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# Cyclic Peptide Metal Salt Adducts.
# II. Crystal Structure of the Silver Nitrate Cyclosarcosylsarcosine 2:1 Adduct

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## Abstract

The crystal structure analysis of the 2:1 adduct of cyclosarcosylsarcosine with silver(I) nitrate shows that the Ag(I) ion directly interacts with the carbonyl oxygen atoms of the peptide moiety. The independent unit is composed of a half cyclosarcosylsarcosine molecule, which sits on a crystallographic center of symmetry, per each silver nitrate unit. The crystal is held together by strong coulombic interactions between the silver and the nitrate ions and by ion–dipole interactions between the silver ion and the organic molecule. The coordination at the Ag(I) ion cannot be described in terms of a regular geometry; each silver ion experiences different types of contacts with the surrounding oxygen atoms. Six Ag–O interactions are in the range 2.35–2.68 Å; a seventh Ag–O interaction presents a distance of 2.90 Å. This latter contact is perhaps the cause of the severe distortion from the ideal octahedral geometry observed experimentally. The nitrate ion and the cyclic peptide molecule are both nearly planar.

## Introduction

Metal cations such as copper, lithium, barium and silver form complexes [1] with cyclic peptides such as *N,N*-dimethylpiperazine-1,5-dione (or cyclosarcosylsarcosine). The study of the interactions between cyclic peptides and metal ions is relevant to the understanding of the stereochemical requirements needed for the occurrence of binding and for the determination of the types of force and the factors responsible for coordination together with the type and mode in which it occurs.

In a previous study [2, 3] we have reported the structure of the hexaaquocopper(II) perchlorate cyclosarcosylsarcosine 1:2 adduct, and we have shown that the interactions occurring in this case are different from those previously observed for the lithium perchlorate complex [4]. In fact, while the $Li^+$ ion directly coordinates to the oxygen atoms of the carbonyl groups of the cyclic dipeptide, such interaction does not occur in the case of the Cu(II) adduct because the hydration of the Cu(II) ion leads to the octahedrally coordinated cation $Cu(H_2O)_6^{2+}$, which is linked through hydrogen bonds to the cyclic dipeptide molecules and to the perchlorate anions.

Silver nitrate forms with cyclosarcosylsarcosine a 2:1 adduct with a stoichiometry different from those observed for the perchlorates of several ions for which 1:2 adducts occur. We have investigated by X-ray diffraction the possible structural differences occurring in this metal salt cyclic peptide adduct in order to establish whether direct coordination between peptide carbonyl oxygens and silver ions is present. A preliminary account of the results has been previously reported at the VIIIth American Peptide Symposium in Washington, D.C. [2].

## Experimental

The cyclic peptide silver nitrate 2:1 adduct was obtained by mixing ethyl acetate solutions of the dipeptide and the silver salt. By slow evaporation of the ethyl acetate solution needle-shaped single crystals of the adduct were obtained. Preliminary diffraction spectra by photographic techniques indicate the triclinic system, because no systematic absences were observed. Density measurements by flotation techniques indicate the presence in the unit cell of one silver nitrate formula unit per each half cyclic peptide molecule, with a 2:1 stoichiometry for the adduct.

The CAD 4 Enraf-Nonius diffractometer equipped with PDP-8 and PDP-11 Digital computers of the Centro Interdipartimentale di Metodologie Chimico-fisiche of the University of Naples was used for data collection, structure determination and refinement. The SDP package of crystallographic programs (structure determination programs) was used

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TABLE I. Crystal Data for $AgNO_3 \cdot 0.5c(Sar)_2$

| | |
|---|---|
| Formula unit | $AgNO_3 \cdot 0.5C_6H_{10}N_2O_2$ |
| Formula weight | 240.95 a.m.u. |
| Crystal system | triclinic |
| Space group | $P\bar{1}$ |
| $Z$ | 2 formula units/unit cell |
| $a$ | 5.410(4) Å |
| $b$ | 7.562(4) Å |
| $c$ | 8.020(6) Å |
| $\alpha$ | 92.06(4)° |
| $\beta$ | 105.07(4)° |
| $\gamma$ | 104.60(4)° |
| $V$ | 304.8(9) $Å^3$ |
| Density, measured by flotation | 2.62(1) $g/cm^3$ |
| Density, calculated | 2.625 $g/cm^3$ |
| Reflections, measured | 1154 |
| Reflections observed | 1015 with $I > 3.0\sigma(I)$ |
| Radiation | Mo K$\alpha$ ($\lambda$ = 0.71069 Å) |
| $R$ factor | 0.058 |
| Temperature | 23 °C, ambient |

throughout. Unit cell parameters, orientation matrix, and intensity data collection were carried out using Zr-filtered Mo K$\alpha$ radiation. Crystallographic data are given in Table I.

Diffraction data were collected by an $\omega$–$2\theta$ scan mode with a range of $(0.8 + 0.15\text{tag}\ \theta)°$ for peak measurements. Background counts were taken at each end of each scan and a distance crystal-counter of 368 mm was used with a counter aperture of 4 mm. The tube placed between the goniometer head and the detector was evacuated using a vacuum pump. Prescan runs were made with a speed of 5 deg/min. Reflections with a net intensity $I \leqslant 0.5\ \sigma(I)$ were flagged as 'weak'; those having $I > 0.5\ \sigma(I)$ were measured at lower speed (in the range 1–5 deg/min) depending on the $\sigma(I)/I$ value. The time allowed for the scan was set to a maximum of 60 s. Two intensity control reflections were recorded every 100 reflections and no significant change in their intensity was observed during data collection. A total of 1154 reflections in the range 1–25° of $\theta$ was collected; of these 1015 reflections had a net intensity greater than 3.0 $\sigma(I)$ and were considered as 'observed'. All reflections were corrected for Lorentz and polarization effects.

The structure has been solved by interpreting the Patterson vectors. The silver atom was located, and by successive Fourier syntheses the positions of all non-hydrogen atoms were determined. Refinement by full-matrix least-squares procedure with weight $w = 1/\sigma(F_o^2)$, anisotropic temperature factors for Ag, N, O, and C atoms and isotropic temperature factors for H atoms, led to a final $R$ factor of 0.058 for all observed reflections. The positions of the H atoms were calculated by stereochemical considerations and they were kept fixed. To each hydrogen, a temperature factor equal to the $B_{eq}$ of the atom to which it is linked was assigned and kept fixed in the refinement. Atomic scattering factors for all atomic species were calculated from Cromer and Waber [5]. All calculations were carried out on the PDP-11 computer under the SDP system. The final atomic parameters for the silver nitrate cyclosarcosylsarcosine 2:1 adduct are reported in Table II.

TABLE II. Final Atomic Parameters[a]

| Atom | $x/a$ | $y/b$ | $z/c$ | $B_{eq}$ |
|---|---|---|---|---|
| Ag | 604(2) | 2409(1) | 250(1) | 2.75(3) |
| N(1) | 6594(19) | 3840(14) | 1445(12) | 2.5(4) |
| O(1) | 8929(18) | 4823(14) | 1740(13) | 3.7(4) |
| O(2) | 4860(18) | 4456(14) | 1768(13) | 3.8(4) |
| O(3) | 6042(21) | 2233(14) | 765(14) | 4.4(5) |
| $C^{\alpha}$ | 4503(27) | −1385(18) | 3590(17) | 2.9(5) |
| C′ | 2804(24) | −61(16) | 3495(15) | 2.3(4) |
| O | 1007(18) | −192(12) | 2190(11) | 2.6(4) |
| N | 3396(19) | 1206(13) | 4840(12) | 2.1(4) |
| $C_N$ | 1854(26) | 2555(19) | 4764(15) | 2.8(5) |
| $H(1)C^{\alpha}$ | 5733 | −1037 | 2795 | 2.9 |
| $H(2)C^{\alpha}$ | 3121 | −2471 | 3537 | 2.9 |
| $H(1)C_N$ | 1729 | 3233 | 3742 | 2.8 |
| $H(2)C_N$ | 7639 | 7127 | 4251 | 2.8 |
| $H(3)C_N$ | 966 | 2037 | 3984 | 2.8 |

[a] Corresponding standard deviation (in parentheses). Positional parameters are multiplied by $10^4$.

## Results and Discussion

The Ag(I) ion, as in the case of the lithium perchlorate cyclosarcosylsarcosine 1:2 adduct [4], directly interacts with carbonyl oxygen atoms of the peptide moiety, while in the case of the hexaaquocopper(II) perchlorate cyclosarcosylsarcosine 1:2 adduct [2, 3] no direct interaction occurred because of the shielding by the coordinated water molecules of the Cu(II) ions. The independent crystallographic unit in the lattice is composed of one silver nitrate unit and half of a cyclosarcosylsarcosine molecule lying on a center of symmetry. The crystal is held together by strong coulombic interactions between silver and nitrate ions and by ion–dipole interactions between the silver ion and the organic molecules. Thus, the present structure is different from the structures of both the lithium and the copper(II) adducts. In fact, in the lithium adduct only carbonyl oxygens from the organic molecules act as ligands, and in the copper(II) adduct no carbonyl oxygens from the organic molecules are involved in the coordination; but in the silver adduct a mixed type of coordination takes place due to oxygen atoms from both the inorganic as well as the organic moieties.

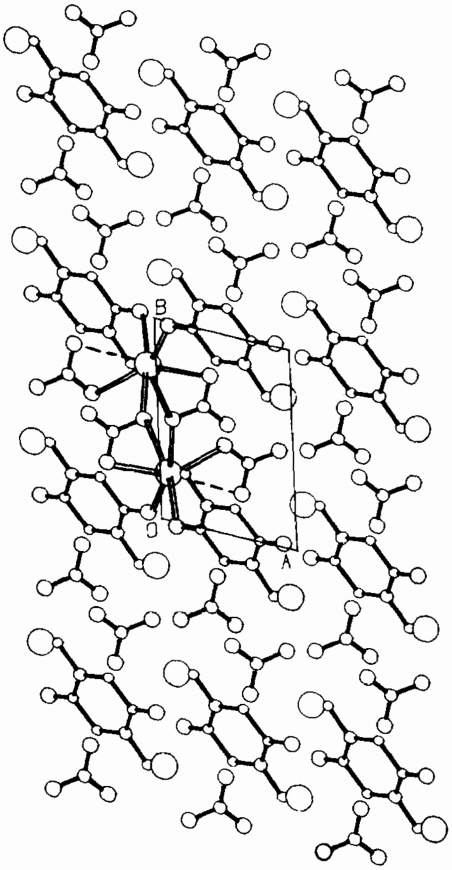

Fig. 1. Mode of packing in the crystal of the silver nitrate cyclosarcosylsarcosine 2:1 adduct as viewed along the *c* direction. Bonding in the nitrate ion and the cyclic organic molecule is represented with darker lines; coordination of the silver(I) ion is shown with empty lines. The weak interaction between the Ag ion and the O(3) atom is indicated as a dashed line.

### *The Coordination of the Ag(I) Ion*

Each Ag(I) ion experiences different types of contacts with the surrounding oxygen atoms, as shown in Fig. 1: (i) two short contacts with the O atom of a cyclic peptide molecule and the O(2) atom of a nitrate ion (2.35 and 2.41 Å, respectively); (ii) four intermediate contacts (between 2.57 and 2.68 Å) with the O(1) and O(3) atoms of a nitrate anion, acting as a bidentate, with the O(1)* of a symmetry-related nitrate anion and the carbonyl oxygen O* of a symmetry-related cyclic peptide molecule; and (iii) a rather weak interaction with the O(3) atom of another nitrate anion (2.90 Å).

The description of the Ag(I) coordination cannot be done simply in terms of a regular polyhedron. Tentatively, it can be considered that the Ag(I) ion is octahedrally coordinated to six oxygen atoms as shown in Fig. 2, but further interaction with a seventh oxygen produces rather severe distortions from the ideal coordination.

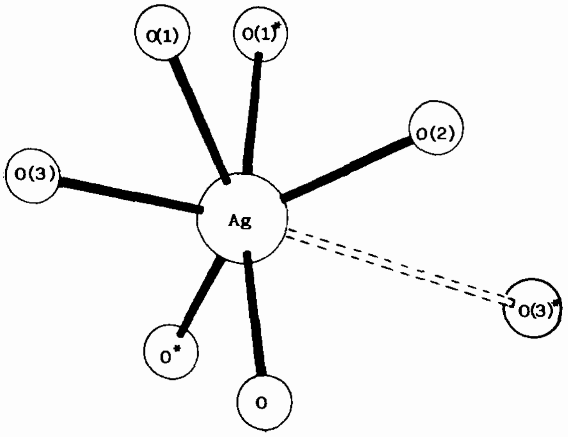

Fig. 2. The coordination around the silver(I) ion. The broken line between the Ag and the O(3)* atoms indicate the weak interaction occurring. Atoms labelled with an asterisk are related to those without asterisk by symmetry element.

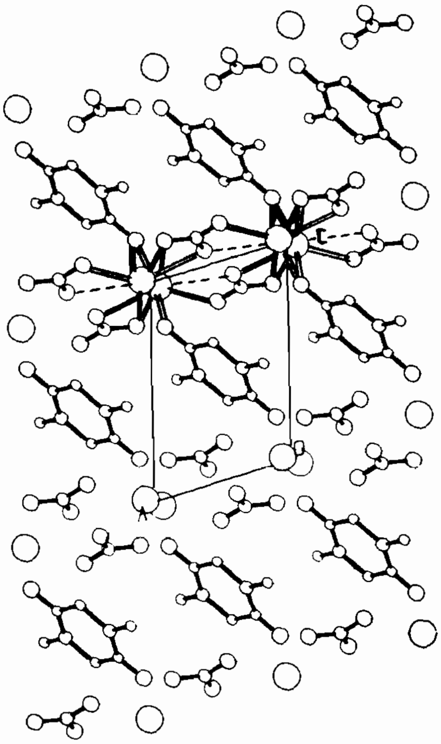

Fig. 3. Mode of packing in the crystal of the silver nitrate cyclosarcosylsarcosine 2:1 adduct as viewed along the *b* direction. Bonding in the nitrate ion and the cyclic organic molecule is represented with darker lines; coordination of the silver(I) ion is shown with empty lines. The weak interaction between the Ag ion and the O(3) atom is indicated as a dashed line.

The O(1) oxygen atom of each nitrate ion and the oxygen atom of each carbonyl group bridge two silver ions, as shown in Figs. 1 and 3, while the O(2) atom is linked to only one silver ion and, finally, the O(3) is strongly linked to one silver ion and weakly inter-

TABLE III. Bond Lengths, Bond Angles and Dihedral Angles[a]

| | | | |
|---|---|---|---|
| Bond lengths | | | |
| Ag–O | 2.568(9) | N(1)–O(1) | 1.250(10) |
| Ag–O* | 2.354(6) | N(1)–O(2) | 1.226(10) |
| Ag–O(1) | 2.612(8) | N(1)–O(3) | 1.245(10) |
| Ag–O(1)* | 2.679(7) | N–$C^{\alpha}$ | 1.436(12) |
| Ag–O(2) | 2.406(8) | N–C′ | 1.332(11) |
| Ag–O(3) | 2.578(9) | N–$C_N$ | 1.466(13) |
| | | C′–O | 1.210(11) |
| | | $C^{\alpha}$–C′ | 1.512(14) |
| Bond angles | | | |
| O–Ag–O* | 88.7(2) | O(1)–N(1)–O(2) | 121.0(9) |
| O–Ag–O(1) | 109.1(2) | O(2)–N(1)–O(3) | 120.4(9) |
| O–Ag–O(2) | 95.5(3) | O(1)–N(1)–O(3) | 118.6(9) |
| O–Ag–O(3) | 88.6(3) | $C^{\alpha}$–N–C′ | 124.9(8) |
| O–Ag–O(1)* | 170.1(2) | $C^{\alpha}$–N–$C_N$ | 115.5(7) |
| O*–Ag–O(1) | 138.2(3) | C′–N–$C_N$ | 119.7(8) |
| O*–Ag–O(2) | 135.5(3) | N–C′–O | 123.6(10) |
| O*–Ag–O(3) | 96.2(3) | N–C′–$C^{\alpha}$ | 118.2(9) |
| O(1)–Ag–O(2) | 81.6(2) | O–C′–$C^{\alpha}$ | 118.2(9) |
| O(1)–Ag–O(3) | 48.8(2) | C′–$C^{\alpha}$–N | 116.9(8) |
| O(1)–Ag–O(1)* | 76.7(3) | | |
| O(2)–Ag–O(1)* | 77.1(3) | | |
| O(3)–Ag–O(1)* | 101.2(3) | | |
| O(2)–Ag–O(3) | 128.1(2) | | |
| O*–Ag–O(1)* | 92.0(2) | | |
| Torsion angles | | | |
| C′*–N*–$C^{\alpha}$–C′ | ($\phi$) | −1.8 | |
| N–C′–$C^{\alpha}$–N* | ($\psi$) | 1.7 | |
| $C^{\alpha}$*–N–C′–$C^{\alpha}$ | ($\omega$) | −1.8 | |

[a] Estimated standard deviations in parentheses.

acts with another symmetry-related silver ion. Ag–O bond distances and O–Ag–O bond angles are listed in Table III. Severe deviations from 90° are observed in the O–Ag–O bond angles.

### *The Nitrate Anion*

Bond distances and bond angles of the nitrate anion are given in Table III. On the average the N–O bond distances and the O–N–O bond angles are 1.24 ± 0.01 Å and 120 ± 1°, respectively, in good agreement with the corresponding values reported in the literature [6]. Deviations from the ideal $D_{3h}$ symmetry are ascribed to the different interactions experienced by each oxygen atom in the crystal lattice.

The O(1) and O(3) atoms of the nitrate ion act as bidentate ligands with respect to each silver ion; consequently the O(1)–N(1)–O(3) bond angle is smaller (118.6°) than the other two (121.0° and 120.4°), and the two bond distances N(1)–O(1) and N(1)–O(3) are larger (1.250 and 1.245 Å, respectively) than the N(1)–O(2) bond distance (1.226 Å).

The four atoms of the nitrate group are nearly planar, with a maximum deviation from the mean square plane of 0.01 Å.

### *The Cyclosarcosylsarcosine Molecule*

In Table III bond lengths and bond angles in the cyclic peptide molecule are given. Comparison with data previously reported [7, 8] shows no significant differences, with average deviations of bond lengths and bond angles from the literature data within 0.02 Å and 2°, respectively.

Each cyclic molecule, sitting with its ideal center of gravity on a crystallographic center of symmetry, shows in the crystal a nearly planar conformation of its six-membered ring. The $\omega$, $\phi$, and $\psi$ conformational angles [9] are close to 0°, with alternating plus and minus signs as in a very flat chair conformation, previously observed in cyclosarcosylsarcosine as well as other *N*-methylated cyclic dipeptide molecules [8]. Each oxygen atom of the C=O groups bridges two Ag(I) ions approximately in the *b* direction, with different bond strengths (2.35 and 2.57 Å, respectively).

### *Packing in the Crystal*

The mode of packing of the silver nitrate cyclosarcosylsarcosine 2:1 adduct is shown in Figs. 1 and 3, where the projections as viewed along the *c* and the *b* directions, respectively, are given. Layers of inorganic material and layers of organic material roughly parallel to the *ac* plane pack alternately with each other. Coulombic and ion–dipole interactions between ions and the organic molecules are mainly responsible for the building up of the crystals. Methyl groups facing each other across centers of symmetry contribute to the packing by idrophobic interactions.

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