

The Structure of (3*S*,6*S*)-3,6-Bis[(2*R*,5*S*)-5-chloro-2-piperidinio]-2,5-piperazinedione Sulfate Pentahydrate

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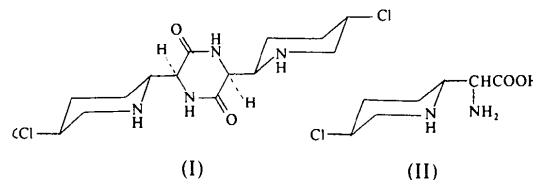
Abstract

The structure of the antineoplastic agent (3*S*,6*S*)-3,6-bis[(2*R*,5*S*)-5-chloro-2-piperidinio]-2,5-piperazinedione sulfate pentahydrate, $\text{cyclo}(-\text{HSlt}-\text{HSlt})^{2+} \cdot \text{SO}_4^{2-} \cdot 5\text{H}_2\text{O}$, has been determined from an analysis of a crystal with $a = 26.570$ (14), $b = 14.913$ (8), $c = 6.006$ (3) Å, $Z = 4(\text{C}_{14}\text{H}_{24}\text{Cl}_2\text{N}_4\text{O}_2^{2+} \cdot \text{SO}_4^{2-} \cdot 5\text{H}_2\text{O})$ and $\rho_c = 1.502 \text{ Mg m}^{-3}$ ($\rho_o = 1.450 \text{ Mg m}^{-3}$) in the space group $P2_12_12_1$. Anisotropic least-squares refinement converged to the residuals $R = 0.0885$ and $R_w = 0.0866$ for the absolute configuration indicated above for 2241 independent observed reflections, recorded with Cu $K\alpha$ radiation on an automated diffractometer. Each piperidinio group has the chair conformation with the Cl atom and the diketopiperazine (DKP) group in equatorial positions. The DKP ring has a boat conformation with the piperidinio groups attached at equatorial positions. The amine protons on the piperidinio groups are involved in an extensive hydrogen-bonding network with the SO_4^{2-} ions and the five water molecules of hydration, forming pleated ribbons of edge-sharing pentagons parallel to the c axis of the structure.

Introduction

The antineoplastic agent *cyclo*-(streptolutyl-streptolutyl-) (I), *cyclo*-(Slt-Slt-), has been shown to have activity in various neoplastic test systems (Gitterman, Rickes, Wolf, Madas, Zimmerman, Stoudt & Demny, 1970; Tarnowski, Schmid, Hutchison & Stock, 1973) and has also undergone preclinical tests (Folk, Peters, Pavkov & Swenberg, 1974). To provide an unequivocal structure determination with absolute configuration we have prepared the sulfate salt and performed a single-crystal X-ray diffraction analysis of this compound (Pettit, Von Dreele, Herald, Edgar & Wood, 1976). During this analysis it became evident that this highly hydrated salt contained a very complex hydrogen-bonding network involving large sheet-like arrays of water molecules. We now report the full structure analysis of this salt and discuss the molecular

conformation of this diketopiperazine and the extensive hydrogen-bonding pattern.



Experimental

Data collection

Single crystals of $\text{cyclo}(-\text{HSlt}-\text{HSlt})^{2+} \cdot \text{SO}_4^{2-} \cdot 5\text{H}_2\text{O}$ were grown from methanol–water solution as long needles. A crystal $0.10 \times 0.20 \times 1.10$ mm cleaved from a much longer one was placed with some of the mother liquor in a glass capillary which was then sealed to prevent dehydration.

Preliminary Weissenberg photographs displayed orthorhombic mmm Laue symmetry and the extinctions $h00: h = 2n + 1$; $0k0: k = 2n + 1$ and $00l: l = 2n + 1$ that uniquely correspond to the space group $P2_12_12_1$. A refinement of the setting angles for 15 reflections ($6.6 \leq 2\theta \leq 23.2^\circ$) obtained on a Syntex $P\bar{1}$ autodiffractometer from this crystal gave the lattice parameters $a = 26.570$ (14), $b = 14.913$ (8), $c = 6.006$ (3) Å which for $Z = 4(\text{C}_{14}\text{H}_{24}\text{Cl}_2\text{N}_4\text{O}_2^{2+} \cdot \text{SO}_4^{2-} \cdot 5\text{H}_2\text{O})$ gives $\rho_c = 1.502 \text{ Mg m}^{-3}$ ($\rho_o = 1.450 \text{ Mg m}^{-3}$).

The diffraction intensities for 2580 unique reflections within the limits of the diffractometer ($2\theta \leq 140^\circ$) were collected with graphite-monochromated Cu $K\alpha$ radiation and the diffractometer operating in the variable-speed θ – 2θ scan mode. For each reflection, the scan speed (between 1 and 8° min^{-1}) was determined from the intensity found in a rapid sampling scan. The scans were taken over the range $\pm 1^\circ$ above and below the $K\alpha_1$ – $K\alpha_2$ doublet with a background count for 0.125 of the total scan time taken at each end of the scan. The intensities of three reflections periodically monitored during the course of the data collection showed an average fluctuation of 3%; a smoothed

average of these intensities was applied to the observed intensities. There were 2241 reflections used in all subsequent calculations for which $|F_o| \geq \sigma_F$; $\sigma_F = 0.025 |F_o| + (C + k^2B)^{1/2} R/(2|F_o|Lp)$, where C is the total count in a scan taken at the rate R and $k (=4)$ is the ratio of scanning time to the time for the total background count B . Corrections were applied for Lorentz and polarization effects for monochromated radiation (Azaroff, 1955), but absorption ($\mu = 3.844 \text{ mm}^{-1}$) and extinction effects were ignored.

Structure determination and refinement

The structure of $cyclo(-HSlt-HSlt)^{2+} \cdot SO_4^{2-} \cdot 5H_2O$ was readily solved with the *MULTAN* 74 system of computer programs (Germain, Main & Woolfson, 1971; Declercq, Germain, Main & Woolfson, 1973; Koch, 1974). A set of normalized structure factors, E_{hkl} , was obtained from a Wilson (1942) analysis of all 2580 reflections. The 270 reflections with $E_{hkl} \geq 1.51$ were expanded over 2000 Σ_2 interactions in the space group $P2_12_12_1$, and were then subjected to a convergence analysis to give the starting set 20,0,2(0); 10,10,0(0); 8,14,0(0); 044(0); 031($\pi/2$); 502(0); 430(0); 474($\pm\pi/4$); 022(0 or π) and 713($\pm\pi/4$ or $\pm 3\pi/4$). The first four phases are fixed from Σ_1 relationships, the next three fix the origin (Hauptman & Karle, 1956) and the next three are variable with the 474 determining the enantiomorph. A multiple-solution tangent refinement of the 16 possible starting sets gave an absolute figure of merit of 0.9065, a Ψ_0 of 387 (Cochran & Douglas, 1955), and a residual of 29.58 for the best overall solution. A Fourier synthesis of these phases revealed the positions of 22 atoms, 21 of which ultimately proved correct. These positions were used to phase ($R = 41\%$) successive difference Fourier syntheses* which revealed the positions of the rest of the 32 atoms in the structure.

The model with isotropic thermal motion was refined by full-matrix least squares with each reflection assigned a weight, $w = 1/\sigma_F^2$, and with the real atomic scattering factors for Cl^0 , S^0 , O^0 , N^0 , C^0 and H^0 and the anomalous-dispersion corrections for Cl and S (*International Tables for X-ray Crystallography*, 1974). At convergence the standard residual was $R = 0.1508$ and the weighted residual $R_w = [\sum w(|F_o| - |F_c|)^2 / \sum w |F_o|^2]^{1/2}$ was 0.1614. The model with anisotropic thermal motion was refined by large-block least squares (289 parameters in 3 blocks) to give the residuals $R = 0.1071$ and $R_w = 0.1145$. The 24 H atoms on the $cyclo(-HSlt-HSlt)^{2+}$ ion were placed at idealized positions and the anisotropic refinement was repeated to yield the residuals $R = 0.0985$ and $R_w = 0.1070$. A difference synthesis permitted placement of

the 10 H atoms on the five water molecules. A repeat of the refinement yielded the residuals $R = 0.0945$ and $R_w = 0.0947$ at convergence. A similar refinement of the structure of the opposite hand yielded the residuals $R = 0.0993$ and $R_w = 0.0998$, thus establishing the absolute configuration of $cyclo(-HSlt-HSlt)^{2+}$ sulfate pentahydrate. Refinement of the H atom positions followed by a repeat of the anisotropic refinement for the correct absolute configuration yielded the final residuals $R = 0.0885$ and $R_w = 0.0866$ for 2241 reflections.*

Results

Final atomic coordinates for $cyclo(-Hstreptolityl-Hstreptolityl)^{2+}$ sulfate pentahydrate, (3*S*,6*S*)-3,6-

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35476 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Fractional coordinates ($\times 10^4$) and equivalent isotropic thermal parameters ($\times 10^3$) for $cyclo(-HSlt-HSlt)^{2+}$ sulfate pentahydrate

The estimated standard deviations are listed in parentheses.

| | <i>x</i> | <i>y</i> | <i>z</i> | $U_{eq} (\text{Å}^2)^*$ |
|--------------------------------------|-------------|-------------|-----------|-------------------------|
| (A) The $cyclo(-HSlt-HSlt)^{2+}$ ion | | | | |
| O(1) | 4538 (2) | 505 (4) | 8213 (9) | 36 |
| C(1 γ) | 4801 (3) | 199 (5) | 6695 (14) | 33 |
| C(1 α) | 4558 (3) | 93 (5) | 4384 (13) | 31 |
| N(1) | 4851 (2) | -473 (5) | 2921 (12) | 36 |
| C(1 β) | 4011 (3) | -202 (5) | 4545 (14) | 34 |
| C(1 γ) | 3710 (4) | -102 (6) | 2428 (16) | 44 |
| C(1 δ) | 3169 (4) | -361 (7) | 2759 (19) | 54 |
| C(1 ϵ) | 3110 (3) | -1290 (6) | 3701 (6) | 46 |
| C(1 ζ) | 3445 (3) | -1429 (6) | 5711 (7) | 48 |
| N(1 η) | 3968 (2) | -1165 (4) | 5255 (12) | 36 |
| Cl(1) | 2485.5 (10) | -1528 (2) | 4547 (6) | 81 |
| O(2) | 5575 (2) | -1041 (4) | 1624 (9) | 39 |
| C(2 γ) | 5326 (3) | -632 (5) | 3067 (13) | 29 |
| C(2 α) | 5612 (3) | -321 (5) | 5159 (14) | 30 |
| N(2) | 5269 (2) | -30 (4) | 6906 (11) | 31 |
| C(2 β) | 5986 (3) | -1043 (5) | 5987 (13) | 30 |
| C(2 γ) | 6404 (3) | -667 (6) | 7474 (16) | 43 |
| C(2 δ) | 6755 (3) | -1396 (6) | 8280 (18) | 47 |
| C(2 ϵ) | 6458 (3) | -2091 (6) | 9490 (16) | 34 |
| C(2 ζ) | 6045 (3) | -2483 (6) | 8085 (16) | 43 |
| N(2 η) | 5712 (2) | -1764 (4) | 7196 (12) | 35 |
| Cl(2) | 6828.8 (10) | -2979 (2) | 10570 (6) | 71 |
| (B) The sulfate ion | | | | |
| S | 565.3 (8) | 2470.0 (14) | 4831 (3) | 34 |
| O(3) | 497 (3) | 1554 (4) | 3976 (9) | 35 |
| O(4) | 936 (2) | 2965 (4) | 3493 (11) | 49 |
| O(5) | 94 (2) | 2924 (4) | 4871 (12) | 58 |
| O(6) | 765 (3) | 2400 (5) | 7153 (9) | 25 |
| (C) Hydration molecules | | | | |
| O(7) | 2577 (4) | 4079 (7) | 1810 (16) | 113 |
| O(8) | 851 (2) | 3926 (4) | 9691 (11) | 53 |
| O(9) | 4638 (3) | 2077 (4) | 888 (11) | 57 |
| O(10) | 1872 (3) | 4357 (7) | 8272 (17) | 101 |
| O(11) | 1939 (3) | 3139 (6) | 4895 (15) | 88 |

* From this point all calculations were performed with the *CRYSTALS* system of computer programs (Rollett & Carruthers, 1974), adapted for the Univac 1110 computer.

* Calculated from $U_{eq} = (U_1 U_2 U_3)^{1/3}$ where U_1, U_2, U_3 are the principal radii of the thermal ellipsoid.

Table 2. Fractional coordinates ($\times 10^3$) and bond distances for hydrogen atoms in *cyclo(-HSlt-HSlt)-²⁺sulfate pentahydrate*

The estimated standard deviations are listed in parentheses.

| | <i>x</i> | <i>y</i> | <i>z</i> | <i>d</i> (Å) |
|------------------|----------|----------|-----------|--------------|
| H(1 α) | 449 (3) | 61 (5) | 402 (14) | 0.81 (8) |
| H(1) | 467 (3) | -71 (5) | 246 (15) | 0.67 (7) |
| H(1 βa) | 385 (3) | 12 (5) | 546 (15) | 0.84 (8) |
| H(1 γa) | 372 (3) | 44 (5) | 209 (15) | 0.83 (8) |
| H(1 γb) | 389 (3) | -43 (5) | 149 (14) | 0.90 (8) |
| H(1 δa) | 297 (3) | -26 (5) | 125 (15) | 1.06 (9) |
| H(1 δb) | 297 (3) | 2 (5) | 366 (15) | 0.95 (8) |
| H(1 ϵ) | 324 (3) | -172 (5) | 253 (15) | 1.01 (8) |
| H(1 ζa) | 342 (3) | -199 (5) | 592 (14) | 0.85 (8) |
| H(1 ζb) | 326 (3) | -104 (5) | 684 (15) | 1.02 (8) |
| H(1 ηa) | 422 (3) | -128 (6) | 573 (15) | 0.74 (8) |
| H(1 ηb) | 407 (3) | -143 (6) | 399 (15) | 0.90 (9) |
| H(2) | 589 (3) | 24 (5) | 469 (14) | 1.15 (9) |
| H(2) | 547 (3) | 17 (5) | 746 (15) | 0.70 (8) |
| H(2 β) | 615 (3) | -129 (5) | 540 (14) | 0.66 (8) |
| H(2 γa) | 622 (3) | -31 (5) | 861 (14) | 0.99 (8) |
| H(2 γb) | 662 (3) | -28 (5) | 672 (15) | 0.94 (8) |
| H(2 δa) | 696 (3) | -173 (5) | 739 (16) | 0.91 (8) |
| H(2 δb) | 697 (3) | -121 (5) | 903 (15) | 0.78 (8) |
| H(2 ϵ) | 627 (3) | -187 (5) | 1031 (14) | 0.78 (8) |
| H(2 ζa) | 585 (3) | -286 (5) | 851 (14) | 0.80 (8) |
| H(2 ζb) | 623 (3) | -279 (5) | 710 (15) | 0.90 (8) |
| H(2 ηa) | 546 (3) | -163 (5) | 802 (15) | 0.85 (8) |
| H(2 ηb) | 543 (3) | -209 (5) | 679 (15) | 0.93 (8) |
| H(7 a) | 236 (3) | 420 (5) | 76 (14) | 0.87 (8) |
| H(7 b) | 258 (3) | 464 (5) | 241 (15) | 0.91 (8) |
| H(8 a) | 110 (3) | 370 (5) | 1033 (15) | 0.84 (8) |
| H(8 b) | 52 (3) | 370 (5) | 980 (14) | 0.95 (7) |
| H(9 a) | 497 (3) | 219 (5) | 97 (14) | 0.91 (7) |
| H(9 b) | 459 (3) | 164 (5) | 17 (15) | 0.79 (8) |
| H(10 a) | 194 (3) | 387 (5) | 753 (15) | 0.87 (8) |
| H(10 b) | 147 (3) | 423 (5) | 855 (15) | 1.09 (8) |
| H(11 a) | 159 (3) | 315 (5) | 476 (15) | 0.93 (7) |
| H(11 b) | 191 (3) | 369 (5) | 424 (14) | 0.91 (8) |

Table 3. Bond distances (Å) for *cyclo(-HSlt-HSlt)-²⁺sulfate pentahydrate*

The estimated standard deviations are listed in parentheses.

(A) The *cyclo(-HSlt-HSlt)-²⁺* ion

| | | | |
|--------------------------------|------------|--------------------------------|------------|
| C(1')N(2) | 1.295 (9) | C(2')N(1) | 1.288 (9) |
| C(1')O(1) | 1.236 (9) | C(2')O(2) | 1.250 (9) |
| C(1')C(1 α) | 1.540 (11) | C(2')C(2 α) | 1.539 (11) |
| C(1 α)C(1 β) | 1.521 (11) | C(2 α)C(2 β) | 1.548 (10) |
| C(1 α)N(1) | 1.446 (10) | C(2 α)N(2) | 1.456 (10) |
| C(1 β)C(1 γ) | 1.510 (12) | C(2 β)C(2 γ) | 1.531 (11) |
| C(1 β)N(1 η) | 1.502 (10) | C(2 β)N(2 η) | 1.488 (9) |
| C(1 γ)C(1 δ) | 1.501 (13) | C(2 γ)C(2 δ) | 1.512 (11) |
| C(1 δ)C(1 ϵ) | 1.504 (13) | C(2 δ)C(2 ϵ) | 1.491 (12) |
| C(1 ϵ)Cl(1) | 1.772 (9) | C(2 ϵ)Cl(2) | 1.773 (8) |
| C(1 ϵ)C(1 ζ) | 1.514 (13) | C(2 ϵ)C(2 ζ) | 1.502 (12) |
| C(1 ζ)N(1 η) | 1.469 (10) | C(2 ζ)N(2 η) | 1.489 (10) |

(B) The sulfate ion

| | | | |
|-------|-----------|-------|-----------|
| SO(3) | 1.471 (6) | SO(5) | 1.423 (6) |
| SO(4) | 1.470 (6) | SO(6) | 1.495 (6) |

Table 4. Bond angles ($^\circ$) for *cyclo(-HSlt-HSlt)-²⁺sulfate pentahydrate*

The estimated standard deviations are listed in parentheses.

(A) The *cyclo(-HSlt-HSlt)-²⁺* ion

| | | | |
|--|-----------|--|-----------|
| N(2)C(1')O(1) | 124.6 (8) | N(1)C(2')O(2) | 124.2 (7) |
| N(2)C(1')C(1 α) | 117.7 (7) | N(1)C(2')C(2 α) | 119.0 (7) |
| O(2)C(1')C(1 α) | 117.7 (7) | O(1)C(2')C(2 α) | 116.8 (7) |
| C(1')C(1 α)C(1 β) | 112.0 (6) | C(2')C(2 α)C(2 β) | 111.7 (6) |
| C(1')C(1 α)N(1) | 112.4 (6) | C(2')C(2 α)N(2) | 111.6 (6) |
| C(1 β)C(1 α)N(1) | 112.5 (6) | C(2 β)C(2 α)N(2) | 112.2 (6) |
| C(1 α)N(1)C(2') | 126.4 (7) | C(2 α)N(2)C(1') | 127.6 (7) |
| C(1 α)C(1 β)C(1 γ) | 115.1 (7) | C(2 α)C(2 β)C(2 γ) | 113.5 (6) |
| C(1 α)C(1 β)N(1 η) | 111.6 (6) | C(2 α)C(2 β)N(2 η) | 110.1 (6) |
| C(1 γ)C(1 β)N(1 η) | 107.1 (6) | C(2 γ)C(2 β)N(2 η) | 109.6 (6) |
| C(1 β)C(1 γ)C(1 δ) | 111.8 (8) | C(2 β)C(2 γ)C(2 δ) | 111.7 (7) |
| C(1 γ)C(1 δ)C(1 ϵ) | 112.8 (8) | C(2 γ)C(2 δ)C(2 ϵ) | 109.3 (7) |
| C(1 δ)C(1 ϵ)Cl(1) | 113.0 (6) | C(2 δ)C(2 ϵ)Cl(2) | 113.8 (6) |
| C(1 δ)C(1 ϵ)C(1 ζ) | 111.4 (8) | C(2 δ)C(2 ϵ)C(2 η) | 112.5 (8) |
| Cl(1)C(1 ϵ)C(1 ζ) | 107.1 (6) | Cl(2)C(2 ϵ)C(2 ζ) | 108.7 (6) |
| C(1 ϵ)C(1 ζ)N(1 η) | 111.7 (7) | C(2 ϵ)C(2 ζ)N(2 η) | 110.8 (7) |
| C(1 ζ)N(1 η)C(1 β) | 112.5 (6) | C(2 ζ)N(2 η)C(2 β) | 113.8 (6) |

(B) The sulfate ion

| | | | |
|-----------|-----------|-----------|-----------|
| O(3)SO(4) | 111.0 (4) | O(4)SO(5) | 111.0 (4) |
| O(3)SO(5) | 109.8 (4) | O(4)SO(6) | 108.0 (4) |
| O(3)SO(6) | 107.7 (4) | O(5)SO(6) | 109.2 (4) |

Table 5. Torsion angles ($^\circ$) for the *cyclo(-HSlt-HSlt)-²⁺* ion

| IUPAC designation | Atoms involved | Residue 1 | Residue 2 |
|-------------------|---|------------|------------|
| ω | C(α)NC'C(α) | 5.0 (11) | 11.0 (12) |
| ψ | NC'C(α)N | 15.6 (10) | 10.1 (10) |
| ϕ | C'C(α)NC' | -24.2 (11) | -18.7 (10) |
| χ_1 | NC(α)C(β)C(γ) | -66.7 (9) | -74.6 (8) |
| χ_2 | C(α)C(β)C(γ)C(δ) | -177.0 (7) | 178.9 (7) |
| χ_3 | C(β)C(γ)C(δ)C(ϵ) | -54.6 (11) | -57.1 (10) |
| χ_4 | C(γ)C(δ)C(ϵ)C(ζ) | 49.1 (11) | 56.9 (10) |
| χ_5 | C(δ)C(ϵ)C(ζ)N(η) | -50.5 (10) | -54.9 (10) |
| χ_6 | C(ϵ)C(ζ)N(η)C(β) | 58.1 (9) | 53.5 (9) |
| χ_7 | C(ζ)N(η)C(β)C(α) | 172.3 (7) | -179.1 (7) |
| - | NC(α)C(β)N(η) | 55.6 (9) | 48.7 (8) |
| - | C(ζ)N(η)C(β)C(γ) | -60.9 (9) | -53.6 (9) |
| - | N(η)C(β)C(γ)C(δ) | 58.3 (9) | 55.3 (9) |

The torsion angles ω_1 , ψ_1 , and ϕ_1 are for the atom sequences C(2 α)N(2)C(1')C(1 α), N(2)C(1')C(1 α)N(1) and C(1')C(1 α)N(1)C(2'), respectively.

bis[(2*R*,5*S*)-5-chloro-2-piperidinio]-2,5-piperazinedi-one sulfate pentahydrate, are given in Tables 1 and 2 with the estimated standard deviations from the last cycle of least-squares analysis. The perspective view in Fig. 1 displays the essential configurational and conformational features of the *cyclo(-HSlt-HSlt)-²⁺* cation. The two residues have identical configurations at the three chiral centers (*S*)-C(α), (*R*)-C(β) and (*S*)-C(ϵ) as established in this analysis. Bond lengths and angles within the cation and sulfate anion are

Table 6. *Hydrogen-bonding contacts* ($<3 \text{ \AA}$)

The estimated standard deviations are given in parentheses.

| Probable donor | Proton | Probable acceptor | d (\AA) |
|----------------|----------------|-------------------|----------------------|
| N(1 η) | H(1 ηa) | O(3) | 2.712 (9) |
| N(1 η) | H(1 ηb) | O(6) | 2.715 (9) |
| N(2 η) | H(2 ηa) | O(2) | 2.893 (9) |
| N(2 η) | H(2 ηb) | O(9) | 2.698 (9) |
| O(7) | H(7a) | O(10) | 2.863 (14) |
| O(7) | H(7b) | O(10) | 2.889 (14) |
| O(8) | H(8a) | O(4) | 2.705 (9) |
| O(8) | * | O(6) | 2.750 (9) |
| O(9) | * | O(5) | 2.820 (9) |
| O(9) | H(9b) | O(1) | 2.885 (8) |
| O(10) | H(10a) | O(11) | 2.728 (12) |
| O(10) | H(10b) | O(8) | 2.917 (11) |
| O(11) | H(11a) | O(4) | 2.808 (9) |
| O(11) | H(11b) | O(7) | 2.877 (14) |

* No proton found near the hydrogen-bonding position.

Table 7. *Hydrogen-bonding angles* ($^\circ$) (*distances* $<3 \text{ \AA}$) for *cyclo(-HSlt-HSlt-)²⁺ sulfate pentahydrate*

The estimated standard deviations are given in parentheses.

| | | | |
|-------------------------------------|------------|-------------------------------|------------|
| S-O(3)···N(1 η) | 114.9 (7) | O(10)···O(7)···O(10) η' | 116.0 (8) |
| S-O(4)···O(8) | 132.2 (6) | O(10)···O(7)···O(11) | 99.4 (12) |
| S-O(4)···O(11) | 121.2 (7) | O(10) η' ···O(7)···O(11) | 119.7 (9) |
| O(8)···O(4)···O(11) | 106.5 (7) | O(4)···O(8)···O(6) | 92.1 (8) |
| S-O(5)···O(9) | 113.1 (8) | O(4)···O(8)···O(10) | 106.6 (8) |
| S-O(6)···N(1 η) | 141.3 (6) | O(6)···O(8)···O(10) | 95.6 (9) |
| S-O(6)···O(8) | 119.2 (7) | O(5)···O(9)···O(1) | 123.2 (5) |
| N(1 η)···O(6)···O(8) | 99.2 (8) | O(5)···O(9)···N(2 η) | 140.2 (5) |
| C(1 η')···O(1)···O(9) | 131.7 (7) | O(1)···O(9)···N(2 η) | 96.2 (9) |
| C(2 η')···O(2)···N(2 η) | 152.4 (6) | O(7)···O(10)···O(7) η' | 90.7 (12) |
| C(1 β)···N(1 η)···O(3) | 113.5 (11) | O(7)···O(10)···O(8) | 111.1 (9) |
| C(1 β)···N(1 η)···O(6) | 115.6 (11) | C(7 η')···O(10)···O(8) | 137.5 (6) |
| C(1 ζ)···N(1 η)···O(3) | 106.6 (14) | O(7)···O(10)···O(11) | 114.4 (9) |
| C(1 ζ)···N(1 η)···O(6) | 101.2 (14) | O(7 η')···O(10)···O(11) | 106.2 (10) |
| O(3)···N(1 η)···O(6) | 106.4 (7) | O(8)···O(10)···O(11) | 97.5 (11) |
| C(2 β)···N(2 η)···O(2) | 103.9 (13) | O(4)···O(11)···O(7) | 114.3 (9) |
| C(2 β)···N(2 η)···O(9) | 107.2 (9) | O(4)···O(11)···O(10) | 102.0 (19) |
| C(2 ζ)···N(2 η)···O(2) | 90.8 (17) | O(7)···O(11)···O(10) | 101.1 (10) |
| C(2 ζ)···N(2 η)···O(9) | 89.4 (5) | | |
| O(2)···N(2 η)···O(9) | 145.8 (4) | | |

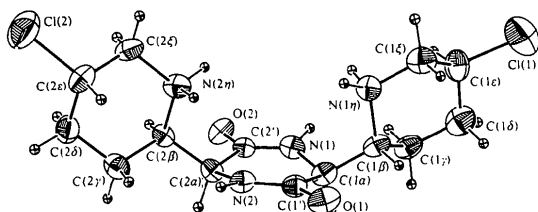


Fig. 1. A perspective view of the (3*S*,6*S*)-3,6-bis-(2*R*,5*S*)-5-chloro-2-piperidinyl-2,5-piperazinedione cation.

recorded in Tables 3 and 4. The set of torsion angles in Table 5 fully characterizes the conformation of the *cyclo(-HSlt-HSlt-)²⁺* cation. All the hydrogen-bonding parameters for contacts between the two ions and the five water molecules of hydration are listed in Tables 6 and 7. A stereoscopic drawing of the unit cell and its

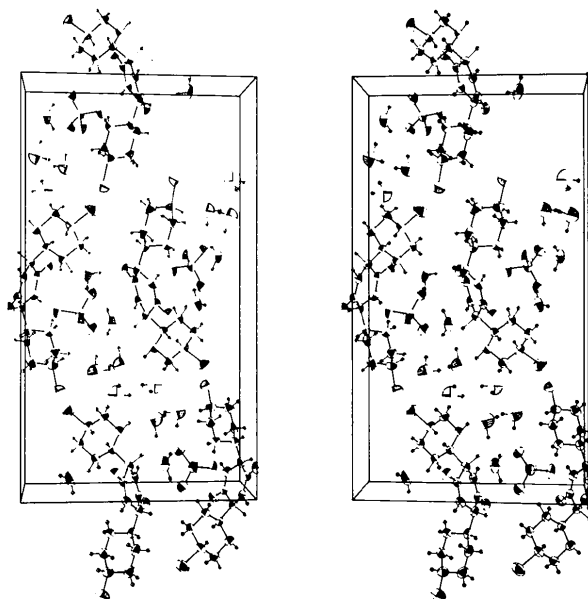


Fig. 2. A stereoscopic view of the unit cell and four formula units of *cyclo(-HSlt-HSlt-)²⁺ \cdot SO₄²⁻ \cdot 5H₂O*. An additional cation and water molecule are also shown. The *a* axis is vertical, *b* is horizontal and *c* is into the paper.

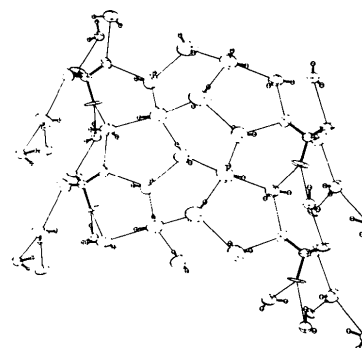


Fig. 3. A perspective view of the ribbon of hydrogen-bonded water molecules. Thin lines connect atoms within a possible hydrogen-bonding distance ($<3 \text{ \AA}$). The vertical axis is parallel to the *c* axis.

contents is shown in Fig. 2 and a perspective view of the hydrogen-bonding network across two unit cells is shown in Fig. 3.

Discussion

The molecular ion *cyclo(-HSlt-HSlt-)²⁺* is a diketopiperazine (DKP) with identical (5*S*)-5-chloropiperidinium substituents on the α -carbon atoms of the DKP ring, in agreement with the structure assigned by Arison & Beck (1973). The parent amino acid, (2*S*)-2-amino-[(2*R*,5*S*)-5-chloro-2-piperidyl]acetic acid (II), has been designated streptolutine (Pettit *et al.*, 1976) and abbreviated Slt. The absolute configurations of both amino acid residues are identical; the α -carbon

(*S*) is the same as typical naturally occurring amino acids such as L-alanine. The other two chiral C atoms are (*R*)-C(β) and (*S*)-C(ϵ) for both residues. In this study the piperidine N atoms, N(η), are both protonated, thus giving the dipositive cation.

As can be seen by comparing equivalent torsion angles the molecular ion has an approximate twofold axis passing through the center of the DKP ring and perpendicular to it. Thus both piperidine rings are in the chair conformation and positioned so that the N atoms, N(η), are on the same side of the DKP ring. Inspection of the packing diagram, Fig. 2, shows that this orientation is achieved to permit the closest possible contact between the cationic centers on the *cyclo*-(HSl-t-HSl-t)²⁺ ion and the sulfate anions; in fact, one amino group, N(1 η), forms hydrogen bonds to two O atoms, O(3) and O(6), on adjacent sulfate ions. The other amino group forms hydrogen bonds with some of the surrounding water molecules (see below).

The bonding within the piperidine rings is quite uniform; all C—C single bonds are normal, as are the C—N bonds, and are similar to those found for piperidine.H₂S (Smail & Sheldrick, 1973) and piperidine.HCl (Dattagupta & Saha, 1975). The angles are also normal and, as found for the above structures and other six-membered rings, are generally slightly larger than the ideal tetrahedral angle. The Cl atom is attached equatorially to the piperidine ring; the C—Cl bonds are normal in both residues. The piperidine rings are subject to some thermal motion, with the major-axis r.m.s. displacements in the range 0.20–0.27 Å. However, the Cl atoms have larger r.m.s. displacements, ~0.33 Å, so we have applied riding corrections (Busing & Levy, 1964) to the C—Cl bonds to obtain 1.789 and 1.794 Å for residues 1 and 2, respectively.

The DKP ring is in a twist-boat conformation similar to that found for *cyclo*-(L-Ala-L-Ala-) (Sletten, 1970), but with somewhat less distortion from planarity. However, the amide bonds, C'—N, in the present compound are appreciably twisted with ω angles of 5.0 and 10.1° for residues 1 and 2, respectively. By comparison, *cyclo*-(L-Ala-L-Ala-) had ω angles of 8.1 and 0.7° for the two residues. The symmetric DKP rings in *cyclo*-(L-Ala-D-Ala-) (Sletten, 1970) and DKP itself (Degeilh & Marsh, 1959) have much smaller ω angles, 3.2 and 1.3°, respectively, and are much flatter. The boat conformation in the present case is clearly a result of repulsion between the bulky and charged side groups; if the DKP ring were flat the piperidine groups would be closer and suffer appreciable steric interference.

The bonding parameters for the DKP ring are reasonably uniform; the carbonyl bond lengths are normal, average 1.243 Å, and only slightly longer than those found for *cyclo*-(L-Ala-L-Ala-). The C(α)—C(β), average 1.535 Å, and the C(α)—C', average 1.539 Å, bonds are both much longer than found in *cyclo*-

(-L-Ala-L-Ala-), 1.516 and 1.517 Å, respectively, but are more typical for open peptides (Ramachandran & Venkatachalam, 1968). However, the C'—N bonds are much shorter, average 1.292 Å, despite the greater twist, than for *cyclo*-(L-Ala-L-Ala-), 1.329 Å, while the C(α)—N bonds for both compounds are nearly the same, 1.457 versus 1.451 Å for this study. Despite these differences in bond lengths, *cyclo*-(L-HSl-t-L-HSl-t)²⁺ and *cyclo*-(L-Ala-L-Ala-) have identical bond angles within the DKP ring and also show much less variation between equivalent angles than was found for the bond lengths.

Neither amide proton participates in the hydrogen-bonding network; however, the carbonyl O atoms each form hydrogen bonds. One, O(1), forms a hydrogen bond to a water molecule, H₂O(9), and the other forms an intermolecular hydrogen bond with a piperidine amine group, O(2)···H—N(2 η), on an adjacent molecular ion.

The sulfate anion has bond lengths quite close to the average value, 1.49 Å, reported by Wells (1967). One bond is somewhat shorter, 1.423 Å, with two others slightly short, both 1.470 Å, and one longer, 1.495 Å. Despite this variation the angles are all very close to the ideal tetrahedral angle. Three of the O atoms each apparently participate in just one hydrogen bond but the other, O(4), participates in two hydrogen bonds with surrounding water molecules and amine groups.

The hydrogen-bonded network of water molecules, as shown in Fig. 3, is a pleated ribbon of edge-sharing pentagons. The central row of pentagons is made up entirely of water molecules: O(7), O(10), O(7'), O(10'), O(11) joined at two of the O(7)—O(10) edges. Pairs of these pentagons each share edges with a pentagon made up of four water molecules and a sulfate oxygen O(10), O(8), O(2), O(11), O(7). The remaining edges in the central-row pentagons are shared with the six-membered rings: O(11), O(10), O(8), O(4), S, O(2). This ribbon of five- and six-membered rings is then bounded by a complex series of hydrogen bonds to the amine groups, carbonyl and sulfate O atoms and the remaining water molecule, O(9). Some of these linkages also form rings of various sizes along the boundary of the ribbon. Very similar networks of hydrogen-bonded water molecules have been found in the higher hydrates of pinacol (Kim & Jeffrey, 1970), piperazine (Schwarzenbach, 1968), 2,5-dimethyl-2,5-hexanediol (Jeffrey & Shen, 1972) and 2,7-dimethyl-2,7-octanediol (Jeffrey & Mastropaolo, 1978). In the first three cases there are extended nets of edge-sharing pentagons of water molecules and hydroxyl groups that link across the sheets to form semi-clathrates (Jeffrey, 1969) enclosing the aliphatic groups. In the octanediol these sheets are sufficiently separated to prevent cross-linking. However, in all these cases the nets are not bounded as is found in this study.

The hydrogen-bonding contacts are all similar to

those observed in these other structures. However, the angles, Table 7, show a larger range of values, 89–152°, than found, for example, in the octanediol, 100–114°. The H atoms generally were found in appropriate hydrogen-bonding positions but due to the lower quality of the data they cannot unambiguously be assigned to these positions.

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Structure of the 1:1 Complex Between *N,N*-Dimethyl-*p*-toluidine and Hexafluorobenzene

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Abstract

The 1:1 complex between *N,N*-dimethyl-*p*-toluidine, $C_9H_{13}N$, and hexafluorobenzene, C_6F_6 , crystallizes in a monoclinic cell. In order to avoid a too oblique β angle a lattice with space group $I2/m$ and $a = 6.566$ (2), $b = 16.539$ (5), $c = 7.206$ (3) Å, $\beta = 97.97$ (3)° was chosen rather than the conventional Bravais lattice with space group $C2/m$ and $a = 6.566$ (2), $b = 16.539$ (5),

$c = 9.051$ (3) Å, $\beta = 127.96$ (3)°. $V = 775.0$ Å³, $Z = 2$ (assumed), $D_c = 1.38$ Mg m⁻³ (not measured). The structure was refined by constraints to $R = 0.078$ for 164 observed reflections. The structure is disordered with the *N,N*-dimethyl-*p*-toluidine molecule in two equivalent orientations. The thermal vibrations of the hexafluorobenzene molecule are unusually large, especially along [010]. The partner molecules are stacked alternately with an interplanar distance of 3.50 Å. The overlap of the benzene rings of the partner molecules is very similar to that observed in other complexes of hexafluorobenzene with π donors, and the

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