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Bi- and polynuclear coordination compounds of d-elements as catalysts of homogeneous selective oxidation of thiol groups

Natalie Sergeevna Panina[1], Alisher Talgatovich Talgatov[1], Roman Vladimirovich Suezov[1], Nicolay Leonidovich Medvedskiy[1], Aleksei Vladimirovich Eremin[2,*] and Alexandr Nicolaevich Belyaev[1]

[1] St. Petersburg State Technological Institute (Technical University), Moskovskii pr. 26, 190013, Saint Petersburg, Russia

[2] Peter the Great St.Petersburg Polytechnic University, Politekhnicheskaya Str., 29, 195251, Saint Petersburg, Russia

Abstract: This research aims to study the catalytic cycle reactions for homogeneous selective oxidation of thiol RSH groups to RSSR with the participation of coordination compounds for d-element ions-Ni^{II}, Pd^{II}, Pt^{II}, Cu^{I}, Cu^{II}. We used the DFT M06, PBE0 / Def2-TZVP methods to build the quantum chemical models of the reactions. We have developed a mechanism for the functioning of the catalytic system in which primary active centers are either binuclear **{**$M(\mu\text{-}OH)_2M\}^{n+}$ or polynuclear $\{M(\mu\text{-}OH)_2M(\mu\text{-}OH)_2M\}^{2+}$ sites. Catalysts under consideration should retain stable spatial complementarity at all stages of the process. The main interrelated functions of the binuclear catalysts are the spatial approaching of anions RS^- in the inner sphere of the bridged coordination compound required for the disulfide (–S–S–) cross-linking and the two-electron redox transfer during the transformation of these anions into disulfide $(CH_3)_2S_2$.

Keywords: Palladium, platinum, copper, catalysis, coordination compounds, quantum chemical modeling.

Introduction

The oxidative process associated with the transformation of endogenous thiols as regulators of redox processes in all living organisms is schematically represented by the reaction:

$$2R\text{-}SH - 2\bar{e} \rightleftarrows R\text{-}S\text{-}S\text{-}R + 2H^+ \quad \textbf{(1)}$$

In biological systems, the processes of oxidation are performed by endogenous oxidants, one of which is hydrogen peroxide [1]. In a living organism, the signal processes of this type are catalyzed by enzymes, including metalloenzymes [2].

In patented investigation [3,4] binuclear coordination compounds of palladium are proposed as catalysts for homogeneous selective oxidation of thiol groups of aliphatic thiols, peptides, proteins, etc. The estimation of the catalytic activity of the coordination compounds $[Pd_2(\mu\text{-}OH)_2(dipy)_2]^{2+}$ and $[Pd_2(\mu\text{-}OH)_2(NH_3)_2]^{2+}$ in the process of oxidation of glutathione (GSH) performed by of high performance liquid chromatography (HPLC) has shown their larger catalytic effectiveness as compared to that of Cisplatin (*cis*-$[Pt(NH_3)_2Cl_2]$), the catalyst widely used in pharmaceutical industry. The study of the samples of the oxidized form of glutathione (GSSG) containing ultra-small amounts of complexes *cis*-$[Pd_2(\mu\text{-}OH)_2(NH_3)_2]^{2+}$and $[Pd_2(\mu\text{-}OH)_2(dipy)_2]^{2+}$and their thiolate derivatives was performed in the Institute of Cytology RAS against human epidermoid carcinoma A431 and acute myeloid leukemia HL-60 cells. The studies have shown that these samples have a toxic modifying effect comparable with that of the Glutoxim® drug [5,6]. Similar systems are used as accompanying drugs in chemotherapy of oncological diseases as modulators of the system of internal protection of the organism [7].

Besides the palladium compounds, copper ions are the catalysts of many redox processes. The research of the catalytic activity of complexes of Cu(II) using the HPLC method showed that these coordination compounds demonstrate high efficiency in the glutathione oxidation with hydrogen peroxide. However, the results of the biochemical study carried out in our group on living organisms (mice) indicate that the use of ultra-small amounts of Cu(II) compounds as catalysts of glutathione oxidation does not affect therapeutic effectiveness of the final medical drug. At the same time experimental studies have shown that the inclusion of small amounts of Cu^{II} ions in the drugs containing coordination compounds of Pd^{II} (in the ratio not exceeding 2: 1) substantially increases the catalytic activity of these drugs [8].

**Corresponding author: Aleksei Vladimirovich Eremin*
Email address: ha9room@gmail.com
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The purpose of this work is to develop a mechanism for the functioning of the suggested catalytic systems based on quantum-chemical modeling of individual stages of the catalytic cycle. By analogy with the ideas developed in the theory of enzymatic catalysis, the convergence of reagents during their sorption in the active center is considered as a reason for the high activity of the catalysts [9]. At that the increase in the reaction rate is connected with the pre-exponential term in the Arrhenius equation $k = Ae^{-Ea/RT} = A'e^{\Delta S\#/R}e^{-Ea/RT}$, that is, with the entropy of activation $\Delta S^{\#}$ [10,11]. The $\Delta S^{\#}$ value is negative because it is connected to a decrease in the number of degrees of freedom when the activated complex is formed. However, in the case of binding the properly oriented particles reacting on the topologically suitable catalytic center, the $\Delta S^{\#}$ value is substantially less negative than in the case of their scattering.

To explain the experimentally obtained increase in the rate of thiol oxidation reactions [4,8], we consider the factor of the most favorable orientation of the RS^- groups in the coordination compound necessary for disulfide (-S-S-) cross-linking and the formation of the disulfide R_2S_2. We did not perform calculations of activation barriers in this work because of complexity of the structure of the transition state of the catalytic centers of transition metals having different multiplicity and diversity of channels of the reaction when H_2O_2 is used as an oxidant.

Results and discussion

The key point in the catalytic oxidation reactions of thioaminoacids involving *d*-element complexes is the preliminary processes of hydrolysis of these *d*-element complexes [12,13], leading to a structure with the binuclear core **{**$M(\mu\text{-}OH)_2M\}$ [14-16] imitating the active site of a metalloenzyme. Processes of hydrolysis generally take place to a greater extent with a decrease in the concentration of the complex in solution.

The main reactions of the catalytic cycle of oxidation of RSH to RSSR involving binuclear hydroxo-bridged complex $[L_2M(\mu\text{-}OH)_2ML_2]^{2+}$ by analogy with [17-19] are the following:

$$[L_2M(\mu\text{-}OH)_2ML_2]^{2+} + 2RSH \rightleftarrows [L_2M(\mu\text{-}SR)_2ML_2]^{2+} + 2H_2O \quad \textbf{(2)}$$

$$[L_2M(\mu\text{-}SR)_2ML_2]^{2+} + H_2O_2 \rightleftarrows \{[M_2(\mu\text{-}SR)_2(OH)_2L_4]^{2+}\} \quad \textbf{(3)}$$

$$\{[M_2(\mu\text{-}SR)_2(OH)_2L_4]^{2+}\} \rightleftarrows [L_2M(\mu\text{-}OH)_2ML_2]^{2+} + RSSR \quad \textbf{(4)}$$

Equations (**2**) and (**4**) represent respectively the stages of the catalyst $[L_2M(\mu\text{-}OH)_2M'L_2]^{2+}$ consumption and regeneration. Reaction (**3**) is the key step which represents the formation of the intermediate $\{[M_2(\mu\text{-}SR)_2(OH)_2L_4]^{2+}\}$ capable of the intramolecular redox process (**4**).

In the experimental study [17] of the catalytic system based on binuclear hydroxo-bridged dipyridyl complex $[Pd_2(\mu\text{-}OH)_2(2,2'\text{-dipy})_2]^{2+}$ we have isolated and characterized the binuclear complex $[Pd_2(\mu\text{-S-Cys})(\mu\text{-S-CysH})(dipy)_2](NO_3)_3\cdot 4.5H_2O$ (dipy = 2,2′-bipyridyl). Its reaction with the oxidant (H_2O_2) leads to precipitation of cystine, the disulfide form of cysteine. The formation of the intermediate cysteine-containing coordination compound is an indirect confirmation that the catalytic process under scrutiny proceeds via the formation of $[L_2M(\mu\text{-}SR)_2ML_2]^{2+}$ cation. Complexes with a similar fragment $M(\mu\text{-}SR)_2M$, readily formed in aqueous solutions, were described by structural and spectral methods [20,21].

For the Pd^{II} complexes and their isoelectronic analogs - the Pt^{II} coordination compounds, the energy changes were calculated during the reactions of the catalytic cycle in the gas phase and in the solution (H_2O). The data presented in Table 1 (see Supplementary Materials) indicate a decrease in the total energy of the systems in the reactions of formation (**2**) and oxidation (**3**) of bridging coordination compounds. Under the oxidation of the metallic core of $M_2^{II}(\mu\text{-}S)_2$ by hydrogen peroxide in the intermediate bimetallic compound, the most energetically favorable is the addition of both OH-groups to the same metal atom. This allowed us to consider the intermediate $[(NH_3)_2(OH)_2M(\mu\text{-}SCH_3)_2M(NH_3)_2]^{2+}$ formed at stage (**3**) as a binuclear mixed-valence complex with the $M^{IV}(\mu\text{-}S)_2M^{II}$ core. Such a core, being restored in its own turn, oxidizes the bridging thiolate groups. The reason of instability of the intermediate coordination compound $M^{IV}M^{II}$ is related to the presence of an oxidant (M^{IV} ion) and reducers (ligands $\mu\text{-}SCH_3^-$) in its inner sphere, which leads to the inner-sphere redox process (**4**).

In the case of the Ni^{II} ion, isoelectronic to the ions Pd^{II} and Pt^{II}, we considered the coordination compounds of various multiplicities. In order to estimate the energy variations in the separate stages of the catalytic cycle with participation of nickel complexes, we chose the most stable triplet structures $[L(OH)Ni(\mu\text{-}SCH_3)_2(\mu\text{-}OH)NiL]^{2+}$ (L = en). The results obtained for reactions (**2**) - (**4**) of the catalytic cycle under consideration with the participation of paramagnetic Ni^{II} compounds are presented in Table 2 (Supplementary Materials).

The performed study of the catalytic systems for selective oxidation of thiols on the basis of binuclear coordination compounds of Ni^{II}, Pd^{II} and Pt^{II} demonstrates differences in energy effects of separate steps of the catalytic cycle connected to the nature of the metal (see Table 3, Supplementary

Materials). For the complex of Ni^{II}, as compared with the similar palladium analogue, substitution of hydroxo bridges by the thiolate ions in reaction (**2**) results only in a small decrease in the total energy of the system. At the same time, for the coordination dimer of Pt^{II} the total energy is substantially increased in the stage of redox disproportionation (**4**). The obtained energy differences are in qualitative agreement with the theory of hard and soft acids and bases (HSAB) [22]. According to HSAB theory, in reaction (**2**) the "hard" acid Ni^{II} ion is stronger bound with the "hard" base oxygen atoms of the μ-OH-groups than with the "soft" base sulfur atoms of the μ-SCH_3-groups. For Pt complexes in reaction (**4**), the bonds of a "soft," easily polarizable metal ion is much stronger with the "soft" base S atoms in μ-SCH_3- than with the "hard" O atoms in μ-OH. A higher stability of the coordination core $Pt^{IV}(\mu\text{-}SCH_3)_2Pt^{II}$ can slow down the inner-sphere redox process leading to the recovery of the catalyst. The coordination compounds of Pd ion which according to their acidity property lies between the isoelectronic Ni and Pt ions turn out to be the most suitable for the reactions of the catalytic cycle under consideration.

Total stabilization achieved in the course of reactions (**2**) – (**4**) for the coordination metal ions which can again provide the formation of the hydroxo-bridged dimer $[L_2M(\mu\text{-}OH)_2M'L_2]^2$ and the disulfide $(CH_3)_2S_2$, is 2.99 eV in the gas phase and 3.19 eV in aqueous solution. These values, due to the additivity of the energy variations in the coupled reaction stages, coincide with the energy effects calculated for reaction (**5**).

$$2CH_3SH + H_2O_2 \rightleftarrows (CH_3)_2S_2 + 2H_2O \qquad \textbf{(5)}$$

With ultra-small concentrations of metal ions, the most important condition for the action of the catalyst should be its ability for stable regeneration during the catalytic cycle. In catalytic systems based on M^{II} ions, the active sites of compounds (Fig. 1, Table 1) retain a stable spatial correspondence in the reactions (**2**) - (**4**) of the catalytic cycle, which allows the catalyst to be regenerated.

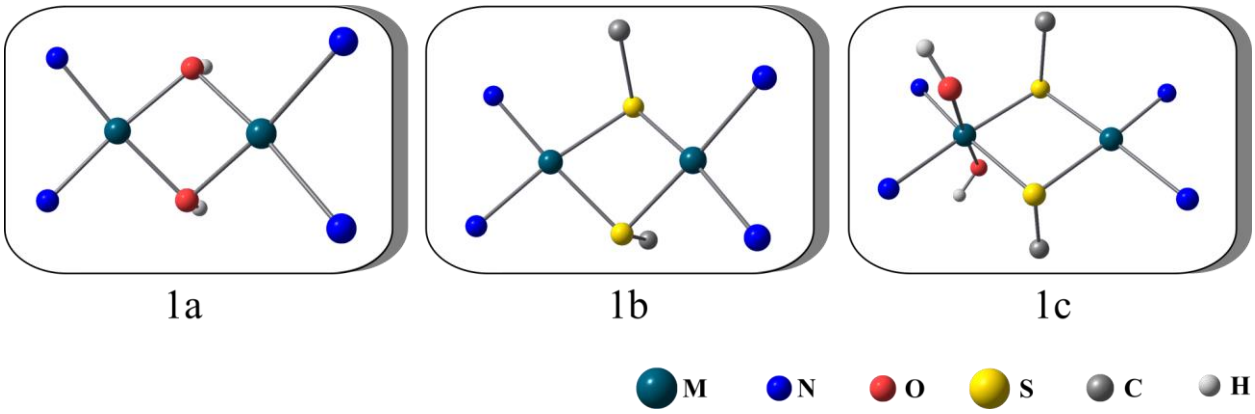

Figure 1. Structure of active sites of the catalytic system (M = Pd, Pt):
(1a) -$\{M^{II}(\mu\text{-}OH)_2M^{II}\}^{2+}$, (1b) $\{M^{II}(\mu\text{-}SR)_2M^{II}\}^{2+}$, (1c) -$\{M^{II}(\mu\text{-}SR)_2M^{IV}(OH)_2\}^{2+}$.
Hydrogen atoms of amino ligands are omitted for clarity.
Key distances (Å) for active sites:

1a	1b	1c
Pd-(μ-OH): 2.045 (all); Pd-Pd: 2.985; O-O: 2.718	Pd-(μ-SR): 2.326, 2.321, 2.326, 2.321; Pd-Pd: 3.334; S-S: 2.993	Pd-(μ-SR): 2.322, 2.346, 2.322, 2.346; Pd-Pd: 3.508; S-S: 3.079
Pt-(μ-OH): 2.060, 2.060, 2.060, 2.060; Pt-Pt: 3.036; O-O: 2.702	Pt-(μ-SR): 2.332, 2.325, 2.332, 2.325 Pt-Pt: 3.390; S-S: 3.038	Pt-(μ-SR): 2.329, 2.329, 2.352, 2.352 Pt-Pt: 3.486; S-S: 3.124

The calculations which take into account the solvent effect (H_2O) demonstrated only a slight decrease (not exceeding 0.01 Å) in the main interatomic distances as compared to the corresponding values for gas phase. It was the spatial similarity that allowed regeneration of the catalytic system starting state due to the inner-sphere redox process (**4**). The process included the synchronous transfer of two electrons from the pair of coordinated thiol bridges to ion M^{IV}, leading to the breakage of the bridge bonds M–S(CH_3), to the recombination of two thiol radicals $(CH_3)S\cdot$ into the disulfide $(CH_3)_2S_2$, and to the rearrangement of two axial OH^- ligands into the original bridge positions.

The obtained results are in good agreement with the principle of retention of the reaction site at the initial and at the end of the catalytic cycle and with a fundamental principle of the least action [23]: lower energy of activation corresponds to the least motion of nuclei and the least violation of the original electron distribution, that is, to minimal electron

perturbation. The principle of complementarity (mutual structural complementarity) widely used in biochemistry for the explanation of the nature of the enzyme catalysis can be considered from the point of view of the fundamental principle of the least action [24] too. L. Pauling stated as early as in 1948 [25] that enzyme molecules were structurally complementary to the activated complexes formed in the course of the reactions they catalyze. The principle of complementarity provides mutual correspondence between the chemical structure of the substrate and the active site of the enzyme for the interaction of the molecules [26]. The results of the presented study show that the principle of complementarity can be also applied in quantum-chemical modeling of catalytic systems for selective oxidation of aliphatic thiols RSH involving coordination compounds of *d*-elements.

Let us consider the suggested mechanism of selective oxidation of aliphatic thiols in more detail. Binding of thiols RSH at the active site $\{M(\mu\text{-}OH)_2M\}$ occurs when they neutralize the μ-OH-groups of the coordination compound via reaction (2), leading to the appearance of the catalytic site $\{M(\mu\text{-}SR)_2M\}$, the latter being responsible for the process development. The first essential function of this bimetallic site is the spatial approaching of the two thiolate anions RS^- upon their entering as ligands in the inner sphere of the coordination compound required for the disulfide (–S–S–) cross-linking and formation of the disulfide $(CH_3)_2S_2$. Spatial complementarity of the bridged coordination center in the considered reactions can provide the start and end of the catalytic cycle.

The last step of the considered catalytic cycle includes the electron transfer reaction. Free radicals RS· are formed via single-electron oxidation of the ligand RS^-. The formation of the disulfide molecule R_2S_2 requires the presence of two radicals RS· and, respectively, transfer of two electrons. In agreement with the least action principle, the simplest way for oxidation with hydrogen peroxide and further regeneration of the catalytic center should include two-electron redox processes. According to [27], if the number of electrons accepted by one part of the catalytic center coincides with the number of electrons donated by the other part, the reaction is complementary. Therefore, besides the spatial complementarity, the second essential function of the bimetallic catalytic center is the redox complementarity, that is, providing the possibility of two-electron transfer both during oxidation of this center by hydrogen peroxide and in the reaction of intramolecular disproportionation with the formation of the oxidized product disulfide. These two-electron transfers occur in the systems under consideration with active centers including M^{II} and M^{IV} ions (Fig. 1).

Complex ions Cu^I and Cu^{II} act as catalysts in many redox processes. In this paper, for the catalytic cycle of oxidation of RSH to RSSR with participation of binuclear complexes of *d*-elements we examined the effectiveness of systems including copper ions in different oxidation states and multiplicity: $Cu^I(3d^{10})$, $Cu^{II}(3d^9)$ и $Cu^{III}(3d^8)$. The requirement of complementary *n*-electron transition [27] limits the choice of acting pairs for the analyzed catalytic centers: Cu^I- Cu^I, Cu^{II}- Cu^{II}, Cu^I- Cu^{III}, Cu^{III}- Cu^{III}.

According to the results obtained for Cu^I ions, dimer $[(NH_3)_2Cu^I(\mu\text{-}OH)_2Cu^I(NH_3)_2]^0$, which is initial for the catalytic cycle, can only by convention be considered as having binuclear structure which is stabilized only by hydrogen bonds of the aminate ligands and hydroxo groups, as well as electrostatic interactions of the oppositely charged atoms (Fig. 2a). The key active center $\{(OH)Cu^I\ldots Cu^I(OH)\}^0$ (Fig. 2b) must provide the beginning of the cycle in the catalytic system under consideration.

In the subsequent steps of the catalytic cycle the stability of the binuclear active center on the basis of Cu^I ions can be increased. Thus, in the step of neutralization of the μ-OH groups, Cu^I ions, which are soft Lewis acids, form stronger bonds with thiolate bridges $\mu\text{-}SCH_3$ (Fig. 2). At the same step, an active dimeric center (2c) is formed with short interatomic distance $d_{Cu(I)–Cu(I)}$ = 2.568 Å. The formation of such an active center in binuclear coordination compounds of Cu^I with close interatomic distance ($d_{Cu(I)–Cu(I)}$ = 2.575 Å) was presumed from the results of DFT calculations in [28]. The oxidation of $\{Cu^I(\mu\text{-}SCH_3)_2Cu^I\}^0$ with hydrogen peroxide can result in the most energetically and complementarily stable triplet active site $\{(OH)Cu^{II}(\mu\text{-}SCH_3)_2Cu^{II}(OH)\}^0$ (2d). However, stable spatial complementarity of active sites required in all stages of the catalytic cycle for regeneration of the catalyst can be lost due to instability of the primary link, $\{(OH)Cu^I\ldots Cu^I(OH)\}^0$ leading to violation of functioning of the whole system. Possibly, in the catalytic system based on Cu^I ions it would be more promising to search for terminal ligands which would better stabilize binuclear hydroxo systems than the aminate ligands.

To elucidate possible reasons for the discrepancy between the experimental facts mentioned above and the high catalytic activity of Cu(II) coordination compounds in the reactions of glutathione oxidation with hydrogen peroxide and the absence of their effect on the therapeutic efficacy of the final drug in living organisms, we performed quantum-chemical modeling of the catalytic cycle based on Cu(II) binuclear coordination compounds of different multiplicity and obtained the following results.

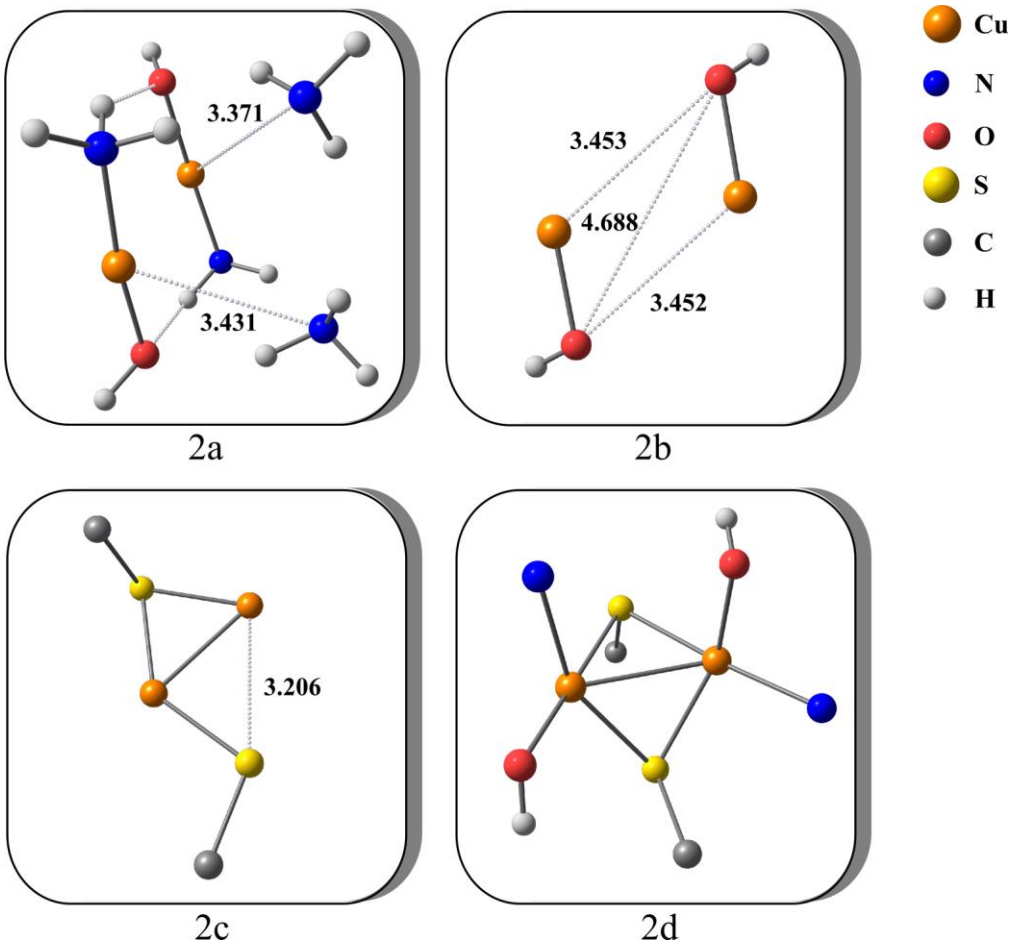

Figure 2. Optimized structure of dimer $[(NH_3)_2Cu^{I}(\mu\text{-}OH)_2{}^{I}(NH_3)_2]^0$ (**2a**) and active sites $\{(OH)Cu^{I}\ldots Cu^{I}(OH)\}^0$ (**2b**), $\{Cu^{I}(\mu\text{-}SCH_3)_2Cu^{I}\}^0$ (**2c**), $\{(OH)Cu^{I}(\mu\text{-}SCH_3)_2Cu^{I}(OH)\}^0$ (**2d**). In structures **2b** and **2c**, amino ligands are omitted for clarity.

Key distances (Å) for active sites:

2a	2b
Cu-NH_3 1.911; Cu-(μ-OH) 1.823 H_{NH3}-OH 1.867, 1.862 Cu-Cu 2.911	Cu-OH 1.823; O-O 4.688 Cu-Cu 2.911
2c	**2d**
Cu-(μ-SR) 2.322, 2.220, 2.244 S-S 4.246 Cu-Cu 2.568	Cu-NH_3 2.058, 2.035 Cu-OH 1.889, 1.918 Cu-(μ-SR) 2.369, 2.342, 2.389, 2.346 Cu-Cu 2.5918; S-S 3.168

For the binuclear compounds with $Cu^{II}(d^9\text{-}d^9)$ ions, the reactions (**2**) and (**3**) with the lowest-energy triplet center $\{Cu^{II}(OH)_2Cu^{II}\}^{2+}$ (3a) (Fig. 3) lead further to the formation of spatially similar structures - the triplet one with the center (3c) - $\{Cu^{II}(\mu\text{-}SCH_3)_2Cu^{II}\}^{2+}$ and the oxidized singlet (3e) - $\{(OH)Cu^{III}(\mu\text{-}SCH_3)_2Cu^{III}(OH)\}^{2+}$.

The lowest in energy triplet spin-asymmetric oxidized binuclear active center 3f is characterized by the loss of complementarity in the course of reaction (3). As to high-spin quintet structure 3g with low energy, it can also be included in reactions (2)–(4) of the catalytic cycle. If the reaction follows this path, the structure 3g would geometrically correspond to the starting state 3a. However, in 3g, two particles $(CH_3)S\cdot$ with unpaired electrons could not combine to give the molecule of $(CH_3)_2S_2$ because they are located on different sites of the plane of the active center. Possibly, this is related to the initial arrangement of the M–μS(CH_3) bonds. Nevertheless, the considered catalytic cycle including the formation of high-spin quintet structure 3g with hydroxo-bridges $Cu^{III\text{-}d8}(\uparrow\uparrow)(\mu\text{-}OH)_2Cu^{III\text{-}d8}(\uparrow\uparrow)$ is capable of generation of free radicals $(CH_3)S\cdot$.

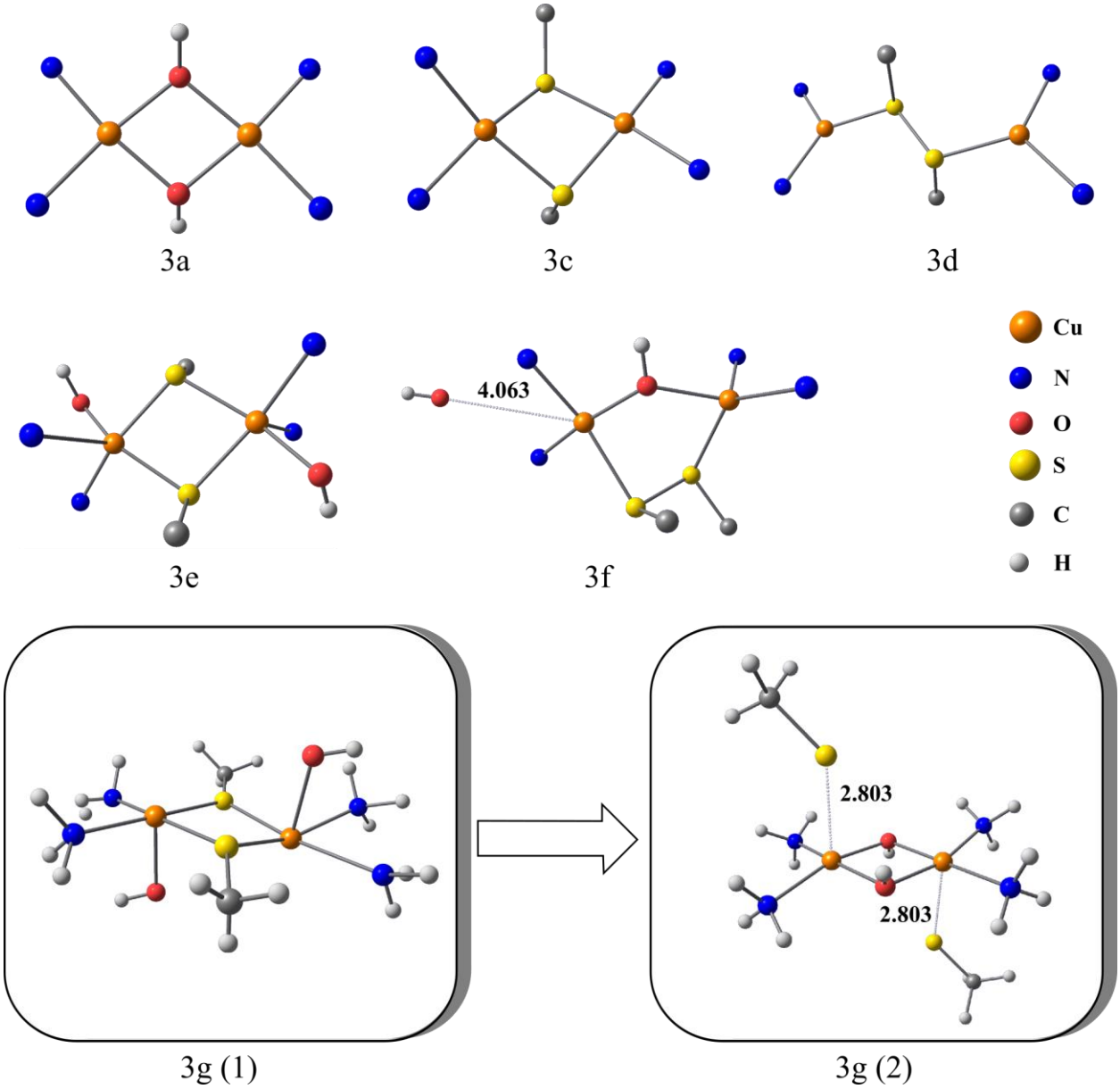

Figure 3. Structure of active sites **3a–3f** of the catalytic system; **3g (1)** - starting position, **3g (2)** – optimized structure. In the structures **3a-f**, the hydrogen atoms are omitted for clarity.
Key distances (Å) for active sites:

3a	3c	3d
Cu-(μ-OH) 1.939 (all); O-O 2.494; Cu-Cu 2.971	Cu-(μ-SR) 2.310, 2.353, 2.295, 2.348; S-S 3.001; Cu-Cu 3.410	Cu-SR 2.265, 2.265; S-S 2.120; Cu-Cu 5.719
3e	3f	
Cu-(μ-SR) 2.229, 2.244, 2.229, 2.244; Cu-OH 1.821, 1.821 S-S 2.835; Cu-Cu 3.460	Cu-(μ-OH) 2.190, 1.866; Cu-SR 2.482, 2.355 S-S 2.055; Cu-Cu 3.673	
3g (1)	3g (2)	
Cu-(μ-SR) 2.200, 2.226; O-O 5.190; Cu-Cu 3.261; S-S 3.032	Cu-(μ-OH) 1.952, 1.947, 1.952, 1.947; O-O 2.539; Cu-Cu 2.960; S-S 6.270	

Therefore, quantum-chemical modeling shows that transformation of binuclear system on the basis of Cu^{II} ions gives rise to the formation of stable complementary active centers, which make possible the two-electron redox reaction within the catalytic cycle under consideration. Along with this, transformation of the starting triplet hydroxo-bridged dimer $\{Cu^{II}(\mu\text{-}OH)_2Cu^{II}\}^{2+}$ with center 3a to the compound with thiolate bridges can generate another route of the reaction leading to degradation of the

catalyst. The fact is that in the triplet state the active centers $\{Cu^{II}(\mu\text{-}SCH_3)_2Cu^{II}\}^{2+}$ 3c have higher energy than in the singlet state 3d, $\Delta(E + ZPE) = 0.70$ eV. The conservation of spin in elementary reactions has an imp ortant consequence: chemical reactions with spin change are forbidden. However, the reconstruction of geometry during the reaction may cause the situation when crossing the singlet and the triplet potential energy surfaces minimizes the energy difference between the two spin conformers. This opens the way for transition of the high-energy triplet structure $\{Cu^{II}(\mu\text{-}SCH_3)_2Cu^{II}\}^{2+}$ (3c) to the more stable in energy singlet structure 3d. The search for a minimum at the crossing of the triplet (T) and singlet (S) surfaces of potential energy for the 3c→3d transition (Fig. 3) was performed using the MEX routine of the GAMESS program package [29,30]. During the geometry optimization, the energies of the spin isomers become practically equal. The geometry of complex $\{(NH_3)_2Cu^{II}(\mu\text{-}SCH_3)_2Cu^{II}(NH_3)_2\}^{2+}$ corresponding to the minimum at the crossing of the triplet and singlet surfaces of potential energy ($E_T = E_S$) is shown in Fig. 4 in comparison with the optimized structures of the spin isomers 3c and 3d.

At the point ($E_T = E_S$) the triplet structure of the coordination polyhedron 3c suffers substantial changes. Interatomic distances $d_{Cu(II)\ldots Cu(II)}$ essentially increase and $d_{RS\ldots SR}$ decrease. Geometric structure of 3d, corresponding to one of such local minima with the highest energy, is shown in Fig. 5. The low-energy singlet active center 3d represents an electrostatic complex. It is stretched diagonally relative to other complementary catalytic centers of this cycle: the pair of covalent interactions Cu–S is lost and the interatomic distance Cu–Cu is too large (>5.5 Å), while the S–S atoms of the two thiol ligands are already practically ready by their structural parameters for the formation of the bond in disulfide. These conditions provide a possibility of direct oxidation of thiol groups with hydrogen peroxide to produce the disulfide bypassing the copper ions of the binuclear active site. High efficiency of oxidation of thiols by hydrogen peroxide can be revealed by the HPLC method. Further relaxation of the singlet isomer 3d results in full destruction of the coordination polyhedron to three independent centers (Fig. 5). This route leads to the loss of complementarity and degradation of the catalytic cycle. Therefore, in a living organism the described triplet-singlet transition can be the reason of the irreversible inhibition of activity of the considered catalyst on the basis of compounds of Cu^{II} binuclear complexes.

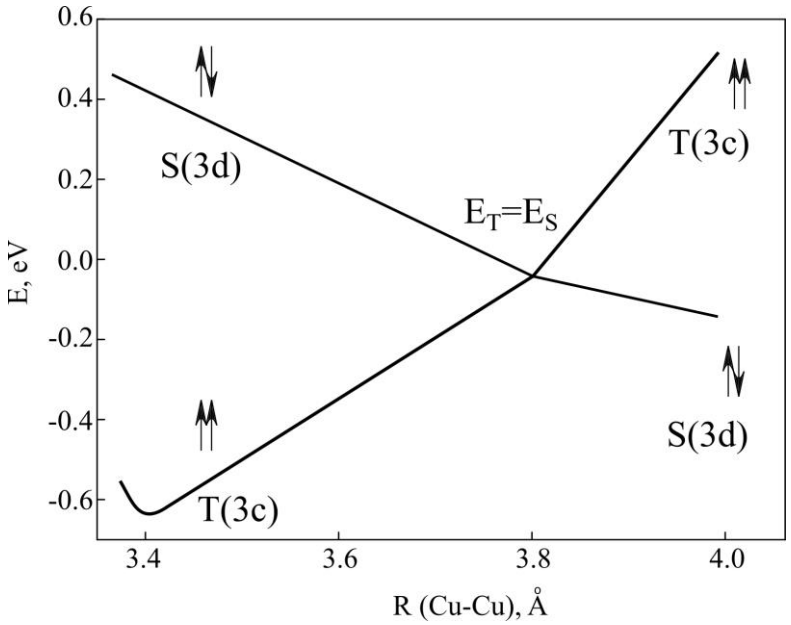

Figure 4. Schematic representation of changes in the energies of the triplet-singlet transition for coordination polyhedron $\{(NH_3)_2Cu^{II}(\mu\text{-}SCH_3)_2Cu^{II}(NH_3)_2\}^{2+}$.

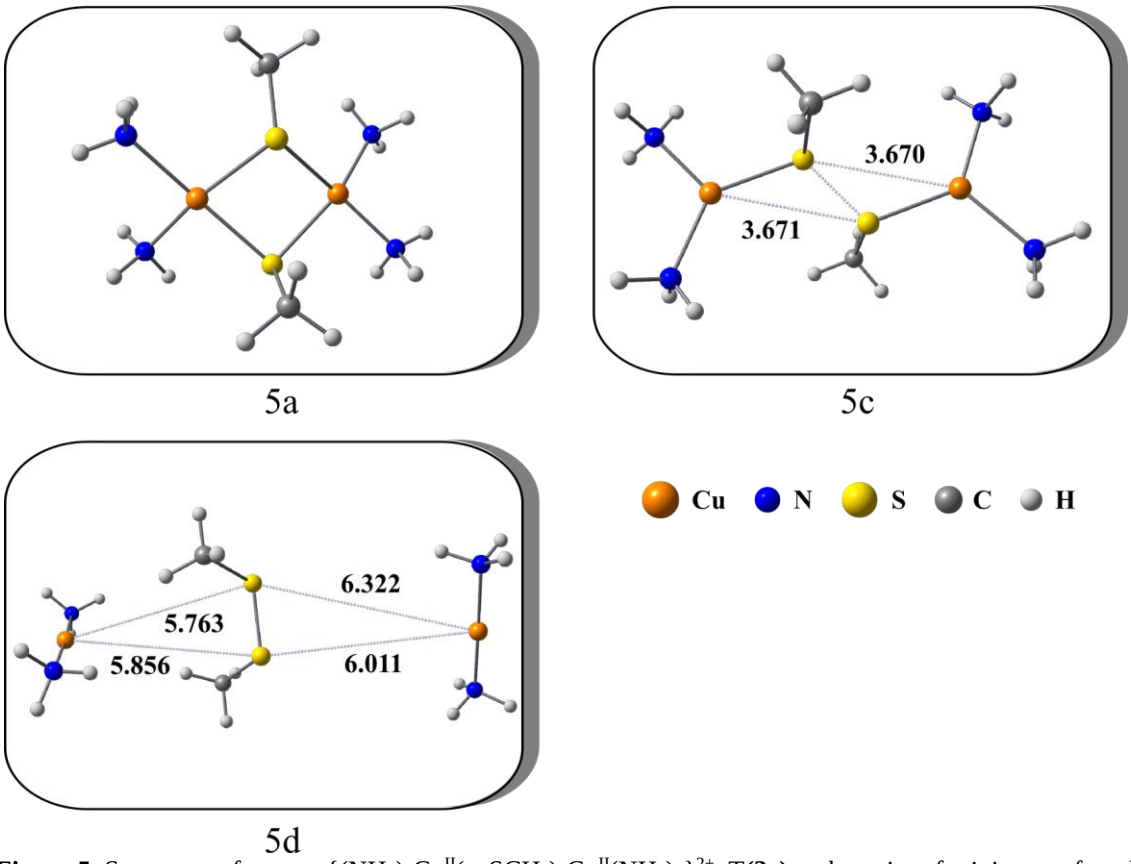

Figure 5. Structures of center $\{(NH_3)_2Cu^{II}(\mu\text{-}SCH_3)_2Cu^{II}(NH_3)_2\}^{2+}$: T**(3c)** at the point of minimum of total energy (a) and at crossing of the triplet and singlet potential energy surfaces (b, $E_T = E_S$) and S(**3d**) in the point of local minimum (c), and decomposition of active site of coordination polyhedron (d). Key distances (Å) for active sites:

5a	5c	5d
Cu-(μ-SR): 2.310, 2.353, 2.295, 2.384; Cu-Cu: 3.410; S-S: 3.001	Cu-SR: 2.265, 2.265; Cu-Cu: 5.719; S-S: 2.120	Cu-Cu: 11.698; S-S: 2.032

It was shown previously that experimental studies on the inclusion of small amounts of Cu^{II} ions in preparations containing Pd^{II} coordination compounds indicated that the catalytic activity of these preparations is significantly increased [8]. Therefore it is possible to suggest a scheme allowing enhancing the action of the catalyst. In view of close radii of Cu^{2+} and Pd^{2+}, upon introduction of aqua complexes of Cu^{II} in the catalytic system on the initial stages of the hydrolysis reactions, their incorporation occurs in the polymeric palladium-containing particle. As a result, a hydroxo-bridged structure with mixed Pd^{II}–Cu^{II}–Pd^{II} bimetallic centers is formed. A fragment of such a structure can be a three-nuclear core $\{Pd^{II}(\mu\text{-}OH)_2Cu^{II}(\mu\text{-}OH)_2Pd^{II}\}^{2+}$ (Fig. 6).

According to reaction (**2**), the substitution of μ-OH groups in the active site $\{Pd^{II}(\mu\text{-}OH)_2Cu^{II}(\mu\text{-}OH)_2Pd^{II}\}^{2+}$ (6a) by $\mu\text{-}SCH_3$ groups gives rise to the formation of the structure $\{Pd^{II}(\mu\text{-}SCH_3)_2Cu^{II}(\mu\text{-}SR)_2Pd^{II}\}^{2+}$ (6b). A specific feature of this structure is that four SCH_3^- anions are spatially oriented and brought closer around the Cu^{II} ion for the disulfide cross-linking. The formation of similar arrangement at the Pd^{II} ion is prevented by the *cis*-structure of the starting aminate complexes. Nevertheless, in the case of four-coordinate aquo complexes of Pd^{II} ion the growth of polymeric hydroxo-bridged chain resulting further to a large amount in the bound thiolate anions is also possible.

The subsequent oxidation of the mixed copper-palladium complex by reaction (**3**) with hydrogen peroxide is the reason of incipience of the intermediate coordination compound having the core 6c,$\{(OH)Pd^{IV}(\mu\text{-}OH)(\mu\text{-}SCH_3)_2Cu^{II}(\mu\text{-}SCH_3)_2(\mu\text{-}OH)Pd^{IV}(OH)\}^{2+}$. Redox processes occurring inside this core give two bound molecules R_2S_2. As a result, the amount of RS^- ions spatially oriented and brought closer for the disulfide cross-linking increases and, as a con-sequence, the aforementioned probability of formation of the transition state with a large number of thiolate bridges also increases. This may explain the experimentally observed increase in the catalytic activity of coordination compounds based on Pd^{II} with the inclusion of small amounts of Cu^{II} ions. For three-nuclear bimetallic Pd^{II}–Cu^{II}–Pd^{II} centers providing the formation of two molecules of R_2S_2 the processes under consideration are complementary and four-electron.

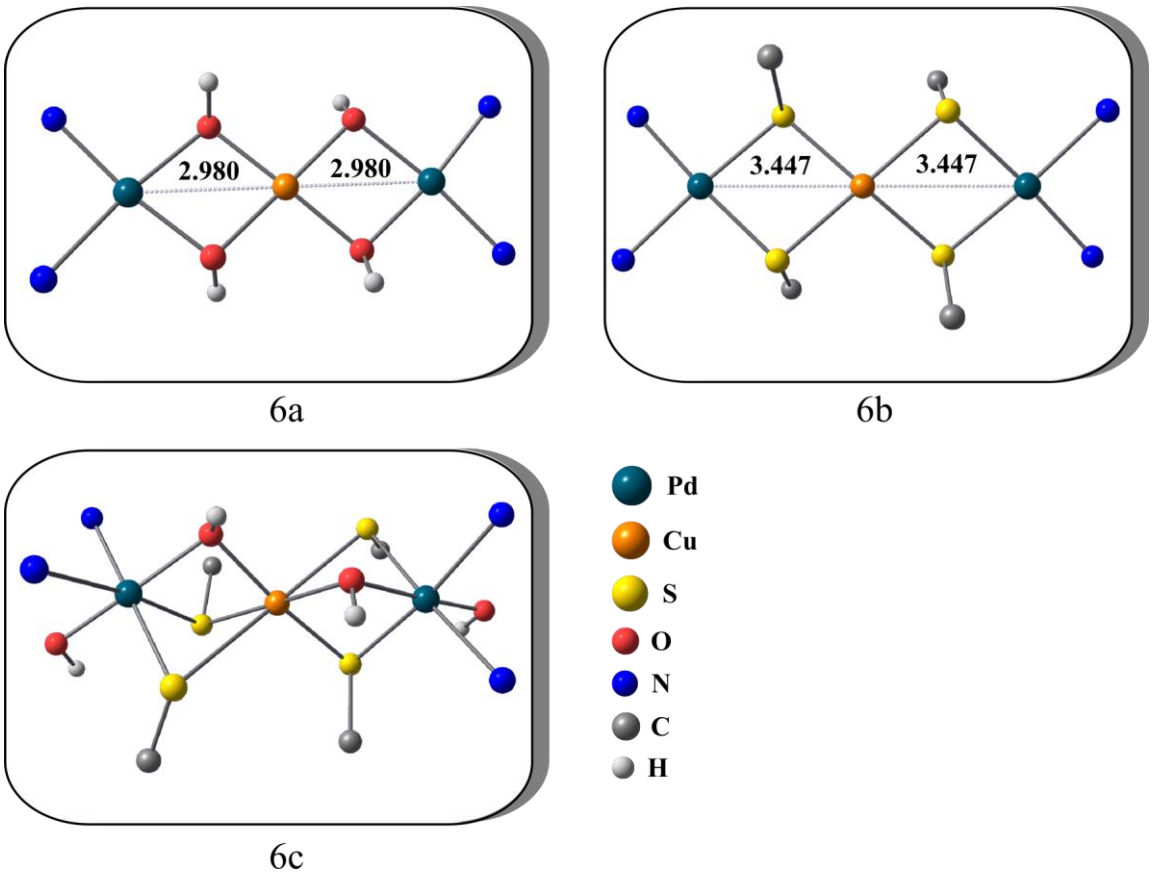

Figure 6. Structure of active sites **6a–6c** of the catalytic system. The hydrogen atoms of the amino ligands and R are omitted for clarity. Key distances (Å) for active sites:

6a	6b	6c
Pd-(μ-OH) 2.016 (all); Cu-(μ-OH) 1.948 (all); O-O 2.614	Pd-(μ-SR) 2.316 (all); Cu-(μ-SR) 2.341 (all); S-S 3.132	Pd-(μ-SR) 2.335, 2.337; Pd-SR 2.337 Cu-(μ-SR) 2.355 (all); Cu-(μ-OH) 3.024, 3.043 Pd-Cu 3.042, 3.024; S-S 3.156, 3.109

It was shown above that participation of binuclear ions including only Cu^{II} with their subsequent oxidation to Cu^{III} may result in destruction of the catalytic cycle. In the assumed copper-palladium catalytic scheme, the coordinated ions of copper(II) not involved in the redox reactions (**2**)–(**4**), play a role of the coordinator of the polynuclear core providing bringing together of a large number of thiolate ligands. However, if there are too many copper(II) ions, the redox reactions in the formed polymeric compound would be retarded by the lack of Pd^{II} ions suffering such processes. It is worth noting that from the data of quantum-chemical modeling, in all stages of the catalytic cycle with participation of the metal center Pd^{II}–Cu^{II}–Pd^{II} the spatial complementarity is retained. Distortion in the structure 6c caused by non-spherical $3d^9$-shell of Cu^{II} ions leads to octahedral arrangement of two sulfur atoms with elongated distances Cu–S [31]. Two axial thiol ligands RS can depart first from the complex-forming ion Cu^{II} at the stage (**4**) of the reaction of disproportionation of the compound 6c. As a result, the initial complex 6a is formed again with the arrangement of the ligand atoms around Cu^{II} ions close to square-planar.

Conclusion

In the given paper the quantum-chemical modeling of catalytic cycle reactions for homogeneous selective oxidation of thiol RSH groups to RSSR with the participation of coordination compounds for d-element ions-Ni^{II}, Pd^{II}, Pt^{II}, Cu^{I}, Cu^{II}, was carried out by DFT M06, PBE0 / Def2-TZVP methods. It is shown that among the isoelectronic ions of the 10th group of the periodic system for the reactions of the catalytic cycle under study the most appropriate are the coordination compounds of the Pd^{II} ion which is situated between the Ni^{II} and Pt^{II} ions according to HSAB theory.

The mechanism has been developed for the functioning of the catalytic system under consideration. Its primary active centers are

binuclear **{**$M(\mu\text{-}OH)_2M\}^{n+}$ or polynuclear $\{M(\mu\text{-}OH)_2M(\mu\text{-}OH)_2M\}^{2+}$ sites. Catalysts on the basis of such active centers of the *d*-element ions retain stable spatial complementarity in all stages of the process. The chief interrelated functions of the binuclear catalysts are the spatial approaching of two thiolate anions RS^- in the inner sphere of the bridged coordination compound required for the disulfide (–S–S–) cross-linking and the provision of the condition for n-electron redox transfer during the transformation of these anions into disulfide $(CH_3)_2S_2$.

It is shown that the catalytic systems based on binuclear coordination compounds including only Cu^I and Cu^{II} ions can be ineffective for this purpose because of the loss of complementarity and destruction of the catalytic cycle. In polymeric copper-palladium active centers formed due to the hydrolysis of the starting mononuclear coordination compounds, Cu^{II} ions act as coordinators of formation of the starting polynuclear site $\{Pd^{II}(\mu\text{-}OH)_2Cu^{II}(\mu\text{-}OH)_2Pd^{II}\}^{2+}$ bringing together a large number of thiolate ligands, which influences the rate of formation of disulfide R_2S_2. The spatial complementarity is retained in all stages of the catalytic cycle with participation of the metal center Pd^{II}-Cu^{II}-Pd^{II}.

Computational details

The series of quantum chemical calculations of the complexes were carried out by the DFT M06 [12] and PBE0 [13] methods using SDD [14-16] and def2-TZVP basis sets [18]. All calculations were performed using Gaussian09 program package [17]. Quantum-chemical data used to calculate the energy changes during catalytic cycle reactions are presented in Table 1 (Supplementary Materials). Molecular structures and normal modes were visualized using Chemcraft program [19]. In order to reduce the number of basic functions, the simplest methane-thiol CH_3SH was taken as thiol. The effect of water as a solvent was accounted for within the model of polarizable continuum [20, 21].

Due to the fact that ultra-small metal ion concentrations not exceeding the level of natural bioregulators (10^{-7}-10^{-9} mol/L) were used in experimental studies, in quantum-chemical modeling the assessment of the possibility of chemical reactions at each stage was carried out using the requirement of stabilization of the reacting system to reduce its total energy and not to reduce the thermodynamic potential Gibbs ΔG^0 in the reacting system calculated per 1 mole of substance.

Conflict of Interest

The authors declare no conflict of interest.

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