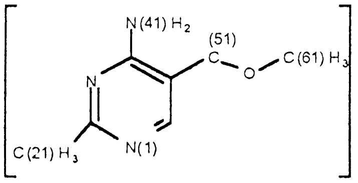
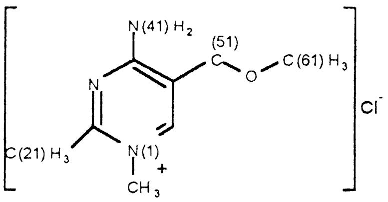
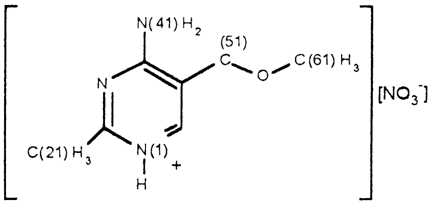
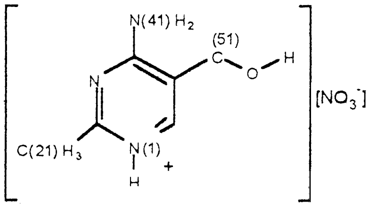
Scheme 4

Degradation studies

It has been observed in attempts to crystallize the [L]$^{6+}$ cation with certain anions that although the pure hexacationic salt was originally used it was the tetracationic analogue, the 16-pyrimidinium crown 4 salt,[11] that was isolated. Indeed, our ^{1}H NMR studies have indicated that dissolution of [L][NO$_3$]$_6$·16H$_2$O in D$_2$O at pH 1.5 leads to the degradation of the compound to the 16-pyrimidinium crown 4 salt after only 2 h. These results have been the impetus behind the desire to understand the reactivity of the larger cation towards weak nucleophiles in pure and mixed aqueous solvents.

To facilitate solubility, the [L]$^{6+}$ nitrate salt was dissolved in methanol–water (3:2). This mixture was refluxed for periods

Table 5 Proton NMR shifts (δ) for some pyrimidine analogues[a]

	$C(21)H_3$	$C(61)H_3$	N(1)H	$N(1)CH_3$	$C(51)H_2$	C(6)H	$N(41)H_2$	Ref.
	2.33	3.26	—	—	4.26	7.95	6.60	18
	2.59	3.35	—	3.76	4.32	8.35	8.22, 8.98	18
	2.55	3.34	7.02 $J_{NH} = 52$ Hz	—	4.34	8.09	8.54, 9.33	*b*
	2.47	—	7.21 $J_{NH} = 49$ Hz	—	4.36	8.08	8.93	*b*

[a] In $(CD_3)_2SO$. [b] This work.

of up to 1 week, leading to the degradation of the starting material. Attack at the bridging methylene group by an incoming methanol nucleophile, followed by the loss of an oligopyrimidinium leaving group, caused the $[L]^{6+}$ cation to break apart, as in Scheme 3. Deprotonation of the methoxide oxygen and protonation of the pyrimidine portion at the N(1) position lead to the production of the ionic compound $[C_6H_9N_3OCH_3][NO_3]$. While the free base 4-amino-5-methoxymethyl-2-methylpyrimidine has been reported,[17] this is the first report of the nitric acid salt. Mass spectrometry showed the compound to possess a molecular weight consistent with the structure reported herein for the cation. The melting point was determined to be 161 °C, 45 °C above that of the neutral analogue.[17] X-Ray crystallography confirmed that the compound prepared was the nitric acid salt of 4-amino-5-methoxymethyl-2-methylpyrimidine, as seen in Fig. 5.

In Table 5 the ^1H NMR data for the nitric acid salt reported here are compared to those of the previously reported free base.[18] The free base shows only a single time-averaged amino peak, while the nitric acid salt exhibits a pair of amino resonances which are shifted well downfield. This agrees with a previous report of the ^1H NMR spectrum of the chloride salt of the N(1)-methylated analogue which also exhibits a pair of amino peaks.[18] This is attributed to an increased contribution of resonance structures containing a C(4)–N(41) double bond in the N(1)-methylated and -protonated compounds, which raises the rotational barrier about this C–N bond, freezing the two amino protons in inequivalent environments. These resonance structures also place positive charge at the N(41) position, leading to increased hydrogen bonding resulting in the substantial downfield chemical shift as compared to the free base.

Since most studies of the $[L]^{6+}$ cation are undertaken in pure aqueous solutions, reflux of the nitrate salt was also performed in water. Following a period of 1 d, the ^1H NMR spectrum indicated that the macrocycle had begun to react in a manner analogous to that seen in the mixed methanol–water studies. After 7 d the spectrum of the resultant compound indicated that it was the nitric acid salt of 4-amino-2-methylpyrimidine-5-methanol. As indicated in Table 5, there was evidence of protonation at the N(1) position due to a 1 : 1 : 1 triplet centred at δ 7.21 similar to that seen in the spectrum of the nitric acid salt of 4-amino-5-methoxymethyl-2-methylpyrimidine centred at δ 7.02. In a reaction similar to that shown in Scheme 3, water, acting as a nucleophile, is added at the methylene carbon, with the oligopyrimidinium acting as the leaving group.

In an attempt to determine the stability of the $[L]^{6+}$ cation in aqueous solution over long periods of time, the compound was dissolved in D_2O and monitored by means of ^1H NMR spectroscopy. These studies demonstrated that, at ambient temperatures over a period of several weeks in D_2O at pH 6, degradation of the $[L]^{6+}$ cation takes place, yielding the nitric acid salt of the 4-amino-2-methylpyrimidin-5-methanol compound and some of the smaller 16-pyrimidinium crown 4 cation, $[L']^{4+}$. As the reaction temperature is lowered to ambient levels the nucleophilic addition of water to the methylene bridge becomes slower. This allows a newly formed terminal pyrimidine group to act as an incoming nucleophile on a methylene bridge four units away, generating the 16-pyrimidinium crown 4 species, as seen in Scheme 4. Lowering the pH of the solution has a similar, yet more pronounced effect. At pH 1.5, adjusted by the addition of HNO_3, the complete conversion of the $[L]^{6+}$ cation into the $[L']^{4+}$ species takes place within a few hours at ambient temperature. In this case none of the nitric acid salt of the

4-amino-2-methylpyrimidine-5-methanol compound is seen. Raising the pH to above 7 leads to the rapid decomposition of the macrocycle, generating several unidentified products. Since thiamin is known to produce 4-amino-2-methylpyrimidine-5-methanol upon heating to 37 °C at pH 8.2,[19] this is also one of the likely degradation products of the $[L]^{6+}$ cation in basic solution.

Conclusion

The reflux reaction of thiamin in alcohols to prepare an oligopyrimidinium species has been known for some twenty years. It has been shown that the result of this procedure is the synthesis of the $[L]^{6+}$ cation.[4] However, due to disorder in the minor nitrate ion of the $[L]^{6+}$ hexanitrate species, its structure has only recently been solved to our satisfaction.

Despite its ability to produce well formed crystals from aqueous solutions, degradation of the $[L]^{6+}$ cation over long periods of time in water and water–methanol mixtures has been observed. Complete degradation at elevated temperatures to the nitric acid salts of the pyrimidinium alcohol and methoxide products has been confirmed. The partial degradation of the macrocycle to the smaller 16-pyrimidinium crown 4 cation, $[L']^{4+}$ is also observed as both the temperature and the pH are lowered.

These results indicate that further studies involving the $[L]^{6+}$ cation in aqueous media need to be carried out at slightly acidic pH, ambient temperatures and for a limited amount of time in order to minimize the degradation of the macrocycle to either the monopyrimidinium alcohol or to the smaller macrocyclic species.

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