A COMBINED *ab initio* AND DENSITY FUNCTIONAL STUDY OF THE ELECTRONIC STRUCTURE OF THYMINE AND 2-THIOTHYMINE RADICALS

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Dedicated to Professor Rudolf Zahradník on the occasion of his 75th birthday.

The electronic and energetic properties of thymine (**1**) and 2-thiothymine (**2**) and their neutral and positively charged radicals are considered by a combined *ab initio* and density functional theory approach. It is conclusively shown that ionization of **1** and **2** greatly facilitates deprotonation of the formed radical cations thus making the proton transfer between charged and neutral precursor species thermodynamically favourable. The adiabatic ionization potential of **1** and **2** are analysed. It appears that ADIP(**1**) is larger than ADIP(**2**) by 10 kcal/mol, because of greater stability of the highest occupied molecular orbital (HOMO) of the former. It is also shown beyond any doubt that the spin density in neutral and cationic radical of **2** is almost exclusively placed on the σ-3p AO of sulfur implying that these two systems represent rather rare sigma-radicals. In contrast, the spin density of radicals of **1** is distributed over their π-network.
Keywords: Nucleic acids; DNA; Nucleobases; Pyrimidines; Thymine; 2-Thiothymine; Spin density; Ionization potentials; *Ab initio* calculations; DFT.

The effects of ionizing radiation on DNA have attracted a lot of research interest in the last few decades, since it can cause dramatic effects such as genetic mutations. The radiation damage predominantly occurs *via* the formation of the nucleic acid bases and sacharide radicals, which may lead to single-strand breaks[1] and DNA-DNA or DNA-protein crosslinks[2–4]. It is very difficult to investigate the effects of radiation on DNA by experimental techniques and methods like electron spin resonance (ESR) and/or electron nuclear double resonance (ENDOR) because of the complexity of the full DNA. The most accurate studies are those for simple crystals of the nucleic

bases and some related derivatives at low temperatures, but even in this case the spectra are "contaminated" by the presence of the hydrogen bonding between subunits of the crystal structures[4]. It is gratifying that the computational chemistry can supply important complementary information and provide help in interpreting the measured data. In the present work we examine the spatial and electronic structure of radicals of thymine and 2-thiothymine and their deprotonated forms by using reliable theoretical models. The former compound is one of the more important nucleic acid bases, which by absorption of UV radiation undergoes photodimerization leading to carcinogenic effects[5]. The latter molecule is an unnatural nucleic base, which serves as an intrinsic photo label for specific targeting of the selected sites in nucleic acids[6,7]. In addition, 2-thiothymine seems to be the first σ-radical produced by γ-radiation[8], which makes this system particularly interesting. The studied molecules are depicted in Fig. 1.
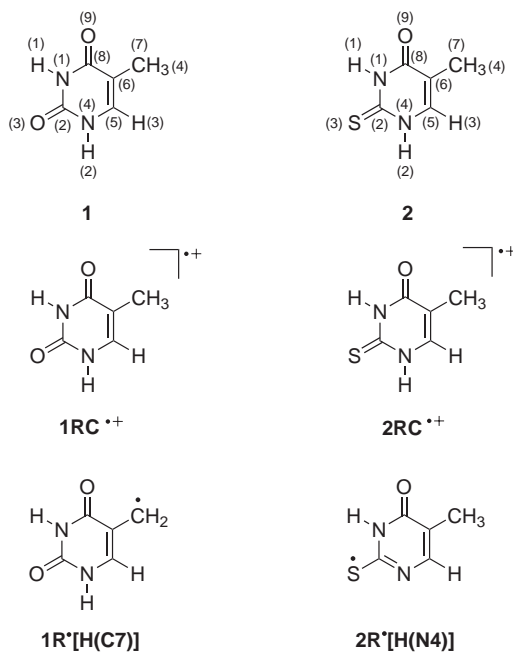

Fig. 1

Schematic representation and atom numbering of thymine (**1**), 2-thiothymine (**2**) and their radical cations **RC**$^{•+}$ and neutral radicals **R**$^{•}$. Atoms given within square parentheses denote proton detached in the deprotonation process

THEORETICAL METHODOLOGY

A theoretical model of choice should be the best compromise between accuracy and reliability on one hand and feasibility and economy on the other. Since we would like to use the selected model in studying interactions and dimerization of pyrimidine bases later on, the theoretical level of choice should be as simple as possible. There are two ways in studying open-shell radicals. One can use either spin-restricted or spin-unrestricted wave functions. The former involves doubly occupied molecular orbitals with one or more singly occupied MOs. They are eigenfunctions of the spin-squared operator and give pure spin states. Their drawback is that the spin localization in radicals is sometimes unrealistic[9]. The spin-unrestricted approach optimizes α and β MOs independently thus leading to lower Hartree–Fock energies than the restricted procedure, because there is a greater flexibility in accommodating electrons with the same spin. Spin-unrestricted wave functions are in addition less computationally demanding than spin-restricted wave functions[10], but suffer from contamination of higher spin states, since they are no longer eigenfunction of the $\hat{S}^2$ operator. Although this shortcoming can be alleviated by introducing spin-projected energy corrections[11], we would prefer using the restricted open-shell formalism in optimizing the total molecular energy and spatial structure, All calculations are performed by using Gaussian 98 suite of programs[12].

Selection of the Theoretical Model

The most economical approach in optimizing molecular geometries, which takes into account a large portion of the electron correlation effects, is DFT Becke's three-parameter exchange functional (B3)[13,14] combined with Lee, Young and Parr correlation term (LYP)[15]. Further, a reasonably efficient and well balanced basis set is provided by Pople's 6-31G* functions[10,12] giving rise to the B3LYP/6-31G* model. The next step in designing a more accurate theoretical procedure is selection of the method, which should be used in executing the single-point calculations on the B3LYP/6-31G* optimized geometries. For this purpose, we have to test the model against the experimental data related to some critical molecular properties. One of them is certainly the ionization potential (IP), which influences to a large extent basicity and acidity of molecules[16,17] and affects the molecular reactivity in general. Protonation of the radical anions and deprotonation of the radical cations in production of neutral nucleotide radicals are in particular important[4,18,19] to mention just these two processes, where

the IPs play an important role. The ionization potentials (IPs) for thymine and 2-thiothymine (depicted in Fig. 1) are calculated by several theoretical models and compared with available experimental data[20,21] in Table I. The models employed encompass the standard B3LYP DFT scheme, ROHF/6-311+G**//B3LYP/6-31G* model abbreviated thereafter as M(I) and ROMP2(fc)/6-311+G**//B3LYP/6-31G* approach, which in a shorthand notation will read M(II). Perusal of the presented data shows that the M(II) model gives both the vertical ionization potentials (VIP) and the adiabatic ionization potentials (ADIP) of thymine in excellent agreement with experiment. On the other hand simple B3LYP/6-31G* and the HF (M(I)) model fail to provide quantitative information on VIP and ADIP of thymine, thus being unsatisfactory for our purposes. Since the employed basis set 6-311+G** is quite flexible, we believe that the M(II) model offers also reliable VIP and ADIP values for 2-thiothymine, where the measured data are not existent. In this context it is useful to mention that the ROMP2(fc)/6-311+G** theoretical framework proved very useful in reproducing VIPs and ADIPs of organic molecules[22]. Hence, results obtained by the M(II) model calculations will be used in the forthcoming discussion, if not stated otherwise.

RESULTS AND DISCUSSION

It is convenient to break down VIPs and ADIPs of **1** and **2** into various contributions according to our earlier analysis[22] and to briefly discuss changes

TABLE I
Koopmans' vertical and adiabatic first ionization potentials of thymine (**1**) and 2-thiothymine (**2**) by various theoretical models (in eV)[a]

Molecule	Model	Koopmans	Vertical	Adiabatic
1	B3LYP/6-31G*	6.57	8.72	8.50
	M(I)	9.67	8.52	8.11
	M(II)	–	9.15 (9.14)[b]	8.86 (8.87)[c]
2	B3LYP/6-31G*	6.21	8.24	8.16
	M(I)	9.02	7.82	7.70
	M(II)	–	8.34	8.41

[a] Experimental values are given in parentheses. M(I) and M(II) models are: M(I), ROHF/6-311+G**//B3LYP/6-31G*; M(II), ROMP2(fc)/6-311+G**//B3LYP/6-31G*. [b] Ref.[20]. [c] Ref.[21]

in various terms. They are displayed in Table II. It can be shown that the vertical ionization potential is a sum of four terms:

$$\text{VIP[M(II)]} = -\varepsilon_1 + E_\text{r}(\text{orb})_{n-1}^{\text{CN}} + \Delta E(\text{corr})_{n,n-1}^{\text{CN}} + \Delta(\text{ZPVE})_{n-1,n}^{\text{CN}} \ , \qquad (1)$$

where ε_1 is the orbital energy of the HOMO calculated in Koopmans' clamped nuclei-frozen electron density approximation. The orbital relaxation energy of the radical cation computed at the clamped nuclei (CN) geometry is given by:

$$E_\text{r}(\text{orb})_{n-1}^{\text{CN}} = E(\text{HF})_{n-1}^{\text{CN}} - E(\text{HF})_n + \varepsilon_1 \ , \qquad (2)$$

where the Hartree–Fock energies $E(\text{HF})_n$ and $E(\text{HF})_{n-1}^{\text{CN}}$ of the ground state and the radical cation are calculated by using the B3LYP/6-31G* geometry of the ground state. The basis set employed in Hartree–Fock calculation was 6-311+G**. Further, the term $\Delta E(\text{corr})_{n,n-1}^{\text{CN}}$:

$$\Delta E(\text{corr})_{n,n-1}^{\text{CN}} = E(\text{corr})_n - E(\text{corr})_{n-1}^{\text{CN}} \qquad (3)$$

gives a difference in the correlation energy between the molecular ground state and molecular radical cation employing geometry of the neutral molecule (CN). Finally, $\Delta(\text{ZPVE})_{n-1,n}^{\text{CN}}$ provides a difference in the zero point vibrational energies between the molecular cation and neutral molecule:

TABLE II
Breakdown of VIP and ADIP values for thymine (**1**) and 2-thiothymine (**2**) into various contributions (in kcal/mol)[a]

Contribution	Thymine (**1**)	2-Thiothymine (**2**)
$-\varepsilon_n$(Koopmans)	$(223.0)_1$	$(208.1)_1$
$E_\text{r}(\text{orb})_{n-1}^{\text{CN}}$	–18.4	–27.8
$\Delta E(\text{corr})_{n,n-1}^{\text{CN}}$	33.5	15.8
$\Delta(\text{ZPVE})(\text{corr})_{n-1,n}^{\text{CN}}$	–1.2	–0.9
VIP[M(II)]	236.9	195.2
$E_\text{r}(\text{nucl})_{n-1}$	–17.6	–2.9
$\Delta E(\text{corr})_{n-1,n-1}^{\text{RN}}$	–16.1	1.5
$\Delta(\text{ZPVE})_{n-1,n-1}^{\text{RN}}$	0.2	–0.7
ADIP[M(II)]	203.4	193.1

[a] Subscript 1 denotes the first Koopmans' ionization potential.

$$\Delta(\text{ZPVE})_{n-1,n}^{\text{CN}} = (\text{ZPVE})_{n-1}^{\text{CN}} - (\text{ZPVE})_n \ . \tag{4}$$

The adiabatic ionization potential can be expressed as VIP and some correction terms:

$$\text{ADIP}[\text{M(II)}] = \text{VIP}[\text{M(II)}] + E_r(\text{nucl})_{n-1} + \Delta E(\text{corr})_{n-1,n-1}^{\text{RN}} + \Delta(\text{ZPVE})_{n-1,n-1}^{\text{RN}} \ . \tag{5}$$

Here, the nuclear relaxation effect on the HF energy is given as:

$$E_r(\text{nucl})_{n-1} = E(\text{HF})_{n-1} - E(\text{HF})_{n-1}^{\text{CN}} \tag{6}$$

and the corresponding change in the correlation energy is:

$$\Delta E(\text{corr})_{n-1,n-1}^{\text{RN}} = E(\text{corr})_{n-1}^{\text{CN}} - E(\text{corr})_{n-1} \tag{7}$$

Finally, $\Delta(\text{ZPVE})_{n-1,n-1}^{\text{RN}} = (\text{ZPVE})_{n-1} - (\text{ZPVE})_{n-1}^{\text{CN}}$. Inspection of the results presented in Table II shows that a lion's share in determining both VIP and ADIP potentials has Koopmans' IP^{Koop} term. Let us consider VIP of thymine first. The outgoing electron comes from π-MO depicted in Fig 2. It appears that $\text{IP}^{\text{Koop}}(\mathbf{1})$ is diminished by 18.4 kcal/mol by the orbital relaxation while keeping the nuclei fixed. In contrast, the electron correlation term $\Delta E(\text{corr})_{n,n-1}^{\text{CN}}$ increases $\text{IP}^{\text{Koop}}(\mathbf{1})$ by an overwhelming amount of 33.5 kcal/mol leading to increased VIP($\mathbf{1}$) relative to the IP^{Koop} by 13.9 kcal/mol. This is a consequence of the fact that the electron correlation in the ground state of the neutral molecule is larger than in its radical cation. It should be mentioned that higher VIP($\mathbf{1}$) than $\text{IP}^{\text{Koop}}(\mathbf{1})$ is more an exception than a rule, as the earlier analysis shows on a large set of small molecules involving first- and second-row atoms[22]. Both nuclear relaxation and $\Delta E(\text{corr})_{n-1,n-1}^{\text{RN}}$ term lead to lowering of VIP($\mathbf{1}$) by –17.6 and –16.1 kcal/mol, respectively, yielding the adiabatic ionization potential ADIP($\mathbf{1}$) = 203.4 kcal/mol.

A different picture takes place in 2-thiothymine ($\mathbf{2}$), although the ejected electron originates also from the π-MO of the ring (Fig. 2). The orbital relaxation is a predominating term leading to a decrease in VIP($\mathbf{2}$) compared with $\text{IP}^{\text{Koop}}(\mathbf{2})$. Somewhat surprisingly, both the nuclear relaxation term and a change in the correlation energy $\Delta E(\text{corr})_{n-1,n-1}^{\text{RN}}$ due to the geometry optimization of the radical cation are very small and of different sign. Consequently, they practically cancel out implying that ADIP($\mathbf{2}$) $\cong$ VIP($\mathbf{2}$). It should be mentioned that the changes in ZPVEs in both systems $\mathbf{1}$ and $\mathbf{2}$ upon ionization are small and can be neglected at least in the qualitative discussions of VIPs and ADIPs. As a final comment, we would like to point
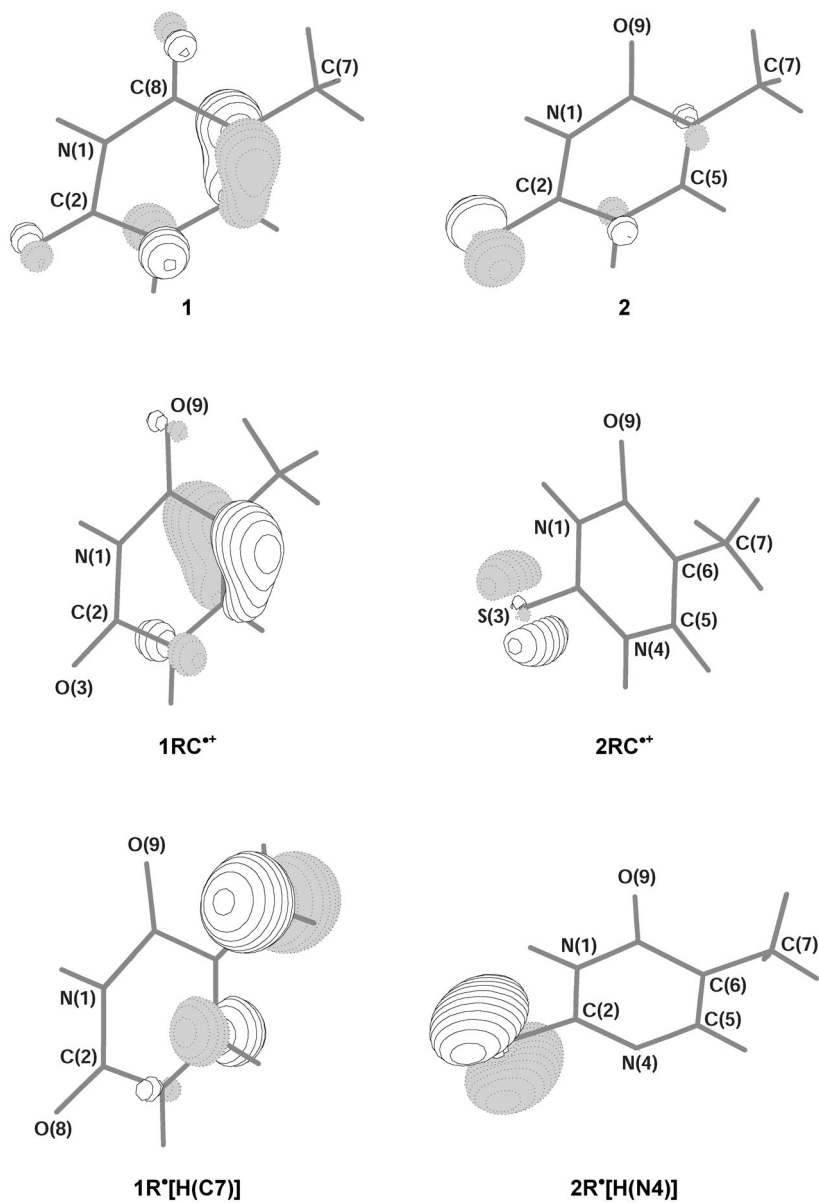
FIG. 2
HOMO orbitals in **1**, **2** and their neutral and cationic radicals

out that ADIPs of **1** and **2** are smaller than the corresponding IP^{Koop} values by 19.6 and 15.0 kcal/mol, respectively. The difference ADIP(**1**) – ADIP(**2**) = 10.3 kcal/mol is *inter alia* a consequence of the fact that it is far less costly to ionize HOMO in **2** than to eject an electron from the π-system of **1**.

The main focus of the present work is the relative stability of radical cations and neutral radicals of **1** and **2** as well as their spin-density distributions. The energetic properties are summarized in Table III. A point of considerable interest is deprotonation of radical cations since the latter are not stable and easily give up proton in real environment. Moreover, it seems that proton-transfer reactions between the ionized nucleic acid base pairs are important ingredients of the ion radical stabilization and charge migration in DNA[23]. It appears that the lowest deprotonation energy (DPE) in thymine radical cation is required for abstraction of the H4 proton attached to the methyl carbon atom C(7) thus forming methylene radical center. The corresponding DPE value is rather small, which bears some relevance for the deprotonation process (see below). In 2-thiothymine radical cation, there are two competitive sites for efficient deprotonation. The first is proton of the methyl group with DPE[H(C7)] = 206.0 kcal/mol, and a slightly more favourable deprotonation N(4) position with DPE[H(N4)] = 205.4 kcal/mol. It is interesting to compare DPEs of radical cations with the corresponding DPEs of neutral species for the same positions. It appears that radical cation formation greatly facilitates deprotonation process. For instance, it is easier to deprotonate H(N4) position in both radical cations by some 120 kcal/mol than in neutral thymine and 2-thiothymine. An even more dramatic change is found for the H(C7) position, where this difference assumes values as high as 172 and 160 kcal/mol for thymine and 2-thiothymine, respectively (Table III). The most interesting finding, however, is that the proton affinities of thymine and 2-thiothymine are 204.1 and 204.5 kcal/mol, respectively. In both cases the most basic position is the carbonyl oxygen O(9). Thus we can conclude that the proton transfer from radical cations of **1** and **2** to nucleic acid bases like, *e.g.*, neutral thymine is a thermodynamically favourable process.

The structural data and spin-density distributions are presented in Table IV. The molecular geometries are calculated by the B3LYP/6-31G* method, which is generally considered as reliable enough for predicting molecular equilibrium structures. As to the spin densities, they are computed at the simple ROHF/6-311+G** level of theory by using B3LYP geometries. Consequently, some care has to be exercised in interpreting the spin-density results in view of the approximate nature of the restricted open shell Hartree–Fock model. This is the reason why we shall use it only for qualitative pur-

TABLE III
Total molecular energies of radical cations and neutral radicals (in a.u.) and deprotonation energies DPEs (in kcal/mol) obtained by the M(II) theoretical model[a] and acidity of thymine and 2-thiothymine

Molecule energies	Radical cation	Neutral radical H(N1)	Neutral radical H(N4)	Neutral radical H(C5)	Neutral radical H(C7)	Neutral molecule	Anion H(N4)	Anion H(C7)
Thymine								
E[M(II)]	-452.72564	-452.34377	-452.38798	-452.36437	-452.40068	-453.05135	-452.50551	-453.43269
DPE	–	242.2	214.5	229.3	206.5		334.0	378.0
2-Thiothymine								
E[(MII)]	-775.31213	-774.95193	-774.97216	-774.93353	-774.97122	-775.62103	-775.08643	-775.02416
DPE	–	218.1	205.4	229.6	206.0		327.1	365.4

[a] Position of the abstracted proton is given in parentheses.

poses. In discussing geometry parameters of radical cations and neutral radicals it is useful to have visual representations of HOMOs of these species and compare them with HOMO orbitals in the parent compounds **1** and **2**. It was mentioned already that ionization of **1** involves ejection of an electron from the π-HOMO of the ring thus forming radical cation **1RC•+**. This leads to a rearrangement of the π-density in the ring as evidenced by changes in bond distances. For instance, bond distances in the O(3)=C(2)–N(1)–C(8) fragment are shortened, whereas C(2)–N(4) bond

TABLE IV
Selected geometric parameters obtained at the B3LYP/6-31G* level of theory and total atomic spin densities of radical cation and neutral (deprotonated) radical of thymine and 2-thiothymine calculated by the ROHF/6-311+G**//B3LYP/6-31G* model[a]

Molecule	Bond	Neutral molecule	Radical cation	Neutral radical[b]	Atom	Radical cation	Neutral radical[b]
1	N1–C2	1.387	1.373	1.391	N1	0.001	0.000
	C2–O3	1.218	1.201	1.218	C2	0.005	0.008
	C2–N4	1.390	1.449	1.387	O3	0.017	0.007
	N4–C5	1.380	1.327	1.378	N4	0.113	0.016
	C5–C6	1.352	1.409	1.393	C5	0.168	0.179
	C6–C7	1.500	1.475	1.390	C6	0.601	0.000
	C6–C8	1.468	1.493	1.492	C7	0.013	0.769
	C8–O9	1.222	1.211	1.218	C8	0.007	0.006
	C8–N1	1.408	1.402	1.400	O9	0.039	0.002
2	N1–C2	1.370	1.347	1.377	N1	–0.008	0.002
	C2–S3	1.667	1.704	1.705	C2	0.046	0.012
	C2–N4	1.373	1.363	1.344	S3	0.950	0.975
	N4–C5	1.380	1.367	1.347	N4	–0.011	–0.008
	C5–C6	1.353	1.374	1.386	C5	0.013	0.006
	C6–C7	1.500	1.484	1.491	C6	–0.004	–0.001
	C6–C8	1.466	1.480	1.466	C7	0.001	0.002
	C8–O9	1.220	1.205	1.223	C8	0.006	0.010
	C8–N1	1.413	1.431	1.400	O9	0.001	0.002

[a] Löwdin partitioning[24] of the mixed density is utilized in extracting the spin densities on atoms. [b] Neutral radical corresponds to **1R•[H(C7)]** for thymine and **2R•[H(N4)]** for 2-thiothymine.

length is significantly stretched. In addition, N(4)–C(5) is substantially condensed, whilst both C(5)=C(6) and C(6)–C(8) bonds are lengthened. Interestingly, deprotonation of **1RC•+** at C(7) atom yielding **1R•[H(C7)]** make the bond distances practically equal to those of the neutral molecule **1** with a notable exception at the C(6) center. This is in accordance with intuition since deprotonation introduces a rehybridization of the C(7) atom, leading to shortening of the C(6)–C(7) bond due to increased hybridization s-character. Moreover, the unpaired spin density is placed on the π-AOs at atoms C(7) and C(5) (Table IV), which is well described by the HOMO in **1R•[H(C7)]**. Further, an efficient bonding interaction along the C(5)=C(6) bond is obviously destroyed in **1R•[H(C7)]**, in contrast to the situation in both **1** and **1RC•+**. Concomitantly, the C(5)=C(6) bond is lengthened in neutral radical **1R•[H(C7)]**. There is a qualitative similarity in the HOMOs of **1** and **1RC•+** with a notable difference that there is one electron less in the latter. Hence, the C(5)=C(6) should be extended in **1RC•+** relative to the parent molecule **1**. By the same token, the N(4)–N(5) bond should be shortened in **1RC•+**, because the antibonding out-of-phase density is decreased. All these conjectures deduced by inspection are corroborated by the calculated distances given in Table IV. In 2-thiothymine, the situation is less transparent because there is an inversion of HOMOs in going from **2** to **2RC•+** and **2R•[H(N4)]**. In **2**, the highest occupied orbital is π-HOMO, whereas the spin-density in **2RC•+** and **2R•[H(N4)]** is placed almost exclusively on the in-plane 3p AO of sulfur (by 0.95|e| and 0.98|e|, respectively), which subsequently becomes HOMO. Therefore, a more detailed analysis of the σ- and π-bond orders would be necessary here to interpret the changes in bond distances. The most important conclusion, however, is that **2RC•+** radical cation and **2R•[H(N4)]** radical are the sigma radicals, which is in accordance with the experimental evidence[8]. It appears that it is a very rare case as far as their production by the γ-radiation technique is concerned. On the other hand, it seems that the π-radicals occur more readily, which is also the case with **1RC•+** and **1R•[H(N4)]** systems, where the π-spin density is distributed preponderantly over C(5), C(6) and C(7) carbon atoms. Although the ROHF/6-311+G** results should be taken *cum grano salis*, these qualitative conclusions seem to be warranted.

CONCLUSIONS

We have shown that ionization of thymine (**1**) and 2-thiothymine (**2**) greatly facilitates deprotonation of these two species. The latter is energetically slightly smaller than the proton affinities of **1** and **2** implying that

proton transfer between radical cations and their neutral precursor compounds should be thermodynamically favourable. The adiabatic ionization potentials of **1** and **2** are analysed and it is shown that the former is larger due to properties of the initial state mirrored by the Koopmans theorem, *i.e.*, by the greater stability of the highest occupied molecular orbital. The spin density in **2RC$^{\bullet+}$** and **2R$^{\bullet}$[H(N4)]** is placed almost exclusively in the σ-3p AO of sulfur in accordance with experiment[8] implying that they both belong to a class of the σ radicals. In contrast, the spin density is placed in π-MOs and distributed predominantly over C(5) and C(6) atoms (0.17|e| and 0.60|e|, respectively) in **1RC$^{\bullet+}$** and over C(5) and C(7) atoms (0.18|e| and 0.77|e|, correspondingly) in **1R$^{\bullet}$[H(N4)]**.

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