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Reductive Desulfurization of Allylic Thiols by HS$^-$/H_2S in Water Gives Clue to Chemical Reactions Widespread in Natural Environments

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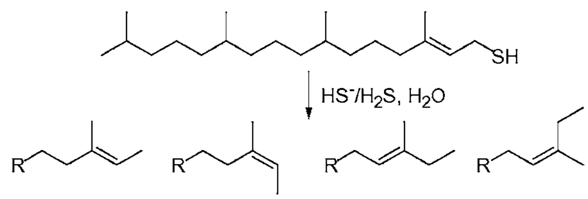
ABSTRACT



The reduction of allylic thiols to alkenes by hydrogen sulfide in aqueous solutions, a novel reaction that may explain reduction processes widely occurring in natural environments, has been discovered. Its mechanism has been studied and suggested to follow an S_{RN}1-like pathway involving radical intermediates undergoing 1,4 hydrogen shifts.

Efficient reduction of sedimentary organic matter is observed in oxygen-depleted environments where intense bacterial sulfate reduction occurs.[1,2] The mechanisms involved in such reactions, which play a key role in the transformation and preservation of organic matter in the subsurface, are far from being fully understood. There is clear evidence that these reactions are partly due to abiotic processes in which sulfides formed by bacterial sulfate reduction may play an important role.[3] We have now investigated the possible role of H_2S as a potential reducing agent for sedimentary organic matter by means of simulation experiments and observed an unprecedented reduction reaction: the reductive desulfurization of allylic thiols induced by hydrogen sulfide in water leading to a mixture of corresponding olefins. Furthermore, we have focused our study on the mechanism of this reaction, which involves the replacement of a sulfhydryl group by a hydrogen atom.

(*E*)-Phyt-2-ene-1-thiol ((*E*)-3,7,11,15-tetramethylhexadec-2-ene-1-thiol **1**) was used as a model compound since it is generally present in sulfur-rich recent sediments[1] and representative of a widely distributed class of lipids found in these environments deriving from phytol, the side-chain of chlorophyll.

(*E*)-phyt-2-ene-1-thiol **1** was reacted with H_2S as the only reactant under our simulation conditions (aqueous solutions, pH = 8−9, and mild temperature).[4] The sodium salt of a carboxylic acid (sodium laurate) was added to reproduce the lipophilic environment of lipids in water in natural environments (micelles, membrane remains, etc.). Gas chromatog-

(1) Adam, P.; Schneckenburger, P.; Schaeffer, P.; Albrecht, P. *Geochim. Cosmochim. Acta* **2000**, *64*, 3485.

(2) Behrens, A.; Schaeffer, P.; Bernasconi, S.; Albrecht, P. *Geochim. Cosmochim. Acta* **2000**, *64*, 3327. Schaeffer, P.; Schmitt, G.; Behrens, A.; Adam, P.; Hebting, Y.; Bernasconi, S.; Albrecht, P. 20th International Meeting on Organic Geochemistry, Nancy, France, Sept 10−14, 2001; Géologie et Gestion des Ressources minérales et énergétiques (G2R): Nancy, France; Abstracts Vol. 2, p 365.

(3) Schouten, S.; van Driel, G.; Sinninghe Damsté J.; de Leeuw, J. *Geochim. Cosmochim. Acta* **1993**, *57*, 5111. Schneckenburger, P.; Adam P.; Albrecht, P. *Tetrahedron Lett.* **1998**, *39*, 447.

(4) Typically, 20 mg of phyt-2-ene-1-thiol **1** (0.40 g/L) was reacted at 50 °C in a septum-sealed vial with an argon-degassed H_2S-saturated aqueous solution (50 mL) containing lauric acid sodium salt (1, 5, or 10 g/L) for 15−180 days. The highest yields of phytenes (3.8%) were obtained after 180 days with 10 g/L of surfactant; after 15 days with 1 g/L of surfactant, 0.1% yield was obtained.

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raphy-mass spectrometry (GC-MS) analyses of the reaction products revealed the presence of several phytene isomers: (*Z*)- and (*E*)-phyt-2-ene (**2** and **3**, respectively, in a 1/2 ratio), as well as two yet unreported compounds (*Z*)- and (*E*)-phyt-3-ene (**4** and **5**, respectively, in a 1/2 ratio). The residual sulfur compounds are composed of a mixture of (*E*)- and (*Z*)-phyt-2-ene-1-thiols (**1** and **6**, respectively, in a 2/1 ratio) as well as of the corresponding polysulfide cross-linked dimers **7** (Figure 1).

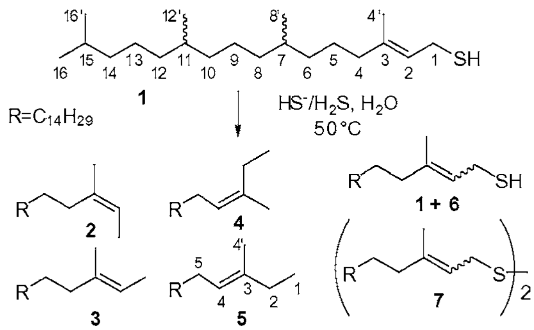
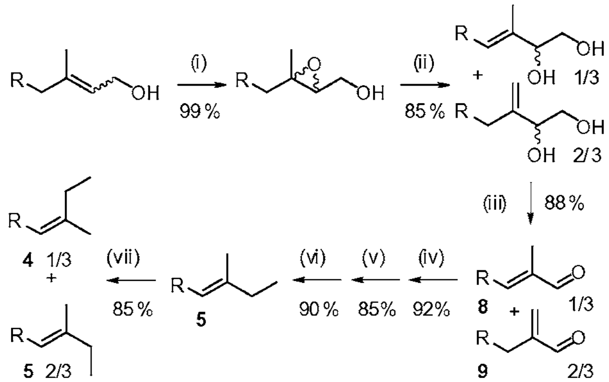


Figure 1. Desulfurization of (*E*)-phyt-2-ene-1-thiol **1** by H_2S yields (*Z*)- and (*E*)-phyt-2-ene (**2** and **3**, respectively) as well as (*Z*)- and (*E*)-phyt-3-ene (**4** and **5**, respectively). Mixtures of (*E*)- and (*Z*)-phyt-2-ene-1-thio1 **1** and **6**, respectively, as well as the corresponding polysulfides **7** are also recovered.

Separation of the phytene isomers by GC was difficult and only obtained using a capillary column coated with a poly(ethylene glycol)-bonded phase.[5] The structural assignment of the two unknown phytenes **4** and **5** was made possible by comparison of mass spectral data and chromatographic behavior with synthetic standards. In this regard, compound **5** was synthesized following the procedure described in Scheme 1. A commercially available mixture of (*E*)- and (*Z*)-phytol was first oxidized to epoxides by

Scheme 1. Synthesis of (*Z*)- and (*E*)-Phyt-3-ene **4** and **5**[a]



[a] Reaction conditions: (i) *m*-CPBA/DCM; (ii) Ti(*i*-OPr)$_4$/DCM; (iii) $NaIO_4$/EtOH−H_2O; (iv) LC separation and then DIBAH/THF; (v) TsCl, DMAP, TEA/DCM; (vi) CH_3MgI/Et_2O, (vii) *hν*, PhSSPh/hexane.

m-CPBA. The unseparable diols obtained after opening of the epoxyalcohols by titanium(IV) isopropoxyde[6] were then cleaved by sodium periodate to yield two unsaturated aldehydes **8** and **9**. After separation, aldehyde **8** was reduced to the corresponding alcohol and subsequently chlorinated.[7] Finally, the substitution of the chloride by methylmagnesium iodide yielded (*E*)-phyt-3-ene **5**, which was fully characterized using MS and NMR spectroscopy. Particularly, the nuclear Overhauser effect observed between methyl 4′ and methylene 5 confirmed the stereochemistry of the double bond. To obtain **4**, **5** was isomerized photochemically in the presence of diphenyl disulfide.[8] Pure **4** was isolated by reverse-phase HPLC from the mixture[9] (**4** and **5**; 1/2 ratio) and characterized by MS and NMR.

When (*E*)-phyt-2-ene **3** was reacted with hydrogen sulfide under our simulation conditions (60 days), it was quantitatively recovered and no isomerized phytenes could be detected by GC and GC-MS analyses. This rules out the possibility that (*E*)-phyt-2-ene **3** is the initial product formed by reduction of (*E*)-phyt-2-ene-1-thiol **1** and that further double-bond isomerization and migration reactions account for the presence of the phytene isomers in the reaction products. Consequently, the formation of the mixture of the phytene isomers resulting from *E*/*Z* isomerization and migration of the double bond from initial position 2 to position 3 must be directly related to the nature of the reaction intermediates.

By analogy with experiments on the replacement of nitro groups by hydrogen induced by thiolates,[10] the reduction of phyt-2-ene-1-thiol **1** could be related to $S_{RN}1$ reactions involving radical intermediates (Scheme 2). Hydrogen sulfide is, indeed, known to be a good hydrogen atom donor, while thiols are able to induce $S_{RN}1$ reactions.[10]

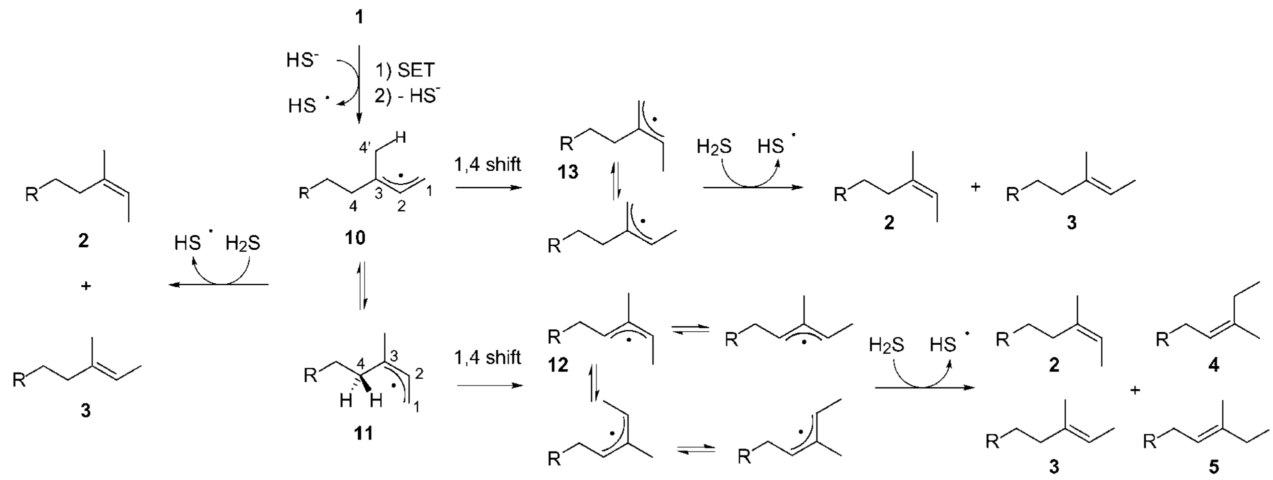
Furthermore, it has also been shown that carbon−sulfur bonds can be cleaved under $S_{RN}1$ conditions.[11] Thus, we propose in the first step of the reaction the formation of a radical anion by a single-electron transfer (SET) from hydrogen sulfide ions. Further loss of a sulfhydryl group by a heterolytic cleavage of the carbon−sulfur bond would then yield a delocalized radical **10**.

Quenching of radical **10** by abstraction of a hydrogen atom from an H_2S molecule would give (*E*)-phyt-2-ene **3** exclusively and no phyt-1-ene, in agreement with the fact that radicals generally abstract hydrogen by the less substituted carbon when delocalization is possible.[12]

Formation of (*Z*)-phyt-2-ene **2** might be explained by isomerization of the allylic radical **10** to allylic radical **11**,

(5) J&W DB-WAX, 30 m × 0.254 mm, film thickness = 0.15 μm.
(6) Morgans, D. J.; Sharpless, K. B.; Traynor, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 462.
(7) Hwang, C. K.; Li, W. S.; Nicolaou, K. C. *Tetrahedron Lett.* **1984**, *25*, 2295.
(8) Moussebois, C.; Dale, J. *J. Chem. Soc. C* **1966**, 260.
(9) Du Pont Zorbax ODS 250 × 9.4 mm, 8 μm; MeOH−H_2O 94:6 v:v; 5 mL/min.
(10) Kornblum, N.; Carlson, S.; Smith, R. *J. Am. Chem. Soc.* **1978**, *100*, 289. Kornblum, N.; Carlson, S.; Smith, R. *J. Am. Chem. Soc.* **1979**, *101*, 7086.
(11) Cheng, C.; Stock, L. *J. Org. Chem.* **1991**, *56*, 2436. Rossi, R.; Bunnett, J. *J. Org. Chem.* **1973**, *38*, 1407. Rossi, R.; Bunnett, J. *J. Am. Chem. Soc.* **1974**, *96*, 112.

Scheme 2. Postulated Mechanism of the Formation of Phytenes **2**−**5** from the Reduction of Phyt-2-ene-1-thiol **1** by H_2S via an $S_{RN}1$-Type Reaction and Involving 1,4 Hydrogen Shifts



which is again quenched by a hydrogen atom from H_2S. The isomerization of allylic radicals is not very common[13] but has been shown to occur depending upon the conditions,[14] a fact that has lately been corroborated by activation energy calculations.[15]

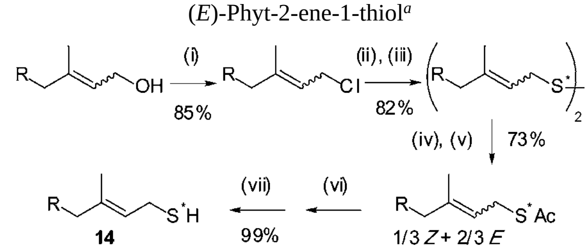
The only plausible explanation, considering the reaction conditions, for the formation of the (*Z*)- and (*E*)-phyt-3-enes **4** and **5**, respectively, would involve a 1,4 shift of a hydrogen atom from position C-4 to C-1, which are spatially close in radical **11** leading to a secondary allylic radical **12**. This delocalized radical, as well as the related radicals formed by isomerization (Scheme 2), could then be quenched either at C-4 to give **2** and **3**, or at C-2 to give **4** and **5**. Furthermore, a 1,4 shift could have taken place between C-1 and C-4′ on radical **10**, resulting in an allylic radical **13**. When quenched at the less substituted C-4′, this radical and the related radical formed by isomerization would yield **2** and **3**, respectively.

Although several examples of 1,4 hydrogen shift in radicals have been reported,[16] our case would be the first evidence of a 1,4 shift between two allylic positions.

When the reaction involving the same substrate ((*E*)-phyt-2-ene-1-thiols **1**) was carried out in DMF/H_2O (3/1; v/v) using NaSH as a nucleophile, the allylic desulfurization and formation of phytenes (**2**−**5**) is also observed. However, phyt-3-enes **4** and **5** are not formed if the reaction is performed in pure DMF, suggesting that under these conditions, 1,4 hydrogen atom shift reactions do not occur. This suggests that the presence of water under the experimental conditions used might induce significant solvent effects upon the 1,4 shift reaction, in agreement with the effects observed for instance in radical cyclization reactions when performed in water as compared to organic solvents.[17]

An $S_{RN}1$-like mechanism brings up the question of whether the sulfhydryl group on the residual phyt-2-ene-1-thiols **1** and **6** has undergone substitution by hydrogen sulfide. To test this hypothesis, we have synthesized ^{34}S-labeled (*Z*)- and (*E*)-phyt-2-ene-1-thiols. The labeled thiols, with an isotopic enrichment ratio of $^{32}S/^{34}S = 1/1$, were obtained by addition of the Grignard reagent of (*Z*)- and (*E*)-1-chloro-phyt-2-enes, synthesized with Riecke magnesium,[18] on isotopically enriched elemental sulfur ($^{32}S/^{34}S = 1/1$). The resulting polysulfides were reduced with sodium ethanethiolate to the corresponding thiols, which were acetylated with acetic acid anhydride (Scheme 3). The (*Z*)- and (*E*)-acetates were separated by reverse-phase HPLC and saponified. ^{34}S-Labeled (*E*)-phyt-2-ene-1-thiol **14** was reacted with $H_2{}^{32}S$

Scheme 3. Synthesis of the ^{34}S-Labeled (*E*)-Phyt-2-ene-1-thiol[a]



[a] Reaction conditions: (i) TsCl, DMAP, TEA/DCM; (ii) Riecke Mg/THF, −100 °C; (iii) $^{32}S/^{34}S$ (1/1)/THF; (iv) EtSH−MeONa/MeOH−Et_2O; (v) Ac_2O−Py; (vi) HPLC separation; (vii) KOH/MeOH.

(12) Oswald, A.; Griesbaum, K.; Thaler, W.; Hudson, B., Jr. *J. Am. Chem. Soc.* **1962**, *84*, 3897.

(13) Walling, C.; Thaler, W. *J. Am. Chem. Soc.* **1961**, *83*, 3877.

(14) Thaler, W.; Oswald, A.; Hudson, B. *J. Am. Chem. Soc.* **1965**, *87*, 311. Denney, D. B.; Hoyte, R. M.; MacGregor, P. T. *J. Chem. Soc., Chem. Commun.* **1967**, 1241. Hoyte, R. M.; Denney, D. B. *J. Org. Chem.* **1973**, *39*, 2607.

(15) Mo, Y.; Lin, Z.; Wu, W.; Zhang, Q. *J. Phys. Chem.* **1996**, *100*, 6469.

(16) Milosavljevic, S.; Jeremic, D.; Mihailovic, M. *Tetrahedron* **1973**, *29*, 3547. Beckwith, A. L.; Ingold, K. U. In *Free Radicals Rearrangements*; de Mayo, P., Ed.; Academic Press: New York, 1980; p 182. Hart, D. J.; Wu, S. C. *Tetrahedron Lett.* **1991**, *32*, 4099. Journet, M.; Malacria, M. *Tetrahedron Lett.* **1992**, *33*, 1893. Crich, D.; Sun, S.; Brunckova, J. *J. Org. Chem.* **1996**, *61*, 605. Gulea, M.; López-Romero, J.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2000**, *2*, 2591.

(17) Yoromitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041.

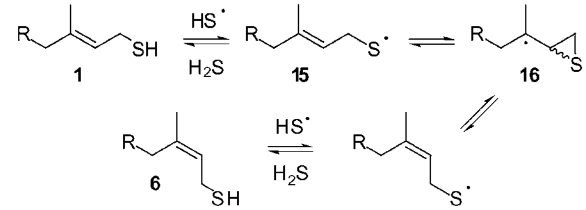
under our simulation conditions for 120 days. The analysis by GC-MS of the (*E*)- and (*Z*)-phyt-2-ene-1-thiols obtained in a 2/1 ratio, besides the isomeric mixture of phytenes, did not reveal any sulfur exchange, as it would have been expected in a standard $S_{RN}1$ reaction. This suggests that, under our experimental conditions, the postulated allylic radical intermediates are preferentially quenched by hydrogen from H_2S.

However, when the reaction involving ^{34}S-labeled (*E*)-phyt-2-ene-1-thiol **14** was performed in a DMF/H_2O mixture (3/1; v/v) with NaSH as the nucleophile, the GC-MS analysis of the (*E*)- and (*Z*)-phyt-2-ene-1-thiols present in the reaction mixture besides the desulfurization products (phytenes) showed that both (*E*)- and (*Z*)-isomers have undergone sulfur atom exchange ($^{32}S/^{34}S$ isotopic ratio increasing from 1/1 to 2/1), thus showing that ^{34}S atoms are replaced by ^{32}S atoms from the NaSH nucleophile. This result clearly supports in this case the occurrence of an $S_{RN}1$ reaction, involving the formation of intermediate allylic radicals.

Since (*E*)-phyt-2-ene **3** does not isomerize under the reaction conditions, the isomerization of (*E*)-phyt-2-ene-1-thiol **1** via an intermolecular addition/elimination[8] of thiyl radicals can be ruled out. In addition, as mentioned above, no sulfur exchange was observed when the reaction was performed in water with the ^{34}S-labeled substrates. This clearly shows that isomerization of (*E*)- to (*Z*)-phyt-2-ene-1-thiol in water does not involve the allylic radicals **10** and **11** formed during an $S_{RN}1$-type reaction. We therefore envisage an intramolecular cyclization of the thiyl radical **15** of the (*E*)-phyt-2-ene-1-thiol **1** on the double bond forming a radical thiirane **16** to explain the isomerization of the double bond. Such a species has never been encountered, and ab initio calculations have shown that its opening would be spontaneous.[19] Since the π bond character is lost upon formation of the radical thiirane, the newly formed σ bond allows rotation and, thus, a nonselective opening of the radical thiirane (Scheme 4).

In conclusion, we have shown that HS^-/H_2S is able to desulfurize allylic thiols in aqueous solutions probably by an $S_{RN}1$-related mechanism involving single-electron transfers from hydrogen sulfide ions. The intermediary occurrence of allylic radical species is notably supported by the formation of the phyt-3-ene isomers, due to unprecedented 1,4 hydrogen shifts, and the exchange of the sulfur atoms at least when the reaction is performed in DMF/H_2O.[20]

Scheme 4. Mechanism of the Isomerization of (*E*)-Phyt-2-ene-1-thiol **1** into (*Z*)-Phyt-2-ene-1-thiol **6**



This newly discovered reduction process might be widely operative in sulfide-rich anoxic environments, which are widespread among marine and terrestrial settings. It is noteworthy, in this respect, that (*E*)- and (*Z*)-phyt-2-ene-1-thiols[1] and the four isomeric phytenes (**2**−**5**) do indeed occur in recent sulfur-rich sediments in the same proportions as in our experiments in water. This reaction thus gives clues to abiotic reduction processes taking place in water in natural environments[21] that are still unknown from a chemical point of view and often simply referred to as “hydrogenations”. These reductive processes are not only important for the long-term preservation of organic compounds in the subsurface but may also have been relevant in prebiotic chemistry.[2,22]

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Supporting Information Available: ^1H and ^{13}C NMR and MS spectral data of compounds **4**, **5**, and **14**, as well as the procedure for the reductive desulfurization of allylic thiols in water and for the $S_{RN}1$ reaction performed in a DMF/H_2O mixture with ^{34}S-labeled phyt-2-ene-1-thiol **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 5893.
(19) Pasto, D. *J. Org. Chem.* **1996**, *61*, 252.
(20) Reaction has not been optimized for preparative purposes but gave a yield of 7% phytenes after 3 h in pure DMF.
(21) Hebting, Y.; Schneckenburger, P.; Adam, P.; Schaeffer, P.; Albrecht, P. 20th International Meeting on Organic Geochemistry, Nancy, France, Sept 10−14, 2001; Géologie et Gestion des Ressources minérals et énergétiques (G2R): Nancy, France; Abstract Vol. 1, 138.
(22) Wächtershäuser, G. *Prog. Biophys. Mol. Biol.* **1992**, *58*, 85.