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# Synthesis and structure of a water-soluble nitrosyl iron complex with cysteamine ligand

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**A water-soluble nitrosyl complex of iron $\{Fe_2[S(CH_2)_2NH_3]_2(NO)_4\}SO_4 \cdot 2.5H_2O$, belonging to a structural type '$\mu_2$-S' and containing a ligand of natural origin, cysteamine, was synthesised and studied by X-ray crystallography, IR and Mössbauer spectroscopy.**

Nitrosyl complexes of iron and sulfur-containing ligands are structural and spectroscopic models of natural NO depots represented by active centers of nitrosyl iron-sulfur proteins found in all living forms.[1] These complexes display high mutagenic,[2] vasodilatory[3] and antineoplastic[4] activities at moderate toxicity and are considered as promising prodrugs, NO donors of new generation for curing of socially important disorders.[5] Broad clinical applications of synthetic neutral nitrosyl complexes of $[Fe_2(SR)_2(NO)_4]$ with R = Alk[6–10] (μ-S type) and R = Aryl[11–13] (μ-N-C-S type) are limited by their low solubility in water and physiological solutions. Thus, a search for water-soluble and, therefore, more bioavailable NO donors of that class with higher effectiveness and lower toxicity is warranted.

This study aimed to synthesize a water-soluble binuclear nitrosyl iron complex with the sulfur-containing ligand of natural origin (cysteamine) and to investigate molecular and crystal structures of the complex. It is known that cysteamine (β-mercaptoethylamine) is an effective radioprotector and antioxidant; it is used in therapeutic practice as detoxifying agent,[14] can protect cells from DNA damages due to its anti-mutagenic activity;[15,16] can be used for the treatment of some cancer forms as it inhibits proliferation of neoplastic cells.[17–19]

Complex **1** was obtained by a reaction of iron(II) sulfate dissolved in water with the solution of cysteamine hydrochloride at a mole proportion of 1:1. The reaction in a flow of nitrogen monoxide obtained by a published method[20] was conducted for 1–1.5 h at 40 °C until crystals started to form in the solution. The reaction mixture was incubated at 6–8 °C for 15 h and then the resulting fine crystalline brown-red sediment was filtered off and dried in air for 24 h. The yield was 16.5%.† In contrast to the synthesis of $\{Fe_2[S(CH_2)_2NH_3]_2(NO)_4\}X$ (X = Cl, I) complex[5] where reactions are to be conducted in toxic tetrahydrofuran using iron dinitrosyls $Fe(CO)_2(NO)_2$ or $[Fe(NO)_2I]_2$ obtained by multistage reactions, the method we used to obtain **1** is simple and economical.

The obtained complex is highly soluble in water, DMSO, less soluble in methanol, ethanol and TGP; insoluble in heptane, acetonitrile and diethyl ether. Polycrystals of **1** are stable in air at room temperature.

† *Elemental analysis* of complex **1** was performed at the Analytical Centre, Institute of Problems of Chemical Physics of the Russian Academy of Sciences (IPCP RAS). Found (%): C, 8.53; H, 4.06; N, 15.70; S, 17.71. Calc. for $C_4H_{19}Fe_2N_6O_{10.5}S_3$ (%): C, 9.10; H, 3.60; N, 15.93; S, 18.27.

According to X-ray diffraction analysis (Figure 1),‡ **1** is the sulfate salt of the $\{Fe_2[S(CH_2)_2NH_3]_2(NO)_4\}$ dication crystallizing with 2.5 water solvate molecules per anion.

In the crystal of **1**, the unit cell contains two almost identical independent centrosymmetric dications $\{Fe_2[S(CH_2)_2NH_3]_2(NO)_4\}^{2+}$ in which iron atoms are bonded to two nitrogen atoms of the nitrosyl ligands and two μ-sulfur atoms of the protonated cysteamine ligands. The latter ones are characterized by antiperiplanar conformation with the SCCN torsion angles of 169.1 and 179.8°. The iron atoms, except for those in the Fe(1)–Fe(1A) bond, are characterized by slightly distorted tetrahedral configuration with the maximum deviation of NO–Fe–NO angle up to 121.3(2)°. Although the geometry of two independent dications is almost identical, the Fe···Fe distances in them are slightly different: 2.672(1) and 2.682(1) Å. The Fe–NO bonds are off linearity by an average of ~10° and bend toward each other.

‡ *Crystals of* **1** ($[C_4H_{14}Fe_2N_6O_4S_2]^{2+}$, $[SO_4]^{2-}$, 2.5[$H_2O$], $M$ = 527.13) are triclinic, space group $P\bar{1}$, at 100 K: $a$ = 6.850(1), $b$ = 10.575(2) and $c$ = 13.723(2) Å, $\alpha$ = 90.884(3)°, $\beta$ = 95.900(3)°, $\gamma$ = 90.635(3)°, $V$ = = 988.6(3) Å$^3$, $Z$ = 4/2, $d_{calc}$ = 1.771 g cm$^{-3}$, $\mu$ = 1.839 mm$^{-1}$. Intensities of 23140 reflections were measured with a Bruker SMART APEX2 CCD diffractometer [$\lambda$(MoKα) = 0.71072 Å, $\omega$-scans, $2\theta < 56°$] at 100 K and 5969 independent reflections were used in the further refinement. The results of index procedure as well as visual inspection of the 3-dimensional and rocking curves of spots revealed that the crystal was a twin. All attempts to find a single crystal without twining even with extremely small dimensions (the crystal finally chosen was 0.35×0.04×0.03 mm$^3$) were unsuccessful. Collected dataset was indexed using cell_now software and then intensities of collected reflections were described as the superposition of two crystal components with a rotation angle of 179.5° along the (0 0 1) direction. The frames were integrated separately for each component and then reflections of two components were separately included in refinement *via* HKLF 5 format (BASF is 0.21). All equivalent reflections were merged using the TWINABS program. The structure was solved by the direct method and refined by the full-matrix least-squares technique against $F^2$ in the anisotropic-isotropic approximation. The hydrogen atoms were located from the Fourier synthesis of the electron density and refined in the riding model. For **1** the refinement converged to $wR_2$ = 0.1204 and GOF = 0.930 for all independent reflections [$R_1$ = = 0.0548 was calculated against $F$ for 3632 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using the SHELXTL PLUS 5.0 software.[33]

CCDC 663194 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2009.

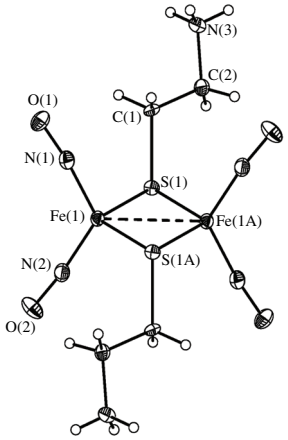


**Figure 1** The general view of one of the independent dications $\{Fe_2[S(CH_2)_2NH_3]_2(NO)_4\}^{2+}$ in representation of atoms by thermal ellipsoids ($p$ = 50%). Selected bond lengths (Å): Fe(1)–N(2) 1.665(2), Fe(1)–N(1) 1.675(5), Fe(1)–S(1) 2.244(1), Fe(1)–S(1A) 2.252(1), Fe(1)–Fe(1A) 2.672(1), S(1)–C(1) 1.837(5), N(1)–O(1) 1.164(5), N(2)–O(2) 1.180(5); bond angles (°): N(1)–Fe(1)–N(2) 121.6(2), N(2)–Fe(1)–S(1) 106.6(2), N(1)–Fe(1)–S(1) 104.6(1), N(2)–Fe(1)–S(1A) 108.0(2), N(1)–Fe(1)–S(1A) 108.1(2), S(1)–Fe(1)–S(1A) 107.07(5), N(2)–Fe(1)–Fe(1A) 120.1(2), N(1)–Fe(1)–Fe(1A) 118.2(2), S(1)–Fe(1)–Fe(1A) 53.68(4), S(1A)–Fe(1)–Fe(1A) 53.40(4), C(1)–S(1)–Fe(1) 106.78(17), Fe(1)–S(1)–Fe(1A) 72.93(5), O(1)–N(1)–Fe(1) 171.4(4), O(2)–N(2)–Fe(1) 173.7(4).

Taking into account the fact that this complex is diamagnetic, the rather small Fe···Fe distance can be interpreted as the presence of the Fe–Fe bond. On the other hand, it can result solely from the geometry of four-membered $Fe_2S_2$ ring.[21] Note that the Fe···Fe separation in such complexes is rather sensitive to crystal packing effects and, for example, in the iodine salt it is 2.715(1) Å.[5]

Summarizing the data on the dication geometry, we can conclude that the structure of **1** can be considered as the Roussin's red ethers type.[22]

The cysteamine molecule is a potential ambident ligand, and the metal atom coordination occurs in various complexes by a monodentate way through the sulfur atom while an amino group remains free, or by a chelate way through the sulfur and nitrogen atoms of primary amine. In case of silver complexes, the coordination by the monodentate way[23,24] is more likely due to the lack of coordination sites of the metal atom because, for instance, the coordination in rhenium complexes occurs by the chelate way.[25]

According to the crystal packing analysis, **1** is characterized by the layered structure (Figures 2 and 3) with alternating water···anion (**A**) and dication (**B**) layers interconnected through

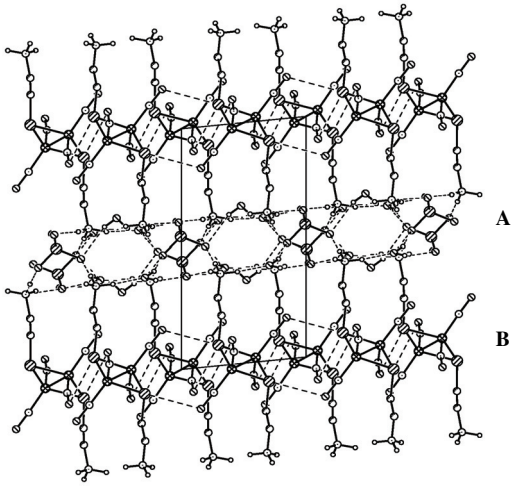


**Figure 2** The projection of crystal packing illustrating the layered type structure in **1**.

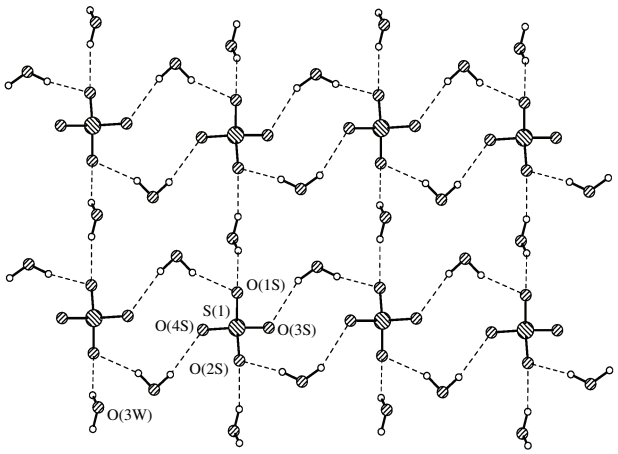


**Figure 3** The structure of water-sulfate sublattice in a crystal of complex **1**. Selected distances (Å): H(1WB)···O(3S) 1.986, H(1WA)···O(2S) (–$x$, –$y$ + 2, –$z$ + 1) 1.958, H(2WA)···O(4S) (–$x$, –$y$ + 1, –$z$ + 1) 1.979, H(2WB)···O(1S) 1.949, H(3WB)···O(2S) ($x$ + 1, $y$, $z$) 2.467; H(3WA)···O(1S) 2.225.

$H_2N$–H···O hydrogen bonds with both water molecules [N···O 2.726(3)–2.732(2) Å] and $SO_4^{2-}$ anions [2.757(3)–2.796(4) Å]. In the layers of **A** type $SO_4^{2-}$ anions and $H_2O$ molecules are assembled by the H-bonds with the O···O separation in the range of 2.766(6)–3.292(6) Å. In layers **B** dications are connected through the NO···S contacts with S(1)···O(1′) and S(1′)···O(1) [1 – $x$, 1 – $y$, 2 – $z$] distances equal to 3.222(2) and 3.282(2) Å, respectively. Note that the latter ones are characterized by a high degree of directionality with S(1)O(1′)N(1′) and S(1′)O(1)N(1) angles (85.7–85.8°) close to 90°.

The data obtained by Mössbauer spectroscopy[§] are in a good agreement with X-ray data. The Mössbauer spectrum of **1** at $T$ = 293 K, as well as spectra of other diamagnetic binuclear compounds of structural type $\mu_2$-S, have a single doublet[26] thus indicating structural equivalency of the iron atoms. The parameter values of the Mössbauer spectrum of $^{57}$Fe for isomeric shift and quadrupole split at 294 K in **1** are $\delta$ = 0.0595(5) mm s$^{-1}$ and $\Delta E_Q$ =1.098(1) mm s$^{-1}$, respectively.

Two distinctive absorption bands of the NO groups with frequencies of valency vibrations in the range of 1657–1807 cm$^{-1}$ were found in the IR spectra[¶] of **1**. However, the fact that both bands are slightly shifted to a higher frequency region suggests that the NO group has a partial positive charge due to the shift of the electronic density from the NO groups to the Fe atoms. According to the Enemark–Feltham formalism[27–29], the Fe configuration is $d^7$, (oxidation state +1, $S$ = 1/2).

In order to analyze the specific features of chemical bonding in **1**, we performed the DFT (BP86/TZVP) calculation of the isolated dication (Figure 4). The optimisation[††] of **1** in $C_i$ symmetry leads to geometrical parameters that are close to the experimental ones. In particular, the Fe···Fe distance is 2.652 Å, the distances in the Fe–S and Fe–N bonds are 2.242 and 1.664–1.668 Å, respectively, and the SFeS bond angle is 72.5° (see Figure 1 for comparison). The consequent frequency calculations for **1** revealed that $C_i$ symmetry corresponds to the

[§] *Mössbauer absorption spectra of $^{57}$Fe* were obtained using WissEl equipment at the constant acceleration mode. $^{57}$Co in a Rh matrix was used as a source. Spectrum measurements at low temperatures were conducted using a CF-506 flow-through helium cryostat (Oxford Instruments) with a temperature control. Mössbauer spectra were analyzed by the least squares method at the assumption of Lorents' form for individual spectrum components.

[¶] *IR spectra* of specimens were measured using a Spectrum BX-II Fourier spectrometer at the Analytical Center of IPCP RAS. Specimens were prepared as tablets with KBr (1 mg of the compound per 300 mg of KBr, $\nu_{max}$/cm$^{-1}$): 3453 (s), 2920 (s), 2360 (m), 1773 (vs), 1733 (vs), 1267 (m), 1200 (s), 1120 (s), 773 (m), 653 (s), 1773, 1733 (NO).

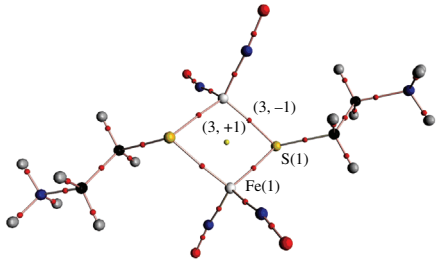


**Figure 4** Molecular graphs of dication **1** obtained from the wavefunction produced by BP86/TZV calculation.

minimum on the potential energy surface (PES). The frequencies were scaled by a factor of 0.975 that was chosen to match the experimental values for the Fe–NO frequency vibration of compound **1** leading to the values of 1750.1 and 1774 $cm^{-1}$. In order to additionally justify the accuracy of *ab initio* calculation, we estimated the quadrupole splitting for **1** using the procedure described in detail elsewhere.[30] The BP86/TZVP calculation resulted in $\Delta E_Q$ value 0.92±0.02 mm $s^{-1}$ (quadrupole moment of $^{57}Fe$ $Q$ was 0.15±0.02 barn[30]).

Taking into account quite good agreement of calculated geometry with the experimental one, as well as with the Fe–NO frequency vibration and $\Delta E_Q$ values, we expect the results of electron density function $\rho(r)$ analysis at the chosen level of theory to be reasonable. In order to check the presence of the Fe–Fe bond in **1**, we performed the topological analysis of $\rho(r)$ within Bader's 'Atoms in Molecule' theory.[31] The charges of the NO groups in **1** (–0.27 and –0.29 e) are almost identical to those observed in sodium nitroprusside.[32] The critical point (CP) search unexpectedly revealed the presence of CP (3, +1) at the center of Fe(1)–Fe(2) line instead of CP (3, –1). Note that the observed characteristic set persists in the case of B3LYP functional with 6-311+G(d,p) basis set. The analysis of chemical bonding within above scheme clearly showed that Fe–S and Fe–N bonds were characterized by significant degree of π-component: the values of ellipticity were found to be in the range of 0.09–0.118.

Thus, we can expect that the interaction of two unpaired electrons is realized not through the direct Fe···Fe bonding but rather due to superexchange *via* μ-S bridges. Further investigations of chemical binding in compounds of Roussin's red ethers type, especially the experimental analysis of $\rho(r)$ function, may clarify the chemical bonding pattern in this quite interesting class of complexes.

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†† *Geometry optimization* and frequency calculation of dication **1** were performed with the Gaussian03 program package[34] at the BP86/TZVP level. As the convergence criteria, the default threshold limits 0.00045 and 0.0018 au were applied for the maximum force and displacement, respectively. The absence of imaginary frequencies indicates that $C_i$ point group corresponds to the minima. The frequencies were scaled by a factor of 0.975 that was chosen to match the experimental value for the Fe–NO frequency vibration of compound **1**. Topological analysis of the $\rho(r)$ function (AIMPACK[35]) was based on the wave functions obtained by isolated molecule calculations.