Quantum chemical investigation on photodegradation mechanisms of sulfamethoxypyridazine with dissolved inorganic matter and hydroxyl radical

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ABSTRACT

Sulfamethoxypyridazine (SMP) is one of the commonly used sulfonamide antibiotics (SAs). SAs are mainly studied to undergo triplet-sensitized photodegradation in water under natural sunlight with other coexisting aquatic environmental organic pollutants. In this work, SMP was selected as a representative of SAs. We studied the mechanisms of triplet-sensitized photodegradation of SMP and the influence of selected dissolved inorganic matter, i.e., anions (Br⁻, Cl⁻, and NO₃⁻) and cations ions (Ca²⁺, Mg²⁺, and Zn²⁺) on SMP photodegradation mechanism by quantum chemical methods. In addition, the degradation mechanisms of SMP by hydroxyl radical (OH•) were also investigated. The creation of SO₂ extrusion product was accessed with two different energy pathways (pathway-1 and pathway-2) by following two steps (step-I and step-II) in the triplet-sensitized photodegradation of SMP. Due to low activation energy, the pathway-1 was considered as the main pathway to obtain SO₂ extrusion product. Step-II of pathway-1 was measured to be the rate-limiting step (RLS) of SMP photodegradation mechanism and the effect of the selected anions and cations was estimated for this step. All selected anions and cations promoted photodegradation of SMP by dropping the activation energy of pathway-1. The estimated low activation energies of different degradation pathways of SMP with OH• radical indicate that OH• radical is a very powerful oxidizing agent for SMP degradation via attack through benzene derivative and pyridazine derivative ring.

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Introduction

Sulfonamide antibiotics (SAs) are beneficial sulfanilamide derivative antibacterial chemical compounds, which were verified by the Nobel laureate Gerhard Domagk (Domagk, 1935). Since 1940s, more than 150 different SAs have been frequently used in the treatment of bacterial infected diseases in human and veterinary (Baran et al., 2012), such as including urinary tract infections, gastrointestinal, and respiratory infections (Hemstreet, 2006; Huovinen, 2001; Could, 1999). These popular antibiotics are also used in aquaculture (Sarmah et al., 2006; Fang et al., 2006; Kummerer, 2009), and in cultivation (Battaglin et al., 2000; Could, 1999; Shao et al., 2005; Hirsch et al., 1999). The universal production and usage of antibiotics have been extensively increased for the last ten years, it is probably due to the wide range of excellent...
activity and low price. The global annual usage was estimated between 100,000 and 200,000 tons (Baran et al., 2011, 2012; Nan et al., 2014; Shao et al., 2005). Only in China more than 25,000 tons of antibiotics are ingested annually (L. Gao et al., 2012; P. Gao et al., 2012), and in the USA consumption of antibiotics is about 16,000 tons, including the 2.3% of SAs (Fabianska et al., 2014). In Europe, per year usage of SAs has been estimated about 11% to 23% from the total production of antibiotics (Sarmah et al., 2006). SAs are regularly released into the aquatic environments through different pathways and their universal detection in the natural water (Anna et al., 2011; Kummerer, 2009; Nan et al., 2014; Bu et al., 2013; Guangshui et al., 2013; Jia et al., 2011), including sulfamethoxypyridazine (SMP). The transmitted SAs could prevail in natural water for a period of time and transfer into many other organisms through food cycle (Fang et al., 2006; Shao et al., 2005; Boxall et al., 2006).

Thus, occurrence of SAs in various aquatic environments has been measured as emergent issue of particular concern because of their possible harmful effects on terrestrial organisms (Kummerer, 2009; Nan et al., 2014; Bu et al., 2013; Sarmah et al., 2006), on the aquatic organisms, and green plants (Ferrari et al., 2004; Brain et al., 2008; Yang et al., 2008; Garcia-Galan et al., 2009). Their effects are including as carcinogenic potency (Baran et al., 2011; Cabello, 2006; Fletcher, 2015), drug-resistance of pathogenic bacteria, and the appearance of superbugs (L. Gao et al., 2012; P. Gao et al., 2012; Woodward, 2010). Therefore, it is very urgent to eliminate SAs from the aquatic environment and to investigate suitable pathways for their elimination. According to current literature, photodegradation pathway has been found to be one of the most suitable pathways to access the fate and behavior of SAs in the natural aquatic environments (Braschi et al., 2016; Li et al., 2015; Batchu et al., 2014a, 2014b; Zessel et al., 2014; Garcia-Galan et al., 2012). Zhang et al. (2013) and Boreen et al. (2005) have studied the formation of SO2 extortion product in photolysis of selected SAs and fast rate of photolysis in natural water was attributed to the influences coexisting pollutants of aquatic environment and hydroxyl radical (OH•). The effective role of OH• radical generated by electrochemical and electro-catalytic process has been described in degradation and toxicity elimination of SAs (Haidar et al., 2013; Fabianska et al., 2014; Y. Wang et al., 2016; Z. Wang et al., 2016). Khaleel et al. (2013) studied photodegradation and biodegradation of SMP in different aqueous media, and the hydroxylation of SMP was found to be the main photodegradation path. Chuang et al. (2011) reported the ozonation and photocatalysis degradation of SMP in water.

Despite of many studies, the triplet-sensitized photodegradation mechanisms of SMP have not been thoroughly investigated yet. In real aquatic environmental conditions; SMP photodegradation could also be affected by coexisting dissolved inorganic matter, i.e., anions and cations (Hafuka et al., 2014; Hubicka et al., 2012; Selvam et al., 2007; Quivet et al., 2006). In new trends of research, quantum chemical computation has been verified to be a reasonable substitute of experimental study for saving cost and time as well as for assessing the fate organic pollutants, and it has also provided significant informations about reaction mechanisms, intermediates and products (Shah et al., 2015; Wang et al., 2014; Ren et al., 2011). In addition, theoretical calculations have been recognized in the studies of OH• radical-initiated oxidation degradation mechanisms of atmospheric pollutants (Dang et al., 2015; Sun et al., 2015; Zhang et al., 2014). Thus, in this research the density functional theory (DFT) method with the 6-31 + G(d,p) theory level was employed to study the mechanisms of triplet-sensitized photodegradation SMP, and to estimate the influences of the selective dissolved inorganic matter, i.e., anions (Br−, Cl−, and NO3) and cations ions (Ca2+, Mg2+, and Zn2+) on the rate-limiting step (RLS) in SMP degradation as well as the hydroxylation mechanisms of SMP.

1. Computational methods

As shown in Fig. 1, SMP (CAS # 80-35-3) was selected as a representative of SAs for this study. The geometries of reactants, intermediates, and products of each elementary reaction were optimized by using DFT (Shah et al., 2015; Wang et al., 2014; Ren et al., 2011) and Becke’s three-parameter (B3) hybrid method (Becke, 1993, 1988) with Lee-Yang-Parr (LYP) gradient-correlation function (Lee et al., 1988; Miehlich et al., 1989), and 6-31 + G(d,p) basis set (Frisch et al., 1984; Krishnan et al., 1980). Gaussian09 software package was used in the entire study (Frisch et al., 2009). All calculations were considered of the solvation environment. Since the geometry of each reacting molecule depends on the interaction between the system (molecule) and surrounding (solvent), integral equation formalism polarized continuum model (IEFPCM) was used with solvent (water) to simulate the SMP photodegradation in water environment (Miertus et al., 1981; Miertus and Tomasi, 1982). The harmonic vibrational frequency computations of reactants and products were characterized without any imaginary frequency. Whereas, the transition states (TSs) were obtained with one imaginary frequency. The advancement of reactant molecule toward the TS and product of each elementary reaction was made by means of the intrinsic reaction coordinates (IRC). Zero point energy (ZPE) comparisons between reactant and TS were considered for estimation of activation energies of each pathway. Time-dependent density functional theory (TD-DFT) was used along with the 6-31 + G(d,p) level of theory for the computation of ultraviolet absorbance spectra.

2. Results and discussion

2.1. Geometries of SMP conformers

Optimized structures of the three possible conformers (SMP-I, SMP-II, and SMP-III) of the model compound (SMP) are depicted in Supplementary material (Fig. S1) with labeling of the atoms. The ZPE-corrected energies of these three optimized conformers and their S–N1 bond cleavage activation energies were compared to select the most stable conformer of SMP for further studies. As presented in (Fig. S1), the maximum difference in ZPE-corrected energies conformer SMP-I is less than (2.1 kcal/mol) and activation energy is higher than (0.7 kcal/mol) than SMP-II and SMP-III. According to these results, the SMP-I was confirmed to be the most stable conformer of SMP, and this conformer was selected for
further detail study of the triplet-sensitized photodegradation mechanisms.

2.2. Computational and experimental geometrical parameters of SMP

In order to insure the reliability of selected theoretical method, optimized structural parameters of SMP at B3LYP/6-31+G(d,p) level of theory were compared with the experimental structural data available in the literature (Basak and Mazumdar, 1987). The maximum differences in bond lengths (Å) and bond angles (°) between the computational and experimental structures are shown in Fig. 1. For example; in the calculated SMP structure, S–N1 bond is longer than and N3–N4 bond is shorter than the experimental values by a magnitude of 0.09 and 0.02 Å, respectively. The largest difference in bond angle was (6.1°) observed in O2–S–N1 between the structures. Additionally, TD-DFT with the 6-31G+(d,p) level of theory calculation was performed to determine the maximum absorption peak (λmax) of SMP. As represented in Supplementary material (Fig. S2), calculated λmax of 258.9 nm is in good agreement with the experimental value 260.0 nm in water reported by Rajendiran et al. (2014). This comparison showed that the selected level of theory is a useful method for further comprehensive photodegradation mechanistic study of SMP.

2.3. Photodegradation mechanisms of SMP

The creation of SO2 extrusion product was calculated as a primary photoproduct by two minimum energy pathways (pathway-1 and pathway-2) in photodegradation of SMP (Fig. 2). The activation energy profile with optimized structure of reactant (SMP), intermediate (IM), and the products with the numbering atoms are shown in Fig. 2. Both the pathways were accessed by following two steps (step-I and step-II), in which the step-I (S–N1) bond cleavage is the same as the step-I for pathway-1 and pathway-2. In pathway-1; step-I, an IM was obtained with activation energy 2.8 kcal/mol by S–N1 bond cleavage in SMP. This IM was used as a reactant for the step-II of pathway-1 and pathway-2, respectively. In the step-II of pathway-1, SO2 extrusion product (N-(6-methoxy-3-pyridazinyl)-1, 4-benzenediamine) was obtained by a chemical bond formation between C1 and N1 in the IM with the activation energy 22.3 kcal/mol.

As described in pathway-1, the step-I of pathway-1 was also considered as the step-I for pathway-2. In step-II of pathway-2, a chemical bond (C1–N3) is formed in the IM and SO2 extrusion product (2-(4-aminophenyl)-6-methoxy-2,3-dihydropyridazin-3amine) was obtained with the activation energy 26.2 kcal/mol. Due to high activation energy, the step-II of pathway-2 is difficult to carry out as compared to the step-II of pathway-1. In addition, enthalpy change (ΔH) in step-II of pathway-1 and pathway-2 was also calculated. As can be seen in Fig. 2; according to the estimated value of ΔH (−9.1 kcal/mol) of pathway-1 of step-II, the IM can undergo an exothermic reaction by C1–N1 bond formation. While, the value of ΔH (+13.0 kcal/mol) of pathway-2 of step-II indicated that the C1–N3 bond formation in the IM is an endothermic reaction. Thus, pathway-1 was considered as the main pathway and step-II of pathway-1 was measured to be the RLS for SMP photodegradation mechanisms. The IRC of RLS of pathway-1 along with the optimized reactant, TS, and product can be seen in Supplementary material (Fig. S3), and the coordinates “of mol2 file” of the IM, and TS of RLS are also presented in Supplementary material (Tables S1, and S2).
2.3.1. Influences of anions and cations on photodegradation of SMP

It is well known fact that dissolved inorganic matter (anions and cations) has been found with organic pollutants in the contaminated aquatic environments, and these ions could affect on the degradation of organic pollutants. Therefore, anionic and cationic influence on the RLS of pathway-1 in SMP photodegradation was studied. As defined above, the step-II of pathway-1 is the RLS for SMP photodegradation. Selected anions (Br\(^-\), Cl\(^-\), and NO\(_3^-\)) and cations (Ca\(^{2+}\), Mg\(^{2+}\), and Zn\(^{2+}\)) are optimized with the reactant (IM) of pathway-1. Three geometries with anions (IM\(\cdot\)Br\(^-\)), IM\(\cdot\)Cl\(^-\)), and IM\(\cdot\)NO\(_3^-\)) and three geometries with cations (IM\(\cdot\)Ca\(^{2+}\)), IM\(\cdot\)Mg\(^{2+}\), and IM\(\cdot\)Zn\(^{2+}\)) were obtained, respectively. Different locations on the IM for each selected ion were investigated by optimization and geometry of the lowest energy of each ion was considered as a reactant to obtain SO\(_2\) extrusion product (N-(6-methoxy-3-pyridazinyl)-1, 4-benzenediamine). Additionally; as representatives, the IRC of RLS (without the interaction of these ions) and IRC of RLS with the interaction of Br\(^-\) and Zn\(^{2+}\) ion are presented in Supplementary material (Fig. S3), and their coordinates of mol2 file of TSs are also given in Supplementary material (Tables S2, S3, and S4).

As shown in Fig. 3, the computed activation energy of RLS of pathway-1 without the interaction of these anions ions and cations is 22.3 kcal/mol. In the case of anions, the role of Br\(^-\) ion was more pronounced to promote the photodegradation of SMP by decreasing the activation energy of RLS of pathway-1. The computed activation energy of RLS of pathway-1 with Br\(^-\) is 12.1 kcal/mol, whereas, the activation energy of RLS of pathway-1 was slightly affected by Cl\(^-\), and NO\(_3^-\) ions only up to a magnitude of 0.8 kcal/mol. Similarly, estimated activation energies with the interaction of cations (Ca\(^{2+}\), Mg\(^{2+}\), and Zn\(^{2+}\)) are 14.7, 13.3, and 12.4 kcal/mol, respectively (Fig. 3). These results indicated that all the selected anions and cations can promote photodegradation of SMP. Therefore, it is concluded that Br\(^-\) ion and the selected metal ions or their salts can be suitable catalyst for degradation of SAs.

2.4. Mechanisms of SMP degradation by hydroxyl radical

OH\(^*\) radical has played an important character in degradation of organic pollutants. In this section we have investigated the mechanisms of SMP degradation by OH\(^*\) radical and defined the most easy attacking positions in SMP molecule for HO\(^*\) radical. As represented in Figs. 4 and 5; SMP molecule has two cyclic rings, (I) benzene derivative and (II) pyridazine derivative, and two amine groups (H\(_2\)N\(_2\))- and (H\(_1\)N\(_1\))- . Therefore, OH\(^*\) radical can attack in both rings and amine groups.

In case of benzene derivative (I), five pathways (pathway-1 to pathway-5) were studied in SMP degradation by OH\(^*\) radical reactions. The representatives IRCs of some reactions are presented in Supplementary material (Fig. S4) along with the optimized reactant, TS, and product, and the coordinates “of mol2 file” of some selective IMs and TSs are also given in Supplementary material (Tables S5 to S10). As presented in Fig. 4, in pathway-1 and pathway-2, the substitution of OH\(^*\) radical at the meta- and ortho-position (C\(_6\) and C\(_3\)) in benzene ring of SMP was performed with the activation energies of 2.1 and 5.1 kcal/mol, respectively. Due to the low activation energy of step-I of pathway-1, this path was followed and additional two steps (II and III) were further investigated for decomposition of SMP. In pathway-1 of step-II, an intermediate-2 (IM\(_2\)) was obtained with the activation energy of 24.1 kcal/mol by S\(\cdot\)N\(_1\) bond cleavage in the intermediate-1 (IM\(_1\)) of step-I. The step-III of pathway-1 was accessed through C\(_1\) – N\(_1\) bond making in the IM\(_2\), in which SO\(_2\) product
was obtained with the activation energy of 21.7 kcal/mol. In pathway-3, OH• radical reaction is studied with C1 of benzene ring, at the same time C1 – S bond in SMP was cleaved. The activation energy of this pathway was equal to 2.4 kcal/mol. Whereas in pathway-4, elimination of primary amine group (H2N2−) was carried out with two consecutive steps. The step-I was performed by a chemical bond formation between OH• radical and C4 of benzene ring, while in step-II a chemical bond (C4 – N2) is cleaved in the IM3 (product of step-I). The calculated activation energies of step-I and II of this path are 4.4 and 19.9 kcal/mol, respectively (Fig. 4). In pathway-5, H from primary amine (H2N2−) group of SMP is abstracted by OH• radical through benzene derivative ring. SMP: sulfamethoxypyridazine.
OH• radical. In this path, water (H2O) and SMP radical (SMP*) were obtained as degradation products with the activation energy of 1.8 kcal/mol. That is to say, in degradation mechanism of SMP by OH• radical step-II is estimated to be the RLS for pathway-1 and pathway-4.

In the case of pyridazine derivative (II), five pathways (pathway-6 to pathway-10) were also investigated in degradation of SMP by OH• radical reactions. The representative IRCs of some reactions are shown in Supplementary material (Fig. S5) along with the optimized reactant, TS, and product, and the coordinates of some selective IMs and TSs are also given Supplementary material (Tables S11 to S18). As can be seen in Fig. 5, pathway-6 was assessed with two steps; in step-I, OH• radical attacked on C7 of SMP and a chemical bond between C7 and OH• radical is formed that lead to formation of an intermediate-4 (IM4), and in step-II elimination of methoxy group was carried out by C7O3 bond cleavage in the IM4. The computed activation energies of both steps of pathway-6 are 3.1 and 14.0 kcal/mol, respectively. Pathway-7 was studied with a three steps reaction; in step-I, a chemical bond is created between OH• radical and C8 of SMP that lead to formation of an intermediate-5 (IM5). The estimated activation energy of this step is 0.5 kcal/mol. In step-II, the IM5 was used as reactant and bond is cleaved between S and N1 in the IM5 and intermediate-6 (IM6) was obtained with the calculated activation energy of 30.3 kcal/mol. While in step-III, a chemical bond (C1−N1) is formed in the IM6 and SO2 product was obtained. The estimated activation energy of this step was equal to 19.0 kcal/mol. Pathway-8 was accessed with a single step reaction, in which the reaction between OH• radical and N4 of SMP was carried out with the activation energy of 13.9 kcal/mol. In pathway-9, in step-I, a bond is formed between N1 (secondary amine group of SMP) and OH• radical that lead to formation of an intermediate-7 (IM7). The calculated activation energy of this step is 16.9 kcal/mol. And in step-II, a chemical bond (C1−N1) is formed in the IM7 and SO2 product was obtained with the activation energy of 25.4 kcal/mol. Pathway-10 was studied with a single step reaction in which H of secondary amine (−HN1−) is abstracted by OH• radical. In this path H2O and SMP radical (SMP*) were obtained as degradation products of SMP. The computed activation energy of this pathway is 2.2 kcal/mol. Thus, the step-II of pathway-6, 7, and 9 is measured to be the RLS for these paths in SMP degradation by OH• radical.

### 3. Conclusions

This research presented an insight into the photodegradation mechanisms of SMP and how it is affected by selected dissolved inorganic matter, i.e., anions (Br−, Cl−, and NO3−) and cations (Ca2+, Mg2+, and Zn2+), and hydroxylation of mechanisms SMP. Theoretical optimized geometrical parameters and λmax of SMP to be in a better agreement with the experimental values indicated that the selected level of theory is reasonable for further mechanistic study. In photodegradation of SMP, formation of SO2 product was studied with two different minimum energy pathways. Pathway-1 was measured as the main pathway and step-II of this path was confirmed to be the RLS for SMP photodegradation. All the selected anions and actions promoted the photodegradation of SMP by reducing the activation energy of RLS of pathway-1. The results obtained in the hydroxylation of SMP indicated that the OH• radical is a very powerful oxidizing agent for the degradation SMP. This theoretical mechanistic study of SMP will deliver new insight into the photodegradation mechanisms of SAs and other...
organic pollutant of aquatic environment. In addition, information of the influence of anions and cations, and the active role of OH\(^+\) radical on degradation of SMP will be helpful for better understanding of photochemical behavior of organic pollutants in different aquatic environments.

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jes.2016.09.023.

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