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Reviews

Transformations of arsenic in the marine environment

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Summary. It is ten years since arsenobetaine was first isolated from the western rock lobster *Palinurus cygnus*. Subsequently this naturally-occurring arsenical has been found in many species of marine animals contributing to the human diet. The identification of arsenic-containing ribofuranosides in algae and the production of dimethylarsinoylethanol from their anaerobic decomposition has allowed speculation on arsenic metabolism in marine organisms and has suggested a possible route to arsenobetaine from oceanic arsenate.
Key words. Arsenobetaine; arsenic-containing ribofuranosides; dimethylarsinoylethanol; marine-derived foodstuffs; marine algae; arsenic metabolism.

Although it has been known since the 1920s that marine organisms contain substantial quantities of arsenic[12, 14] it is only 10 years since the first isolation and identification of an arsenic compound from this source; that of arsenobetaine (fig. 1, **13**) from the western rock lobster, *Palinurus cygnus*[20]. Since then the virtual ubiquity of arsenobetaine in marine animals (particularly those contributing to the human diet) has been demonstrated[26] and interest has developed in toxicological aspects of arsenic in marine-derived foodstuffs[27, 47] and in the biochemical transformations of arsenic in marine food chains[16, 17, 26]. It is this latter aspect that we wish to consider here.

Arsenobetaine was first prepared 50 years ago for pharmacological studies examining the possible physiological role of arsenic analogues of some simple nitrogen-containing metabolites[48, 49]. Certainly, the chemical structure of arsenobetaine suggests the possibility of close parallels to nitrogen metabolism, with the probability that arsenobetaine is biosynthesised by a pathway analogous to that for glycine betaine. This apparent similarity has been used as a basis for speculation on the metabolism of arsenic in marine organisms[39]. We consider that the biotransformations of arsenic in the marine environment show only a superficial resemblance to nitrogen metabolism (reflected in the structure of some compounds) and are fundamentally different with a detoxifying rather than central metabolic role. An overall outline of the scheme that we propose is shown in figure 1. Rigorously characterised compounds are shown in heavy type; the remainder is, to an extent, speculation. We will consider the scheme as a number of separate stages.

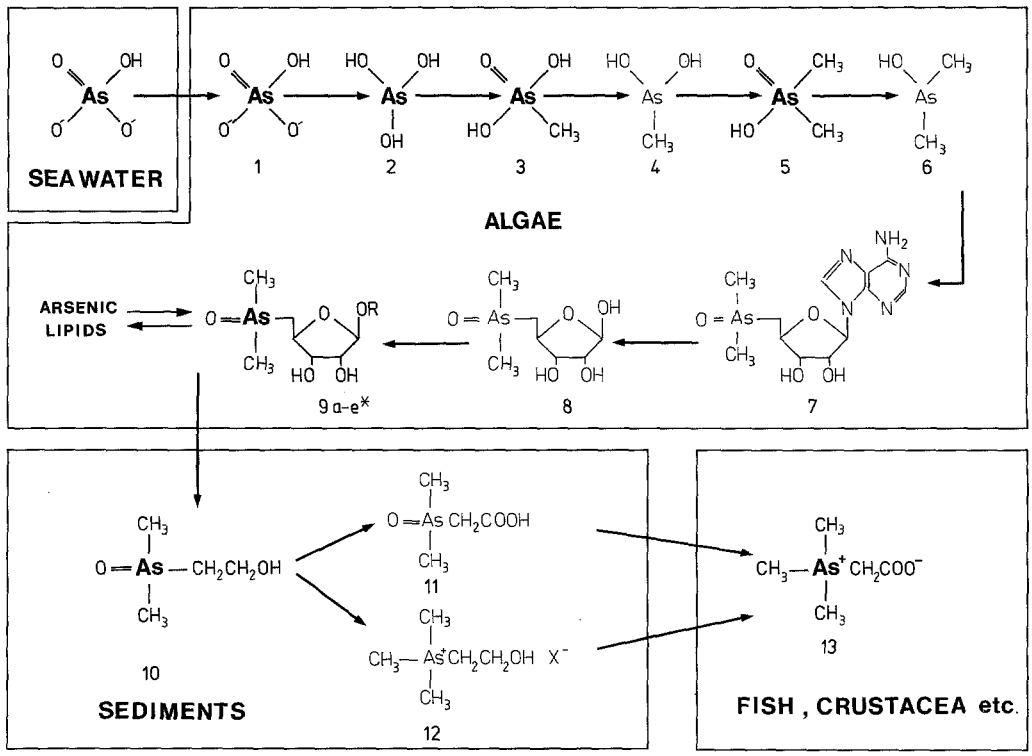


Figure 1. Proposed scheme for transformations of arsenic compounds in the marine environment leading to the production of arsenobetaine from oceanic arsenate. Identified compounds are shown in heavy type.

* Compound **9**

(a) R = $-CH_2CH(OH)CH_2OH$

(b) = $-CH_2CH(OH)CH_2SO_3H$

(c) = $-CH_2CH(OH)CH_2OSO_3H$

(d) = $-CH_2CH(NH_2)CH_2SO_3H$

(e) = $-CH_2CH(OH)CH_2OP(O)(OH)OCH_2CH(OH)CH_2OH$

The biosynthesis of arseno-sugars from arsenate by marine algae

It has been suggested[34] that arsenate (**1**), the predominant form of arsenic in seawater[1], is absorbed by algae because of its similarity to the essential phosphate. Competitive absorption with phosphate, it is claimed[40], results in arsenate being toxic to phytoplankton at levels only a little above ambient. On the other hand, independent mechanisms for arsenate and phosphate absorption have been demonstrated for both phytoplankton[2] and macroalgae[28] at close to normal concentrations. No role has been proposed for cellular arsenic and it seems likely that it is adventitiously absorbed. As a consequence algae have a need to control the concentrations and chemical forms of arsenic in their tissues. In the case of the brown algae *Ecklonia radiata*[17] and *Hizikia fusiforme*[23] and an unspecified symbiotic, unicellular, green alga in the clam *Tridacna maxima*[22], the products of these requirements are arsenic-containing ribofuranosides **9a–9e**. The diverse nature of these algae, together with published information on arsenic compounds in others[2, 13, 30], suggests the likely ubiquity of arseno-sugars as algal metabolites. The compounds **9a–9e** differ from one another only in the nature of their side-chains. It seems likely that they are biosynthesised by the mechanisms outlined initially by Challenger[10, 11] for the methylation of inorganic arsenic by microorganisms, and involving sequential reduction and methylation by S-adenosylmethionine[9] (under the control of methyltransferases) of arsenate to produce, initially, methylarsonic acid and then dimethylarsinic acid. However, the final reduction and methylation to trimethylarsine (as is the case with microorganisms) does not occur, but instead the adenosyl group of the methylating agent is transferred to the arsenic atom. The key intermediate in this stage of the scheme would be **7**. This compound has yet to be found, and those few algae examined to date could have contained it only in undetectably low levels. Enzymatic, hydrolytic removal of adenine to produce **8** (also currently undetected) would be followed by formation of the glycosides **9a–9e** by reaction with available algal metabolites[7]. Compound **9e** is of particular interest and will be considered further below.

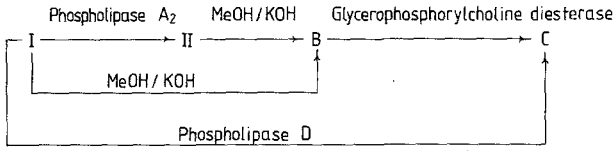
Although it seems likely that the order in the above scheme (fig. 1, **1–9**) will be followed, we cannot be sure whether attachment of the adenosyl group precedes or follows (or indeed comes between) the two methylation steps in some or all cases. If, as seems unlikely, attachment of the ribo- group should precede at least one methylation, then it is necessary to allow the possibility that enzymic removal of the adenine residue (and possible attachment of a sidechain) may also precede at least one methylation step at the arsenic atom. None of the additional range of compounds allowed by these possibilities has yet been detected in marine algae.

Marine waters containing phytoplankton contain dimethylarsinic acid and methylarsonic acid in addition to arsenate and arsenite[1]. Presumably such compounds are released by the phytoplankton and may result from par-

tial completion of the Challenger pathway or from decomposition of arsenic-containing ribofuranosides.

Biosynthesis of lipid-soluble arsenic

Some algae (notably *Fucus* spp.) contain the bulk of their arsenic burden as lipid-type compounds[30], whereas others, *Ecklonia radiata* for example, have only a few percent in lipid form[17]. All, however, appear to contain some lipid-type arsenic compounds and none of these has yet been fully characterised. Most progress in the identification of lipid-soluble arsenic compounds has been made by Benson's group[13], and their results are best interpreted in the light of the subsequent work noted above which rigorously characterised the water-soluble organic arsenic compounds elaborated by algae[17,22,23]. It is worth considering the work of Benson's group in some detail. After subjecting phytoplankton *(Chaetoceros concavicornis)* to radio-labelled arsenate for four days and then harvesting and extracting the crop, three main lipid-type arsenic compounds (I, II and III; 33% of total arsenic) and four water-soluble compounds (A, 40% of total arsenic; B, 14%; C, 8%; and D, 2%) were distinguished. The individual contributions of the three lipid forms were not stated. Judicious use of enzymatic and chemical techniques facilitated the following conversions:



It is obvious that the correct identification of compounds I, II and B depended upon correct identification of compound C. However Benson's group incorrectly identified compound C as the then unknown trimethylarsonium lactate $(CH_3)_3As^+CH_2CH(OH)COO^-$, on the basis of chromatographic, electrophoretic and chemical manipulations. Subsequent synthesis of trimethylarsonium lactate[42] revealed their error and they have retracted this aspect of their work[3,31]. Compound D was identified as dimethylarsinic acid but apparently no attempts were made to identify lipid III or compound A (the major water-soluble component).

Irrespective of the misidentification of compound C, Benson's group provided a plausible scheme for the degradation of arseno-lipids which is compatible with the system based upon rigorously proven chemical structures that we can now postulate. Chromatographic co-ordinates[13] of compounds A, B and C suggest their identity with compounds **9b** (or possibly, **9c**) and **9a** respectively (fig. 1), and we can tentatively rewrite Benson's scheme as shown in figure 2. Compound **9e**, which has been identified in *Ecklonia radiata*[17] and *Hizikia fusiforme*[23], has some analogy to glycerophosphoryl choline and esterification by long-chain fatty acids of the two free hydroxy groups of the terminal glycerol residue would produce a phospholipid analogous to lecithin. It is thus likely to occupy a key position in the biosynthetic/degradative pathway between arseno-lipids and water-soluble arsenic compounds. Benson has speculated[4] that the biosynthesis of arsenic-containing phospholipids may facilitate the incorporation of arsenic into membrane lipid bilayers and, ultimately, its passage across membranes with resulting excretion.

The presence of a small quantity of dimethylarsinic acid could be explained by some accumulation occurring along the postulated biosynthetic pathway or by decomposition of arsenic-containing ribofuranosides during work-up.

The conversion of arseno-sugars to arsenobetaine

Limited experimentation has indicated that marine animals acquire their arsenic burdens through the food web rather than directly from ambient water[25,29,38]. If it is accepted that most such animals contain some, if not all, of their arsenic as arsenobetaine, and that the production and retention of arseno-sugars is a general property of marine algae, then it is probable that arseno-sugars are converted to arsenobetaine within the food chain.

It is, of course, possible that the arseno-sugars are dissipated and degraded on senescence of the algae or not retained by herbivores, and that arsenobetaine has its origin elsewhere; in bacterial action on arsenate from sediments by the gut flora of detritovores for example. However, the latter seems unlikely and experimentation suggests that bacterial methylation of arsenate in the gut tract of fishes does not go beyond the production of trimethylarsine oxide[18].

The conversion of arsenic-containing ribofuranosides to arsenobetaine requires the cleavage of the C_3–C_4 bond of the sugar residue with subsequent oxidation at the C_4 position, and reduction and further methylation at the

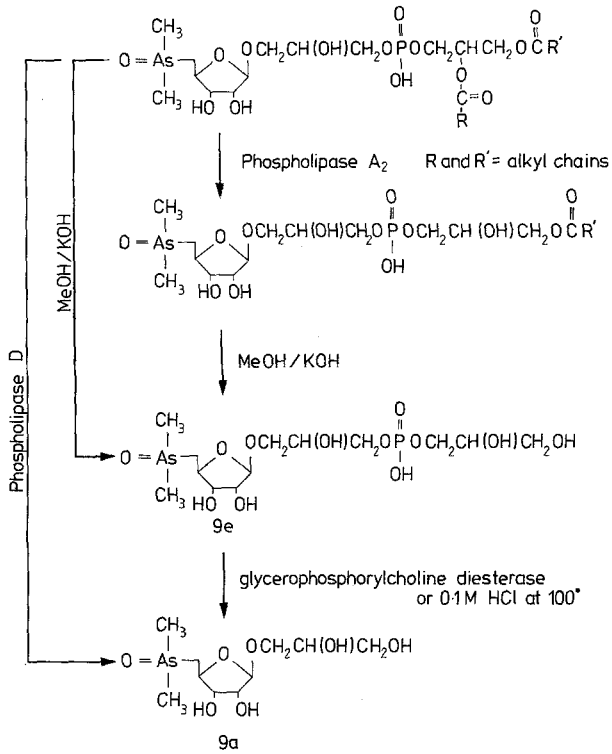


Figure 2. Benson's scheme[13] for the degradation of algal arseno-lipids to water-soluble compounds modified in the light of knowledge of arsenic-containing ribofuranosides in algae[16,17,22,23].

arsenic atom[16,21]. Such processes are most likely to occur (probably microbially mediated) in marine sediments and both oxidising and reducing conditions, within the limits imposed by such an environment, will be required for their completion. When fragments of fresh *Ecklonia* were allowed to decompose under controlled anaerobic conditions, the arseno-sugars they contained were quantitatively converted to dimethylarsinoylethanol (**10**)[21]. Thus, in conditions such as might be found in marine sediments or in beach deposits of kelp, cleavage of the C_3–C_4 bond of the sugar residue occurred with generation of the two carbon sidechain necessary for the subsequent production of arsenobetaine. Of the remaining steps, the oxidation of the terminal $-CH_2OH$ to $-COOH$ suggests no difficulties, but the further methylation of the arsenic atom appears to be less straightforward.

Quaternary (tetraalkylated) arsonium compounds have not been observed as metabolites in studies involving the administration of inorganic arsenic to microorganisms[10,11] or to experimental animals (mice[43,45], rats[43], rabbits[44], hamsters[33] and monkeys[46]) or, indeed, to humans[50]. Challenger's[10,11] and subsequent studies[15] suggest that the conversion of trimethylarsine oxide to trimethylarsine is the final stage of the methylation pathway involving microorganisms. And, although most mammals (the marmoset monkey was an exception[46]) respond to administered inorganic arsenic by methylation, the end product in most cases is methylarsonic or dimethylarsinic acids. Only a single case of the production of a trimethylated species has been reported; that of an uncharacterised trimethylarsenic compound (probably trimethylarsine oxide) produced as a minor metabolite after administration of dimethylarsinic acid to the hamster[51]. Quaternary arsenic compounds have never been observed. In addition, as noted above, alkylation in marine algae does not appear to proceed beyond the trialkyl stage[17]. There is consequently an intriguing problem as to the origin of the final methyl group in the ubiquitous arsenobetaine.

Further methylation and quaternisation of arsenic is most likely to occur in marine sediments and it may be worthwhile looking for parallels with the methylation of mercury under similar conditions. Microbial methylation of inorganic mercury salts has been demonstrated in both aerobic[6] and anaerobic[37] sediments, but in even the most grossly contaminated systems, methylated mercury represented only a very small percentage (usually $< 0.1\%$) of the total mercury present[5]. The accurate estimation of such small quantities is possible because the nature of methylmercury renders it amenable to gas chromatographic analysis with highly sensitive electron capture detection. If trialkylated arsenic species (in this case dimethylarsinoylethanol) methylate under similar conditions and to a similar extent, detection and estimation would be considerably more difficult because of the polar and involatile nature of the end product (arsenocholine or arsenobetaine). So in the limited experimentation that has been carried out to date[19,21], the presence of small, but possibly significant, quantities of arsenocholine or arsenobetaine may have gone undetected.

The possible parallels with methylmercury may be taken further; although fish do not themselves methylate mercury[24], they possess the greater part of their mercury burden (usually $> 70\%$) as methylmercury[41]. Consequently, considerable selection in favour of methylmercury over inorganic or other organic species must occur in the processes by which fish acquire and retain mercury. Such selection is usually explained in terms of the lipid solubility of methylmercury and its strong bonding to the protein sulphydryl groups in biological tissue. It is not so easy to offer a reasonable explanation as to why fish and crustaceans selectively accumulate arsenobetaine over other arsenic species that may be available in marine waters and sediments. Although arsenobetaine is apparently tenaciously retained by marine animals, no function can be suggested for it beyond that of an opportunistically utilised and unimportant osmolyte[52]; and the ease with which arsenobetaine can be removed from fresh muscle tissue by solvent extraction[8] suggests that it is held by nothing stronger than electrostatic bonding. Furthermore, the similarities between dimethylarsinoylethanol and arsenobetaine, in terms of solubilities, size, polarity and basicity, render unlikely a selection process as clear cut as that involving methylmercury.

The termination of alkylation at, or before, the tri-alkyl stage in microorganisms, algae and mammals suggests that substantially different conditions may be involved in the final methylation and also that a different mechanism may be employed. For further methylation of dimethylarsinoylethanol to occur by a scheme involving S-adenosylmethionine (i.e. the transfer of a positively charged carbonium methyl group), it is mechanistically necessary for reduction to the arsine, $(CH_3)_2AsCH_2CH_2OH$, to occur prior to methylation. Although this arsine has not been detected in experiments with anaerobically decomposing *Ecklonia*, its presence in small quantities cannot be ruled out. However, dimethylarsinoylethanol at neutral and acidic pH exhibits a basicity comparable to that of arsenobetaine, and may well be more susceptible than the corresponding arsine to methylation by processes other than those involving S-adenosylmethionine.

At present it is not known whether the route to arsenobetaine from dimethylarsinoylethanol would proceed via arsenocholine (**12**) or dimethylarsinoylacetic acid (**11**). The former would require that the final methylation precede the oxidation of the sidechain; the latter that methylation follow oxidation. The reported presence of arsenocholine[32,35,36] in samples of shrimps might, if confirmed, suggest its involvement as an immediate precursor of arsenobetaine.

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