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REGULAR ARTICLES

Proposing boric acid as an antidote for aluminium phosphide poisoning by investigation of the chemical reaction between boric acid and phosphine

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KEYWORDS

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Abstract Aluminium phosphide (AlP) is a storage fumigant pesticide, which is used to protect stored grains especially from insects and rodents. It releases phosphine (PH_3) gas, a highly toxic mitochondrial poison, in contact with moisture, particularly if acidic. Although the exact mechanism of action is unknown so far, the major mechanism of PH_3 toxicity seems to be the inhibition of cytochrome-c oxidase and oxidative phosphorylation which eventually results in adenosine triphosphate (ATP) depletion and cell death. Death due to AlP poisoning seems to be as a result of myocardial damage. No efficient antidote has been found for AlP poisoning so far, and unfortunately, most of the poisoned human cases die. PH_3, like ammonia (NH_3), is a Lewis base with a lone-pair electron. However, boric acid ($B(OH)_3$) is a Lewis acid with an empty p orbital. It is predicted that lone-pair electron from PH_3 is shared with the empty p orbital from $B(OH)_3$ and a compound forms in which boron attains its octet. In other words, PH_3 is trapped and neutralised by $B(OH)_3$. The resulting polar reaction product seems to be excretable by the body due to hydrogen bonding with water molecules. The present article proposes boric acid as a non-toxic and efficient trapping agent and an antidote for PH_3 poisoning by investigating the chemical reaction between them.

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Introduction

Aluminium phosphide (AlP) as a pesticide is present in the forms of tablet, dust, pellet and grains [1]. In Iran, the tablet form of AlP is called 'rice tablet' because it is used for protection of rice [2]. It reacts with moisture and water and produces phosphine gas (PH_3) [3], a colourless, flammable and highly toxic gas, with an odour of garlic or decaying fish [4]. Thus, it is called a fumigant pesticide [5]. AlP is not toxic *per se* but the toxic gas PH_3, which is formed in contact to moisture, is responsible for toxicity of AlP [6]. Although the exact mechanism of action is unknown so far, the major mechanism of PH_3 toxicity seems to be the inhibition of cytochrome-*c* oxidase and oxidative phosphorylation [7], which eventually results in adenosine triphosphate (ATP) depletion and cell death [4]. AlP is a multi-organ poison. It has toxic effects on cardiovascular, respiratory, hepatic and gastrointestinal systems and induces acid–base disturbances [7]. Death due to PH_3 poisoning seems to be as a result of myocardial damage and cardiovascular collapse [8]. Unfortunately, no specific antidote has been found for routine treatment of AlP poisoning so far and most of the poisoned human cases die [7].

Boric acid ($B(OH)_3$) is a colourless, odourless, transparent material with a slightly unctuous touch [9]. It has a water solubility of about 50 g l^{-1} (21 °C). The pH value of a 0.1 M solution of boric acid is 5.1; thus, it is considered as a weak acid [10]. Boric acid is considered as a non-toxic material with a 5.14 g kg^{-1} oral median lethal dose (LD_{50}) in rats [11].

Boric acid with an empty p orbital is considered as a Lewis acid (electron acceptor), which theoretically can react with a Lewis base (electron donor). A Lewis base has a lone-pair electron that can be shared with empty p orbital of $B(OH)_3$. Boron attains its octet in the resulting compound [12].

In the present study, the possibility of a reaction between a non-toxic Lewis acid (boric acid) and a highly toxic Lewis base (PH_3) has been investigated and thus a new antidote for PH_3 is proposed.

Hypotheses/ideas

Reaction between boron triflouride (BF_3) and ammonia (NH_3) has been well described long time ago [13–15]. In this reaction, NH_3 as a Lewis base shares its lone-pair electron with an empty p orbital of a Lewis acid (BF_3). Thus, NH_3 acts as an electron donor and BF_3 acts as an electron acceptor. After reaction, the B–N bond has been shown to have a covalent bond characteristic [13–15]. A similar reaction between $B(OH)_3$ (Lewis acid) and PH_3 (Lewis base) is theoretically expected. It is predicted that boric acid as a non-toxic weak Lewis acid chemically bonds with highly toxic phosphine gas. In this reaction, phosphine gas is trapped and neutralised by boric acid. The resulting polar reaction product seems to be excretable by the body due to hydrogen bonding with water molecules. Thus, boric acid is proposed as a possible efficient non-toxic antidote for phosphine gas poisoning.

Evaluation of hypotheses/ideas

To evaluate the effectiveness of boric acid to trap and neutralise phosphine gas, the chemical reaction between these two substances should be first studied. The volume of released phosphine gas and the rate of phosphine gas release in boric acid solution are determined and compared (at the same pressure and temperature) with the condition where boric acid is replaced with water (control). The pH of the reaction media will be monitored continuously to evaluate the increase in pH because PH_3 is a base. Addition of hydrochloric acid to boric acid solution and reaching the solution pH to 2 (approximate pH of the stomach) and determination of the volume of released phosphine gas and the rate of phosphine gas release will reveal the efficiency of boric acid in trapping and neutralising phosphine in the stomach. Released phosphine will be collected in and its volume measured by an upside-down water-filled glass measuring cylinder in a water basin. Rate of phosphine gas release will be determined by measuring the produced phosphine gas at appropriate time intervals. To confirm the reaction between boric acid and phosphine gas and formation of a P–B bond, infrared spectroscopy will be used using a sodium chloride (NaCl) cell.

Discussion/conclusion

Although digoxin [16], *N*-acetylcysteine [17], hyperbaric oxygen [18], $^{25}Mg^{2+}$-carrying nanoparticles [7], intragastric irrigation with sweet almond oil [19], combination of vitamin C and methylene blue [20], extensive gastric lavage with coconut oil and sodium bicarbonate solution with simultaneous aspiration [21], intra-aortic balloon pump [22], *N*-omega-nitro-L-arginine methyl ester (L-NAME) [17], combination of atropine and pralidoxime [23] and trimetazidine [24] have been reported efficient either experimentally or in case reports, unfortunately, no specific antidote has been found for routine treatment of AlP poisoning so far and most poisoned human cases do not survive [7].

The reaction between BF_3 as a Lewis acid and NH_3 as a Lewis base is schematically depicted in Fig. 1(a). In this reaction, ammonia and boron triflouride act as an electron donor and electron acceptor, respectively. The resulting reaction product is polar with hydrogen bonding with water molecules [12–15].

The reaction between boric acid ($B(OH)_3$ as a Lewis acid and PH_3 as a Lewis base is comparable with the reaction between BF_3 and NH_3 (Fig. 1(b)). It is predicted that the product of this reaction is a polar adduct with hydrogen bonding with water molecules.

Unlike BF_3 which is a toxic substance and cannot be used medically, boric acid is a non-toxic weak Lewis acid [11], which has several medical uses such as antiseptic, insecticide, eyewash solution and etc [25]. Although many studies reviewed boric acid toxicity in humans, most of them have focussed on infants and children who are inherently susceptible to xenobiotics [26–33]. A review of acute human exposure to boric acid indicated that the effects of any particular dose can vary dramatically among individuals. The average dose for asymptomatic ingestion cases, which accounts for 88% of all ingestions, is around 0.9 g. However, the range of reported asymptomatic doses is wide, from 0.01 to 88.8 g. The average dose causing symptoms was 3.2 g, but it was also highly variable with individual values ranging from 0.1 to 55.5 g. Further, minimum oral lethal doses of boric acid in humans have been estimated from accidental poisonings to be in the range of 5–20 g for adults, 3–6 g for children and < 5 g for infants [34].

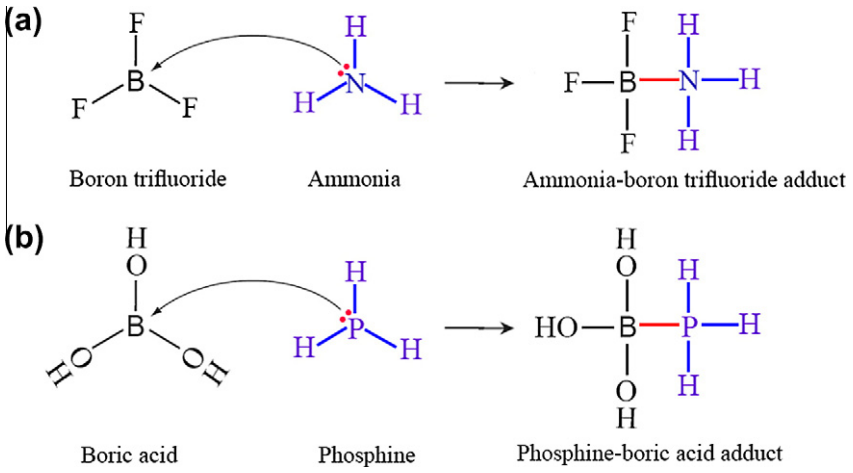

Figure 1 Chemical reaction between boron trifluoride and ammonia (a) and proposed chemical reaction between phosphine and boric acid (b).

Boric acid does not liberate a proton in water, but rather bonds to the O atom of an H_2O molecule, which then releases an H^+ ion to form the $B(OH)^{4-}$ ion (with a pK_a of 9.23) according to the following chemical equation [10,12–15]:

$$B(OH)_3 + H_2O \rightarrow B(OH)_4^- + H^+ \qquad \text{(Reaction1)}$$

The pK_a's of boric acid are 9.24, 12.40 and 13.40, respectively [10]. According to the Henderson–Hasselbalch equation equation, in the acidic pH of the stomach (about 2.0), almost all boric acid molecules exist as $B(OH)_3$ [10] and at physiologic pH of the human body (7.4), about 1.8% of boric acid molecules exist as $B(OH)^{4-}$ and 1.4% of those exist as $H_2BO_3^-$. PH_3 is more basic than water; thus, it is predicted that at the pH of stomach and of blood, a reaction between PH_3 and boric acid is more probable.

It has been shown that 500 mg of a 3-g AlP tablet (which contains about 56% pure AlP (equal to 1680 mg pure AlP)) is lethal for an adult human being [1]. According to the chemical reaction of AlP with water, 1 mol (57.96 g) of AlP produces 1 mol (34 g) phosphine gas [3]:

$$AlP + 3H_2O \rightarrow Al(OH)_3 + PH_3 \uparrow \qquad \text{(Reaction2)}$$

Therefore, it is expected that 500 mg of a 3-g AlP tablet (equivalent to 280 mg pure AlP) releases 164.13 mg phosphine. One mole (34 g) of phosphine at standard pressure (1 atm) and temperature (273.15 K or 0 °C) occupies 22,400 ml volume. Thus, it is expected that under these conditions, 164.13 mg phosphine occupies 108.13 ml volume. It is predicted that at normal human body temperature (310.15 K or 37 °C), phosphine gas molecules have more energies and hence have more toxicity than under ambient conditions [12].

According to the following chemical reaction, in the presence of hydrochloric acid of the stomach, a faster reaction occurs [3]:

$$AlP + 3HCl \rightarrow AlCl_3 + PH_3 \uparrow \qquad \text{(Reaction3)}$$

The proposed neutralisation reaction of phosphine by boric acid is as follows:

$$PH_3(g) + B(OH)_3(aq) \rightarrow H_3P - B(OH)_3(aq) \qquad \text{(Reaction4)}$$

This reaction seems to be exothermic because an aqueous solution of an adduct with lower entropy is formed from a gas (with higher entropy) and an aqueous solution of boric acid.

According to reactions 2 (occurred in water), 3 (occurred at stomach pH) and 4, it is predicted that 164.13 mg phosphine (from 500 mg of a 3-g AlP tablet) is stoichiometrically and theoretically neutralised by 298.47 mg boric acid, which is very low to poison an adult human. Therefore, the minimum efficient dose of boric acid for neutralisation of AlP and phosphine is proposed to be 1.06 times of the weight of the former and 1.81 of that of the latter.

According to the following chemical calculation, it is predicted that an absorption peak at about 1029 cm^{-1} due to P–B bond stretching in the $(OH)_3B–PH_3$ adduct appears in the infrared spectrum [35]:

$$\bar{\nu} = 4.12\sqrt{\frac{K}{\mu}} = 4.12\sqrt{\frac{(5 \times 10^5)}{8.013}} = 1029.16 \text{ cm}^{-1}$$

where $\bar{\nu}$ is the frequency in cm^{-1}, K is the force constant in dynes cm^{-1} and μ is reduced mass which can be obtained by following calculation:

$$\mu = \frac{M_P M_B}{(M_P + M_B)} = \frac{30.97 \times 10.81}{(30.97 + 10.81)} = \frac{334.78}{41.78} = 8.013$$

where M_P and M_B are the atomic masses of phosphorous and boron atoms, respectively.

The reaction of ammonia with boric acid which results in ammonium borate is another evidence that phosphine gas can chemically react with boric acid [36].

This article proposes boric acid as a new and efficient antidote for trapping and neutralising phosphine gas by investigating the chemical reaction between these two compounds. Although the present study predicted that boric acid chemically reacts with phosphine gas, which results in more polar and may be a more excretable product than phosphine, further extensive chemical, *in vitro* and *in vivo* studies should be done to show the integrity of the present study.

Overview Box

First Question: What do we already know about the subject?

There is no specific efficient antidote for AlP and PH_3 poisoning so far. Mortality due to AlP poisoning is very high.

Second Question: What does your proposed theory add to the current knowledge available, and what benefits does it have?

Boric acid is a non-toxic Lewis acid which efficiently traps PH_3 gas. In this reaction, boric acid acts as a Lewis acid and phosphine acts as a Lewis base. The resulted polar reaction product which has H and OH groups can form hydrogen bonds with water molecules and hence can be excreted in urine by the body.

Third question: Among numerous available studies, what special further study is proposed for testing the idea?

The chemical reaction between PH_3 and boric acid should be first studied. The volume of released PH_3 gas and rate of PH_3 release in boric acid solution should be compared (at the same pressure and temperature) with the condition where boric acid is replaced with water (control). *In vitro* and *in vivo* studies should also be done to confirm the present idea. Moreover, cytochrome-*c* oxidase activity in cardiomyocytes and mortality rate should be determined.

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