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Full Articles

Quantum chemical modeling of possible reactions of mononuclear iron nitrosyl complex $[Fe(SC(NH_2)_2)_2(NO)_2]Cl \cdot H_2O$ in an aqueous solution

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Possible reactions of the mononuclear iron nitrosyl complex $[Fe(SC(NH_2)_2)_2(NO)_2]Cl \cdot H_2O$ in an aqueous solution were studied using quantum chemical modeling. The electronic structures of the possible intermediates were examined by the NBO and AIM methods. The substitution of the thio ligand in the iron—sulfur nitrosyl complex by a water molecule and the formation of dimeric intermediate complexes were found to facilitate the NO-donation process.

Key words: iron—sulfur nitrosyl complexes, DFT, PCM, NBO, AIM.

It is reliably established by numerous investigations than NO possesses a wide range of biological activity.[1—9] Depending on the local concentration *in vivo*, the effect exerted by NO on cell targets can be divided into three categories: regulatory, protective, and pathologic. At low concentrations NO acts as a signal transductor in many physiological processes (for example, for blood flow regulation, relaxation of unstriped muscles, iron homeostasis, thrombocyte activity, and as a neurotransmitter), whereas at high concentrations NO serves as a cytotoxic protector against pathogenesis and tumor,[10] which can be used for the treatment of oncological diseases. At the same time, an NO excess leads to the development of pathological processes.[11] Therefore, the application of exogenic NO donors with certain NO-activity seems to be especially urgent. On the one hand, the concentration of nitrogen monoxide should exceed the exogenic concentration. On the other hand, the amount of evolved NO should not assuredly achieve pathological values. The iron—sulfur nitrosyl complexes recommended themselves very well for this purpose[12—14]: they show significant results as anticancer drugs of a wide application spectrum.

We have earlier established by the electrochemical study of the NO-donor activity of the iron—sulfur nitrosyl complexes of various classes using the sensor electrode that all the compounds studied evolve from 5 to 50 nmol L^{-1} NO per 1 mole of the complex at pH 6.5 and temperature 25 °C.[15] Evidently, the quantity of NO evolved by these complexes is far from the stoichiometric amount; however, it is quite sufficient for NO therapy.

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Therefore, the iron—sulfur nitrosyl complexes are NO donors evolving nitrogen monoxide in the therapeutical concentration.

The object of the study in this work is the mononuclear iron nitrosyl complex $[Fe(SC(NH_2)_2)_2(NO)_2]Cl \cdot H_2O$ (**1**). In an aqueous solution under anaerobic conditions, similarly to the aforementioned compounds, this complex also evolves NO: 31.7 nmol L^{-1} (mole of complex)$^{-1}$.[16] In our previous works,[17,18] we repeatedly considered the problem of searching for the mechanism of NO-donation using quantum chemical modeling. It should be mentioned that the energy of the Fe—NO bond for all types of the complexes, including considered complex **1**, is fairly high (~23 kcal mol^{-1} (B3LYP)). We have previously assumed that, most likely, the reaction proceeds *via* the formation of intermediate complexes, for example, aqua complexes of diverse compositions and structures when water molecules are coordinated on the Fe atom and form hydrogen bonds between each other.[16] For these compounds, the NO-donation reaction became exothermic; however, it is very difficult to experimentally confirm the existence of these complexes. Obviously, there are other routes for the transformation of complex **1** in solutions, including the Fe—S bond cleavage and dimerization, and the products formed can also be intermediate in the elimination of a nitrogen monoxide molecule. The purpose of this study is to consider possible reactions that occur in an aqueous solution of complex **1** using quantum chemical modeling for the understanding of the mechanism of NO-donation and factors affecting this process.

Calculation Methods

Quantum chemical calculations were performed in the framework of the density functional theory (DFT) with the full optimization of geometric parameters of the starting and formed complexes using Gaussian 09 program (Version D),[19] as well as the B3LYP hybrid functional and 6-311++G**//6-31G* basis set, taking into account solvation in an aqueous solution in terms of the polarizable continuum model (PCM). The B3LYP method well recommended itself earlier for this complex.[20] The optimization of geometric parameters and calculation of frequencies were performed using the 6-31G* basis set, and the energies were calculated in the extended 6-311++G** basis set. The calculations showed the absence of imaginary frequencies and, hence, all optimized structures correspond to minima on the potential energy surface. The NBO (Natural Bond Orbital) calculation procedure implemented in the Gaussian 09 program was applied. The AIMAll program package (Version 15.05.18)[21] was used to analyze the wave function by methods of the AIM (Atom in Molecule) theory. The wave functions and topological characteristics of the electron density distribution were calculated in the same approximation. The optimization of the geometric parameters was performed for the doublet state in the case of the starting complex and mononuclear complexes containing the $Fe(NO)_2$ fragment. For the mononuclear complexes with the Fe(NO) fragment, the optimization was performed for the triplet state.[16] The geometric parameters of the binuclear complexes were optimized for the triplet state[22] and quartet state after NO ligand elimination, since the triplet state turned out to be lower-lying in energy than the doublet state.

Results and Discussion

The main characteristics of the bonds, which were earlier considered in detail for complex **1**,[20] are presented in Table 1.

The bond order obtained from the natural analysis of occupancies and the Wiberg index characterizing the bond multiplicity for Fe—S are significantly lower than those for Fe—N (see Table 1). Therefore, according to the NBO analysis, the Fe—S bond in this complex is much weaker than the Fe—N bond. A similar conclusion can be drawn from the topological analysis of the critical points of the (3, −1) type between the Fe and S atoms, as well as between the Fe and N atoms. Although the bond is covalent and strongly polar ($\nabla^2 \rho(r) > 0$, $h_e(r) < 0$) in both cases, the values of $|\nabla^2 \rho(r)|$ and $\rho(r)$ for the Fe—S bond are considerably lower than those for Fe—N, and this also concerns the modulus of the local electron energy $|h_e(r)|$, as well as $v_e(r)$, which is the potential energy density at the critical point of this bond. Thus, as in the case of the binuclear iron nitrosyl compounds,[23] the Fe—S bond in this complex is covalent strongly polar, but it is weaker than Fe—N. Therefore, when considering the dissociation of the complex in water, it seems reasonable to take into account the elimination of the thiourea ligand and all subsequent possible processes in an aqueous solution as well.

The optimized structures of the starting complex and products of three possible reactions, *viz*., NO elimination, addition of the water molecule, and elimination of the thiourea ligand (the energies of these processes are given in kcal mol^{-1} in Schemes 1—4) are presented in Scheme 1.

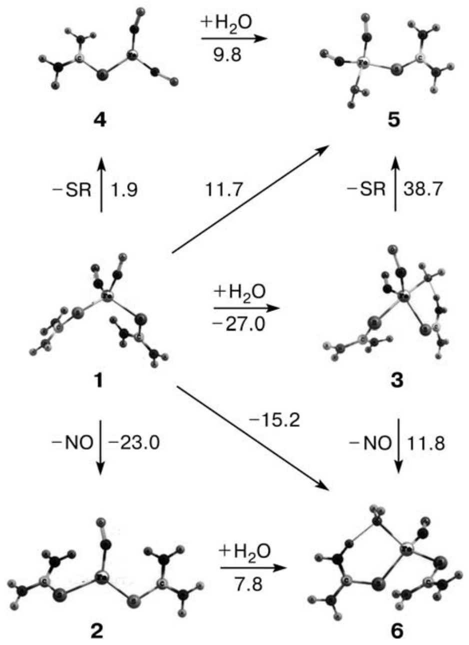
We believe that molecules of the medium (water molecules in the case) can occupy the liberated coordination site instead of the leaving thiourea or NO ligand. It is

Table 1. Comparison of the main parameters of the Fe—S and Fe—N bonds from the NBO and AIM calculations

Bond	NBO		AIM			
	Bond order	Wiberg index	ρ	$\nabla^2\rho(r)$	$h_e(r)$	$v_e(r)$
Fe—S	1.049	0.543	0.062	0.103	−0.021	−0.067
Fe—N	1.597	1.407	0.158	0.966	−0.047	−0.335

Note. Here and in Table 2, ρ is the electron density, $\nabla^2\rho(r)$ is the electron density Laplacian, $h_e(r)$ is the local electron energy, and $v_e(r)$ is the potential energy density at the critical point.

Scheme 1

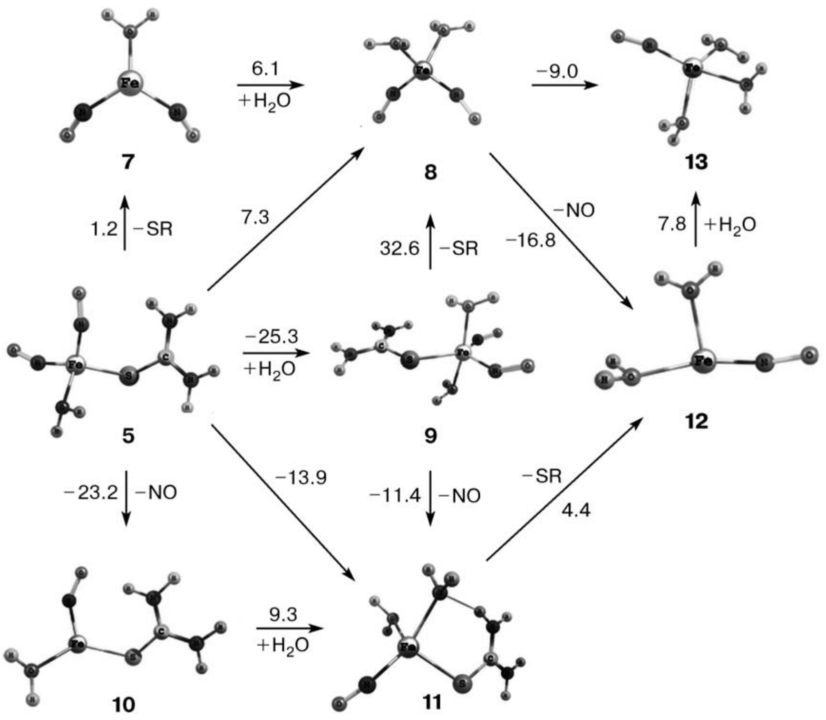


seen from Scheme 1 that the products of the considered reactions can be complexes **5** (for the substitution of the thiourea ligand by a water molecule) and **6** (for the substitution of the nitrosyl ligand by a water molecule), but the formation of complex **5**, as follows from the calculations, is an exothermic process, whereas 15.2 kcal mol^{-1} are required for the formation of complex **6**. Scheme 1 also presents another route of formation of complexes **5** and **6** *via* the primary addition of the water molecule to the starting complex **1** to form intermediate pentacoordinated complex **3**, which further dissociates with the elimination of any ligand. However, the energy of the total processes of formation of complexes **5** and **6** remained unchanged and, hence, the substitution of the thio ligand by the water molecule (11.7 kcal mol^{-1}) is more favorable than the substitution of NO by the water molecule (−15.2 kcal mol^{-1}). Then, based on the assumption that the formed complex **5**, can undergo the same transformation as the starting complex, we can consider the reactions of thio ligand elimination, nitrogen monoxide, and the addition of the water molecule already to the latter (Scheme 2).

As in the case of the starting complex, the substitution of the thiourea ligand by the water molecule with the formation of complex **8** (7.3 kcal mol^{-1}) is most energetically favorable, and the substitution of the nitrosyl ligand leading to complex **9** is an endothermic process (−13.9 kcal mol^{-1}), regardless of the fact what process, *i.e.*, ligand elimination or water molecule addition, occurs first.

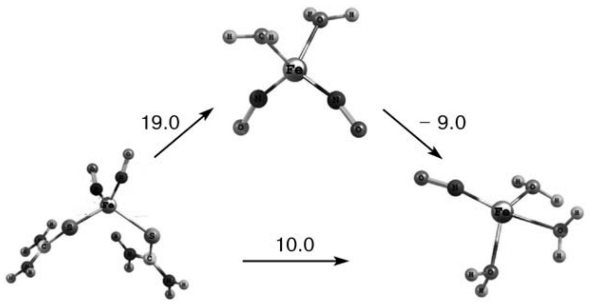
Only NO ligand elimination with the formation of mononitrosyl complex **13** can already be considered for complex **8**. This process of NO ligand substitution by the water molecule is endothermic, as in the case of two previous cases, but, first, it requires only 9.0 kcal mol^{-1} unlike the starting complex (−15.2 kcal mol^{-1}) and complex **5** (−13.9 kcal mol^{-1}). Thus, it can be concluded that

Scheme 2



the substitution of the thio ligand in the iron—sulfur nitrosyl complex by the water molecule facilitates the NO-donation process, which is presented in Scheme 3 (the energies of the intermediate steps are summated).

Scheme 3



We can see that the whole process of NO-donation by the starting complex is exothermic and can occur in an aqueous solution. It is most likely that the both thiosulfate ligands are first substituted by water molecules to form intermediate product **8**, in which the substitution of the NO ligand by water molecules occurs.

In all cases, we assumed that the water molecule occupies the free coordination site, but the formed complexes of tricoordinated iron can also be dimerized to form binuclear complexes of various compositions. The possible structures that could be formed by the dimerization of complex **4** are presented in Scheme 4. As can be seen from Scheme 4, the dimerization can also proceed with the formation of both the Fe—S and Fe—N bonds (nitrogen of the NO or NH_2 group).

Dimerization with the formation of two new Fe—S bonds and the formation of a dication of Roussin´s salt with thiourea (**14**) are most energetically favorable processes. The formation of dimers with μ-NO-bridging bonds (**15**—**17**) needs higher energy expenses, although they are slightly higher. At the same time, the dissociation at the Fe—NO bridging bond for these complexes proceeds more easily than for the Fe—NO terminal bonds of the starting complex and many bonds calculated in this work, which is unambiguously associated with the fact that this bond is very weak. The main characteristics of the Fe—NO bonds, terminal for **14** and bridging for **15**—**17**, are presented in Table 2.

Interestingly, even in dimer **14** with the terminal NO ligands the Fe—N bond is somewhat weaker than that in the starting mononuclear complex (see Tables 1 and 2). The bridging μ-NO bonds in complexes **15** and **16** are nearly the same by topological characteristics, which is evident, since these dimers are close in structure and dif-

Scheme 4

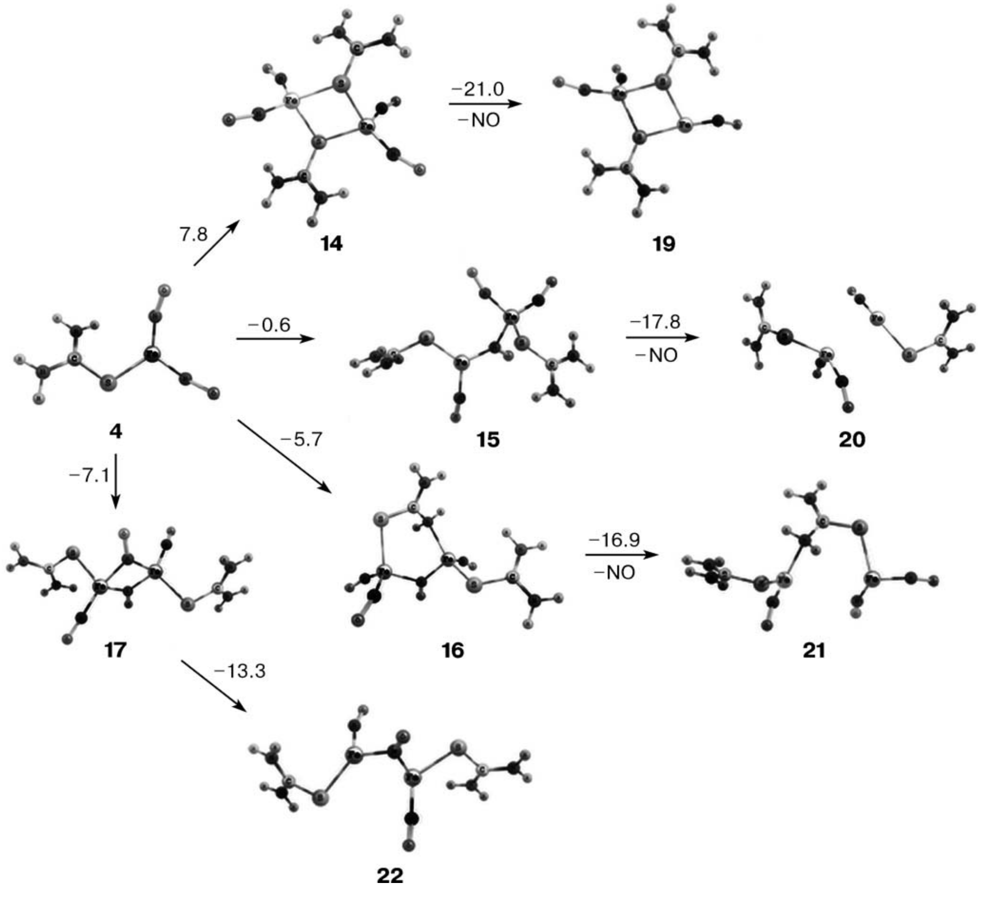


Table 2. Selected characteristics of the Fe—NO bonds in the dimers obtained by the NBO and AIM methods

Compound	Wiberg index	Bond order	ρ	$\nabla^2\rho(r)$	$h_e(r)$	$v_e(r)$
14	1.044, 1.055	1.440, 1.442	0.153, 0.155	0.871, 0.948	−0.043, −0.046	−0.324, −0.312
15	0.617, 0.373	0.958, 0.796	0.116, 0.074	0.495, 0.248	−0.029, −0.017	−0.172, −0.083
16	0.674, 0.338	1.042, 0.746	0.120, 0.070	0.498, 0.229	−0.032, −0.015	−0.189, −0.088
17	0.536, 0.630	0.581, 0.624	0.090, 0.101	0.363, 0.352	−0.018, −0.025	−0.138, −0.127

fer only by the fact that in complex **16** one of the thiourea ligands forms the bridging μ-CNS bond, which is often met for the iron—sulfur clusters. In compounds **15** and **16**, the Fe—NO bonds are almost two times weaker than the terminal bonds for the starting complex and dimer **14**. Nitrogen monoxide is bound less strongly to iron in complex **17**, where the nitrosyl ligands are bridging and thiourea ligands are terminal, as we considered earlier.[23] The energy of NO elimination (see Scheme 4), as can be seen, correlates well with the parameters of the bond (see Table 2), *i.e.*, according to the NBO and topological analysis, the weaker the bond, the lower the energy, and *vice versa*. Evidently, the elimination of NO from dimer **17** occurs most easily and, possibly, the dimerization process that takes place in solutions of the mononuclear iron nitrosyl complex facilitates NO-donation in some cases.

To conclude, selected reactions that can occur in an aqueous solution of the nitrosyl complex $[Fe(SC(NH_2)_2)_2(NO)_2]Cl \cdot H_2O$ were modeled using quantum chemical calculations, namely, the substitution of the thiourea and nitrosyl ligands by an aqua ligand, dimerization, and NO-donation. On the whole, we may conclude that the NO-donation process in the sulfur-containing iron nitrosyl complexes is fairly complicated and can proceed *via* various intermediate complexes with a weaker Fe—NO bond: aqua complexes and dimers of diverse composition, which are direct NO donors in aqueous solutions of the studied complex.

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