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Review

Biological methylation of less-studied elements

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Biological methylation is an enzymatic process in which a methyl group is transferred from one atom to another. For elements having atomic number greater than 11, biological methylation has been most extensively studied for three elements: arsenic, mercury and sulfur. However, many other elements also undergo biological methylation but have received less attention. Recent work on these less-studied elements and new applications of biological methylation to environmental remediation, along with a description of these reactions in terms of bonding models, is the focus of this review.

KEYWORDS: adenosylmethionine; biomethylation; bioremediation; Challenger mechanism; environment; methylcobalamin; methyltransferase; toxicity; volatilization

SOME GENERAL CONSIDERATIONS

Terminology

The term biological methylation (usually contracted to biomethylation) refers to an enzymatic transfer of a previously formed methyl group from some donor atom to some acceptor atom within a living organism. Enzymes controlling such transfers are termed *methyltransferases*. The more general term of transmethylation refers to ***any*** methyl transfer reaction, whether or not living cells are involved; thus, biomethylation is equivalent to an enzymatic transmethylation occurring in cells. Biomethylations of carbon, nitrogen, oxygen or sulfur atoms are used regularly by organisms as a part of their metabolism.[1–4] Investigations involving enzymatic transmethylation have become increasingly important in genetic and cancer research,[5–7] where the terms hypomethylation and hypermethylation are frequently encountered.

Other elements with atomic number greater than 11 also undergo biomethylation.[8–13] A substantial and growing research literature on this topic currently exists for arsenic and mercury. Additional elements that also undergo biomethylation have received considerably less attention. Such less-studied elements are the focus of this review, along with possible roles that their biomethylation might play in health hazards and environmental pollution.

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Organisms causing biomethylation

As far as is known, enzymatic transmethylation occurs in all organisms. However, not all organisms will necessarily methylate every element. Table 1 shows those elements for which biomethylation has been reported, and the type of organism performing it. The largest number of elements (especially metals) are methylated primarily (possibly exclusively) by bacteria, usually in sediments or soils. Fungi, yeasts and algae methylate metalloids and nonmetals (arsenic, antimony, chalogens); the halogens undergo methylation primarily in marine kelps and seaweeds. Plants and animals

Table 1. Element biomethylation by type of organism[a]

Periodic group number								
9	10	11	12	13	14	15	16	17
				Al	Si	P	S	Cl
				NR	NR	1	1–4	2,3
Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br
1–4	1	NR	NR	NR	1(?)	1–4	1–4	2,3
			Cd	In	Sn	Sb	Te	I
			1(?)	NR	1,2	1,2	1,2,4	1–3
			Hg	TI	Pb	Bi	Po	At
			1	1	1,2(?)	1	1,2	NR

[a] Methylation and classes of organisms: (1) bacteria; (2) fungi/algae/yeast; (3) plants; (4) animals. NR: biomethylation not reported.

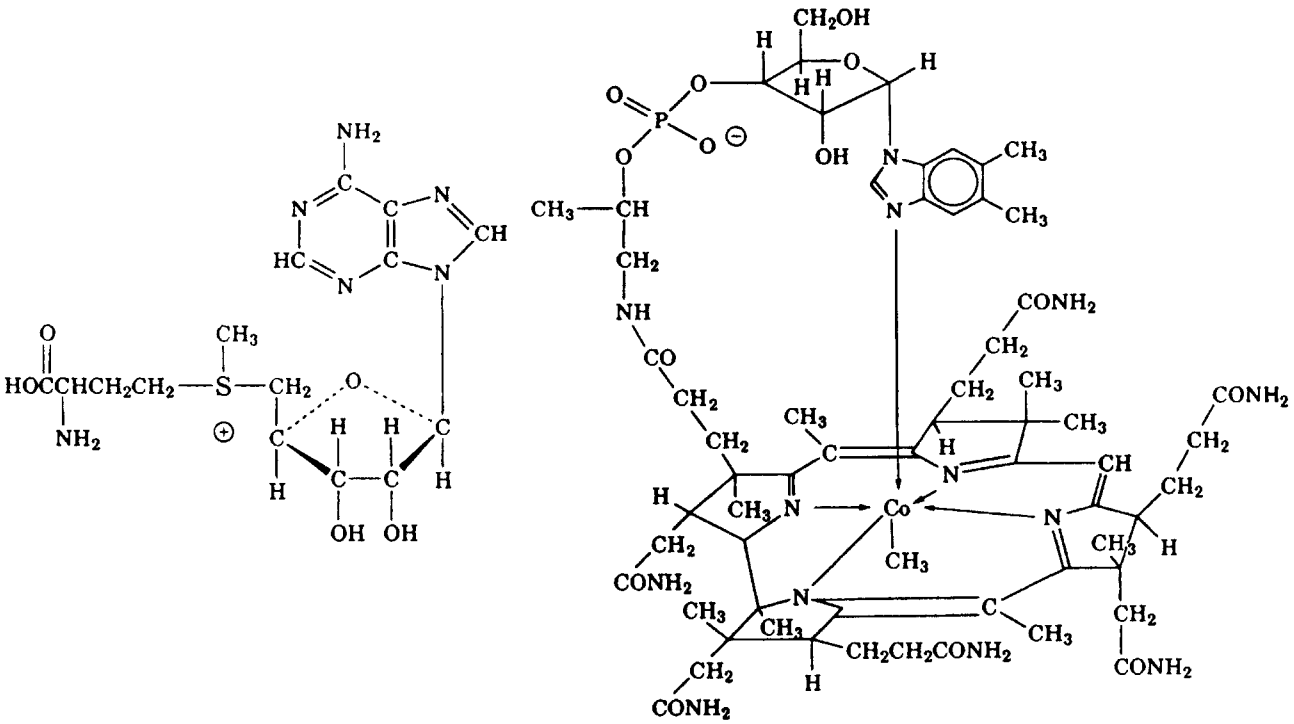

Figure 1. Structures of *S*-adenosylmethionine (**I**) and methylcobalamin (**II**).

appear to be more limited in the scope of their biomethylation, especially where their own organismal processes (as opposed to biomethylation by symbiotic bacteria) are involved. However, plants and animals have been much less investigated as biomethylating systems than unicellular organisms, and generalizations are therefore speculative. It should be stressed that the *rates* of biomethylation will vary substantially and will depend on the organism(s) involved, the nature of the substrate and its concentration.

Biomethylation and molecular properties

Elements undergoing biomethylation are nearly always already incorporated into a chemical compound. Introduction of a methyl group generally requires replacement of some other ligand (usually an inorganic group, e.g. halide, hydrogen, hydroxide, etc). Such replacement may weaken intermolecular attractive forces originally present, thereby altering those physical properties (e.g. volatility, solubility) that depend on such forces. For example, chemical methylation of the oxygen atom in water (b.p. 100 °C) gives first methanol (b.p. 65.2 °C) and then dimethyl ether (b.p. −25 °C). For heavier elements, the most drastic change caused by methylation seems to occur when the first and/or last methyl group is introduced. Subsequent methylations continue such changes until the 'permethyl' compounds [e.g. $As(CH_3)_3$, $Pb(CH_3)_4$, $(CH_3)_2Se$], which are gases or volatile liquids at room temperature,[13] are formed. Introduction of methyl groups onto atoms also enhances solubility in lipids and (usually) decreases solubility in water. One chemical consequence of methylation is a change in the ability of the acceptor atom to form complexes with ligands or bind to surfaces.

These effects arising from biomethylation markedly alter the biological activity of the acceptor element, usually substantially changing its toxicity. In fact, poisonings and deaths resulting from methylated derivatives of mercury and arsenic (despite a general reduction in toxicity for arsenic on biomethylation) have provided the major impetus for research on biomethylation. Challenger's pioneering work on arsenic volatilization by the fungus *Scopulariopsis brevicaulis* arose from numerous cases of arsenic poisoning, and first introduced the concept of biomethylation.[14–16] Biomethylation of arsenic under environmental conditions remains an area of great research activity.[17–19] Poisonings arising from biomethylation of mercury in the sediments of Minamata Bay (Japan), and elsewhere, have also generated an enormous research effort.[8,20] Other consequences of physical changes resulting from biomethylation, such as enhancement/dimunition in the movement of elements through the terrestrial biosphere or possible use in bioremediation (see section entitled 'Biomethylation, volatilization and bioremediation'), have also provided incentives for research on this process.

MECHANISMS OF BIOMETHYLATION

Introduction

During biological methylation, the methyl group is most likely transferred as a bridging intermediate **[donor---CH_3---acceptor]** rather than as a free entity. Such an intermediate would form during an associative mechanism, especially an associatively activated intimate mechanism (I_a; see Ref. 21, p. 33) The methyl group may be cationic (electrophilic), radical, or anionic (nucleophilic), depending on the specific donor atom, which in turn will determine the type of substrate atom that can serve as an acceptor. If the transmethylation is also an oxidation–reduction reaction, then the inner-sphere model for electron transfer reactions might be applicable (see Ref. 21, p. 51).

Heavy elements usually undergo biomethylation from one of two biological donors: *S*-adenosylmethionine (**I**), or methylcobalamin (**II**) (see Fig. 1). Nonenzymatic transmethylation can also occur in the natural environment, and may be important in the formation/decomposition of methylmetal compounds.

The Challenger mechanism

Challenger formulated a mechanism (now named for him) to describe the biomethylation of arsenic.[15] In biological systems, arsenate ion (As^V) would be reduced to arsenite (As^{III}).[17] At the pH levels found within most living organisms, arsenite ion would exist primarily as $H_2AsO_3^-$ and the methylation reaction can be written as

$$:As(:O)(OH)_2^- + RR'SCH_3^+ \rightarrow CH_3As(:O)(OH)_2 + RR'S \quad (1)$$

The methyl donor, $RR'SCH_3^+$ is **I**, whose metabolism[14] and methylating abilities[22–25] have been extensively studied. Equation (1) shows an oxidation–reduction reaction, with the sulfur atom of **I** being reduced from +4 to +2, and the arsenic atom being oxidized from +3 to +5. The reactive form of **I** has (*S*)-configurations at both the amino acid center and the sulfonium center (which has three organic groups and a stereochemically important lone pair of electrons).[1]

This form of transmethylation might be viewed as an inner-shell electron pair transfer (see Ref. 21, p. 51), as a nucleophilic attack on the methyl group by the acceptor atom (see Refs 21 (p. 380), 24, 26), or as an acid–base reaction using the hard–soft acid–base (HSAB) model.[27–29] Model studies using methylsulfonium compounds indicated that the reaction could be described by a second-order nucleophilic attack mechanism (S_N2), and that the intermediate had a linear structure.[24] If such a mechanism applies to methylations involving **I**, this would require any acceptor atom to have a lone pair of electrons available. However, the mere presence of one (or more) electron pairs does not automatically render an atom susceptible to biomethylation. The degree of 'softness' is a crucial factor. In the HSAB model, soft bases will react preferentially with soft acids (and *vice versa*), as shown by the values of log K_1 for halide ions listed in Table 2. Fluoride ion is a hard base, iodide ion is a soft base, and the other two halide ions are intermediate. The log K_1 for hard acids decreases going from fluoride to iodide, whereas exactly the opposite trend occurs for soft acids. The methyl carbocation appears to behave as a soft acid (see Refs 21 (p. 380) and 28), indicating that it should bond preferentially to soft bases. This is borne out by the observation that the trimethyloxonium ion, $(CH_3)_3O^+$, nominally containing a methyl carbocation bonded to an oxygen atom (a hard base), transferred that group to an organic sulfide (a soft base).[30] Similarly, methyl iodide forms more readily in biomethylation than either the chloride or bromide (see section entitled 'Chlorine, bromine and iodine'). When arsenite ion undergoes biomethylation, the arsenic atom, not an oxygen atom, receives the methyl group. The softness of an acceptor base will depend very much on its chemical environment, and, in biological systems, it seems likely that one role of methyltransferases will be to make the electron pair on the substrate more available for bonding.

Table 2. The log K_1 values for halides bonding to metal cation

Metal cation	F^-	Cl^-	Br^-	I^-
Zn^{2+}	0.77	−0.19	−0.60	−1.3
Cd^{2+}	0.57	1.59	1.76	2.08
Hg^{2+}	1.03	6.74	8.94	12.87
Ga^{3+}	5.86	−0.6	nl	nl
In^{3+}	3.78	2.36	2.01	1.64
Tl^{3+}	nl	8.1	9.7	nl
Tl^+	0.10	0.68	0.93	nl
Sn^{2+}	3.95	1.15	0.73	nl
Pb^{2+}	<0.3	0.96	1.11	1.26

[a] K_1 is the first association constant for the hydrated metal ion with halide.
[b] Values taken from Reference 27, p. 34. nl: not listed.

Biomethylation of carbon requires formation of a stabilized carbanionic intermediate.[1] Some 120 adenosylmethionine-dependent methyltransferases have been assigned Enzyme Commission (E.C.) numbers;[25] of these, 55 methylate oxygen atoms, 41 methylate nitrogen atoms, 14 methylate carbon atoms, and the remainder methylate sulfur and/or other elements. Such specialization is consistent with the HSAB model, since transmethylation from **I** onto nitrogen, oxygen or carbon atoms should require different conditions than for a corresponding transmethylation onto sulfur, arsenic or other atoms of heavier elements.

Complexation by thiols appears to be required for arsenic atoms to undergo biomethylation, probably because replacement of oxygen atoms by less electronegative sulfur atoms would render the electron pair on arsenic 'softer' and more available to an incoming methyl group. Also, arsenic(V) is less stable and more easily reduced when bonded to sulfur.

Aqueous arsenate is converted to arsenic(III) by H_2S, even at neutral pH.[31] Although arsenic(V) sulfide and $(CH_3)_3AsS$ are stable moieties, the sulfur counterpart to methylarsonic acid is unknown, and dithiocacodylate ion is stable only in salts and complexes,[32,33] decomposing readily in acidic aqueous media:

$$2(CH_3)_2AsS_2^- + 2H^+ \rightarrow 2[(CH_3)_2AsS_2H] \rightarrow \{(CH_3)_2As\}_2S + H_2S + 2S \quad (2)$$

By contrast, numerous methylarsenic(III)–sulfur compounds are known, including polymeric $[CH_3AsS]_x$ and various ring systems[34] of general formula CH_3AsS_x. **II** will methylate arsenite ion in the presence of glutathione.[35]

Arsenic can undergo successive methylations, with each methyl transfer being preceded by reduction of arsenic(V) to arsenic(III). Intermediate methylarsenic(III) species have been detected *in vivo*[36–42] and may be a carcinogenic risk factor.[41,43–46] Mixtures of methylarsenicals are usually found in organisms, although the relative concentrations of the different components may vary substantially. In vertebrates, cacodylate ion is the primary metabolite and is excreted in urine, whereas microorganisms frequently generate (and emit) gaseous trimethylarsine. Some invertebrates can form $(CH_3)_4As^+$ ion,[47] making arsenic the only element so far reported that is able to accept four methyl groups during biomethylation. Though pentamethylarsenic ($(CH_3)_5As$) is a known compound,[48,49] it reacts with water and appears very unlikely to form under biological conditions.

Various other elements undergo biomethylation by this mechanism. Those whose initial form does not have an available lone pair (usually oxyanions) must be reduced before a methyl group can be transferred. Application of this mechanism to specific elements will be discussed in their respective sections.

Methylcobalamin

The second major biomethylating agent is methylcobalamin (**II**), one form of vitamin B_{12}, whose extensive chemistry and biochemistry are reviewed in two recent volumes.[50,51] Unlike **I, II** may transfer its methyl group as a cation, radical or anion, thereby allowing a range of possible acceptor atoms. One especially important acceptor species is homocysteine, which, through the intermediacy of the enzyme methionine synthase, reacts with **II** to form methionine.[50–53] This in turn can be converted to **I**. Thus, methyl groups transferred via the Challenger mechanism previously came from **II**. Methylcobalamin can also methylate heavy elements directly. Methylcobalamin-dependent methyltransferases are known,[50–53] and the structure of one such enzyme has recently been reported.[54] To date, the most commonly reported heavy element acceptor species for **II** are mercury (II) derivatives. Hg^{II} is a soft acid and methyl carbanion is a soft base;[27–29] thus, the HSAB model predicts that the two should combine readily, probably *via* the previously mentioned I_a mechanism. Biomethylation of mercury has been extensively reviewed[8,9,55–57] and will not be considered further.

ELEMENTS REPORTED TO UNDERGO BIOMETHYLATION

Introduction

Cadmium, mercury, cobalt, nickel and almost all of the heavier main-group elements have been reported to undergo biomethylation (see Table 1). There are substantial variations in the rates and degrees of methylated product formation. Certain elements (e.g. arsenic, mercury, antimony, tin, lead, selenium) in their methylated forms pose public health problems and have been investigated primarily for this reason. Cobalt undergoes methylation only in vitamin B_{12} to form **II** and will not be discussed here.

Selenium

Selenium, along with arsenic and tellurium, were first investigated by Challenger.[15] Selenium has an extensive biochemistry,[58,59] in which biomethylation plays an important part. Methylselenium compounds, especially selenomethionine, occur in many organisms,[60,61] and *Se*-adenosylselenomethionine (the selenium analog of **I**) can form in cells.[62] The ratio of this compound to its demethylated product, *Se*-adenosylselenohomocysteine, is lower than the ratio of **I** to *S*-adenosylhomocysteine, suggesting that the methylating ability of the seleno compound may be greater than **I**.

Selenium biomethylation, like its arsenic counterpart, proceeds *via* the Challenger mechanism. However, chemical dissimilarities between the two elements result in markedly different metabolic products:

1. Selenium–oxygen bonds are more easily cleaved than arsenic–oxygen bonds;[8] thus, while arsenic biomethylation yields methylarsonic and cacodylic acids as major metabolites excreted in the urine of vertebrates, the major selenium species excreted in vertebrate urine is trimethylselenonium ion $(CH_3)_3Se^+$, although selenomethionine and other selenium-containing amino acids have also been detected.[62,63]
2. Selenium is less likely to complex with thiols than arsenic; indeed, one report indicates that methylation and glutathione complexation compete with each other in bilary selenium excretion.[64] How this affects the rate and direction of biomethylation is yet to be determined.
3. Methylselenol, CH_3SeH, and its anion have been proposed as contributing to the toxicity[65] and anticarcinogenic effects[66] of selenium.

A selenocysteine methyltransferase has been detected in some species of *Astragalus*.[67]

Dimethylselenide[68–70] and selenomethionine[71] were formed by Indian mustard (*Brassica juncea*) seedlings

Table 3. Some standard electrode potentials[a]

Group 13			
Ga_2O_3/Ga_2O	−0.5	In^{3+}/In^{+}	+0.443
In_2O_3/In^{+}	−0.216	Tl^{3+}/Tl^{+}	+1.05
Group 14			
Ge^{4+}/Ge^{2+}	0.00	SnO_3^{2-}/Sn^{2+}	+0.844
Sn^{4+}/Sn^{2+}	+0.154	SnO_2/Sn^{2+}	−0.77
Pb^{4+}/Pb^{2+}	+1.7(est)	PbO_2/Pb^{2+}	+1.455
Group 15			
$H_2PO_4^-/H_2PO_3^-$	−0.260		
$H_2AsO_4^-/H_2AsO_3^-$	+0.666		
$SbO_3^-/HSbO_2$	+0.678		
Group 16			
$HSeO_4^-/H_2SeO_3$	+1.090	Se/Se^{2-}	−0.92
$HTeO_4^-/HTeO_3^-$	+0.813	Te/Te^{2-}	−1.14
TeO_3/TeO_2	+1.026	Po/Po^{2-}	−1.4 (approx)
PoO_3/PoO_2	+1.524		
Group 17			
I_2/I^-	+0.621		
At_2/At^-	+0.3		

[a] The standard electrode potential is the potential relative to the standard hydrogen electrode under standard conditions. Values are in volts and are taken from Ref. 79

exposed to selenite and selenate salts. Bacteria in the plant rhizosphere are necessary for this biomethylation,[69] and the dimethylselenide generated appears to require 3-dimethylselenopropionate, $(CH_3)_2Se^+CH_2CH_2CO_2^-$,as a precursor.[70] A hybrid poplar volatilized dimethylselenide 232 times faster from selenomethionine than from selenite.[72] Bacteria can generate dimethyldiselenide as well as dimethylselenide.[73,74] Thus selenium, like sulfur, apparently has two pathways for the generation of environmentally occurring dimethylselenide.

Like some other heavier elements, selenium is biologically necessary at low concentrations and becomes toxic at higher levels. Biomethylation is being used more and more to remove selenium from soils, sediments and solid wastes; this aspect is discussed in the section entitled 'Biomethylation, volatilization and bioremediation'.

Tellurium

Much less work has been done on tellurium biomethylation than for its selenium counterpart. Telluromethionine is a known compound, and, through laboratory procedures, has been incorporated into various proteins for the purpose of using the tellurium atom as a tracer.[75–78] This compound has not yet been observed *in vivo*, nor has the tellurium analog of **I** been reported.

Most biomethylation research involving tellurium has utilized unicellular organisms as the generating agents. As Table 3 shows, elemental tellurium is more difficult to reduce to its dinegative anion than either sulfur or selenium, and is occasionally found as a metabolite of tellurite ion.[80] Generation of volatile dimethyltelluride occurred by fungal action on tellurite salts,[80,81] by action of the facultative anaerobe *Pseudomonas fluorescans* on both tellurite and tellurate salts,[80] and through anaerobic digestion of sewage sludge.[82] Although both $(CH_3)_4Te$ and $(CH_3)_6Te$ are known compounds, only the dimethyl compound is known (or likely) to form through biomethylation.

Tellurium biomethylation apparently occurs *via* the Challenger mechanism, although it remains to be determined whether the same enzymes are used for both selenium and tellurium. Tellurium may have a more extensive biochemistry than has yet been reported, and apparently offers a rich field for enterprising research investigators.

Chlorine, bromine and iodine

Only the methyl halides have been reported as forming through biomethylation. Although dimethylhalonium ions, $(CH_3)_2X^+$, have been reported,[83,84] they are probably too reactive to be detected in biological systems. Investigations into biomethylation of the halogens are usually connected to their occurrence in the natural environment and their participation in environmental transportation/distribution processes; biomethylation of iodine in Antarctica, for example, strongly contributes to its biogeochemical cycle.[85] Thus far, fungi, algae and plant cells have been the primary methylating organisms reported,[86] but, recently, various species of bacteria have been found to form CH_3I, using **I** as the methyl source.[87]

Three biomethylation pathways apparently exist:[86]

1. direct biomethylation of halide anions via the Challenger mechanism
2. formation of methyl–halogen bonds by haloperoxidase enzymes
3. reaction of halide anions with dimethylsulfiopropionate.

The alga *Phaeocystis* showed a positive correlation between CH_3Br formation and dimethylsulfiopropionate levels,[88] but no such correlation was observed in Antarctic macroalgae.[89] Positive correlations between CH_3Br and CH_3I levels were reported,[90] as well as between CH_3I and $(CH_3)_2S$ levels.[91] CH_3Cl was apparently formed by more species than CH_3Br.[80,92] In a comparative investigation involving salt marsh environments, CH_3Cl and CH_3Br formed in a 20:1 ratio.[93] Other comparative studies found that fungal biomethylation varied in the order I >Br >Cl.[86] This is the order of their nucleophilicity[26] and their 'softness' as bases,[27] which is consistent with biomethylation via the Challenger mechanism.

Considerably more systematic work is needed to draw firm conclusions about the mechanistic and other details of halogen biomethylation.

Tin

Investigations into environmental biomethylation of tin compounds has grown out of the use of tri-*n*-butyltin (and, more recently, triphenyltin) compounds in antifouling paints. The release of these compounds into natural waters and sediments with subsequent accumulation by invertebrates (especially shellfish) has posed a potentially serious health problem.[94–96] Biomethylation of tin compounds has occurred under environmental conditions, and various laboratory investigations into this process have been reported.[8,13,97–100] Tin-containing substrates may be conveniently divided into two major categories: acceptor species that initially have no tin–carbon bonds (inorganic tin) and those that initially have at least one tin–carbon bond (organic tin).

The term 'inorganic tin', frequently mentioned in literature reports, represents something of a confession of ignorance as to the actual tin species present and may include a variety of possible compounds. Tin has two stable oxidation states: +2 and +4; the energetics of their interconversion depends very much on the specific chemical forms (see Table 3). Both oxidation states are hard acids,[27] with tin(II) being less hard than tin(IV). In laboratory experiments, the chemical form of inorganic tin that actually underwent biomethylation was probably not the one originally added. If the substrate actually accepting a methyl group contains tin(II), then biomethylation should follow the Challenger mechanism. Several complexes of tin(II) have been reported;[98] these possess a trigonal pyramidal structure, with the electron pair on tin situated at the apex and available for bonding. Tin(II) within a cell most probably would exist as a complex. The tin(II) species most readily methylated by the yeast *Saccharomyces cerevisiae* was a penicillamine complex containing an Sn—S linkage.[99] Similarly, amino acid complexes of tin(II) reacted faster with **II** than did uncomplexed tin(II).[100] What chemical form a tin(IV) compound might take in a biological system can only be hypothesized. In aqueous solution, at biological pH values, tin(IV) is most likely to exist as hydrated $Sn(OH)_4$, which, upon absorption into cells, would quite probably form complexes through esterification of the hydroxyl groups and/or bonding to oxygen or nitrogen atoms through expansion of the coordination shell. In anoxic sediments (and probably within cells), tin(IV) may well undergo reduction to tin(II), particularly with enzymatic assistance.

Organic tin substrates under environmental conditions would include methyl-, butyl-, octyl- and phenyl-tin containing varying numbers of organic groups attached to the tin atom. Like arsenic, selenium and tellurium, tin can undergo successive methylations. Reactivity of organotin intermediates towards further methylation seems to decrease as the number of organic groups increases.[100] Tetramethyltin was one component of a mixture of volatile gases (including other methylmetals) formed in anaerobic digestion of sewage sludge.[82]

Tri-*n*-butyltin compounds (oxide, fluoride, etc.) have comprised the active component of antifouling paints used on watercraft or other water-exposed surfaces. These would slowly leach out into adjacent waters, and eventually become incorporated in sediments.[94,95] Their primary route of decomposition proceeded through successive loss of butyl groups, forming dibutyltin, monobutyltin and finally inorganic tin species. Mixed methylbutyltin compounds have also been reported,[8,101,102] with methyltributyltin being the most abundant. Tetramethyltin was also found, but, interestingly, as yet, no tetrabutyltin.[101] *In vitro* methylation studies of tri-*n*-butyltin chloride in seawater–sediment mixtures, using methanol as a methyl source, showed formation of methyltributyltin and methyltin compounds.[103] Triphenyltin compounds have been used to replace the tributyltin analogs in antifouling paints in recent years.[94,95] Both phenyltin and *n*-octyltin compounds have been discovered in the environment,[102] but, so far, no mixed methylphenyl- or methyloctyl-tin species have been reported.

Inorganic ligands attached to tin in organotin derivatives almost always bond through more electronegative elements (fluorine, oxygen, chlorine, sulfur etc). Hydrogen bonded to tin is anionic in nature, as shown by the following reactions:[104]

$$(C_6H_5)_3SnH + RLi \rightarrow (C_6H_5)_3SnR + LiH \quad (3)$$

$$(C_6H_5)_3SnH + HCl \rightarrow (C_6H_5)_3SnCl + H_2 \quad (4)$$

This suggests that a methyl group entering such a chemical environment is likely to be nucleophilic (i.e. carbanionic) in nature, making **II** the probable methyl source. Tin–carbon bonds are sufficiently labile that rearrangement of the organic groups must always be considered as a possibility. However, the detection of methyltributyltin suggests that, under those conditions, rearrangement is slow at best. Reports of methylbutyltin compounds have been rather infrequent, suggesting that biomethylation may be merely a secondary metabolic route for the environmental transformation of tri-*n*-butyltin compounds.

Lead

The biomethylation of lead has not yet been unequivocally established[8,13,105,106] and has been the center of some controversy. Three factors contribute to this situation:

1. Methyllead compounds have been introduced into the environment as pollutants, making it difficult to establish that methyllead compounds reported in water or sediments might have a biogenic origin.
2. Monomethyllead(IV) compounds decompose so rapidly at ambient temperatures that they have yet to be isolated.
3. The methyl–lead linkage is very labile, and the methyl group can be readily transferred to other acceptors, especially mercury. Such transfer may contribute to the

instability of monomethyllead(IV) intermediates (e.g. through reductive elimination):

$$Pb(II) + CH_3^+ \rightarrow [CH_3Pb(IV)]^+ + Cl^- \rightarrow CH_3Cl + Pb(II) \quad (5)$$

Such reactivity would ordinarily prevent a monomethyllead intermediate from existing sufficiently long to allow the introduction of additional methyl groups. As Table 2 shows, the pattern of halides bonding to lead(II) is similar to those shown by other soft acids, suggesting that it should be able to accept a methyl group from **I**. If a potential lead(II) substrate were complexed by appropriate ligands, it might undergo biomethylation to form a monomethyllead(IV) intermediate sufficiently long-lived to receive a second methyl group (or undergo rearrangement) and form a stable dimethyllead(IV) compound. Early work indicated that **II** could methylate lead compounds under abiotic conditions,[105] but did not indicate whether this reaction might occur *in vivo*. Tetramethyllead did form in the reaction of **II** with lead dioxide,[106] but it seems unlikely that this reaction would occur in the natural environment.

Nevertheless, methyllead compounds have been discovered under environmental conditions that are consistent with the biomethylation of lead.[97] $(CH_3)_4Pb$ was found as one component of a gaseous mixture emitted by landfills[107] and was formed both by polar macroalgae[108] and by polar marine bacteria,[109] presumably through biomethylation, Trimethyllead compounds were found in seawater.[110] In a comparative study, bioactive sediments methylated mercury, tin and lead substrates;[111] mercury underwent methylation 10^4 times faster than either of the other two, and lead was methylated more readily than tin. Lead(II) compounds, like tin(II), would almost certainly undergo biomethylation via the Challenger mechanism. In anoxic sediments or within cells, any inorganic lead(IV) compounds would be rapidly reduced to lead(II).

Workers investigating biomethylation of lead have used the presence or absence of methyllead products as a measure of the occurrence of that process. Such a criterion may not in itself be valid, since biomethylation of lead, more than any other element, might well ultimately yield products other than methyllead compounds. In this author's view, biomethylation of lead can and does occur, but methyllead compounds are not the only products formed (e.g. Eqn. (5)) and the role of this reaction in the biogeochemical cycling of lead is probably marginal.

Antimony

The biomethylation of antimony, like that of tellurium, has languished under the shadow of a more thoroughly studied lighter congenor (arsenic). Though methylantimony compounds had been previously reported in natural waters,[8] their formation through biomethylation has been confirmed only in the past 3 years,[112–122] and have been detected almost exclusively from fungi and bacteria as the generating organisms. These investigations got an initial impetus from the investigation of a possible role of trimethylstibine as a contributor to sudden infant death syndrome.[113,115] Most reported research has utilized the fungus *S. brevicaulis* (used by Challenger in his arsenic studies[15]) as a methylating organism, although soil bacteria also generated trimethylstibine.[112,115] Biomethylation was observed under both anaerobic[114,117] and aerobic conditions,[117,119–122] with trimethylstibine being the primary product. A nonvolatile dimethylantimony compound (possibly dimethylstibinic acid) also formed,[117,120] and methylstibine and dimethylstibine have also been reported.[122] When $^{13}CD_3$-labeled methionine was incorporated into the growth media of *S. brevicaulis*, the label was incorporated into the methylantimony products.[120] The fungus *Cryptococcus humicolus* generated methylantimony compounds from both antimony(III) and antimony(V) substrates;[122] however, stibine was the major product from antimony(V), and trimethylstibine was the exclusive product from antimony(III).

In comparative studies, antimony was methylated much less rapidly and less extensively than arsenic.[119,121] Antimony(III) compounds inhibited the biomethylation of arsenic substrates [arsenic(III) being more strongly affected than arsenic(V)], whereas $KSb(OH)_6$ did not inhibit this reaction.[121] By contrast, the presence of small quantities of sodium arsenite *stimulated* biomethylation of antimony![121] Volatile methylantimonials have been detected in gases emitted from sludges and landfills[82,107,123]—primarily trimethylstibine, though mono- and di-methylstibine have also been reported.[82]

Thus, the biomethylation behavior of antimony strongly parallels that of arsenic. One major difference may arise from the greater tendency of antimony(V) to attain a coordination number of six, often through bridging in the solid state; for example, the antimony analog of monosodium methylarsonate is actually dimeric, with bridging oxygen atoms.[124] This additional coordination might make a methyl transfer intermediate more difficult to form; indeed, $KSb(OH)_6$ is more reluctant to undergo biomethylation than its arsenic counterpart.[121,125] Coordination number differences may also account for the difference in methylation rates between potassium antimony tartarate and antimony(III) oxide,[125] with the former reacting considerably more slowly. Tetramethylstibonium ion, unlike its arsenic counterpart, has yet to be reported as a biomethylation product. Pentamethylstiborane, $(CH_3)_5Sb$, like its arsenic analog, is reactive towards water and is very unlikely to be detected in organisms.[48]

As with tellurium compared with selenium, the biochemistry of antimony has been much less investigated than that of arsenic. The occurrence of methylantimony species within vertebrates remains to be demonstrated. The extensive chemistry of methylarsenicals in marine kelp and other organisms has not yet been duplicated for antimony; one report[126] does suggest that many such compounds may well

exist. Arsenobetaine, $(CH_3)_3As^+CH_2CO_2^-$,is widespread in the environment.[17–19] The antimony analog has recently been prepared and characterized,[127] thereby providing a valuable reference standard for investigators.

Bismuth

Environmentally occurring trimethylbismuth was first detected in gases emitted from sewage sludge[82,128] and has subsequently been detected in other environmental sources.[129,130] Formation of monomethylbismuth(III),[129,130] dimethylbismuth(III)[130] and even bismuthine[130] by the methanogen *Methanobacterium formicicum* from bismuth(III) nitrate or some bismuth-containing pharmaceuticals has been reported. Treatment of cell extracts of *M. formicicum* with **I** failed to yield any trimethylbismuth, but treatment of those extracts with **II** did form this compound.[130] *In vitro* treatment of bismuth(III) nitrate with **II** also yielded $(CH_3)_3Bi$.[130]

Bismuth differs from arsenic and antimony in the much lower stability of the +5 oxidation state relative to the +3 state. No mono- or di-methylbismuth(V) compounds are known. $(CH_3)_3BiCl_2$ decomposes rapidly at room temperature,[131] and $(CH_3)_4Bi^+$ was isolated only as the trifluoromethylsulfonate salt.[131] Transient methylbismuth(V) intermediates may have formed in the reaction of **II** with sodium bismuthate.[106] Oxidation of bismuth(III) to bismuth(V) by methylation through the Challenger mechanism does not seem likely. Biomethylation of bismuth very likely involves nonoxidative methyl transfer, suggesting that **II** is the methyl source.[130] The narrowing biological scope of methylmetal compounds that occurs going from arsenic to antimony continues with bismuth, and the biochemistry of methylbismuth compounds will most probably be that of $(CH_3)_3Bi$.

Phosphorus

Although numerous compounds containing phosphorus–carbon linkages can be formed biogenically,[132,133] these have, by and large, been alkylphosphonic acids. The only methylphosphorus compound thus far known to form through biomethylation is phosphinothricin, $CH_3P(:O)(OH)CH_2CH_2CH(NH_2)CO_2H$.[132] Investigations[132] on the formation of this compound have shown that the methyl group came from methionine, that **II** was a required cofactor, and that the immediate precursor of phosphinothricin was the phosphonous acid, $HP(:O)(OH)CH_2CH_2CH[NHC(:O)]CO_2H$.

Phosphonous acids exist primarily as tetravalent phosphorus(V) tautomers that can be in equilibrium with phosphorus(III) species:[134]

$$RPH(:O)(OH) \rightleftharpoons :PR(OH)_2 \qquad (6)$$

If the phosphorus(III) tautomer were stabilized by complexation, then methylation might proceed *via* the Challenger mechanism. There have been no systematic investigations into the possible biomethylation of phosphorus compounds. Stabilized phosphorus(III) compounds, such as triarylphosphines (e.g. $(C_6H_5)_3P$:) or esterified phosphates, would appear to make appropriate substrates for laboratory investigations into phosphorus biomethylation, by analogy with the reported preparation of methylphosphonate esters by treatment of trimethylphosphite with iodomethane.[134]

Cadmium

When $CdCl_2$ was added to marine sediment samples, an unidentified organocadmium species was detected.[136] Monomethylcadmium species were detected in seawater samples and also in arctic ice melts,[110] where they reached levels of 1.2 ng dm^{-3} and accounted for 48% of total cadmium. Whereas polar macroalgae failed to form methylcadmiun compounds,[108] polar bacteria[109] generated monomethylcadmium species along with trimethyllead compounds, but **not** mono- or di-methylmercury, dimethylcadmium or tetramethyllead. Dimethylcadmium was formed by *Pseudomonas* species,[137] and has also been detected in gases from sewage sludges.[129,138]

From the limited data currently available, cadmium apparently undergoes biomethylation under conditions similar to its Group 12 congener mercury. Like Hg^{II+}, Cd^{II+} is a soft acid (see Table 2), and can also form both mono- and di-methyl derivatives, although the monomethyl species seems to be more widespread and is apparently stable in aqueous solution. In all likelihood, therefore, **II** would be the methyl donor. Reported natural concentrations of monomethylcadmium are generally low: the detection level is 470 pg dm^{-3}, and most reported values[110] fall in the range 450–720 pg dm^{-3}. Dimethylcadmium seems to form under volatilizing conditions where water is absent. The ubiquity of methylcadmium compounds in the environment and their role(s) in the natural cycling of this element still remain to be determined.

Nickel

Biomethylation of nickel occurred when the metal was incorporated into the F-430 cofactor of methanogenic bacteria.[8,139,140] Acetylcoenzyme A was involved in reaction(s) leading to formation of both a methylnickel linkage in the cofactor and also an iron–carbon monoxide linkage at a nearby site.[140,141] EPR studies suggested that the nickel in methylcoenzyme M reductase existed as nickel(I).[142–145] Like cobalt in **II**, the nickel–methyl bond must be stabilized by a special chelating environment in order to form without immediate decomposition.

Nickel biomethylation apparently occurs only in methanogenic bacteria. However, the importance of nickel biomethylation is considerably greater than this limitation might suggest. Methane generation by bacteria (methanogenesis) plays an important role in terrestrial ecology, and occurs over virtually the entire Earth. Methanogenesis has been extensively investigated,[145] and nickel is a required trace element for methanogenic *Archaea*.[146] Though mechanistic details are still being determined, the final step in

methanogenesis is the 'biomethylation of hydrogen', in which a methyl group bonded to nickel is converted to methane. Whether additional examples of nickel biomethylation will be reported, and whether other organisms might perform this reaction, remains to be seen.

Polonium

One group has reported that appreciable quantities of a gaseous polonium compound formed in the presence of bread mold, but not in its absence,[147] and that the volatile product was destroyed by reaction with a nitric–perchloric acid mixture.[147] Their evidence suggested that this compound was $(CH_3)_2Po$ (estimated boiling point: 138 °C).[147] A second group found that ^{209}Po (probably as PoO_2) added to a culture treated with seaside sediments gave a volatile polonium compound (probably also dimethylpolonide).[148] Dimethylsulfide was emitted when very dilute ^{35}S-sulfuric acid was added to these sediments.[148] Treatment of a polonium sample with **II** produced a volatile product, but this did not happen with methyl iodide.[148] Although all polonium isotopes are radioactive, three have relatively long half-lives: (^{208}Po: 2.9 years; ^{209}Po: 102 years; ^{210}Po: 138.4 days), and ^{210}Po occurs in nature as part of the ^{238}U decay series.[148] By analogy with its lighter congeners, polonium might be expected to form methyl derivatives *via* the Challenger mechanism; however, polonium(IV) is much more difficult to oxidize than either selenium(IV) or tellurium(IV) (see Table 3), and formation of methylpolonium-(VI) compounds seems unlikely. This idea is supported by the above-mentioned unreactivity of a polonium(IV) species with methyl iodide. However, polonium in the oxidation states of either +2 or −2 might well accept a methyl group from **I** under appropriate conditions. Like bismuth(III) nitrate, polonium(IV) reacted with **II** to form a volatile product[148] (presumably dimethylpolonide, although not specifically identified as such), suggesting biomethylation by **II**. Since biomethylation of polonium may play a part in its environmental cycling,[147] and possibly present a health problem, more research is needed to answer these questions.

Thallium

Although thallium was reported to undergo biomethylation under laboratory conditions more than 20 years ago,[149] methylthallium species have been discovered in natural waters only very recently.[150,151] Measured concentrations of $(CH_3)_2Tl^+$ (the only naturally occurring methylthallium compound thus far reported) fell in the range 0.4–3.2 ng dm^{-3}. These values correlated well with both methylcadmium and trimethyllead levels.[151] Total dissolved thallium levels in the Atlantic Ocean[151] varied between 1.6 and 20.1 ng dm^{-3}, not too different than the range of 4.3 to 10.8 ng dm^{-3} reported for the Great Lakes.[152] Levels in other waters were much higher, especially in industrial wastewaters, where values exceeding 1000 ng dm^{-3} were reported.[153] The proportion of $(CH_3)_2Tl^+$ ion to total thallium (where the former could be detected at all)[151] ranged from 3 to 48%, but there was no correlation between the two sets of concentrations. In fresh water, the proportion of thallium(III) to total dissolved thallium was $68 \pm 6\%$.[152] Experiments using bacterial incubation and added $TlNO_3$ solution showed that dimethylthallium ion formed only in anaerobic samples.[151]

Unlike lead or bismuth, thallium does form a stable monomethyl compound:[154]

$$(CH_3)_2TlOAc + Hg(OAc)_2 \rightarrow CH_3HgOAc + CH_3Tl(OAc)_2 \quad (7)$$

Methylthallium diacetate decomposed slowly in water at room temperature, and reacted with halide ions to precipitate thallous halides.[154] This compound methylated various amines in methanol,[155] through a proposed intermediate CH_3TlOAc^+. Thus, stability of the monomethyl derivatives varies in the order mercury(II) > thallium(III) ≫ lead(IV) ≫ bismuth(V). Since both thallium(I) and thallium(III) are soft acids (Table 2), and compounds in both states occur in nature, there may be more than one possible biomethylation route. Whether **I** methylates thallium(I) or **II** methylates thallium(III), the monomethylthallium species initially formed would have to be sufficiently stabilized, probably through complex formation, to enable a second methyl group to be introduced. The importance of biomethylation in the biogeochemical cycling of thallium is still to be determined.

Germanium

Germanium is perhaps the most enigmatic of those elements known to undergo biomethylation. Mono- and di- (but not tri-)methylgermanium compounds have been reported in natural waters,[8,97,156] with a uniform level of 16 ng dm^{-3} throughout the ocean water column.[156] Recently, tetramethylgermane has been reported in geothermal gases,[123] and a trimethylgermanium species was excreted in human urine after consumption of germanium-containing fish.[157] Since there is no anthropogenic source for methylgermanium compounds, the species detected must arise from biomethylation. Both silicon(IV) and tin(IV) are hard acids[27] and presumably germanium(IV) is likewise. Germanium(IV) is only slightly more difficult to reduce than tin(IV) (see Table 3), so formation of a germanium(II) species *in vivo* is not unlikely. Such a species would very probably exist as a complex, and this might then undergo biomethylation *via* the Challenger mechanism. Some reported model studies support this idea;[123,158] however, more research is required before any firm conclusions can be drawn.

BIOMETHYLATION, VOLATILIZATION AND BIOREMEDIATION

Introduction

In recent years, investigations involving biomethylation

have expanded into newer areas, exploring its occurrence in waste dumps/landfill (with resulting formation of volatile species that escape into the atmosphere), and its potential use for removal of contaminating elements from soils, sediments or other solid wastes. The enormous increase in usage and disposal of semiconductors (especially III–V or II–VI materials such as GaAs or CdSe) have generated new potential substrates for biomethylating bacteria; such materials might be contributing to the growing problem of electronic wastes.[159] Also, employment of natural organisms, especially plants, to remove and/or destroy toxic compounds through biomethylation is becoming increasingly common. Volatilization can be an entry/dispersal route for elements in environmental cycles; it might also be used to transfer solids from one place to another.

Volatilization

As mentioned in the section entitled 'Biomethylation and molecular properties', bonding of methyl groups to the heavier elements increases their volatility. Though most pronounced for the permethyl compounds, this enhancement is also found for partially methylated metal(loid) species [e.g. $(CH_3)_2AsH$, $(CH_3)_3SnCl$, $(C_4H_9)_3SnCH_3$]. Such compounds are toxic and have caused health problems in the past, e.g. the fungal generation of 'Gosio-gas' (trimethylarsine).[8,15,16] Volatile compounds of heavy metals have long been known to form in refuse dumps,[160] and, recently, methyl derivatives of various heavy elements have been discovered in vapors emitted by landfills and sewage digestors.[82,108,123,128,129,137,161] Such vapors included other volatile compounds not previously detected in the environment (e.g. $Mo(CO)_6$ and $W(CO)_6$).[107] Dimethylmercury has recently been identified in sewage gases,[162] and gaseous organotin compounds are given off in estuaries and coastal areas.[95,101] As knowledge about emission of gaseous organometal(loid)s from landfills and other waste sites increases, the role(s) of biomethylation in such systems will become more fully appreciated.

Bioremediation

Volatilization through biomethylation has considerable potential for use as a method of remediation. To date, the most investigated application has been the removal of unwanted elements (primarily selenium and arsenic) from soils. Removal of selenium by biomethylation and subsequent volatilization has already been mentioned (see section entitled 'Selenium'), and has been reviewed.[163,164] Both $(CH_3)_2Se$ and $(CH_3)_2Se_2$ were generated by soil microbes.[165] Addition of methionine enhanced dimethylselenide volatilization (by increasing the concentration of **I**?).[72,166] Selenium volatilization was reported to require both a reduced precursor form of selenium and the presence of dioxygen.[167] Arsenic can also be volatilized from soils[168–171] through biomethylation, as can iodine.[172] The rate of volatilization depends very much on specific conditions: trace elements can enhance or inhibit fungal biomethylation of arsenic,[168] and in wastewater sludges this process proceeded best over a pH range 6.5 to 8.0 and was sharply curtailed at pH 5.0.[170] The possible use of arsenic volatilization in bioremediation has recently been proposed.[171] Dimethyltelluride could be generated from electrolytic slimes by *Penicillium chrysogenum*.[173]

Volatility is not the only physical property affected by biomethylation (see section entitled 'Biomethylation and molecular properties'). Changes in solubility (both in lipids and in water) alter the ability of an element to be absorbed by plants. Phytoremediation of polluted soils and waters has become a rapidly developing area,[174–176] and biomethylation will probably play an important part in it. Methylarsenicals were detected in plants and lichens growing near an old arsenic smelter site.[177] Methylmercuric species can be absorbed by plants under flooding conditions,[178] and organotin compounds can be accumulated by aquatic plants.[179–181]

CANDIDATE ELEMENTS FOR BIOMETHYLATION

Introduction

Biomethylation involves a complex set of processes occurring in many organisms under a wide range of conditions. Elements that undergo biomethylation do so at widely varying rates and to greatly differing extents. In order to determine that biomethylation has indeed occurred, a methylmetal product usually needs to be detected. Since such species typically occur at extremely low levels (often 1 ng dm^{-3} or less), their detection requires both specially designed equipment and an investigator specifically searching for them! Also, the ability of any element to undergo biomethylation depends very much on the chemical form of that element, as has already been illustrated. Keeping these limitations in mind, we now consider additional elements and the likelihood, based on available information, of their undergoing biomethylation.

Aluminum, gallium and indium

Of these three elements, indium is the most promising candidate. Indium(III) is readily reduced to indium(I) (see Table 3), it forms isolable compounds in this oxidation state, it forms water-stable methyl derivatives (especially dimethylindium compounds), and it is flanked on three sides in the periodic table by elements already known to undergo biomethylation. Unlike thallium(III), indium(III) is a hard acid, but less strongly so than others in Table 2. Thus, like thallium, it has the possibility of methylation by either **I** or **II**. The very low natural abundance of indium would appear to make detection of methylindium in the natural environment quite unlikely; however, like thallium, indium seems to be a good candidate for laboratory investigation.

Gallium and aluminum are more difficult to reduce than indium, and the high energies of these elements' bonds to oxygen preclude ready cleavage to open up a coordination

site, especially in aqueous media. Both are hard acids, making biomethylation by **I** unlikely. If these two elements ever do undergo biomethylation, it is most likely to occur under anaerobic, strongly reducing conditions, with gallium being the more favorable prospect.

Silicon and boron

Methylsilicon compounds have, of course, been detected in the natural environment.[182–185] However, in every case they seem to have been formed through bacterial degradation of methylsilicone polymers to dimethylsilanediol,[182] which was subsequently converted to CO_2, SiO_2 and H_2O. The high silicon–oxygen and boron–oxygen bond energies render their reduction under biological conditions very unlikely. Even the direct reaction of silicon with methyl chloride requires high temperatures and a metal catalyst to occur.[186] If these elements were present as reduced forms (e.g. metal silicides and borides), such substrates might indeed undergo biomethylation under laboratory conditions, although probably at a very slow rate. Organo-boron or -silicon sulfides might also be possible substrates. Environmental biomethylation, however, seems quite improbable, based on present knowledge.

Fluorine and astatine

These elements—the lightest and heaviest of the halogens—would appear to be potential candidates for biomethylation. Fluoride ion is the least nucleophilic of the halide ions,[26] and is also a hard base,[27] making it the least likely of the halides to react with **I**. A culture of the fungus *Phellinus pomaceus*, which methylated chloride, bromide and iodide ions, did not methylate fluoride ion.[86,187] Methyl fluoride has been predicted to have a longer tropospheric lifetime than methyl chloride—3.7 versus 1.54 years[188] — but does not appear to enter the atmosphere by any biogenic pathway. Biomethylation of fluoride ion seems improbable. However, there has as yet been no systematic search for evidence of fluoride biomethylation, and it may well occur under laboratory conditions.

Methyl astatide is a known compound[189] with an estimated boiling point of about 70 °C,[190] and might easily form through biomethylation. However, all isotopes of astatine are radioactive with short half-lives (the most stable,[210] At, has a half-life of 8.1 h), making their detection difficult, to say nothing of harming the potential methylating organisms. Astatide ion is more easily oxidized than iodide ion (Table 3) and should be as soft, if not softer as a base. Hence, biomethylation of astatide ion seems chemically possible, and laboratory investigations appear to provide the most promising route approach to a possible biogenic CH_3At.

Zinc

Unlike its heavier congeners cadmium and mercury, Zn^{II} is a hard acid (Table 2), and is therefore less likely to react with **II**. Furthermore, the reactivity of dimethylzinc towards air and water would apparently make it unlikely to be detected if formed by biomethylation, especially under environmental conditions. However, the same also holds for cadmium, which **has** been detected (see section entitled 'Cadmium'). Chemical reactivity of methylmetals at very low concentrations often differs from that at macroscopic levels, and monomethylzinc derivatives at extremely low levels might actually last long enough for detection, especially if stabilized by chelating agents. Dimethylzinc seems likely to be found, if at all, as part of gas mixtures formed under anaerobic, reducing conditions, whereas monomethylzinc compounds, like the cadmium and mercury analogs, might form in anaerobic environments and be stable enough for detection.

Transition metals

Apart from cobalt and nickel, transition metals are not known to undergo biomethylation. Even cobalt and nickel must be located in specific chemical environments formed by special chelating agents in order to form stable biogenic methyl derivatives. Given that an iron–carbon monoxide linkage can form *in vivo*,[152,156] there is no apparent reason why a biogenic iron–methyl linkage might not also form under appropriate conditions. Stable methyl compounds of platinum and gold are known, suggesting that these metals might also serve as substrates for biomethylation under appropriate conditions. Other transition metals appear very unlikely as candidates at this time, but cannot be totally ruled out.

CONCLUSIONS

Research involving biomethylation of the heavy elements has always had a strongly practical aspect. The two most thoroughly investigated elements, arsenic and mercury, have been closely involved in human health and poisoning from environmental sources. Recent reports of poisoning by methyltin-contaminated lard in China provide another example.[191] Antimony biomethylation studies (see section) were carried out in part because of its possible participation in sudden infant death syndrome. Recent reports that landfills, sewage sludges and wastewater treatment gases generate or include volatile methylmetal compounds provide new and additional avenues for research. The increasing range of applications of biomethylation for remediation of polluted soils and waters has given still further impetus for research in this area. Semiconducting compounds (e.g. GaAs) contain electron-rich elements that might undergo biomethylation; in fact, gallium arsenide[192] and metal chalcogenides[193] readily reacted with methyl iodide in the presence of water to form methyl derivatives. Quite possibly, biomethylation may find uses for the recycling of these materials, particularly considering the growing concern over electronic wastes.[159]

As more becomes known about the mechanisms of biomethylation, investigations into its occurrence with lesser-studied and even previously unstudied elements should become more common and more focused. Research into the biomethylation of the heavier elements has largely developed in relative isolation from other areas. Biomethylation in genetics and medicinal research, mentioned in the section entitled 'Terminology', is receiving extensive and intensive research. Findings in these areas, especially relating to the details of methyl transfer, should provide additional impetus to research on the heavier elements. Enzymatic transmethylation is one continuous subject and needs to be recognized as such; but it is circumstance that has caused it to be so fragmented. Biomethylation of elements has often provided unexpected results and developments. The deepening knowledge of this process and its widening scope of applications strongly suggest that additional developments will be reported in future years.

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NOTE ADDED IN PRESS

The formation of a methyl–nickel bond during methanogenesis has been called into question by quantum chemical calculations,[194] which propose an alternative mechanism in which the nickel activates a methyl group bonded to sulfur. Emission of trimethylarsine through biomethylation of arsenic in soils was observed,[195] but only 0.5% of the arsenic content was so volatilized. Tropical plants were found to emit substantial quantities of methyl chloride.[196]

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