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Gas-Phase Interaction of Calcium (Ca^{2+}) with Seleno Derivatives of Uracil

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Abstract: The structures and relative stabilities of the complexes between Ca^{2+} and 2-selenouracil, 4-selenouracil, and 2,4-diselenouracil have been investigated through the use of B3LYP/6−311++G(3df,2p)//B3LYP/6−31+G(d,p) density functional theory (DFT) calculations. In those systems where both types of basic centers, a carbonyl or a selenocarbonyl group, are present, Ca^{2+} association with the oxygen is favored. For 2,4-diselenouracil the nitrogen atom at position 3 is the most basic site toward Ca^{2+} attachment followed by heteroatoms attached to positions 4 and 2. Although the enolic and selenol forms of selenouracils should not be observed in the gas phase, the corresponding Ca^{2+} complexes are the most stable ones. More importantly, all the activation barriers associated with the corresponding tautomeric processes are lower than the entrance channel, and therefore not only these complexes should be observed but also they should be the dominant species in the gas phase. Also, Ca^{2+} association has a clear catalytic effect on these tautomerization processes, whose activation barriers decrease between 10 and 15 kcal mol^{-1}.

Introduction

Genetic information storage, gene expression, and catalysis are some of the important biological functions in living systems in which nucleic acids participate.[1–4] Watson and Crick base pairing and π stacking allow the formation of stable duplexes that are central to genetic information storage, transcription, and replication. The replacement of the oxygen on the nucleobases with sulfur[5,6] has provided insight into DNA duplex stability, recognition, and replication at the atomic level.[7,8] Recent studies on these sulfur modifications have revealed enhanced base-pairing selectivity[9]and replication efficiency and fidelity, especially with the 2-thiothymidine.[10] What would be the implications if oxygen is replaced by selenium? As selenium is in the same group, but is much larger than oxygen, the replacement of O by Se will provide insight into base pairing selectivity. Recently, Salon et al.[11,12] have synthesized some Se derivatives of the DNA nucleobases and studied their crystal structures, their thermostabilities, and the impact of their incorporation into oligonucleotides. In addition, specific pyrimidines in natural tRNAs have been derivatized by incorporation of Se on the nucleobases. The functionality of Se is not well understood although it was suggested that Se might be involved in the tRNA anticodon.[13–15] In view of the increased interest in nucleobase seleno derivatives, our attention has been directed to the exploration of the reactivity changes caused by replacing oxygen by selenium in small biochemical systems. In this respect we have recently found, for instance, that the reactivity of selenourea with respect to Ca^{2+} mimics that of thiourea but presents significant dissimilarities with respect to urea.[16] The aim of this paper is to investigate the Se derivatives of uracil, namely, 2-selenouracil (2SeU), 4-selenouracil (4SeU), and 2,4-diselenouarcil (24dSeU), in order to contribute to the understanding of its involvement in biological compounds when interacting with Ca^{2+}. It is well-known that Ca^{2+} takes part in a wide range of biological processes, including the regulation of muscle contraction, transduction, glycolysis, gluconeogenesis, ion transport, and the stabilization of interprotein complexes.[17,18] This moti-

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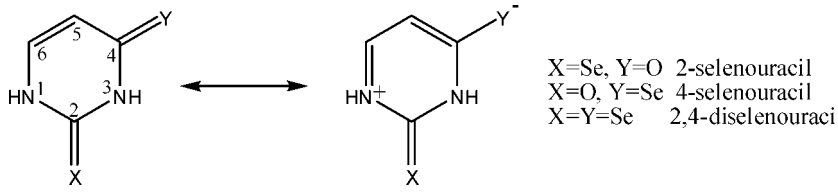
Scheme 1



vated a growing interest in the study of the interaction of biochemical systems with this metal dication, both from the experimental and the theoretical viewpoints.[19–31]

Computational Details

Geometries were optimized by using density functional theory with the hybrid functional B3LYP[32,33] as implemented in the Gaussian 03 suite of programs,[34] in conjunction with the 6−31+G(d,p) basis set. Harmonic vibrational frequencies were computed (at the same level) to classify stationary points as local minima or transition structures (TS) and to estimate their zero-point vibrational energy (ZPVE) corrections (scaled by 0.986).[35] In order to obtain more reliable energies for the local minima, single point energies have been evaluated by using the same functional combined with the 6−311++G(3df,2p) basis set at B3LYP/6−31+G(d,p) geometries.

The corresponding Ca^{2+} binding energies, D_0, were evaluated by subtracting from the energy of the most stable complex the energy of the neutral and that of Ca^{2+}, after including the corresponding ZPE corrections. The basis set superposition error (BSSE) was not included in the calculation of D_0, because as it has been previously reported that for DFT and DFT/HF hybrid methods this error is usually small, when the basis set expansion is sufficiently flexible.[36]

The bonding characteristics were analyzed by means of the atoms in molecules (AIM) theory.[37,38] For this purpose we have located the relevant bond critical points (BCP) and evaluated the electron density for each of them, by means of the AIMPAC series of programs.[39] With the aim of further exploring the nature of calcium bonding in these complexes, we turn here to the usefulness of the topological analysis of the electron localization function (ELF), a direct measure of the local Pauli principle. The reader is referred to several reviews on this powerful technique of bonding analysis.[40–42] As the ELF is a scalar function, the analysis of its gradient field can be carried out in order to locate its attractors (the local maxima) and the corresponding basins. To carry out these calculations the TopMod suite of programs has been used.[43]

Results and Discussion

Structure and Stability of Selenouracils−Ca^{2+} Adducts. Since selenouracils may exist in several tautomeric forms, the first question to be addressed, in order to rationalize their intrinsic reactivity is which tautomers are predominant in the gas phase. Previous studies have shown,[44,45] that oxo-seleno and diseleno are the most stable forms and that the energy barriers connecting them with other tautomers are very high, and therefore the oxo-seleno and diseleno forms will be the only ones present in the gas phase under normal conditions.

As expected the heteroatoms bonded to carbons at positions 2 and 4 are the most favorable sites for electrophilic attack, as was previously found for uracil and its thio-derivatives.[46–51] These interactions lead to complexes **1** and **4,** as presented in Figure 1. Another possibility is π bonding, where the metal lies perpendicular to the plane of the molecule, as it has been found[47,52,53] for the thio-analogues. However, for selenouracils all attempts to locate a conventional π-complex failed, as they collapsed to structure **7** where the metal interacts with the lone pair of the nitrogen at position 3. Conversely, structure **7** has never been observed before in uracil−M^{2+} complexes (where M = Be, Mg, Ca, Cu)[48,52,53] where the topology of the electron density favors a π interaction. This is not surprising if we consider that oxygen is much more electronegative than selenium, so when oxygen is replaced by selenium there is an accumulation of electron density on the N3 lone pair. To this first effect, a second important one is added. Selenium is much more volumi-

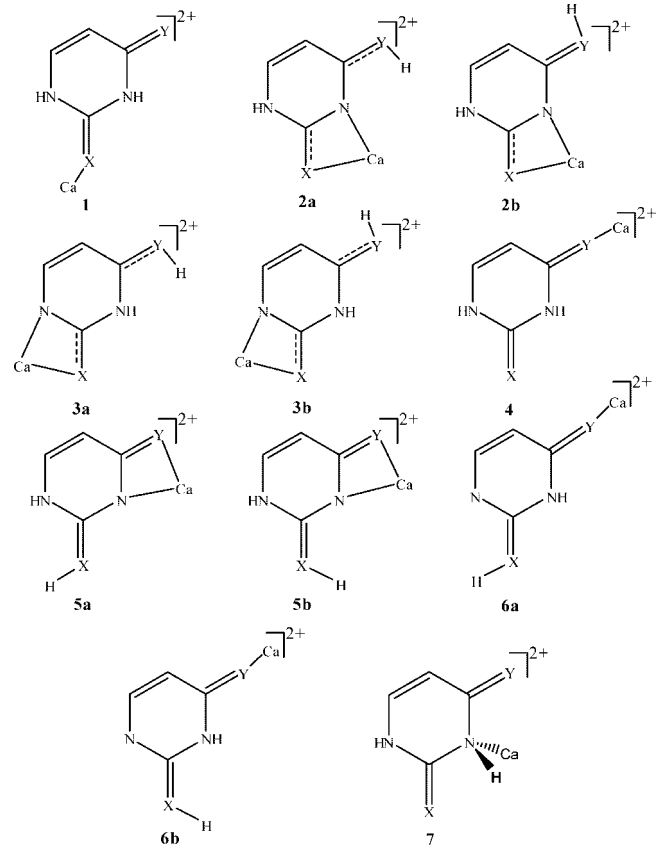


Figure 1. Schematic representation of different tautomers of selenouracil−Ca^{2+} complexes in all possible conformers.

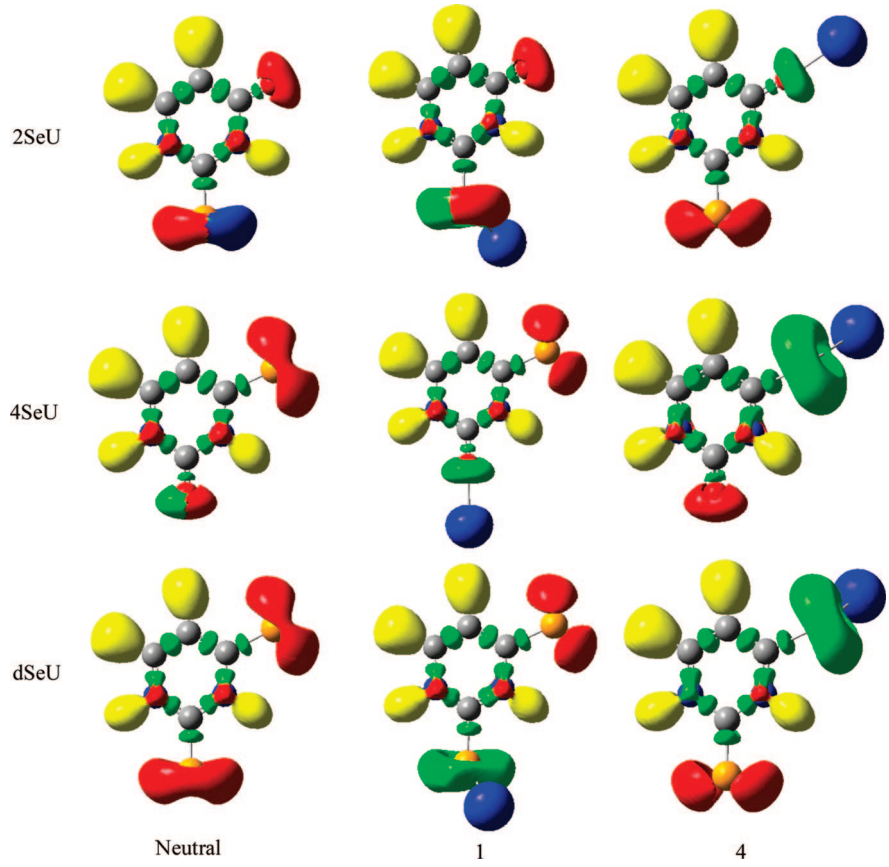


Figure 2. Schematic representation of attractors localized in neutral 2- and 4-selenouracils and their associated Ca^{2+} complexes **1** and **4** at ELF = 0.8. Yellow lobes correspond to V(C,H) or V(N,H) basins, and red lobes correspond to V(O) or V(Se) basins associated with O or Se lone pairs. Green lobes correspond to V(C,C), V(C,O), V(C,N), and V(C,Se) basins. Blue lobes correspond to the metal core, C(Ca).

nous and much more polarizable than oxygen, as clearly reflected in the ELF description of the neutral compounds (see Figure 2). Therefore, the interaction with the metal dication is much more favorable when the molecule contains only seleno groups (24dSeU). In fact, in the case of diselenouracil, complex **7** is more stable than the complex in which the metal interacts with the heteroatom at position 4 by approximately 2 kcal/mol (see Table 1). The strong polarization of both Se atoms is mirrored in the existence of BCPs between them and Ca^{2+} (see Figure 3). Conversely, the presence of a carbonyl group in the molecule significantly decreases the stability of structure **7** which, for 2-selenouracil, becomes 21.7 kcal mol^{-1} less stable than the complex in which Ca^{2+} binds the carbonyl group.

Table 1 also shows that for 2,4-diselenouracil, complex **4** is 5.9 kcal mol^{-1} more stable than complex **1**. A similar behavior was reported for the protonation[46] and the Cu^{+} association[47] of uracil and 2,4-dithiouracil, reflecting the contribution of zwitterionic resonance structures (see Scheme 1) which accumulate negative charge on the heteroatom at position 4. It is worth noting that this resonance structure also locates a positive charge at N1, explaining why π-type complexes evolve to an N3 attached species (complex **7**) but never to a N1 attached structure.

This explanation in terms of the contribution of the zwiterionic forms of Scheme 1, which may be valid for 2,4-diselenouracil, 2,4-dithiouracil, and uracil, where the heteroatoms at positions 2 and 4 are identical cannot be extended to the 2- and 4-derivatives, in which the heteroatom's nature at these positions differs. Indeed, as shown in Table 1 for 2SeU complex **4** is more stable (16.6 kcal mol^{-1}) than complex **1**; but for 4SeU both complexes are nearly degenerate, indicating that the ability of the basic center to bind Ca^{2+} depends not only on its position within the ring but also on

Table 1. Relative Energies (ΔE, kcal mol^{-1}) of the Different Stationary Points of the [Selenouracil−Ca]$^{2+}$ Complexes

	2-selenouracil ΔE	4-selenouracil ΔE	2,4-diselenouracil ΔE
1	**31.5**	25.1	33.6
2a	8.3	2.2	3.5
2b	**0.0**	0.0	0.8
3a	7.6	0.4	0.1
3b	**3.9**	0.2	0.0
4	**14.9**	25.7	27.7
5a	**1.1**	8.2	4.3
5b	3.1	12.3	6.9
6a	17.6	30.2	28.4
6b	18.6	39.2	29.2
7	**36.8**		**25.9**
TS1_4		25.7	
TS1_7	36.8		36.7
TS7_4	35.3		34.0
TS7_5a			51.6
TS7_2d			50.7
TS5a-4	37.8	63.3	51.6
TS2b-1	62.4	43.8	52.8

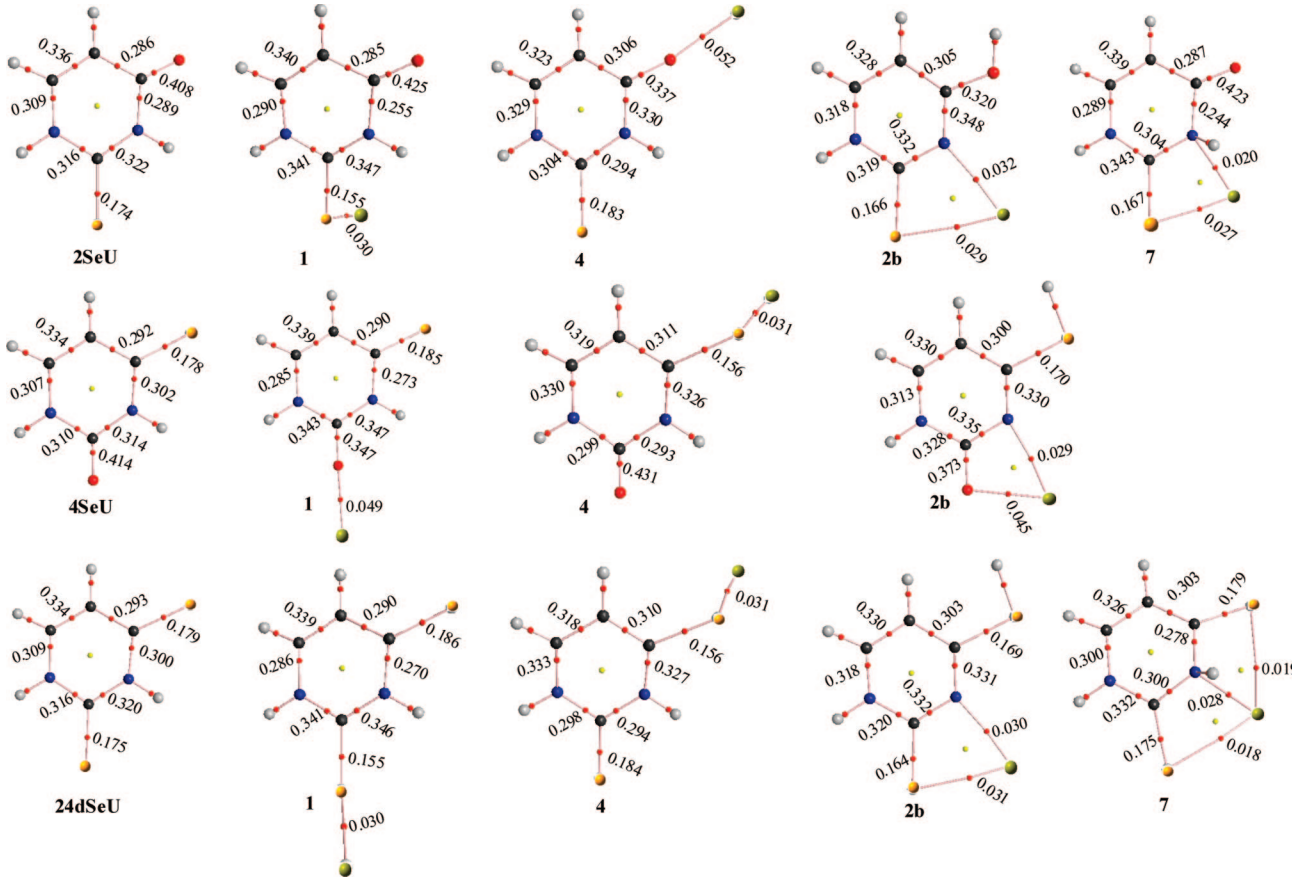


Figure 3. Molecular graphs of some selected selenouracil−Ca^{2+} complexes. Red dots represent bond critical points and yellow dots ring critical points. Electron densities are in au.

its nature. As a matter of fact the binding energy when Ca^{2+} is attached to the oxygen atom at position 4 in uracil (−104.7 kcal mol^{-1})[54] is greater than that computed for 4SeU (−94.5 kcal mol^{-1}), where this position is occupied by a Se atom. In order to separate both effects we have considered it useful to add to the set of uracil and selenouracils the subset of noncyclic molecules which contain the same basic sites in similar molecular environments, namely, acetamide, urea, and their Se-containing analogues. The corresponding binding energies are plotted in Figure 4, and the calculated values are reported in Table S3 of the Supporting Information. In this figure, points named [Ca4,O2] and [Ca4,Se2] correspond to complexes in which Ca^{2+} is attached to the heteroatom at position 4 (O or Se), and the heteroatom at position 2 is O or Se, respectively. Similarly, [Ca2,O4] and [Ca2,Se4] correspond to complexes in which Ca^{2+} is attached to the heteroatom at position 2 (O or Se), and the heteroatom at position 4 is O or Se, respectively (see Scheme 2).

It is apparent that, in agreement with our previous discussion, Ca^{2+} binding energies are always greater when the metal is attached to position 4. It is also worth noting that the binding energy to the heteroatom in position 4 (or 2) is not affected much by the nature of the heteroatom at position 2 (or 4). It is also evident that the Ca^{2+} binding energy for urea (selenourea) is larger than that of acetamide (selonoacetamide), because the presence of two amino groups bonded to the carbonyl (selenocarbonyl) group enhances the resonance stabilization of the molecular dication. However, one of the most significant findings of the plot in Figure 4 is the preference of Ca^{2+} to attach to the oxygen atoms. In fact, the Ca^{2+} binding energy of selenourea is estimated to be −97.5 kcal mol^{-1} while that of urea is about −107.3 kcal mol^{-1} which shows the preference of Ca^{2+} for oxygen. The same conclusion is reached when acetamide is compared with selenoamide. In the case of 2-selenouracil and 4-selenouracil, the preference of calcium to interact with the carbonyl group is in competition with the enhanced basicity of the heteroatom at position 4. This is evident if we analyze the relative stability of complexes **1** and **4.** Indeed, for 2SeU both effects are in the same direction, and accordingly complex **4** (in which Ca^{2+} is attached to a C═O group in position 4) is about 16.6 kcal mol^{-1} more stable than complex **1** (where Ca^{2+} is attached to C═Se group in position 2). Conversely, for 4SeU both effects counterbalance each other. Although in general oxygen attachment should be preferred to selenium attachment, the selenocarbonyl group exhibits an enhanced basicity because it occupies position 4, and the result is that complexes **1** and **4** are nearly degenerate.

Bonding and Bonding Perturbation upon Ca^{2+} Association. The small value of the electron density at the BCPs of the Ca−Se, Ca−N, and Ca−O bonds (see Figure 3) as well as the fact that the energy density is positive[55] indicates that the bonding in [Ca−selenouracils]$^{2+}$ complexes is essentially ionic. However, a comparison between the values obtained for the isolated bases and the bases within the complexes clearly shows the existence of strong polariza-

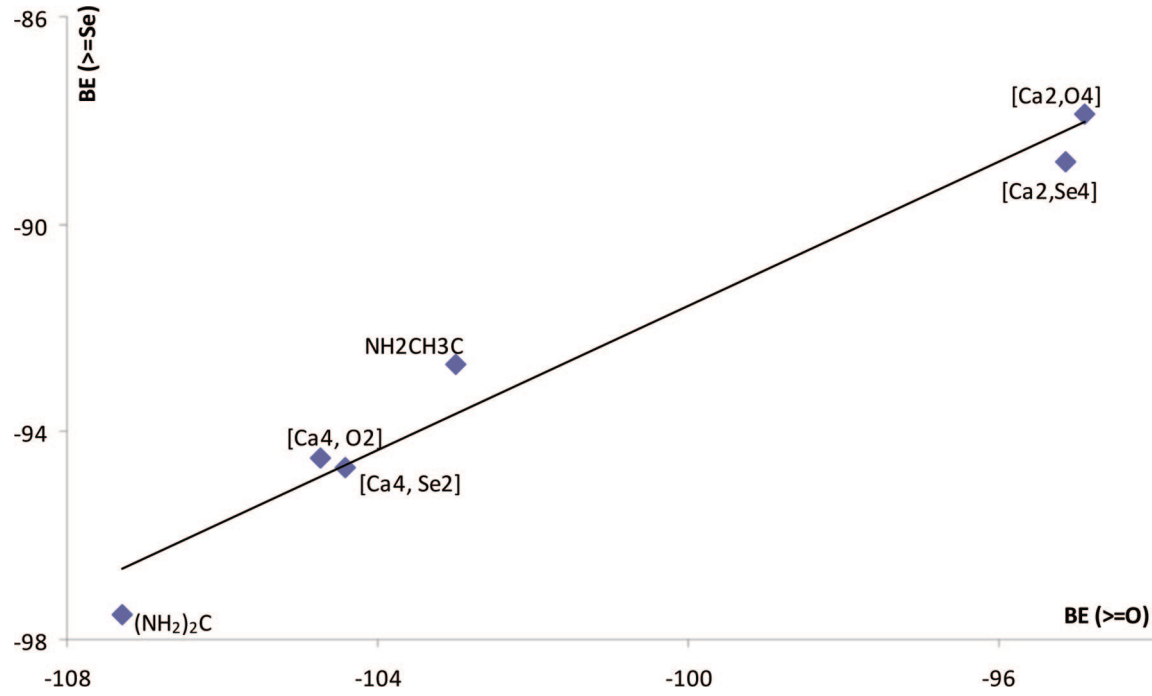
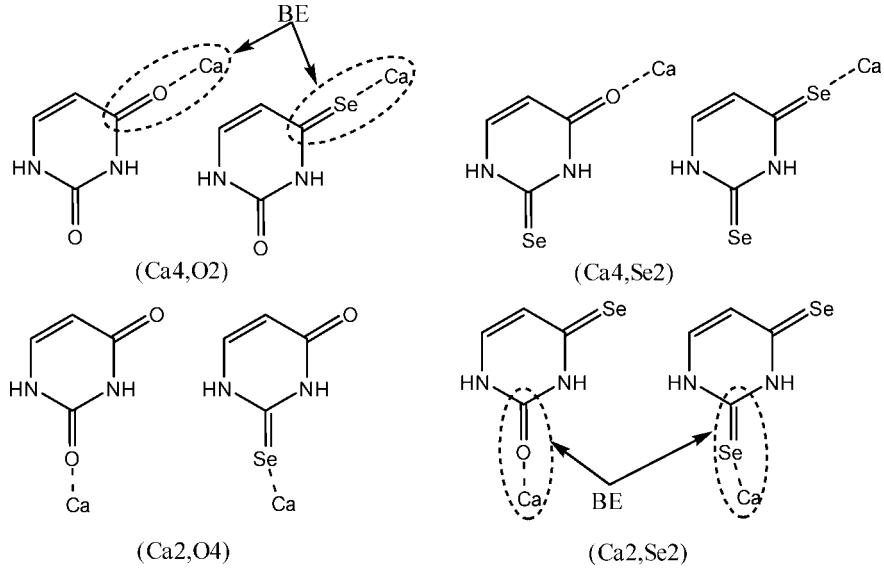


Figure 4. Carbonyl−Ca^{2+} binding energies versus selenocarbonyl−Ca^{2+} ones in the different selenouracils under consideration ($r^2 = 0.968$). $(NH_2)_2C$ and NH_2CH_3C denote urea and acetamide, respectively. [Ca4,O2], [Ca4,Se2], [Ca2,O4], and [Ca2,Se4] are defined in Scheme 2 (see also text).

Scheme 2



tion effects which cause a significant reorganization of the electron density of the base. For instance, when the alkaline-earth metal is associated directly with one of the heteroatoms at position 2 or 4, the electron density at the C═X (X = O, Se) BCP decreases significantly (by about 0.02 e.au^{-3} when X═Se and by about 0.07 e.au^{-3} when X = O). The much smaller effect observed for C═Se bonds clearly reflects the larger polarizability of Se with respect to oxygen. This different behavior of O-attached and Se-attached complexes is also reflected in the ELF of complexes **1** and **4** (see Figure 2), which shows that, upon Ca^{2+} association, an expansion of the basin associated with the basic site lone pairs takes place when this site is a Se atom, whereas a contraction of this basin is observed when the basic site is oxygen. Similar polarization effects are detected when complexes **7** are formed. In fact, the electron density at the bonds in which N3 participates also decreases significantly ($\Delta\rho_{C2-N3} = 0.020$ and $\Delta\rho_{N3-C4} = 0.022$) (see Figure 3).

The fact that electrostatic and polarization interactions are the dominant factors in these complexes explains the structural differences between urea−Ca^{2+} and selenouracil−Ca^{2+} adducts. While the angle C═O−Ca in urea−Ca^{2+} adducts[56] is 180°, the C═Se−Ca angle in selenouracil−Ca^{2+} adducts is about 110°. This behavior resembles that found for the attachment of Li^+ to formaldehyde and thioformaldehyde.[57] In the former case, a linear C−O−Li arrangement is predicted for the equilibrium conformation of the H_2CO-Li^+ complex, while a bent C−S−Li conformation

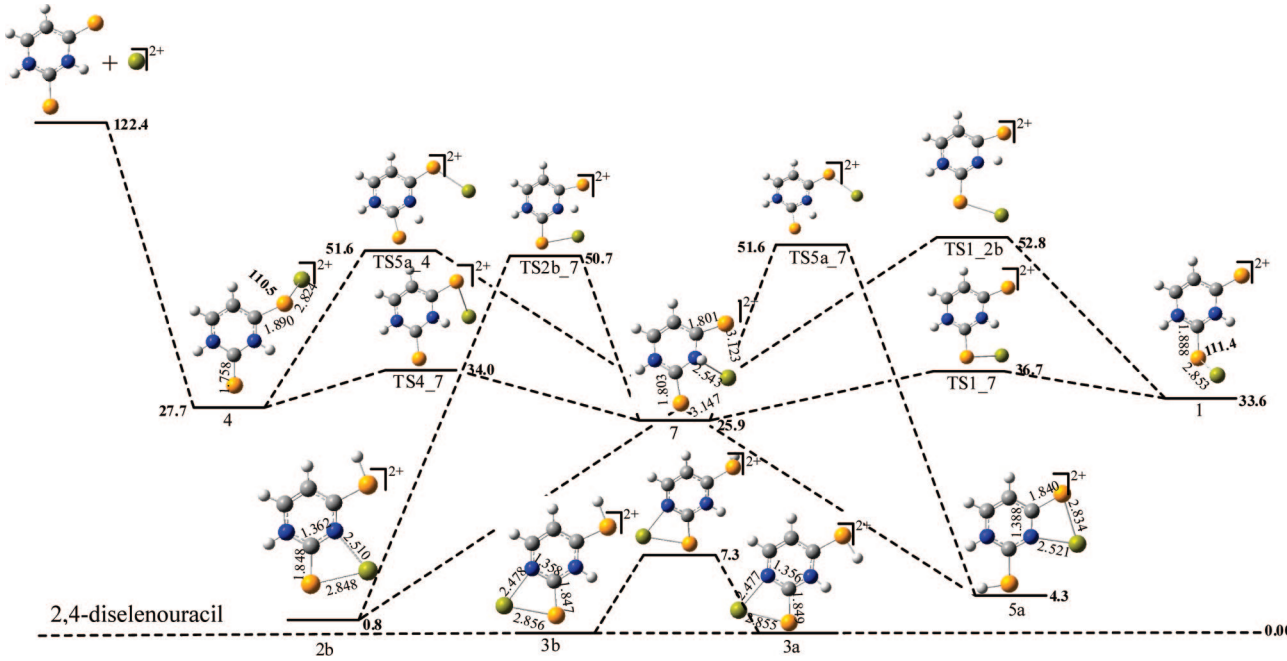


Figure 5. Energy profile for the isomerization process of dSeU−Ca^{2+} adducts. Relative energies are in kcal mol^{-1}.

is found for the equilibrium structure of the H_2CS-Li^+ system. A suitable explanation in terms of the differences in the molecular electrostatic potentials associated with the two neutral systems and polarization effects was offered by Alcamí et al.[58] The same arguments apply here. The primary interaction between the neutral molecule and the dication is electrostatic. Due to the size difference between oxygen and selenium atoms, the distance from the nuclei to the electrostatic potential minima is not only much shorter for oxygen than for selenium but also shorter than the typical dication-oxygen distance in the complex. As a consequence, the dication moves along isopotential lines connecting the two minima associated with the oxygen lone pairs. Since the potential is the same whatever the position of the dication along these lines, it nests between the two lone pairs to favor its simultaneous polarization. Conversely, when the cation approaches a selenium atom, the Ca−Se distances are similar to the distance between Se nuclei and the potential minima associated with its lone pairs, and the cation is trapped in either of these minima. This is nicely reflected in the ELF analysis of the valence basin associated with the reactive heteroatoms (see Figure 2). As far as the carbonyl group is concerned the electronic population in both monosynaptic basins associated with the oxygen lone pairs decreases. Conversely, for the selenocarbonyl only one monosynaptic basin of the selenium atom is actually affected (see Table S1).

Catalytic Effects on the Tautomerization Processes. In addition to the complexes resulting from the direct attack of Ca^{2+} on selenouracil (**1**, **4**, **7**), we have also considered the complexes that can be formed by Ca^{2+} attachment to the different tautomers formed by suitable hydrogen shifts (structures **2**, **3**, **5**, and **6** in Figure 1). The letters ***a*** and ***b*** have been added in order to distinguish between the various conformers with a different orientation of the hydrogen bonded to X or Y (see Figure 1). Their relative energies are summarized in Table 1. Total energies and ZPE corrections are given in Table S2 of the the Supporting Information. It should be mentioned that in some cases 4 conformers might be presented; in Figure 1 we have only included the two most stable ones. The optimized geometries of the global minima and transition states are given in the Supporting Information.

The data in Table 1 indicate that all complexes **2, 3,** and **5**, in which Ca^{2+} interacts simultaneously with the carbonyl (selenocarbonyl) group and the adjacent deprotonated ring nitrogen, are among the most stable selenouracils−Ca^{2+} complexes. As a matter of fact all of them are more stable than complexes **1** and **4**. The enhanced stability of complexes **2, 3**, and **5** arises from the fact that the alkaline-earth dication is able to polarize simultaneously both the heteroatom at positions 2 or 4 and the imino-type nitrogen which is very basic. This is nicely reflected in the topology of the corresponding electron densities. Although in complexes **2** the electron density at the X−Ca (X = O, Se) BCP is slightly smaller than in complexes **1** or **4**, this effect is clearly counterbalanced by the formation of a new N−Ca bond, which in complexes **1** and **4** is not possible (see Figure 3).

In view of the high stability of tautomers **2, 3,** and **5**, we investigated the possible tautomerization processes which connect them with the adducts **1**, **4**, and **7**. The corresponding energy profiles are plotted in Figures 5–7. The most significant finding is that all activation barriers lie below the entrance channel. This means that although the direct association of Ca^{2+} to selenouracils should lead exclusively to complexes **1**, **4**, and **7** since the neutrals only exist in the oxo-seleno and diseleno forms in the gas phase, the exothermicity of Ca^{2+} association is enough to trigger the tautomerization of the system, and, therefore, complexes **2b** should be the dominant ones for 2SeU−Ca^{2+} and 4SeU−Ca^{2+} species. For 2,4-SeU, a mixture of forms **3a** (34%), **3b** (41%), and **2b** (25%) should be found, because these three forms are very close in energy. The isomerization process connecting form **1** with forms **3a** and **3b** of 2,4-

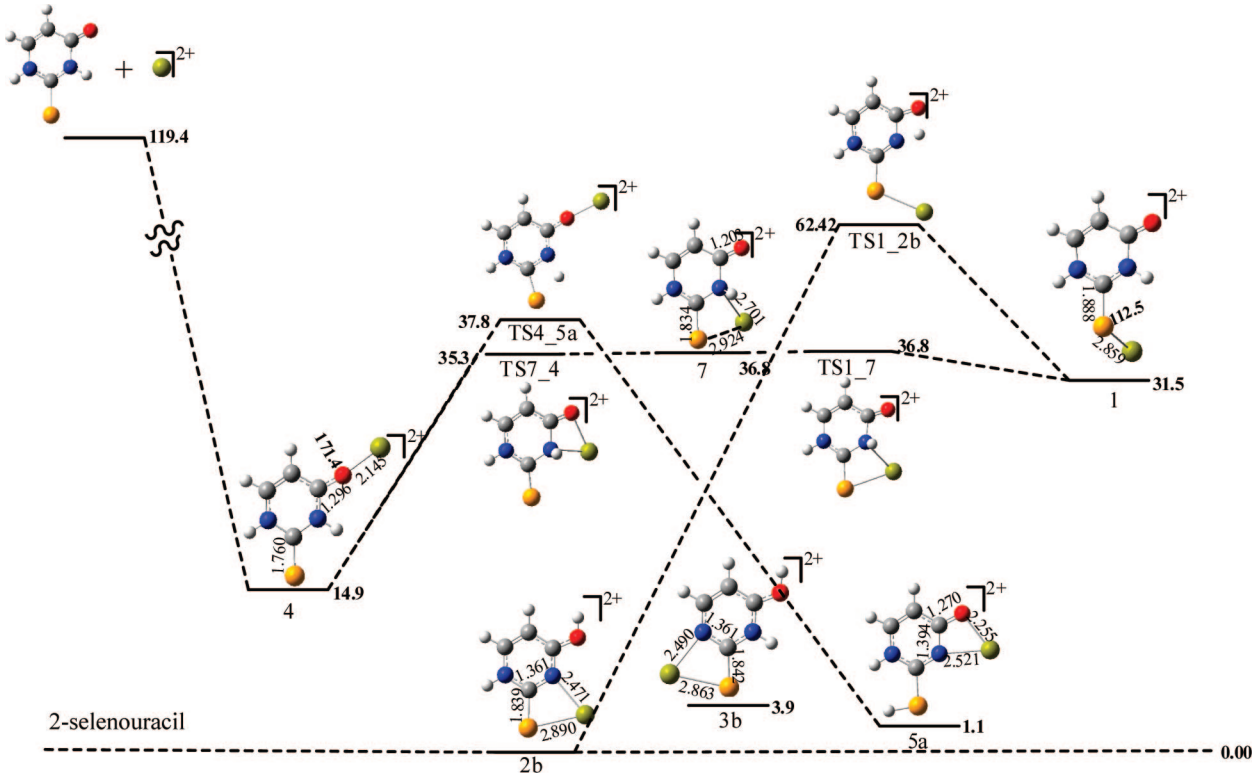


Figure 6. Energy profile for the isomerization process of 2SeU−Ca^{2+} adducts. Relative energies are in kcal mol^{-1}.

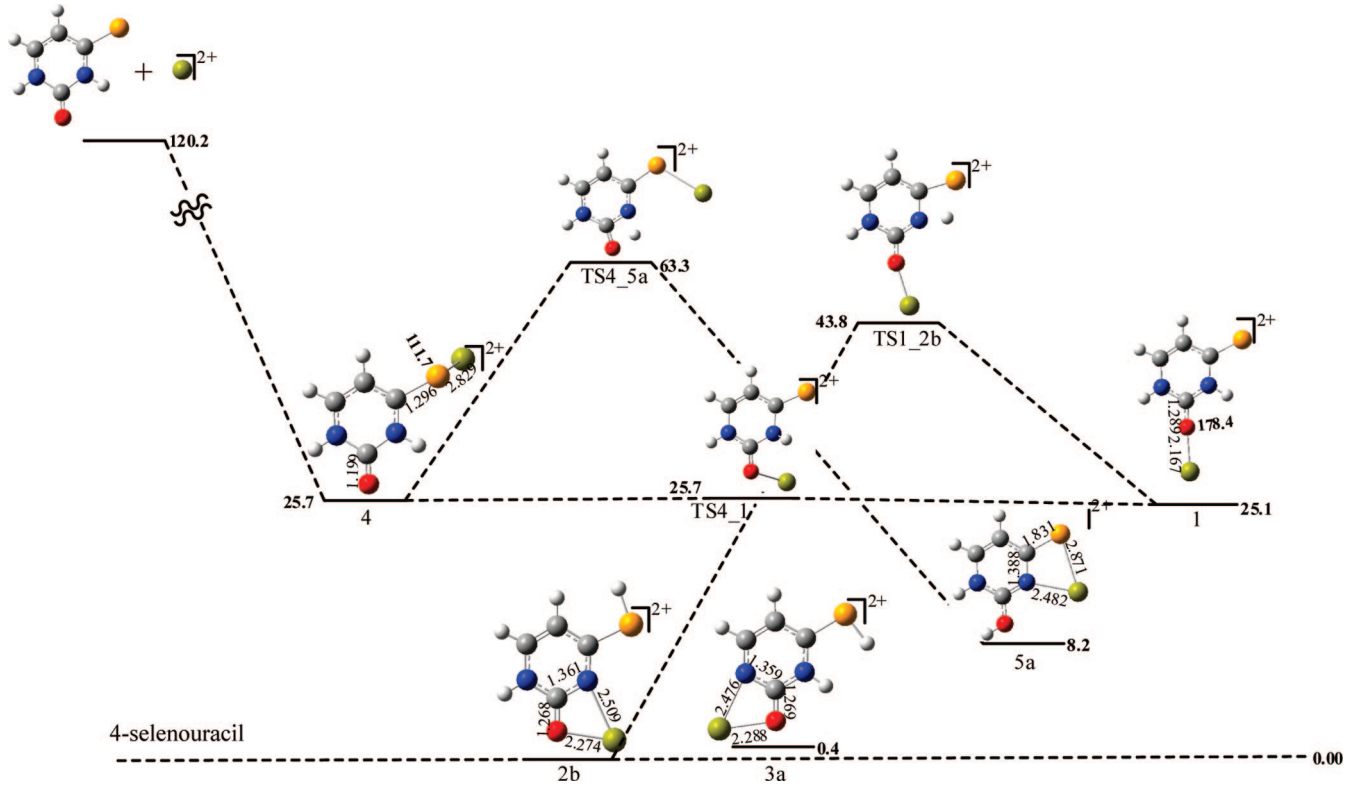


Figure 7. Energy profile for the isomerization process of 4SeU−Ca^{2+} adducts. Relative energies are in kcal mol^{-1}.

diselenouracil is presented in Figure S1 of the Supporting Information, to not overload Figure 5.

Figures 6 and 7 also show that the connections between forms **1** and **4** for 2SeU and 4SeU are essentially barrierless processes, either through form **7** as an intermediate (in the case of 2SeU) or directly (in the case of 4SeU, for which form **7** does not exist). The barriers for the same interconversion in the case of 2,4-diselenouracil are not negligible, but still rather small, so the **1**−**4** isomerization process must be also very facile.

To reach forms **2b** and **5a** a hydrogen shift is implicated, but these processes are clearly catalyzed by the presence of Ca^{2+}. If one refers, for instance, to 2-SeU, the activation barrier associated with the H-shift that connects forms **1** and **4** which for the isolated base is 40.9 kcal/mol,[45] for the Ca^{2+} complex reduces to 30.9 kcal mol^{-1}. The same applies to the barrier connecting forms **4** and **5**. For the Ca^{2+} complexes this barrier is 22.9, while for the isolated base it rises to 37.7 kcal mol^{-1}.[45] The same applies to 4-SeU and 2,4-SeU. For 4-SeU the **1**-**2b** and **4**-**5a** activation barriers change from 32.9 kcal mol^{-1} and 47.1 kcal mol^{-1} for the isolated base[45] to 18.7 and 37.6 kcal mol^{-1} in the corresponding Ca^{2+} complexes, respectively. The corresponding values for 2,4-SeU are 32.5 and 36.6 kcal mol^{-1} (isolated base) vs 19.2 and 23.9 kcal mol^{-1} (Ca^{2+} complexes).

Conclusions

The substitution of oxygen by selenium in uracil leads to significant changes in the reactivity of the system. The most important variation is the increased electron density of the nitrogen lone pair at position 3 and therefore its increased basicity. While in uracil and thiouracils the association of Cu(II)[49], Cu(I),[47] and proton[46] takes place exclusively at positions 2 and 4, in selenouracil−Ca^{2+} complexation at the nitrogen atom at position 3 leads to an alternative local minimum of the potential energy surface in the case of 2-SeU and 2,4-SeU. Furthermore, this adduct is predicted to be the most stable one in the case of 2,4-SeU, because in this position Ca^{2+} is able to interact with both Se atoms which are very polarizable.

Our results also show a clear preference of Ca^{2+} to be attached to oxygen, even though the enhanced basicity of the heteroatom at position 4 may alter this tendency, and in 4-SeU, the O-attached and the Se-attached complexes are nearly degenerate.

Perhaps the most important conclusion of this study is that although the enolic and selenol forms of selenouracils should not be observed in the gas phase,[44,45] the corresponding Ca^{2+} complexes are the most stable ones. More importantly, all the activation barriers associated with the corresponding tautomeric processes are lower than the entrance channel, and therefore not only these complexes should be observed but also they should be the dominant species in the gas phase. Also, Ca^{2+} association has a clear catalytic effect on these tautomerization processes, whose activation barriers decrease between 10 and 15 kcal mol^{-1}.

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Supporting Information Available: Tables of total energies, zero-point energies of the different selenouracil−Ca^{2+} complexes, binding energies plotted in Figure 4, and electronic populations in some relevant structures and the optimized geometries of the global minima and the transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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