ISSN 1070-3632, Russian Journal of General Chemistry, 2015, Vol. 85, No. 7, pp. 1655–1660. © Pleiades Publishing, Ltd., 2015.
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Effect of Metal Nature (Ni, Pd, Pt) on the Catalytic Oxidation of Aliphatic Thiols: Quantum-Chemical DFT Modeling of Separate Steps of the Catalytic Cycle

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Received March 2, 2015

Abstract—Quantum-chemical DFT modeling of the reagents and products of selective oxidation of aliphatic thiols RSH to disulfides RSSR' with participation of coordination compounds of Ni, Pd, and Pt was performed. For Ni(II) ions, structures of different multiplicity were analyzed. The revealed differences in energy effects of the separate studies of the catalytic cycle for Ni, Pd, and Pt ions comply with the notions of hard and soft acids and bases. The obtained results open prospects for the search of effective catalysts of the oxidation of glutathione not only among binuclear coordination palladium compounds, but also among those of nickel and platinum.

Keywords: catalysis, coordination compounds, reaction mechanisms, thiols

DOI: 10.1134/S1070363215070142

Earlier we have shown that one of the most probable functions of the metal in catalytic oxidation of aliphatic thiols RSH to disulfides RSSR' is the formation of coordination compounds with thiolate ions RS^- with their subsequent oxidation and destruction of the coordination polyhedron [1]. For the modeling of the process of oxidation of thiolate ions we considered the catalytic cycle with participation of the hydroxo-bridged complex of Pd(II) with terminal 2,2'-dipyridyl (dipy) ligands, $[Pd_2(\mu\text{-}OH)_2(dipy)_2]^{2+}$, for which the following reactions were suggested as the principal processes:

$$[Pd_2(\mu\text{-}OH)_2(dipy)_2]^{2+} + 2RSH \leftrightarrow [Pd_2(\mu\text{-}SR)_2(dipy)_2]^{2+} + 2H_2O, \quad (1a)$$

$$[Pd_2(\mu\text{-}SR)_2(dipy)_2]^{2+} + H_2O_2 \leftrightarrow \{[Pd_2(\mu\text{-}SR)_2(dipy)_2(OH)_2]^{2+}\}, \quad (2a)$$

$$\{[Pd_2(\mu\text{-}SR)_2(dipy)_2(OH)_2]^{2+}\} \leftrightarrow [Pd_2(\mu\text{-}OH)_2(dipy)_2]^{2+} + RSSR. \quad (3a)$$

Equations (1a) and (3a) represent reaction steps in which the catalyst $[Pd_2(\mu\text{-}OH)_2(dipy)_2]^{2+}$ is consumed and regenerated. Reaction (2a) is the key step in which the formation of an unstable intermediate palladium complex $\{[Pd_2(\mu\text{-}SR)_2(dipy)_2(OH)_2]^{2+}\}$ is possible.

The possibilities of the proposed scheme of catalytic oxidation of glutathione (L-γ-glutamyl-L-cysteinyl-glycine, GSH) we investigated on the basis of the results of quantum-chemical DFT calculations of the model aminate palladium complexes, isoelectronic and isostructural to the dipyridyl complexes. The performed calculations have shown that upon the oxidation of binuclear metal core $Pd_2^{II}(\mu\text{-}S)_2$ with hydrogen peroxide in the intermediate bimetallic compound the most energy favorable process is the addition of two OH-groups to the same palladium atom. This allows considering this intermediate as a binuclear mixed-valent complex with the core $Pd^{IV}Pd^{II}(\mu\text{-}S)_2$. In turn, this core, being reduced, oxidizes the bridging thiolate groups.

The estimation of the effectiveness of the catalytic activity of 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 performed by the method of high-performance liquid chromatography has shown their greater catalytic effectiveness as compared to that of the catalyst widely used in pharmaceutical industry, *cis*-platinum (*cis*-$[Pt(NH_3)_2Cl_2]$). The investigation of the samples of the oxidized form of glutathione (GSSG) containing ultramicro amounts of complexes $[Pd_2(\mu\text{-}OH)_2(NH_3)_2]^{2+}$ and $[Pd_2(\mu\text{-}OH)_2(dipy)_2]^{2+}$ and their thiolate derivatives was performed in the Institute

Table 1. Total energies of compounds in gas phase [E(gas)] taking into account zero point energy (ZPE) and solvation energies [$E(H_2O)$] used in calculations of energy variations in the steps of the catalytic cycle

Compound	E(gas) + ZPE, a.u.	$E(H_2O)$, eV
H_2O	–76.353972	–0.29
H_2O_2	–151.434240	–0.27
H_3O^+	–76.633089	–3.32
CH_3SH	–438.545522	–0.13
CH_3SSCH_3	–875.927296	–0.15
$[(NH_3)_2Pd(\mu\text{-}OH)_2Pd(NH_3)_2]^{2+}$	–632.877693	–7.19
trans-$[(NH_3)_2Pd(\mu\text{-}SCH_3)_2Pd(NH_3)_2]^{2+}$	–1357.344578	–6.80
$[(NH_3)_2(OH)_2Pd(\mu\text{-}SCH_3)_2Pd(NH_3)_2]^{2+}$	–1508.803177	–7.07
$[(NH_3)_2Pt(\mu\text{-}OH)_2Pt(NH_3)_2]^{2+}$	–615.808327	–7.24
trans-$[(NH_3)_2Pt(\mu\text{-}SCH_3)_2Pt(NH_3)_2]^{2+}$	–1340.273012	–6.91
$[(NH_3)_2(OH)_2Pt(\mu\text{-}SCH_3)_2Pt(NH_3)_2]^{2+}$	–1491.810528	–7.12
$[(en)Ni_2(\mu\text{-}OH)_2Ni(en)]^{2+}$	–873.677236	–6.93
$[(en)Ni(\mu\text{-}SCH_3)_2Ni(en)]^{2+}$	–1598.087750	–6.68
$[(en)(OH)Ni(\mu\text{-}SCH_3)_2(\mu\text{-}OH)Ni(en)]^{2+}$	–1749.597594	–6.62

of Cytology RAS on the cells of A431 human epidermoid carcinoma and the cells of HL-60 acute myeloid leukemia. The studies have shown that these samples have a toxic modifying effect comparable with that of the drug Glutoxim® [2, 3]. Similar systems are used as accompanying drugs in chimiotherapie of oncological diseases [4, 5] as modulators of the system of internal protection of the organism.

In the present work the search for new catalytic systems for selective oxidation of thiols was extended by including in the described scheme the coordination compounds of other *d*-elements of the 10th Group of the Periodic Table, Pt(II) and Ni(II).

Table 2. Energy changes ΔE (eV) in steps (1)–(3) in the gas phase and solution (H_2O) in the catalytic cycle of oxidation of thiols

Reaction	(1)	(2)	(3)
Ni(gas) (c)	–0.74	–2.06	–0.19
Ni(H_2O) (c)	–0.81	–1.73	–0.65
Pd(gas) (a)	–2.28	–0.66	–0.05
Pd(H_2O) (a)	–2.21	–0.66	–0.32
Pt(gas) (b)	–2.22	–2.81	+2.04
Pt(H_2O) (b)	–2.21	–2.75	+1.77

Quantum-chemical calculations of the complexes were carried out by the DFT M06 method [6] using GAUSSIAN09 program package [7] and SDD basis set [8–11]. Chemcraft graphical program was used for visualization of molecular structures and normal modes [12]. The energies of solvation of the compounds were calculated using the polarizable continuum model [13, 14]. To reduce the number of basis set functions the molecule of glutathione RSH was simulated by the simplest analog, methanethiol CH_3SH.

The results of quantum-chemical calculations are presented in Table 1. For analogs of palladium complexes, coordination compounds of Pt(II), quantum-chemical calculations of the reaction of neutralization of the inner-sphere bridging OH-groups and their substitution by the thiolate SCH_3-bridges according to Eq. (1b)

$$[(NH_3)_2Pd(\mu\text{-}OH)_2Pd(NH_3)_2]^{2+} + 2CH_3SH \leftrightarrow [(NH_3)_2Pd(\mu\text{-}SCH_3)_2Pd(NH_3)_2]^{2+} + 2H_2O \quad (1b)$$

show a decrease in the total energy of the system by 2.22 eV in the gas phase, and by 2.21 eV in water solution (Table 2). The geometry optimization of the

complex $[(NH_3)_2(OH)_2Pt(\mu\text{-}SCH_3)_2Pt(NH_3)_2]^{2+}$, an intermediate compound similar to the palladium complex formed by the oxidation reaction (2b) led to the structure shown in Fig. 1.

$$[(NH_3)_2Pt(\mu\text{-}SCH_3)_2Pt(NH_3)_2]^{2+} + H_2O_2 \leftrightarrow [(NH_3)_2(OH)_2Pt(\mu\text{-}SCH_3)_2Pt(NH_3)_2]^{2+}. \quad (2b)$$

Coordination cations of palladium and platinum $[(NH_3)_2(OH)_2M(\mu\text{-}SCH_3)_2M'(NH_3)_2]^{2+}$ are similar in structure: one of metal M ions becomes six-coordinate, whereas the other ion M' remains tetracoordinate. Tetracoordinate complexes of palladium and platinum are low-spin and are described by dsp^2-hybrid orbitals. They originate from the state Pd(II). At the same time, six-coordinate polyhedra with d^2sp^3-hybrid orbitals of the metal belong to complex compounds of Pd(IV). Thus, as in [1], in the complex cation $[(NH_3)_2(OH)_2\cdot M^{IV}(\mu\text{-}SCH_3)_2M^{II}(NH_3)_2]^{2+}$ we assign to the six-coordinate metal ion the state Pt(IV), and to the tetracoordinate metal ion, Pt(II).

The reason of instability of the intermediate coordination compound $M^{IV}M^{II}$ is related with the presence in its inner sphere of an oxidant (M^{IV} ion) and reducers (ligands $\mu\text{-}SCH_3^-$) leading to the inner-sphere redox process. This process includes a synchronous transfer of two electrons from the pair of coordinate thiol bridges on the M^{IV} ion leading to the rupture of the M–S(CH_3) bridging bonds and recombination of two thiol radicals $(CH_3)S^{\cdot}$ to give disulfide $(CH_3)_2S_2$. This must be followed by the intramolecular rearrangement in the coordination sphere of the reduced dimer by shifting of the OH^- ligands coordinated to M^{IV} to the bridging position. In the result, compounds $[(NH_3)_2M\cdot(\mu\text{-}OH)_2M(NH_3)_2]^{2+}$ are formed, which are the starting compounds of the catalytic cycle under consideration.

The analysis of total energies of platinum compounds showed that the process of formation of complex $[(NH_3)_2(OH)_2Pt^{IV}(\mu\text{-}SCH_3)_2Pt^{II}(NH_3)_2]^{2+}$ [reaction (2b)] is preferable over its palladium analog (Table 2). However, the stability of the platinum complex makes it less prone to intramolecular redox process

$$[(NH_3)_2(OH)_2Pt^{IV}(\mu\text{-}SCH_3)_2Pt^{II}(NH_3)_2]^{2+} \leftrightarrow [(NH_3)_2Pt^{II}(\mu\text{-}OH)Pt^{II}(NH_3)_2]^{2+} + (CH_3)_2S_2, \quad (3b)$$

whose calculated energy characteristics are positive and suggest destabilization of the system: ΔE(gas) (3b) = 2.04 eV, ΔE_{solv} (3b) = 1.77 eV.

For the nickel coordination compounds, the calculations of complexes with bidentate terminal ligand ethylenediamine $NH_2(CH_2)_2NH_2$(en) were performed. The RSH molecules were also simulated by the methanethiol CH_3SH. For nickel complexes, unlike similar compounds of palladium and platinum, different spin complexes are possible depending on the strength of the ligand field. In the present work, coordination nickel compounds of different multiplicity were analyzed: singlet (all electrons on the metal atoms are paired); triplet [two unpaired electrons in the central fragment $Ni_2(\mu\text{-}L)_2$]; quintet (four unpaired electrons).

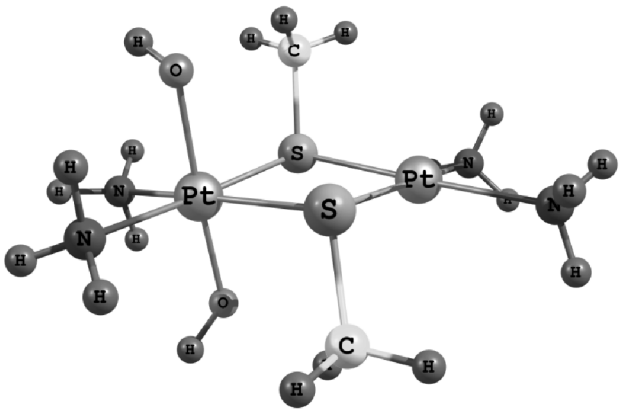

Fig. 1. Optimized structure of coordination cation *trans*-$[(NH_3)_2(OH)_2Pt(\mu\text{-}SCH_3)_2Pt(NH_3)_2]^{2+}$.

The $[(en)Ni_2(\mu\text{-}OH)_2Ni(en)]^{2+}$ cation in the gas phase was found to be the most stable in the singlet state of the bimetal core. In this case, the closest surrounding of the metal centers is nearly square-planar. In aqueous solution, the most stable are dimers $[(en)Ni(\mu\text{-}OH)_2Ni(en)]^{2+}$ in the quintet state, which is related to a larger polarity of the studied systems in the high-spin state. Four unpaired electrons of the quintet structure are localized practically identically on the nickel atoms, with small delocalization of the spin density to the bridging OH-groups. The closest surrounding of the metal atoms is a distorted tetrahedron. Both in the gas phase and in solution the triplet structure possesses the energy between that of the singlet and quintet. Note, however, that the spin density in the triplet structure is so delocalized that both unpaired electrons are localized on only one nickel atom. Therewith the closest surrounding of the nickel atom is a distorted tetrahedron, whereas for the other metal atom having no unpaired electrons the surrounding is close to square-planar. The energy difference of the considered structures of different multiplicity in aqueous solution is less than in the gas phase.

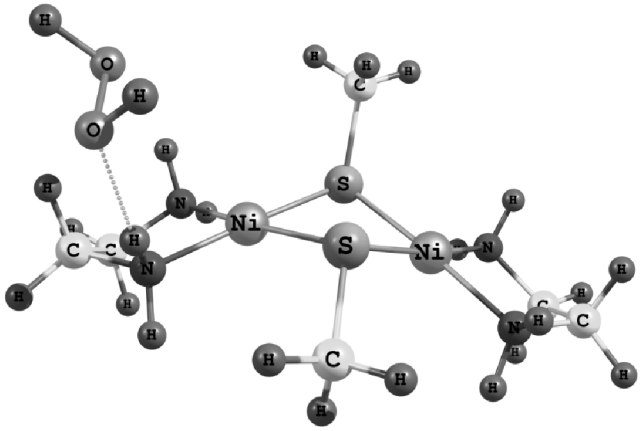

Fig. 2. Singlet structure **I**, *trans*-{[(en)Ni(μ-SCH_3)$_2$Ni(en)]$^{2+}$·H_2O_2}.

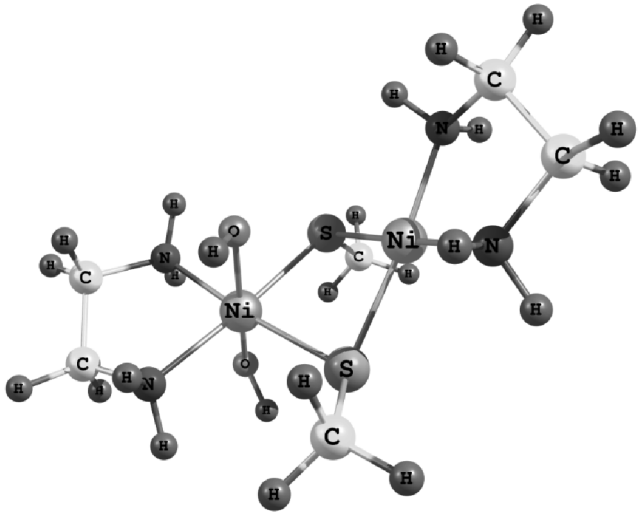

Fig. 3. Singlet structure **II**, *trans*-[(en)$_2$(OH)$_2$Ni$_2$(μ-SCH_3)$_2$]$^{2+}$.

Substitution of bridging OH^- groups with SCH_3^- anions by reaction (1c) results in the formation of dimers [(en)Ni(μ-SCH_3)$_2$Ni(en)]$^{2+}$. The most stable in the gas phase are singlet structures with paired *d*-electrons on the nickel atoms. In aqueous solution, as in the case of μ-OH-dimers, complex cations in the quintet state with substantial delocalization of the two unpaired electrons on each metal atom are of lower energy. The triplet structures possess energy, as above, between that of the singlet and quintet structures.

For the oxidized dimer [(en)$_2$(OH)$_2$Ni$_2$(μ-SCH_3)$_2$]$^{2+}$ we also obtained dissimilar in energy optimized structures of coordination polyhedral of different multiplicity. These dimers having SCH_3-groups on the same side of the plane of the central fragment (designated by us as *cis*-isomers) and those obtained by inversion turning of these groups (*trans*-isomers) are only slightly different in energy. In view of close energies of the *cis* and *trans*-isomers the obtained results were not distinguished in the following discussion. Besides, as a starting approximation for the oxidized coordination compound [(en)$_2$(OH)$_2$Ni$_2$(μ-SCH_3)$_2$]$^{2+}$ we considered different types of coordination of the μ-OH-groups, originating from hydrogen peroxide, to a single and to different nickel atoms.

Table 3. Energies of coordination compounds [(en)$_2$(OH)$_2$Ni$_2$·(μ-SCH_3)$_2$]$^{2+}$ of different multiplicity in gas phase and solution (H_2O) (eV) relative to the energy of structure **I** (eV)

[(en)$_2$(OH)$_2$Ni$_2$(μ-SCH_3)$_2$]$^{2+}$	Gas *cis*-	Gas *trans*-	H_2O *cis*-	H_2O *trans*-
I (singlet)	0.00	0.00	0.00	0.00
II (singlet)	–0.84	–0.66	–0.99	–0.87
III (triplet)	–1.05	–1.05	–1.29	–1.35
IV (quintet)	–0.85	–0.68	–1.04	–1.04

In the optimized structure **I**, *trans*-{[(en)Ni(μ-SCH_3)$_2$Ni(en)]$^{2+}$·H_2O_2} (Fig. 2) corresponding to a local minimum on the potential energy surface of the system in the gas phase, the molecule of H_2O_2 appears close to the singlet binuclear cation although does not form Ni···OH bonds. The distance between its oxygen atom and the nearest hydrogen atom of ethylenediamine is 1.931 Å. In aqueous solution this distance is increased to 2.085 Å, but the arrangement of the intramolecular bonds in the coordination polyhedron is retained. The energies (in eV) of coordination compounds [(en)$_2$(OH)$_2$Ni$_2$(μ-SCH_3)$_2$]$^{2+}$ of different multiplicity relative to the energy of structure **I** are given in Table 3.

For the oxidized by hydrogen peroxide dimer [(en)$_2$(OH)$_2$Ni$_2$(μ-SCH_3)$_2$]$^{2+}$ in the singlet structure **II** (Fig. 3) both OH-groups are coordinated to the same metal atom. The triplet structure of **III** [(en)(OH)Ni(μ-SCH_3)$_2$(μ-OH)Ni(en)]$^{2+}$ (Fig. 4) was found to be the most stable both in gas phase and in aqueous solution. Two unpaired electrons in the triplet structure **III** are localized mainly on the Ni atom, connected only with the bridging OH-group, with insufficient shift of the spin density to the ligand sulfur, oxygen and nitrogen atoms lying near this metal atom. The least stable is the quintet structure **IV** (Fig. 5). Two unpaired electrons in structure **IV** practically completely belong

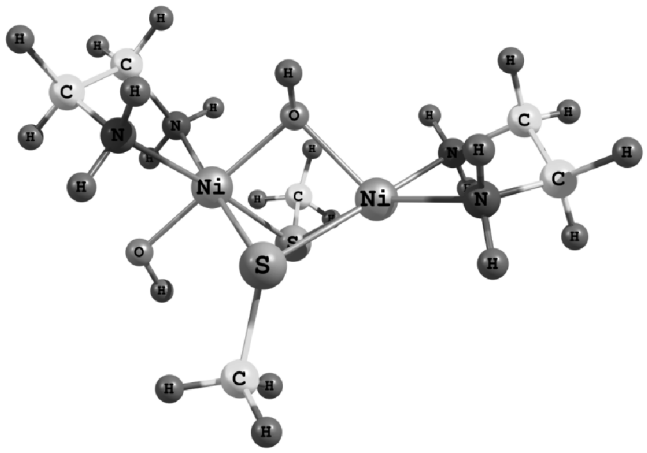

Fig. 4. Triplet structure **III**, *trans*-[(en)(OH)Ni(μ-SCH_3)$_2$·(μ-OH)Ni(en)]$^{2+}$.

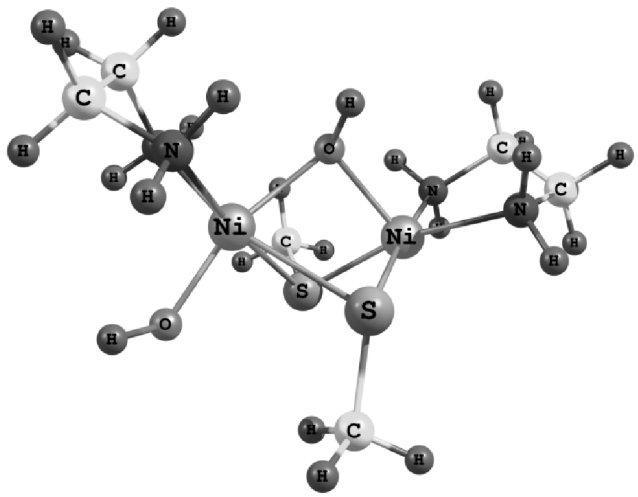

Fig. 5. Quintet structure **IV**, *trans*-[(en)(OH)Ni(μ-SCH_3)$_2$·(μ-OH)Ni(en)]$^{2+}$.

to the nickel atom connected with two OH-groups (bridging and terminal). A slightly more than one electron of the spin density is localized on the other metal atom. The other part of the spin density is nonuniformly distributed between the ligand atoms coordinated to the first of the described nickel atoms, with predominate contribution of the rest of spin density to the terminal oxygen atom of the OH-group.

For estimation of energy variations in the separate stages of the catalytic cycle with participation of nickel complexes triplet *trans*-structures **III** have been chosen. These structures turned out to be the most stable for the nickel binuclear core oxidized by hydrogen peroxide, whereas for dimers [(en)Ni(μ-$OH)_2$·Ni(en)]$^{2+}$ and [(en)Ni(μ-$SCH_3)_2$Ni(en)]$^{2+}$, described in reactions (1c) and (2c), the differences in the energies of the isomers of different multiplicity, according to calculations, were negligible.

For the reaction of neutralization of the hydroxo-bridged dimer

$$[(en)Ni(\mu\text{-}OH)_2Ni(en)]^{2+} + 2CH_3SH \leftrightarrow [(en)Ni(\mu\text{-}SCH_3)_2Ni(en)]^{2+} + 2H_2O, \quad (1c)$$

the variation in the total energy was ΔE(gas) (1c) = –0.74 eV, ΔE_{solv} (1c) = –0.81 eV (Table 2). The decrease in the total energy upon oxidation of the S-bridge dimer with hydrogen peroxide according to reaction (2c) was 2.06 eV.

$$[(en)Ni(\mu\text{-}SCH_3)_2Ni(en)]^{2+} + H_2O_2 \leftrightarrow [(en)(OH)Ni(\mu\text{-}SCH_3)_2(\mu\text{-}OH)Ni(en)]^{2+}. \quad (2c)$$

Taking into account the solvent effect (water) this value decreased to 1.73 eV.

The scheme of the catalytic cycle similar to the earlier considered [1] for coordination compounds of Pd(II) assumes the destruction of the species [(en)(OH)·Ni(μ-$SCH_3)_2$(μ-OH)Ni(en)]$^{2+}$ with the formation of the hydroxo-bridged dimer [(en)Ni(μ-$OH)_2$Ni(en)]$^{2+}$ and dimethyl disulfide CH_3SSCH_3 by reaction (3c).

$$[(en)(OH)Ni(\mu\text{-}SCH_3)_2(\mu\text{-}OH)Ni(en)]^{2+} \leftrightarrow [(en)Ni(\mu\text{-}OH)_2Ni(en)]^{2+} + (CH_3)_2S_2. \quad (3c)$$

The calculated changes in the total energies of the products and the reagent in reaction (3c) are ΔE(gas) (3c) = –0.19 eV, ΔE_{solv} (3c) = –0.65 eV. The decrease in the total energies for reaction (3c) obtained both for the gas phase and the aqueous solution allows concluding on the instability of the intermediate compound [(en)(OH)Ni(μ-$SCH_3)_2$(μ-OH)Ni(en)]$^{2+}$.

Total stabilization achieved in the course of reactions (1c)–(3c), which can again provide the formation of the hydroxo-bridged dimer [(en)Ni(μ-$OH)_2$Ni(en)]$^{2+}$ and the disulfide $(CH_3)_2S_2$, is 2.99 eV in the gas phase and 3.19 eV in aqueous solution. These values, in view of the additivity of the energy variations in the coupled reaction stages, coincide with the energy effects calculated for reaction (4).

$$2CH_3SH + H_2O_2 \leftrightarrow (CH_3)_2S_2 + 2H_2O. \quad (4)$$

The performed study of the catalytic systems for selective oxidation of thiols on the basis of binuclear coordination compounds of nickel, palladium, and platinum are indicative of differences in energy effects of separate steps of the catalytic cycle connected with the nature of the metal (Table 2). For the aminate nickel complex, as compared with the similar

palladium analog, substitution of hydroxo bridges by the thiolate ions with the formation of H_2O by reaction (1c) results only in a small decrease in the total energy of the system. At the same time, for the coordination platinum dimer, the total energy is substantially increased in the stage of redox disproportionation [reaction (3b)]. The obtained energy differences are in qualitative agreement with the notions of the theory of hard and soft acids and bases (HSAB) [15]. According to HSAB theory, in reaction (1c), a "hard" acid, Ni ion, is stronger bound with "hard" bases, oxygen atoms of the μ-OH groups in the coordination species $[(en)Ni_2(\mu\text{-}OH)_2Ni(en)]^{2+}$, than with "soft" bases, sulfur atoms of the μ-SCH_3 groups in the product $[(en)Ni(\mu\text{-}SCH_3)_2Ni(en)]^{2+}$. For Pt complexes in reaction (3b), the bonds of a "soft," easily polarizable metal ion are much stronger with "soft" bases, S atoms in the starting compound $[(NH_3)_2\cdot(OH)_2Pt(\mu\text{-}SCH_3)_2Pt(NH_3)_2]^{2+}$, than with "hard" O atoms in the product $[(NH_3)_2Pt(\mu\text{-}OH)_2Pt(NH_3)_2]^{2+}$. 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 recovery of the catalyst. The coordination compounds of Pd ion, which in these properties lies between the isoelectronic Ni and Pt ions, turn out to be most suitable for the reactions of the catalytic cycle under consideration.

A special role in the investigated processes can play the nature of the terminal ligands in the starting compounds of the catalytic cycle. The decrease in both the rigidity of the binuclear core $Ni(\mu\text{-}OH)_2Ni$ favorable for reaction (1c) and the softness of the core $Pt(\mu\text{-}SR)_2Pt$ promoting the rupture of the Pt–S bridge bonds in reaction (3b) can be favored by terminal ligands with optimal combination of the donor-acceptor properties for the given catalytic cycle. In [1], the effectiveness of the catalytic action of ultramicro amounts of the studied binuclear palladium compounds on the process of oxidation of a biologically important endogenic thiol, glutathione, was experimentally proved. The present work opens a prospect for the search of effective nickel and platinum catalysts of selective oxidation of biologically active thiols.

ACKNOWLEDGMENTS

This work was supported by the Russian Foundation for Basic Research (grant no. 14-08-00923).

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