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Thioketones as key intermediates in the reduction of ketones to thiols by HS^- in natural environments

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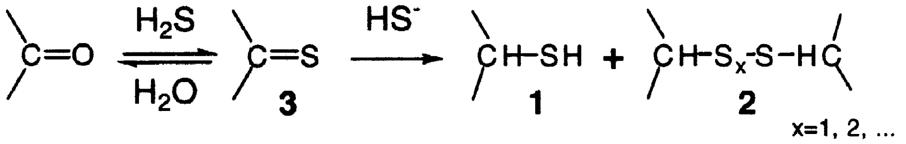
Abstract: Thioketones have been shown to be likely intermediates in the reduction of ketones and aldehydes to thiols by hydrogen sulfide ions, a reaction which plays an important role in the natural sulfurization of organic matter in sediments. The reduction proceeds by a thiophilic addition of HS^- on the thioketone most likely *via* a single electron transfer mechanism.

The study of the biotic and chemical tranformations undergone by biological material in actual environments is essential for understanding its short term fate and the mode of functioning of these complex ecosystems. In this respect, sulfur rich environments are of particular interest since they often contain sediments with high amounts of organo-sulfur compounds likely to be formed at early stages of diagenesis by the reaction of reduced organic sulfur species, produced by bacterial processes, with functionalised lipids of biological origin.[1] Simulation experiments conducted recently under plausible natural conditions have shown that polysulfide ions react with linear aldehydes as well as with linear and steroid ketones to form, in good yield, the corresponding thiols, mainly as dimers linked by polysulfide bridges.[2] Such a reaction could, at least partly, explain the occurrence of sulfur-rich macromolecules in sediments and petroleum.[3] However, the nature of this reaction and, in particular, the mechanism of the reduction process still remain unclear. We report evidence, here, that the formation of thiols **1** and related dimers **2** from ketones and aldehydes is likely to occur *via* the corresponding thiocarbonyls **3**, and that the latter are reduced by a thiophilic addition of the hydrogen sulfide ions *via* a radical anion process.



Investigation of the reaction on several cyclic and steroid ketones and on aldehydes (phytenal, dodecanal) confirmed that these carbonyl groups are indeed reduced into thiols **1** and mainly related dimers **2** by sodium hydrogen sulfide in water or aqueous DMF.[4] As an example, reduction of cholestan-3-one mainly led, in 30% yield, to dimers **5**, along with small amounts of cholestane-3α- and 3β-thiols **4a** and **4b** and cholestane-3-thione **6** as deduced from probe MS and GC-MS of the volatile fraction. Treatment of the reaction mixture with lithium aluminium deuteride essentially gave non deuteriated cholestane-3α- and 3β-thiols **4a** and **4b**, along with small amounts of monodeuteriated thiols formed by reduction of the thioketone **6**. The compounds were identified by comparison with authentic standards.[3a,5] No alcohols which could be formed by a direct reduction of the ketones under the reaction conditions could be detected. Furthermore, alcohols were unaltered under these

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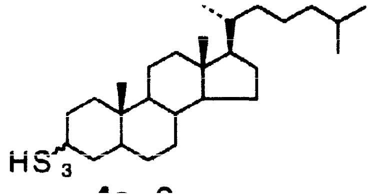
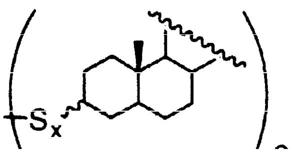
conditions. Further indications that thiocarbonlys are probable intermediates in the reduction of ketones to thiols were inferred from their recent characterization in sulfur rich actual environments.[6]



4a: 3α
4b: 3β



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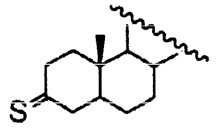

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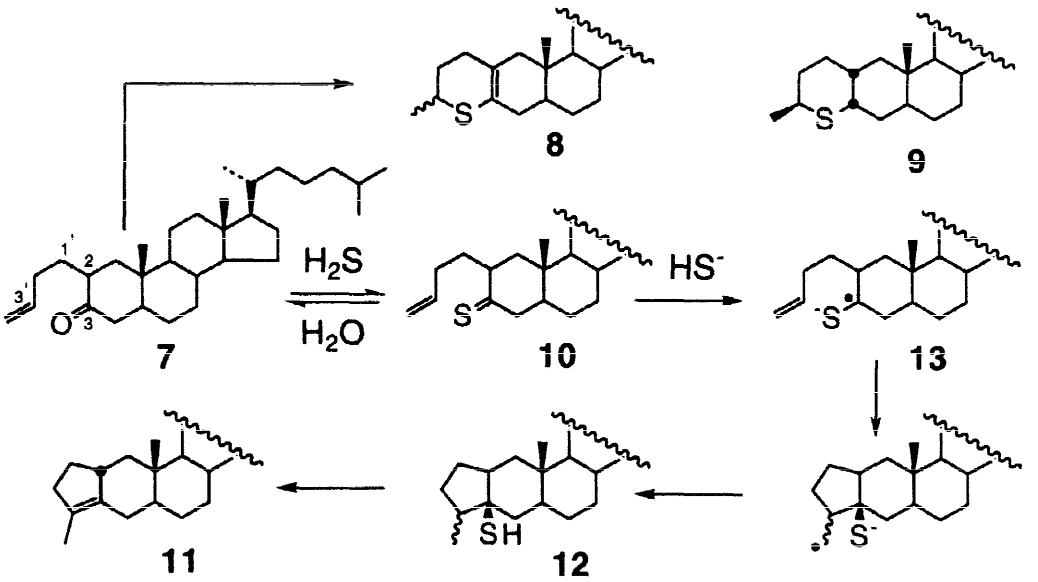
The mechanisms involved in the thiophilic additions of sulfur nucleophiles to thiocarbonyls have been little studied. In the case of the reduction of hexafluorothioacetone to the corresponding disulfide in the presence of thiols[7], the only reported example of thiophilic reaction of thioketones with sulfur nucleophiles, an ionic mechanism has been proposed. An ionic mechanism has also been proposed for the reductive thiophilic addition of alkyllithium and aryllithium compounds on thiocarbonyls.[8] However, in this case, detection of thioether radicals by ESR,[9a] as well as the observation of some typical radical reactions[9b] allowed several authors[9] to propose a SET mechanism implying an electron transfer from the organometallic compound to the thiocarbonyl forming a radical anion.



Therefore, for a closer investigation of the reaction of ketones with hydrogeno-sulfide and sulfide ions and, in particular, of its mechanism, steroid ketone **7** (2α-but-3'-en-1'-yl 5α-cholestan-3-one) bearing an unsaturated C_4 side-chain was prepared[10] and treated with HS^- in aqueous DMF[11] in order to test whether a radical at C-3 formed during the reduction of the thione could eventually be quenched by reaction with the side-chain double bond. Steroid sulfides were the main reaction products obtained. The two major sulfides **8** and **9** were isolated by HPLC from the reaction mixture and characterized by NMR (500MHz) studies comprising homo- (^{1}H-^{1}H: COSY and NOESY) and heteronuclear (^{1}H-^{13}C: HMBC and HSQC) correlation experiments. The configuration of the carbon atom bearing the methyl group on the thiane ring of compound **8** could, however not be established. Sulfurization at position 3—with reduction in the case of compound **9**—has occurred on both compounds. Compound **8** could be formed by cyclisation[12] of thioketone **10** (in fact the thioenol) on the double bond of the butene side-chain. A similar process could lead to compound **9** but would require reductive sulfurization of ketone **7** prior to cyclisation.[12]

Beside the major sulfides **8** and **9**, minor amounts of a C_{31} steroid hydrocarbon could also be detected by GC-MS. Its structure **11** was confirmed by comparison of its chromatographic behaviour (coinjection experiments on a polar and an apolar GC column) and mass spectral data with those of a reference compound. The latter was synthesized by acid catalyzed water elimination on the cyclopentanol (OH instead of SH in **12**) obtained by photochemically induced electroreductive cyclisation of 2α-but-3'-en-1'-yl 5α-cholestan-3-one **7** in acetonitrile with triethylamine as electron donor.[13] Its structure was established by NMR studies comprising homonuclear (^1H-^1H: COSY and NOESY) and heteronuclear (^1H-^{13}C: HSQC, HMBC) correlation experiments.[14]

Formation of hydrocarbon **11** must arise from elimination of the sulfhydryl group on an intermediate cyclopentanethiol derivative **12** resulting from the *5-exo-trig* cyclisation[15] of a transient species **13** bearing a radical at position 3. This species may possibly be a radical anion resulting from a single electron transfer from hydrogen sulfide ions on an intermediate thioketone **10**. The cyclopentanethiol derivative **12**, could, however, not be detected, which may be due to easy elimination of tertiary sulfhydryl groups.

From these results, it could hence be proposed that hydrogen sulfide ions are able to reduce thiocarbonyls in water or aqueous DMF in a process implying formation of a radical species deriving from an intermediate thiocarbonyl rather than by an ionic mechanism as previously proposed for the reaction of thioketones with sulfur nucleophiles.[7] The radical species, which could be a radical anion formed by single electron transfer would then rapidly be quenched by abstracting hydrogen from hydrogen sulfide or hydrogen sulfide ions. The resulting thiols would subsequently react with the polysulfide species formed in the process to yield the dimeric entities.

The simultaneous observation of steroid ketones and of their related thioketones and thiols in sulfur rich sediments from an actual lake (Siders Pond, USA)[6] further underlines the key role played by thioketones as intermediates in the process leading from carbonyls to thiols in natural environments. These results further suggest that single electron transfers from hydrogen sulfide ions may also play a role in other reductive processes affecting organic matter from anoxic environments.

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4. In a typical experiment, 270μmol of ketone were treated under argon with 2.0g (27mmol) of sodium hydrogen sulfide in 30ml of a mixture of DMF and water (2:1 v/v) during 20 hours at 70°C. After cooling at room temperature, the mixture was poured into water and extracted with hexane. Chromatography of the crude extract on silicagel (elution with hexane) yielded 10%-30% of an apolar fraction (Rf> 0.1, SiO_2, hexane) containing the sulfur compounds (thiols, thioketones, ...). Higher yields were obtained with longer reaction times and with aldehydes. Similar experiments were performed in water : typically 10-25μmol of ketone and 1ml of a 0.18M sulfuric acid solution were placed in a glass ampula and purged with argon. The suspension was frozen at -78°C and 45mg (0.18mmol) of solid sodium sulfide were added. After sealing under vacuum at -20°C the ampula was heated at 100°C for a period of time extending from one week to several months after which the aqueous phase was extracted with hexane and chromatographed on silica gel prior to GC-MS analysis.
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10. 2-but-3'-en-1'-yl 5α-cholestan-3-one **7**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ ppm : 0.67 (3H, *s*, H-18), 0.86 (6H, *d*, H-26 et H-27, *J* = 7.0 Hz), 0.90 (3H, *d*, H-21, *J*=6.5 Hz), 1.04 (3H, *s*, H-19), 4,96 (1H, *m*, H-4'*trans*), 5,04 (1H, *m*, H-4' *cis*), 5.78 (1H, *ddt*, *J* = 6.5, 10, 17, H-3'). GC-MS (EI, 70 eV), *m/z* (rel. int.) : 440 [M$^+$] (52%), 411 (6), 386 (100), 316 (54), 55 (74).
11. 29mg (60μmol) of 2α-but-3'-en-1'-yl 5α-cholestane-3-one **7** were reacted under argon with 950mg (13mmol) of sodium hydrogen sulfide in 10ml DMF containing 300μl of water during 20 hours at 70°C. After cooling at room temperature, the mixture is poured into water and extracted with hexane. The crude extract was chromatographed on a silicagel column (elution with hexane) to yield 8mg of an apolar fraction (Rf> 0.1, SiO_2, hexane).
12. Formation of **8** and **9** as predominant sulfides may be the result of polysulfide-catalyzed *exo*-cyclisations of thiols on double bond similar to those described in Poinsot, J.; Schneckenburger, P.; Adam, P.; Schaeffer, P.; Trendel, J.; Albrecht, P. *J. Chem. Soc., Chem. Commun.*, in press.
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14. 4',5'-dihydro-3'-methyl-1'H-cyclopenta [2,3] cholestane **11** : ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm : 0.64 (*s*, 3H, H-18), 0.82 (*s*, 3H, H-19), 0.85 (*d*, 6H, *J*=6.5 Hz, H-26 and H-27), 0.89 (*d*, 3H, H-21, *J*=6.5 Hz), 1.59 (*s*, 3H, CH_3-3'). ^{13}C-NMR δ ppm : 12.07 (18), 12.09 (19), 13.5 (CH_3-3'), 18.7 (21), 22.7 (26 and 27). GC-MS (EI, 70 eV), *m/z* (rel. int.) : 424 [M$^+$] (100%), 409 (50), 315 (11), 269 (14), 161 (27), 95 (20).
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