

Synthesis and Crystal Structure of a Spiro Amine: 3,9,12-Triaza-6-azoniaspiro[5,8]tetradecane Chloride Trihydrochloride Dihydrate

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The spiro amine L1·Cl·3HCl·2H₂O, 3,9,12-triaza-6-azoniaspiro[5,8]tetradecane chloride trihydrochloride dihydrate, has been synthesized by the reaction of 1-(toluenesulfonyl)-1,3,7-triazacyclononane with *N,O,O'*-tris(*p*-toluenesulfonyl)-bis(2-hydroxyethyl)amine followed by removal of the tosyl groups by acid hydrolysis. The structure of L1·Cl·3HCl·2H₂O has been solved by the X-ray diffraction technique at *T* = 120 K; *M_r* = 380.2, orthorhombic, *Pbca*, *a* = 18.922(4), *b* = 21.706(4), *c* = 8.512(4) Å, *Z* = 8, *D_x* = 1.44 g cm⁻³, MoKα = 0.71073 Å, μ = 6.9 cm⁻¹, *F*(000) = 1624, *R* = 0.056 for 1921 unique reflections. The nine-membered ring adopts a triangular [333] conformation with the nitrogen atoms occupying the corner positions. The six-membered ring has a chair conformation. The H₃L1⁴⁺ cations are connected through hydrogen bonds to the chloride ions and the water molecules. The concentration acid dissociation constants have been determined potentiometrically, and the following values were obtained: p*K*_{a1} = 0.55(6), p*K*_{a2} = 5.23(3), p*K*_{a3} = 7.11(5) (1 M NaCl, 25°C). The ¹³C NMR spectrum is in agreement with a time-averaged C_{2v} symmetry in solution.

Macrocyclic and macrobicyclic polyamines are of current interest and exhibit unusual basicity and coordination chemistry.^{1–8} Cross-bridging of cyclam or cyclen, i.e. bridging of nonadjacent nitrogens, leads to bicyclic tetraamines which may adopt conformations having all four nitrogen lone pairs pointing inside the cavity for complexation of metal ions (for ligand abbreviations see the Experimental). Cross-bridging of cyclam has been reported by Weisman *et al.*,⁹ who synthesized the ethylene cross-bridged cyclam shown in Fig. 1A. Micheloni and co-workers^{10–12} have reported the synthesis of cyclen analogues (Figs. 1B–1D). Some of these cages react as proton sponges (stronger bases than OH⁻ in water) and form stable complexes with small cations such as reported for lithium. We reported recently an alternative method for synthesis of such small bicyclic tetraamines.¹³ The reaction of cyclen (protected at two nonadjacent nitrogens by tosylation) with trimethylene bis(*p*-toluenesulfonate) was shown to give the macrocycle shown in Fig. 1E. We are currently investigating the prospects of this method for the synthesis of new members within this interesting class of macrobicyclic ligands. We are also looking for alternative methods, and in this paper we de-

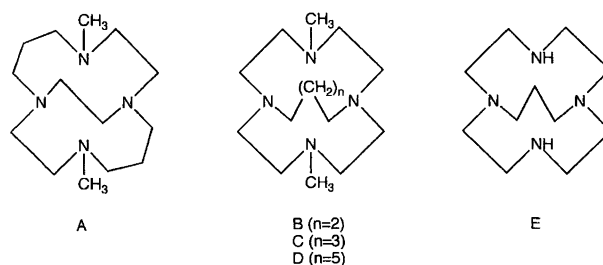


Fig. 1. Cross-bridged derivatives of cyclen and cyclam.

scribe an attempt to synthesize an analogue to E by reacting the monotosylate of tacn with the tritosylate of bis(2-hydroxyethyl)amine.

Experimental

Abbreviations. ts, *p*-toluenesulfonyl; DMF, dimethylformamide; bhea, bis(2-hydroxyethyl)amine; bhea·ts₃, *N,O,O'*-tris(*p*-toluenesulfonyl)bis(2-hydroxyethyl)amine; cyclen, 1,4,7,10-tetraazacyclododecane; cyclam, 1,4,8,11-tetraazacyclotetradecane; tacn, 1,4,7-triazacyclononane; tacn·ts, 1-(toluenesulfonyl)-1,4,7-triazacyclononane;

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tacn · ts₂, 1,3-bis(toluenesulfonyl)-1,3,7-triazacyclononane; L1⁺, 3,9,12-triaza-6-azoniaspiro[5,8]tetradecane; L1 · ts₂, 3,9-bis(*p*-toluenesulfonyl)-3,9,12-triaza-6-azoniaspiro[5,8]tetradecane; L1 · ts₃, 3,9,12-tris(*p*-toluenesulfonyl)-3,9,12-triaza-6-azoniaspiro[5,8]tetradecane.

Materials. The preparations of the compounds tacn · ts and bhea · ts₃ have been published previously.^{14–16} All other chemicals were of analytical grade.

Analyses. C, H, N and Cl analyses were made by Preben Hansen at the Microanalytical Laboratory at the H. C. Ørsted Institute, Copenhagen.

Mass spectra. Positive ion FAB mass spectra were obtained on a Jeol AX505W mass spectrometer using glycerol or 3-nitrobenzyl alcohol as matrix.

NMR spectra. ¹H and ¹³C NMR spectra were measured at 5.87 T on a Bruker AC 250 NMR spectrometer equipped with a 5 mm probe. ¹³C chemical shift values (δ) are reported in ppm relative to internal TMS in CDCl₃ [δ(TMS) = 0 ppm] and referenced to internal dioxane in D₂O or H₂O [δ(dioxane) = 67.4 ppm]. ¹³C DEPT NMR spectra were used to distinguish CH₃ and CH₂ carbon atoms.

Determination of acid dissociation constants. The pH measurements were made using Radiometer equipment as reported previously.¹⁷ The concentration acid dissociation constants of H₃L⁴⁺ were determined by titration of a solution of L1 · Cl · 3HCl · 2H₂O with sodium hydroxide at ionic strength 1 M kept constant with sodium chloride.

Synthesis. A solution of tacn · ts · 2HBr (4.45 g, 0.01 mol), bhea · ts₃ (5.68 g, 0.01 mol) and sodium carbonate (4.45 g, 0.042 mol) in DMF (80 ml) was heated to 105 °C

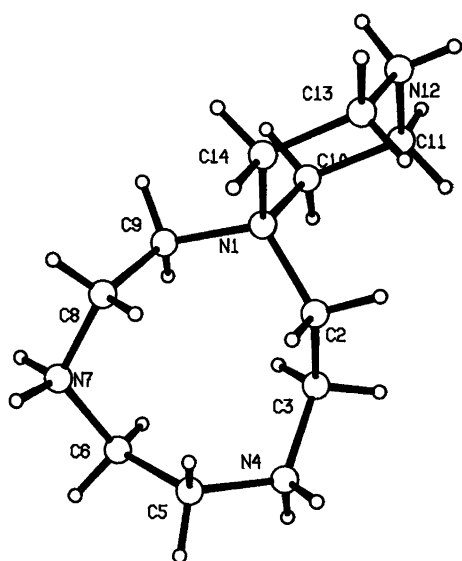


Fig. 2. View of the H₃L⁴⁺ cation with its atomic labelling.

for 20 h. The solution was filtered and the filtrate was evaporated on a rotary evaporator (80 °C) to give an oil. Addition of 96% ethanol (150 ml) gave a white precipitate, which was filtered off. The filtrate was evaporated on a rotary evaporator (80 °C), the resulting oil was extracted twice with water (150 ml) and the residue of water was removed by evaporation on a rotary evaporator. This gave a yellow powder of the ditosylate of the product (1.9 g). FABMS *m/z*: 507 (*M* = L1 · ts₂⁺). The crude ditosylate (1.9 g) was added to 98% H₂SO₄ (2 ml) and the mixture was heated to 100 °C for 43 h. The black solution was then cooled in ice and the chloride salt was precipitated by addition of 12 M HCl (4.5 ml) and methanol (10 ml). The precipitate was filtered off, washed with methanol and dried in air (0.6 g). The crude product was recrystallized by dissolution in water (6 ml g⁻¹), filtration and addition of one volume of 12 M HCl and seven volumes of methanol. The white, crystalline precipitate was filtered off, washed with methanol and dried in air. Yield: 220 mg (6%) of a pure product. Analytical data: Calculated for C₁₀H₃₀Cl₄N₄O₂: C, 31.59; H, 7.95; Cl, 37.3; N, 14.74. Found: C, 31.47; H, 7.84; Cl, 37.1; N, 14.56. FABMS *m/z*: 199, (*M* = L1⁺). ¹³C NMR (D₂O): δ = 58.1 [C–N(quat.)]; δ = 56.8 [C–N(quat.)]; δ = 46.9 [C–N(sec.)]; δ = 42.2 [C–N(sec.)]; δ = 38.0 [C–N(sec.)]. The product was also identified by its tritosylate prepared by reaction of pure L1 · Cl · 3HCl · H₂O with *p*-toluenesulfonyl chloride (mole ratio 1:4) in pyridine using standard procedures. The product was washed thoroughly with water and dried in air. FABMS *m/z*: 661 (*M* = L1 · ts₃⁺). ¹³C NMR (D₂O): δ = 58.8 [C–N(quat.)]; δ = 56.1 [C–N(quat.)]; δ = 45.8 [C–N(ts)]; δ = 45.4 [C–N(ts.)]; δ = 39.5 [C–N(ts.)]; δ = 20.0 and 20.1 (CH₃, ratio 2:1).

X-Ray techniques. Crystal and experimental data for the compound are listed in Table 1. The possible space groups were established from rotation and Weissenberg photographs using Cu radiation. The reflecting power of the crystals was rather poor, and furthermore it was not possible to get a good single crystal. The crystal was cooled to 120 K using a Crystream nitrogen gas cooler System.¹⁸ The unit-cell parameters were derived from a least-squares fit of refined diffractometer setting angles for 25 reflections. Four standards were measured for intensity and orientation control after every 200 reflections; no fading was observed. The intensities were corrected for Lorentz and polarization effects, but not for absorption. The structure was solved by direct methods and refined by a full-matrix least-squares technique. The hydrogen atoms were all located from electron density difference maps. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms in the molecules of water were refined isotropically, whereas the hydrogen atoms in the H₃L⁴⁺ cation were refined with fixed isotropic thermal parameters, *U*(H) = *U* for attached C or N. The crystallographic computations were performed with SHELXS86¹⁹ and SHELX76.²⁰ The atomic scattering

Table 1. Crystal and experimental data.

Formula	$C_{10}H_{26}N_4^{4+}, 4Cl^-, 2H_2O$
Formula weight	380.2
Crystal system	Orthorhombic
Space group	<i>Pbca</i> (No. 61)
Unit-cell dimensions	
<i>a</i> /Å	18.922(4)
<i>b</i> /Å	21.706(4)
<i>c</i> /Å	8.512(4)
Unit-cell volume, <i>V</i> /Å ³	3496(2)
Formula units per unit cell, <i>Z</i>	8
<i>F</i> (000)	1616
Calculated density <i>D_x</i> /g cm ⁻³	1.44
Radiation	MoKα
Wavelength, λ/Å	0.71073
Linear absorption coefficient/cm ⁻¹	6.9
Temperature, <i>T</i> /K	120
Crystal description	Colourless
Crystal size/mm	0.27 × 0.18 × 0.025
Diffractometer	Enraf-Nonius CAD-4F
Unit-cell determination	
No. of reflections used	25
θ-range/°	10.3–13.9
Intensity data collection	
θ _{max} /°	35
Range of <i>h</i>	0–30
Range of <i>k</i>	0–35
Range of <i>l</i>	–0–13
Scan mode	ω
Scan range, Δω	1.00 + 0.35 tan θ
Total number of unique reflections	7669
No. of independent reflections, [<i>I</i> > 3σ(<i>I</i>)]	1960
No. reflections used in refinement	1921
Corrections	Lorentz polarization
Structure refinement	
Minimization of	$\sum w(F_o - F_c)^2$
Anisotropic thermal parameters	All non-hydrogen atoms
Isotropic thermal parameters	Hydrogen atoms
No. of refined parameters	275
Weighting scheme	$[\sigma^2(F_o) + 0.0004 F_o ^2]^{-1}$
$R = \sum F_o - F_c / \sum F_o $	0.056
$Rw = [\sum w(F_o - F_c)^2 / \sum w F_o ^2]^{1/2}$	0.049
$S = [\sum w(F_o - F_c)^2 / (N_{obs} - N_{var})]^{1/2}$	1.12
Final (Δ/δ) _{max}	0.25
Final Δ <i>Q</i> _{min} and Δ <i>Q</i> _{max} /e Å ⁻³	–0.57 and 0.60

factors were taken from literature.²¹ The PLUTO program²² was used for the illustrations and PLATON²³ for molecular geometry calculations.

The final positional parameters are listed in Table 2. Anisotropic thermal parameters, positional parameters for the hydrogen atoms and a list of observed and calculated structure factors may be obtained from one of the authors (I. S.) on request.

Results

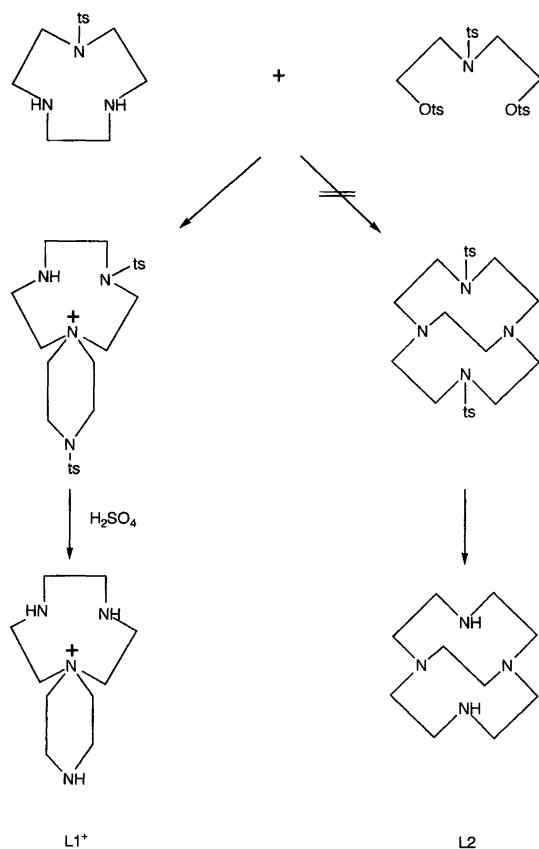
Synthesis. The reaction of tacn · ts with bhea · ts₃ (DMF, sodium carbonate, reflux) and removal of the tosyl groups

by hydrolysis in sulfuric acid (98%, 100 °C) gave the spiro amine L1⁺, which was isolated as the hydrochloride, L1 · Cl · 3HCl · 2H₂O, as shown in Scheme 1. As mentioned in the introduction, the experiment was an attempt to obtain the cross-bridged macrobicyclic ligand L2 as shown in the right-hand part of Scheme 1. The elemental analysis and the FABMS of the product are both in agreement with the two possible structures, L1⁺ and L2. Likewise, the ¹³C NMR spectrum exhibits five signals of equal intensity (see Experimental), which is in agreement with structure L1⁺, but it does not unambiguously exclude structure L2, for which the number of signals could be three (2:2:1) or five (1:1:1:1:1) depending on the conformation(s) of the macrocycle and its dynamic proper-

Table 2. Fractional atomic coordinates and equivalent isotropic thermal parameters (in Å²).

Atom	x	y	z	U_{eq}^a
N(1)	0.4249(3)	0.1129(2)	0.5566(6)	0.013(1)
N(4)	0.2317(3)	0.1007(2)	0.5923(6)	0.013(2)
N(7)	0.3094(3)	0.1130(2)	0.2066(6)	0.017(1)
N(12)	0.5404(3)	0.1308(3)	0.7832(6)	0.021(2)
C(2)	0.3578(3)	0.1291(3)	0.6424(7)	0.015(2)
C(3)	0.3022(3)	0.0789(3)	0.6480(7)	0.011(2)
C(5)	0.2257(3)	0.1272(3)	0.4314(7)	0.014(2)
C(6)	0.2534(4)	0.0848(3)	0.3039(7)	0.015(2)
C(8)	0.3728(3)	0.1388(3)	0.2862(7)	0.016(2)
C(9)	0.4121(3)	0.0920(3)	0.3865(7)	0.013(2)
C(10)	0.4626(3)	0.0600(3)	0.6358(7)	0.015(2)
C(11)	0.4914(3)	0.0768(3)	0.7964(7)	0.018(2)
C(13)	0.5041(4)	0.1843(3)	0.7133(8)	0.020(2)
C(14)	0.4744(3)	0.1683(3)	0.5548(7)	0.017(2)
Cl(1)	0.36631(7)	0.00695(6)	0.0070(2)	0.0183(4)
Cl(2)	0.15099(8)	0.06358(6)	-0.0648(2)	0.0172(4)
Cl(3)	0.32316(9)	0.27998(7)	0.4655(2)	0.0228(5)
Cl(4)	0.03930(9)	0.16061(8)	0.3697(2)	0.0269(5)
O(1)	0.1868(3)	0.2995(2)	0.2538(7)	0.028(2)
O(2)	0.1554(4)	0.1899(3)	0.1289(7)	0.049(2)

$$^a U_{eq} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j.$$



Scheme 1. An attempt to synthesize the bicyclic tetraamine L2 by the reaction path shown on the right-hand side failed, and the spiro amine L1⁺ was obtained.

ties. In order to obtain an unambiguous assignment of the structure, the tosylate of the product was made using an excess of *p*-toluenesulfonyl chloride. FABMS for this products gave a dominant peak corresponding to a tritosylated product (as expected for L1⁺) and only a very weak peak for a ditosylated product (as expected for L2). The ¹³C NMR spectrum showed five signals of equal intensity for CH₂-N carbon atoms and two signals for CH₃ carbon atoms (tosylate) in the ratio 2:1. Thereby the structure of L1⁺ was established with certainty, as confirmed by an X-ray structure analysis as described below.

The low yield in the synthesis of L1⁺ · Cl⁻ · 3HCl · H₂O is probably caused by formation of oligomacrocyclic by-products in the first step and formation of side-products during the detosylation reaction. Several synthetic conditions were tried without any improvement in the yield. No evidence for the formation of the originally desired product L2 was obtained. It is likely that the yield of L1⁺ may be improved considerably if tacn · ts₂ is used instead of tacn · ts, but this has not been attempted.

Crystal structure. Bond lengths and bond and torsion angles are listed in Table 3. The labelling of the atoms in the H₃L1⁴⁺ ion is shown in Fig. 3. Although the substituents at N(1) are different from those at N(4) and N(7), the conformation of the nine-membered ring of the protonated H₃L1⁴⁺ cation is best described as a triangular [333] conformation²⁴ with the three nitrogen atoms situated at the corner positions. A similar conformation is found in 1,4,7-trithiacyclononane 1,1,4,4,7,7-hexaoxide,²⁵ the three sulfur atoms being located at the corners

Table 3. Bond lengths (in Å) and bond and torsion angles (in °).

N(1)–C(2)	1.506(8)	N(12)–C(11)	1.499(9)
N(1)–C(9)	1.537(8)	N(12)–C(13)	1.475(9)
N(1)–C(10)	1.511(8)	C(2)–C(3)	1.515(9)
N(1)–C(14)	1.524(8)	C(5)–C(6)	1.516(9)
N(4)–C(3)	1.493(8)	C(8)–C(9)	1.521(9)
N(4)–C(5)	1.490(8)	C(10)–C(11)	1.516(8)
N(7)–C(6)	1.478(9)	C(13)–C(14)	1.502(9)
N(7)–C(8)	1.487(8)		
C(2)–N(1)–C(9)	113.1(5)	N(1)–C(2)–C(3)	115.6(5)
C(2)–N(1)–C(10)	111.0(5)	N(4)–C(3)–C(2)	112.5(5)
C(2)–N(1)–C(14)	109.8(4)	N(4)–C(5)–C(6)	113.4(5)
C(9)–N(1)–C(10)	105.7(4)	N(7)–C(6)–C(5)	113.4(5)
C(9)–N(1)–C(14)	108.7(4)	N(7)–C(8)–C(9)	113.5(5)
C(10)–N(1)–C(14)	108.3(5)	N(1)–C(9)–C(8)	114.1(5)
C(3)–N(4)–C(5)	118.8(5)	N(1)–C(10)–C(11)	112.9(5)
C(6)–N(7)–C(8)	118.6(5)	N(12)–C(11)–C(10)	110.1(5)
C(11)–N(12)–C(13)	111.0(5)	N(12)–C(13)–C(14)	110.8(5)
		N(1)–C(14)–C(13)	113.8(5)
C(9)–N(1)–C(2)–C(3)	56.1(6)	C(5)–N(4)–C(3)–C(2)	57.2(7)
C(10)–N(1)–C(2)–C(3)	–62.5(6)	C(3)–N(4)–C(5)–C(6)	54.6(7)
C(14)–N(1)–C(2)–C(3)	177.7(5)	C(8)–N(7)–C(6)–C(5)	54.6(7)
C(2)–N(1)–C(9)–C(8)	57.1(6)	C(6)–N(7)–C(8)–C(9)	57.6(7)
C(10)–N(1)–C(9)–C(8)	178.8(5)	C(13)–N(12)–C(11)–C(10)	58.0(6)
C(14)–N(1)–C(9)–C(8)	–65.2(6)	C(11)–N(12)–C(13)–C(14)	–57.3(7)
C(2)–N(1)–C(10)–C(11)	–67.4(6)	N(1)–C(2)–C(3)–N(4)	–127.6(5)
C(9)–N(1)–C(10)–C(11)	169.5(5)	N(4)–C(5)–C(6)–N(7)	–123.3(6)
C(14)–N(1)–C(10)–C(11)	53.2(6)	N(7)–C(8)–C(9)–N(1)	–127.1(5)
C(2)–N(1)–C(14)–C(13)	68.9(6)	N(1)–C(10)–C(11)–N(12)	–57.2(6)
C(9)–N(1)–C(14)–C(13)	–166.9(5)	N(12)–C(13)–C(14)–N(1)	55.7(7)
C(10)–N(1)–C(14)–C(13)	–52.5(6)		

of the triangle. The nitrogen atoms being at the corners of the conformation is also found in 1,4,7,10-tetraazacyclododecane tetrahydrochloride,²⁶ where the four nitrogen atoms in the 12-membered $H_4cyclen^{4+}$ ring occupy the four corners of the quadrangular [3333] conformation. In the nine-membered ring in the present structure the six N–C bond lengths average 1.498(8) Å and the three C–C bond lengths 1.517(2) Å, which are in agree-

ment with values found in other azacycloalkanes. The C(2)–N(1)–C(9) angle is somewhat smaller than the other two C–N–C angles. This might indicate that the substituted six-membered ring has some effect on the geometry of the nine-membered ring. The six-membered ring of the H_3L^{4+} cation has a slightly distorted chair conformation. The four N–C bond lengths average 1.502(10) Å. The C(10)–N(1)–C(14) angle is somewhat smaller than

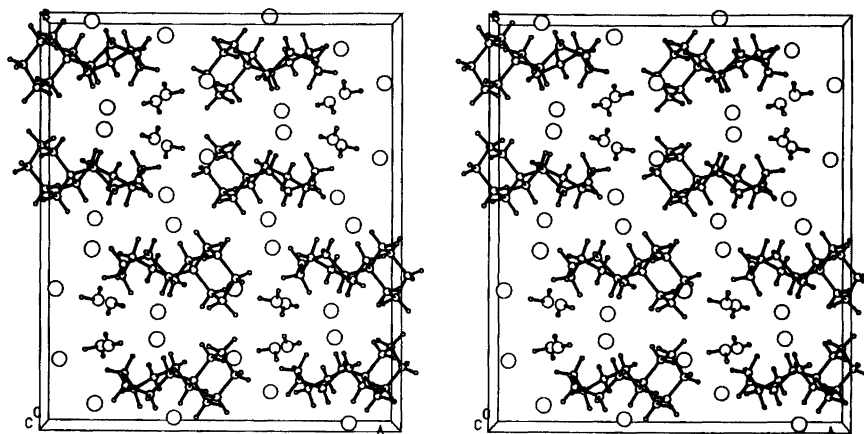
Fig. 3. Stereoview of the unit cell seen along the c -axis.

Table 4. Hydrogen-bond geometry (in Å, °)

D—H···A	D···A	H···A	D—H···A
O(1)—H(O12)···O(2)	2.673(8)	1.93(9)	155(9)
N(4)—H(41)···Cl(1) ⁱ	3.070(5)	2.12(6)	155(4)
N(4)—H(42)···O(1) ⁱⁱ	2.703(7)	1.87(6)	178(6)
N(7)—H(71)···Cl(3) ⁱⁱⁱ	3.111(5)	2.33(6)	147(5)
N(7)—H(72)···Cl(1)	3.057(5)	2.12(6)	171(5)
O(1)—H(O11)···Cl(3)	3.175(6)	2.37(6)	174(6)
N(12)—H(121)···Cl(4) ^{iv}	3.025(6)	2.26(7)	150(5)
N(12)—H(122)···Cl(2) ^{iv}	3.156(6)	2.27(6)	164(5)
O(2)—H(O21)···Cl(2)	3.201(7)	2.43(9)	162(9)
O(2)—H(O22)···Cl(4)	3.071(7)	1.93(9)	174(9)

Symmetry code: ⁱ 1/2-x, -y, 1/2+z; ⁱⁱ x, 1/2-y, 1/2+z; ⁱⁱⁱ x, 1/2-y, -1/2+z; ^{iv} 1/2+x, y, 1/2-z.

the C(11)–N(12)–C(13) angle. Thus the substituted nine-membered ring might have a small effect on the geometry of the six-membered ring. In 1,4-dinitro-2,5-dioxo-1,4-diazacyclohexane²⁷ the ring adopts a twisted conformation. Also the N–C bonds of 1.399(3) and 1.466(4) Å are smaller than the N–C bonds observed in the present structure. This might be due to substitution effects of the NO₂ groups. Therefore, a close comparison between the two structures is not possible. The crystal packing (Fig. 3) is influenced by hydrogen bonds, which are described in Table 4.

Acid dissociation constants of H₃L1⁴⁺. The concentration acid dissociation constants (K_{ai}) of H₃L1⁴⁺ were determined by potentiometric titrations which gave the values [$pK = -\log(K)$]: $pK_{a1} = 0.55(6)$, $pK_{a2} = 5.23(3)$, $pK_{a3} = 7.11(5)$ (1 M NaCl, 25 °C). It seems reasonable to assume that the acid strength of the secondary NH₂⁺ groups in the six- and twelve-membered rings, respectively, are influenced strongly by the charge(s) of the other group(s) in the ring they belong to, but only marginally to charge(s) of the group(s) in the other ring. It is therefore anticipated that one pK_a value is close to that of H₂pip²⁺ (pip = piperazine, $pK_{a1} = 5.2$)²⁸ and that two pK_a values are close to pK_{a1} and pK_{a2} of H₃tacn³⁺ ($pK_{a1} = 0.5$ and $pK_{a2} = 7.0$).²⁹ These predicted values are very close to the observed pK_a values for H₃L1⁴⁺, which therefore may be assigned to the three secondary NH₂²⁺ groups as follows: pK_{a1} (nine-membered ring), pK_{a2} (six-membered ring) and pK_{a3} (nine-membered ring).

The observation that HL1²⁺ ($pK_{a3} = 7.11$) is a much stronger acid than, e.g., NH₄⁺ ($pK_a = 9.465$)³⁰ indicates that L1⁺ will coordinate only weakly to metal ions. In fact preliminary experiments have shown that the amine forms a blue copper(II) complex in aqueous solution at ca. pH 6. The amine is not bound very strongly, as shown by the observation that addition of NaOH (pH ca. 13) results in hydrolysis of the amine complex and precipitation of copper(II) hydroxide. We are now studying this aspect and are also looking at the prospect of coordinating L1⁺ to robust metal ions such as cobalt(III).

Conclusions

The observation that L1⁺ and not L2 is formed by the studied reaction is, unfortunately, an experimentally very clear illustration of the well known fact that six-membered rings are kinetically as well as thermodynamically very stable. Following the results reported by Micheloni and co-workers^{3,4} it seems likely that a similar reaction using tsN(CH₂COCl)₂ (followed by reduction of the amide) would afford L2. Also, the corresponding reaction using tsN(CH₂CH₂CH₂OTs)₂ might give a bicyclic species rather than a spiro compound. These aspects are now being pursued.

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