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Sulfur dioxide, source of (bi)sulfite

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Abbreviations:

GSH, glutathione; **GSH-Px**, glutathione peroxidase; **$HO^{\bullet}$**, hydroxyl radical; **H_2O_2**, hydrogen peroxide; **$HS^{\bullet}$**, thiyl radical: **H_2S**, hydrogen sulfide; **H_2SO_3**, sulfurous acid; **HSO_3^-**, bisulfite (hydrogen sulfite); $HSO_3^{\bullet}$, bisulfite radical; **NAD**, nicotinamide adenine dinucleotide; **$O^{\bullet}$**, oxygen atom; **O_2**, oxygen; $O_2^{\bullet-}$, superoxide; **ppm**, part per million; **$SO^{\bullet}$**, sulfur monoxide radical ; **SO_2**, sulfur dioxide; **SO_3**, sulfur trioxide; **$SO_3^{\bullet-}$**, sulfur trioxide radical anion; **SO_3^{2-}**, sulfite; **SO_4^{2-}**, sulfate; **$SO_5^{\bullet-}$**, peroxysulfate radical anion; **SOD**, superoxide dismutase; **TBARS**: thiobarbituric acid reactive substance.

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Abstract

Sulfur dioxide (SO_2) is a colorless, non-flammable gas pollutant with a pungent odor. One of its major sources in air is the burning of fossil fuels. It reacts with water in the atmosphere to form sulfuric acid, which is the chief constituent of acid rain. In the body, SO_2 can easily be hydrated to produce sulfurous acid in the respiratory tract, which subsequently dissociates to form its derivatives, bisulfite and sulfite, which contribute to human toxicity. Sulfur dioxide was reported to be a clastogenic and a genotoxic agent for which necessary precautions must be taken. Ion chromatography is the most sensitive and a well established method for the detection of SO_2 in an environment. Thus, it is necessary to understand the physicochemical properties and biological aspects of SO_2 that contribute to its harmful effects on human health and to find ways to treat people who have been harmed.

Introduction

Sulfur dioxide (SO_2) is a colorless, non-flammable gas pollutant with a strong, suffocating odor. It is considered a toxic gas that people may be exposed to either by inhalation or by skin contact [1]. The health hazards and toxicity of SO_2 exposure are well documented [1, 2]. Sulfur dioxide inhalation can cause oxidative stress and lead to changes in antioxidant status of various organs of mice [3]. Several studies have also shown SO_2 and its derivatives are clastogenic and genotoxic agents [4, 5]. In order to avoid these harmful effects and to find ways to treat people who have been injured, it is necessary to understand how SO_2 is absorbed, used, and released by the body. This review paper will mainly focus on routes of SO_2 formation, its derivatives, physicochemical properties, detection, toxicity, and biological/health aspects.

Route of SO_2 formation in the atmosphere

In nature, SO_2 can be released to the air from volcanic eruptions. However, the release of SO_2 into the air primarily comes from electric utilities, which are associated with the burning of fossil fuels. It is also released into the atmosphere through several manufacturing process such as production of sulfuric acid, fertilizers, food preservative, paper pulp, coal-fire power plant, smelter, steel works and other chemical industry [1]. In the atmosphere, natural decay of organic matter releases hydrogen sulfide gas (H_2S), which can be oxidized by hydroxyl radical ($HO^{\bullet}$). H_2S is transformed to SO_2 in a three step process, **reactions (1-3)** and the overall reaction is shown in **reaction (4)**[1].

$$2H_2S + 2HO^{\bullet} \rightarrow 2HS^{\bullet} + 2H_2O \quad \textbf{(1)}$$

$$2HS^{\bullet} + 2O_2 \rightarrow 2HO^{\bullet} + 2SO^{\bullet} \quad \textbf{(2)}$$

$$2SO^{\bullet} + 2O_2 \rightarrow 2SO_2 + O_2^{\bullet} \quad \textbf{(3)}$$

$$2H_2S + 4O_2 \rightarrow 2SO_2 + 2H_2O + O_2^{\bullet} \quad \textbf{(4)}$$

[1] http://jan.ucc.nau.edu/~doetqp-p/courses/env440/env440_2/lectures/lec37/lec37.htm accessed on Feb 25, 2005

Physicochemical properties of SO_2

Sulfur dioxide is heavier than air and also called sulfurous anhydride, sulfur oxide, sulfurous oxide and sulfurous acid anhydride. It has a chemical formula SO_2 and a chemical structure of O=S=O with the molecular weight of 64.06 Daltons. Its physical state is a colorless gas with a density of 2.927 g/L at 0^oC and 760 mmHg. The solubility in water is 23 g/100 mL at 0^oC and can dissolve in organic solvents such as acetic acid, alcohol, chloroform, ether, and in inorganic solvents such as sulfuric acid [1]. In the atmosphere, SO_2 can be converted to sulfuric acid (H_2SO_4), sulfur trioxide (SO_3), and sulfate. As shown in **reaction (5)** and **(6),** in the atmosphere SO_2 reacts with the $HO^\bullet$ to form a bisulfite radical ($HSO_3^\bullet$), which can react with another $HO^\bullet$ to form H_2SO_4.

$$SO_2 + HO^\bullet \rightarrow HSO_3^\bullet \quad \textbf{(5)}$$

$$HSO_3^\bullet + HO^\bullet \rightarrow H_2SO_4 \quad \textbf{(6)}$$

When SO_2 is dissolved in water, it forms sulfurous acid (H_2SO_3), **reaction (7)**, which is an unstable and relatively weak acid dissociates to form bisulfite (HSO_3^-), **reaction (8)** and sulfite, **reaction (9)** [10].

$$SO_2 + H_2O \rightarrow H_2SO_3 \quad \textbf{(7)}$$

$$H_2SO_3 \rightarrow H^+ + HSO_3^- \quad pK_a = 1.86 \quad \textbf{(8)}$$

$$HSO_3^- \leftrightarrow H^+ + SO_3^{2-} \quad pK_a = 7.2 \quad \textbf{(9)}$$

In **reaction (10)**, SO_2 can be gradually oxidized to sulfur trioxide (SO_3) which then reacts with water to form sulfuric acid, **reaction (11).**

$$2SO_2 + O_2 \rightarrow 2SO_3 \quad \textbf{(10)}$$

$$SO_3 + H_2O \rightarrow H_2SO_4 \quad \textbf{(11)}$$

Sulfur dioxide also combines with H_2O_2 to form sulfuric acid, **reaction (12).**

$$SO_2 + H_2O_2 \rightarrow H_2SO_4 \quad \textbf{(12)}$$

Biochemical aspects and derivatives

Many of the general biochemical properties of SO_2 and its derivatives have been reported [5, 6, 8]. Inhaled SO_2 can easily be hydrated to produce sulfurous acid in the respiratory tract, which subsequently dissociates to form its derivatives, bisulfite and sulfite, **reactions (8, 9).** The nomenclature (bi)sulfite is used when it is not known which of these species is involved in a reaction [6]. The derivatives can be absorbed into blood and other body fluid. However, besides inhalation and skin contact, bisulfite and sulfite can enter the body from foods, beverages, and drugs due to its use as a preservative [2]. In addition, endogenous bisulfite/sulfite is regularly generated during the normal processing of sulfur-containing amino acids [7] and can be formed by the metabolism of sulfur-containing drugs, including N-acetyl-cysteine [8]. The reactions of (bi)sulfite are considered to be occur by both one- and two-electrons oxidation, where sulfur trioxide radical anion ($SO_3^{\bullet-}$) and sulfate (SO_4^{2-}) are formed, **reactions (13-15)** [6, 9, 10, 26].

$$SO_3^{2-} + HO^{\bullet} \rightarrow SO_3^{\bullet-} + OH^- \quad k = 5.5 \times 10^9\ M^{-1}\ s^{-1} \quad \textbf{(13)}$$

$$SO_3^{2-} \rightarrow SO_3 + 2e^- \quad \textbf{(14)}$$

$$SO_3 + H_2O \rightarrow SO_4^{2-} + 2H^+ \quad k = 9.4 \times 10^5\ M^{-1}\ s^{-1} \quad \textbf{(15)}$$

Sulfite oxidase, a mitochondria enzyme, is considered to be a two-electron acceptor of electron from (bi)sulfite while the one-electron oxidation is catalyzed by peroxidases [27]. Superoxide ($O_2^{\bullet-}$) initiates (bi)sulfite oxidation by forming $SO_3^{\bullet-}$ but is not a chain propagator, implying $O_2^{\bullet-}$ is not a significant reaction product of the $SO_3^{\bullet-}$ [28]. Sulfur trioxide radical anion reacts with a molecule of oxygen forming a $O_2^{\bullet-}$ and peroxysulfate radical anion ($SO_5^{\bullet-}$), **reaction (16) and (17)** [10]**.** However, $O_2^{\bullet-}$ formed during sulfite oxidation is considered to be a relatively minor product [29].

$$SO_3^{\bullet-} + O_2 \rightarrow SO_3 + O_2^{\bullet-} \quad \textbf{(16)}$$

$$SO_3^{\bullet-} + O_2 \rightarrow SO_5^{\bullet-} \quad k = 1.5 \times 10^9\ M^{-1}\ s^{-1} \quad \textbf{(17)}$$

Peroxysulfate radical anion is a stronger oxidant than $SO_3^{\bullet-}$. After one-electron oxidation initiation, subsequent formation of $SO_5^{\bullet-}$ may then proceed autocatalytically *via* two possible propagation steps to generate sulfate radical anion ($SO_4^{\bullet-}$), **reaction (18).** Sulfate radical anion is a strong oxidant which rapidly oxidizes (bi)sulfite, **reaction (19)** and reacts with water molecule to generate hydroxyl radical, **reaction (20)** but this reaction is not important in propagating the chain reaction because $SO_4^{\bullet-}$ will preferentially react with (bi)sulfite [6]**.**

$$SO_5^{\bullet-} + SO_3^{2-} \rightarrow SO_4^{\bullet-} + SO_4^{2-} \quad k = 1.3 \times 10^7\ M^{-1}\ s^{-1} \quad \textbf{(18)}$$

$$SO_4^{\bullet-} + SO_3^{2-} \rightarrow SO_4^{2-} + SO_3^{\bullet-} \quad k = 2.6 \times 10^8\ M^{-1}\ s^{-1} \quad \textbf{(19)}$$

$$SO_4^{\bullet-} + H_2O \rightarrow HSO_4^{-} + HO^{\bullet} \quad k < 3 \times 10^3\ M^{-1}\ s^{-1} \quad \textbf{(20)}$$

The main metabolite produced in the blood after respiratory exposure to SO_2 is sodium sulphite (Na_2SO_3) [4]. It was reported that SO_2 and sulfur (IV) oxoanions (SO_4^{2-}) in solution undergo pH-dependent equilibration reactions between SO_2, H_2SO_3, HSO_3^-, and SO_3^{2-}. At normal physiological pH values and concentrations of greater than 1 M, the equilibrium is between approximately equal proportions of SO_3^{2-} and HSO_3^-**,** while at lower pH such as that of the stomach of fasting humans, the equilibrium is essentially between HSO_3^- and free SO_2 [11].

Sulfur dioxide can form adducts with many biological molecules, such as DNA or protein. For example, SO_2 reacts irreversibly with thiamine (vitamin B-1) to yield pyrimidine sulfonic acid and 4-methylhydroxyethyl thiazole [13]. At high concentrations, SO_2 may destroy cobalamins (vitamin B-12) *via* the formation of photolabile complexes [14]. Sulfite forms adducts with nicotinamide adenine dinucleotide (NAD), flavins, and reversible adducts with the 5, 6-double bond of cytosine and uracil, their nucleosides, and nucleotides [15, 16]. Non-enzymatic reactions of sulfite with tissue components include cleavage of disulfide bonds, with the formation of S-sulfonates and thiols [17]. The sulfitolysis reaction of sulfite was suggested to be the common reaction mechanism mediating the underlying biochemical reactions leading to

both toxic and carcinogenic properties of SO_2 [18]. It has been reported that sulfites are capable of reacting with nitric oxide and its derivatives, which then affected nitric oxide's ability to function in cell signaling process [19].

Detection

The natural SO_2 concentration in the atmosphere is 0.04-0.45 mg/m^3 (0.01-0.17 ppm [1]. There are several established analytical methods used to measure SO_2 in the environment. These methods include ion chromatography, titration, colorimetry, mass spectroscopy, conductimetry, amperometric detection, flame photometric detection and turbidimetry. Ion chromatography seems to be the most sensitive of among these methods [1]. In contrast, the methods for determining exposure to SO_2 in biological materials are not well established. These techniques lack sensitivity and precision for SO_2 because of the rapid conversion of SO_2 to sulfur-containing metabolites, such as S-sulfonate [20]. However, sulfite free radicals can be detected using EPR spectroscopy [6, 9].

Health and environmental effects

The people most often exposed to SO_2 are workers in industries where SO_2 is produced as a by-product. Sulfur dioxide can easily and rapidly enter the bloodstream through the lungs and break down to sulfate, which is then excreted through urine [1]. One human health concern is for short-term exposure to SO_2 concentrations above 1,000 μg/m^3 or 0.38 ppm, measured as a 10-minute average[2]. Under this condition a person may develop burning of the nose and throat, breathing difficulties, severe airway obstruction, bronchitis and bronchoconstriction. Another concern is for long-term exposure to persistent levels of SO_2 which can change lung function [21]. Long term exposure to SO_2 pollution even at low concentrations in the environment, may be a potential risk for the induction of cytogenetic damage in human [22]. From the same study,

[2] http://lnweb18.worldbank.org/essd/essd.nsf/GlobalView/PPAH/$File/46_soxc.pdf accessed on Feb 25, 2005

low concentrations SO_2 induced only chromatid-type chromosome aberration while at high concentrations of SO_2 induced both chromatid-type and chromosome-type chromosome aberration. Sulfur dioxide is reported to be a clastogenic and genotoxic agent that decreased mitotic index, induced chromosome aberration and sister-chromatid exchange [4].

In addition, it is reported that SO_2 is a systemic oxidative damaging agent that causes various organ damage in animals including brain, lung, heart, liver, stomach, intestine, spleen, kidney, and testis [3]. Inhalation of SO_2 significantly decreased levels of GSH and decreased activity of SOD and GSH-Px, while catalase activity was not altered. Significant increases in TBARS levels were also observed [3, 23]. The antioxidant levels of vitamin C and ceruloplasmin in plasma were reported to be decreased upon exposure to SO_2. The decreased vitamin C might be due to the reactions with sulfur-centered radicals from SO_2 metabolite while the decreased in ceruloplasmin might be due to the presence of bisulfite in the plasma that interacts with the copper ion, and leads to inhibition of ceruloplasmin [24]. It is also reported that SO_2 and its *in vivo* derivatives can cause a prolongation effect of the nerve pathway [23] and are toxic to central neural cells of animals [25].

Summary

Sulfur dioxide is a dangerous air pollutant that is considered to have adverse health effects on humans due to its carcinogenicity, clastogenicity, and genotoxicity. The major health concerns associated with exposure to high concentrations of sulfur dioxide are effects on various organ systems, especially the respiratory system. Moreover, SO_2 derivatives are considered to be an important source of free radicals generated in biological system. Sensitive methods of detection and understanding of the interactions of SO_2 and its derivatives with biomolecules are necessary to help protect the public from the harmful effects of SO_2.

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