Solvation Effects Alter the Photochemistry of 2-Thiocytosine

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Abstract

Radiationless deactivation channels of 2-thiocytosine in aqueous environment are revisited by means of quantum-chemical simulations of excited-state absorption spectra, and investigations of potential energy surfaces of the chromophore clustered with two water molecules using the algebraic diagrammatic construction method to the second-order (ADC(2)), and multireference configuration interaction with single and double excitations (MR-CISD) methods. We argue that interactions of explicit water molecules with thiocarbonyl group might enable water-chromophore electron transfer (WCET) which leads to formation of intersystem crossing that was not considered previously. This is the first example of a WCET process occurring in the triplet manifold of electronic states. This phenomenon might explain nonradiative decay of the triplet state population observed in thiopyrimidines in the absence of molecular oxygen. According to our calculations this WCET process might also entail a subsequent, virtually barrierless, electron-driven proton transfer (EDPT) resulting in the formation of hydroxyl radical which could further participate in photohydration or deamination reactions.

1. Introduction

Photochemistry and photophysics of thiated nucleobases has recently attracted increasing attention, owing to to their potential use as photosensitizers in pharmacological
applications [11], nanotechnology [2], and their intriguing properties in promoting prebiotically credible chemical reactions and processes [3–7]. For instance, α-2-thioribocytidine was recently demonstrated to be a crucial intermediate in the photochemical synthesis of β-ribonucleosides under the conditions of the early Earth [7]. The prebiotic background of thiated nucleobases is also supported by presence of naturally occurring thiobases in mitochondrial tRNA of some bacteria and yeasts [8–10]. However, the main focus on thiated nucleobases stems from their potential applications in photochemotherapy [11–13], photodynamic therapies in treating skin disorders [14], superficial tumors [15–16] and bladder cancer [12]. It is worth noting that thioguanine is already used as a therapeutic agent for lymphoblastic leukemia [17] and breast cancer [18], while 2-thiocytosine influences the mitosis of human lymphocytes [19] and shows cytotoxic [20], anticancer [21] and antibacterial activity [22].

Characterization of photochemical and photophysical properties of thiated nucleobases is crucial for understanding the mechanisms governing their phototherapeutic activity and photoinduced chemical reactions. In the past decade, various spectroscopic and theoretical studies aimed to scrutinize the photophysics and photochemistry of thiocytosine, thioguanine, thioracil, and thiothymine [13, 23–34]. It is now well established that the most attractive features of thionucleobases are their structural similarity to canonical nucleobases combined with considerable singlet-triplet spin-orbit couplings (SOC) that enables efficient population of long-lived triplet states and efficient generation of singlet oxygen [1, 35]. Recently joint transient absorption spectroscopy (TAS) and computational studies of Mai et al. [33] revealed that near unity triplet yields often observed in thionucleobases may also be explained by relatively high energies and consequently lower accessibility of $S_1/S_0$ conical intersections when compared to the lowest-energy intersystem crossings.

Although many aspects of the photophysics of thionucleobases are now quite well understood, previous computational studies focused predominantly on isolated chromophores. This may be a serious limitation obscuring interpretation of the experimental results, since recently there is a growing amount of data suggesting that water molecules may actively participate in photochemistry of hydrated heterocycles by modifying state crossings and, more importantly, opening new photorelaxation channels which are not
accessible in the gas phase. The examples include microhydrated adenine \cite{36-39}, cytosine and cystidine \cite{40}, eumelanine \cite{41}, and azole chromophores \cite{42, 43}. For instance, Barbatti demonstrated that water molecules may stabilize the excited $^1n_N\pi^*$ state in 7H-adenine through the interaction of the $n_N$ orbital of adenine with the $p_z$ orbital of the neighbouring water molecule \cite{37}. This permits radiationless deactivation through the $n\pi^*/S_0$ state crossing, which is induced by \textit{water-to-chromophore electron transfer} (WCET). More recently, some of us suggested that the long-lived dark state observed experimentally in aqueous cytidines might correspond to the $^1n\pi^*_CT$ excited state also involved in WCET \cite{40}. Consequently, understanding how the surrounding water molecules could affect the photochemistry of thionucleobases (\textit{e.g.} thiocytosine) is the obvious next step in providing their complete photochemical characteristics in native environments.

In this work, we show that microhydration of 2-thiocytosine by two water molecules [2tCyt-(H$_2$O)$_2$] may enable a similar WCET process, which could lead to the formation of yet another intersystem crossing in microsolvated 2tCyt that was not considered previously. This phenomenon might also explain nonradiative decay of the triplet state population observed in thiopyrimidines in the absence of molecular oxygen \cite{35}.

2. Computational methods

The ground-state minimum energy geometries and harmonic vibrational frequencies of microhydrated 2tCyt were computed at the MP2/cc-pVTZ level \cite{44-47}. The stationary points on excited state potential energy surfaces were located using the algebraic diagrammatic construction to the second order method [ADC(2)] method \cite{48-50} and the cc-pVTZ basis set as implemented in the \textsc{Turbomole} 7.1 package \cite{51}. Vertical excitation energies were obtained at the ADC(2)/cc-pVTZ level, assuming the $S_0$ geometry optimized using the MP2/cc-pVTZ method. Solvation effects on the vertical excitation energies exerted by bulk water were estimated using the non-equilibrium polarizable continuum solvation model (PCM) combined with ADC(2)/cc-pVTZ method which are implemented in the \textsc{Q-Chem} 5.0 package \cite{52}. The perturbed state specific (ptSS) approach was used either in a fully consistent perturbation-energy-and-density (PTEED) or perturbation-density (PTD) variant \cite{53-54}. The orbital character of the considered excited states was assigned based on natural transition orbitals \cite{55} (NTOs).
obtained using TheoDore package \[56\]. The potential energy (PE) profiles for WCET mechanism were calculated using the ADC(2) and MP2 methods for the excited and ground electronic states, respectively, using the TURBOMOLE 7.1 package. The PE scans were performed based on linear interpolation in internal coordinates (LIIC) between the appropriate stationary geometries.

The minimum-energy crossing points (MECPs) were located using the sequential penalty constrained optimization method proposed by Levine et al. \[57\] employing energies and analytical gradients computed at the ADC(2) and MP2 levels, for the excited and ground state, respectively, and assuming the cc-pVTZ basis set. The MECPs were optimized using CIOpt package \[57\] which was interfaced with the TURBOMOLE 7.1 program. This approach was also employed to locate $T_2(^3\pi_S\pi^*)/T_1(^3n_S\pi^*)$ MECP, which in terms of non-adiabatic transition state theory \[58\] represents the saddle point (transition state) separating the ring-puckered and WCET minima on the $T_1$ hypersurface. The transition state structure was verified by the assignment of the orbital character of the degenerated $T_2$ and $T_1$ states, and the dominant contributions were associated with the $^3\pi_S\pi^*$ (ring-puckered) and $^3n_S\pi^*$ (WCET) characters respectively.

To validate whether the ADC(2) method is appropriate for the studied case the $T_1$ ($n_S\pi^*$) minimum-energy and $T_1/S_0$ MECI structures of microhydrated 2tCyt obtained using ADC(2) method were reoptimized at MR-CISD(2,3)/6-31++G(d,p) level using the Columbus 7.0 package \[59\]. The reference configurations were obtained by distributing two electrons among occupied $n_S$ and two virtual $\pi^*$ orbitals. The Davidson size-extensivity correction was applied to all MR-CISD energies (MR-CISD+Q). The spin-orbit coupling (SOC) was computed for the $S_1/T_2$ MECP ISC at the MS-CASPT2/cc-pVTZ-DK level using MOLCAS 8.0 package \[60\]. The 2nd order Douglas–Kroll–Hess Hamiltonian was adopted in these computations to include scalar relativistic effects.

The excited-state absorption (ESA) spectra of isolated and microhydrated 2tCyt were simulated employing the nuclear ensemble method \[61\], with 500 initial conditions generated from a Wigner distribution for all vibrational normal modes calculated for the appropriate minimum-energy excited state structures using the ADC(2) method and the cc-pVTZ basis set. The required excitation energies and oscillator strengths for the 11 lowest excited states were obtained using ADC(2) method and the same basis set. The
ESA spectra were simulated using the modified Newton-X 2.0 program [62] which was interfaced with the Turbomole 7.1 package.

3. Results and Discussion

3.1. Vertical excitations in the light of UV-absorption spectrum of 2-thiocytosine

The stationary absorption spectrum of 2tCyt in water solution shows a broad band with maxima at 270 nm (4.59 eV), 240 nm (5.17 eV) and a shoulder at about 220 nm (5.64 eV) [63]. Based on the results of ab initio calculations, the first peak was assigned by Mai et al. to S_4 and S_2 states having similar ^1π_Sπ^* character (centered around the thiocarbonyl group but associated with different π^* orbitals), and the remaining features to the S_6 and S_8 states, respectively, arising from ^1ππ^* transitions within the aromatic ring [63]. The 2tCyt water cluster used in these calculations was constructed by saturating all the possible water-chromophore hydrogen bonds, and the vertical excitation energies were computed using the multi-state complete active space perturbation theory method (MS-CASPT2) including the non-equilibrium polarizable continuum (PCM) implicit solvation model.

The vertical excitations of the 2tCyt-(H_2O)_2 cluster considered in present contribution (cf. Fig. 1), computed using the ADC(2)/cc-pVTZ method with non-equilibrium ptSS-PCM implicit solvation model of bulk water in a fully self-consistent PTED variant, are shown in Tab. 1. The corresponding gas-phase data are shown in Tab. S1 in the Supplementary Information (SI). Generally, our results are in agreement with earlier MS-CASPT2 predictions with one notable exception. In both ADC(2) and MS-CASPT2 calculations the low-lying ^1n_Sπ^* and ^1π_Sπ^* states are destabilized in polarizable medium but to different extent. That is why we do not observe the change of ordering of S_1 and S_2 states in our ADC(2) results that is predicted by the MS-CASPT2/PCM approach [63]. It is worth noting that the reaction field in MS-CASPT2 calculations was computed at the CASSCF level, thus lacking the dynamic correlation effects, while the ADC(2)/ptSS-PCM(PTED) calculations were self-consistent with the correlated electron density. Our assumption is further confirmed by the fact that the ordering of the ^1n_Sπ^* and ^1π_Sπ^* states is exchanged only in the MS-CASPT2 calculations including the PCM solvation.
Table 1: Vertical excitation energies of microhydrated 2tCyt, computed using ADC(2)/ptSS-PCM(PTED)/cc-pVTZ approach, assuming the S\textsubscript{0} structure optimized at the MP2/PCM/cc-pVTZ level. The corresponding MS-CASPT2(14,10)/PCM/cc-pVDZ values were taken from Ref. \textsuperscript{63} and are shown for the reference.

| State / Transition | ADC(2) | MS-CASPT2 |
|--------------------|--------|-----------|
|                    | E\textsubscript{exc}/[eV] | f\textsubscript{osc} | E\textsubscript{exc}/[eV] | f\textsubscript{osc} |
| S\textsubscript{1}  | 4.00   | 2.1·10\textsuperscript{-4} | 4.50  | 0.02   |
| S\textsubscript{2}  | 4.30   | 0.10    | 4.23  | 0.01   |
| S\textsubscript{3}  | 4.40   | 1.7·10\textsuperscript{-3} | 5.12  | 0.02   |
| S\textsubscript{4}  | 4.52   | 0.30    | 4.60  | 0.40   |
| T\textsubscript{1}  | 3.73   | -       | -     | -      |
| T\textsubscript{2}  | 3.93   | -       | -     | -      |
| T\textsubscript{3}  | 4.00   | -       | -     | -      |

model, while inclusion of five explicit water molecules without polarizable dielectric environment in the MS-CASPT2 calculation yielded a result which is in qualitative agreement with the ADC(2)/ptSS-PCM(PTED) calculations \textsuperscript{63}.

Since the ordering of states is important for further discussion, we decided to reoptimize the structure with five explicit water molecules from Ref. \textsuperscript{63} at the MP2/PCM/cc-pVTZ level. This geometry was further used to compute vertical excitation energies using the ADC(2)/ptSS-PCM(PTED)/cc-pVTZ approach. The results indicate that the \textsuperscript{1}n\textsubscript{S}π\textsuperscript{*} transition is still the lowest-lying state (4.40 eV) and the second one is the \textsuperscript{1}π\textsubscript{S}π\textsuperscript{*} state (4.54 eV), albeit the energy difference between these excitations has decreased. We also performed calculations with the same cluster surrounded by more than 200 water molecules represented by the effective fragment potentials (EFP) and implicit solvent model at the ADC(2)/EFP/ptSS-PCM(PTD)/cc-pVDZ level which also show the same ordering of the low-lying states (cf. SI for details).
Figure 1: The geometries of microhydrated 2tCyt optimized using the ADC(2)/cc-pVTZ method. The $n_S$ and $\pi^*$ molecular orbitals indicate WCET character of lowest-lying $T_1$ triplet state.
3.2. Nonradiative deactivation channels of microsolvated 2-thiocytosine

The experimental transient absorption spectra (TAS) recorded for 2tCyt show broad and featureless absorption during the early 100 fs which was tentatively assigned to population of singlet $\pi_S\pi^*$ and $n_S\pi^*$ states [33]. After the initial 120 fs, the spectrum exhibits two distinct absorption maxima at about 350 and 550 nm. The former maximum is decaying after 320 fs while the latter is continually rising during the first 3.0 ps. These bands were assigned to the singlet $^1\pi_S\pi^*$ and triplet $^3\pi_S\pi^*$ states, respectively (possibly with some contribution from $^3n_S\pi^*$ transition), and the latter peak does not decay within 20 ps which confirms its assignment to the long-lived triplet state [1]. Two time constants of 210 and 480 fs were fitted for the initial dynamics, and tentatively assigned to the $S_1$/$T_2$ intersystem crossing and the $T_2$/$T_1$ internal conversion, and near unity triplet yield was reported [33]. Consequently, a substantial population of the $T_1$ ($\pi\pi^*$) state was reported after the initial 400 fs. Much less is known about deactivation of this reactive triplet state. Generally, for all thiobases solvent quenching dominates the deactivation of $T_1$ ($\pi\pi^*$) state in polar solvents while triplet self-quenching is otherwise important [35].

In order to further interpret the experimental TAS results [33] and the possible effects of explicit solvation we optimized stationary points and identified relevant MECPs of microhydrated 2tCyt at the ADC(2)/cc-pVTZ level. Here, we discuss the plausible radiationless relaxation channels (Fig. 2) upon photoexcitation at 274 nm (4.52 eV). According to Kasha’s rule, the initial population of optically bright $S_4$ state (4.52 eV) should undergo ultrafast internal conversion to the $S_2$ ($\pi\pi^*$) state. The population of the latter state may further lead to the efficient population of the $S_1$ state, which might be attained through the $S_2$/$S_1$ MECP at 3.04 eV. A competitive relaxation channel might drive the system towards the $T_2$ triplet state which could be reached by intersystem crossing in the vicinity of the $S_2(\pi\pi^*)$/$T_2(n_S\pi^*)$ MECP, which is isoenergetic with the aforementioned $S_2$/$S_1$ conical intersection (3.04 eV). The lowest-lying $T_1$ triplet state can be also accessed through ISC at $S_1(\pi_S\pi^*)$/$T_2(n_S\pi^*)$ MECP at 3.04 eV with SOC of about 163 cm$^{-1}$ and the subsequent $T_2$/$T_1$ conical intersection at 2.98 eV. In fact, the $S_1\rightarrow T_2$ ISC should be very efficient due to the molecular orbital character change, what is confirmed by sizable SOC matrix elements and nearly degenerate energy levels at the
stationary points lying close to the $S_1/T_2$ MECP. We located ring-puckered and S-out-of-plane minimum-energy structures having the energies of 2.91 and 2.95 eV (with respect to the ground state geometry), on the $T_1$ hypersurface of the 2tCyt-(H$_2$O)$_2$ cluster. These results show that the ADC(2) picture of radiationless deactivation of microsolvated 2tCyt system is compatible with the previous interpretation of TAS results and MS-CASPT2 calculations [33].

![Figure 2: Schematic representation of plausible photodeactivation channels in microsolvated 2tCyt estimated at the ADC(2)/MP2/cc-pVTZ level.](image)

Interestingly, the ring-puckered $T_1$ minimum energy structure at 2.91 eV shown in Fig. 1 displaying $3\pi_2\pi^*$ character, was also observed by Mai et al. [33]. However, according to our calculations, water molecules may significantly stabilize the $3\pi_2\pi^*$ component of the $T_1$ state through the water-chromophore electron transfer (WCET) phenomenon which leads to formation of another minimum energy structure at 2.87 eV that is accessible from the ring puckered $T_1$ minimum after passing through a modest energy barrier.
of ∼0.1 eV. This WCET process might, in fact, facilitate a radiationless deactivation channel which ensues quenching of triplet of states in aqueous 2tCyt. Below, we show a possible mechanism of such deactivation via a consecutive electron-driven proton transfer mechanism.

3.3. Water-chromophore electron transfer in microhydrated 2-thiocytosine

Fig. 1 shows minimum-energy structures of the ground and lowest-lying triplet electronic states of 2tCyt-(H₂O)₂ cluster. The 3ⁿSπ⁺ WCET minimum is characterized by substantial rearrangement of water molecules with respect to the ground-state geometry. More specifically, the water molecule which in the ground state was hydrogen-bonded to the N3 atom of 2tCyt is partially rotated in a way allowing attractive interaction between its lone-pair pₓ orbital and the nₛ orbital of thiocarbonyl group (see also Tab. S2 in the SI). This dispersion-like interaction is associated with charge transfer from the water molecule to the chromophore which amounts to approximately 0.15 electron (according to particle-hole analysis of the electronic wave-function at ADC(2)/cc-pVTZ level) [56]. The corresponding distance between the sulphur and the interacting oxygen atoms amounts to 2.40 Å and is noticeably shorter than H₂O···S distance in the electronic ground state. In contrast, the O–H bond in this water molecule, interacting through a hydrogen bond with the N3 atom of 2tCyt is extended to 1.07 Å. This structure is similar to the WCET minimum-energy crossing points reported previously for 7H-adenine and cytosine [37, 40], however, it is the first time that this phenomenon is found also in the triplet manifold and with the involvement of the thiocarbonyl group.

The 3ⁿSπ⁺ minimum-energy structure lies only 0.36 eV above the closed-shell ground state at the ADC(2) level, and the corresponding SOC between the 3ⁿSπ⁺ and S₀ amounts to 46 cm⁻¹. This indicates that 2tCyt might in fact undergo relatively efficient ISC to the electronic ground state from this T₁ minimum. The 3ⁿSπ⁺–S₀ energy gap is further reduced to 0.22 eV when more explicit water molecules are considered (i.e. in [2tCyt(H₂O)₄] cluster, cf. the SI for details). Thus the observed charge transfer and elongation of the O–H bond might initiate a proton transfer from water molecule to the N3 atom of 2tCyt. According to our calculations, such electron-driven proton transfer results in the formation of the T₁/S₀ state crossing. The corresponding MECP geometry
located at the ADC(2)/MP2/cc-pVTZ level is shown as inset in Fig. 3. This photochemical reaction leads to the formation of radical form of 2tCyt and hydroxyl radical which is known to be highly reactive and mobile. This implies that such mechanism might initiate photoinduced conversion of 2-thiocytosine to thiouracil after the subsequent migration of the hydroxyl radical to the C4 atom of the pyrimidine ring and extrusion of ammonia. The UV-induced deamination reaction was in fact observed experimentally in canonical cytosine and cytidine [64].

![Figure 3: The PE surface cuts of the lowest-lying states of microsolvated 2tCyt showing stabilization of the $3n_S\pi^\ast$ hypersurface by WCET. The PE profiles suggest that this process enables radiationless deactivation channel in polar solvent that proceeds through the $3n_S\pi^\ast \rightarrow S_0$ ISC. The plot shows linear interpolation in internal coordinates (LIIC) between the T$_1$ WCET minimum-energy geometry and the $3n_S\pi^\ast \rightarrow S_0$ MECP ISC, both located employing the ADC(2)/MP2/cc-pVTZ method.](image)

Fig. 3 shows potential energy profile corresponding to the photorelaxation pathway connecting the minimum-energy structure of $3n_S\pi^\ast$ state stabilized by WCET and the $3n_S\pi^\ast / S_0$ MECP ISC, all located at the ADC(2)/MP2/cc-pVTZ level. The shallow $3n_S\pi^\ast$ minimum visible on the left-hand side of the PE profile actually vanishes when the water cluster is extended to several explicit water molecules (cf. SI for details), indicating that in this case the electron-driven proton transfer may be a virtually barrierless process. The spin-orbit coupling (SOC) between the T$_1$ and S$_0$ states calculated for this MECP
geometry amounts to 63 cm\(^{-1}\), what suggests that the closed-shell S\(_0\) state might be efficiently repopulated at this state crossing. It should be noted though that the foregoing photodeactivation channel may also lead to the formation a triplet biradical system.

To assess applicability of ADC(2) method to describe the partially biradical \(^3n_S\pi^*\) state of microhydrated system, we employed the multireference configuration interaction with single and double excitations MR-CISD(2,3)/6-31++G(d,p) method to reoptimize its minimum-energy structure and \(^3n_S\pi^*/S_0\) state crossing. Both of these MR-CISD optimizations resulted in geometries characterized by degenerate \(^3n_S\pi^*\) and \(S_0\) states. Even though the ADC(2) results suggested a T\(_1\)-S\(_0\) energy gap of 0.36 eV in the \(^3n_S\pi^*\) minimum, such \(\Delta E\) is in fact in the infrared spectral region and consequently the corresponding state crossing might be accessible under ambient conditions. Therefore, despite small quantitative differences between the MR-CISD and ADC(2) methods, the qualitative features of the WCET minimum are correctly reproduced at the ADC(2) level. In contrast, the \(^3n_S\pi^*/S_0\) MECP associated with the proton transfer process and optimized at the MR-CISD level is higher in energy by 0.43 eV than the corresponding T\(_1\) WCET minimum. This suggests lower availability of the EDPT process than that implied by the ADC(2) method.

### 3.4. Simulations of excited-state spectra of \(2\text{-thiocytosine}\)

In order to verify our findings and compare our results to previous experimental and theoretical results of Mai at al. [33], we performed simulations of excited-state absorption (ESA) spectra for isolated \(2\text{tCyt}\) (Fig. 4a) and microhydrated \(2\text{tCyt}\) (Fig. 4b) molecules employing the nuclear ensemble method. The simulated ESA spectra can be further used in assignment of transient absorption (TAS) UV measurements. The simulated ESA spectra for the isolated molecule were obtained using the minimum-energy structures corresponding to the \(S_1\), \(S_2\), T\(_1\) ring-puckered and T\(_1\) S-out-of-plane minima optimized at the ADC(2)/cc-pVTZ level, whereas in the case of microhydrated molecules the ESA spectra were simulated assuming \(S_1\), T\(_1\) ring-puckered, T\(_1\) S-out-of-plane and T\(_1\) WCET excited state potential energy surfaces.

Comparison of the ESA spectra (Fig. 4) obtained for both isolated and microhydrated \(2\text{tCyt}\) shows similar features with somewhat redishifted absorption bands for the latter. According to the experimental TAS spectrum of \(2\text{tCyt}\) in water solution [33], there are
two distinct absorption maxima at about 350 and 525 nm which were assigned based on MS-CASPT2 calculations to the $^1\pi_S\pi^*$ and $^3\pi_S\pi^*$ states, respectively. Our simulated ESA spectra (Fig. 4a) of 2tCyt are generally consistent with these findings and show that these bands may refer to the $S_2$ (or $S_1$) and $T_1$ states in ADC(2) calculations, respectively, for which the computed absorption maxima are located at about 310 and 400 nm, respectively. It is worth noting that the latter state ($T_1$ ring-puckered minimum) has two components, mixing the $^3\pi_S\pi^*$ and $^3n_S\pi^*$ transitions, in line with what was suggested in the previous work conducted at the MS-CASPT2 level [33]. The disparity between experimental and simulated maxima (310 nm vs 350 nm) assigned to the singlet $^1\pi_S\pi^*$ state ($S_2$ or $S_1$) may be due to lack or inappropriate description of solvent effects in the simulated ESA spectrum. It should be noted though that our ESA spectra are simulated from the corresponding minimum energy geometries distorted along vibrational normal modes, and thus do not correspond to fully relaxed PE surfaces. Even more pronounced differences in the experimental and theoretical absorption bands (400 nm compared to 525 nm) are apparent for the $T_1$ ring-puckered state. However, vibrational cooling effects result in systematic blue-shift of this band during the excited state dynamics of the system and the position of the experimental maximum (525 nm) was reported at 3.7 ps. Consequently, we expect this band to undergo further hypsochromic shift at longer time delays.

The ESA spectrum simulated for the $T_1$ ring-puckered state ($^3\pi_S\pi^*$) of microhydrated 2tCyt-(H$_2$O)$_2$ reveals slight redshift of the predicted absorption maximum to 450 nm. In addition, the simulated ESA spectrum (Fig. 4b) of the $T_1$ S-out-of-plane ($^3\pi_S\pi^*/^3n_S\pi^*$) minimum-energy structure exhibits an overlapping band at 450 nm, similar to the ESA spectrum of the $T_1$ ring-puckered state. This indicates that both the $T_1$ ring-puckered and $T_1$ S-out-of-plane minima could be populated during the excited-state dynamics of aquated 2tCyt. As shown in Fig. 4b, the simulated ESA spectrum for the $T_1(^3n_S\pi^*)$ WCET minimum is characterized by high absorption in the same spectral range as the $S_1$ and $S_2$ states of both microhydrated and isolated 2tCyt. Consequently, the absorption band visible at 350 nm between 2 and 4 ps in the experimental TAS spectrum might be also the result of partial population of the $T_1(^3n_S\pi^*)$ WCET state [33]. Unfortunately, the corresponding excited-state absorption band overlaps with that of the $T_1$ S-out-of-
plane with dominant contribution from the $^3\pi_\text{S}^\pi_\text{S}^*$ configuration. Therefore, analysis of TAS measurements is probably not sufficient to provide unambiguous identification of the different states contributing to the excited-state absorption in the triplet manifold.

![Excited-state absorption (ESA) spectra for the isolated 2tCyt (a) and microsolvated 2tCyt (b) at the ADC(2)/cc-pVTZ level.](image)

Figure 4: Excited-state absorption (ESA) spectra for the isolated 2tCyt (a) and microsolvated 2tCyt (b) at the ADC(2)/cc-pVTZ level.
It is worth noting, that the WCET process is characterized by very small $T_1/S_0$ energy gaps and relatively high SOC matrix elements ($46 \text{ cm}^{-1}$) what suggests that it might not be observable in TAS measurements due to rather short lifetimes. However, population of the $^3\pi_S\pi^*$ WCET state might lead to efficient proton transfer and formation of the hydroxyl radical or even unreactive repopulation of the electronic ground state. Another scenario induced by the characteristic WCET interaction may be related to the population of the S-out-of-plane $T_1$ minimum, which according to our preliminary XMS-CASPT2 optimizations has sufficient contribution from the $^3n_S\pi^*$ state to induce the characteristic $\text{H}_2\text{O} \cdots \text{S=C}$ interaction (cf. SI for details). In each of these cases, we expect that the WCET photodeactivation channel described in detail in the previous paragraphs could efficiently quench triplet states of 2tCyt with the direct involvement of solvent molecules. Consequently the WCET process could explain the weak photosensitizing properties of aqueous 2tCyt solutions.

4. Conclusions

In order to elucidate radiationless deactivation of 2tCyt in aqueous environment, we performed computational explorations of excited-state potential energy surfaces of microhydrated 2tCyt model system. We discovered that water-chromophore electron transfer (WCET) might be the potential driving force responsible for quenching excited triplet states of the studied molecule. For the first time, we show that this characteristic WCET interaction may involve a thiocarbonyl group leading to an interaction between the $p_z$ orbital of water and the $n_S$ orbital of the chromophore. Furthermore, this is the first example of a WCET process occurring in the triplet manifold of electronic states [37, 40]. In particular, our results demonstrate that the $T_1$ topography of aqueous thionucleobases cannot be limited to the sole consideration of S-out-of-plane and ring-puckered $^3\pi\pi^*$ minima (as suggested by Bai et al.) [65], and in specific cases $^3n\pi^*$ electronic states might come into play. As shown above, very low $T_1$-$S_0$ energy gap and considerable SOC matrix elements could provide an efficient channel for the repopulation of the closed-shell electronic ground state.

Since photoinduced electron transfer processes often entail subsequent proton transfer, we considered similar possibility from the WCET minimum of microhydrated 2tCyt.
According to our ADC(2) simulations this virtually barrierless EDPT process might be resulting in the formation of hydroxyl radical which could further participate in photohydration or deamination reactions. It should be noted though that the additional MR-CISD results suggest existence of a modest energy barrier (below 0.5 eV) for this process. In fact, this phenomenon is closely related to UV-induced water splitting reactions observed for pyridine [66, 67], acridine [68] and heptazine [69]. Therefore, we suggest that further studies of thionated compounds with similar photochemical properties might be an interesting further direction for photochemical water splitting, particularly since, the aforementioned nitrogenous heterocycles exhibit predominantly singlet and not triplet reactive photochemistry.

Resuming, our study demonstrates that water molecules may modify the shapes of excited-state PE surfaces in thionucleobases, stabilize exciplex interactions and open photorelaxation channels which are not available in isolated chromophores. Since these effects cannot be reproduced theoretically by sole use of implicit solvation models or hybrid quantum mechanics/molecular mechanics (QM/MM) approach, we suggest that the inclusion of explicit QM water molecules might be the necessary next step in determining the important details of the photochemistry of aqueous thionucleobases.

**Supplementary data**

Supplementary data associated with this article can be found, in the online version including: vertical excitation energies of microhydrated 2-thiocytosine (2tCyt) in gas phase; detailed discussion of the $T_1$ minimum energy structures of microhydrated 2-thiocytosine (2tCyt) located using various methods; properties of larger microhydrated clusters and the results of QM/EFP calculations.

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