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Ascorbic acid acts as a hydride donor towards 2-arsonocarboxylic acids

Panayiotis V. Ioannou[1]* and Michael G. Siskos[2]
[1]Department of Chemistry, University of Patras, Patras, Greece
[2]Department of Chemistry, University of Ioannina, Ioannina, Greece

2-Arsonohexanoic acid is decomposed during its attempted reduction to 2-arsenosohexanoic acid by triphenylphosphine in the presence of a catalytic amount of iodine. When ascorbic acid is substituted for the triphenylphosphine, hexanoic acid is obtained, implying that the arscorbic acid acts as a hydride donor. Copyright © 2001 John Wiley & Sons, Ltd.

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INTRODUCTION

L-Ascorbic acid, or vitamin C, is a plant product, but it occurs to some extent in human tissues.[1,2] Hydrogen peroxide is removed through the Ascorbate-Glutathione Cycle and by its scavenging of the $O_2^{\cdot -}$, $HO^{\cdot}$ and singlet oxygen, it is important for plant growth and protection.[2] Ascorbic acid in man is mainly involved in proline and lysine hydroxylation for formation of collagen, and its deficiency leads to scurvy.[1] It is also involved in other biochemical events.[1,2]

Ascorbic acid (AH_2) in water is a weak acid[3] (pK_a 4.17) and a mild reducing agent.[4] It acts as a one-electron donor to various electron acceptors, especially inorganic compounds,[5,6] giving, through the highly acidic radical $AH^{\cdot}$, a comparatively stable[7] radical anion $A^{\cdot -}$, which, upon donation of its electron, gives dehydroascorbic acid.[5] The stability of the radical anion is attributed to its pseudo-aromaticity.[7]

The use of arscorbic acid as a reducing agent with organic oxidants is little reported. Substituted nitrobenzenes have been reduced to the corresponding amines.[8] Quinones are reduced in methanol or water, by one-electron transfer followed by hydrogen atom transfer, to hydroquinones, the hydrogen ascorbate ion being oxidized faster than the undissociated ascorbic acid.[9] In aqueous solution, ascorbic acid reduces the dye 2,6-dichloroindophenol to its leuco base faster than does hydrogen ascorbate.[10] In this work an H^+ and an $H:^-$ transfer are implied in the activated complex.

The displacement of a halide by the AsO_3^{3-} nucleophile[11] is known as the Meyer reaction.[12] It works well with substrates that are soluble in the aqueous alkaline arsenite, but with less-soluble substrates the reaction is very slow.[13] A carboxy group geminal to a halide will render this part of a molecule water soluble and will also make the displacement of the halide faster. Then, decarboxylation of the geminal diacid will give the required arsonic acid. These two reactions represent a general route to arsonic acids.[14] We prepared 2-arsonohexanoic acid from 2-bromohexanoic acid in order to study the conditions of its preparation and decarboxylation to pentylarsonic acid.[15]

With another line of reasoning, we proposed that by reducing a 2-arsonocarboxylic acid to its arsenoso compound[16] and then applying the Auger reaction[17] we could eventually obtain novel arsinolipids having an HOOC—CH(R)—AsO_2H— head group. In this communication we describe an unusual reaction of ascorbic acid, in the presence of traces of iodine, towards 2-arsonohexanoic acid. The product is not the expected arsenoso compound but hexanoic acid, which may have arisen by hydride transfer from ascorbic acid.

EXPERIMENTAL

Materials

2-Arsonohexanoic acid[15] was prepared as a very

* Correspondence to: P. V. Ioannou, Department of Chemistry, University of Patras, Patras, Greece.

viscous oil from 2-bromohexanoic acid[18] by a procedure similar to that described for the preparation of arsonoacetic acid,[19] but it was purified by column chromatography. Triphenylphosphine was from Aldrich and ascorbic acid from Merck. Methanol was *not* dried over A_4 molecular sieves, because wet methanol is used for reduction with ascorbic acid.[20] De-aerated methanol or water solutions were prepared by boiling, stoppering and cooling to room temperature (RT). Silica gel Si60 (Serva) was used for column chromatography, and silica gel H (Merck) for thin-layer chromatography (TLC).

Instruments and analyses

TLC analyses were run on microslides using, where possible, appropriate standards. Visualization was effected by iodine vapour (for hexanoic acid, triphenylphosphine, triphenylphosphine oxide and arsenite (AsO_3^{3-}/$HAsO_3^{2-}$ in MeOH/conc. NH_3(4:1))[21,22] followed by spraying with 35% sulfuric acid and charring. Arsenic(III) oxide was detected, as 'AsO_3^{3-}', by TLC and confirmed by IR spectroscopy (sharp peak at 802 cm^{-1}).[23] IR spectra were taken on a Perkin–Elmer model 16PC FT-IR spectrometer. ^{1}H NMR spectra were run on a Brucker DPX Avance (400 MHz) spectrometer. Electron spin resonance (ESR) measurements were made using a Varian E-109 spectrometer.

Attempted iodide-catalysed reduction of 2-arsonohexanoic acid

With triphenylphosphine

Reduction of 2-arsonohexanoic acid with triphenylphosphine to produce the —As═O group was unsuccessful (see Discussion).

With ascorbic acid in undried methanol

The 2-arsonohexanoic acid (592 mg, 2.47 mmol) was dissolved in de-aerated methanol (10 ml), flushed with nitrogen, and ascorbic acid (521 mg, 2.96 mmol) was added. TLC revealed no reaction after stirring at RT for 30 min. Iodine (19 mg, 3 mol%) was then added and stirred at RT. TLC in Et_2O/Me_2CO 1:1 revealed that ascorbic acid (R_f 0.68) reacted smoothly to give dehydroascorbic acid (R_f 0.81) and in MeOH/conc. NH_3 4:1 showed the disappearance of the 2-arsonohexanoic acid. After 3 h the solvent was removed and the yellowish oil was dried in vacuo to give a yellowish foam. To this solid, water (2 ml) was added and extracted with ether (2 × 5 ml) to give an ether phase, an aqueous phase and a white solid. The solid (119 mg) was, by IR, As_2O_3 corresponding to 49% C—As bond cleavage. The ether phase gave an oil (221 mg), which, by IR [neat: 1708 vs] and ^{1}H NMR [$CDCl_3$, δ: 2.36 (t, J 7.6 Hz, 2H, CH_2COOH)], was slightly impure hexanoic acid, corresponding to 77% recovery. The spectra were identical to those of pure hexanoic acid.

For the detection of ascorbic acid free radical the solution of the reactants was prepared under argon. No ESR signal was detected in either the absence or the presence of iodine (3 and 15 mol%) at 20 min, 55 min and 19 h after its addition.

With ascorbic acid in methanol/water 1:1 v/v

The diacid (141 mg, 0.59 mmol) was dissolved in de-aerated methanol/water 1:1 v/v (2 ml), flushed with nitrogen, and then ascorbic acid (124 mg, 0.7 mmol) and iodine (5 mg, 3 mol%) were added. The colourless solution was stirred at RT for 22 h. TLC (Et_2O/Me_2CO 1:1) showed traces of dehydroascorbic acid. Evaporation (rotary, 50 °C) and drying gave a yellowish solid, which, by TLC, was mostly dehydroascorbic acid. Dissolution in water (1 ml) and extraction with ether (1 × 5 ml) gave a yellowish film (19 mg) with no smell of hexanoic acid. No precipitated As_2O_3 was seen.

With ascorbic acid in water

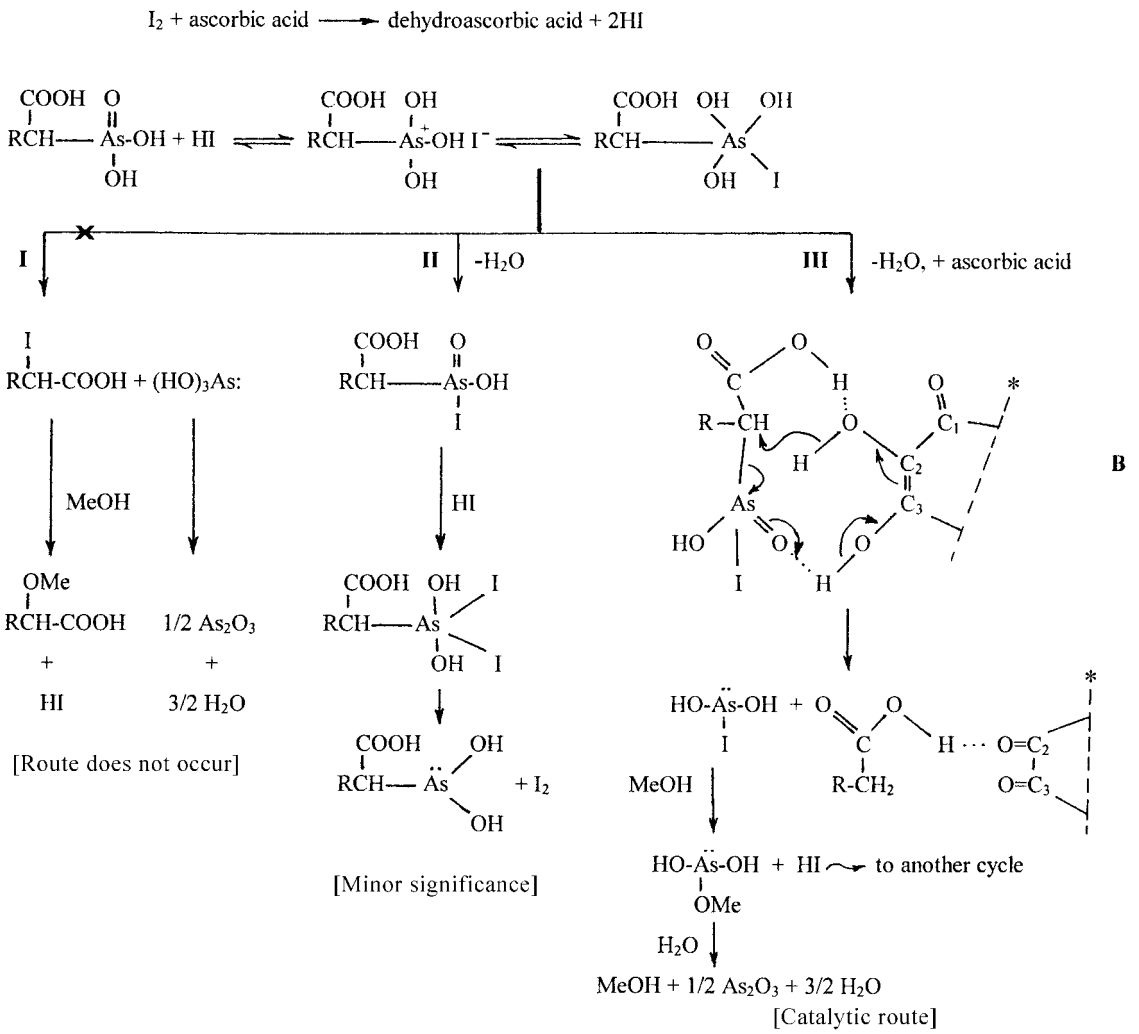
Following the above procedure, we obtained the same results.

Attempted chloride-catalysed reduction of 2-arsonohexanoic acid with ascorbic acid

The title acid (266 mg, 1.11 mmol) dissolved in de-aerated methanol (2 ml) was flushed with nitrogen, and ascorbic acid (235 mg, 1.33 mmol) and methanolic hydrochloric acid (5 mol%) were added. After stirring at RT for 3 h, TLC again revealed that no reaction had taken place (i.e. as for MeOH/water 1:1 above). Iodine (9 mg, 3 mol%) was then added and stirred at RT for 3 h, whereupon reaction took place. Work up, as above, gave As_2O_3 (47 mg, corresponding to 42% C—As bond fission) and hexanoic acid (111 mg, 86% recovery).

RESULTS AND DISCUSSION

We have used a methanolic solution of triphenyl-

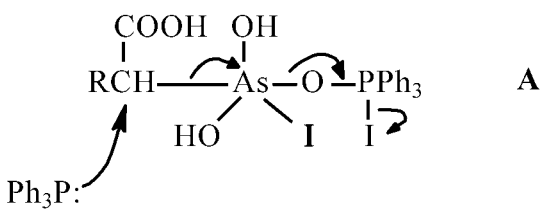


*Showing only functioned parts of ascorbic acid

Scheme 1.

phosphine or ascorbic acid in the presence of catalytic amounts of iodine to reduce some aliphatic and aromatic arsonic acids, $RAsO_3H_2$, to arsonous acid [$RAs(OH)_2$] or arsenoso compounds [$(RAsO)_x$].[16] In the case of ascorbic acid, it first reduces the iodine to hydroiodic acid, the actual reducing agent of the —AsO_3H_2 group, the iodide being oxidized to iodine (e.g. Route II, Scheme 1).

The attempted reduction of 2-arsonohexanoic acid by Ph_3P/I_2 gave a clear solution, implying that no substantial amounts of As_2O_3 were produced, but on work up As_2O_3 was obtained corresponding to ~50% C—As bond fission. The bond fission comes from the attack of the Ph_3P nucleophile to the α-carbon of the diacid by the mechanism suggested[16] or as shown in **A**:



The I—$As(OH)_2$ produced should solvolyse and hydrolyse as shown in Scheme 1. Because of the similar solubilities of $[RCH(COOH)AsO]_x$, $RCH(COOH)PPh_3{}^+HO^-$, Ph_3P and $Ph_3P{=}O$ we were not able to separate them.

With the milder[16] reducing system ascorbic acid/iodine, the 2-arsonohexanoic acid gave a clear solution and, on work up, the isolated As_2O_3 indicated at least 50% C—As bond fission. Slightly impure hexanoic acid (75–85%) was recovered. No signal coming from ascorbic acid radical was detected by ESR, implying that the reduction is not a one-electron process. Since ascorbic acid alone or in the presence of a catalytic amount of hydrochloric acid does not react with the substrate, but it does react in the presence of hydroiodic acid, it seems that the latter is required, as shown in Scheme 1.

Iodide does not attack the α-carbon, Route **I**, because we did not detect the —OCH_3 protons at ~3.30 ppm in the ^{1}H NMR spectrum of the crude hexanoic acid.

Route **II** was not followed to a significant extent. If a small triplet in the ^{1}H NMR spectrum of the isolated crude hexanoic acid at 2.91 ppm (J = 7.6 Hz) is assigned to the $[RCH(COOH)AsO]_x$ then this product constitutes 8% of the mixture.

Route **III** leads to the observed products through the activated complex **B**. The hydride comes from the C_2-OH, probably aided by the hydrogen bonding of the carboxylic group, while the proton comes from the more acidic[24] C_3-OH. The soft iodide is required to attack the soft As^+, Scheme 1, and by being large may also help the formation of the activated complex, **B**, because it is Route **III** and not Route **II** that is being preferred. This mechanism shows that ascorbic acid and not hydroiodic acid is the true reductant for this arsonic acid.

In water, which is a stronger base than methanol,[25] no reaction took place. The explanation may be that in water the reactants (2-arsonohexanoic acid and ascorbic acid) are to a certain degree ionized and the hydroiodic acid completely ionized to H_3O^+ and I^-. Then protonation of the As=O oxygen does not take place and, therefore, there is no path to the activated complex **B**. Also, hydrogen ascorbate in water is a stronger one-electron reducing agent than two-electron reducing agent,[5] and in our system it seems that the substrate cannot accept only one electron at a time.

CONCLUSIONS

This work reveals that arsonic acids having a geminal carboxy group cannot be reduced to their corresponding arsonous acids by the mild reducing systems triphenylphosphine/iodine or ascorbic acid/iodine. At the same time, evidence is obtained that ascorbic acid can act as a reductant by hydride transfer rather than by a free radical mechanism.

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