ISSN 1070-3632, Russian Journal of General Chemistry, 2011, Vol. 81, No. 3, pp. 576–585. © Pleiades Publishing, Ltd., 2011.
Original Russian Text © G.V. Baryshnikov, B.F. Minaev, V.A. Minaeva, 2011, published in Zhurnal Obshchei Khimii, 2011, Vol. 81, No. 3, pp. 481–490.

Theoretical Study of the Models of Ca^{2+} and Mg^{2+} Ions Binding by the Methylidene Rhodanine Neutral and Anionic Forms

G. V. Baryshnikov, B. F. Minaev, and V. A. Minaeva

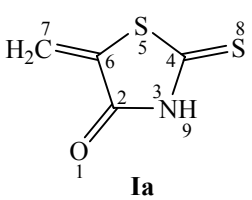
Khmelnitskii Cherkassy National University, ul. Shevchenko 81, Cherkassy, 18031 Ukraine
e-mail: glebchem@rambler.ru

Received April 13, 2010

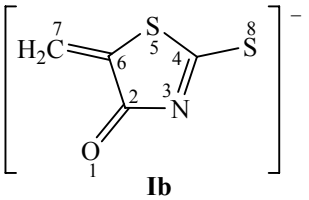
Abstract—The equilibrium geometry and energy parameters of the complexes of Ca^{2+} and Mg^{2+} with 5-methyl-2-thioxotiazolidin-4-one (methylidene rhodanine) and its anion in a 1:1 ratio in different conformations were calculated by the quantum-chemical method with the density functional theory on the level of hybrid functional B3LYP in the basis of atomic orbitals 6-31+G(d). The influence of metal ion size on the number of possible isomeric coordinations was indicated. The principles of stabilization and destabilization of the structures depending on their conformations al structure were described. Based on the calculated equilibrium geometry parameters of the complexes conformations the effect of complexation on the structure of rhodanine ligand was elucidated. In the framework of a polarizable continuum the relative stability of the possible tautomeric forms of methylidene rhodanine in water was investigated. A new structure of the methylidene rhodanine anion distinquished by a specific distribution of negative charge is suggested.

DOI: 10.1134/S1070363211030248

Rhodanines comprise a vast class of non-aromatic five-membered heterocycles, which are widely used in analytical chemistry and medicine. However, much more interesting for medicine are the rhodanine derivatives at the methylene group, the rhodanine ylides. According to the publications, the rhodanine ylides possess antibacterial [1], fungicidal [2–4], antidiabetic [5], anticancer [6] activity, antiviral, anti-inflammatory properties, and a number of other features [7]. Such biological activity is defined by the possibility of rhodanine ylides to block the active centers of certain enzymes like cyclooxygenase, 5-lipoxygenase, aldose reductase, β-lactamase, and others [8], through the formation of stable hydrogen bonds between the enzyme active center and the ketone or thioketone group of the rhodanine ring, leading to blocking metabolic processes. It has been also reported on the possibility of rhodanine ylides to form stable complex with the metal ions included in the composition of the metal-containing proteins and enzymes [9], as well as present in the free state [10–12]. Therefore the study of the mechanism of binding the metal ions by rhodanine ylides is certainly relevant for the understanding of their biological activity. With this aim we have carried out a quantum-chemical study of the possible models of Ca^{2+} and Mg^{2+} binding by neutral and anionic forms of 5-methyl-2-thioxotiazolidin-4-one (methylidene rhodanine), the simplest representative of the rhodanine ylides (**Ia**). A possibility of dissociation of methylidene rhodanine (mRd) at the N–H bond with the formation of methylidene rhodanine anion (**Ib**) has been shown in [9, 13].



Ia



Ib

The Ca^{2+} ions are contained in the composition of calmodulin, the universal calcium sensor of the protein nature, as well as of the other calcium-dependent enzyme systems. It was reported in [9] on the possibility of blocking the calcium-dependent enzymes, namely, the calcium aspartame protease, by methylidene rhodanine. The Mg^{2+} ions being isomorphic to Ca^{2+} ions, were detected in similar sensory systems in the human body, and were contained in the composition of some cofactors and activators of enzymes: the cofactors of replication of nucleic acids,

protein biosynthesis, Mg^{2+}-dependent ATPase, acethylcholinesterase, etc. Taking this fact into account, we predict also a possibility of blocking by methylidene rhodanine of Mg^{2+} ions as isomorphous to the Ca^{2+} ions. In order to understand the mechanism of blocking action of the methylidene rhodanine and its anion, we examined possible models of mono- and bidentate binding of Ca^{2+} and Mg^{2+}. Considering the structural features of the rhodanine ring, we further investigated the structure and stability of the possible methylidene rhodanine tautomers in order to determine the most probable form of existence of methylidene rhodanine in the blood.

Calculation procedure. The initial geometry of the studied conformers was optimized by the semiempirical Hartree–Fock self-consistent field method of molecular orbitals [14] in the PM3 approximation [15]. The final optimization of the possible conformers of the complexes $[Ca(mRd)]^{2+}$, $[Mg(mRd)]^{2+}$, $[Ca(mRd)]^{+}$, and $[Mg(mRd)]^{+}$, the calculation of their total energies and IR absorption spectra were performed in the framework of the density functional theory (DFT) in the vacuum approximation using the hybrid functional B3LYP [16, 17] in the double valence-split basis 6-31+G(d) [18] with the additional polarization of *d*-orbitals and diffuse components. The optimization of the possible tautomeric forms of methylidene rhodanine was performed in the larger triple valence-split basis 6-311+G(d) [19] using a polarized continuum model (solvent water, ε = 78.39) that enables simulating the real conditions of existence of the tautomers in the human body. The 6-311+G(d) basis allows a more accurate accounting for the effects of electron correlation in the molecules of tautomers and an accurate calculation of their total energies. In the calculated IR absorption spectra of the complexes and tautomers, all vibration modes are characterized by positive value of the wave number, indicating that the true minimum of the system is found and the compound is stable. All calculations were performed with the software package GAUSSIAN 03 [20] on a supercomputer PDC at the High Royal Technical School (Stockholm, Sweden).

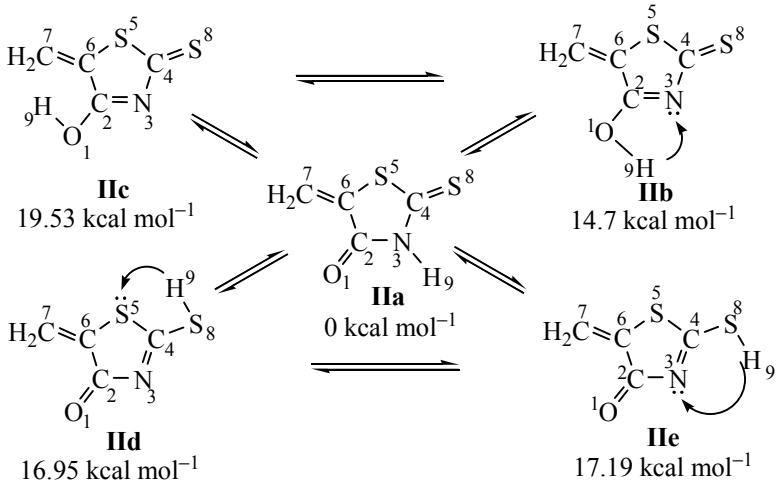
Analysis of the structure and stability of tautomeric forms of methylidene rhodanine. In [9, 12, 21] a possibility was reported of the existence of the yiliden–rhodanine ring in three tautomeric forms: ketone, enol and thioenol, due to a significant polarity of the rhodanine N–H bond and to the possibility of the proton migration to the oxygen or sulfur atoms of the C=O and C=S groups, respectively (**Ia**). Enol and thioenol forms, as we believe, can exist in two equivalent conformations differing by the direction of the S^8–H^9 and O^1–H^9 bonds. This conclusion is confirmed by the data [13].

In order to determine the predominant form of the methylidene rhodanine in blood we calculated the total energies of each tautomer and rotamer. As the model of the solvent we chose water that was the main component of the human blood and tissue.

We found that the most stable form of the rhodanine ring was the ketone form **IIa**. The total energy of the studied tautomers relative to the total energy of the methylidene rhodanine keto form **IIa** are shown in Scheme 1.

The instability of the conformations **IIb**–**IIe** with respect to the conformation **IIa** can be understood by analyzing the energy of the process of transformation

Scheme 1.



of the most stable and predominant in an organism conformation **IIa** into any other conformation. The first step of the transformation is the dissociation of the keto form **IIa** at the N–H bond under the action of water, to form solvated methylidene rhodanine anion and hydroxonium cation. Calculations show that this leads to a significant energy consumption (~37.6 kcal mol^{-1}) that results in the low ability of methylidene rhodanine to dissociation (K_d = 10^{-8} [9, 13]). We believe that under standard conditions the dissociation is defined solely by the probability of the energy distribution.

Although the reaction of the tautomerization proceeds most likely by synchronous mechanism, not in two stages, but in one (breaking N–H bonds with a simultaneous proton transfer), we considered two stages in order to approximately estimate the process energy.

The second step is the formation of the conformers **IIb–IIe** and water from the methylidene rhodanine anion and hydroxonium ion. This reaction is accompanied by the energy release (18.1, 22.9, 19.7, 20.5 kcal mol^{-1} for conformers **IIb**, **IIc**, **IId**, and **IIe**, respectively), however, not compensating the energy consumption in the first stage. Thus, the ketoenol and keto–thioenol transformations are to a great degree endothermic, and under the conditions *in vivo* they are not fully realized that is consistent with the data of [22].

The methylidene rhodanine anions formed at the dissociation can reversibly transform into the tautomer **IIa** with the energy gain, but the formation of tautomers **IIb–IIe** is more probable, taking into account the features of localization of the extra electron in the anion of the methylidene rhodanine **IIIb** (Scheme 2.)

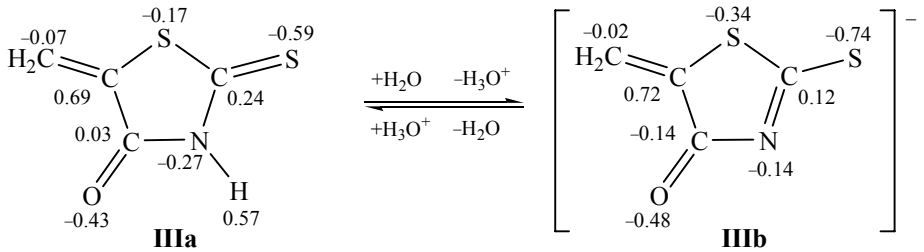
The negative charge in the anion **IIIb** is basically localized evenly on the ketone and thioketone groups, which leads to significant changes in the anion structure compared with the neutral methylidene rhodanine molecule **IIIa**. The electron density is redistributed over the N–C=S fragment with the formation of a new structure N=C–S (Scheme 2). Such a transformation, in our view, greatly stabilizes the resulting anion and favors the formation of conformers **IIb–IIe** due to the interaction with hydroxonium cation. Note that the suggested scheme of the charge distribution in the methylidene rhodanine anion **IIIb** is fundamentally different from the scheme proposed in [13]. This is due to the use of a more precise DFT method in our study.

As seen from Scheme 1, the **IIb** conformer of the methylidene rhodanine enol form is more stable than the **IIc** conformer by 4.83 kcal mol^{-1}. This can be attributed to the fact that the electrostatic attraction between the hydrogen atom H^9 and the N^3 lone electron pair is rather weak, and just this situation provides the energy gain. A similar effect is typical for thioenol form **IIe**, but it is weaker because of the relatively greater distance between the hydrogen atom and the N^3 lone pair compared with the enol form **IIb** (2.626 Å compared with 2.392 Å), and significantly lower polarization of S–H bond compared with the O–H. In this regard, the electrostatic attraction of the hydrogen atom H^9 to the lone electron pair on S^5 is energetically more favorable than the attraction to the lone pair of N^3 atom, and conformer **IId** is by 0.24 kcal mol^{-1} more stable than **IIe**.

For a more detailed understanding of the optimization results of the studied tautomers and to illustrate the changes in the structure of the rhodanine ring in the processes of tautomerization we carried out a com-parative analysis of the obtained geometric parameters (Table 1).

As seen from Table 1, the optimized geometric parameters of the keto form **IIa** (the only possible in the crystalline state) is in good agreement with the X-ray diffraction data [9, 13, 23, 24]. Calculations show that the tautomers **IIa–IIe** have a planar structure (deviation from the ideal plane is no more than 0,07°),

Scheme 2.



IIIa **IIIb**

but we do not exclude the possibility of existence of the tautomeric forms **IIb–IId** in other conformations as a result of free rotation of bonds O^1–H^9 and S^8–H^9 relative to the molecule plane. We also found that in the process of tautomerization the rhodanine ring does not suffer a significant deformation, and all changes in the structure of methylidene rhodanine are caused by the changes in the C=O, C=S, and C–N bond orders.

Thus, based on the values of the total energy of the methylidene rhodanine tautomers we found that the most probable form of existence of methylidene rhodanine is the ketone form. In [9, 13] an experimental evidence was obtained of the higher stability of keto form of rhodanine ring compared with other possible tautomers. This conclusion was also confirmed in several theoretical publications concerning the tautomerism of rhodanine [22, 25] and related compounds [21, 25]. Accounting for this fact, we have studied the models of the Ca^{2+} and Mg^{2+} binding just with the ketone form of the methylidene rhodanine.

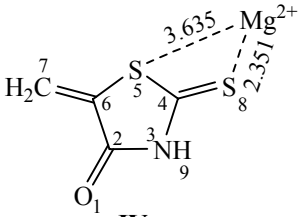
Structure of possible conformations of $[Mg(mRd)]^{2+}$ and $[Ca(mRd)]^{2+}$ complexes. When optimizing the conformations of the complexes of Ca^{2+} and Mg^{2+} with methylidene rhodanine we considered the possibility of coordination of metal ions to each of the sites of the molecule. We predicted and optimized seven stable conformations of the complexes of methylidene rhodanine with Mg^{2+} ions and 4 con-formations with the Ca^{2+} ions. Unfortunately we were not able to optimize and obtain stable conformations of the $[Ca(mRd)]^{2+}$ corresponding to conformers **IVc**, **IVf**, and **IVg** of the $[Mg(mRd)]^{2+}$ complex. In the process of optimizing the conformers of type **IVc** and **IVf** of the complex $[Ca(mRd)]^{2+}$ they transformed into a stable conformer **IVk**. Conformers of the type **IVg** at the optimization transformed to the stable form **IVh**. The attempted optimization of the conformations of both complexes with the coordination of metal ions to the sulfur atom S^5 of the rhodanine a strong deformation of the cyclic molecular structure occurred leading to the cleavage of the ring at the C^4–S^5 bond. This coordination is accompanied by a considerable consumption of energy and therefore is hardly probable.

The relatively smaller number of possible conformations for the Ca^{2+} we attribute to its larger ionic radius compared with the Mg^{2+} ion. This leads to a decrease in the options for the coordination of Ca^{2+} ions around the ligand molecule and decreases the number of stable conformations. At the Mg^{2+} and Ca^{2+} binding the structure of methylidene rhodanine is changed substantially (Table 2), which is caused by a significant redistribution of electron density in the mRd molecule at the binding.

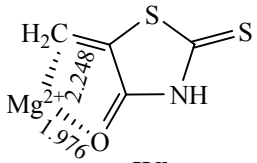
Table 1. Bond lengths (Å) and bond angles (deg) for the ground state of the methylidene rhodanine tautomers calculated by the PCM DFT B3LYP/6-311+G(d)

Bond, angle	**IIb**	**IIc**	**IId**	**IIe**	**IIa**	**IIa** [9, 13]
O^1–C^2	1.311	1.316	1.218	1.218	1.215	1.218
C^2–N^3	1.305	1.305	1.394	1.396	1.389	1.390
N^3–C^4	1.370	1.368	1.297	1.296	1.365	1.349
C^4–S^5	1.787	1.783	1.775	1.778	1.765	1.748
C^4–S^8	1.657	1.657	1.740	1.740	1.653	1.627
S^5–C^6	1.771	1.772	1.773	1.773	1.778	1.751
C^6–C^7	1.337	1.338	1.333	1.333	1.334	1.364
C^2–C^6	1.471	1.478	1.509	1.508	1.493	1.459
O^1–H^9	0.997	0.987	–	–	–	–
S^8–H^9	–	–	1.379	1.379	–	–
N^3–H^9	–	–	–	–	1.031	0.969
$\angle O^1C^2N^3$	123.4	117.5	123.8	123.7	124.1	122.8
$\angle C^2N^3H^9$	–	–	–	–	120.4	120.3
$\angle H^9N^3C^4$	–	–	–	–	120.7	121.5
$\angle N^3C^4S^8$	125.0	125.0	119.8	124.7	125.8	126.4
$\angle S^8C^4S^5$	122.0	122.0	121.9	117.0	124.1	124.0
$\angle S^5C^6C^7$	128.1	126.0	126.5	126.4	126.8	130.3
$\angle C^7C^6C^2$	125.5	127.5	124.4	124.4	123.5	120.2
$\angle C^6C^2O^1$	118.5	125.1	123.8	123.8	126.7	127.2
$\angle C^6C^2N^3$	118.1	117.4	112.4	112.5	109.2	110.0
$\angle C^2N^3C^4$	112.3	112.9	112.2	112.1	119.0	118.2
$\angle N^3C^4S^5$	113.0	113.0	118.2	118.3	110.1	109.6
$\angle C^4S^5C^6$	90.1	90.2	88.1	88.0	92.1	92.7
$\angle S^5C^6C^2$	106.4	106.5	109.1	109.1	109.7	109.5
$\angle C^2O^1H^9$	111.0	116.8	–	–	–	–
$\angle C^4S^8H^9$	–	–	97.5	95.4	–	–

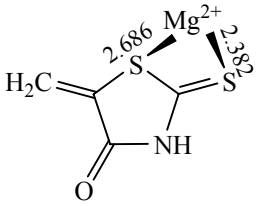
This redistribution is due to the partial compensation of the positive charge of the metal cation by the electron density of the methylidene rhodanine ligand. In this case the ligand itself obtains a partial positive charge, which significantly affects its structure. The optimized conformations of both complexes can be classified according to their spatial structures as the planar and non-planar. The planar conformations



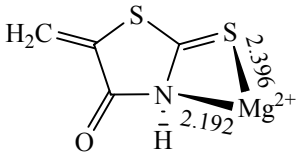
IVa
4.88 kcal mol^{-1}



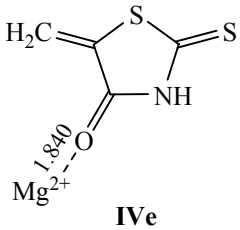
IVb
0 kcal mol^{-1}



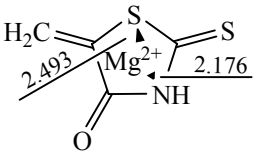
IVc
4.24 kcal mol^{-1}



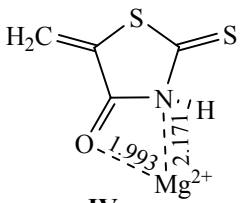
IVd
11.53 kcal mol^{-1}



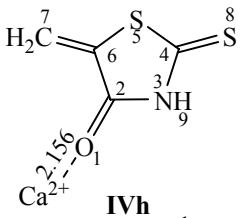
IVe
6.26 kcal mol^{-1}



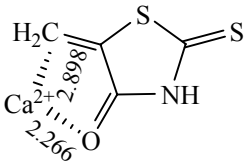
IVf
37.88 kcal mol^{-1}



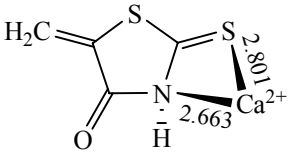
IVg
23.87 kcal mol^{-1}



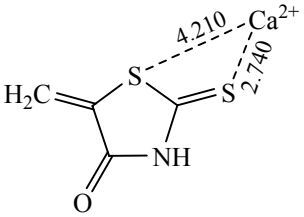
IVh
0 kcal mol^{-1}



IVi
6.12 kcal mol^{-1}



IVj
16.35 kcal mol^{-1}



IVk
7.76 kcal mol^{-1}

comprise **IVa**, **IVe**, and **IVg** structures of the $[Mg(mRd)]^{2+}$ complex and **IVh**, **IVk** structures of the $[Ca(mRd)]^{2+}$ complex. To the non-planar conformation belong structures **IVb–IVd** and **IVf** of the $[Mg(mRd)]^{2+}$ complex and **IVi, IVj** of the $[Ca(mRd)]^{2+}$ complex.

By the multiplicity of the binding of metal ions by methylidene rhodanine, the conformations obtained can be divided into mono- and bidentate. Monodentate conformations comprise the conformers **IVe** and **IVh**, in which the metal atom is coordinated at the methylidene rhodanine carbonyl group. This results in the redistribution of electron density over the Me^{2+}–O^1=C^2 fragment, which greatly increases the C^1=O^2 bond length compared with the free methylidene rhodanine optimized by the same method in the vacuum approximation (1.289 Å and 1.286 Å in complexes $[Mg(mRd)]^{2+}$ and $[Ca(mRd)]^{2+}$, respectively, compared with 1.216 Å in mRd). Note that the monodentate conformation of the $[Ca(mRd)]^{2+}$ complex is the most stable since the planar coordination of Ca^{2+} with the partially negatively charged oxygen atom O^1 of carbonyl group (–0.51 e) (Scheme 2, **IVh**) is the most energetically and sterically advantageous among the possible coordinations, which is consistent with the data of [9].

The planar conformations **IVa** and **IVk** are intermediate between the mono- and bidentate coordinations. In this case, the coordination of metal ion to the methylidene rhodanine occurs through thioketone group C^4=S^8. Therewith there is a long-range interaction of metal ions with the sulfur atom S^5 of the thio fragment of rhodanine ring (Scheme 2, **IVa, Vk**). It should be noted that the long-range interaction is rather weak due to the long distance between the metal cation and the sulfur atom of the thio fragment (Scheme 2), and the coordination of metal ions with the sulfur atom of the C^4=S^8 group is hardly probable taking into account a too low negative charge (–0.08 e) on the sulfur atom of the group. The conformers **IVa** and **IVk** are characterized by a redistribution of electron density over the S^5–C^4=S^8 fragment compared with the free methylidene rhodanine molecule. The C^4=S^8 bond is lengthened (1.744 Å and 1.719 Å in the complexes $[Mg(mRd)]^{2+}$ and $[Ca(mRd)]^{2+}$, respectively, compared with 1.641 Å in mRd), while the S^5–C^4 is shortened (1.728 Å and 1.737 Å in the complexes $[Mg(mRd)]^{2+}$

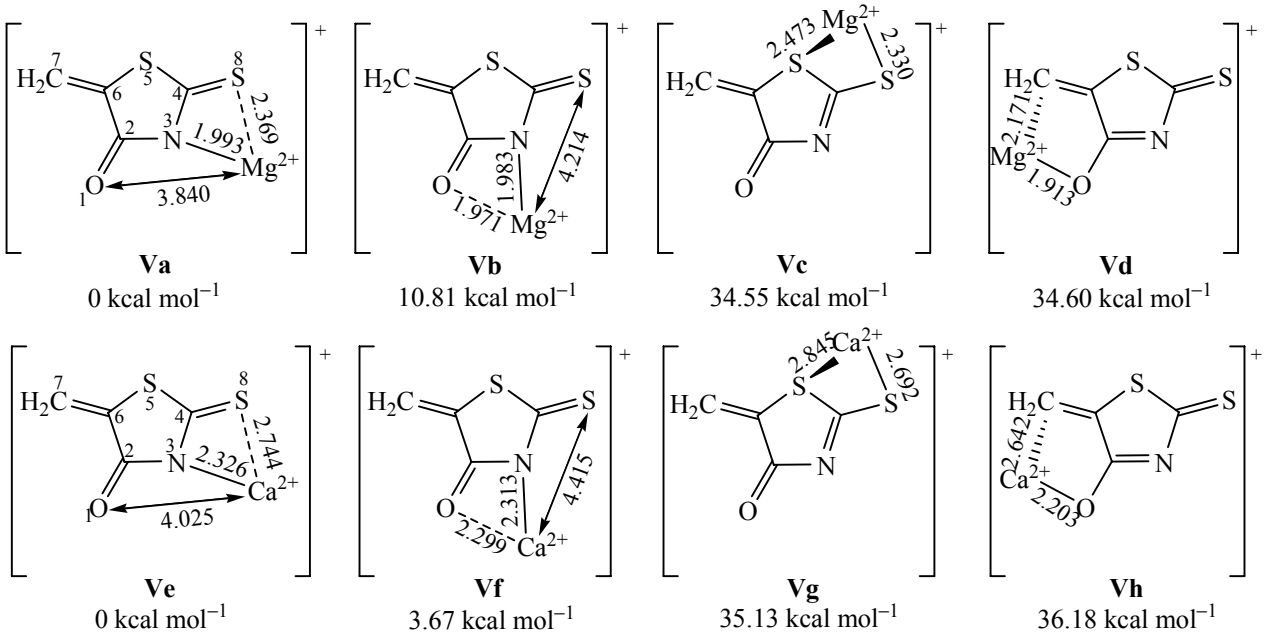
Table 2. Bond lengths (Å) and bond angles (deg) for the ground state of the possible conformations of the $[Ca(mRd)]^{2+}$ and $[Mg(mRd)]^{2+}$ complexes calculated by the DFT B3LYP/6-31+G(d) method in the gas phase

Bond, angle	**IVa**	**IVb**	**IVc**	**IVd**	**IVe**	**IVf**	**IVg**	**IVh**	**IVi**	**IVj**	**IVk**	**Ia**	**Ia** [9, 13]
O^1–C^2	1.193	1.263	1.190	1.188	1.289	1.188	1.261	1.286	1.263	1.196	1.197	1.216	1.218
C^2–N^3	1.462	1.334	1.467	1.540	1.334	1.532	1.449	1.332	1.335	1.496	1.447	1.395	1.390
N^3–C^4	1.325	1.412	1.318	1.446	1.426	1.452	1.523	1.428	1.417	1.424	1.331	1.375	1.349
C^4–S^5	1.728	1.825	1.775	1.698	1.751	1.890	1.761	1.766	1.802	1.713	1.737	1.778	1.748
C^4–S^8	1.744	1.604	1.716	1.701	1.627	1.589	1.604	1.617	1.608	1.688	1.719	1.641	1.627
S^5–C^6	1.797	1.704	1.810	1.794	1.787	1.832	1.802	1.780	1.743	1.792	1.795	1.779	1.751
C^6–C^7	1.340	1.405	1.338	1.345	1.348	1.342	1.358	1.346	1.366	1.343	1.339	1.339	1.364
C^2–C^6	1.487	1.502	1.496	1.478	1.461	1.482	1.434	1.469	1.494	1.479	1.489	1.497	1.459
N^3–H^9	1.022	1.023	1.024	1.034	1.020	1.029	1.034	1.019	1.021	1.028	1.021	1.015	0.969
$\angle O^1C^2N^3$	122.3	126.5	122.4	120.1	121.5	121.2	114.2	122.5	125.9	120.5	122.7	124.2	122.8
$\angle C^2N^3H^9$	118.7	122.6	118.5	104.8	123.2	110.8	110.6	123.5	122.6	108.2	119.2	120.4	120.3
$\angle H^9N^3C^4$	124.4	120.0	123.5	109.5	118.9	114.1	105.1	117.8	119.5	111.9	123.1	119.9	121.5
$\angle N^3C^4S^8$	119.6	127.4	127.7	117.9	123.3	130.9	122.5	123.6	126.0	120.6	120.7	125.9	126.4
$\angle S^8C^4S^5$	127.0	125.0	120.7	127.6	127.9	128.5	129.2	128.6	126.0	125.9	126.8	125.1	124.0
$\angle S^5C^6C^7$	126.0	131.0	126.9	124.7	125.3	125.1	127.2	126.1	129.4	125.4	126.3	127.4	130.3
$\angle C^7C^6C^2$	124.4	118.9	124.8	123.7	125.3	124.8	123.1	124.4	120.9	123.6	124.2	122.6	120.2
$\angle C^6C^2O^1$	129.6	121.1	128.2	131.4	126.6	131.1	131.1	126.0	122.3	130.3	129.1	127.0	127.2
$\angle C^6C^2N^3$	108.1	112.1	109.3	108.4	111.9	107.7	114.0	111.5	111.7	109.2	108.2	108.8	110.0
$\angle C^2N^3C^4$	116.9	117.0	117.6	111.3	117.9	109.9	110.8	118.8	117.7	113.3	117.7	119.8	118.2
$\angle N^3C^4S^5$	113.4	107.6	111.6	114.2	108.8	100.6	108.2	107.8	108.0	113.3	112.5	109.0	109.6
$\angle C^4S^5C^6$	91.9	92.4	92.3	93.6	92.1	89.1	94.2	92.4	92.2	93.2	92.1	92.5	92.7
$\angle S^5C^6C^2$	109.6	110.0	108.1	111.5	109.4	110.0	109.6	109.5	109.7	110.9	109.5	110.0	109.5

and $[Ca(mRd)]^{2+}$, respectively, compared with 1.778 Å in mRd). Thus, the coordination of Ca^{2+} and Mg^{2+} through the S^5 and S^8 atoms of the methylidene rhodanine leads to the formation of the conjugated system S^5...C^4...S^8 in the rhodanine ring, which, as we believe, stabilizes conformers **IVa** and **IVk**, characterized by low total energy of the most stable conformations **IVb** and **IVh**.

The non-planar conformation **IVb–IVd, IVf, IVi**, and **IVj** are certainly bidentate. Their relative stability is affected by two opposing factors: the stronger binding due to the formation of two coordination bonds (energy gain) and the deviation of the metal ions and the atoms of the methylidene rhodanine molecule from the plane (energy loss). The preferential contribution of the first or second factor fully defines the stability of a conformer. Therefore the **IVb** conformation (Scheme 2) of the $[Mg(mRd)]^{2+}$ complex is the most stable, since the factor of the double binding of Mg^{2+} ion with the negatively charged oxygen atoms O^1 (–0.51 e) of carbonyl group and C^7 (–0.66 e) of methylene group prevails considerably over the destabilizing factor of deviation of the metal cation from the plane. In the **IVi** conformer of the $[Ca(mRd)]^{2+}$ complex the contribution of the steric factor is greater and that leads to the energy loss of 6.12 kcal mol^{-1} compared with the planar monodentate conformer **IVh**.

The **IVc** conformer of the $[Mg(mRd)]^{2+}$ complex deserves special attention. In this case, the deviation of the metal cation from the plane (energy loss) and as a



consequence its stronger binding to the methylidene rhodanine molecule (energy gain) results in a net gain in energy of 0.64 kcal mol^{-1} compared to the planar conformation **IVa**. Therefore the **IVc** conformer is the second in stability. Note that the additional stabilization of the **IVc** conformer, like conformers **IVa** and **IVk**, is accomplished by forming a conjugated system S^5...C^4...S^8 capable of binding the metal cation more firmly.

The conformers **IVd, IVf, IVg,** and **IVj** corresponding to bidentate binding of Ca^{2+} and Mg^{2+} through the partially negative nitrogen atom (–0.37 e) are the least stable among other possible conformers. This is due primarily to the deviation of the N–H bond from the molecule plane at binding the metal cation that leads to significant energy loss, and taking into account the activation barrier, this coordination is virtually impossible. However, the coordination of the metal cation via the nitrogen atom is possible in the case of dissociation of methylidene rhodanine keto form at the N–H bond or at its tautomeric transformation. In this case, the coordination of the metal ion through the nitrogen atom is not hindered sterically and can be realized without significant loss in energy.

Structure of the possible conformers of the [Mg(mRd)]$^+$and [Ca(mRd)]$^+$ complexes. The coordination of Ca^{2+} and Mg^{2+} with the deprotonated methylidene rhodanine anion we investigated in view of above results. At the optimization of possible conformations of Ca^{2+} and Mg^{2+} complexes with the methylidene rhodanine anion we started with the already optimized conformers of the complexes $[Mg(mRd)]^{2+}$ and $[Ca(mRd)]^{2+}$, taking into account all possible stable versions of the coordination of metal cations with the mRd molecule. As a result, we found four most stable conformation of each $[Mg(mRd)]^+$ and $[Ca(mRd)]^+$ complexes.

Optimized geometric parameters of the studied conformations and of the isolated methylidene rhodanine anion are given in Table 3.

We found that the main changes in the structure of the anion in the complexes, in comparison with the isolated mRd anion, are associated with the changes in the bond orders upon binding. The values of the bond angles show a weak strain of the methylidene rhodanine cyclic structure.

Taking into account the features of distribution of negative charge in the methylidene rhodanine anion, it is logical to assume that the most probable and energetically favorable is the coordination of the metal ion via the sulfur atoms S^5 (–0.74 e) and S^8 (–0.34 e) and the oxygen atom O of ketone group (–0.48 e). On the nitrogen atom N (–0.14 e) of the rhodanine ring a small negative charge and the lone pair of 2*s* electrons are also localized, therefore the coordination of Ca^{2+} and Mg^{2+} through the nitrogen atom is also quite probable. These assumptions are fully consistent with the results of optimization of the possible conformers of the $[Mg(mRd)]^+$ and $[Ca(mRd)]^+$ complexes and

Table 3. Bond lengths (Å) and bond angles between the bonds (deg) for the ground state of the possible conformations of the $[Ca(mRd)]^+$ and $[Mg(mRd)]^+$ complexes calculated by DFT B3LYP/6-31+G(d) in the gas phase

Bond, angle	**Va**	**Vb**	**Vc**	**Vd**	**Ve**	**Vf**	**Vg**	**Vh**	**Ib**
O^1–C^2	1.209	1.294	1.199	1.293	1.216	1.283	1.204	1.289	1.232
C^2–N^3	1.417	1.347	1.427	1.308	1.407	1.349	1.418	1.310	1.372
N^3–C^4	1.345	1.394	1.266	1.345	1.342	1.383	1.272	1.354	1.319
C^4–S^5	1.735	1.786	1.928	1.934	1.751	1.785	1.913	1.891	1.861
C^4–S^8	1.740	1.632	1.748	1.617	1.726	1.642	1.735	1.624	1.680
S^5–C^6	1.791	1.787	1.784	1.677	1.785	1.781	1.781	1.708	1.756
C^6–C^7	1.338	1.345	1.335	1.425	1.339	1.343	1.335	1.388	1.342
C^2–C^6	1.500	1.461	1.532	1.529	1.500	1.474	1.529	1.528	1.533
$\angle O^1C^2N^3$	123.5	116.8	124.7	125.6	122.9	118.9	124.6	125.8	125.5
$\angle N^3C^4S^8$	119.5	125.3	129.6	131.5	122.3	124.4	128.9	129.6	129.1
$\angle S^8C^4S^5$	124.9	125.4	116.1	118.5	122.5	124.9	117.4	119.3	117.7
$\angle S^5C^6C^7$	126.0	128.7	127.4	130.2	126.6	128.4	127.6	129.4	128.7
$\angle C^7C^6C^2$	124.0	124.1	123.7	120.2	123.9	124.0	123.5	121.9	122.6
$\angle C^6C^2O^1$	126.9	128.3	122.4	118.0	126.3	126.5	122.3	118.0	121.1
$\angle C^6C^2N^3$	109.7	114.8	112.8	116.2	110.8	114.6	113.0	116.0	113.4
$\angle C^2N^3C^4$	114.8	116.3	115.1	114.3	114.4	115.5	115.5	114.1	115.1
$\angle N^3C^4S^5$	115.6	109.3	114.0	110.0	115.3	110.7	113.7	111.1	113.2
$\angle C^4S^5C^6$	89.9	92.4	87.6	89.3	90.0	91.7	88.4	89.5	89.6
$\angle S^5C^6C^2$	110.0	107.3	108.6	109.6	109.5	107.6	108.7	108.7	108.7

their calculated total energies. The most stable conformers of the complexes $[Mg(mRd)]^+$ and $[Ca(mRd)]^+$ are the structures **Va** and **Ve**, respectively. The stability of these conformations is primarily attributable to their planarity and strong bidentate binding of the metal to form a strong ionic bond N^3–Mg^{2+} (Ca^{2+}) and to the stabilizing S^3–Mg^{2+} (Ca^{2+}) coordination interaction. Additional stabilization of conformers **Va** and **Ve** is due to the long-range binding between the metal cation and the O^1 atom of the carbonyl group (Scheme 2). The second by stability are the conformers **Vb** and **Vf** of the $[Mg(mRd)]^+$ and $[Ca(mRd)]^+$ complexes respectively. They, like the conformers **Va** and **Vb**, are consistent with the planar bidentate coordination of metal ions with the methylidene rhodanine anion. The metal cation binding is performed by the formation of a ionic bond N^3–Mg^{2+} (Ca^{2+}) and a coordination bond O–Mg^{2+} (Ca^{2+}). These conformers are relatively unstable because the bond O^1–Mg^{2+} (Ca^{2+}) in the conformations of **Vb** and **Vf** is less polarized than the S^8–Mg^{2+} (Ca^{2+}) bond in the **Va** and **Ve** conformers, in correspondence with the distribution of negative charge in the anion mRd. The lower stability of the structures **Vb** and **Vf** is also a result of relatively weak long-range interaction due to a considerably long distance between the interacting atoms. Note that the instability of **Vb** conformer compared to **Va** is larger than that of **Vf** compared to **Ve**. We think that this is because of the larger contribution of the long-range interaction in the stabilization of conformer **Va** as compared with that in the case of **Ve**, owing to the greater electrostatic attraction to the oxygen atom of the carbonyl group O atom (–0.50 e) of the ion Mg^{2+} compared with the ion Ca^{2+}, given the shorter distance O^1–Mg^{2+} compared with O^1–Ca^{2+}. Thus, the relative weakening of the long-range S^1–Mg^{2+} (Ca^{2+}) interaction in the structures **Vb** and **Vf** compared with the **Va** and **Ve** due to the significant distance between the interacting atoms and the lack of electrostatic attraction of Mg^{2+} and Ca^{2+} to the sulfur atom of the thioketone group S (0 e) destabilizes the structure **Vf** to a greater extent compared with **Vb**.

The conformations **Vc**, **Vd** and **Vg**, **Vh** of the complexes $[Mg(mRd)]^+$ and $[Ca(mRd)]^+$ are equally

unstable relative to conformers **Va** and **Vg**. This is due primarily to the nonplanarity of these conformers that is energetically unfavorable compared with structures **Va** and **Vg**. The stabilization of conformation **Vc, Vd** and **Vg, Vh** due to weak coordination bonds S^5–Mg^{2+} (Ca^{2+}) and C^7–Mg^{2+} (Ca^{2+}) is insignificant, which also causes instability of these structures. Considering the relative values of total energy of the conformers **Vc, Vd, Vg,** and **Vh** it is possible to predict the negligible probability of their formation in the human body.

Thus, the binding of Ca^{2+} and Mg^{2+} ions by the methylidene rhodanine anions occurs to a greater extent in accordance with models **Va** and **Vg**, respectively. However, we also do not exclude the possibility of binding of Ca^{2+} and Mg^{2+} according to structures **Vb** and **Vf**.

Thus, on the basis of our quantum-chemical calculations of the models of binding of Ca^{2+} and Mg^{2+} by the neutral and anionic forms of methylidene rhodanine, we reached the following conclusions:

Methylidene rhodanine in aqueous solution exists mainly as the ketone form, which is due to the low probability of keto-enol and keto-thioenol transformations. The limiting stage of the tautomeric transformation is the heterolytic dissociation of the methylidene rhodanine N–H bond.

The binding of Ca^{2+} and Mg^{2+} by the methylidene rhodanine neutral form can occur in correspondence with the mono- and bidentate schemes with the formation of planar and nonplanar conformations. The most probable model for the binding is bidentate coordination of the metal cation through the oxygen atom of the carbonyl group and the carbon atom of the methylene group.

The binding of ions Ca^{2+} and Mg^{2+} by the methylidene rhodanine anionic form can correspond to the bidentate scheme exclusively. The most probable model for the binding is bidentate coordination of the metal cation through the thioketone group sulfur atom and the nitrogen atom of the rhodanine ring.

ACKNOWLEDGMENTS

The authors express their deep gratitude to the head of the Laboratory of Theoretical Chemistry, Royal Technical High School (Stockholm, Sweden), Professor Hans Ogren for the opportunity to use resources of the PDC supercomputer.

REFERENCES

1. Bryk, R., Gold, B., Venugopal, A., Singh, J., Sam,y R., Pupek, K., Cao, H., Popescu, C., Gurney, M., Hotha, S., Cherian, J., Rhee, K., Ly, L., Converse, P.J., Ehrt, S., Vandal, O., Jiang, X., Schneider, J., Lin, G., and Nathan, C., *Cell Host & Microbe*, 2008, vol. 3, no. 3, p. 137.
2. Sortino, M., Delgado, P., Juárez, S., Quiroga, J., Abonía, R., Insuasty, B., Nogueras, M., Rodero, L., Garibotto, F.M., Enrize, R.D., and Zacchinoa, S.A., *Bioorg. & Med. Chem*., 2007, vol. 15, no. 1, pp. 484–494.
3. Orchard, M.G., Neuss, J.C., Galley, C.M.S., Carr, A., Porter, D.W., Smith, P., Scopes, D.I.C., Haydon, D., Vousden, K., Stubberfield, C.R., Young, K., and Page, M., *Bioorg. & Med. Chem. Lett.,* 2004, vol. 14, no. 15, pp. 3975–3978.
4. Dolezel, J., Hirsova, P., Opletalova, V., Dohnal, J., Marcela, V., Kunes, J., and Jampilek, J., *Molecules,* 2009, vol. 14, no. 10, pp. 4197–4212.
5. Lesyk, R.B., Zimenkovsky, B.S., and Troc'ko, N.Y., *Ukrainica Bioorganica Acta*, 2004, vol. 1, pp. 29–38.
6. Russell, A.J., Westwood, I.M., Crawford, M.H.J., Robinson, J., Kawamura, A., Redfield, C., Laurieri, N., Lowe, E.D., Davies, S.G., and Sim, E., *Bioorg. and Med. Chem*., 2009, vol. 17, no. 2, pp. 905–918.
7. Verma, A. and Saraf, S.K., *Europp. J. Med. Chem*., 2008, vol. 43, pp. 897–905.
8. Irvine, M.W., Patrick, G.L., Kewney, J., Hastings, S.F., and MacKenzie, S.J., *Bioorg. & Med. Chem. Lett*., 2008, vol. 18, no. 6, pp. 2032–2037.
9. Loncharich, R.J., Nissen, J.S., and Boyd, D.B*., Struct. Chem*., 1996, vol. 7, no. 1, pp. 37–49.
10. Fabretti, A.C., Franchini, G., Peyronel, G., and Ferrari, M., *Polyhedron*, 1982, vol. 1, nos. 7–8, pp. 633–635.
11. Zaki, M.T.M., Abdel-Rahman, R.M., and El-Sayed, A.Y., *Anal. Chim. Acta*, 1995, vol. 307, pp. 127–138.
12. Tang, E., Yang, G., and Yin, J., *Spectrochimica Acta, Part A,* 2003, vol. 59, no. 3, pp. 651–656.
13. Boyd, D.B., *J. Mol. Struct.: Theochem*, 1997, vol. 401, no. 3, pp. 227–234.
14. Dewar, M.J.S. and Theil, W., *J. Am. Chem. Soc*., 1977, vol. 99, no. 15, pp. 4899–4907.
15. Stewart, J.J.P., *J. Comp. Chem*., 1989, vol. 10, no. 2, pp. 209–220.
16. Becke, A.D., *J. Chem. Phys*., 1993, vol. 98, no. 7, pp. 5648–5652.
17. Lee, C., Yang, W., and Parr, R.G., *Phys. Rev., B*, 1988, vol. 37, no. 2, pp. 785–789.
18. Francl, M.M., Petro, W.J., Hehre, W.J., Binkley, J.S., Gordon, M.S., DeFrees, D.J., and Pople, J.A., *J. Chem. Phys*., 1982, vol. 77, no. 7, pp. 3654–3665.

19. Krishnan, R., Binkley, J.S., Seeger, R., and Pople, J.A., *J. Chem. Phys*., 1980, vol. 72, no. 1, pp. 650–654.
20. Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Montgomeri, J.A Jr., Vreven, T., Kudin, K.N., Burant, J.C., Millam, J.M., Iyengar, S.S, Tomasi, J., Barone, V., Mennucci, B., Cossi, M., Scalmani, G, Rega, N., Petersson, G.A., Nakatsuji, H., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Klene, M., Li, X., Knox, J.E., Hratchian, H.P., Cross, J.B., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazyev, O., Austin, A.J., Cammi, R., Pomelli, C., Ochterski, J.W., Ayala, P.Y., Morokuma, K., Voth, G.A., Salvador, P., Dannenberg, J.J., Zakrzewski, V.G., Dapprich, S., Daniels, A.D., Strain, M.C., Farkas, O., Malick, D.K., Rabuck, A.D., Raghavachari, K., Foresman, J.B., Ortiz, J.V., Cui, Q., Baboul, A.G., Clifford, S., Cioslowski, J., Stefanov, B.B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Martin, R.L., Fox, D.J., Keith, T., Al-Laham, M.A., Peng, C.Y., Nanayakkara, A., Challacombe, M., Gill, P.M.W., Johnson, B., Chen, W., Wong, M.W., Gonzalez, C., and Pople, J.A. *Gaussian 03,* Revision C.02, Gaussian, Inc., Wallingford, CT, 2004.
21. Ray, J., Panja, N., Nandi, P.K., Martin, J.J., and Jones, W.E., *J. Mol. Struct*., 2008, vol. 874, nos. 1–3, pp. 121–127.
22. Al-Sehemi, A.G. and El-Gogary, T.M., *J. Mol. Struct.: Theochem*, 2009, vol. 907, nos. 1–3, pp. 66–73.
23. Shahwar, D., Tahir, M.N., Raza, M.A., Iqbal, B., and Naz, S*., Acta Cryst*., 2009, vol. 65, no. 11, p. o2637.
24. Barreiro, E., Casas, J.S., Couce, M.D., Sánchez, A., Sordo, J., Varela, J.M., and Vázquez-López, E.M., *Cryst. Growth & Design*., 2007, vol. 7, no. 10, pp. 1964–1973.
25. Tahmassebi, D., *J. Mol. Struct.: Theochem*., 2003, vol. 638, nos. 1–3, pp. 11–20.