

Mesomeric tautomerism of ligand is a novel pathway for synthesis of cationic dinitrosyl iron complexes: X-ray structure and properties of nitrosyl complex with thiourea



Nataliya A. Sanina*, Sergey M. Aldoshin, Natal'ya Yu. Shmatko, Denis V. Korchagin, Gennadii V. Shilov, Nikolay S. Ovanessian, Alexander V. Kulikov

Institute of Problems of Chemical Physics, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russia

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ABSTRACT

A new cationic dinitrosyl iron complex (DNIC) with thiourea of the formula $[\text{Fe}(\text{SC}(\text{NH}_2)_2)_2(\text{NO})_2]\text{Cl} \cdot \text{H}_2\text{O}$ (**I**) has been obtained in the reaction of aqueous solutions of salts $\text{Na}_2[\text{Fe}_2(\text{S}_2\text{O}_3)_2(\text{NO})_4] \cdot 4\text{H}_2\text{O}$ and $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ in the presence of $\text{SC}(\text{NH}_2)_2$ in acidic medium for the first time. Structure and properties of **I** have been studied by X-ray analysis, Mössbauer, IR- and EPR spectroscopy and amperometry. Complex **I** generates NO in aqueous anaerobic solutions (at $T = 25^\circ\text{C}$) without additional activation; NO amount at pH 7 and 8 is ~ 36 nM, at pH 9 a smaller (~ 24 nM) but more prolonged release of NO was observed, thus suggesting the potential of this method for synthesis of a new class of DNIC for medicine.

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In addition to cellular S-nitrosothiols ($R_{\text{protein}}\text{SNO}$), dinitrosyl iron complexes with proteins (protein-bound DNICs) and low molecular weight dinitrosyl iron complexes (LMW-DNICs) are the most important forms of storage and transportation of nitric oxide (NO) in vivo [1–3]. Search for new experimental approaches to the synthesis of analogues of LMW-DNICs, and investigation of their properties, including NO-donating activity, open possibilities for practical application of mimetics of active centers of nitrosyl [1Fe–2S] ferredoxins as effective NO generating compounds for the therapy of socially significant diseases [4,5].

In the present work, the method for synthesis of cationic [1Fe–2S] DNIC with thiourea has been developed for the first time, and its structure and properties in the solid phase and solutions have been studied as compared to the synthetic equivalents of LMW-DNICs studied previously, i.e., neutral [6–8] and anionic [9–18] mononuclear dinitrosyl iron complexes with various thiols.

Single crystals of complex **I** were obtained by the substitution of the corresponding functional ligand (thiourea) for the thiosulfate ligands in the sodium salt of tetranitrosyl binuclear anion in the presence of sodium thiosulfate as a reducing agent (Scheme 1).

As distinct from the substitution of thiosulfate ligands with aromatic thiols, which needs the alkaline medium [19], in this method the acidic solution of the ligand was used. The structure of thiourea can be

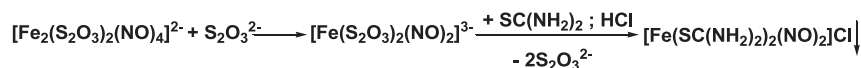
presented by two mesomeric forms: canonic thioamide and zwitterionic thioimide, the latter having a negative charge on the sulfur atom and a positive charge on the nitrogen atoms of the amidine fragment (Scheme 2). NRT (Natural Resonance Theory) analysis performed in the frame of NBO 6.0 [20] shows that the contributions of these resonance structures are comparable, with a small superiority of the basic thion form **1** (40.2%). The total contribution of equally probable structures **2a** (26.5%) and **2b** (26.5%) exceeds the contribution of the basic thion form **1**, thus pointing to a preferably zwitterionic form of thiourea molecule in the gaseous phase. In the solution, these forms are in equilibrium, which depends on the medium acidity.

As a result, the sulfur atom is a strong nucleophilic center, and thiourea is protonated at the sulfur atom to yield thiol salts with strong acids. Thiourea chloride easily participates in substitution reactions of thiosulfate ligands in the thiosulfate DNIC (Scheme 1). Complex **I** is isolated as single crystals with high yield. The crystals are stable upon storing in the inert atmosphere at $T = -8$ – 10°C for a long time (above 6 months), this being confirmed by IR spectra of the obtained samples. Complex **I** is soluble in water and other polar solvents.

From X-ray analysis data, the independent part of the structure of **I** is presented by one cationic DNIC with thiocarbamide ligands, chlorine anion and a solvate water molecule (Fig. 1). The iron atom in the cationic complex **I** is coordinated by two thiocarbamide ligands (S1, S2 are marked according to the sulfur atom numeration in Fig. 1) and two NO groups, and has a distorted tetrahedral structure. Ligands $\text{SC}(\text{NH}_2)_2$

* Corresponding author.

E-mail address: sanina@icp.ac.ru (N.A. Sanina).



Scheme 1. The formation of DNIC $[\text{Fe}(\text{SC}(\text{NH}_2)_2)_2(\text{NO})_2]\text{Cl} \cdot \text{H}_2\text{O}$.

have a planar structure and a *sin*-orientation to each other at 82.1° (S1) and 84.7° (S2) angles to plane S(1)Fe(1)S(2). The planes of S1 and S2 ligands are not parallel; the angle between them is 34.5°. The bond length S(1)–C(1) is 1.748(1) and S(2)–C(2) is 1.742(1) Å, corresponding to the length of a single C–S bond, which is longer than the double S=C bond (1.684 Å) [21,22]. This fact, together with the shortened lengths of C–N_{avg} 1.320(2) Å (as compared to the length of a single C–N bond 1.43 (aromatic)–1.48 Å (alkyl) [22] in S–C(NH₂)₂ ligands) is consistent with the results of NRT analysis, which demonstrated preferably zwitterionic nature of the thiourea molecule.

The bond lengths in the nitrosyl groups of DNIC differ inconsiderably and are equal to: Fe(1)–N(1) 1.688(1), Fe(1)–N(2) 1.684(1), N(1)–O(1) 1.168(1), and N(2)–O(2) 1.165(1) Å, while valence angles at the nitrogen atoms of the nitrosyl groups differ more substantially (164.92(9) and 170.22(9)°). The structural difference between ligands S1 and S2 was also minor (see cif-file from the Supporting information, SI), this being due, like for the nitrosyl groups, to the different participation of these ligands in intermolecular interaction. For the crystalline structure of **I**, the intermolecular H-bonds between the amidine fragment of the thiourea ligand of the cationic DNIC and the oxygen atoms of the solvate water molecule, and H-bonds between the oxygen atoms of the solvate water molecule and the chlorine anions are the main type of intermolecular interaction.

Hence, the structure of **I** suggests that the Fe atom has a high-spin d^7 Fe^{+1} configuration, which is characterized by antiferromagnetic coupling of two of the three unpaired electrons of Fe with unpaired electrons of the NO ligands to yield a paramagnetic unit $\{\text{FeS}_2\text{N}_2\}$ with one unpaired electron.

For $[\text{Fe}–2\text{S}]$ DNIC of various structural types, positions of the absorption bands (AB) of the NO stretching vibrations are essentially different: for anionic DNIC $\nu_{\text{NO}} = 1766$, and 1674 cm^{-1} [9–18], while for neutral DNIC $\nu_{\text{NO}} = 1807$, and 1695 cm^{-1} [6–8]. The complexes of both structural types, which contain aromatic thiolyls, are characterized by the shift of the absorption band to (?in?) the positive region. It is known [23] that the AB position in IR spectra correlates with the N–O bond lengths: for anionic complexes the average bond length is 1.180 Å, for neutral ones it is 1.166 Å. As follows from IR spectra, AB of the stretching vibrations of the NO groups in **I**, similar to neutral DNIC, are shifted to more positive values ($\nu_{\text{NO}} = 1807$, 1744 cm^{-1}), and the average bond of the N–O bond is 1.167 Å.

The values of ^{57}Fe Mössbauer spectrum parameters for polycrystals of **I** (quadrupole splitting $\Delta E_{\text{Q}} = 1.167(1) \text{ mm/s}$, isomeric shift $\delta_{\text{Fe}} = 0.194(1) \text{ mm/s}$ and the width of the absorption lines $\Gamma = 0.243(1) \text{ mm/s}$ at 296 K) are close to those for neutral DNIC with 1,2,4-triazole-3-thiolyl (**II**) ($\Delta E_{\text{Q}} = 1.118(1) \text{ mm/s}$, $\delta_{\text{Fe}} = 0.188(1) \text{ mm/s}$ at 296 K) [7] and differ from those of anionic DNIC $[\text{N}(\text{C}_2\text{H}_5)_4][\text{Fe}(\text{SC}_6\text{H}_5)_2(\text{NO})_2]$ (**III**) ($\Delta E_{\text{Q}} = 0.78(1) \text{ mm/s}$, $\delta_{\text{Fe}} = 0.08(1) \text{ mm/s}$ at 296 K) [9]. As shown [24], such values of the Mössbauer parameters fall into the region where the different redox states of iron overlap [25], thus making it difficult for an unambiguous determination of the oxidation state. δ_{Fe}

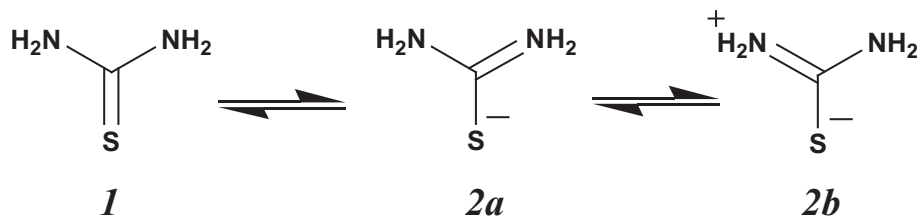
value for cationic complex **I** is almost twice as high as for the anionic one, thus pointing to the decrease of the charge density on the iron atom. This is consistent with the increase of the Fe–S_{avg} bond length (2.328 Å). For comparison, the average Fe–S bond length in anionic mononuclear complexes [9–18] is 2.308 Å, and in $[\text{N}(\text{C}_2\text{H}_5)_4][\text{Fe}(\text{SC}_6\text{H}_5)_2(\text{NO})_2] - 2.280 \text{ Å}$ [9]. It should be noted that in this anionic complex the δ_{Fe} value lies in the region of such values for tetranitrosyl binuclear dianionic nitrosyls of “ μ -S” structural type $\text{Q}_2^+[\text{Fe}_2\text{S}_2(\text{NO})_4]^{2-}$ that have even shorter average bond lengths Fe–S (2.235 Å) [19]. In neutral complex **II** triazolethiol ligands are in different tautomeric forms (thiol and thion) and coordinate the Fe atom differently, forming the covalent and donor–acceptor Fe–S bonds. In complex **I** the elongation of the Fe–S bond also points to a considerable contribution of the thion form in the structure of thiocarbamide ligand.

In Fig. 2 EPR spectra of polycrystalline powder of **I** and its solution in DMSO are shown. In the powder of **I** 0.88 spins per complex have been detected, this being the evidence of a paramagnetic state of the complex with one unpaired electron, while in DMSO solution there are 0.18 spins/complex in 10 min after dissolution, thus pointing to a fast decomposition of the complex. The amplitude of the spectrum in DMSO reduced by ten times within a day. In ethanol and in water no spectra were detected in 10 min after dissolution.

The EPR spectrum is typical for axial symmetry of *g*-tensor (Fig. 2A). *g*-Factors are close to those we have obtained earlier [7] for neutral DNIC with an aromatic ligand 1,2,4-triazole-3-thiol $[(\text{NO})_2\text{Fe}(\text{SC}_2\text{H}_3\text{N}_3)(\text{SC}_2\text{H}_2\text{N}_3)] \cdot 0.5\text{H}_2\text{O}$, $g_{\perp} = 2.04$ and $g_{\parallel} = 2.02$. Quantum-chemical calculations yielded parameters of EPR spectra: $g_x = 2.013$, $g_y = 2.034$, $g_z = 2.038$, and $g_{\text{iso}} = 2.029$. Anisotropic *g*-factors are close to *g*-factors of powders; *g*-factor of the solution somewhat exceeds the calculated one, probably due to the influence of the solvent (acetonitrile).

In the EPR spectrum of **I** HFS is not resolved, only weak bands can be seen. As follows from quantum-chemical calculations, the largest HFS constants from two nitrogen nuclei that are the closest to the Fe atom are 5.77 and 3.12 Gs, all other constants from the protons and nitrogen nuclei are below 1 Gs. In Fig. 2 the dotted line presents the EPR spectrum calculated with all HFS constants and the width of Lorentzian individual lines of 4.4 Gs using Program Simfonia (Bruker). The width of simulated EPR line is similar to the experimental one. The spectrum of powders of **I** is similar to the EPR spectra of frozen solutions of anionic DNIC with an aliphatic ligand $[\text{PPN}][(\text{NO})_2\text{Fe}(\text{SCH}_2\text{CONH}(\text{CH}_3))_2]$ [15] (PPN-*bis*(triphenyl phosphine)iminium). It can be seen that for complex **I** intermolecular distances Fe...Fe are also long (>5.90 Å), and exchange interactions are weak.

As follows from electrochemical analysis (see the Supporting information, SI), complex **I** decomposes to yield NO within seconds after dissolution in anaerobic aqueous solution (Fig. 3). The maximum amounts of NO generated by complex **I** at pH 7 and pH 8 are almost equal (~36 nM per mole of the complex). The time dependence of NO amount has the maximum: in ~1.5 min after the start of decomposition of **I** NO release decreases, and in ~8 min NO amount decreases to ~25 nM. At



Scheme 2. Tautomeric (thioamide (**1**) and thioimide (**2a**, **2b**)) forms of thiourea.

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