Editor HONGZHE SUN

# Biological Chemistry of Arsenic, Antimony and Bismuth

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Editor

HONGZHE SUN

Department of Chemistry, University of Hong Kong, P. R. China



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### Preface

Arsenic (As), antimony (Sb) and bismuth (Bi) are in Group 15 in the periodic table together with nitrogen and phosphorus. All of them are directly and indirectly related to human life. Both nitrogen and phosphorus are essential to life whereas arsenic (and antimony) is double-edged. The therapeutic effect of arsenic has been recognized even in ancient China and arsenic minerals have often been used in traditional Chinese medicine (e.g., realgar and orpiment). Partially based on this application, arsenic trioxide (Trisenox) was tested and subsequently approved to be used as an anticancer drug against leukaemia. In fact the first modern pharmaceutical is an organoarsenic compound, arsphenamine (Salvarsan or Ehrlich 606). Ironically, the structure of the drug in solution was not clear until recently. Both antimony and bismuth have been used in clinics for decades. The toxicity of arsenic (and antimony) is also well-known and indeed the contamination of groundwater by arsenic is becoming a major health problem in Asian countries such as India and Bangladesh. In spite of their importance to our lives and the environment, there is no book that reports the latest progress of biological chemistry of arsenic, antimony and bismuth.

This book gives readers a comprehensive update of the progress, particularly in the past decade. The 15 chapters which constitute the book have been written by leading scientists who are experts in their relevant field. Chapter 1 is an overview of the current knowledge of the chemistry of arsenic, antimony and bismuth. Chapters 2 and 3 are devoted to the biological chemistry of arsenic, antimony and bismuth. The latest information on structures of clinically used antimony and bismuth drugs, and arsenic/antimony-protein complexes, is described extensively. The transport and trafficking of the metalloid (As and Sb) is summarized in Chapter 8. Chapters 6 and 7 are devoted to biotransformation and biomethylation of arsenic, antimony and bismuth, one of the most important metabolism processes in biological systems. Chapter 5 is devoted the application of arsenic minerals in traditional Chinese medicine whereas Chapter 11 summarizes the modern applications of arsenic trioxide for leukaemia. Subsequently, Chapter 12 reviews the latest progress of the development of anticancer agents based on arsenic, antimony and bismuth complexes. Chapters 9 and 13 are devoted to medical applications of (radio)bismuth especially for potential anticancer treatment. Since the discovery of the bacterium Helicobacter pylori and its role in gastritis and peptic ulcer disease by Warren and Marshall in the 1980s, bismuth containing drugs has been commonly recommended in clinics together with antibiotics. Chapter 10 summarizes clinical applications of bismuth for Helicobacter pylori infection and the potential mechanism of action. Chapter 14 is devoted to the genetic toxicology of arsenic and antimony. In view of the rapid development of modern bioanalytical techniques such as metallomics and metalloproteomics, Chapters 4 and 15 review the concept and methodology of these techniques and more importantly, the application of the '-omics' towards our understanding of the biological chemistry of arsenic, antimony and bismuth.

Such topics will be of particular interest to researchers, scientists and postgraduate students working in the fields of chemistry, biochemistry, environmental chemistry, toxicology and medicine.

I would like to thank all contributors for the hard work and tremendous effort that they have put into writing this book. During the preparation of the book chapter, Professor Toshikazu Kaise (Tokyo University of Pharmacy and Life Sciences, Japan) passed away suddenly. He was an excellent scholar and he promoted the work of the younger generation of scientists in various countries. Professor Kaise will be remembered by all his colleagues and friends. This book, therefore, is dedicated to him for his outstanding contributions to biological chemistry of arsenic. I would also like to express my sincere appreciation to Dr. Nan Yang, Dr. Hongyan Li, and Cheuk-Nam Tsang and Commissioning Editor Paul Deards, and Rebecca Ralf from John Wiley & Sons, Ltd. Without their kind help and strong support, the publication of this book would be impossible. Hongyan and Frances are acknowledged for their endless support and encouragement. And last but not least, I hope that you, the reader, will enjoy reading this book and develop the interdisciplinary spirit that lives in biological inorganic chemistry.

Hongzhe Sun Hong Kong, China

### 1

### The Chemistry of Arsenic, Antimony and Bismuth

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Arsenic, antimony and bismuth are the heavier pnictogen (Group 15) elements and consistent with their lighter congeners, nitrogen and phosphorus, they adopt the ground state electron configuration  $ns^2np^3$ . Arsenic and antimony are considered to be metalloids and bismuth is metallic, while nitrogen and phosphorus are non-metals. Arsenic and antimony are renowned for their toxicity or negative bioactivity [1, 2] but bismuth is well known to provide therapeutic responses or demonstrate a positive bioactivity [3]. As a background to the biological and medicinal chemistry of these elements, the fundamental chemical properties of arsenic, antimony and bismuth are presented in this introductory chapter.

### **1.1 Properties of the Elements**

Selected fundamental parameters that define the heavier pnictogen elements are summarized in Table 1.1 [4]. While arsenic and bismuth are monoisotopic, antimony exists as two substantially abundant naturally occurring isotopes. All isotopes of the heavy pnictogens are NMR active nuclei, indicating that the nuclear spin will interact with an applied magnetic field. However, as the nuclear spins of these isotopes are all quadrupolar, NMR spectra generally consist of broad peaks and provide limited information. The atoms As, Sb and Bi all have the same effective nuclear charge ( $Z_{eff} = 6.30$ , Slater), which estimates the charge

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Parameter	As	Sb	Ві
Atomic Number Natural Isotopes (abundance)	33 <sup>75</sup> As (100) <i>Stable</i>	51 <sup>121</sup> Sb (57.4) <i>Stable</i>	83 <sup>209</sup> Bi (100) <i>a-decay</i> [5]
Radioactive Stability	busic	<sup>123</sup> Sb (42.6) Stable	$t_{1/2}$ : $(1.9 \pm 0.2) \times 10^{19} yr$
Nuclear Spin, I	-3/2	+5/2 ( <sup>121</sup> Sb) +7/2 ( <sup>123</sup> Sb)	-9/2
Ionization Energies (kJ mol <sup>-1</sup> )			
$M \rightarrow M^+$	947	833.7	703.2
$M^+ \rightarrow M^{2+}$	1798	1794	1610
$M^{2+} \rightarrow M^{3+}$	2735	2443	2466
$M^{3+} \rightarrow M^{4+}$	4837	4260	4372
$M^{4+}  ightarrow M^{5+}$	6043	5400	5400
Electron Affinity	78	101	91.3
$(kJ \text{ mol}^{-1}) M(g) \rightarrow M(g)$			
Electronegativity, $\chi^{P}$ ( <i>Pauling scale</i> )	2.18	2.05	2.02
Atomic Radius (Å)	1.25	1.82	1.55
Single-bond Covalent Radius (Å)	1.21	1.41	1.52
Van der Waals Radius (Å)	2.00	2.20	2.40
Ionic Radii (Å)			
$M^{5+}$	0.46	0.62	0.74
M <sup>3+</sup>	0.58	0.76	0.96

**Table 1.1**Elemental parameters for arsenic, antimony and bismuth (adapted with permission<br/>from [4]). Copyright Springer Science + Business Media

experienced by a valence electron taking into account shielding by the other electrons. As a consequence, the ionization energies and electron affinities for As, Sb and Bi are very similar. The ionization energy is the energy required to remove a valence electron from an atom or an ion in the gas phase. The ionization energies are predictably greater for ions with higher positive charge and are typically lower for atoms or ions with higher principal quantum number (n). The electron affinity is the energy released when an atom gains an electron to form an anion in the gas phase. The electronegativity ( $\chi^P$ ), defining the relative ability of an atom to attract electrons to itself in a covalent bond, is sufficiently larger for arsenic than for antimony and bismuth. The atomic radii, covalent radii and ionic radii are smallest for arsenic and largest for bismuth atoms consistent with the relative atomic mass and number of electron shells.

Selected biological and toxicity data for As, Sb and Bi are summarized in Table 1.2. While some arsenic compounds are essential to certain animal species [4], most arsenic compounds display toxic biological effects even when present in only small amounts. Some compounds, such as Salvarsan 606 [6], are therapeutic, although there are reported side effects, including death in high dosages. Neither antimony nor bismuth has any known natural biological function. While antimony has toxicity comparable with that of arsenic, bismuth can be tolerated in large quantities. Bismuth compounds have been used for more than two centuries to treat many medical disorders and are now commonly available in the preparations known commercially as Peptobismol and DeNol [3].