



*Federal Research Center of Problems of Chemical Physics
and Medicinal Chemistry RAS*

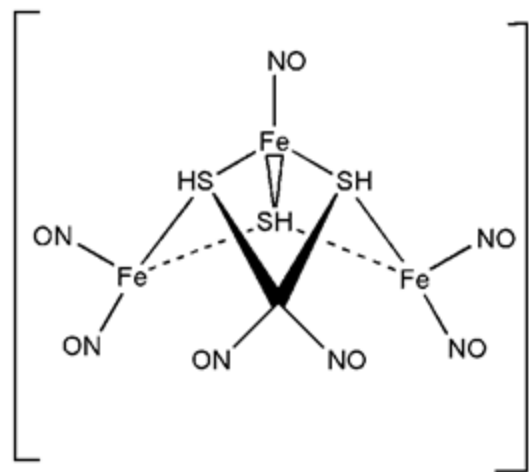
The QSAR Study of the Hydrolysis of Dinitrosyl Iron-Sulfur Complexes

Victor B. Luzhkov, Vladimir B. Krapivin, Natalya A. Sanina

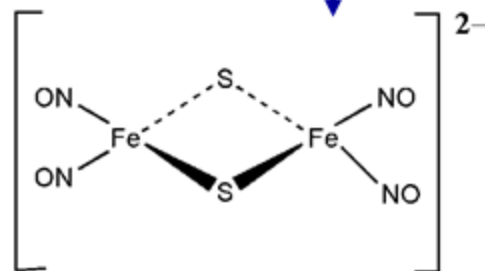
Roussin esters and dinitrosyl iron-sulfur complexes (DNICs)

Playfair (1849), sodium nitroprusside $\text{Na}_2[\text{Fe}(\text{CN})_5(\text{NO})]^{2-}$

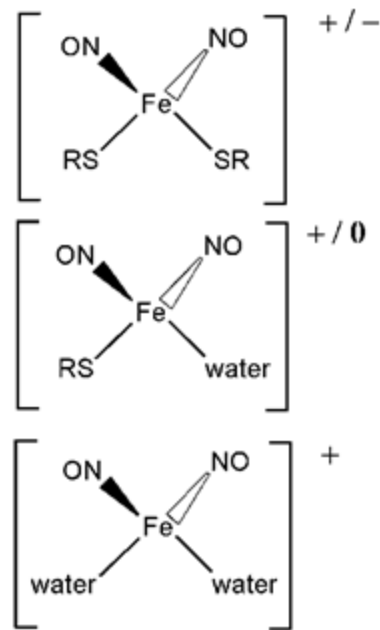
Roussin salts and esters (1858)



← black red



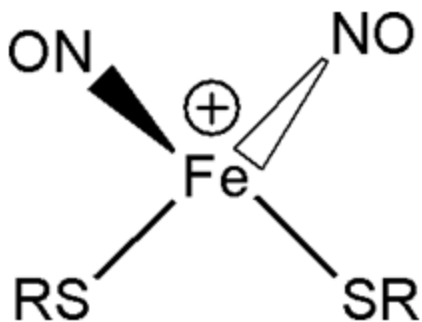
DNICs (1965)



Biological activity of DNICs

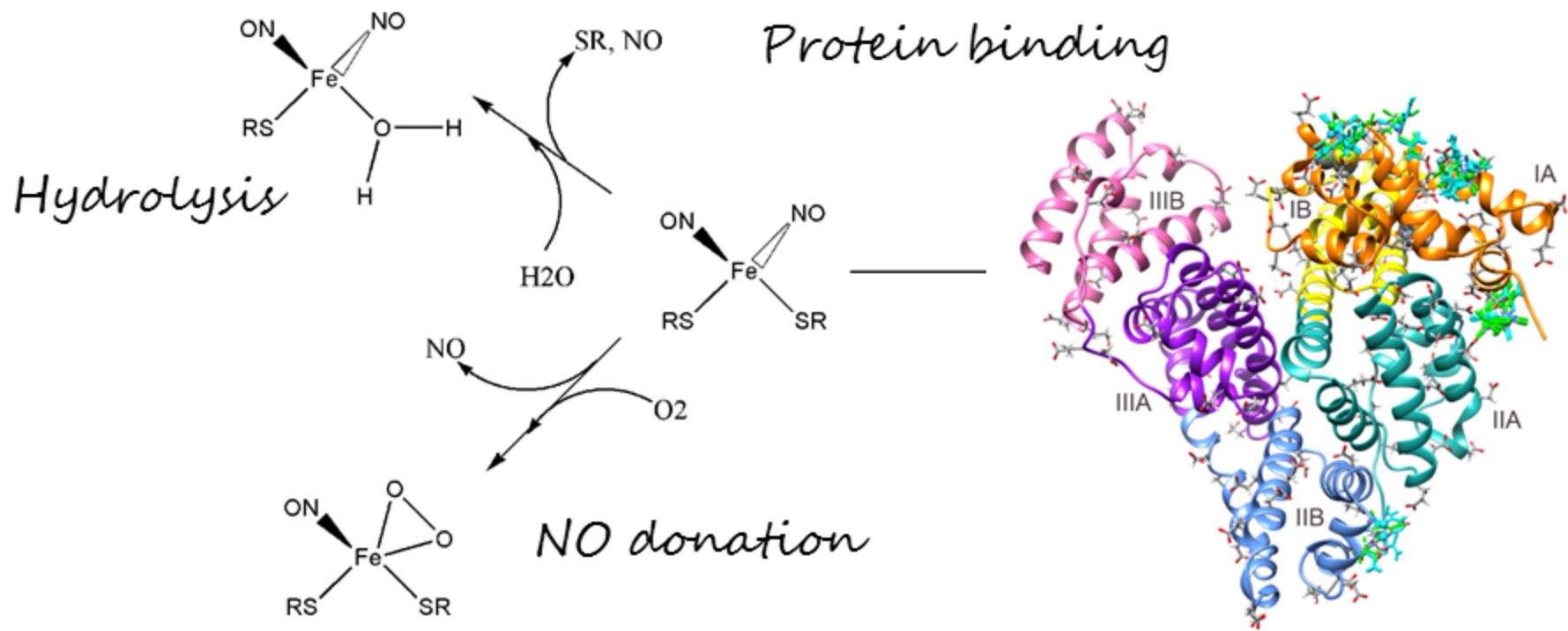
Sodium nitroprusside $\text{Na}_2[\text{Fe}(\text{CN})_5(\text{NO})]^{2-}$ –
lowers blood pressure (1929)

Exogenous DNICs – vasodilators,
treatment of cardiovascular diseases
and ischemia reperfusion injuries,
antitumor activity,
cytoprotective action,
antiinflammation effect,
antibacterial action,
neurostimulating effect,
involvement in signaling function



DNICs with iron-sulfur sites in proteins – storage of NO

Biochemical transformations of DNICs



The aim of the work is to study the effect of the chemical structure of thio ligands on their binding in DNICs

Methods of computational modeling

Density Functional Theory (DFT) calculations using hybrid meta-GGA functional TPSSH and the triple-zeta valence basis set def2-TZVP. Full geometry optimization and harmonic frequencies calculation in gas phase and water. Single-conformation approximation used.

Treatment of solvent effects employed the standard model density (SMD) approach and the polarizable continuum model (PCM) with integral equation formalism.

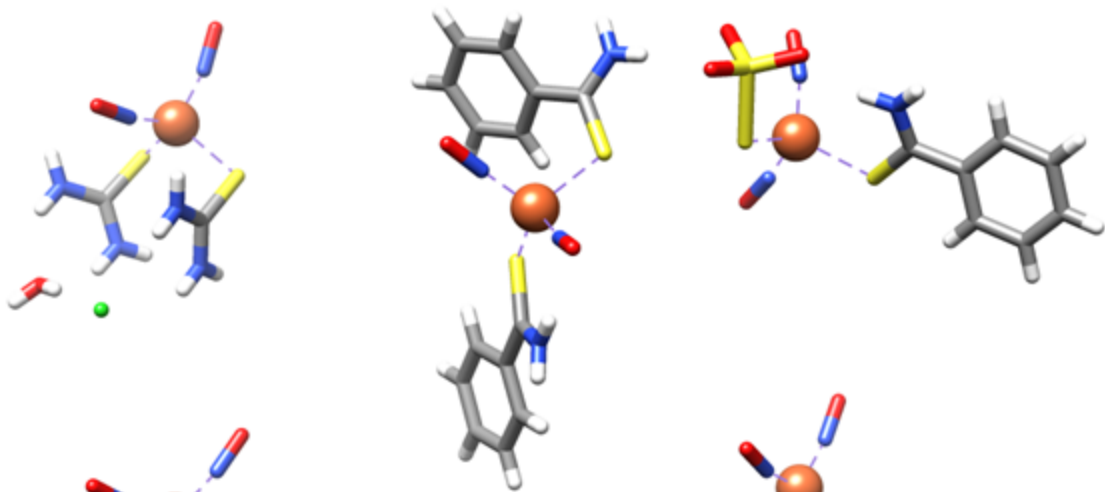
The Fe–S bond energies were calculated from the enthalpies of reactants and products

$$D_{298}(\text{Fe-S}) = H_{298}(\text{R}) + H_{298}(\text{L}) - H_{298}(\text{R-L})$$

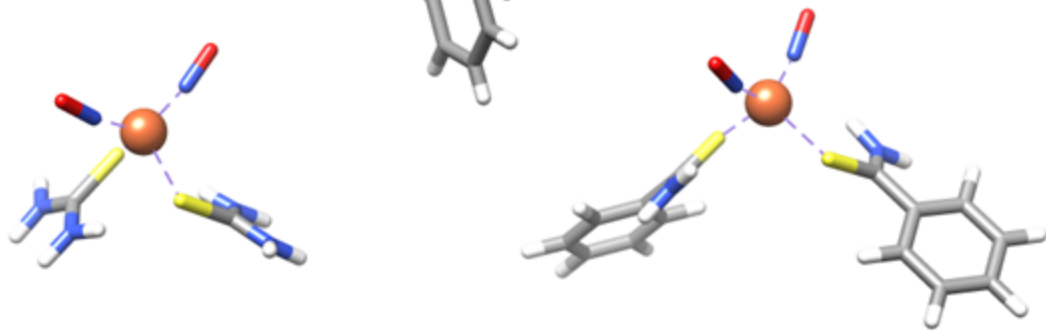
$$\Delta D_{298}(\text{Fe-S}) = H_{298}(\text{R-W}) + H_{298}(\text{L}) - H_{298}(\text{R-L}) - H_{298}(\text{W})$$

Molecular structure of DNICs

X-ray structures

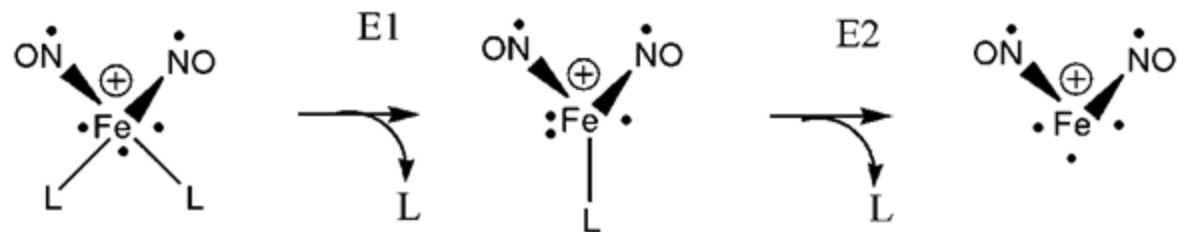


Structures from the DFT calculations in water

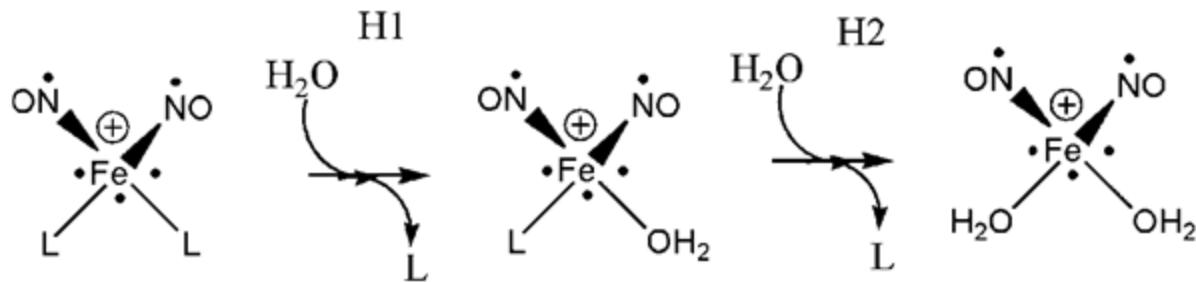


Routes of the thio ligand hydrolysis

Thio ligand abstraction
(dissociative path)



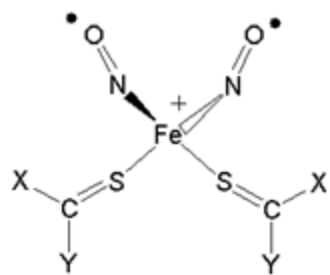
Thio ligand replacement
(associative path)



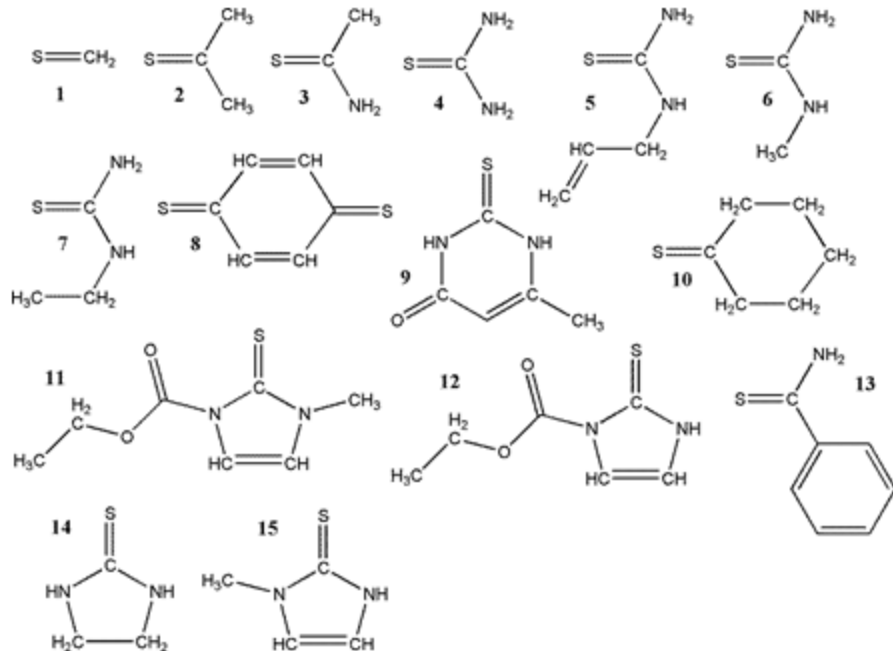
Theoretical study of the hydrolysis of iron-sulfur-nitrosyl complex.

Luzhkov et al., *Russ. J. Phys. Chem. A*, 2023, **97**, 813

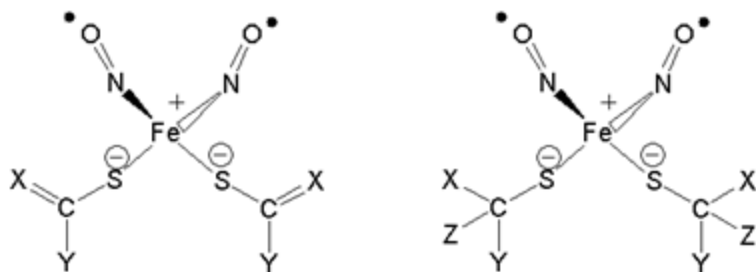
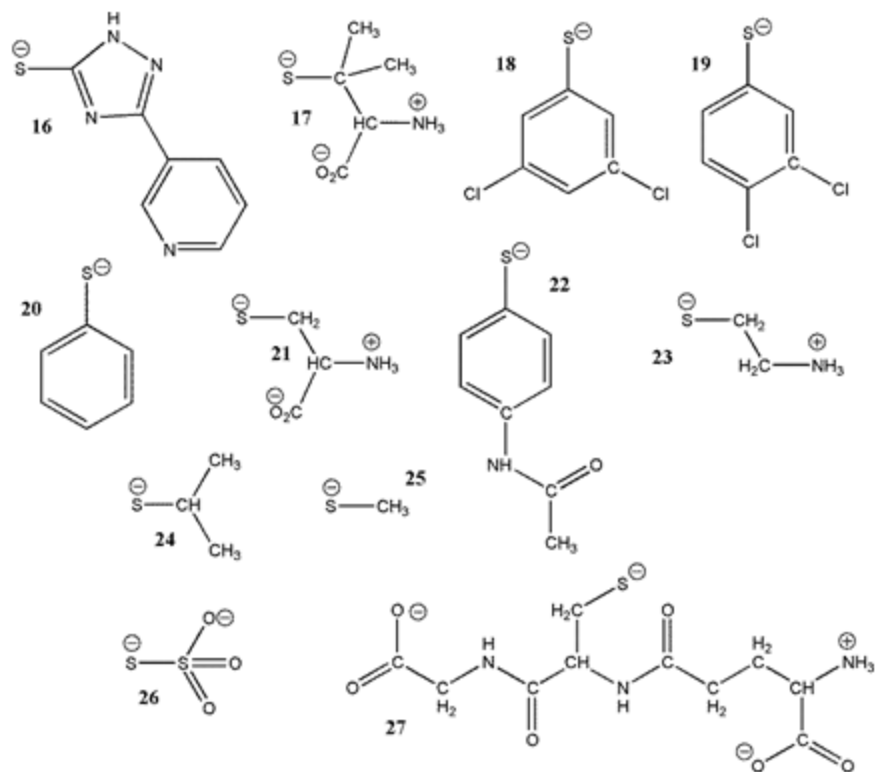
The Fe-S bond energies in the thiocarbonyl DNICs $[\text{Fe}(\text{NO})_2\text{L}_2]^+$



L	$D_{298}(\text{Fe}-\text{S})^{\dagger}$	$\Delta D_{298}(\text{Fe}-\text{S})^{\dagger}$	$D_{298}(\text{Fe}-\text{S})^{\ddagger}$	$\Delta D_{298}(\text{Fe}-\text{S})^{\ddagger}$
1	16.6	-22.5	13.3	-9.6
2	32.5	-1.4	29.3	1.3
3	54.7	21.2	44.2	15.7
4	58.5	29.8	52.5	19.3
5	60.8	28.9	48.0	18.0
6	61.0	30.0	51.9	21.0
7	65.4	32.7	53.0	23.8
8	20.4	-13.7	19.8	-8.0
9	32.0	-3.4	23.9	-2.7
10	35.2	2.2	31.0	2.1
11	43.0	14.5	38.3	4.8
12	51.6	18.4	42.8	14.0
13	52.4	17.7	39.8	12.5
14	59.6	27.2	47.7	18.2
15	60.8	31.2	54.9	22.6

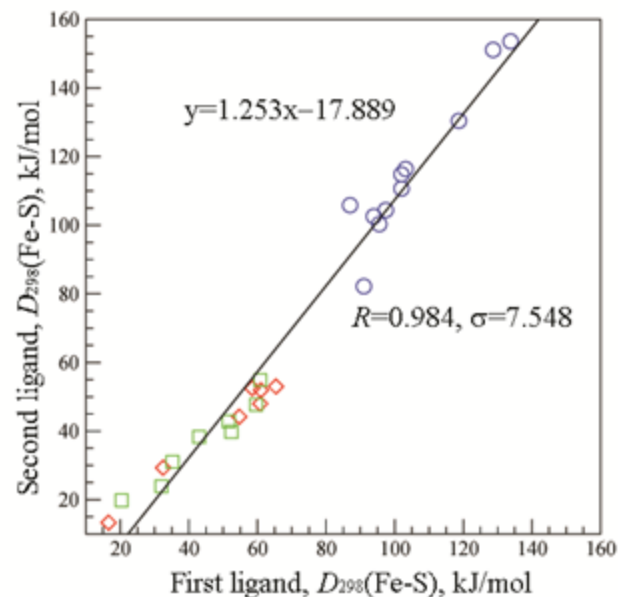
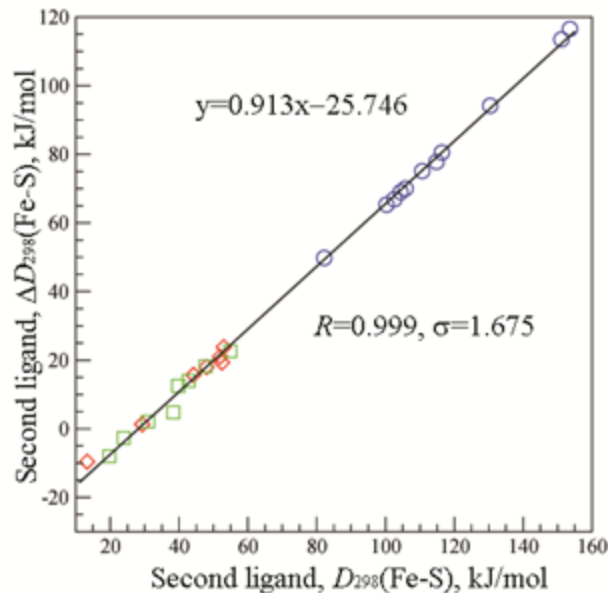
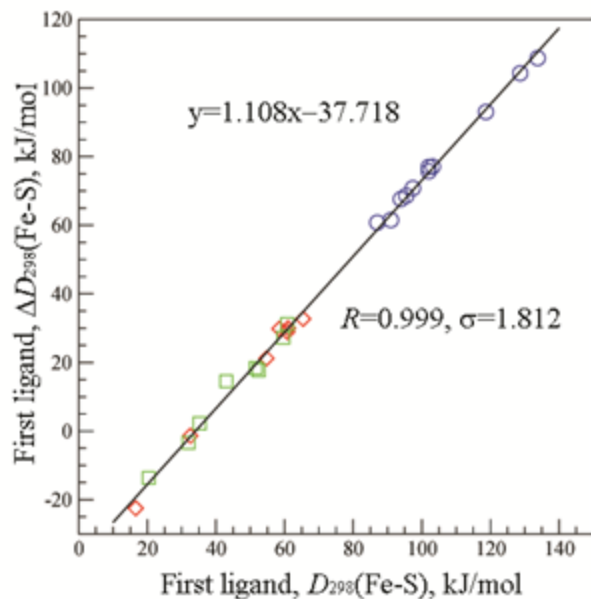


The Fe-S bond energies in the thiolate DNICs $[\text{Fe}(\text{NO})_2\text{L}_2]^-$



L	$D_{298}(\text{Fe-S})^1$	$\Delta D_{298}(\text{Fe-S})^1$	$D_{298}(\text{Fe-S})^2$	$\Delta D_{298}(\text{Fe-S})^2$
16	91.0	61.5	82.2	49.8
17	93.9	67.6	102.6	66.9
18	95.5	68.6	100.3	65.3
19	97.4	70.8	104.4	69.0
20	102.0	77.0	114.8	77.8
21	102.0	75.7	110.7	75.1
22	103.2	77.1	116.4	80.5
23	118.7	93.0	130.4	94.2
24	128.7	104.3	151.1	113.5
25	133.8	108.7	153.6	116.6
26	87.0	60.8	105.8	70.0

Pairwise comparison of the Fe-S bond energies

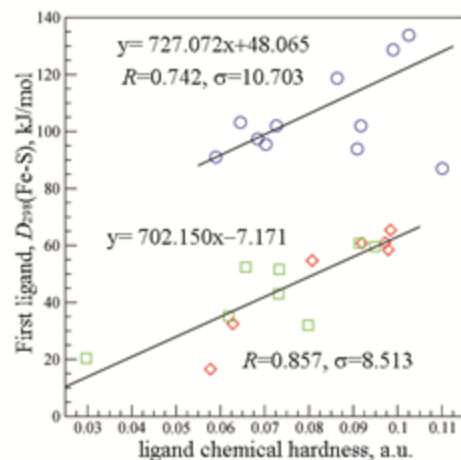
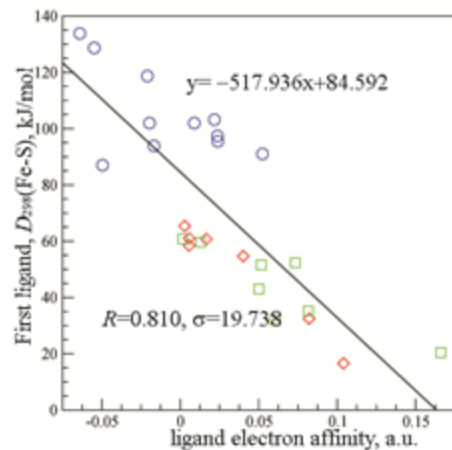
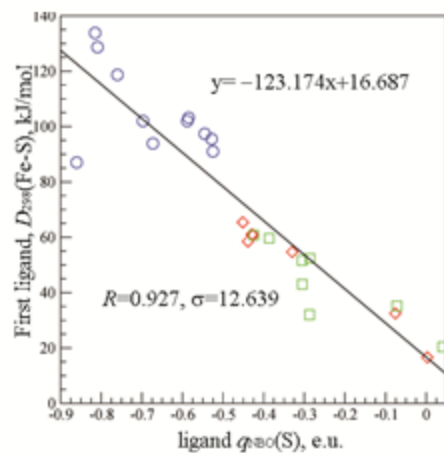
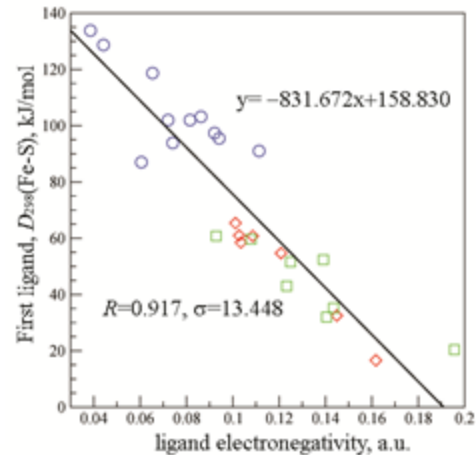
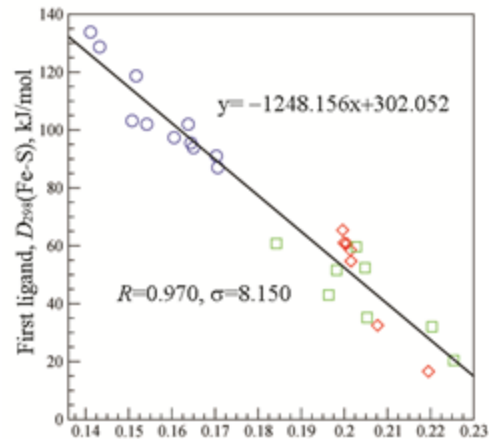
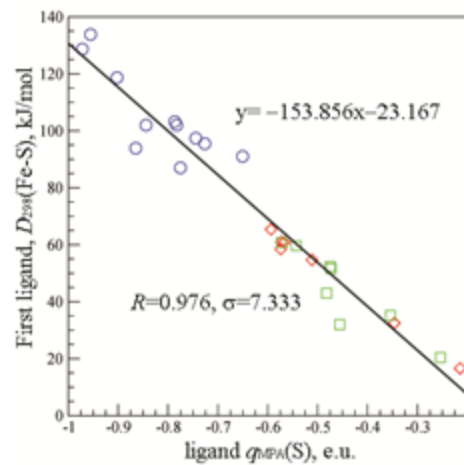


The reactivity indices of thio ligands vs. the Fe-S bond energy. Linear correlations

$$q_{\text{MPA}}(\text{S}), q_{\text{NBO}}(\text{S}), I, A, \chi, \eta, \alpha : \\ I = -\varepsilon_{\text{homo}}, A = -\varepsilon_{\text{lumo}} \quad \chi = \left(\frac{\partial E}{\partial q} \right)_{\text{ao}} \quad \eta = \frac{1}{2} \left(\frac{\partial^2 E}{\partial q^2} \right)_{\text{ao}}$$

Bond energy	Correlation coefficient, R					
	$q_{\text{MPA}}(\text{S})$	$q_{\text{NBO}}(\text{S})$	I	A	χ	η
$D_{298}(\text{Fe}-\text{S})^1$	0.976	0.927	0.970	0.810	0.917	0.857/0.742*
$\Delta D_{298}(\text{Fe}-\text{S})^1$	0.979	0.930	0.974	0.813	0.920	0.848/0.754*
$D_{298}(\text{Fe}-\text{S})^2$	0.962	0.910	0.978	0.783	0.901	0.836/0.767*
$\Delta D_{298}(\text{Fe}-\text{S})^2$	0.958	0.904	0.974	0.778	0.895	0.847/0.765*

The Fe-S bond energy correlations with $q(S)$, I , A , χ , η



Two-parameter models for correlating the Fe-S bond energy correlations with the reactivity indices

$$D(\text{Fe-S})^1 = -86.381(\pm 13.976)q_{\text{MPA}}(\text{S}) - 587.607(\pm 114.053)I + 126.891(\pm 29.297) \quad (1)$$

$n=26, R^2=0.978, \sigma = 5.104$

$$D(\text{Fe-S})^1 = -182.357(\pm 13.356)q_{\text{MPA}}(\text{S}) + 131.653(\pm 54.177)A - 44.035(\pm 9.534) \quad (2)$$

$n=26, R^2=0.962, \sigma = 6.682$

$$D(\text{Fe-S})^1 = -176.608(\pm 23.208)q_{\text{MPA}}(\text{S}) + 137.346(\pm 133.565)\chi - 51.590(\pm 28.011) \quad (3)$$

$n=26, R^2=0.955, \sigma = 7.324$

$$\Delta D(\text{Fe-S})^1 = -94.467(\pm 12.730)q_{\text{MPA}}(\text{S}) - 668.403(\pm 103.885)I + 106.853(\pm 26.685) \quad (4)$$

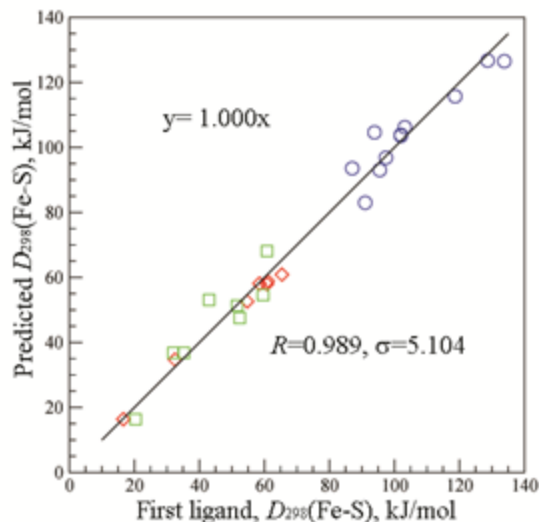
$n=26, R^2=0.985, \sigma = 4.649$

$$\Delta D(\text{Fe-S})^1 = -202.859(\pm 13.613)q_{\text{MPA}}(\text{S}) + 146.149(\pm 55.220)A - 87.003(\pm 9.717) \quad (5)$$

$n=26, R^2=0.968, \sigma = 6.810$

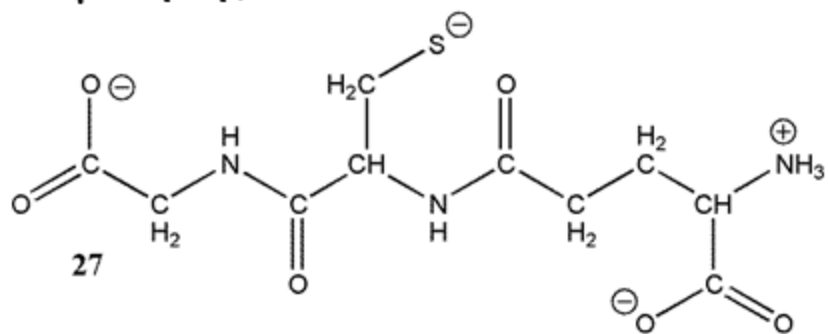
$$\Delta D(\text{Fe-S})^1 = -195.589(\pm 24.065)q_{\text{MPA}}(\text{S}) + 147.110(\pm 138.497)\chi - 94.281(\pm 29.045) \quad (6)$$

$n=26, R^2=0.960, \sigma = 7.595$



The Fe-S bond energy of glutathione in DNIC

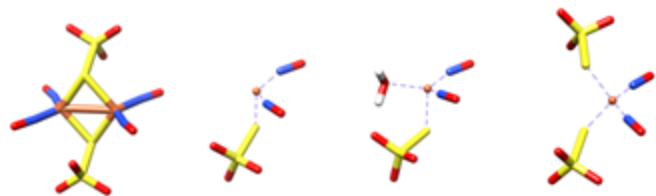
Glutathione



$$D_{298}(\text{Fe-S})^1 = 116.1 \pm 8.0 \text{ kJ/mol}$$

$$\Delta D_{298}(\text{Fe-S})^1 = 91.1 \pm 8.2 \text{ kJ/mol}$$

TNIC to DNIC



- replaces in DNIC ligands **4, 7**

- replaces in TNIC ligands **19, 20, 21, 23(118.7)**,
does not replace ligand **22(103.2)**

Conclusions

The Fe–S bond energies have calculated for 26 DNICs with thiocarbonyl and thiolate ligands in water using DFT methods. Structure–activity relationships are explored for a set of reactivity indices of thio ligands.

Linear correlations have been found for the calculated Fe–S bond energies with the partial electronic charge on atom S and the energies of frontier MOs of the free thio ligands in water. These correlations include also linear combinations of the MO energies (electron negativity χ and chemical hardness η). The reactivity indices reflect the contributions of electrostatic interactions and electron delocalization in the energy of coordination bonds Fe–S.

The formulated two-parameter models can be used to predict thermodynamic stability of new DNICs in the hydrolysis of thio ligand and/or substitution for other thio ligands from the reactivity indices of only the ligand alone. The predicted in this way Fe–S bond energy of glutathione agrees with the experimental data on thio ligand substitution by this thiol.

Thank you for attention!