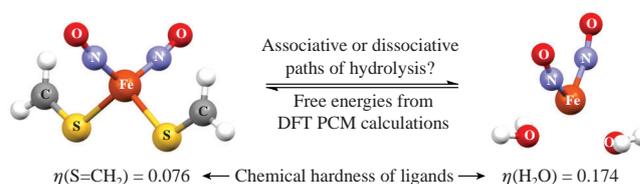


Decomposition of dinitrosyl iron complex with thioformaldehyde ligands in water: reaction mechanisms and the role of chemical hardness of ligands

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The mechanisms of hydrolysis of a model cationic dinitrosyl iron complex with a prototypic thioformaldehyde ligand have been studied using the density functional theory and polarizable continuum water model. The free-energy calculations have predicted that the associative mechanism of the thioformaldehyde ligand removal has a ~ 34 kJ mol⁻¹ lower activation barrier in water than the dissociative mechanism. The additional estimates of chemical hardness have provided useful qualitative characterization of the thio ligands binding.



Keywords: iron complexes, sulfur complexes, nitrosyl complexes, thioformaldehyde, density functional theory, hydrolysis, chemical hardness.

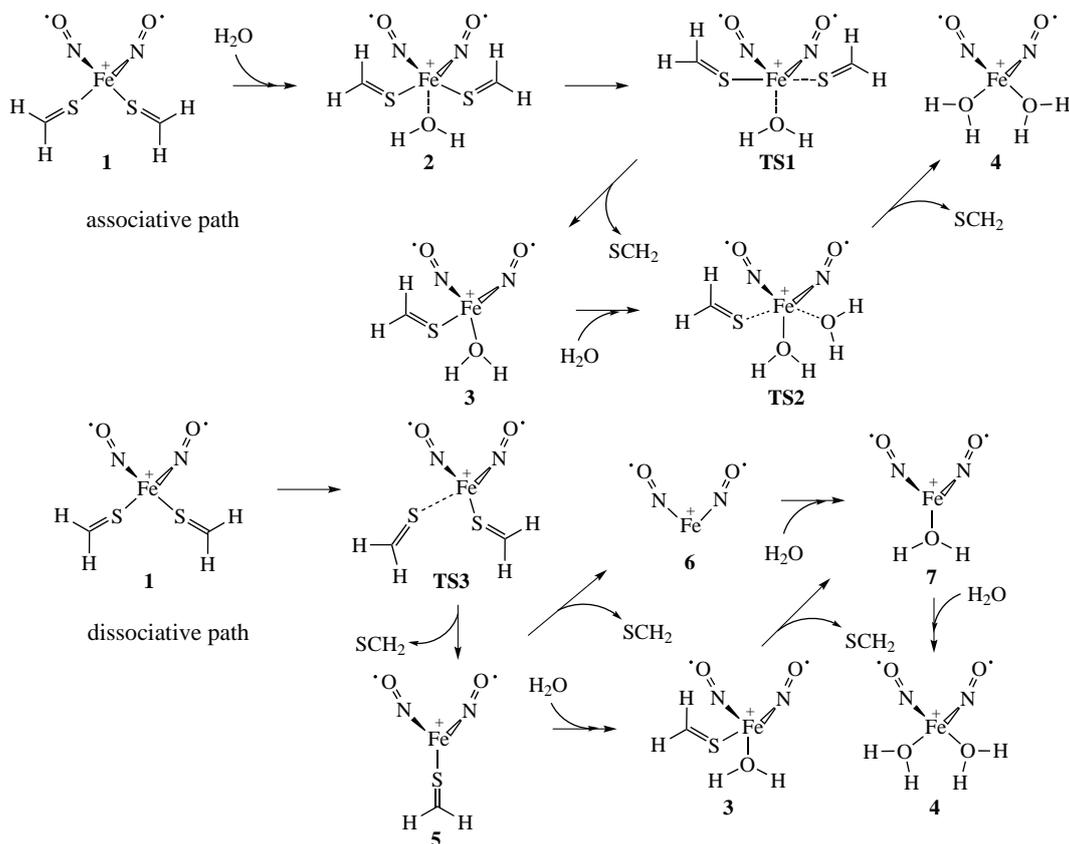
The iron–sulfur–nitrosyl complexes (ISNC) are actively studied compounds due to their applications as nitric oxide (NO) carriers and donors.^{1–3} The synthetic [Fe–S] complexes are analogous to ubiquitous [Fe–S] centers in proteins.^{4,5} Diverse thiol ligands are used in functionalized [Fe–S] complexes including sulfur-containing amino acids, sulfates, thiocarbonyl groups. Iron of the [Fe–S] units in chemical and biological systems readily forms coordination complexes with NO molecules. Such reversible NO binding to iron centers in biological and synthetic ISNC plays important role in signaling mechanisms in living systems and therapeutic action of related pharmacological drugs.^{4–6} The chemical reactivity of ISNC is to a large extent determined by interplay of the thio and NO ligands at iron center. The ISNC can undergo transformations in water with production of free NO, and this process goes with higher speed under aerobic conditions than anaerobic.^{7–9} The NO donor activity of ISNC also depends on the type of participating thio ligands.⁹ The thio ligands in ISNC are in many cases readily detached from coordinated metal. For instance, exchange reactions of thio ligands are observed in solution.^{10–12}

In this work we consider hydrolysis of a model cationic dinitrosyl iron complex (DNIC) $\text{Fe}(\text{NO})_2(\text{SCH}_2)_2^+$ **1** with a small prototypic ligand thioformaldehyde (Scheme 1). Thioformaldehyde is a well-recognized ligand in metal complexes.^{13,14} The aim of the work was to explore the mechanisms of hydrolysis of complex **1** by means of the density functional theory (DFT) method. Such calculations have been widely used for characterization of molecular properties of iron complexes with thiol ligands and NO (*e.g.*, refs. 4, 5, 9, 13, 15). The mechanistic study of transformations of complex **1** in water can provide better understanding of the reactivity of cationic DNICs despite the fact that **1** is not characterized experimentally.

The electronic structures of molecules were calculated using the hybrid meta exchange–correlation functional M06¹⁶ and the triple-zeta valence basis set def2-TZVP¹⁷ that had been derived and widely applied for the studies of transition metals. The calculations of electronic structures, molecular geometries and free energies were performed using Gaussian-09.Rev.D.01 method. The open-shell calculations employed unrestricted wave functions. Solvent effects were considered using the polarizable continuum model (PCM)¹⁸ and the standard model density (SMD) approach.¹⁹ The Gibbs free energy of molecules in water G_w includes the total electronic energy in water $E_{\text{el,w}}$, translational, rotational, harmonic vibrational contributions obtained from the Gaussian-09 calculations including solvent effects, and the corrections for changing the standard state of 1 atm (in Gaussian-09) to the 1 M standard state in liquid water [we used water concentration of 55.5 M and the corrections of $RT \ln(24.4 \cdot 55.5)$ for water molecules and $RT \ln(24.4)$ for other reacting species].

In the calculations, the multiplicity of complex **1** equaled 2 and the Fe atom in **1** was considered in the oxidation state 1+ like in a related thiourea complex $\text{Fe}(\text{NO})_2[\text{SC}(\text{NH}_2)_2]^+$.²⁰ The results of the M06 calculations predict that the lowest-energy conformation of complex **1** in water has the 3D structure (Figure 1; see also Online Supplementary Materials, Figure S1 and Table S1) similar to that of the D_{2d} conformer of the quarternary ammonium ion N^+Et_4 .²¹ The potential energy barriers for rotations of thiocarbonyl ligands are less than 4 kJ mol⁻¹ that indicates labile structure of this coordination compound.

The associative mechanism of the thio ligand hydrolysis of complex **1** involves exchange of the thiocarbonyl ligands for H_2O molecules (see Scheme 1). The reaction route includes several intermediate complexes and transition states with a



Scheme 1 The associative and dissociative paths of thioformaldehyde ligand hydrolysis of DNIC 1.

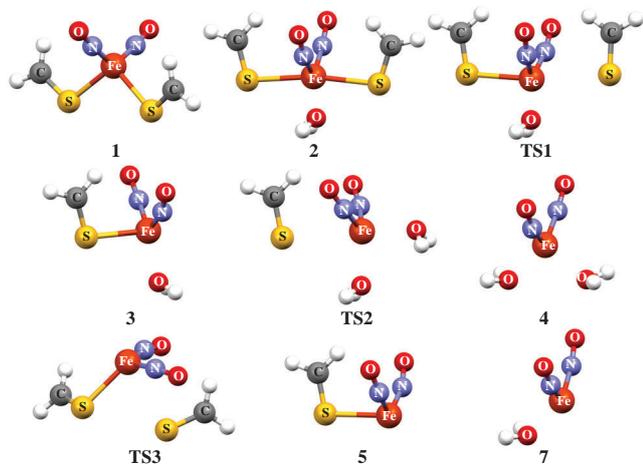


Figure 1 Optimized structures of the reactive species.

penta-coordinated central iron (see Figure 1 and Table 1 and S2). The addition of water molecule at the central Fe atom leads to complex **2** with the shape of trigonal bipyramid where the approaching water occupies a horizontal equatorial position (see Figure 1). This atomic configuration had already been described in earlier work on phosphate ester hydrolysis.^{22–24} The free energy of the prereactive complex at the step of the first water binding is 7.1 kJ mol^{-1} lower than the free energy of reactants by a factor of several tens (Figure 2). The activation free energy of the transition state **TS1** measured relative to **2** has a quite low value of 2.9 kJ mol^{-1} . The attack of the first water molecule in the end leads to formation of a stable intermediate DNIC **3** with the shape of trigonal pyramid (see Figure 1). The free energy activation barrier for the second transition state **TS2** measured relative to **3** has a low value of 3.5 kJ mol^{-1} . The overall free-energy change in the route from **1** to the final complex **4** is $\sim 70.3 \text{ kJ mol}^{-1}$. Thus, the DFT calculations predict low activation

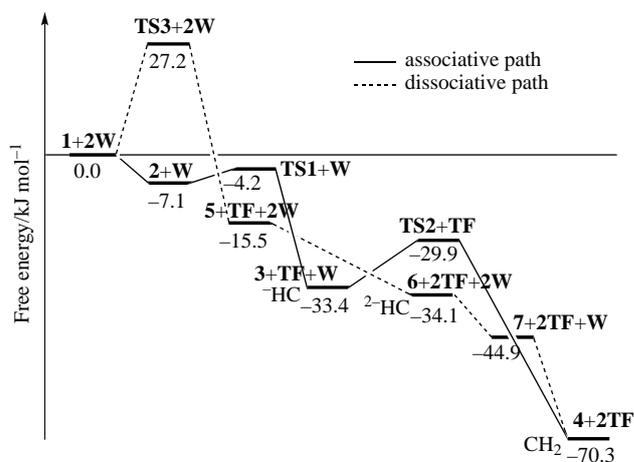


Figure 2 The cumulative free-energy profile of DNIC **1** hydrolysis (see Scheme 1). Symbol W stands for water molecule, TF stands for thioformaldehyde.

barriers for the displacement of thioformaldehydes by water molecules and a pronounced stabilization of DNIC **4** $\text{Fe}(\text{NO})_2(\text{H}_2\text{O})_2^+$.

The hydrolysis of complex **1** can also proceed under anaerobic conditions *via* elimination of the NO^\bullet ligands and occupation of their positions in the $[\text{Fe}-\text{S}]$ complex by water molecules. The free energies of the corresponding products with one and two NO^\bullet ligands exchanged for water are destabilized by 27.8 and 91.9 kJ mol^{-1} , respectively. This allows one to exclude abstraction of NO^\bullet in **1** from further consideration.

In the dissociative route (see Scheme 1), the rupture of the coordination $\text{Fe}-\text{S}$ bond of complex **1** in water proceeds *via* transition state **TS3** with the activation free energy of 27.2 kJ mol^{-1} (see Figures 1, 2). The intermediate complex $\text{Fe}(\text{NO})_2(\text{SCH}_2)^+$ **5** is downhill relative to **1** by $-15.5 \text{ kJ mol}^{-1}$.

Table 1 The calculated energies^a of the reactants in associative and dissociative reaction paths (see Scheme 1).

Molecule	$E_{el,w}/a.u.^b$	$ZPVE_w/a.u.^b$	$\Delta G_{298,w}/a.u.^b$
1	-2398.296819	0.067027	0.023299
2	-2474.748518	0.091800	0.047171
TS1	-2474.745584	0.090645	0.045327
3	-2037.304651	0.064813	0.026423
TS2	-2113.747896	0.088666	0.045844
4	-1676.307515	0.062502	0.023216
TS3	-2398.287498	0.066533	0.024323
5	-1960.848853	0.040166	0.002578
6	-1523.399815	0.012399	-0.020387
7	-1599.853604	0.038440	0.004112

^aCalculations at the M06/def2TZVP PCM-SMD level of theory. ^b $E_{el,w}$, $ZPVE_w$, $\Delta G_{298,w}$ – total electronic energy, zero-point vibrational energy, and thermal correction to the Gibbs free energy at 298.15 K, respectively, in water; the harmonic frequencies were scaled by 0.982.¹⁶

The removal of the second thioformaldehyde ligand from complex **5** produces the compact cationic complex $Fe(NO)_2^+$ **6** that is stabilized in water by -34.1 kJ mol⁻¹. The addition of one water molecule to **6** leads to an even more stable intermediate **7** that is converted to the final product **4** after addition of the second water molecule. The structures of the complexes with partial occupation of coordination sites around Fe⁺ retain tetrahedral configuration of ligands around central iron (see Figure 1).

Reactions of water molecules with mononuclear [Fe–S] complexes had been examined in several computational works.^{25–27} The DFT and QM/MM calculations of the hydrolysis of ferric anionic complex $Fe(SMe)_4^-$ with four thiolate S–Me⁻ ligands²⁷ predict associative mechanism with water being in equatorial position in the first transition state, similar to the mechanism of hydrolysis of complex **1**. However, the predicted free energy 43 kJ mol⁻¹ for substitution of the S–Me⁻ group by H₂O in the anionic complex $Fe(SMe)_4^-$ from the M06/def2TZVP COSMO calculations²⁷ is significantly higher than that for the S=CH₂ ligand in cationic complex **1** from our results. The DFT calculations of cationic DNIC with thiourea ligands also indicate exothermic changes of potential energies in its hydrolysis.²⁶

It is of interest to explain the thermodynamics of ligand exchange at the central iron on the basis of their electronic properties. A useful qualitative option in this respect is provided by the concept of chemical hardness η in inorganic chemistry that is numerically defined as half the difference between ionization potential I and electron affinity A of the considered compound.^{28,29} The common meaning of η is resistance to change or deformation of electronic structure.²⁸ Estimates of η employ Koopmans theorem for definition of I and A in closed-shell systems.²⁹ The calculations of η based on the gas-phase HOMO and LUMO energies show that η increases in the row 0.076 (S=CH₂) < 0.095 (S–Me⁻) < 0.174 (H₂O). Certainly, the thio ligand exchange in $Fe(SMe)_4^-$ and $Fe(NO)_2(SCH_2)_2^+$ by water cannot be directly compared using only the properties of isolated ligands. Yet, we can notice that the softest ligand S=CH₂ also most easily undergoes hydrolysis. This observation can probably be interpreted on the basis of principles that inorganic systems tend to form pairs with similar hardness²⁸ or tend to attain maximum hardness.²⁹

In conclusion, we have studied hydrolysis of a model cationic DNIC with a prototypic thioformaldehyde ligand. Small size of the model allowed us to use the basis set of a sufficient quality in order to accurately grasp structural and energy changes that accompany hydrolysis. The free-energy calculations with the implicit aqueous medium demonstrated exothermic character of

hydrolysis (about -70 kJ mol⁻¹) and preference for the associative mechanism of this reaction. The dissociative mechanism involves ~ 34 kJ mol⁻¹ higher activation barrier than the associative one. Also, the reaction intermediates with unfilled vacant position after removal of SCH₂ at the central iron are less stable than the intermediates where the positions of the SCH₂ ligand are filled with water molecules. The exchange of NO⁺ for H₂O is unfavorable by several tens kJ mol⁻¹. In addition, chemical hardness can be considered as a useful qualitative descriptor of the binding propensity of thio ligands.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.07.010.

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