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Computational Studies of Structural, Electronic, Spectroscopic, and Thermodynamic Properties of Methylmercury-Amino Acid Complexes and Their Se Analogues

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Quantum chemical calculations have been carried out to study the structural, electronic, spectroscopic, and thermodynamic properties of five methylmercury-amino acid complexes and their selenium analogues. The structural properties of methylmercury-amino acids are very similar to their Se analogues except for those properties that are directly related to the Se atom which has a larger covalent radius. Characteristic stretching frequencies are observed for Hg−S/Se and Hg−C bonds. Electronic properties of both methylmercury-amino acids and their Se analogues are different from each other, with the S complexes showing stronger electrostatic attractions which leads to stronger bonds to mercury. The methylmercury complexes with selenoamino complexes, however, are thermodynamically more favorable (ΔG of formation from suitable model reactants) than those of the corresponding amino acid complexes. This can be traced to the lower stability of the reactant selenoamino acids. Such different stability and favorability of formation might be responsible for the different physiological activity in biological systems such as the Hg−Se antagonism.

1. Introduction

Methylmercury (MeHg) biomagnifies through the food chain and is a neurotoxin to aquatic organisms and humans.[1−4] The toxicity of the MeHg stems from the "soft" Lewis acid nature of the species, which can effectively bind with "soft" Lewis bases, including the sulfhydryl group of any amino acid. For instance, MeHg-L-cysteinate is thought to be the main MeHg species that is transported by the amino acid transport system to cross the blood-brain barrier.[5−8] Despite their high thermodynamic stabilities (stability constants in the order of 10^{16}), MeHg can rapidly exchange among various sulfhydryl ligands by bimolecular nucleophilic substitution or via proton-assisted dissociation, which could potentially change the mobility and toxicity of the MeHg species.[9]

Sulfur and selenium belong to the same group in the periodic table. Both of them show similar chemical characteristics. However, owing to the decreasing electronegativity or increasing metallic behavior down the group, the properties change accordingly. For example, both of them form alkali metal derivatives which contain X^{2-} ions, but owing to the higher metallic character of selenium, the stability of Se^{2-} is lower. The formation constants of sulfur and selenium complexes, however, depend on the relative stability of reactants and products. The formation constant of a reaction can be determined from a set of reactants and products at a given set of reaction conditions (e.g., temperature, solvent, etc.).

Because of the chemical similarity, selenium can be incorporated in place of sulfur in amino acids, or attached to the sulfur atoms of cysteine residues as selenotrisulfide. In this way, it can interact with mercury, but the extent to which such interactions contribute to the well-documented Hg−Se antagonism in many animals including humans[10] remains unclear. One commonly held view attributes the Hg−Se antagonism to the higher Hg−Se binding affinity compared to that of Hg−S in biomolecules. This hypothesis goes back to the work of Sugiura et al.[11] who investigated the binding affinity of Hg to selenium and sulfur by proton magnetic resonance for MeHg cysteine and selenocysteine complexes

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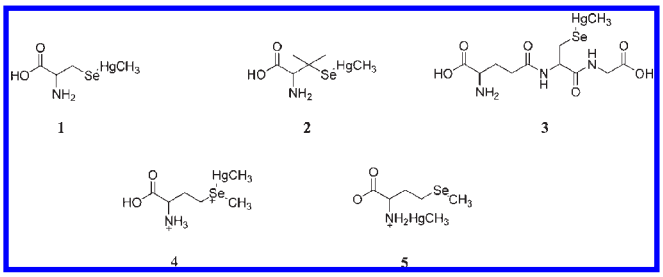

Figure 1. MeHg complexes with seleno amino acids. (1) Methylmercury-L-selenocysteinate, (2) methylmercury-D,L-selenopenicillaminate, (3) methylmercury-L-selenoglutathionate, (4) methylmercury-L-selenomethionate (via Hg−Se bonding; low pH), and (5) methylmercury-L-selenomethionate (via Hg−N bonding; high pH).

and reported smaller mercury-proton coupling constants in the Hg−Se compounds than those in the corresponding Hg−S compounds. This was supported by Carty et al.[12] who reported that the Hg−Se bond length in the MeHg selenocysteine complex is marginally smaller than the expected value based on the Hg−S bond length and the respective covalent radii. On the other hand, Peterson et al.,[13] Cremer et al.,[14] and Filatov and Cremer[15] performed high-level theoretical calculations on the stability of Hg-chalcogenides and showed that Hg−S bonds are stronger than the corresponding Hg−Se bonds. These findings are in contradiction with those of Sugiura[11] and Carty.[12] Therefore, it is imperative to study the interactions of MeHg with amino and selenoamino acids to resolve the conflict about the stability of Hg−S/Se bonds and understand the toxicity and antagonism phenomena.

Aiming to better understand the toxicity of MeHg and the antagonism between Hg and Se, we have recently synthesized four new MeHg-selenoamino acid complexes and characterized them experimentally.[16] In the current paper, we report results of a detailed computational study on the structural, electronic, spectroscopic, and thermodynamic properties of these MeHg-amino acids, as well as the previously reported MeHg-cysteine, and their Se analogues and examine their differences, with a particular interest in the comparative bonding strength between Hg−Se and Hg−S and favorability of the formation of complexes with MeHg. Specifically, we have considered four amino acids, that is, cysteine, penicillamine, glutathione, and methionine, and their selenium analogues. The complexes that will be studied are MeHg-L-cysteinate (MeHgCys), MeHg-L-selenocysteinate (MeHgSeCys), MeHg-D,L-penicillaminate (MeHgPen), MeHg-D,L-selenopenicillaminate (MeHgSePen), MeHg-L-gluthionate (MeHgGlu), MeHg-L-selenoglutathionate (MeHgSeGlu), MeHg-L-methionate via a Hg−S bond (MeHgMeth_lowpH), MeHg-L-selenomethioninate via a Hg−Se bond (MeHgSeMeth_lowpH), MeHg-L-methioninate via a Hg−N bond (MeHgMeth_highpH), and MeHg-L-selenomethioninate via a Hg−N bond (MeHgSeMeth_highpH). Figure 1 shows the structures of the MeHg complexes with selenoamino acids. The sulfur analogues have similar structures.

2. Computational Procedure

Unless otherwise noted, all calculations were performed with the Gaussian-03 (g03)[17] program suite and in the framework of density-functional theory (DFT).[18] The three-parameter functional developed by Becke, which combines the Becke[19] gradient-corrected hybrid exchange functional that contains part of the exact Hartree−Fock exchange and the Lee−Yang−Parr[20] correlation functional, has been employed (denoted as B3LYP). In addition, some of the calculations are performed with the Perdew gradient-corrected exchange and correlation functional (denoted as PBE).[21]

Three types of basis sets for different atoms have been used throughout the calculations. The Stuttgart-Dresden basis set (SDD)[22] for the Hg atom, 6-311+G(p) for S and Se atoms and 6-31+G(p) basis for H, C, N, and O are used. To treat the (scalar) relativistic effects resulting from the presence of the heavy Hg atom, the SDD basis set for the Hg atom is used with the corresponding relativistic effective core potential.

Geometry optimizations and other electronic and spectroscopic calculations for the systems of interest are carried out in the gas phase. The geometries of some compounds are also optimized in solution (solvent water) using the Conductor Polarizable Continuum Model (CPCM)[23] as implemented in the Gaussian-03 package. Solvation free energies in water are calculated for all the systems of interest. No symmetry constraints were imposed during the optimizations. Gas-phase frequency calculations are performed on every optimized structure to verify the nature of the stationary point. We have, however, not found any imaginary frequency for any of the systems of interest, proving that true minima were obtained in each case.

In simulations such as the current ones, four principal levels of approximation have to be chosen.[24] These concern (i) the model chemistry (basis set convergence and, in the case of DFT, choice of exchange-correlation (XC) functional), (ii) a solvation model, (iii) an approximate relativistic method, and (iv) a realistic chemical model for experimental situations that are too complex to model in their entirety. Regarding the model chemistry, we have tested the convergence of the basis sets and functionals for our systems. Using a relatively small basis of 6-31+G(p) for S and Se, we have obtained reasonable structural properties. But the free energies of formation for most of the complexes are hugely underestimated, especially for the selenoamino acid complexes; see the Supporting Information, Table S1. On the other hand, employing the 6-311+G(p) basis sets for H, C, N, and O leads to insignificant changes in structural properties and energetics. For MeHgCys and MeHg-SeCys, we have tested a pure GGA functional (PBE).[21] The calculated properties and energetic values (Supporting Information, Table S2) are very much similar to the B3LYP calculations. To also test the influence of the relativistic approximation, we have used the Priroda code,[25,26] where relativity is treated by a scalar four-component all-electron relativistic method. By using the PBE functional and a triple-ζ basis[27] with

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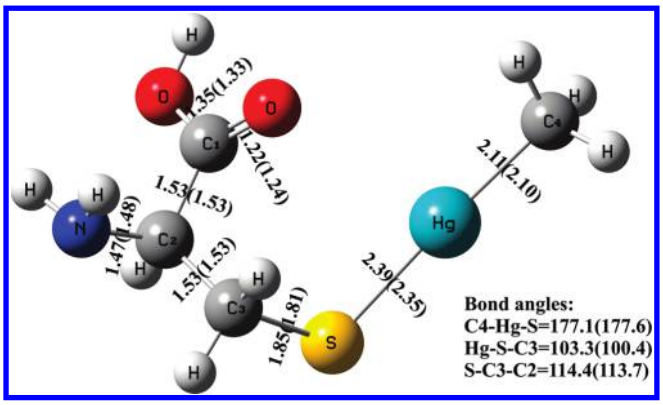

Figure 2. Bond distances (shown between two atoms) and key bond angles (lower right corner) of the optimized structure of MeHgCys along with the corresponding experimental parameters[37] (in parentheses). The units of bond length and angles are Å and degree (deg), respectively.

Table 1. Selected Bond Lengths and Bond Angles for MeHgSeCys[a]

	C−Hg	Hg−Se	Se−C	C−Hg−Se	C−Se−Hg
calculation	2.13	2.52	2.00	178.0	99.9
experiment[12]	2.10	2.47 ± 4	1.99 ± 3	177 ± 2	98 ± 8

[a] Bond length and angle are in Å and degree (deg), respectively.

one polarization function we have again found very similar structural and energetic values for MeHgCys and MeHgSeCys (Supporting Information, Table S3). To analyze the electronic properties and to perform a bond decomposition analysis,[28,29] we have employed the ADF code.[30−35] Both geometry optimizations (with the PBE functional[21]) and single point energy calculations (with the B3LYP functional[19,20]) on g03 optimized geometry were performed. Unless otherwise noted, the ADF results presented are from PBE-optimized calculations.

3. Results and Discussions

a. Structural Parameters and Solvation. We have started our study with the optimization of MeHgCys in the gas phase and compared the structural parameters with the available experimental results. MeHgCys is the most studied MeHg-amino acid complex because of its toxicological relevance. The calculated and experimental structural parameters are shown in Figure 2. From the figure it is clear that structural parameters from our calculations are in good agreement with their corresponding experimental values.[36,37] Similar agreement is found between the calculated and experimental structural properties of MeHgSeCys (Table 1), the only experimentally studied MeHg-selenoamino acid complex[12] until our recent work.[16] Such agreement between calculations and experiments lays the foundation to extend our computational protocol to study other, similar MeHg complexes including MeHgPen, MeHgGlu, and MeHg methionine and their selenium analogues.

Key structural parameters of all complexes other than those of cysteine are listed in Table 2. In the MeHgPen, two hydrogen atoms attached to the carbon atom which is bonded to the sulfur atom are replaced by methyl groups. The optimized structural parameters of MeHgPen are very close to those of MeHgCys. We have obtained C−Hg, S−Hg and C−S bond lengths of 2.12, 2.42, and 1.88 Å, respectively, which are very close to the corresponding values of MeHgCys (Figure 1). Similarly, the bond angle of C−Hg−S we have obtained is 174.9°, which too is very close to the corresponding value of MeHgCys (177.1°). However, the C−S−Hg bond angle in the MeHgPen is 108.4° which is 5° higher than the corresponding value of MeHgCys, because of the steric effects as the large (compared to hydrogen) methyl groups push the MeHg part away. In the MeHgSePen, the structural parameters show a similar pattern as in MeHgPen, that is, because of the larger groups attached to the carbon atom, the C−Se−Hg angle is wider compared to its analogue MeHgSeCys.

The structure of MeHgGlu is different from that of the corresponding complexes of cysteine and penicillamine. The amino and carboxylic acid groups are attached differently in the glutathione complexes. However, the MeHg part is similar to the corresponding section of the cysteine and penicillamine complexes. The structural parameters related to the MeHg part of MeHgGlu are similar to the corresponding values of MeHgCys. The bond lengths we obtained for C−Hg, S−Hg, and C−S are 2.11, 2.43, and 1.85 Å, respectively. The bond angle of C−S−Hg we found is 106.6°, which is slightly higher than in MeHgCys but comparable to MeHgPen. However, the C−Hg−S bond angle is around 3° lower than in MeHgCys. The large tail groups (amino and carboxylic) might induce this steric effect and hence the lower bond angle. Other than the bond length elongation of the metal−ligand bond length on replacing sulfur by selenium like in the cysteine and penicillamine complexes, there are no significant structural modifications or changes in the MeHgSeGlu. The structural parameters related to the carboxylic and amino groups are very similar to those of the cysteine and penicillamine complexes.

The binding of MeHg to methionine depends on the chemical environment, that is, the pH of the medium. At low pH (pH = 1), the MeHg group binds to the protonated sulfur atom similar to the cases of the other three amino acids. However, at higher pH of the medium (pH = 8), the MeHg group binds to the amino group of the methionine.[9,38,39] We have optimized both complexes at their local energy minima. In the MeHgMeth_lowpH, there are two positive charges on the nitrogen and sulfur atoms. Therefore, the bond distances between Hg and either N or S are longer than what we have obtained

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Table 2. Bond Lengths (Å) and Bond Angles (deg) of MeHg Complexes with Penicillamine, Glutathione, and Methionine and Their Se Analogues

	bond length				bond angle		
complexes	C−Hg	Hg−S/Se	S/Se−C	Hg−N	C−Hg−S/Se/N	Hg−S/Se/N−C	S/Se/N−C−C
MeHgPen	2.12	2.42	1.88		174.9	108.4	113.2
MeHgSePen	2.13	2.53	2.04		175.2	106.3	113.3
MeHgGlu	2.11	2.43	1.85		174.2	106.6	115.5
MeHgSeGlu	2.12	2.54	2.00		174.0	104.1	115.7
MeHgMeth_lowpH	2.12	2.61	1.86		177.8	107.9	113.6
MeHgSeMeth_lowpH	2.12	2.70	2.00		177.7	105.7	114.0
MeHgMeth_highpH[a]	2.10			2.08	177.2	120.9	109.0
MeHgSeMeth_highpH[a]	2.10			2.09	177.1	120.8	111.6
MeHgMeth_highpH[b]	2.17			2.34	149.2	113.5	112.2
MeHgSeMeth_highpH[b]	2.18			2.35	148.3	113.3	112.2

[a] Charge-compensated with H atoms, see the text. [b] For the optimized structure in water (CPCM optimization).

for those parameters in the other amino acid complexes. For example, the C−N distance in MeHgCys is 2.47 Å and the same distance in MeHgMeth_lowpH is 2.53 Å. The S−Hg bond distance, we have obtained 2.61 Å, is around 0.18 Å longer than the corresponding bond distances in the other three amino acid complexes. The C−S bond distances (both terminal and chain), however, do not change significantly. An electron releasing methyl group attached to the S counterbalanced the positive charge and hence the bond distances are found to be changed insignificantly. The C−Hg−S bond angle is 177.8°, very similar to that in the MeHg-cysteine complex. The methyl group attached to the sulfur atom induces some steric interactions and hence widens the C−S−Hg angle to 108.0°. The structural parameters for MeHgSeMeth_lowpH are very similar to those of the sulfur analogue, with the only exception that the bond distances to the selenium atom are lengthened.

We experienced difficulties in optimizing the MeHg-Meth_highpH structure. At higher pH, the amino and carboxylic acid groups developed positive and negative charges, respectively, which are difficult to stabilize in the gas phase. In the gas phase calculations, instead of two separate charges, we have found that the hydrogen atoms attached to the amino groups move toward the carboxylic group and neutralize both the amino and carboxylic groups. We then optimized these complexes in water using the CPCM[23] continuum solvation model. Using the CPCM model, we have obtained an optimized structure with two separated charges on the carboxylic acid and amino groups. The optimized structural parameters, however, are not consistent with the experimental data determined by X-ray crystallography.[40,41] The calculated Hg−N distance is longer (by 0.27 Å) than the experimentally reported value. The calculated N−Hg−C bond angle (149.2°) is about 27° smaller than the experimental value (see Table 2). Although we have obtained an optimized structure in the solution, from this observation, we can fairly assume that this single molecule complex is nowhere near to the true picture of a crystal. The experimental work was done on the three-dimensional (3D) solid-state structure of the complexes.

In the 3D network of amino acids or MeHg-amino acid complexes in the crystal structure, there are some intermolecular interactions which hold them in the 3D frame. These interactions are even stronger for molecules that have two functional groups with opposite charge, as the charge of the molecule is counterbalanced by these intermolecular interactions. We assume that this is the case for MeHg-methionine which has a strong charge. To obtain meaningful structural parameters of a charged system in the solid state, we would need to consider a 3D periodic model which is beyond the scope of the present study. Alternatively, one could model a system by compensating for the charge on the molecule by adding or removing small atoms such as hydrogen so that the structure of the system of interest changes insignificantly. To address the latter hypothesis, we have modeled MeHg-methionine at high pH by adding one hydrogen atom to the carboxylic group and removing one hydrogen atom from the amino group. The optimized Hg−N bond distance and N−Hg−C bond angle (see Table 2) are 2.08 Å and 177.2°, respectively, which are in agreement with the corresponding experimental values (2.08 Å and 177.0°). The corresponding bond lengths and angles for charge-compensated MeHgSeMeth_highpH are very similar to those for MeHgMeth_highpH, and are in agreement with our recent experimental results.[16]

Having found the structure of MeHg-methionine in water, we are prompted to test the optimization of other charge-neutral amino acid complexes in water. In particular, we have reoptimized the cysteine complexes in water. The optimized structural parameters, however, are not consistent with the gas phase calculations but rather consistent with the MeHg methionine at high pH complexes (in water). These calculations suggest that there are some strong interactions between the amino acid complexes and the solvent (water) molecules. We hope to study these in more detail in the future, using explicit solvent molecules as well as continuum solvation. However, to get an idea how the solvent interacts with MeHg-amino acid complexes, we have calculated solvation free energies in water of the gas-phase optimized structures, using g03.

Calculated solvation energies of all the complexes can be found in the Supporting Information, Table S4. The data confirms that a polar solvent such as water interacts strongly with the MeHg-amino acid complexes. The solvation free energies for sulfur complexes (Supporting Information, Table S4) are higher than those of the

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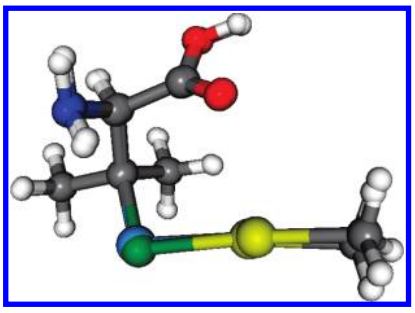

Figure 3. Superimposed structures of MeHgPen and MeHgSePen. White, red, blue, ash, yellow, light blue, and green balls are for hydrogen, oxygen, nitrogen, carbon, mercury, sulfur, and selenium atoms, respectively.

corresponding selenium complexes. The solvation free energy for the glutathione complexes is higher than for the cysteine and penicillamine complexes. Glutathione has more amino and carboxylic groups which can be expected to be more partially charged and hence result in a higher solvation free energy. The solvation free energy for the methionine complexes is much higher (by almost an order of magnitude) than those of the rest of the complexes. This can be understood from the fact that the methionine complexes are charged (+2) molecules. Such strongly charged molecules can easily be stabilized in a polar solvent like water, resulting in very high solvation free energy. Indeed, to first order, the solvation free energy of ions is proportional to the charge squared.

Overall, our structural data suggest that, as far as structural properties are concerned, there is not much difference in the MeHg complexes between amino acids and their corresponding Se analogues other than bond lengthening related to Se. A superimposed structure of MeHgPen and its selenium analogue is shown in Figure 3. The close structural similarity between the two complexes is clearly evident from the figure.

b. Vibrational Frequencies. IR spectra (calculated in the gas phase) of all compounds show characteristic frequencies at ~1700 cm^{-1} for C=O, 3400 cm^{-1} for N−H stretching, and 3600 cm^{-1} for OH stretching. The calculated stretching frequencies of Hg−S for MeHgCys, MeHgPen, MeHgGlu, MeHgMeth_lowpH are 318, 312, 312, and 302 cm^{-1}, respectively, which are in good agreement with the experimental values for MeHgCys (325 cm^{-1})[37] and MeHgPen (322 cm^{-1}).[41] On the other hand, the calculated stretching frequencies of Hg−Se for MeHgSeCys, MeHgSePen, MeHgSeGlu, and MeHgSeMeth_lowpH are 215, 245, 199, and 243 cm^{-1}, respectively. Again these are in good agreement with the corresponding experimental values for MeHgSeMe (218 cm^{-1}),[42] MeHgSeBu^t (199 cm^{-1}),[43] and MeHgSeCys (214 to 218 cm^{-1}).[42] The calculated Hg−C stretching frequencies are 509, 509, 511, 482, and 526 cm^{-1} for MeHgCys, MeHgPen, MeHgGlu, MeHgMeth_lowpH, and MeHgMeth_highpH, respectively, and are 500, 501, 505, 482, and 525 cm^{-1} for their corresponding Se analogues, respectively. These Hg−C frequencies are comparable to those for MeHgSeCys (536 cm^{-1}),[42] MeHgSeBu^t(534 cm^{-1}),[43] MeHgSeCH$_2$Ph(COOH) (542 cm^{-1}),[44] and MeHgCys (538 cm^{-1}).[37] We have obtained the Hg−N stretching frequencies for MeHgMeth_highpH and MeHgSeMeth_highpH at 688 and 716 cm^{-1}, respectively, which are in agreement with the previously reported values of 400 to 700 cm^{-1}.[41] Both Hg−C and Hg−N frequencies are in agreement with the corresponding values of our recent experimental study on these systems.[16]

c. Electronic Structure. Table 3 shows the calculated Mulliken and Hirshfeld charge distributions on the Hg and S/Se atoms along with the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies of MeHg complexes of amino and selenoamino acids.

The Mulliken charge distributions on the Hg and S/Se atoms are in contradiction with the Hirshfeld charge distributions. The Mulliken charge distribution shows a higher charge on the Hg and Se atom in selenoamino acid complexes than those on Hg and S in the amino acid complexes whereas the Hirshfeld charge distribution shows the opposite. Given the known deficiencies in the Mulliken charge analysis and the electronegativity difference between S and Se atoms, the Hirshfeld charge distribution is more acceptable. The charges on Hg in amino acid complexes are slightly higher than those on Hg in selenoamino acid complexes. The charges on S are more negative than those on Se. These observations can be understood from the fact that the S atom is more electronegative than the Se atom. The more electronegative element tends to bind with the metal via an electron transfer (electron accepting-donating) process. In the process, the metal atom donates some fraction of an electron and becomes positively charged, whereas the electronegative element accepts this charge and becomes negatively charged. The less electronegative element has a lower tendency to accept electronic charge and, therefore, the metal and the electronegative element become less positively and negatively charged, respectively. We have obtained charges on Hg and S/Se that are in accordance with this qualitative expectation. Such findings of higher charge distribution on Hg and S would point to stronger ionic interactions, leading to an overall higher complex stability. However, the (Mayer) bond order we have obtained for Hg−S in MeHgCys (0.99) is only a little bit smaller than that for Hg−Se (1.01) in MeHgSeCys and would point to stronger covalent interactions between Hg and Se. The findings of higher bond orders for Hg−Se are in agreement with the experimental report of Sugiura et. al.[11] The relative stabilities of the various complexes are discussed further below (in the Energetics section). The positions of the HOMO and the LUMO of selenoamino acid complexes are marginally shifted compared to those of amino acid complexes to more positive and more negative, respectively. Hence, the HOMO−LUMO gap is narrowed in the selenium complexes (by around 0.25 eV).

The electron densities of the HOMO and LUMO of MeHgCys are shown in Figure 4. The HOMO of MeHgCys is located on the Hg and S atoms, and on the Se atom for its Se analogue. The LUMOs for both complexes are on the carboxylic groups. Looking further

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Table 3. Mulliken and Hirshfeld Charges Distributions (in electron) on the Hg, S/Se, and N Atoms and HOMO and LUMO Energy (in eV) of MeHg Amino Acid and Selenoamino Acid Complexes

	Gaussion-03 calculations					ADF calculations					
	Mulliken charge			energy		Hirshfeld charge			Mulliken charge		
complexes	Hg	S/Se	N	HOMO	LUMO	Hg	S/Se	N	Hg	S/Se	N
MeHgCys	0.51	−0.10		−6.17	−0.89	0.37	−0.19		0.46	−0.26	
MeHgSeCys	0.61	−0.27		−5.94	−0.96	0.35	−0.16		0.49	−0.31	
MeHgPen	0.61	−0.40		−6.16	−0.84	0.37	−0.15		0.45	−0.23	
MeHgSePen	0.63	−0.32		−5.89	−0.88	0.35	−0.12		0.49	−0.27	
MeHgGlu	0.63	−0.13		−6.34	−1.00	0.39	−0.17		0.46	−0.24	
MeHgSeGlu	0.72	−0.32		−6.09	−1.05	0.37	−0.14		0.49	−0.31	
MeHgMeth_lowpH	0.51	0.92	0.55	−14.25	−8.32	0.49	0.17		0.49	0.29	
MeHgSeMeth_lowpH	0.67	0.36	0.55	−13.94	−8.33	0.47	0.25		0.51	0.27	
MeHgMeth_highpH	0.84	0.09		−6.03	−1.22	0.45	−0.01	−0.24	0.71	0.03	−0.74
MeHgSeMeth_highpH	0.84	0.06		−5.75	−1.23	0.45	0.02	−0.25	0.71	−0.03	−0.74

into the contributions to the HOMO and LUMO, mainly the *p* orbitals of the S and Se atoms constitute the HOMO and the *p* orbitals of both the C and O atoms of the carboxylic group constitute the LUMO. The replacement of an S atom by a Se atom does not change the pattern of the electronic characteristics. The electronic properties do change systematically as one could expect from the same group elements, as we have found the shifting of HOMO and LUMO from S to Se containing complexes.

d. Energetics. Although the structural calculations suggested only minor differences in the MeHg complexes with amino and selenoamino acids, electronic calculations, however, showed a change in properties from S to Se complexes, see above. Such differences might be related to differences in the stability between the two types of complexes. Different stabilities under similar reaction conditions could explain the various bonding modes under different physiological conditions.

There are two aspects of the energetics in the current context where MeHg amino acid and seleno amino acid complexes are concerned. First, these are the binding energies of the complexes and second, the free energy of formation of such complexes at the given reaction conditions.

The binding energy of the complexes can be calculated from the energy difference between the complexes and their constituent elements. Although Baerends et al.[45] suggested using the true ground state of the constituent atoms for an accurate estimation of the binding energy, we, however, are more interested in the relative stability between amino and selenoamino acids complexes, rather than the absolute values. Moreover, we have already shown that the only differences in the structures between S and Se containing complexes concern the bonding related to the S and Se atoms. Therefore, any difference in the binding energy between two complexes will be due to the bonding of S and Se. The S and Se atoms bind to the C and Hg atoms in the complexes. The binding energy difference between S−C and Se−C bonds is 10.41 kcal/bond (S−C being stronger) as we have calculated for $(CH_3)_2S$ and $(CH_3)_2Se$ at the same level of theory. Therefore, any difference in the binding energy between the two complexes above 10.41 kcal/mol will be mainly due to Hg−S and Hg−Se bonding. The calculated binding energy (with respect to the atomic fragments) differences between S and Se containing amino acid complexes (with S containing complexes being more stable) for cysteine, penicillamine, glutathione, and methionine (low pH) are 15.93, 17.01, 16.33, and 17.13 kcal/mol, respectively. After subtracting the value of 10.41 kcal/mol, the energy difference between S and Se containing complexes for all four amino acids is around 5.5 to 6.5 kcal/mol. In other words, we can say that the Hg−S bond is stronger by 5.5 to 6.5 kcal/mol than the Hg−Se bond and hence the amino acids complexes are more stable than selenoamino acids complexes. These findings are in agreement with our experimental observations[46] that the decomposition times of synthetic MeHg-selenoamino acids are lower (less than half) than those of the corresponding MeHg-amino acid complexes. Sugiura et al.[11] studied the MeHg complexes with cysteine and selenocysteine and linked the higher binding affinity of Hg−Se (compare to Hg−S) with a smaller mercury-proton spin−spin coupling constant which is in contradiction to our results. The calculated (using ZORA ADF[47,48]) spin−orbit contribution to the bonding energy is slightly higher for Se than S complexes (1.97 kcal/mol higher for MeHgSeCys than MeHgCys). This contribution, however, is not sufficient to offset the much higher electrostatic interactions for S complexes (17.40 kcal/mol higher for MeHgCys than MeHgSeCys, as per the ADF analysis).

Although we have considered so far that the binding energy differences between S and Se containing complexes are only due to the S(Se)−C and S(Se)−Hg bonds, the other structural features might play a role too. Therefore, we have calculated the Hg−S and Hg−Se bond decomposition energies (ΔE) from the following reactions:

$$\mathrm{MeHgCys} \rightarrow \mathrm{MeHg}^{+} + \mathrm{Cysteine}^{-}$$

$$\Delta E_1 = E_{\mathrm{MeHg}} + E_{\mathrm{Cysteine}} - E_{\mathrm{MeHgCys}}$$

$$\mathrm{MeHgSeCys} \rightarrow \mathrm{MeHg}^{+} + \mathrm{Secysteine}^{-}$$

$$\Delta E_2 = E_{\mathrm{MeHg}} + E_{\mathrm{Secysteine}} - E_{\mathrm{MeHgSeCys}}$$

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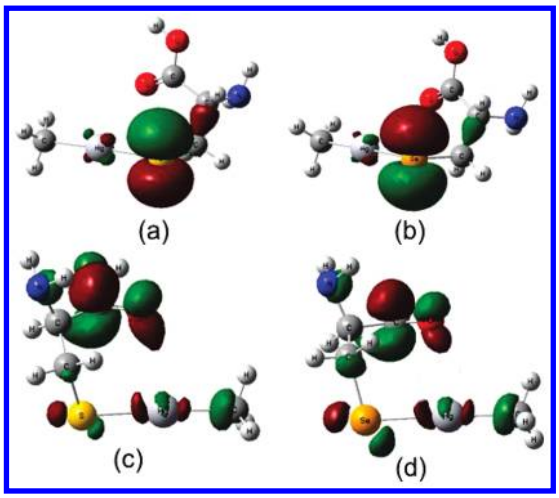

Figure 4. Isodensity surface (0.05/Å^3) of the HOMO (a, b) and LUMO (c, d) of MeHgCys (a, c) and MeHgSeCys (b, d).

where E stands for the respective energy. The calculated value for the difference $\Delta E_1 - \Delta E_2$ is 2.67 kcal/mol, which means 2.67 kcal/mol more energy is required to break the Hg−S bond than the Hg−Se bond. In other words, the Hg−S bond is stronger than Hg−Se by 2.67 kcal/mol. Considering neutral fragments instead of ionic ones on the right-hand side of the above two reactions leads to the same conclusion (with a 0.30 kcal/mol smaller $\Delta E_1 - \Delta E_2$ value). Peterson et al.,[13] Cremer et al.,[14] and Filatov and Cremer[15] performed very high level theoretical calculations on various binary Hg compounds. In their studies, they have found that HgS is more stable than HgSe in both singlet and triplet states. Our findings regarding the relative stability of amino and selenoamino acid complexes are, in fact, in good agreement with their studies.

To further understand the nature of bonding between Hg and S/Se, a Ziegler−Morokuma bond decomposition analysis[28,29,49] has been carried out using the ionic fragments $MeHg^+$ and (seleno)cysteine$^-$. In this scheme, the bond formation energy is separated into two terms: Strain energy plus interaction energy. The strain energy is the energy required for the change in the fragments from their equilibrium geometries to those they will have in the complexes. The interaction energy between two fragments can be further decomposed into three terms: (i) the repulsion between the two fragments according to the Pauli principle, (ii) electrostatic interactions between these two, and (iii) the stabilizing orbital interactions. The decomposed energies between the two fragments of MeHgCys and MeHgSeCys are shown in Table 4.

The favorable electrostatic interactions alone can offset the unfavorable Pauli repulsions and strain energies for both complexes. They provide a larger stabilizing contribution than the orbital interactions, which suggests a greater ionic character (rather than covalent character) in the Hg−S/Se bonding for both complexes. The higher electrostatic energy for the S complex is the result of higher charges on Hg and S atoms as we found in the Hirshfeld charge analysis. The orbital interactions energy for the Se complex is slightly higher than that for the S complex, which indicates slightly more covalent character in the Hg−Se bonding. A more covalent character of a bond arises when the energy difference between interacting atomic orbitals for that bond is getting smaller. Thus, a higher covalent character in Hg−Se can be attributed to the fact that the energy difference between the interacting atomic orbitals of Hg (−6.73 eV for the 6s orbital) and Se (−6.51 eV for the 4p orbitals) is 0.22 eV, which is lower than those of Hg and S (−6.97 eV for the 3p orbitals), 0.24 eV. These small superiority of orbital interactions might be responsible for the slightly higher bond order for Hg−Se in MeHgSeCys.

Table 4. Bond Decomposition Energies (in kcal/mol) between MeHg and (Seleno)cysteine in MeHgCys and MeHgSeCys

energy	MeHgCys	MeHgSeCys
strain energy	7.34	6.92
Pauli repulsions	129.81	126.03
electrostatic interactions	−244.26	−236.68
orbital interactions	−81.49	−82.40

The second energetic factors are the free energies (thermodynamic favorability) for the formation of such complexes. To investigate these thermodynamic factors, we have set up model reactions and calculated the reaction free energies of all complexes by calculating the reaction thermochemistry.

First, we have considered a model system having a bonding between MeHg and S/Se atoms. We have calculated the free energy of formation for MeHgSMe and MeHgSeMe from MeHgOH. We have chosen MeHgOH as one of the reactants keeping in mind that the same compound is used in the synthesis of the current systems of interest. In these model calculations we have optimized all the species involved in those reactions in the gas phase and in water. All calculated energy values are listed in Table 5.

It is clear from Table 5 that all energetic data for the Se complexes are significantly more negative than those of the S complexes. The free energies of formation in water (ΔG_{water}) are higher (by 2−4 kcal/mol) for both S and Se complexes than those in the gas phase (ΔG_{gas}). To the best of our knowledge, there is no experimentally determined data on these reactions. However, Dyrssen and Wedborg[50] indirectly calculated the stability constant (log K) for MeHgSH of 14.5. We therefore decided to calculate the formation constant of MeHgSH from the following reaction:

$$MeHgOH + H_2S \rightarrow MeHgSH + H_2O$$

and obtained a log K value of 13.8, which is in reasonable agreement with their value. This gives further confidence in our computational protocol.

ΔE^s_{water} is the change of the (electronic) energy estimated from single point energy calculations in water using the gas phase optimized geometries. The purpose of this particular calculation is to get an idea about the accuracy of the free energy of formation in water from single point energy calculations by comparing ΔE^s_{water} to the free energy obtained from fully optimized structures,

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Table 5. Free Energy of Formation in Gas Phase (ΔG_{gas}) and in Water (ΔG_{water}) for MeHgSMe and MeHgSeMe[a]

reactions	ΔG_{gas}	ΔG_{water}	ΔE^{s}_{water}	Log K_{water}
$MeHgOH + Me_2S \rightarrow MeHgSMe + MeOH$	−8.36	−6.56	−5.66	4.81
$MeHgOH + Me_2Se \rightarrow MeHgSMe + MeOH$	−14.78	−11.38	−10.58	8.34

[a] ΔE^{s}_{water} is the electronic energy change for single point energy calculations in water of gas phase optimized structures. The units are in kcal/mol. The formation constants (log K_{water}) refer to the solution calculations in water.

Table 6. Free Energy of Formation (ΔG_{gas}) in the Gas Phase[a]

reactions		ΔG_{gas}	ΔE^{s}_{water}
$MeHgOH + Cysteine \rightarrow MeHgCys + H_2O$	(1)	−18.14	−16.77
$MeHgOH + SeCysteine \rightarrow MeHgSeCys + H_2O$	(2)	−22.22	−18.99
$MeHgOH + Penicillamine \rightarrow MeHgPen + H_2O$	(3)	−14.78	−12.12
$MeHgOH + SePenicillamine \rightarrow MeHgSePen + H_2O$	(4)	−22.57	−19.92
$MeHgOH + Glutathione \rightarrow MeHgGlu + H_2O$	(5)	−18.30	−14.61
$MeHgOH + SeGlutathione \rightarrow MeHgSeGlu + H_2O$	(6)	−22.66	−18.81
$MeHg^+ + H^+{}_3O + Methionine \rightarrow MeHgMeth_{lowpH} + H_2O$	(7)	−29.90	7.62
$MeHg^+ + H^+{}_3O + SeMethionine \rightarrow MeHgSeMeth_{lowpH} + H_2O$	(8)	−32.08	7.02
$MeHgOH + Methionine \rightarrow MeHgMeth_{highpH} + H_2O$	(9)	1.76	6.70
$MeHgOH + SeMethionine \rightarrow MeHgSeMeth_{highpH} + H_2O$	(10)	1.32	2.76

[a] ΔE^{s}_{water} is the change in the electronic energy for single point energy calculations in water on the gas-phase optimized geometries. The units are in kcal/mol.

ΔG_{water}. Looking at the numbers in Table 5, it is clear that the ΔE^{s}_{water} values are about 1 kcal/mol higher than the ΔG_{water} values for both S and Se complexes. Assuming, as a hypothesis, the transferability of this result to the amino and selenoamino acid complexes, we will get some idea about the free energy of formation in water without having structures that were optimized in water.

As mentioned above, we have to select a chemically meaningful model for complicated situations, in this case the in vivo thermodynamic favorability of the different Hg complexes. We have chosen the complex formation reactions starting from MeHgOH and the respective free (seleno) amino acids. The free energy of formation and change of electronic energy of all MeHg complexes with amino and selenoamino acids are summarized in Table 6.

For every single set of reactions, the free energies of formation for the selenoamino acids are lower than those for the corresponding amino acid complexes. In other words, the formation of MeHg complexes with a selenoamino acid are more favorable than those of (sulfur containing) amino acids. To the best of our knowledge, there are no experimentally determined thermodynamic parameters available in the literature for any of these complexes. But there is at least one study[51] on MeHg complexes with inorganic anions (SCN and SeCN) where bonding between Hg and S/Se is reported in those complexes. The reported values of the formation constants for Se complexes are higher than for the corresponding S complexes. This result is in agreement with our findings.

Although the stabilities of the S complexes are higher, the free energies of formation of Se complexes are more favorable. It is known that the acid strengths of the hydrides of Se and S are very much different from each other. The pK_a value for H_2Se is 3.80, whereas that for H_2S is 8.25. Because of the difference in the acid strength, the sulfur containing amino acids remain protonated at physiological conditions but selenoamino acids become dissociated. In our calculations, it is also found that selenoamino acids are much less stable than their corresponding amino acids. These less stable selenoamino acids then readily react with MeHg and hence have a more negative free energy of formation. Therefore, it can be assumed that the antagonism and related other physiological activities that occur in the human body and other living mammals might be due to the lower stability of selenoamino acids, which readily react with MeHg, but obviously not due to a stronger Hg−Se bonding over Hg−S.

The first six reactions in Table 6 have negative ΔG values, which means that all six reactions are thermodynamically favorable. The ΔG values for reactions 7 and

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8 are also negative, which implies the thermodynamic stability of the product at least in the gas phase. However, we have found that reactions 9 and 10 are thermodynamically unfavorable. If we look at the third column of Table 6, we notice that the ΔE^{s}_{water} values are of similar order as ΔG_{gas} for reactions 1 to 6, though in each case somewhat less negative. Recalling the hypothesis for MeHgSH and MeHgSeH (Table 5), we can assume that the free energy of reaction in water will follow the same trend as ΔE^{s}_{water} (even if the absolute values are somewhat different). To put it differently, the formation of MeHg complexes with amino and selenoamino acids are thermodynamically favorable in aqueous media and sulfur complexes are more stable.

Although we have found that the ΔG values for reactions 7 and 8 are negative in the gas phase, the ΔE^{s}_{water} values for those two reactions are positive. The reason for this observation is that the solvation energies for the two charged reactants are higher than those of the charged product. This can be related to the different size of the reactants and products:[52] To first order, the solvation energy is proportional to the charge squared and inversely proportional to the distance between charge and polarizable medium. Thus, the small reactants, particularly $MeHg^{+}$ and H_3O^{+}, are disproportionally strongly stabilized relative to the products. As a result, the net energy changes are positive for the model reactions chosen. However, this does not necessarily depict the true picture as to whether these reactions are thermodynamically favorable or not in an experimental setting. To identify the true picture, a complete set of reactants and product (with counterions) need to be considered and optimized in the aqueous media (possibly even including explicit solvation), which is beyond the scope of current computational and theoretical facilities. We are, however, able to firmly establish the fact that the formation of Se complexes is thermodynamically more favorable than that of the S counterparts.

For reactions 9 and 10, we have obtained both ΔG_{gas} and ΔE^{s}_{water} values which are positive. We have discussed in the preceding section that these complexes are model complexes. Although we have found reasonable intramolecular structural parameters for these model compounds, the intermolecular structural parameters are not well matched with the experimental observations as was discussed in our previous paper.[16] This suggests that the addition and removal of a hydrogen atom is not sufficient to counterbalance the intermolecular interactions. Therefore, we have not found these reactions to be thermodynamically favorable.

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4. Conclusion

We have carried out a systematic quantum-chemical study of five biological relevant MeHg-amino acid complexes and their Se analogues. Because of the larger covalent radius of Se (compared to S), the structural parameters directly related to the Se atom are slightly modified in the Se analogues, whereas any other structural parameters are very similar. We have calculated the characteristic IR frequency for Hg−S, Hg−Se, and Hg−C. The HOMO and LUMO for all charge neutral species are situated on S/Se and the carboxylic group, respectively. The HOMO and LUMO are slightly shifted to positive and negative directions for the selenium species, respectively, and hence we find narrower HOMO−LUMO gaps for the Se complexes. Overall, from the structural and electronic characterization, MeHg-amino acid complexes are slightly different from their selenium analogues. From an energetic point of view, the stability (bond strength) and free energy of formation (thermodynamic favorability) of the complexes are opposite to each other. The stabilities of the amino acid complexes are higher than those of the selenoamino acid complexes whereas the formation of selenoamino acid complexes is more favorable than that of amino acids complexes. The higher stabilities of the sulfur complexes are due to the stronger electrostatic interactions between Hg and S, which arise from the higher electronegativity of the S atom. On the other hand, the thermodynamic favorability of the selenium complexes is due to the much lower stability of the (reactant) selenoamino acids. Thus, the lower stability of the selenoamino acids and the resulting thermodynamic favorability of the complex formation with mercury species could explain the well documented antagonism in animals and humans.

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Supporting Information Available: Full citation for reference 17; Tables S1 to S4 showing energetics obtained with smaller basis sets (Table S1), results for Priroda-PBE calculations (Tables S2, S3), and solvation energies (Table S4). This material is available free of charge via the Internet at http://pubs.acs.org.