A theoretical study of hydration effects on the prototropic tautomerism of selenouracils†

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The prototropic tautomerism of 2-, 4-selenouracil and 2,4-diselenouracil has been studied using density functional theory (DFT) methods, at the B3LYP/6–311 + G(3df,2p)//B3LYP/6–31G(d,p) level. The relative stability order of selenouracil tautomers does not resemble that of uracil tautomers, but it is similar to that of thiouracils, even though the energy gaps between the different tautomers of selenouracils are smaller than for thiouracils. The tautomerism activation barriers are high enough as to conclude that only the oxo-selenone or the diselenone structures should be found in the gas phase. The specific interaction with one water molecule reduces these barriers by a half, but still the oxo-selenone form is always the most stable tautomer. The addition of a second water molecule has a relatively small effect, as well as bulk effects, evaluated by means of a continuum-polarized model. For isolated 2- and 4-selenouracils, the more favorable tautomerization process corresponds to a hydrogen transfer towards the selenium atom, the activation barriers for transfer towards the oxygen atom being much higher. This situation changes when specific and bulk effects are included, and the latter process becomes the more favorable one. For 2,4-diselenouracil the more favorable tautomerization, in the gas phase, corresponds to the H shift from N1 to the Se atom at C2, while solvation effects favor the transfer from N3 to the Se atom at C4.

Introduction

A great deal of attention has been devoted over the last decade to investigate the properties and reactivity of uracil and uracil derivatives[1–13] because uracil is one of the five nucleobases and therefore an important component of nucleic acids, among other reasons. Also, the thio-derivatives of uracil have attracted a similar interest[14–18] because 2-thiouracil and 4-thiouracil have been identified as minor components of t-RNA, and they can be used as anticancer and antithyroid drugs.[19] Surprisingly, selenouracils have received much less attention, in spite of the fact that selenium is also present in anaerobic enzymes in the form of selenocysteine,[20–22] and in the t-RNA of some species as 5-methylaminomethyl-2-selenouracil. Furthermore, this compound seems to be involved in condon–anticondon interactions.[20] Also importantly, some selenouracil derivatives, such as the 6-propyl-2-selenouracil, were found to be more potent inhibitors of Type I iodothyronine deiodinase, associated with Grave's disease,[21] than their thio-analogues. The high potency of selenouracils seems to be related to their capacity to form stable enzyme–selenouracil diselenide.[23] It has been also found that the replacement of sulfur by selenium in 6-*n*-propyl-2-thiouracil increases the antiperoxidase activity of this compound.[24]

One of the more important characteristics of uracil and its thio- and seleno-derivatives is that they may exist in many tautomeric forms, which seem to be crucial in order to explain the mutation occurring during DNA duplication.[25,26] Not surprisingly then, the tautomerism in uracil and in thio-uracils is nowadays a well characterized phenomenon.[14,16–18,27] However, the same cannot be said with respect to the tautomerism in selenouracils. As a matter of fact, and to the best of our knowledge, only the relative stabilities of the different tautomers of 2,4-diselenouracil have been reported in the literature,[28] while there is a complete lack of both experimental and theoretical studies on the relative stability of the different tautomers of 2- and 4-selenouracil, and in no cases have the prototropic tautomerization barriers been reported. The aim of this paper is to provide reasonably accurate estimates of these relative stabilities as well as of the activation barriers connecting the different tautomers, through the use of density functional theory calculations. The substitution of oxygen or sulfur by a bulkier and more polarizable selenium atom may significantly alter the structural patterns of nucleic acids as well as their relative stabilities.[22,29–33] Such geometrical and energetic changes might play a role in nucleic acid conformation and in the hydrogen-bonding potentiality of the seleno derivatives. Hence, a good knowledge of the structure and relative stability of the different tautomers of the three selenouracils might constitute a first step in the understanding of reasons behind the differential role of uracil, thiouracil and selenouracil in biological processes. It is also a well established fact that a reduced number of water molecules catalyze this kind of tautomeric processes,[34–41] due to the ability of water to behave both as proton donor and proton acceptor. Hence, our second goal will be to investigate the effect of hydration in this prototropic tautomerism. For this purpose we have also investigated the specific effect of one and two solvating water molecules, and the effect of the bulk on both the relative stability of the more stable tautomers and on the barriers connecting them.

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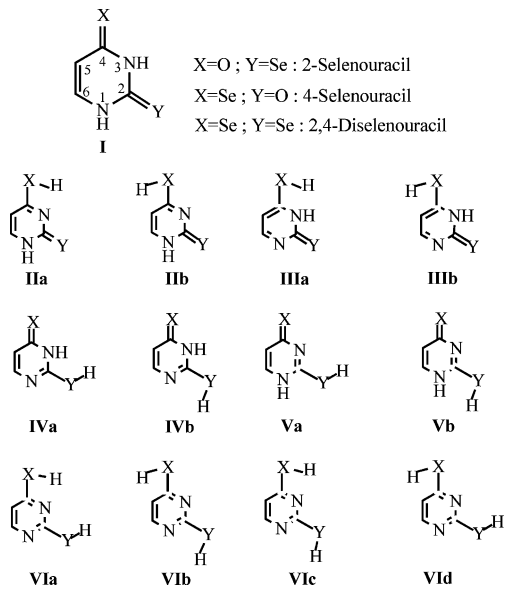
Computational details

The different tautomers (**I–VI**) of selenouracils are shown in Scheme 1. In what follows we will designate as X and Y the heteroatoms bonded to C4 and C2, respectively. It should be noted that most of these tautomers have several conformers, two for tautomers **II**, **III**, **IV** and **V**, and four for tautomers **VI**. Hence, in principle for each derivative there are 13 different structures. The geometries of the 39 different conformers of 2-, 4- and 2,4-selenouracil have been optimized by using the hybrid density functional B3LYP method, which combines the three-parameter nonlocal hybrid exchange potential used by Becke[42] with the nonlocal correlation functional of Lee *et al.*[43] This approach has been shown to yield reliable geometries for a wide variety of systems,[44–48] and in particular for the study of tautomerization processes in compounds similar to those studied here.[14,49–51] All the calculations were performed using the 6–31G(d,p) basis set for all atoms in the system. The harmonic vibrational frequencies of the different stationary points of the potential energy surface (PES) have been calculated at the same level of theory used for the geometry optimization in order to identify the local minima and the transition states (TS), as well as to estimate the corresponding zero-point energy (ZPE) corrections.



Scheme 1

In order to obtain more reliable energies for the local minima as well as for the transition states, final energies have been evaluated by the use of the same functional combined with the 6–311 + G(3df,2p) basis set.

The binding characteristics were analyzed by means of the atoms in molecules (AIM) theory of Bader.[52] For this purpose we have located the relevant bond critical points (bcp) in order to obtain the corresponding molecular graphs. To perform the AIM analysis we have used the AIMPAC series of programs.[53] Also the natural bond orbital (NBO) approach,[54] has been employed to obtain atomic charges and to analyze possible second-order perturbation orbital interactions.

Hydration effects have been analyzed for the three most stable tautomers of each derivative and for the transition states connecting them, using a mixed model as follows. Specific hydration effects were taken into account by considering hydrated complexes with one and two molecules of water. The effect of the bulk was then accounted for by introducing these hydrated complexes in a solvent cavity, through the use of a continuum-polarized model, as implemented in the Gaussian-03 series of programs.[55] The effect of the second solvating water molecule was only investigated for 2-selenouracil and 4-selenouracil.

Results and discussion

Tautomer stability

The energy profiles associated with the tautomerization processes of 2-, 4- and 2,4-selenouracils are given in Fig. 1(a–c). The relative energies of all tautomers, after including the ZPE corrections, are given in Table 1. Tables S1 and S2 in the electronic supplementary information (ESI†) contain the total energies of the different stationary points and their optimized geometries, respectively.

The first conspicuous fact is that, as it has been found previously for uracil and its thio-derivatives, for selenouracils the oxo-selenone form **I** is always the global minimum of the potential-energy surface. Moreover, the energy gap between this form and the remaining tautomers is large enough as to conclude that form **I** will be the only one found in the gas phase for the three derivatives under investigation. Also importantly, the calculated dipole moments of forms **I** are quite large (4.72, 4.97 and 4.88 D, for 2-, 4- and 2,4-selenouracils, respectively) and they decrease significantly on going to the second or third more stable tautomers (**IVb**: 2.97, 4.32, and 3.97 D, respectively, and **VIc**: 1.28, 1.86 and 1.77 D, respectively). Hence, the interaction of forms **I** with polar solvents will be significantly large. We shall show in forthcoming sections, that indeed this form is also the dominant one in aqueous solution.

Similar to what has been found for uracil and thiouracils, the enol-selenol structures (**VIa**–**c**) are systematically among the more stable tautomers, which has been explained by the tendency of the pyrimidine ring to adopt the aromatic structure.[17] However, as shown in Fig. 1(a–c), for the three selenouracils the tautomer **IVb** is equally as stable or slightly more stable than tautomers **VIa** or **VIc**.

It is also worth noting that tautomer **IVb** is always more stable than tautomer **Va**. In other words, the hydrogen shift from N1 towards the heteroatom Y yields a tautomer which is 8–10 kcal

Table 1 Relative energies (ΔE, kcal mol^{-1}) of 2-, 4- and 2,4-selenouracils

	ΔE/kcal mol^{-1}		
Tautomer	2-Selenouracil	4-Selenouracil	2,4-Diselenouracil
I	0.0	0.0	0.0
IIa	11.7	11.4	11.3
IIb	17.9	12.0	11.9
IIIa	22.9	16.0	16.1
IIIb	20.8	16.2	16.3
IVa	9.5	17.2	8.4
IVb	9.3	10.4	8.0
Va	17.5	19.1	17.6
Vb	18.1	28.1	18.2
VIa	9.6	12.3	10.4
VIb	14.0	12.1	8.1
VIc	9.5	11.8	7.9
VId	13.9	12.4	8.1

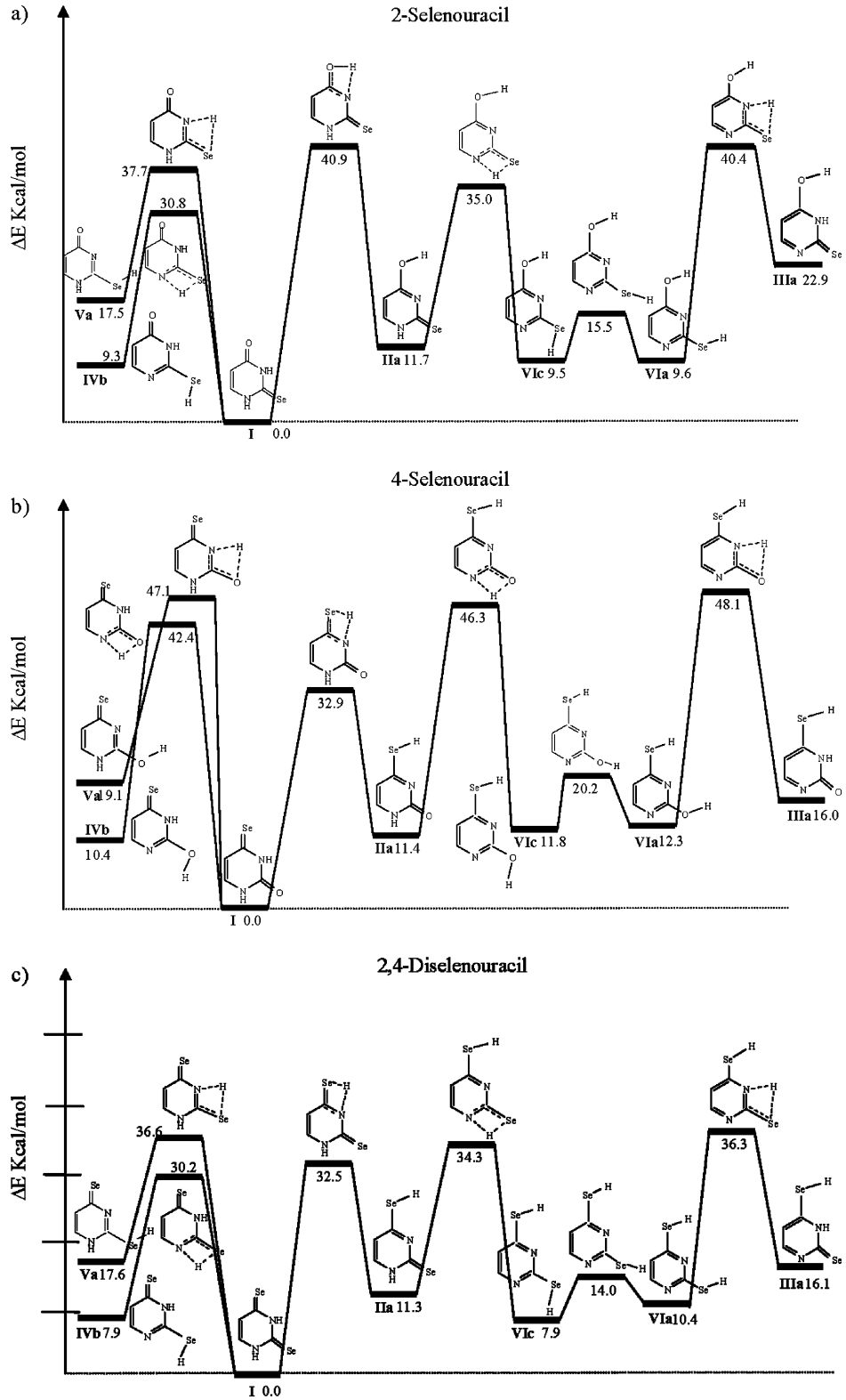


Fig. 1 Energy profile for the different tautomerization processes of a) 2-selenouracil, b) 4 selenouracil, and c) 2,4-diselenouracil. Relative energies in kcal mol^{-1} include ZPE corrections.

mol^{-1} more stable than the tautomer produced when the hydrogen atom is shifted from N3. The lower stability of tautomer **Va** may be understood taking into account that the stabilizing non-bonded interaction between the positively charged hydrogen atom (natural net charge +0.46) attached to N3 and the negatively charged heteroatom X (natural net charge −0.61) that takes place in **I** and in **IVb** is replaced in form **Va** by the repulsive interactions between the N3 nitrogen lone-pair and the lone pairs of X. On the

other hand, a second-order NBO analysis clearly shows that while form **Va** exhibits a typical quinonoid structure, with two double bonds localized at C2N3 and C5C6, in form **IVb**, besides the two double bonds localized at N1C2 and C2C3, there is also a certain delocalization affecting the N1C2 and the C3C4 bonds, which, accordingly, have a partial double bond character. Consistently, these two bonds are 0.008 and 0.024 Å shorter in **IVb** than in **Va**.

For similar reasons, the activation barrier connecting the global minimum with **IVb** is from 5 to 7 kcal mol^{-1} lower than that connecting **I** and **Va**.

Tautomer **IIa** is also always lower in energy than tautomer **IIIa**, because while in the former there is a stabilizing non-bonded interaction between the hydrogen atom of the X–H group and N3, in the latter there is a repulsive one between the hydrogen atom of the X–H group and the hydrogen atom attached to N3. Similar reasons are behind the larger stability of tautomer **IVb** with respect to tautomer **IVa**, particularly for 4-selenouracil.

There are however, some subtle dissimilarities among the three derivatives. For instance, for 2-selenouracil and 2,4-selenouracil form **VIc** is very close in energy to form **IVb**, and form **IIa** lies more than 2 kcal mol^{-1} higher, whereas for 4-selenouracil these three forms are very close in energy, form **IIa** being slightly more stable than form **VIc**. In general, one should expect a stabilization of the system on going from **IIa** towards **VIc**, due to the aromatization of the system. However, in 4-selenouracil this involves going from a keto to an enol function and therefore, in this case, form **VIc** becomes slightly less stable than form **IIa**

However, the larger dissimilarities are associated with the tautomerization barriers. Although, as mentioned above, form **IVb** is always the second most stable tautomer, it is not always the more favorable one from a kinetic point of view. As illustrated in Fig. 1(a), for 2-selenouracil the formation of **IVb** from the global minimum requires a much lower activation barrier than the formation of **IIa**, while for 4-selenouracil it is the other way around (see Fig. 1(b,c)). This can be easily explained if one takes into account that the evolution from **I** to **IIa** in the latter case changes a C=Se group into a C–SeH group, while in 2-selenouracil the same process changes a C=O group into a C–OH group. For 2,4-diselenouracil, both barriers are much closer, since in both cases a C=Se group is changed into a C–SeH group, although the formation of tautomer **IVb** is slightly more favorable than the formation of tautomer **IIa**. The same arguments explain why the **IIa**–**VIc** and the **VIa**–**IIIa** tautomerization barriers are much larger for 4-selenouracil than for 2- and 2,4-selenouracils. Hence, we may conclude that for 2, and 4-selenouracil the more favorable tautomerization process, with origin in the global minimum **I**, corresponds to a hydrogen shift towards the Se atom from N1 in 2-selenouracil and from N3 in 4-selenouracil. Accordingly, although **IVb** is in both cases the second more stable tautomer, in 4-selenouracil form **IIa** is kinetically favored. For 2,4-diselenouracil, **IVb** is thermodynamically and kinetically favored with respect to **IIa**.

We have considered it of interest to compare the relative stabilities of the different selenouracil tautomers with those of their thiouracil counterparts at the same level of theory.[14] This comparison is carried out in Fig. 2(a–c).

It is apparent that there is a reasonably good linear correlation between both sets of values for 2- and 4-substituted derivatives (Fig. 2(a,b)), whereas the scatter is a little bit larger for the 2,4-disubstituted compounds (Fig. 2c). It is also worth noting that the slope of the correlation is always around 0.86, which implies that, although relative stabilities follow similar trends for both families, the energy gaps between the different tautomers of selenouracils are smaller than for thiouracils. The same is observed as far as the tautomerization energy barriers are concerned.

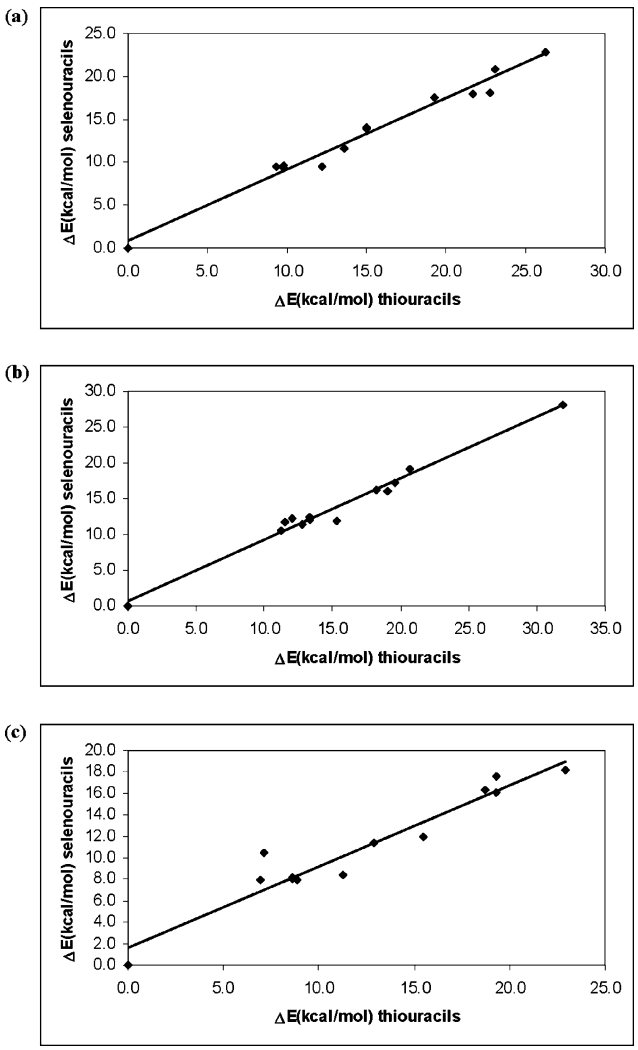


Fig. 2 Linear correlation between the relative stabilities of selenouracils and thiouracils: a) 2-selenouracil *vs.* 2-thiouracil; b) 4 selenouracil *vs.* 4-thiouracil; and c) 2,4-diselenouracil *vs.* 2,4-dithiouracil.

Since, as it has already been reported in the literature, the relative stability order of thiouracil tautomers does not resemble that of uracil tautomers,[14,17,18] we can conclude, in view of the good correlations found above between selenouracils and thiouracils, that the same behavior will be found when comparing uracils and selenouracils. Also, in general, the energy gap between the thione-oxo (or the dithione) forms and the closest hydroxy-mercapto (or dimercapto) tautomers is also much smaller in thiouracils than in uracils,[17,18] and even lower as far as selenouracils are concerned.

Structure and bonding

The optimized geometry of the most stable tautomer for each compound is presented in Fig. S1, ESI†.

Although a detailed discussion of the geometries of these species is not the aim of this paper, some structural features deserve to be commented on. The six-membered rings are rather similar, although both the N1–C2 and the C2–N3 bonds are longer in 4-selenouracil than in 2- and 2,4-selenouracil. In the former compound C2 has an enhanced electronegativity because it is bonded to an oxygen atom, and accordingly it withdraws electron density from the bonds in which it participates. This is actually reflected in the charge densities at the N1–C2 and N3–C2 bond critical points, which are smaller for 4-selenouracil than for the other two derivatives, as illustrated by the corresponding molecular graphs (see Fig. 3). The N1–H bond is systematically slightly shorter than N3–H bond. Consistently the charge density at the corresponding bond critical point is slightly larger in the former than in the latter (see Fig. 3). Also interestingly, as we shall see in forthcoming sections, this difference is also reflected in the molecular force field and the N1–H stretch has a slightly greater frequency than the N3–H stretch. Another interesting structural feature is the fact that the C=Y bond (Y = O, Se) is systematically longer than the C=X (X = O, Se) bond, which can be explained in terms of the bond-activation reinforcement (BAR) rule.[56] In the first case the heteroatom is attached to C2, whose electronegativity is enhanced with respect to that of C4, by being bonded to two nitrogen atoms. Consequently, C2 polarizes the electron density around Y more strongly that C4 polarizes that around X, and therefore the charge density at the C2=Y bcp is always slightly greater than that at the C4=X bcp, and the bond slightly shorter. Also coherently, as we shall see later, the C2=Se stretching frequency in 2-selenouracil is slightly larger than the C4=Se stretching frequency in 4-selenouracil. Similarly, the C2=O stretching frequency in 4-selenouracil is also slightly larger than the C4=O stretching frequency in 2-selenouracil.

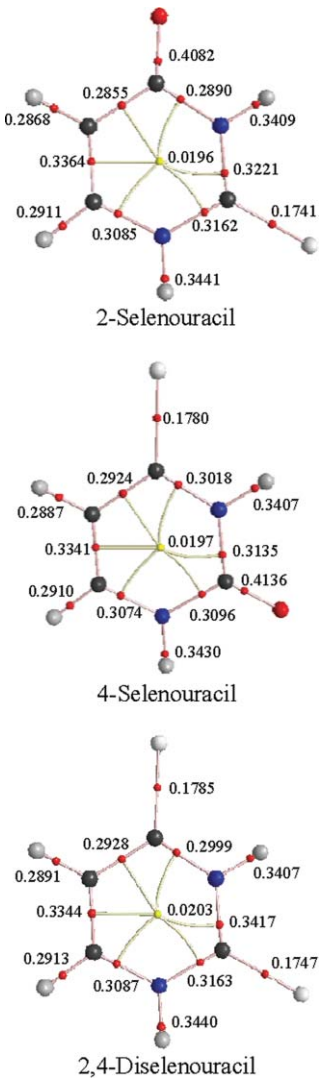


Fig. 3 Molecular graphs of the most stable tautomer of 2-selenouracil, 4 selenouracil, and 2,4-diselenouracil. Red dots denote bond critical points, and yellow dots ring critical points. Electron densities are given in a.u.

Hydration effects

The energy profile corresponding to the prototopic tautomerisms connecting **I** with **IIa**, **IVb** and **Va**, for the corresponding monohydrated species are presented in Fig. 4(a) for 2-selenouracil. For each tautomerization pathway, relative energies are calculated with respect to the corresponding monohydrated clusters, **I1**, **I2** and **I3**, respectively. The relative energies of the mono- and dehydrated clusters are given in Table S3, ESI†. In all cases cluster **I1** is the more stable. Fig. 4(a) clearly shows that the most dramatic effect in the prototopic tautomerism of monohydrated 2-selenouracil is associated with the size of the activation barriers, which become almost half or even less than half of those obtained for the isolated compound. It is also worth noting that the inclusion of a molecule of water closes the gap between **Va** and **IVb**, because N3 in the former is a better hydrogen-bond acceptor than N1 in the latter, yielding a stronger hydrogen bond (HB) with the molecule of water. Also the hydrated form of **IIa** becomes slightly stabilized with respect to the global minimum, because the –OH group is a better hydrogen-bond donor than the NH group. When the effect of the bulk is added, by enclosing this monohydrated species in a solvent cavity, the changes observed in the energy profile are small (see Fig. 4(b)). The energy gap between **Va** and **IVb** decreases further, because the former hydrate has a larger dipole moment than the latter (6.2 *vs.* 2.7 D). Conversely, the effects on the activation barriers are rather small, because the three monohydrated transition states have rather similar (*ca.* 4.6 D) dipole moments.

When a second water molecule is added to the complex, as shown in Fig. 4(c), the energetic profile for the prototropic tautomerism does not change much, but what is more important is that the values of the activation barriers do not change in relative terms, so that the barriers to yield forms **IVb** and **Va** are still about 4 kcal mol^{-1} higher than that to yield form **IIa**.

It is also worth noting that the relative stability of **IIa** monohydrate increases by 2 kcal mol^{-1} when the second molecule of water is added. Bulk effects are in this case quite significant, in particular concerning the barrier to yield tautomer **IIa**, which decreases from 13 to 9 kcal mol^{-1} (see Fig. 4(d)), while those involved in the tautomerization processes leading to **IVb** and **Va** increase slightly. As a consequence, the gap between these barriers increases from about 4 to 10 kcal mol^{-1}, and form **IIa**, which was the less favorable from a kinetic point of view for isolated 2-selenouracil, becomes the more favorable one both thermodynamically and kinetically when specific and bulk solvation effects are taken into account.

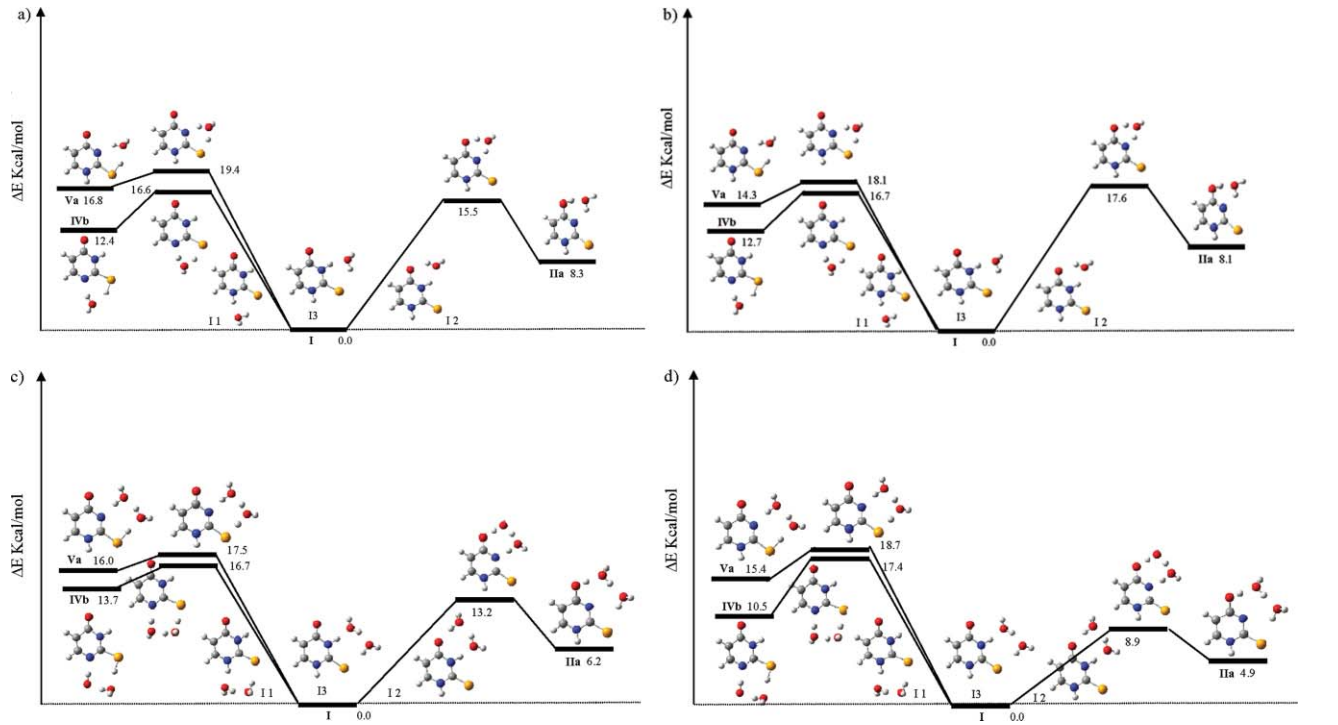


Fig. 4 Energy profile for the tautomerization processes of 2-selenouracil: a) monohydrated species; b) solvated monohydrated species; c) dihydrated species; d) solvated dihydrated species. Relative energies in kcal mol^{-1} include ZPE corrections.

The situation is rather similar as far as 4-selenouracil and 2,4-diselenouracil are concerned (see Fig. S2 and S3, ESI†). The specific solvation effects in the monohydrated complexes slightly reduces the gap between forms **Va** and **IVb**, but have a huge effect on the activation barriers that decrease by a factor greater than 2. However, this effect is quantitatively larger for the transition states connecting form **I** with forms **IVb** and **Va**, than for the transition states connecting **I** with **IIa**. The most obvious consequence is that while for the isolated compound form **IIa** was clearly favored from a kinetic point of view, for the monohydrated species all barriers become rather similar, being that connecting **I** and **IVb** the lowest one. Once more, bulk effects on these monohydrated complexes are rather small, except, as for the case of 2-selenouracil, for the energy gap between forms **Va** and **IVb**, which almost disappear in the case of 2,4-diselenouracil. No significant changes are observed when adding a second water molecule to specifically solvate the system. Hence, for 4-selenouracil the more favorable tautomer, both thermodynamically and kinetically, is **IVb**.

Finally, it is worth mentioning that the profiles of the potential-energy surfaces so far discussed, do not change significantly when they are obtained in terms of free energies, because there are no significant entropic changes on going from one minimum to another, or on going from the minima to the transition state connecting them.

Vibrational frequencies

Very often infrared spectra are used to identify pyrimidinic residues in nucleic acids strands,[57–60] so we have considered it of interest to report and assign the calculated harmonic vibrational frequencies of the more stable tautomers of selenouracils, that may guide future experimental work. The values have been summarized in Table S4, ESI†, together with a short discussion.

As expected, the interaction with water molecules involves a significant red-shifting of the N–H bonds of selenouracil acting as hydrogen-bond donors with respect to the solvating water molecule, while the effect on the C=O or the C=Se stretching frequencies of the groups acting as hydrogen-bond acceptors is rather small. For monohydrated clusters, the red-shifting of the N–H groups are, on average, about 350 cm^{-1}, while the C=O and the C=Se stretching displacements are red-shifted by 27 cm^{-1} and blue-shifted 15 cm^{-1}, respectively. Interestingly, the red-shifting of the NH groups increases significantly (about 200 cm^{-1}) on going from the monohydrated to the dehydrated complexes, because the hydrogen bond between this group and the solvating water molecule becomes reinforced, due to a better orientation of the latter with respect to the former. The inclusion of bulk effects implies a further reduction of the N–H stretching frequency of the order of 50 cm^{-1}, on average.

Conclusions

From the theoretical survey of the prototropic tautomerism of 2-, 4- and 2,4-selenouracils we can conclude that for the three compounds the oxo-selenone form is the more stable tautomer. The relative stability order of selenouracil tautomers does not resemble that of uracil tautomers, but it is similar to that of thiouracils, even though the energy gaps between the different tautomers of selenouracils are smaller than for thiouracils. The tautomerism activation barriers are high enough as to conclude

that only the oxo-selenone or the diselenone structures should be found in the gas phase. This situation does not change in aqueous solution, because, although the tautomerization barriers decrease dramatically when solvent effects are accounted for, they are still high enough in energy as to conclude that only oxo-selenone or diselenone structures will be found in solution.

For isolated 2- and 4-selenouracils, the more favorable tautomerization process corresponds to a hydrogen transfer towards the selenium atom, the activation barriers for transfer towards the oxygen atom being much higher. However, when specific and bulk solvation effects are taken into account, the transfer towards the oxygen atom to produce the corresponding enol becomes clearly favored, for both derivatives. For isolated 2,4-diselenouracil the more favorable tautomerization corresponds to the H shift from N1 to the selenium atom at C2, while solvation effects slightly favor the transfer from N3 to the Se atom at C4.

Although the oxo-selenone forms are the more stable structures, both in the gas phase and in solution, for 2-selenouracil and 2,4-diselenouracil the relative stabilities of the other stable tautomers change when specific and bulk solvation effects are taken into account. In both cases the second most stable tautomer in the gas phase is structure **IVb**, whereas **IIa** is the second most stable in aqueous solution.

Acknowledgements

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References

1 A. K. Chandra, M. T. Nguyen, T. Uchimaru and T. Zeegers-Huyskens, *J. Phys. Chem. A*, 1999, **103**, 8853.
2 S. X. Tian, C. F. Zhang, Z. J. Zhang, X. J. Chen and K. Z. Xu, *Chem. Phys.*, 1999, **242**, 217.
3 M. A. Kurinovich and J. K. Lee, *J. Am. Chem. Soc.*, 2000, **122**, 6258.
4 M. A. Kurinovich and J. K. Lee, *J. Am. Soc. Mass Spectrom.*, 2002, **13**, 985.
5 M. Di Laudo, S. R. Whittleton and S. D. Wetmore, *J. Phys. Chem. A*, 2003, **107**, 10406.
6 M. Haranczyk, R. Bachorz, J. Rak, M. Gutowski, D. Radisic, S. T. Stokes, J. M. Nilles and K. H. Bowen, *J. Phys. Chem. B*, 2003, **107**, 7889.
7 A. M. Lamsabhi, M. Alcamí, O. Mó and M. Yáñez, *ChemPhysChem*, 2003, **4**, 1011.
8 T. M. Miller, S. T. Arnold, A. A. Viggiano and A. E. S. Miller, *J. Phys. Chem. A*, 2004, **108**, 3439.
9 S. Millefiori and A. Alparone, *Chem. Phys.*, 2004, **303**, 27.
10 J. K. Lee, *Int. J. Mass Spectrom.*, 2005, **240**, 261.
11 S. Guillaumont, J. Tortajada, J. Y. Salpin and A. M. Lamsabhi, *Int. J. Mass Spectrom.*, 2005, **243**, 279.
12 A. M. Lamsabhi, M. Alcamí, O. Mó, M. Yáñez and J. Tortajada, *J. Phys. Chem. A*, 2006, **110**, 1943.
13 A. M. Lamsabhi, M. Alcamí, O. Mó, M. Yáñez, J. Tortajada and J. Y. Salpin, *ChemPhysChem*, 2007, **8**, 181.
14 M. Lamsabhi, M. Alcamí, O. Mó, W. Bouab, M. Esseffar, J. L. M. Abboud and M. Yáñez, *J. Phys. Chem. A*, 2000, **104**, 5122.
15 A. R. Katritzky, G. Baykut, S. Rachwal, M. Szafran, K. C. Caster and J. Eyler, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1499.
16 A. R. Katritzky and M. Szafran, *J. Chem. Soc., Perkin Trans. 2*, 1990, 871.
17 A. Les and L. Adamowicz, *J. Am. Chem. Soc.*, 1990, **112**, 1504.
18 J. Leszczynski and K. Lammertsma, *J. Phys. Chem.*, 1991, **95**, 3128.
19 W. Saenger, *Principles of Nucleic Acid Structure*, Springer, New York, 1984.
20 G. F. Kramer and B. N. Ames, *J. Bacteriol.*, 1988, **170**, 736.
21 A. Taurog, M. L. Dorris, W. X. Hu and F. S. Guziec, *Biochem. Pharmacol.*, 1995, **49**, 701.
22 R. Spezia, G. Tournois, T. Cartailler, J. Tortajada and Y. Jeanvoine, *J. Phys. Chem. A*, 2006, **110**, 9727.
23 T. J. Visser, E. Kaptein and H. Y. Aboulenein, *Biochem. Biophys. Res. Commun.*, 1992, **189**, 1362.
24 H. Y. Aboulenein, A. A. Awad and N. M. Alandis, *J. Enzyme Inhib.*, 1993, **7**, 147.
25 Em Gottscha, E. Kopp and A. G. Lezius, *Eur. J. Biochem.*, 1971, **24**, 168.
26 W. Saenger and D. Suck, *Eur. J. Biochem.*, 1973, **32**, 473.
27 B. Lesyng and W. Saenger, *Z. Naturforsch., C: Biosci.*, 1981, **36**, 956.
28 J. Leszczynski and J. Sponer, *J. Mol. Struct. (THEOCHEM)*, 1996, **388**, 237.
29 T. C. Castle, R. I. Maurer, F. E. Sowrey, M. J. Went, C. A. Reynolds, E. J. L. McInnes and P. J. Blower, *J. Am. Chem. Soc.*, 2003, **125**, 10040.
30 J. C. Guillemin, E. H. Riague, J. F. Gal, P. C. Maria, O. Mó and M. Yáñez, *Chem.–Eur. J.*, 2005, **11**, 2145.
31 J. Conradie, E. Tangen and A. Ghosh, *J. Inorg. Biochem.*, 2006, **100**, 707.
32 P. Ramasami, *J. Mol. Struct. (THEOCHEM)*, 2006, **775**, 87.
33 H. Pang, P. J. Skabara, S. Gordeyev, J. J. W. McDouall, S. J. Coles and M. B. Hursthouse, *Chem. Mater.*, 2007, **19**, 301.
34 A. Lledos and J. Bertran, *Tetrahedron Lett.*, 1981, **22**, 775.
35 T. J. Zielinski, R. A. Poirier, M. R. Peterson and I. G. Csizmadia, *J. Comput. Chem.*, 1983, **4**, 419.
36 T. Yamabe, K. Yamashita, M. Kaminoyama, M. Koizumi, A. Tachibana and K. Fukui, *J. Phys. Chem.*, 1984, **88**, 1459.
37 L. Gorb and J. Leszczynski, *J. Am. Chem. Soc.*, 1998, **120**, 5024.
38 J. W. Gauld, H. Audier, J. Fossey and L. Radom, *J. Am. Chem. Soc.*, 1996, **118**, 6299.
39 A. J. Chalk and L. Radom, *J. Am. Chem. Soc.*, 1997, **119**, 7573.
40 L. Rodriguez-Santiago, O. Vendrell, I. Tejero, M. Sodupe and J. Bertran, *Chem. Phys. Lett.*, 2001, **334**, 112.
41 M. K. Shukla and J. Leszczynski, *J. Mol. Struct. (THEOCHEM)*, 2006, **771**, 149.
42 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 1372.
43 C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1988, **37**, 785.
44 A. M. Mebel, K. Morokuma and M. C. Lin, *J. Chem. Phys.*, 1995, **103**, 7414.
45 A. Ricca and C. W. Bauschlicher, *Chem. Phys. Lett.*, 1995, **245**, 150.
46 A. L. Llamas-Saiz, C. Foces-Foces, O. Mó, M. Yáñez, E. Elguero and J. Elguero, *J. Comput. Chem.*, 1995, **16**, 263.
47 J. A. Montgomery, Jr., M. J. Frisch, J. Ochterski and G. A. Petersson, *J. Chem. Phys.*, 1999, **110**, 2822.
48 L. A. Curtiss, P. C. Redfern, K. Raghavachari and J. A. Pople, *J. Chem. Phys.*, 2001, **114**, 108.
49 J. S. Kwiatkowski and J. Leszczynski, *J. Mol. Struct.*, 1996, **376**, 325.
50 A. M. Lamsabhi, T. El Messaoudi, M. Esseffar, M. Alcamí and M. Yáñez, *New J. Chem.*, 2002, **26**, 711.
51 F. Freeman and H. N. Po, *J. Phys. Chem. A*, 2006, **110**, 7904.
52 R. F. W. Bader, *Atoms In Molecules : A Quantum Theory*, Clarendon Press, OxfordUniversity, Oxford, 1990.
53 R. F. W. Bader, J. R. Cheeseman In, 2000.
54 A. E. Reed, L. A. Curtiss and F. Weinhold, *Chem. Rev.*, 1988, **88**, 899.
55 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. J. A. Montgomery, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, J. Austin, R. Cammi, C. Pomelli, J. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y.

Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, In *Gaussian03, Revision C.02* ed.; Gaussian, Inc.: Wallingford CT, 2003.
56 M. Alcamí, O. Mo and M. Yanez, *Mass Spectrom. Rev.*, 2001, **20**, 195.
57 P. D. Schnier, J. S. Klassen, E. E. Strittmatter and E. R. Williams, *J. Am. Chem. Soc.*, 1998, **120**, 9605.
58 N. Leulliot, M. Ghomi, H. Jobic, O. Bouloussa, V. Baumruk and C. Coulombeau, *J. Phys. Chem. B*, 1999, **103**, 10934.
59 G. Shen, M. F. G. Anand and R. Levicky, *Nucleic Acids Res.*, 2004, **32**, 5973.
60 K. I. Miyamoto, K. I. Ishibashi, R. T. Yamaguchi, Y. Kimura, H. Ishii and M. Niwano, *J. Appl. Phys.*, 2006, **99**.