Aerobic oxidation of thiols to disulfides by heterogeneous gold catalysts

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Thiols are smoothly and efficiently oxidized to disulfides (RSSR) with air in the presence of gold nanoparticles supported on CeO_2 in absence of solvent, as well as in aqueous solutions and neutral pH. It is shown that the reaction can occur through the coupling of two sulphur radicals on the metal surface. The sulphur radicals are formed from thiols by one-electron oxidation with the metal. This reaction mechanism strongly resembles that found for sulfhydryl oxidases, a class of enzymes which are involved in the oxidative protein folding through *de novo* formation of disulfides from thiols.

1. Introduction

Disulfide bonds are very important in nature since they are involved in the stabilization of the folded form of proteins.[1,2] Indeed, for many proteins, disulfide bridges are a prerequisite for having their proper biological function. Within the same biological context, the redox state of these bonds has evolved into a *signaling* element for cells since they can be reversibly reduced and re-oxidized. For example it is known that enzymatic reduction of disulfide bonds is linked to the control of numerous metabolic pathways as well as gene expression.[3] The formation of the adequate disulfide bonds is not only an important matter for living cells, but it is also a major challenge when designing and manufacturing proteins by chemical synthesis, semisynthesis and recombinant expression.[4]

The formation of disulfide bonds is also a matter of interest for the industrial production of some pharmaceuticals and agrochemicals,[5] and their formation can be accomplished in the laboratory by means of numerous oxidants and metal catalysts.[6] Cerium(IV) salts, permanganates, transition metal oxides, chromium peroxide, sodium perborate, ferric chloride, sodium chlorite, nitric oxide, copper complexes, and halogens, among others, have been used for oxidation of thiols to disulfides, sometimes in stoichiometric amounts.[6,7] However, the increasing environmental concern associated with the use of toxic and dangerous oxidants and the production of large amounts of subproducts, has directed chemists to develop catalytic oxidation methodologies that use molecular oxygen as primary oxidant. In this context the catalytic oxidation of thiols to disulfides by molecular oxygen using basic alumina,[8] iron[9] and cobalt[10a–c] complexes among others,[10d] has been reported. Similarly, Co(II) and Mn(II) salts of 4-aminobenzoic acid supported on silica gel have also been reported as an example of heterogeneous aerobic catalytic oxidation.[11] Similarly, Corma *et al.* reported that a heterogeneous catalyst consisting of Zn(II)–Al(III) double layer hydroxide with intercalated $[MoVIO_2(O_2CC(S)Ph)_2]_2$ was able to oxidize thiols to disulfides with air, albeit the process required long reaction times.[12] More recently, nickel nanoparticles have also been found to catalyze the oxidation of thiols to disulfides at room temperature, although a large amount of catalyst (15 mol %) was required in this case.[13]

Most methods listed above suffer from one or more of the following disadvantages: long reaction times, difficult work-up, formation of overoxidation products, use of stoichiometric excess of reagents, strong oxidizing agents and strong basic or acidic media. It is then of interest to develop a mild and efficient methodology for synthesizing disulfides from thiols. Since oxygen is a highly desirable oxidizing agent and Au nanoparticles can tolerate sulphur compounds while efficiently use oxygen for achieving many chemical transformations,[14] we have prepared gold nanoparticles deposited on CeO_2 to oxidize thiols with oxygen to the corresponding disulfides at room temperature, working under solvent free conditions or in aqueous media. Within this context we have also successfully attempted to ''mimic'' the peptide bond formation in cells, by performing the oxidation in aqueous medium of different molecules of biological significance such as L-cysteine, the regulator peptide L-glutathione (GSH) and (*R*)-dihydrolipoic acid.

2. Experimental procedures

2.1 Reagents

The reagents benzenethiol (>99%), 4-chlorothiophenol (>97%), 4-methoxythiophenol (>97%), 4-nitrothiophenol (>97%), 1-octanethiol (>98.5%), 2-isopropylbenzenethiol (90%), cyclohexanethiol (97%), naphthalene-2-thiol (>99%), phenylmethanethiol (99%), L-cysteine (>99%), L-gluthatione reduced (>98%), (*R*)-dihydrolipoic acid (>95%), $HAuCl_4 \times 3H_2O$ (>99.99%), $FeCl_3$ (>99.99%), $CuSO_4$(>98%), $NiSO_4$ (>99.99%),

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$Pd(acac)_2$ (>99%) were supplied by Sigma-Aldrich. CeO_2 (Specific Surface Area, BET $ 252 $m^2 g^{-1}$), was supplied by Rhodia. All these reagents were used without any treatment or further purification.

2.2 Preparation of metal supported catalyst

2.2.1 Synthesis of gold nanoparticles supported on CeO_2 (Au/CeO_2). Au/CeO_2 was synthesized by an impregnation procedure. The impregnation was carried out by adding 1 g of support to an aqueous solution of $HAuCl_4 \times 3H_2O$ (16.12 mg, 0.041 mmol) to obtain a catalyst containing 0.8% Au by weight. The mixture was stirred at room temperature for 6 h. Finally, the solvent was removed at reduced pressure, dried under vacuum at 80 °C for about 2 h and then the sample was calcined in air at 250 °C for 5 h (2 °C min^{-1}). The final content of gold in the catalysts was determined by ICP-OES. The catalyst was treated with H_2 at 200 °C under H_2/N_2 (90/10) flow for 3 h (5 °C min^{-1}) before being used in the catalytic tests.

A second Au/CeO_2 catalyst was synthesized according to a method previously described in the literature by adjusting the slurry to pH 10 and washing the solid until free of chloride.[15] The catalyst was treated with H_2 at 200 °C under H_2/N_2 (90/10) flow for 3 h (5 °C min^{-1}) before being used in the catalytic tests.

2.2.2 Synthesis of metal nanoparticles supported on CeO_2 (M/CeO_2); M ¼ Cu, Pd, Ni, Fe. M/CeO_2 were synthesized following an impregnation procedure as for Au/CeO_2 and using $FeCl_3$, $CuSO_4$, $NiSO_4$ and $Pd(acac)_2$ as starting salts. The catalysts were treated with H_2 at 200 °C under H_2/N_2 (90/10) flow for 3 h (5 °C min^{-1}) before being used in the catalytic tests.

2.3. Catalytic reactions

The catalytic experiments were carried out at room temperature in a reactor equipped with a micro-sampling system. This was designed to extract samples at regular reaction times and to follow the reaction evolution. The methodology was as follows: Thiol (1 mmol), dodecane (20mL) as internal standard and 0.0075 mmol of gold supported catalysts were introduced into the reactor that was pressurized with O_2 (5 bar). The experiments were carried out under stirring (500 r.p.m) at room temperature.

The experiments in aqueous media were performed in a discontinuous stirred (500 r.p.m) tank reactor, at room temperature under oxygen (5 bar) and adding the L-cysteine, or reduced L-gluthathione (GSH) (1 mmol), H_2O (1 mL), and 0.0075 mmol of gold in the form of the supported catalyst Au/CeO_2 (0.8% wt). The experiments were carried out at room temperature, setting a level of agitation of 500 r.p.m. Since the reaction products cistine and oxidized gluthatione GSSG were insoluble in water, they were separated from the catalyst by treating the solid residues with acidic water (5% HCl). Water was eliminated under vacuum and the structure of cistine × HCl and GSSG × HCl was confirmed by ^1H and ^{13}C-NMR and Tandem Gas Spectrometry (MS/MS) comparing with authentic commercial samples.

The experiments in EtOH : H_2O (1 mL) were performed in a discontinuous stirred (500 r.p.m) tank reactor, at room temperature under oxygen (5 bar) and adding the thiols (1 mmol), 0.0075 mmol of gold in the form of the supported catalyst Au/CeO_2 (0.8% wt). The experiments were carried out at room temperature, setting the stirring at 500 r.p.m.

2.4. Experimental techniques

The reactions were monitored by gas chromatography using a Varian chromatograph equipped with a flame detector (FID). The products were separated with a HP-5 capillary column (5% phenyl) (30 m × 0.25 m) and identified by GC–MS, using a Fisons GC 8000 gas chromatograph equipped with a DB5 capillary column with a mass spectrometry detector (Fisons MD 800 quadrupole detector).

The identification of the products was also carried out by NMR spectroscopy. NMR spectra were obtained with a Bruker Avance 300 spectrometer working at 300.13 MHz for ^1H and 75.47 MHz for ^{13}C. The ^1H and ^{13}C spectra of the isolated sulfur products were recorded in $CDCl_3$.

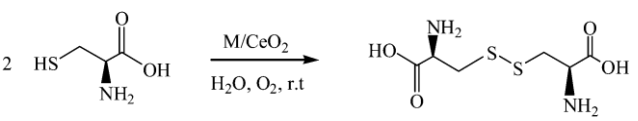
Size distribution of the metal nanoparticles was measured by transmission electron microscopy (TEM), using a bright field microscope with a Philips CM10 at 100 k, and counting more than 150 particles. Samples for TEM were prepared by deposition of a drop containing the catalyst suspended in ethanol, on a copper grid (300 mesh) with a carbon film.

Spin trapping studies were carried out as following: 1.5 mL of a 0.1M toluene solution of the spin trap phenyl *N-t*-butylnitrone (PBN) molecule was incorporated to an EPR probe containing 1.5 mL of a 0.1 M toluene solution of PhSH, and purged with N_2 for 1 min. After this, the EPR spectrum was recorded. Then different Au/CeO_2 catalysts with different metal loadings were incorporated to this EPR probe, being again purged with N_2 for 1 min, and the EPR spectrum recorded.

3. Results and discussion

The oxidation of the aminoacid L-cysteine to the small disulfide cistine in aqueous solutions, was chosen as model reaction to

Table 1 M/CeO_2 catalyzed formation of cistine from L-cysteine in aqueous medium[a,d]



Entry	Catalyst	Time (h)	Conv (%)[b]	Yield (%)[c]
1	Au/CeO_2 (0.8% Au wt)	2	100	90
2	Fe/CeO_2 (1.0% Fe wt)	2.5	84	79
3	Cu/CeO_2 (1.0% Cu wt)	2.5	33	32
4	Ni/CeO_2 (1.0% Ni wt)	2.5	26	25
5	Pd/CeO_2 (1.0% Pd wt)	2.5	14	10
6	CeO_2	2.5	40	39

[a] Reaction conditions: L-cysteine (1 mmol), M/CeO_2 (0.0075 mmol), H_2O (1 mL), P_{O_2} ¼ 5 bar, r.t. [b] Calculated on the basis of recovered aminoacid. [c] Yield of isolated pure product. [d] Reaction carried out without solvent.

study the catalytic behaviour of different metals supported on CeO_2 (see Table 1 and characterization data in Table 1S of Supplementary Material†).

Among all the metals studied, gold afforded the highest yields of cistine (entries 1, Table 1), followed by Fe (entry 2), and Cu, Ni and Pd in much lower yields (see entries 3–5, Table 1). Similarly, a control reaction showed that CeO_2, without any added metal, was able to catalyze the formation of disulfide though with lower yields of the desired dipeptide than Au/CeO_2 and Fe/CeO_2 (see entry 6, Table 1). It is interesting to note that the presence of other metals (Cu, Ni, Pd) that could in principle perform the oxidation reaction when on CeO_2, produced a decrease of the activity of the support as they led to inferior values of the disulfide (see entries 3–6 in Table 1).

It is necessary to point out that the activity of Au/CeO_2 (0.8% Au wt) as catalyst for the oxidation reaction of 1 to 2 was exactly the same, regardless of the type of method used in its preparation (impregnation or deposition-precipitation) (see details of their preparation in the experimental section), as reflected in the kinetic curves of conversion and yield of product 2 *versus* time (Figure 1S in supplementary material†).

Other organosulfur compounds such as the small peptide L-glutathione (GSH) and diverse aryl thiols were also rapidly and efficiently converted to oxidized glutathione (GSSG) and to the corresponding aryl disulfides, with very high yields in the presence of Au/CeO_2 under similar experimental conditions (see entries 1–3 and 6–8, in Table 2).[16]

In this respect, it is important to indicate that the absence of solvent did not prevent the rapid and quantitative transformation of thiol 1 into disulfide 2 (entry 4, Table 2); whereas a control reaction showed that the presence of molecular oxygen was absolutely essential for achieving conversion (entry 5, Table 2).

Finally we observed that the oxidation of (*R*)-dihydrolipoic acid to the corresponding cyclic disulfide (*R*)-lipoic acid (an organosulfur compound essential for life) proceeded with difficulty even at 40 °C (entry 9, Table 2), while the aliphatic thiols in entries 8–9 did not react.

Influence of gold particle size

It is generally observed that for reactions catalyzed by gold nanoparticles, the size of the metal particle is a key variable.[17] Therefore we have prepared a series of Au/CeO_2 catalyst samples in where the crystallite size was varied by changing the metal loading (see Table 2S in supplementary material†). The resultant catalysts were tested for benzenethiol oxidation and the results are given in Fig. 1.

It can be seen there that the initial reaction rate per metal surface atom (turnover frequency, TOF) for the formation of the disulfide compound 2 increases when decreasing the Au crystallite size (Fig. 1). It can also be seen in Fig. 1 that the activity of the catalysts drops practically to zero when the size of the nanoparticles is above 3.5 nm. It appears therefore that the presence of small gold nanoparticles is an absolute requirement for converting thiols into disulfides.

Nature of the active gold species

In order to get further insight into the nature of the gold species responsible for catalytic oxidation, a series of Au/CeO_2 catalysts were prepared keeping constant the total gold content, but changing the ratio $Au^{+\delta}/Au^{T}$ (Au^{T} ¼ total gold atoms), following the experimental procedures described in the literature.[17] The catalytic activity of these samples were tested and Fig. 2 shows that the TON was very close, regardless of the $Au^{+\delta}/Au^{T}$ contained in the samples (see characterization data in Table 2S of supplementary material†). This result suggests that active gold sites are not specifically associated to positively charged species but probably to Au^0 atoms and preferentially to gold atoms with lower coordination numbers whose amount should be proportionally larger in smaller crystallites.

Scope of the reaction

Substituted aryl and alkyl thiols were oxidized in the presence of Au/CeO_2 and molecular oxygen (P_{O_2}¼ 5 bar) under solventless conditions (see Table 3).

As was previously observed for the reaction in H_2O : EtOH media, the transformation of compound 1 into disulfide 2 also takes place rapidly and efficiently with Au/CeO_2 (0.8% Au wt) when working in absence of solvent (entry 1, Table 3). Thiol derivatives with electron donating and electron withdrawing groups at the *para* aromatic position of the benzene ring were also efficiently oxidized to the corresponding disulfides (see entries 2–4, Table 3) as well as other related aromatic thiols (entries 5,6, Table 3).

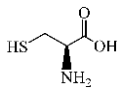
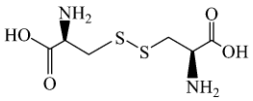
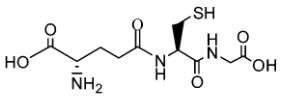
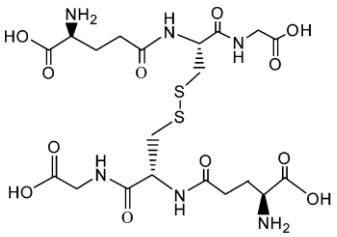
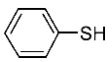
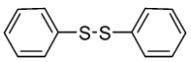
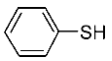
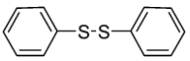
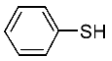
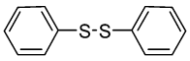
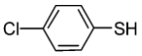
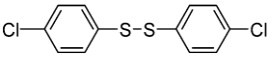
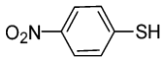
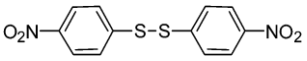
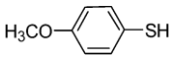
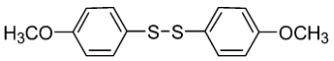
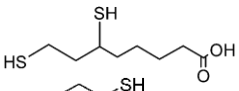
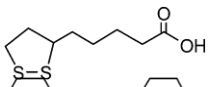
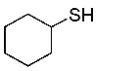
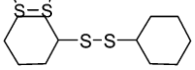
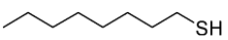
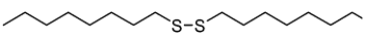
In general, under these reaction conditions, aromatic thiols were found to be much more reactive than aliphatic ones since most aromatic thiols were selectively oxidized to their corresponding disulfides in near quantitative yields (entries 1–9, Table 3).

Reaction mechanism

The oxidation of a mercaptan (R–SH) to a disulfide (RSSR) can follow either a radical or an ionic mechanism, as depicted in Scheme 1 :[18]

In an attempt to detect and identify free-radical intermediates, benzenethiol 1 was oxidized with Au/CeO_2 as catalyst in the presence of styrene. If the reaction occurs through formation of thiyl radicals (Scheme 1), these radicals should be trapped by styrene and the corresponding reaction products would be detected. However, the formation of addition products incorporating the thiyl radical and the alkene residue were not detected by GC, while the disulfide compound 2 was exclusively formed.[18] From these results one may conclude that the radical mechanism was not operative. However, before reaching that final conclusion, it should be taken into account that if RS· radicals are formed they may interact with the gold nanoparticles better than they are trapped by styrene. Indeed the strong dissociation energies of Au–S bonds (418 kJ mol^{-1}), which are only comparable to those for typical chemical bonds of H–H (436 kJ mol^{-1}) and C–C (348 kJ mol^{-1}),[19] may explain the reluctance of gold coordinated thiyl radicals, if formed, to be captured in our case by oxygen or olefins. Then, for better discussing the possible formation of RS· species, spin trapping studies using the spin-trap phenyl-*N*-*t*-butylnitrone (PBN) were performed. In

Table 2 Au/CeO_2 (0.8% Au wt) catalyzed formation of disulfides from thiols in aqueous medium[a]

Entry	Thiol	Disulfide	Time (h)	Yield (%)[b]
1			2	90
2	 GSH	 GSSG	4	85
3[c]			2.5	96
4[d]			2	100
5[de]			24	0
6[c]			2.5	92
7[c]			1.5	88
8[c]			1.5	94
9[cf]			24	21
10[c]			24	0
11[c]			24	0

[a] Reaction conditions: 1 mmol thiol, Au/CeO_2 (0.8% wt, 0.0075 mmol), 1 mL H_2O; P_O ¼ 5 bar. [b] Isolated yield. [c] Solvent: 1 mL of H_2O : ethanol (1 : 1). [d] Solventless conditions. [e] Reaction carried out under inert atmosphere. [f] Reaction carried out at 40 °C.

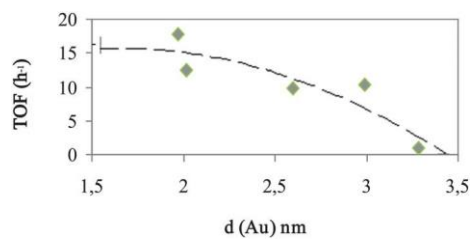


Fig. 1 Plots showing the initial reaction rates (r_0) per surface atom (TOF, h^{-1}) as a function of metal particle size for formation of disulfide compound 2 from thiol 1 with Au/CeO_2 catalysts.

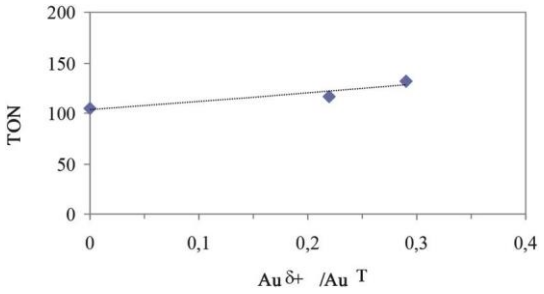
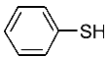
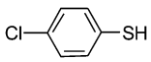
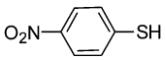
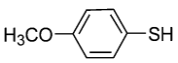
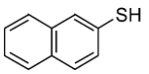
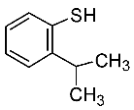
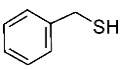
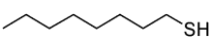


Fig. 2 Correlation between Au^{d+}/Au^{T} ratio of Au/CeO_2, where TON was calculated on the bases of total gold.

this case, a signal that can be associated to the formation of a stable radical adduct between PBN and the thiyl radical ($PHS^{\cdot}$) was identified by EPR (coupling constants aN ¼ 13.8 and aH ¼ 1.8 according to tabulated values).[20a] Additional experiments carried out at increasing gold concentrations in Au/CeO_2 enhanced the intensity of this EPR signal (see experimental section and Fig. 3), whereas a control experiment with CeO_2 and

Table 3 Au/CeO_2 catalyzed synthesis of disulfide compounds from aromatic and aliphatic thiols under oxygen without solvent[a]

R--SH— $\xrightarrow[O_2]{Au}$ R–S–S–R

Entry	Thiol	Time (h)	Conv (%)[b]	Yield (%)[b]	TON[c]	TOF[d]
1		2	100	100	149	14.2
2		1	100	97	121	26.4
3		1	100	100	149	25.3
4		1	100	100	132	23
5[e]		8	92	89	123	4.5
6[e]		24	100	100	123	5.9
7		24	10	10	14	2
8		24	10	0	14	0.1
9		24	0	0	0	0

[a] Reaction conditions: 1 mmol thiol, 0.0075 mmol Au (Au/CeO_2, 0.8% wt), P_O ¼ 5 bar. [b] Determined by GC. [c] Calculated as mmol substrate converted/mmol catalyst. [d] Calculated as mmol substrate converted/mmol catalyst/h. [e] The oxidation was carried out in 0.5 mL toluene as solvent since the thiol was a solid.

Radical pathway, 1

$2RSH \longrightarrow 2\,RS^{\cdot} + 2H^{+} + 2\,e^{-}$

$2RS^{\cdot} \longrightarrow RSSR$

Ionic pathway, 2

$RSH \longrightarrow RS^{+} + H^{+} + 2\,e^{-}$ (or $RSH \longrightarrow RS^{\cdot} + H^{+} + 1\,e^{-}$; $RS^{\cdot} \longrightarrow RS^{+} + 1\,e^{-}$)

$RS^{+} + RSH \longrightarrow RSSR + H^{+}$

Scheme 1 Possible reaction pathways for the formation of disulfide compounds from thiols.

PBN did not show any EPR signal. This observation would be consistent with the existence of a radical mechanism (see Scheme 1) for the aerobic oxidation of thiol to disulfide on the gold catalyst (a related mechanism has been also proposed recently for the gold-catalyzed synthesis of aromatic azo compounds from anilines and nitroaromatics).[20b]

Furthermore, since the oxidation reaction of thiol 1 was strongly dependent upon the OH^{-} concentration, *i.e.* formation of the corresponding disulfide 2 was completely inhibited in the

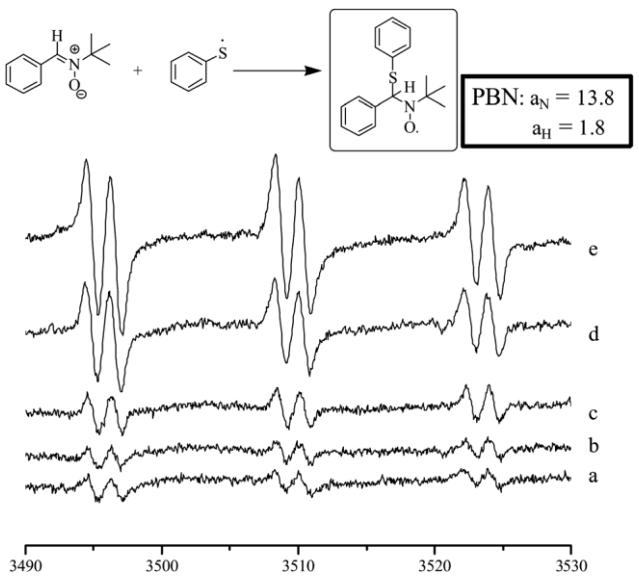


Fig. 3 EPR spectra recorded at different gold metal content: a) 1% mmol Au, b) 2% mmol Au, c) 3% mmol Au, d) 10% mmol Au, e) 16% mmol Au, showing the signal of the radical adduct (aN ¼ 13.8 and aH ¼ 1.8) formed between PBN and the thiyl radical (PHS).

presence of 1 mmol NaOH (with Au/CeO_2 as catalyst), we concluded that one-electron transfer from a thiolate species (RS^-) to one electron acceptor should not be involved in the reaction mechanism.[21]

Besides this, the transformation of thiol 1 into 2 was carried out in the presence of the isotopically labelled triethylsilicon hydride Et_3SiD. This trialkylsilane has an active hydride and it may reduce the cationic species RS^+ to RSD. After 50% of conversion, only the disulfide 2 (major product) and traces of the silanol Et_3SiOH could be detected by GC–MS, hence discarding the cationic pathway.

In view of the above results and according to the radical pathway, the formation of thiolate-Au (RS–Au) species on the metal surface should imply a homolytic S–H scission from the original thiol to form a thiyl radical and hydrogen (see Scheme 1). The thiyl radical may form a thiolate–Au species (RS–Au), whereas hydrogen may bind to the metal surface to form an intermediate Au–H species (in a straightforward fashion) or it may desorb in a molecular form as H_2.

In order to find out on the possible formation of this Au–H intermediate, we thought on performing the oxidation of thiol 1 (1 mmol) to disulfide 2 in the presence of a molecule capable of accepting hydrogen, such as the alkene *p*-methoxystyrene (1 mmol), with Au/CeO_2 (0.0075 mmol) as catalyst and working in absence and in presence of O_2.

Under aerobic conditions (P_{O_2} ¼ 5 bar), thiol 1 (1 mmol) was completely converted into diphenyldisulfide 2 (89% mol) and formation of the hydrogenated product 1-ethyl-4 methoxy-benzene (3) was estimated as 37% mol, by GC after 3.5 h at room temperature. In absence of O_2, the reaction took much longer (12 h) to achieve complete thiol 1 conversion, and the yield of hydrogenated product 3 increased to 53%.

If we take also into consideration the impossibility of the alkene *p*-methoxystyrene (1 mmol) to be hydrogenated (P_{H_2}¼ 5 bar) at room temperature in the presence of Au/CeO_2 (0.0075 mmol) as catalyst, we may conclude that molecular hydrogen is not released during this process, but the Au–H intermediate is necessarily formed on the metal surface upon chemisorption process.

In any case, since the presence of O_2 is absolutely essential for the reaction to take place, *i.e.* for accepting electrons and to regenerate the Au catalytic site,[15] we have also analyzed the amounts of oxygen consumed and the water formed during the oxidation of benzenethiol 1 (reaction conditions: 1 mmol thiol, 0.0075 mmol Au (Au/CeO_2, 0.8% wt), P_{O_2} ¼ 5 bar). It was found that 0.405 mmol of H_2O were formed and 0.28 mmol O_2 were consumed (approximately) per mmol of compound 1.[22] These amounts perfectly match with a chemical balance where unsaturated Au^0 sites mediate the transformation of 1 into 2:

$$2\ PhSH + 2Au^0 \rightarrow PhS{-}SPh + 2Au{-}H \quad (1)$$

$$2\ Au{-}H + 1/2O_2 \rightarrow 2Au^0 + H_2O \quad (2)$$

Nonetheless, taking into account that molecular oxygen forms either H_2O or H_2O_2 when acting as the final electronic sink (*vs.* in living cells), we have also considered the possibility that hydrogen peroxide could be formed. Since a control reaction showed that hydrogen peroxide disproportionates to water and oxygen in the presence of Au/CeO_2, the following two equations must be considered, in which either production of water or hydrogen peroxide might take place:

$$4\ R^{\bullet}C{-}SH + O_2 \rightarrow 2\ R^{\bullet}C{-}S{-}S{-}CR^{\bullet} + 2\ H_2O \quad (3)$$

$$2\ R^{\bullet}C{-}SH + O_2 \rightarrow R^{\bullet}C{-}S{-}S{-}CR^{\bullet} + H_2O_2 \rightarrow H_2O + 1/2O_2 \quad (4)$$

According to the above equations, the amounts of water formed and oxygen consumed can not help to distinguish between the two possible routes because these amounts are exactly the same in both cases.

Although it was not absolutely proven, it is most likely that the formation of disulfides from thiols on gold occurs through a radical path. Thus in Fig. 4 the following mechanism for the gold catalyzed aerobic oxidation of thiols to disulfides has been proposed.

Following the reaction path in Fig. 4, thiol RSH adsorbs on the gold surface inducing an oxidative addition of metal, to give Au–SR and Au–H species. From Au–SR, the assembly of two neighbouring thiyl radicals will take place on the metal surface making possible the formation of the disulfide compound RSSR and the regeneration of the original Au^0 catalyst. The Au–H intermediate will reduce molecular oxygen O_2, hence regenerating the Au^0 catalyst and closing up the catalytic cycle. In anaerobic conditions Au–H will pass its electrons to any other molecule that is prone to be reduced (*i.e.* double bonds).

From the reaction mechanism proposed above it appears that the gold catalyzed formation of disulfides under aerobic conditions with Au/CeO_2 mimics, up to a certain degree, *de novo* formation of disulfides in living organisms by sulfhydryl oxidases.[23] Such enzymes couple the reduction of oxygen to hydrogen peroxide (eqn (5)), albeit sometimes these sulfhydryl oxidases are also referred to thiol oxidases (enzymes that also oxidise thiol groups using oxygen as electron acceptor but reducing it to water) (eqn (6)).

$$2\ R^{\bullet}C{-}SH + O_2 \not\rightarrow R^{\bullet}C{-}S{-}S{-}CR^{\bullet} + H_2O_2 \quad (5)$$

$$4\ R^{\bullet}C{-}SH + O_2 \not\rightarrow 2\ R^{\bullet}C{-}S{-}S{-}CR^{\bullet} + 2\ H_2O \quad (6)$$

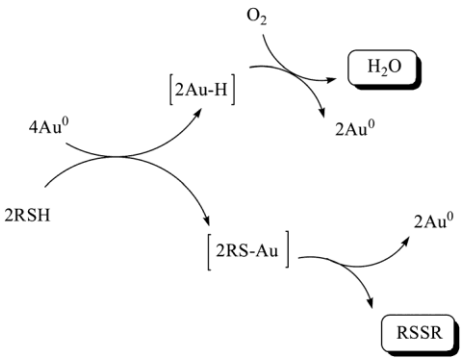


Fig. 4 Plausible reaction mechanism for the gold catalyzed oxidation of thiols to disulfides with molecular oxygen as oxidant.

4. Conclusions

Gold nanoparticles supported on CeO_2 can oxidize smoothly and efficiently at room temperature, a wide variety of aromatic and heterocyclic thiols to disulfides in water as well as in the absence of solvents, using oxygen as electron acceptor. In general, aromatic and aliphatic branched thiols were found to be reactive while the aliphatic thiols were unreactive under these reaction conditions.

Mechanistic studies confirmed that the gold active species are essentially gold atoms, preferentially with lower coordinations, being the oxidation of thiols to give disulfides a structure sensitive reaction. Finally, spin trapping studies by EPR spectroscopy suggest that the reaction follows a radical pathway through the combination of two thiyl radicals, being oxygen the final electron acceptor.

The simplicity of the system, excellent yields and the reasonable reaction time required make Au/CeO_2 an attractive environmentally acceptable catalyst for obtaining disulfides.

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