Antibiotic degradation: a microscopic look at molecular dynamics

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Abstract: In this paper, the effects of active substances in low-temperature plasmas on macromolecular organic compounds are studied by molecular dynamics simulation and reaction force field simulation. Sulfonamide antibiotics were selected as the study subjects. The decomposition process of sulfamethazine at each step is shown at the microscopic level. The ultimate goal is to find a way to degrade antibiotics without pollution, so as to protect the ecological environment. The simulation results show that the sulfamethazine molecule is dehydrogenated into a ring containing nitrogen and a ring containing carbon. The C=N bond of the former will be broken during the simulation, and the product will continue to react with the active particles. Although the carbon-containing ring of the latter is relatively stable and difficult to destroy, the H element on the ring will be replaced by a hydroxyl group to form a new substance, which will continue to react further with other active particles to promote the decomposition of the ring. The benzene ring structure may be broken down into smaller and simpler organic compounds such as short-chain hydrocarbons, aldehydes, or other small molecules. This process not only contributes to the degradation of organic pollutants, but also provides a basis for the development of new chemical reaction pathways and material modification technologies.

1 Introduction

Low-temperature plasma is a non-equilibrium plasma [3], Different from the usual three physical states, it belongs to the fourth state after solid, liquid, and gaseous states [6]. In general, plasma can be divided into plasma in thermal equilibrium and plasma not in thermal equilibrium [5]. In low-temperature plasma, the temperature of electrons is much higher than that of ions and heavy particles, and although the temperature of electrons in the plasma is high, the overall temperature is at a low temperature, so it is called low-temperature plasma.

When the applied voltage reaches the breakdown voltage of the gas, the plasma is ionized by the atoms and atoms after some electrons are deprived, and the gas molecules are ionized to form a mixture including electrons, ions, atoms and atomic clusters, that is, plasma. Among them, the total number of positive ions and electrons in the plasma is approximately equal, and it is generally quasi-neutral [1].

With the rapid development of low-temperature plasma technology, it has been widely used in industry[30]. Plasma engineering is a rapidly evolving field of science and technology, and more and more engineers are using plasma processes in a variety of applications[4]. Its high electron temperature and low gas temperature are non-equilibrium characteristics, on the one hand, because the electron energy is high enough to have high physical and chemical activity[31], and on the other hand, the whole system can maintain a low temperature, which makes it have unique advantages in chemical reaction and material surface modification[7]. A large number of studies have been carried out on plasma physics and the interdisciplinary application of materials modification, biomedicine, energy and chemical engineering, and aerospace, and fruitful research results have been obtained[2].In the field of environmental protection, it is commonly used for waste gas and wastewater treatment because of the high efficiency and energy saving of low-temperature plasma technology and the characteristics of no secondary pollution of products. Low-temperature plasma technology can be used in the field of environmental protection for waste gas and wastewater treatment [8-10]. Through plasma reaction, harmful gases (such as automobile exhaust) can be converted into harmless substances to achieve the effect of purifying the air. In wastewater treatment, low-temperature plasma technology can degrade organic pollutants and improve wastewater treatment efficiency [2] [11]. In recent years, emerging contaminants have begun to be detected in wastewater, including antibiotic contamination[18]. Chemical degradation [12] [13] [14] [15] and microbial degradation [16] [17] are also used to treat antibiotics in wastewater, but both methods have serious drawbacks. The chemical degradation method uses more reactants to react, but the amount of reactants is not easy to control, and once the full reaction is satisfied, there must be the problem of excess reactants, which will introduce secondary pollution at the same time as degradation. In terms of microbial degradation, microorganisms have been used in sewage treatment for a long time, because sewage contains a large number of antibiotics, long-term exposure to antibiotics will slowly cause microorganisms to develop drug resistance, thus greatly reducing the degradation efficiency. The antibiotics in the low-temperature plasma treatment sewage are mainly reactive

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oxygen species (ROS) and reactive nitrogen (RNS) and other substances that play a role, and these substances themselves are non-polluting, so the products after complete reaction with antibiotics are more environmentally friendly to the environment. In literature [19-22], the plasma-reactive oxygen species group has been used to improve the degradation rate of various antibiotics. Reactive oxygen species groups and catalysts can accelerate the degradation of antibiotics without producing contaminants. Ref. [23-25] shows that oxygenated radicals produced in plasma play a crucial role in the decomposition of antibiotics such as ofloxacin, and the degradation products are mainly carbon dioxide and water, which do not pollute the environment.

At present, there are not many experimental studies and real-world application scenarios for low-temperature plasma treatment of wastewater, and there are few microscopic studies in this regard. Computer simulation is a bridge that connects theory and experiment, and molecular dynamics simulation is one of the computer simulation technologies. Molecular dynamics [26] and reaction force fields [27] can simulate the breaking of old bonds and the formation of new bondsand present the dynamic results by computer. The principle of interaction between substances is well explained at the microscopic level. Zhao et al. [28][29]studied the mechanisms of surface modification of materials by plasma. The feasibility of the study at the micro level was confirmed.

In this paper, molecular dynamics and reaction force field simulation methods were used to study the microscopic principle of sulfamethazine (one of the sulfonamide antibiotics) degradation by low-temperature plasma. The reaction between sulfamethazine molecules and particles such as hydroxyl, ozone and oxygen atoms was simulated by computer, and macroscopic experiments were carried out as comparison. The second part of this paper describes the specific methods of modeling, the third part establishes the simulation and analyzes the results, and the fourth part summarizes.

2 Method

2.1 Theory of molecular dynamics

Molecular dynamics [26] is an interdisciplinary discipline that mainly integrates physical mathematics. Molecular dynamics simulation is a method of simulating the motion of molecular systems through mechanics. Molecular dynamics is generally divided into two types. The first one has no chemical reaction, so there is no breaking of old chemical bonds and no production of new chemical bonds. It is mainly used in the study of physical phenomena. The second is related to chemical reactions, where old chemical bonds are broken and new chemical bonds are formed, and the reaction potential is required. These molecular simulations combine the ReaxFF force field and molecular dynamics to simulate both simple and complex chemical reactions. The ReaxFF reaction force field was proposed by van Duin et al[27]. to establish the reaction position at the bond stage. Knowing that the distance between the atoms can determine the bond level, it is clear that the interaction between substances in a chemical reaction based on the bond level is clear. The reaction files used in this article were performed in the Materials Studio software. In the ReaxFF force field [27], the total energy formula for the entire system is as follows:

$$E_{system} = E_{bond} + E_{over} + E_{under} + E_{val} + E_{Coulomb} + E_{vdw} + E_{conj} + E_{tors} + E_{pen} \quad (1)$$

2.2 Sulfamethazine molecular structure and modeling

Sulfamethazine is one of the commonly used sulfonamide antibiotics. Its molecular structure is shown in Figure 1, and its molecular formula is $C_{11}H_{12}O_2N_4S$, which is commonly used in animal husbandry, because it is not easy to degrade and will remain in water and soil to cause environmental pollution.

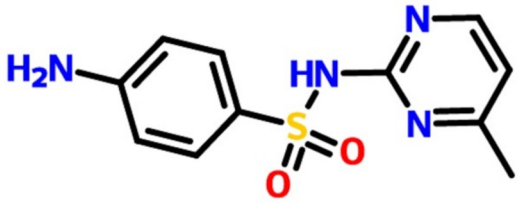

Figure 1. Sulfamethazine molecular structure

The sulfonymethazine molecules were modeled using the Material Studio software. Subsequently, the molecular structure was optimized using the Forcite module to select the NVT ensemble (where V represents the number of determined particles, V represents the volume, T represents the temperature). The initial velocity of the particles was random, the temperature was set to 298K, the time step was set to 0.1 fs, and the total simulation time was 100ps. Figure 2 illustrates the optimized

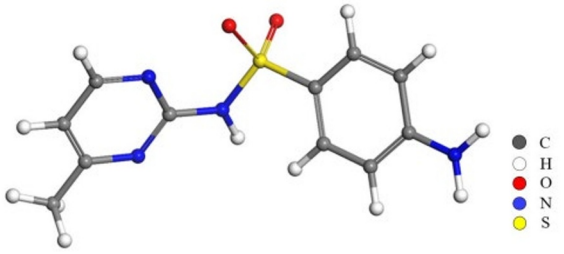

Figure 2. Molecular model of Sulfamethazine

The sulfamethazine molecule is then encapsulated with the active particles, and the size of the reaction cassette is approximately 15 Å×15 Å×15 Å. The kinetic module in the Forcite module is then used to balance the energy of the system, the purpose of which is to keep the system in a stable state with minimal energy by compensating for or removing a portion of the energy of the system.

Figure 3 shows the encapsulation cassette model for the sulfamethazine molecule and reactive oxygen species, as is the case for the other types of particles. According to

the principle of molecular dynamics, if the step size of the molecular dynamics simulation is too large, the energy change during the reaction will be obvious, resulting in the system not conforming to the conservation of energy. The packaging model is imported into LAMMPS for simulation, and the parameter setting method is as follows: reaction time 100ps, temperature 298K, NVT constant temperature system, step size 0.1fs, number of steps is 107 steps, output once every 103 steps, 10 times for each simulation, 20 times can be. Finally, the simulation results can be visualized by importing the simulation results into the Ovito software in Python, and then the experimental data can be graphed.

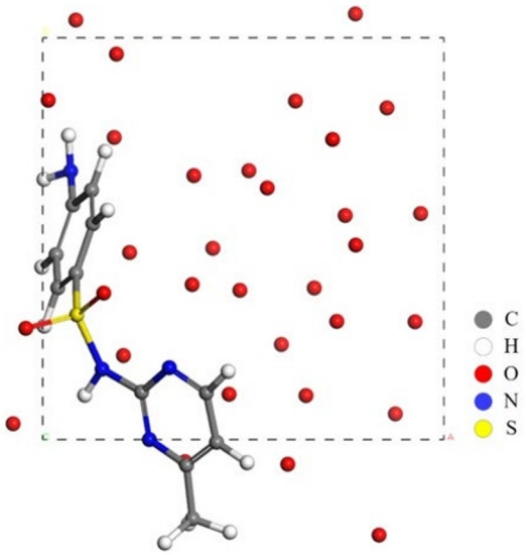

Figure 3. Sulfamethazine and oxygen atom encapsulation reaction box model

3 Simulation Results and Analysis

3.1 Introduction

In this chapter, sulfamethazine, a representative substance of sulfonamides, is selected as the subject of study. The reaction stages, main reaction pathways, phenomena that may occur during the reaction process, and degradation products of sulfamethazine with low-temperature plasma active particles are investigated using molecular dynamics simulations as a tool. The purpose of this research is to provide theoretical support and guidance for the degradation of sulfonamide antibiotics using low-temperature plasma.

3.2 Analysis of the Decomposition Pathways of Sulfamethazine

Under the influence of non-thermail plasma active particles, the sulfamethazine molecule initially breaks into two ring structures, which then continue to decompose. Molecular dynamics simulations reveal that the stability of nitrogen-containing rings is less than that of all-carbon ring structures. In subsequent reactions, the nitrogen-containing rings gradually break into chain structures, which may then further break into smaller molecules as the reaction progresses. In contrast, the all-carbon ring structures are more stable. Sulfur and nitrogen atoms attached to these rings may detach, but the ring structures themselves are not easily destroyed. However, new functional groups, such as hydroxyl groups, may form on the benzene ring molecules. Figure 4 illustrates one of the potential decomposition pathways of the sulfamethazine molecular skeleton for demonstration purposes. It is important to note that in actual simulations, the degradation products are not unique, but their structures are generally similar.

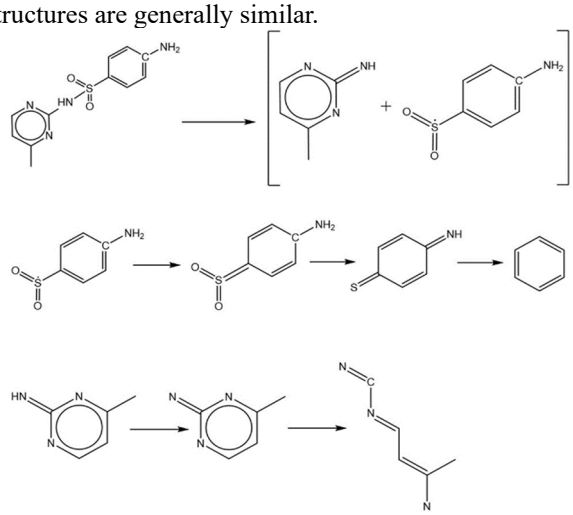

Figure 4. The pyrolysis of sulfamethazine.

3.2.1 Dehydrogenation phenomenon

Figure 5 illustrates the dehydrogenation reaction of the sulfamethazine molecule. According to the figure, the oxygen atom labeled as O1 is capable of capturing a hydrogen atom from the sulfamethazine molecule to form a hydroxyl group, H2-O1. Similarly, a free hydroxyl group in the system captures the hydrogen atom labeled as H4 to form a water molecule. In fact, the dehydrogenation reaction of the sulfamethazine molecule may involve multiple sites. Within the sulfamethazine molecule, aside from the oxygen atom labeled as O1 and the hydroxyl oxygen atom labeled as O3, other atoms may also participate in similar reaction processes. The system contains a large number of nitrogen atoms and their excited state particles or other active particles that could act as acceptors or donors of hydrogen atoms, participating in dehydrogenation or hydrogen transfer reactions. These reactions may lead to molecular structural rearrangements or the formation of new functional groups.

Dehydrogenation reactions not only affect the chemical properties of the sulfamethazine molecule, such as increasing its polarity or altering its electron distribution but may also impact the molecule's biological activity and stability, thereby facilitating subsequent degradation reactions.

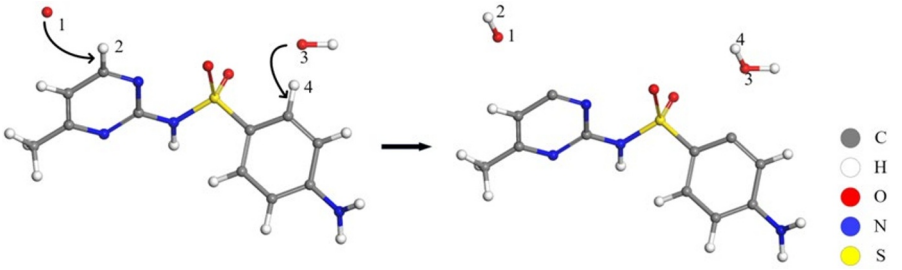

Figure 5. Sulfamethazine dehydrogenation reaction

3.2.2 Ring cleavage

As shown in Figure 6, the sulfamethazine molecule contains two ring structures: one is a benzene ring (ring 2 in the figure), and the other is formed by the combination of an oxygen atom and a nitrogen atom (ring 1 in the figure). These rings are connected together through chemical bonds formed by sulfur atom 4, nitrogen atom 3, and oxygen atom 5. Molecular dynamics simulations have found that the chemical bond between S4 and N3 is prone to breakage. This is because in an oxidative environment, oxidizing agents may accept electrons, causing the sulfur atom to lose electrons and form sulfur oxides, while the nitrogen atom may undergo a reduction reaction, leading to the breakage of the S4-N3 bond. Similarly, for the C5-S4 bond, the sulfur atom undergoes oxidation, and the carbon atom undergoes reduction, which may also lead to the breakage of this bond.

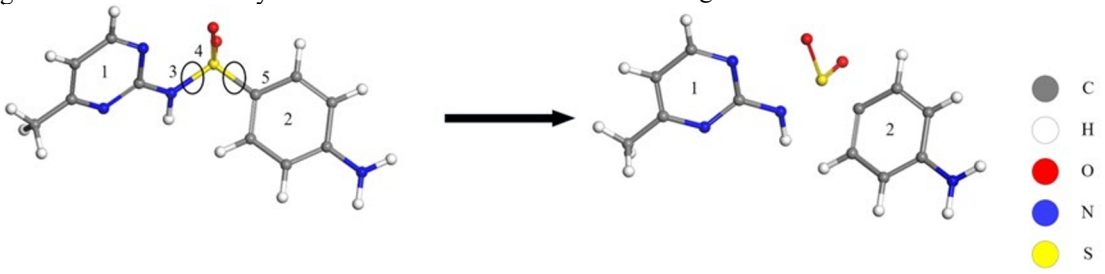

Figure 6. Sulfamethazine inter-ring cleavage reaction.

3.2.3 Cleavage of Nitrogen-Containing Rings

In the previous chapter, it was discussed that the splitting of the two ring structures, ring 1 and ring 2, depicted in Figure 7, resulted in the formation of two new ring structures, with ring 1 being formed by nitrogen and carbon atoms. As shown in Figure 7 a, the nitrogen atom labeled as N2 is bonded to a sulfur atom and a hydrogen atom. With the cleavage of the S-N bond and the removal of the hydrogen atom from N2, an unpaired electron is generated on N2, forming a free radical and altering the electron density around it. Concurrently, the system is abundant in oxidizing and reducing agents, which compel the breaking of the N4=C1 double bond, thereby opening the ring structure. The cleavage of the S-N bond and the removal of the hydrogen atom at position 2 are key steps in this reaction sequence, both leading to a redistribution of electron density and laying the groundwork for subsequent chemical transformations. Specifically, the generation of an unpaired electron on N2 provides an active site for further chemical reactions. The opening of the ring structure offers new pathways for the molecule, potentially involving further oxidation, reduction, polymerization, or rearrangement reactions.

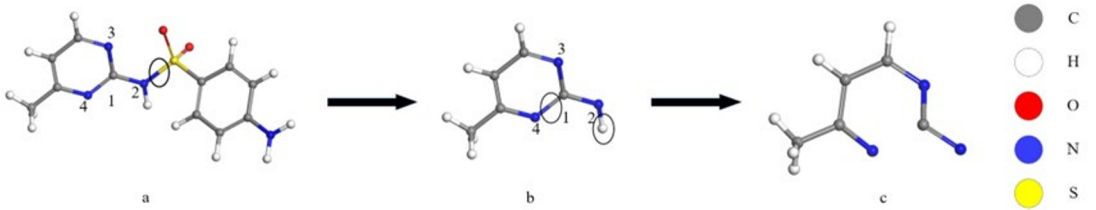

Figure 7. Cleavage of the Nitrogen-Containing Ring in the Sulfamethazine Molecule

3.2.4 Formation of New Functional Groups and Oxidation

In Figure 6, it is revealed that, in addition to the nitrogen-containing ring, the sulfamethazine molecule possesses another ring structure, similar to a benzene ring. This structure may undergo the formation of new functional groups and oxidation under the influence of active particles.

As shown in Figure 8, the benzene-like ring structure can undergo a substitution reaction with hydroxyl groups, specifically manifested as the hydroxyl group replacing a hydrogen atom and bonding with a carbon atom on the ring. The resulting organic compound, having acquired a hydroxyl group, can undergo further oxidation reactions.

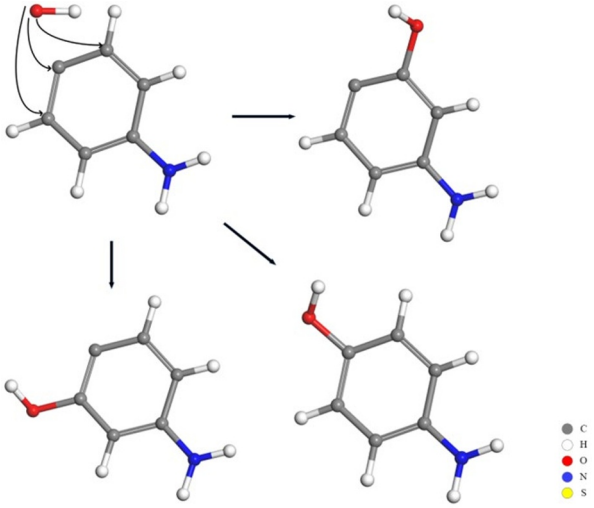

Figure 8. Hydroxyl group substitution reaction with benzene-like ring structure

When benzene-like compounds contain hydroxyl functional groups in their structure, they are prone to undergo oxidation and a series of chemical reactions in an environment rich in oxidants. These reactions can significantly alter the distribution of electron density within the molecule, thereby affecting its chemical properties and reactivity. Particularly under the conditions of low-temperature plasma, a plethora of excited state particles (such as free radicals, excited state oxygen molecules, etc.) have a notable activating effect on the benzene-like ring structures. These high-energy particles are capable of effectively opening the ring structures, leading to the transformation of complex molecules into smaller, simpler molecules, thereby achieving their degradation.

4 Conclusions

In this paper, a model of sulfamethazine molecule was established, and the microscopic reaction between the active particles in the low-temperature plasma and the sulfamethazine molecule was demonstrated by molecular dynamics simulation, and the degradation process of sulfamethazine at the microscopic level was demonstrated. The action of the active particles on the sulfamethazine molecule begins with the dehydrogenation reaction, after which the structure becomes unstable. The MDS-ReaxFF results show that the C=N bond will be broken in the nitrogen-containing ring during the simulation, and the carbon-containing ring (i.e., benzene ring) will first combine with the hydroxyl group and then decompose. The presentation of these results confirms that the active species in low-temperature plasma can degrade antibiotics. Therefore, the results of this computational simulation can provide theoretical support and guidance for subsequent practical experiments. It provides new ideas and ways to solve the emerging pollutants in recent years and protect the environment.

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