Temporary anion states of radiosensitive halopyrimidines: Shape and core-excited resonances

CrossMark

Hsiu-Yao Cheng [a],[*], Yin-Cheng Chen [a], Cheng-Jung Lin [a], Wen-Cheng Liu [a], Sheng-Hwu Hsieh [b]

[a] Department of Chemistry, Tunghai University, Taichung, Taiwan, ROC
[b] Division of Endocrinology and Metabolism, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taiwan, ROC

ABSTRACT

Halopyrimidines are known to be important radiosensitizers in the radiation treatment of cancer. The characterization of their temporary anion states (TASs) is important in the understanding of bond dissociation during such treatment. TASs, in general, can be categorized as shape resonances (SRs) and core-excited resonances (CERs). In this paper, the SRs of example compounds 2-chloro, 2-bromo, and 5-bromopyrimidine are studied via "stabilized Koopmans theorem in the framework of long range corrected density functional theory" and the CERs and possible mixture with SRs are studied via "stabilized long range corrected time-dependent density functional theory". For each of the molecules, π^*, σ^*, and several with strong Cl/Br "d" character SRs are identified below 10 eV. In addition, several π–π^*, π–σ^*, n–π^*, n–σ^*, σ–π^*, and σ–σ^* CERs are also revealed. Moreover, when interpreted as mixture of π_3^* SR with π–π^* CERs, the discrepancy between the calculated π_3^* SR and electron transmission spectroscopy experimental values can be very much reduced. Finally, to have a better understanding of these TASs in human bodies during cancer therapy, the solvent effect of water is also considered via the self-consistent reaction field method using polarized continuum model. Results indicate the TASs of these molecules are more stabilized in water but with different degrees. Our study provides a more detailed analysis of the CERs especially in the 5–10 eV energy range. It will definitely help us in understanding the dissociative electron attachment process of the nucleobases.

1. Introduction

Halopyrimidines have been known as an important class of molecules in cancer treatment. It is believed that the incorporation of these molecules in DNA to replace thymidine can sensitize the tumor cells [1–3]. In radiotherapy, secondary electrons generated from radiation with a most probable energy range of 9–10 eV [4] can attach to DNA subunits so as to result in the formation of temporary anions, or transient negative ions. Temporary anions may decay into dissociative electron attachment (DEA) channels and dissociating electronically excited states. As a sequel, through the decay of temporary anion states (TASs), such processes may lead to the formation of a halogen anion and a reactive nucleobase radical. Ultimately, the breaks of DNA strands, as well as DNA interstrand and intrastrand crosslinks, and DNA–protein crosslinks will be induced [5–14]. In TAS, an extra electron can be added to unfilled orbital of either ground state or excited state of a neutral molecule. The former case is referred to as shape resonance (SR)

or single-particle resonance and the latter as core-excited resonance (CER) or two-particle one-hole resonance [14,15]. SRs often have shorter lifetimes while CERs have longer ones.

To characterize TASs of halopyrimidines properly, both the experimental measurements and computational verification are required. On the side of experimental measurements, the electron transmission spectroscopy (ETS) [16,17] technique is an important means for determining the resonance energies of TASs. For the ETS measurements, Modelli et al. reported 4 features for each of the 2-chloropyrimidine (2-ClPy), 2-bromopyrimidine (2-BrPy) and 5-bromopyrimidine (5-BrPy) [18]. Based on computed unfilled orbital energies and scaled energy shifts, they have assigned the three peaks below 5 eV as π_2^*, σ_{C-X}^* (X = Cl or Br), and π_3^* SRs, and the signals at ca. 5.0–5.5 eV as CERs for all the aforementioned molecules. Other than the ETS, they also carried out the DEA spectroscopy measurements for halopyrimidines in the 0–4 eV energy range. They suggested the two energy signals (ca. 0–0.4 eV) present in each DEA spectrum were ascribed to the electron attachment in π_1^* and π_2^* orbitals, and the dissociative process was relied on σ_{C-X}^*/π^* mixing. For theoretical calculations, Barbosa and Bettega reported cross sections for elastic scattering of low-energy electrons with 2-ClPy,

* Corresponding author. Tel.: +886 4 23590121 32214; fax: +886 4 23590426.
 E-mail address: hycheng@thu.edu.tw (H.-Y. Cheng).

2-BrPy and 5-BrPy using Schwinger multichannel (SMC) method [19]. As for the derivatives of halopyrimidines, Du Penhoat et al. measured the electron stimulated desorption (ESD) for 5-halouracils. They observed the Cl^-/Br^- maximum signals via DEA process are located at 7.2 and 8.7 eV for 5-ClU, and 6.4 eV for 5-BrU [20]. Polska et al. measured ESD for brominated single stranded oligonucleotide trimers. They observed the Br^- maximum signals via DEA process are located 6–6.5 eV for all trimers [21]. The TASs leading to Cl^-/Br^- in the 6–9 eV range are most likely from CERs.

To interpret ETS data properly, computational verification of TASs is imperative. However, to characterize temporary anions accurately and efficiently is a challenging task. For instance, proper size of basis set containing diffuse functions must be employed to accommodate the extra electron [22]. In addition, two more important issues need to be heeded. First of all, TASs are embedded in the continuum and the application of variational calculations for TAS often collapse to a spurious discretized continuum (DC) [23–30] solution upon enlarging the basis set. This issue can be overcome by using the stabilization method (SM) proposed by Taylor [31–33]. Secondly, proper approach that includes electron correlation effects is required because of the considerable correlation energy difference between temporary anion and its parent neutral molecule [22]. Hence, more sophisticated methods beyond Hartree–Fock are required. When density functional theory (DFT) [34] is used, many of its potentials will yield wrong long range behavior and the energies of SRs are often underestimated. However, this drawback can be remedied by using asymptotically corrected exchange–correlation potentials [35–49].

Recently, the SM coupled with Koopmans' theorem (KT) [50], i.e., the stabilized Koopmans theory (SKT) in the framework of long range corrected density functional theory (LC-DFT) has been used successfully in the study of SRs for a series of molecules [43–48]. As for the study of CERs, the excitation energies of vertical anion can be calculated by time-dependent density functional theory (TDDFT) [51]. It is noteworthy that the Kohn–Sham (KS) orbital has a better shape and energy than the Hartree–Fock orbital [52–54]. In molecules, the KS HOMO–LUMO orbital gap is a very good approximation to the first excitation energy [52–54]. Previous studies have demonstrated that long range corrected time-dependent density functional theory (LC-TDDFT) calculations are able to achieve accurate calculation of excitation energies [55–57]. The TDDFT computations on CERs are relatively complex and challenging for (1) multiple electronically excitations may be involved and (2) the spurious excitations of an electron to DC may be included. Recently, we have introduced the stabilized long range corrected time-dependent density functional theory (S-LC-TDDFT) (i.e. SM coupled with LC-TDDFT) to solve the aforementioned problems in the studies of SRs and CERs for p-benzoquinone [49]. Results have indicated that this novel approach can efficiently and successfully generate good agreement in energy results. As to the TASs of halopyrimidines, previous studies mainly focused on the SRs, calculations on CERs have been relatively scarce. Moreover, there are discrepancies between the calculated and experimental positions for the higher-lying π_3^* pure SRs. Furthermore, the information on their lifetimes, which are crucial for the understanding of the dissociation process, is also lacking. In this study, it is then proper and fitting to investigate the resonance energies and lifetimes of SRs and CERs in halopyrimidines. We will first focus on the pure SRs of 2-ClPy, 2-BrPy and 5-BrPy via SKT in the framework of LC-DFT (denoted as SKT^{LC-DFT}), then CERs via S-LC-TDDFT in the 0–10 eV energy range. Furthermore, to have a better understanding of their effects in human body that contains 70–80% of water, it is necessary to take into account the solvent effect of water. Their resonance lifetimes will also be evaluated. Finally, the results of stabilization calculations will be compared with previous studies and their implications in DNA strand breaks will be emphasized.

2. Computational method

First of all, there are multiple variants in the SM. In the present study, the scaling of orbital exponent of the diffuse basis functions is adopted. It is generally accomplished by multiplying each of their orbital exponents by a positive scaling factor η. Five modified Gaussian-type basis sets are selected for testing the stability of stabilization calculations with respect to basis set variation [58,59]. Here, the basis set I denotes the modified 6-311++G(d,p) basis set for C, N, O, and H atoms and 6-311++G(3d,p) basis set for Cl and Br atoms. Basis set II–V represent the modified 6-311++G(d, p), 6-311++G(3d,p), 6-311++G(3df,3dp) and aug-cc-pvtz basis sets, respectively. As to the scaling procedure in SM for these five modified basis sets, the exponents of the outermost diffuse s and p functions on heavy atoms and the outermost diffuses s function on the H atom will be simultaneously multiplied by a scaling factor η. To this end, stabilization calculations are carried out on 2-ClPy using all the I–V basis sets. Results of these calculations revealed that the basis set I is sufficiently flexible to describe the TASs of 2-ClPy. Hence, addition of more diffuse d or f functions on heavy atoms is not necessary for it has no appreciable effect on the calculated resonance energies. As a result, the stabilization calculations of this paper will be based only on the basis set I.

The stabilization plots (SPs) are obtained by plotting the calculated vertical attachment energy (AE), $E(\eta)$, as a function of η. When using the SKT approximation, $E(\eta)$ is equal to the energy of the unfilled orbital at η. As for the S-LC-TDDFT method, $E(\eta)$ is obtained by taking the difference between the total energy of vertical anion $E_{N+1}(\eta)$ and that of ground neutral $E_{N,0}(\eta)$, i.e. $E(\eta) = E_{N+1}(\eta) - E_{N,0}(\eta)$. Notice that $E_{N+1}(\eta) - E_{N,0}(\eta)$ can also be written as $((E_{N+1}(\eta) - E_{N+1,0}(\eta)) + ((E_{N+1,0}(\eta) - E_{N,0}(\eta))$, where $E_{N+1,0}(\eta)$ is the total energy of ground vertical anion. Hence, for excited vertical anion, $E(\eta)$ is equal to the sum of the excitation energy from ground vertical anion to the excited vertical anion state, i.e., $(E_{N+1}(\eta) - E_{N+1,0}(\eta))$, and the total energy difference between the ground vertical anion and the ground neutral state, i.e., $(E_{N+1,0}(\eta) - E_{N,0}(\eta))$.

The eigensolutions in the SKT calculations consist of both SR and DC solutions. As for the eigensolutions in the S-LC-TDDFT calculations, they may consist of the following three solutions: (1) SR and CER, (2) the excitation of an electron to DC (E-DC) solutions, and (3) DC solutions [49]. As η varies, the eigenvalues of the TAS solutions remain stable while those of the DC/E-DC solutions change as η varies. The TAS and DC/E-DC solutions may couple with each other when they are close in energy and may lead to avoided crossings (ACs) between them. The resonance energies (E_R), i.e., calculated AEs, can be extracted from the ACs between the eigenvalues of the SP. In the study of E_R, the midpoint method adopted by Burrow et al. will be used [30]. The energy of TAS is taken as the average value of the two eigenvalues involved in the AC at the η_{ac} of closest approach, if it exists. In case the stabilization plateau of the energy curve $E(\eta)$ over which the energy remains almost constant, the resonance energy can be identified as the energy of the plateau [26,60]. To estimate resonance widths (Γ) from the ACs, the density of states (DOS) [61–67] method is also adopted. The density of resonance states $(|d\eta/dE|)$ around the stabilization plateau for each eigenstate of SP is calculated first. The values of Γ can then be determined via the Lorentzian fitting. The corresponding lifetime τ is obtained as $\hbar/\Gamma$.

For the SRs, we adopt ωB97XD [68] and M11 [69] LC functionals via SKT. As for comparison, the SM in conjunction with the electron-attached (EA) SAC-CI [70–73] and EA EOM-CCSD [74] correlated methods are also included. The former will be denoted as S-EA SAC-CI and the latter as S-EA EOM-CCSD. As for the vertical anions, the same ωB97XD and M11 LC functionals have been chosen in the S-LC-TDDFT computations. In addition, the S-EOM-CCSD