The versatility of gold: from catalysis to biomedicine

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Abstract

This mini-review is to commemorate prof. Renato Ugo introducing a brief overview of our research on gold conducted in the same department at Milan University where he worked as a beloved professor of Inorganic Chemistry and eminent scientist. The aim is to provide a short outline of our main contributions to gold-based heterogeneous catalysis with a look at biomedicine. Gold nanoparticles, alone or alloyed with a second metal, displayed superior performance in the selective aerobic oxidation of a variety of alcohols and aldehydes than the conventional palladium and platinum catalysts, both in liquid and gaseous phase. Whereas supporting nanometric gold on different oxides or carbons allowed to retain its stability and durability over time, the extraordinary properties of colloidal "naked" gold clearly emerged and are herein discussed. In particular, the molecular mechanism underlying the aerobic oxidation of glucose with gold catalysis was disentangled by kinetic studies. Gold has been successfully employed even in glycerol valorisation as well as in the catalytic polymerization of aniline, thus offering an eco-friendly alternative route to conventional polluting syntheses. The way from the discovery to the commercialization of gold-based catalysts has been long and paved with success but even obstacles. Only recently gold catalysis has finally found its first large-scale application in the chemical industry, thus showing how the 'yellow metal' is more than a promise. Last but not least, gold nanoparticles are elective candidates for cancer therapy. On this regard, we have developed a simple approach for the synthesis of extra-small gold nanoparticles to be potentially employed in breast cancer treatment. This adds another gusset to the versatility of the once-considered inert metal.

Keywords: gold, heterogeneous catalysis, selective oxidation, conducting polymers, nanomedicine

1. Introduction

Gold has always held a general fascination in humankind. Symbol of power and nobility, it is the precious metal for excellence as well reflected by the Greek myth of king Midas. Gold has been chosen for some of the most beautiful and ancient artistic handcrafts even because of its impressive durability. This latter peculiarity originates by its high standard electrode potential which leads to gold renowned inertness. Just this intrinsic characteristic has, however, contributed to the initial scepticism towards gold chemistry. It came, thus, as a little shock for the scientific community when this noble element was found to promote highly selective reactions under mild conditions [1, 2]. The turning point was lowering gold particle size down to the nanoscale as its chemico-physical properties markedly change due to its modified electronic structure. Accordingly, a metal to non-metal transition occurs along with an increased surface atom fraction leading to enhanced catalytic performance [3]. Most important, these properties are size-dependant. Three decades have passed by since the starting point for heterogeneous catalysis by gold. Almost simultaneously, at the end of the 80s, Hutchings and Haruta discovered that gold nanoparticles (AuNPs) supported on activated carbon or other reducible supporting materials (i.e. TiO_2) are effective catalysts for gaseous phase acetylene hydrochlorination and CO oxidation respectively [4, 5]. These first papers triggered a general interest for gold catalysis as a precious aid to the then-emerging green chemistry. Hence, a novel era of heterogeneous catalysts entered the scene and stimulated the chemical community to explore gold in a number of selective oxidation reactions both in gaseous and liquid phase. In this context, Rossi et al. gave their own contribution opening up new exciting perspectives in aerobic oxidations, especially conducted in liquid phase although not exclusively [6-43]. One of the key metrics for a catalyst of choice is the high selectivity to a targeted product. This is a challenging issue when the desired product is itself reactive and tends to undergo further oxidative process. Rossi and co-workers were able to convert glycols into monocarboxylates [6-9, 11-18] and unsaturated alcohols into unsaturated aldehydes [19] with almost total selectivity branching out from gold-only catalysts to bimetallic formulations. Notably, these reactions were carried out under mild conditions and employing eco-friendly oxidants as dioxygen or hydrogen peroxide. Moreover, when conducted in liquid phase, only water was used as a solvent. On the occasion of this commemorative Special Issue, the present mini-review reports some of the pioneering studies on gold chemistry carried out by Rossi et al. in the same department at Milan University where prof. Renato Ugo worked.

2. Selective oxidation in liquid phase by gold catalysis

2.1 Glucose aerobic oxidation

Gluconic acid, containing the forms of its δ-lactone and gluconates, is one of the bulk chemicals widely employed in multifaceted areas such as food chemistry, pharmaceutical and construction industries. Its present production is mainly performed by *Aspergillus niger*-enzymatic catalysis starting from glucose with yields higher than 95% in sodium or calcium gluconate. The enzymatic

route displays however some limits to be countered. The most important ones are the low productivity and troublesome separation of the enzyme at the end of the process. Finding out alternative 'green' catalytic routes to overcome these drawbacks is therefore particularly welcome considering that glucose is a low-cost renewable starting material. In 2002 Rossi and co-workers took up the challenge and introduced the first study on the employment of gold supported on carbon catalyst (Au/C) in the liquid phase oxidation of D-glucose to sodium D-gluconate [10]. Previous attempts to substitute the enzymatic process were conducted using palladium and platinum-based catalysts. These ones were taken as a benchmark for the comparative study with Au/C catalyst. Under the same mild conditions (T = 323-373 K, pO_2 = 1-3 atm and pH = 7-9.5), the colloidal gold immobilized on carbon unveiled outstanding catalytic performances. Especially under alkaline conditions (pH = 9.5), gold proved its superiority in terms of activity and stability at similar selectivity when compared to Bi-doped platinum and/or palladium on carbon catalysts [10]. Using either gold or bismuth-modified platinum and palladium catalysts, Rossi and co-workers achieved 99% selectivity to gluconate at almost total conversion. Differences between the two kinds of catalysts were detected by recycling tests, since only gold retained total selectivity after three runs. Such achievements encouraged us to optimize the catalytic system aiming to present gold as a valid alternative to the enzyme. Two years later, a notable 60 000 h^{-1} TOF (turnover frequency) could be reached in the aerobic oxidation of glucose by gold, thus approaching its performance to *Aspergillus niger* catalysis [20]. This study also unravelled the catalytic activity of unsupported AuNPs. The metal-support interaction is still an open question in heterogeneous catalysis. Is the supporting material a catalytic enhancer, a metal stabilizer or both? Far from finding a conclusive answer to the question, as this deeply depends on the nature of supporting material and metal, we could however separate the contribution of gold from carbon. The key role of gold emerged by comparing the catalytic performance of unsupported gold ('naked' AuNPs) to supported Au/C under the same glucose oxidation conditions. Since colloidal gold is known to be unstable without any stabilizing agents (i.e. PVA or PVP), a strategy for obtaining stable 'naked' AuNPs urged to be found. By using glucose in slight excess, acting either as reagent or stabilizer, we successfully reached this goal. Furthermore, a correlation between particle size and activity could be derived by assuming AuNPs as spherical with monomodal distribution. More specifically, an inverse relationship between rate and size was expected according to the simple geometrical model v = k/r, where 'v' stands for the catalytic rate and 'r' for the nanoparticle radius, with constant gold mass of known density. To confirm such a hypothesis, kinetic tests were performed at T = 303 K, glucose/Au molar ratio of 12 000, pO_2 = 1 atm and pH = 9.5 by employing differently sized 'naked' gold (average diameter from 2.5 to 10 nm). The experimental apparatus consisted in a glass reactor interfaced to an automatic titration device equipped with sodium hydroxide. Inverse

correlation between catalytic activity and size was indeed detected in the diameter range 2.5-4.5 nm but, interestingly, followed by deviation from linearity for size larger than 6 nm up to the catalytic inactiveness at 10 nm [Fig. 1] [20, 37].

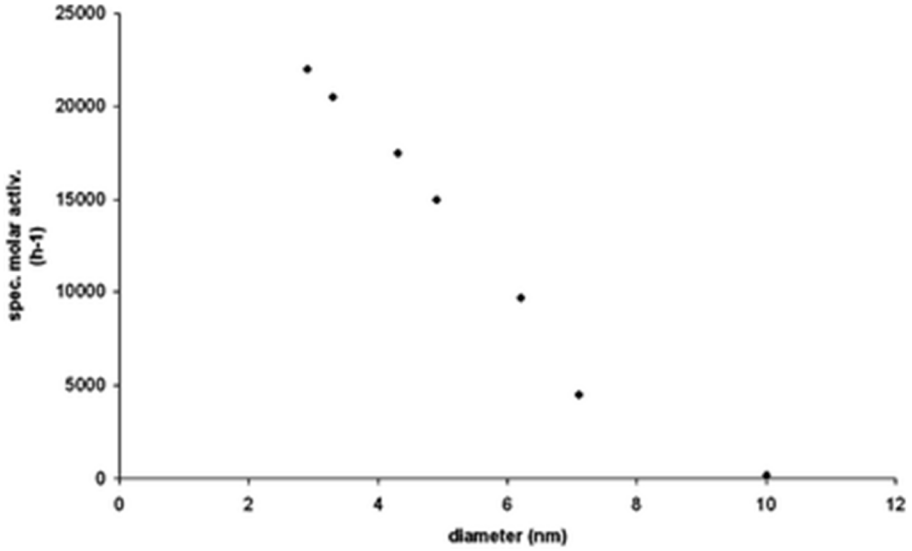

Fig. 1 Aerobic oxidation of glucose by gold catalysis. Correlation between activity and diameter of unsupported ('naked') AuNPs. Experimental conditions: [glucose] = 0.38 M; [Au] = $3.2 \cdot 10^{-5}$ M; glucose : Au = 12 000, T = 303 K, pH = 9.5, pO_2 = 1 bar.

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Such an activity drop means that not only geometrical factors but also electronic modifications might play a role in affecting AuNPs electrophilic properties. On this regard, Bond and Thomson reported marked discontinuity in various chemico-physical properties when gold approaches metal-non metal transition (i.e. gold melting point collapse) [21]. In order to determine the intrinsic catalytic role of gold in glucose oxidation, a comparative study with the supported version of gold nanoparticles was carried out under the same experimental conditions. More in detail, 0.5% Au/C catalyst of 3.6 nm average diameter was prepared by sol immobilization on coconut derived carbon (X40S from Camel, A_s = 1200 m^2 g^{-1}) and compared to the corresponding unsupported AuNPs with the same average diameter. As evinced by the conversion-time plot of the reaction, the two curves overlapped over the first 200 s, afterwards the typical short lifetime of unsupported 'naked' nanoparticles prevented them from retaining stability over time differently from Au/C catalyst [Fig. 2] [20, 37].

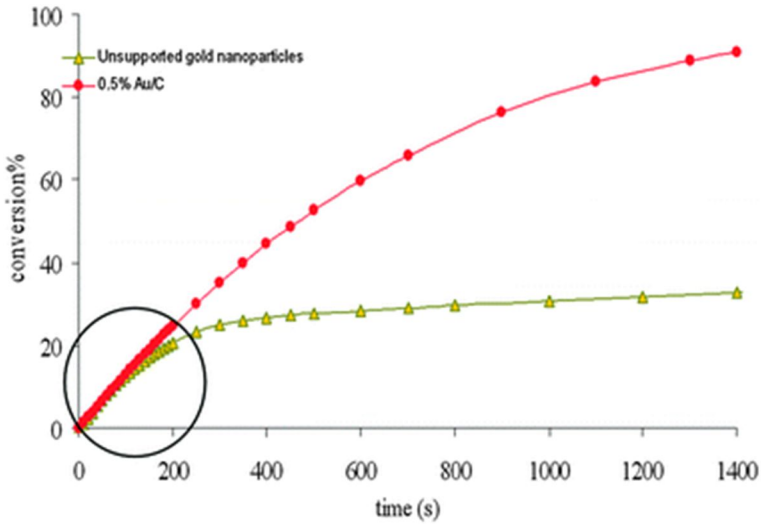

Fig. 2 Aerobic oxidation of glucose by gold catalysis. Comparison between unsupported 'naked' gold nanoparticles (AuNPs) and supported ones (0.5% Au/C). Experimental conditions: [Au] = 10^{-4} M, [glucose] = 0.4 M, T = 303 K, pH = 9.5, pO_2 = 1 bar.

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Nevertheless, the initial activity of 'naked' AuNPs compared to Au/C was crucial for determining metal–support interactions. The two curves overlapping, in fact, indicates no detectable interplay between gold and carbon apart from the stabilizing role of X40S leading to reach total glucose conversion. Inspired by these promising achievements, we felt the time was ripe enough to lead a systematic comparison between gold catalysis and enzymatic catalysis [23]. A gold catalyst, 0.5%wt Au/C with an average particle diameter of 3.6 nm, was synthesized as previously reported by sol immobilization on X40S carbon. *Hyderase*, an enzymatic preparation containing glucose oxidase and catalase as active components and flavine–adenine dinucleotide (FAD) as the rate controlling factor ($1.3 \cdot 10^{-6}$ mol g^{-1}), was purchased from Amano Enzyme Co. Under optimized experimental conditions, higher productivity was achieved by gold catalysis with respect to *Hyderase* (514.3 Kg m^{-3} h^{-1} for Au/C vs 121.7 Kg m^{-3} h^{-1} for *Hyderase*). The reason might be ascribed to the lower FAD concentration in the enzyme, as well as the initial threefold-higher glucose concentration allowed only to Au/C. Conversely the enzyme reached TOF of 600 000 h^{-1}, a markedly higher value than 90 000 h^{-1} calculated for the inorganic catalyst [23].

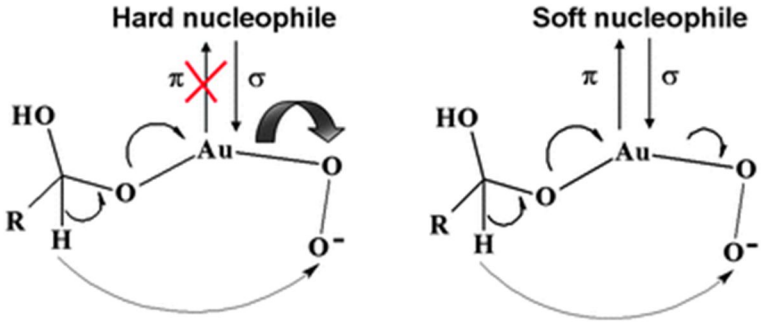
At the time an effective route to directly synthesizing free gluconic acid was unknown, due to low pH conditions required for its manufacture. Unfortunately the enzymatic catalysis is inhibited by acidic conditions and palladium, platinum and gold are scarcely active as well. The only viable way was reacting calcium or sodium gluconate with sulfuric acid, but large production of waste calcium or sodium sulfate represented a limit to be overcome. Alloying gold with a second metal (namely palladium, platinum and copper) was emerging as a new frontier for boosting gold catalytic performance in redox reactions [45]. Eager to find a successful pathway to free gluconic acid

synthesis, we pioneered a Au-Pt/C formulation proved to be more effective to the scope than the monometallic counterparts. An optimized gold-platinum combination (2 Au : 1 Pt, weight ratio) by sol immobilization on carbon successfully led to alkali free oxidation of glucose to gluconic acid, although with modest catalyst lifetime [24]. Despite some limits, a synergistic effect between gold and a second metal stood out markedly, thus kickstarting numerous studies with gold-based bimetallic catalysts in various selective oxidation reactions [27, 29, 35, 38, 45-49].

Unveiling the molecular mechanism underlying glucose aerobic oxidation by gold and enzyme caught meanwhile a general interest. Claus et al. in Germany [50] and our group in Italy [21, 23, 26, 31] presented the first fundamental contributions on this topic based on kinetic investigations over unsupported and carbon supported AuNPs. According to our mechanistic model [23, 26] hydrogen peroxide, instead of water, is the reduction product of dioxygen promoted by gold catalysis. This breakthrough hypothesis was demonstrated by experimental detection of H_2O_2 during glucose aerobic conversion with 'naked' AuNPs. Accordingly, gluconate and hydrogen peroxide were detected with equimolar stoichiometry [26]. Furthermore, a comparative study between enzymatic catalysis and gold catalysis showed that both the systems promote the selective oxidation of glucose sharing the same stoichiometry despite different reaction mechanisms. Concerning the enzymatic catalysis, the rate determining step is the substrate oxidation by *Hyderase* which is reduced according to a faster reaction step of zero order with respect to dioxygen [21]. Differently, glucose adsorption on catalyst represents the rate determining step in the gold-catalysed reaction followed by its oxidation with O_2 dissolved in water. In this latter case, a first-order kinetics depending on dioxygen was detected [23]. Based either on the detection of hydrogen peroxide as by-product or alkali promoting role, we suggested the following molecular mechanism. An electron-rich gold species formed by the hydrated glucose anion with gold is the key for dioxygen activation. This species, in fact, is supposed to promote a nucleophilic attack on dioxygen thus forming a dioxogold intermediate which acts as a bridge for the two-electron transfer from glucose to O_2 [26].

To get further insight into the molecular mechanism, we proceeded evaluating the progressive poisoning of Au/C catalyst during glucose aerobic oxidation [31]. Four probe molecules displaying different soft/hard nucleophilic properties were employed for the tests (thiocyanate, cyanide, cysteine and thiourea). The observed deactivation trend order was crucial. Whereas thiocyanate resulted to be the most powerful in inhibiting the catalytic activity of gold catalyst, the weaker one was thiourea, while cyanide and cysteine presented comparable poisoning effect. Considering the different hard/soft nucleophilic properties of the probe molecules, as well as OH^- promoting role, we concluded that the dioxygen reduction step is markedly affected by the nature of nucleophiles. Accordingly, a hard nucleophile, such as OH^-, seems to retain or even enhance the original catalytic effect since it

prevents the metal from back-donation to the Lewis base. On the contrary, the π back-bonding ability of soft nucleophiles, such as thiocyanate, depresses gold particle catalytic ability because able to withdraw the electron density from the metal thus inhibiting O_2 reduction. Furthermore the overall deactivation kinetics, following an exponential law for all the probe molecules, suggested a long-range interaction between gold and nucleophile thus affecting the entire metal nanoparticle. This might be due to electronic factors overlapping the simple space shielding of active sites (Scheme 1) [31, 37].



Scheme 1 Suggested mechanism for dioxygen activation in gold catalysed oxidation of glucose. Effect of softness and hardness of nucleophiles on gold nanoparticle.

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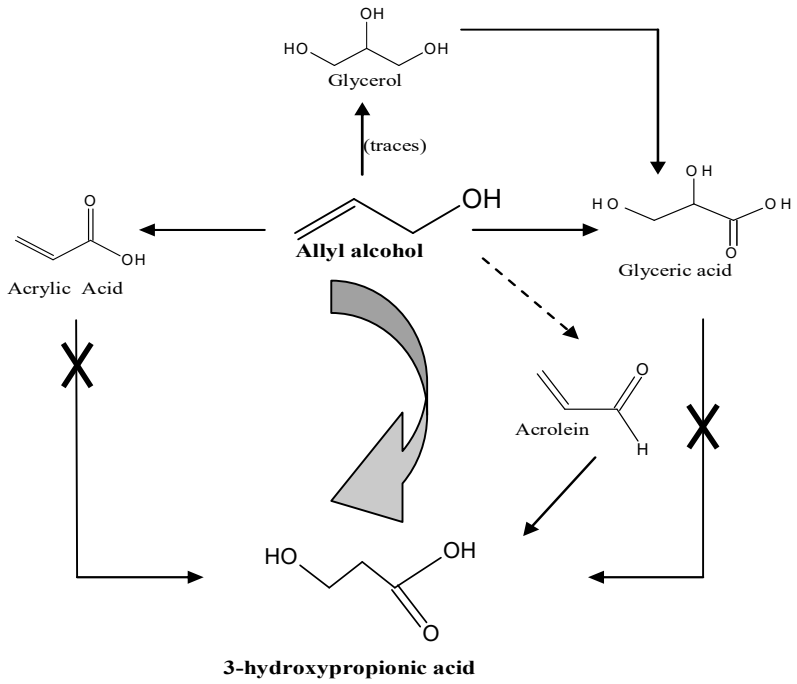
2.2 Allyl alcohol aerobic oxidation

According to a report on top value-added chemicals from biomass presented in 2004 by the Pacific Northwest National Laboratory (US Department of Energy), 3-hydroxypropionic acid (3-HPA) occupies the third position among the twelve most strategic building block chemicals potentially produced from biomass and involved in the manufacture of high performance polymers [51]. The selective oxidation of allyl alcohol, in principle coming from the dehydration of waste glycerol from biodiesel, might offer a renewable green pathway to 3-HPA as we actually found by a lucky case of serendipity. Reacting allyl alcohol in aqueous alkali solution with dioxygen and supported gold catalyst (Au/C or Au/TiO_2), we aimed at achieving acrylate and, after acidification, acrylic acid. Surprisingly, a slow oxidation took place leading to the expected acrylate, along with small amounts of glycerate and, mostly, 3-hydroxypropionate. Properly tuning the experimental conditions ([allyl alcohol] = 1M, pO_2 = 3 atm, allyl alcohol/gold molar ratio = 4000, NaOH/allyl acohol = 3 and T = 323 K) we could optimized 3-hydroxypropionate production finally reaching 79% yield at 100% conversion after one day reaction by Au/C catalysis [32]. We wondered what it might be a possible pathway to 3-HPA. The most reasonable mechanism included acrolein as the intermediate undergoing a Michael-type addition of water to produce 3-HPA as reported in Scheme 2.



Scheme 2. Allyl alcohol oxidation to 3-hydroxypropionic acid by Au/C catalysis: suggested pathway

Another key issue was related to the catalyst reusability, since Au/C underwent selectivity loss to 3-HPA after just the second recycling run. As bimetallic formulations were found to enhance the overall performance and durability of gold catalysts in numerous selective oxidations [29, 38], we decided to adopt this strategy to overcome the problem of selectivity loss. By alloying gold with a second metal (namely, Pt, Pd, Cu and Ag) supported on X40S carbon, we were able to boost conversion, selectivity and life-time of the catalyst [35]. The second metal was added as 1 mol% of the gold concentration and the total amount of the metals was 0.3 weight % of carbon X40S. A notable performance was reached with $Au_{99}Cu_1/C$ which allowed to reach the total conversion retention with a modest selectivity loss from 95.1% (1st run) to 78.3% (4th run). It is surprising that the presence of such a dilute second metal can be so effective in enhancing the catalytic performance of gold. Initially we assumed that copper could play a role in stabilizing the nanoparticles size. STEM analyses performed on fresh and used catalysts rejected such a hypothesis, due to definite signs of metal nanoparticles sintering after use. More likely the low redox potential of copper and, hence, the consequent electronic modifications influencing gold nanoparticles, might be involved in promoting the final catalytic performance despite NPs sintering [35].

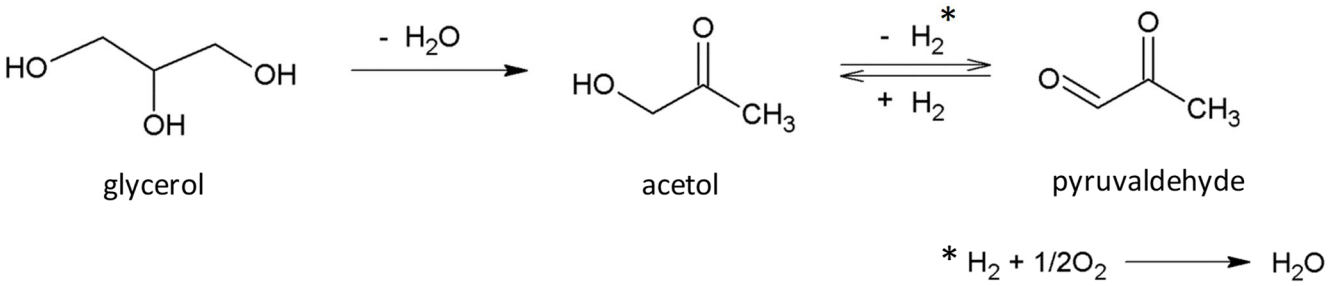
3. Selective oxidation and oxidehydration in gaseous phase by gold catalysis

3.1 Aerobic oxidation of benzyl alcohol

Responsible for the pleasant odor of natural bitter almond oil, benzaldehyde is widely employed in food and cosmetic industry mostly derived from synthetic manufacture. One of the most effective synthetic routes is the oxidation of benzyl alcohol performed with plenty of procedures and catalysts [29, 38, 52-55]. Most of them are carried out in liquid phase leading to benzaldehyde with yields above 95% but, unfortunately, often followed by easy autoxidation to form benzoic acid. A big concern in selective oxidations is just to prevent over-oxidation and stop the reaction at an intermediate stage. This is particularly true in the aerobic oxidation of alcohols to the corresponding aldehydes, since they represent highly desired chemicals especially in pharmaceutics, cosmetics and food industry. Although it is well known that benzaldehyde spontaneously undergoes autoxidation to benzoic acid upon exposure to air at ambient temperature, conducting benzyl alcohol oxidation in alkaline aqueous phase, as requested by gold catalysis, may facilitate this phenomenon during reaction [19, 28, 29]. A strategy to increase selectivity towards benzaldehyde, meanwhile retaining high catalytic activity, is to perform the reaction in gaseous phase. Rossi's first study on gold-catalytic oxidation of benzyl alcohol in gaseous phase led to outstanding selectivity to benzaldehyde but not as much in terms of conversion (selectivity > 99.5% at 50% conversion and T = 523 K; 98% selectivity at 75% conversion and T = 553 K) [19]. Aiming to increase conversion with selectivity retention, gold and copper supported on silica catalysts were prepared as mono- and bimetallic formulations by the incipient wetness method [19, 28]. The series 1%wt Au/SiO_2 and 1%wt Au–Cu/SiO_2 catalysts with different Au/Cu ratio by weight was then tested in the aerobic oxidation of benzyl alcohol employing a fixed-bed vertical glass reactor fitted with a frit carrying the catalyst and provided with an electronically controlled furnace [28]. The experimental thermal range (T = 523-623 K) was selected according to preliminary tests on the reaction feasibility. If on the one hand no benzyl alcohol oxidation was observed at T < 523 K, on the other hand the product underwent degradation with coking at temperature above 623 K, but in between the desired goal was finally reached. The remarkable 99% selectivity to benzaldehyde at 98% conversion highlighted the key role played by gold as well as a synergistic effect between gold and copper. Such a catalytic performance was yielded with the bimetallic Au/Cu = 4 wt/wt formulation (1%wt 4Au–1Cu/SiO_2 catalyst) at a relatively mild temperature (533 K). These achievements might open the door to potential applications in perfumery, where benzaldehyde at high purity grade from synthetic manufacture is always welcome [28].

3.2 Oxidehydration of glycerol

The necessity to find eco-friendly alternatives to petroleum derivatives prompts either academia or industry to search for potential starting materials in biomass. The biodiesel synthesis is one of the most promising answers being a fuel of mono-alkyl esters of long chain fatty acids achieved by *transesterification reaction* of a vegetable oil or animal fat with an alcohol [56]. The increasing overproduction of glycerol, the main by-product of biodiesel synthesis, represents however the other side of the coin. Scientists are now asked to find effective methods for converting glycerol into valuable chemicals such as propylene glycol, acetol, acrolein and pyruvaldehyde commonly yielded from fossil resources. Whereas liquid-phase catalysis by transition metals (i.e. Au, Pt, Pd, Cu, Ni, Ru) supported on different materials (i.e. Al_2O_3, SiO_2, TiO_2, C) seems to offer valid solutions in plenty of cases, some drawbacks still require to be addressed [57-62]. Gaseous-phase research in this area came out later [63-69] but rapidly gained interest since the successful yield of acrolein by glycerol catalytic dehydration [63-65]. Hydroxyacetone (acetol) is another strategic chemical coming from glycerol dehydration, due to its wide employment in food industry, as well as in textile industry and organic synthesis. Acetol, in fact, is a platform molecule used to promote a variety of reactions including dehydration, hydrogenation/dehydrogenation, oxidation and polymerization. Regarding dehydrogenation, methyl glyoxal (pyruvaldehyde) is particularly strategic because can serve as an intermediate towards lactic acid employed in the production of acrylates and biodegradable/biocompatible polymers [69]. Achieving pyruvaldehyde by gaseous-phase conversion of glycerol has been so far scarcely investigated [70, 71]. Recently we presented a viable route for dictating selectivity towards acetol or pyruvaldehyde by simply tuning the experimental conditions in the gaseous-phase conversion of glycerol while retaining the same catalytic system (Scheme 3) [72].



Scheme 3. Oxidehydration of glycerol to pyruvaldehyde

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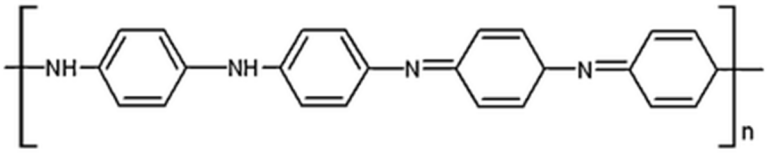
Gold- and copper-based catalysts, including bimetallic formulations, were prepared by incipient wetness impregnation method on γ-alumina. A continuous-flow fixed-bed vertical glass reactor at room pressure and thermal range 523-573 K served as the experimental apparatus. Selectivity could be dictated to acetol (sel. 72%) at 87% conversion at 573 K when adding H_2 to the carrier N_2, or towards pyruvaldehyde (sel. 79%) at 92% conversion with addition of O_2 to N_2 at 523 K. Most important, the catalytic system displaying these best performances was always 1%wt Au/Al_2O_3 [72]. Such relatively mild conditions not only allow for energy savings with respect to other reported procedures, but also for catalyst stability due to its facile regeneration after use. Furthermore, the low metal loading in the catalyst (1% wt) along with its small amount required for each test (0.1 g catalyst) make this procedure economically sustainable thereby offering a viable route for glycerol valorisation.

4. Oxidative polymerization of aniline by gold catalysis

Polyaniline (PANI) belongs to the organic conductive polymers (Scheme 4).



Scheme 4. Polyaniline

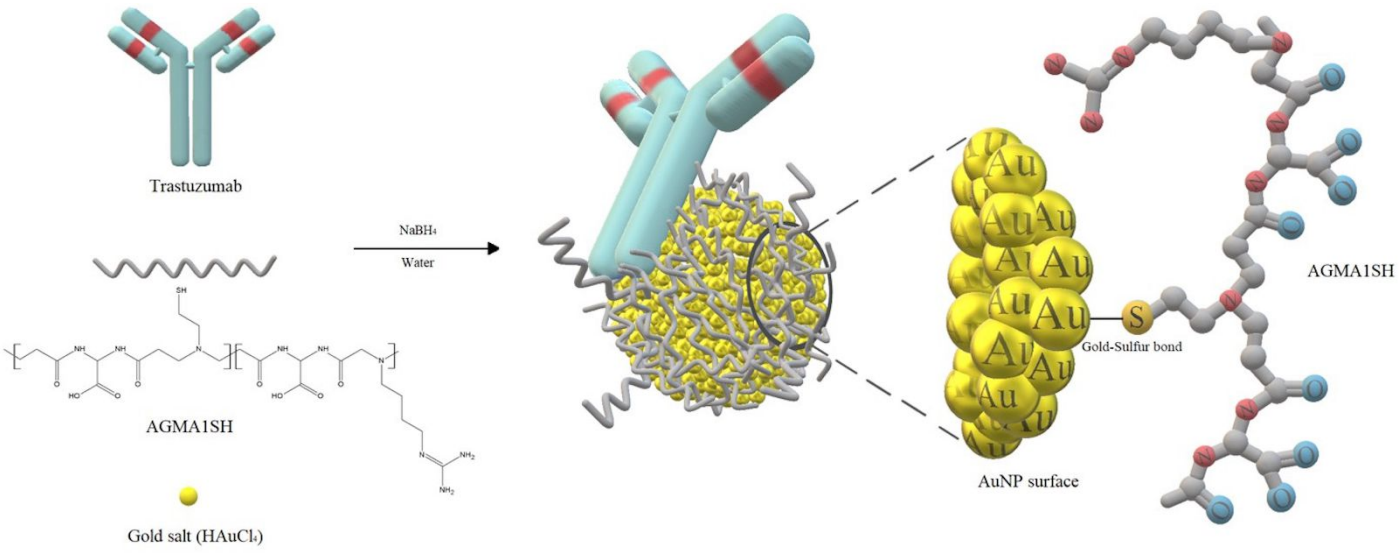
This appealing family of polymeric materials displays eclectic electronic characteristics in between metals and semiconductors, associated with the typical mechanical properties of organic macromolecules. A burgeoning interest has emerged since the end of 1970s when polyacetylene, another important conductive polymer, was successfully synthesized. PANI has drawn particular attention due to its stability in air and tuneable conductivity [30, 33, 36]. Polyaniline conductivity originates from both oxidation state of the material and acidic doping. Moreover the utmost conductivity is reached when PANI is in its *emeraldine* form, this means equal numbers of oxidized and reduced units with one proton doping every two units. The morphology of the conductive polymers is another fundamental factor affecting the final chemico-physical properties. Films, hollow spheres, nanoparticles and many other geometries are now available to be employed as multifaceted materials in different application areas ranging from electronics to biotechnology [73].

Polyaniline (PANI) is commonly achieved from the monomer aniline through oxidative coupling to its dimer, *N*-(4-aminophenyl)aniline, employing strong oxidants in stoichiometric amounts as $(NH_4)_2S_2O_8$ or $Na_2S_2O_8$ but even $K_2Cr_2O_7$ and KIO_3. However, performing the reaction under aqueous acidic conditions as requested, large amount of by-product is delivered as well (i.e. H_2SO_4 when using peroxydisulfate). This represents a big issue due to current environmental restrictions. On the other hand, even high oxidation-state metals do not offer a proper solution. A viable 'greener' pathway may be provided by catalysis which allows to substitute the polluting stoichiometric oxidants with the eco-friendly dioxygen and hydrogen peroxide [30, 33, 36]. Inspired by our positive experience in catalysed-oxidation reactions by gold, we decided to enter this route by employing different gold-based nanoparticles unsupported or supported on carbon and titania. No oxidative polymerization of aniline was observed with all the prepared catalytic systems under a slight oxygen pressure (3 atm) at ambient temperature. Conversely, by using hydrogen peroxide as an alternative oxidant, a catalytic effect was detected with colloidal gold although extremely modest (typically 4–5% yield). No product was isolated without any catalyst and no benefit emerged by employing H_2O_2 in excess. However the yield could be improved by increasing gold amount in the range Au : aniline = 0.001–0.004 (molar ratio) thereby leading to 27% yield after 1 day reaction [30, 36]. Previously we have discussed about the short lifetime typical of unsupported nanoparticles and, hence, of colloidal gold (Section 2.1). This might explain the aforementioned modest conversion of aniline. In order to confirm such a hypothesis, our next step was to carry out the oxidative polymerization with supported gold nanoparticles (0.5%wt Au/C, 1%wt Au/TiO_2), under the same experimental conditions ([aniline] = 0.05 M, [HCl] = 0.025 M, T = 293 K, t = 1 day, H_2O_2/aniline = 1 molar ratio). Actually this was a winning strategy. Supporting gold on P25 titania was particularly effective since 70% yield was achieved, while 0.5%wt Au/C led to a scarce 12% yield. A powerful synergistic effect between gold and titania clearly emerged, furtherly confirmed by blank tests. Accordingly, whereas unloaded carbon resulted to be inert in aniline polymerization with hydrogen peroxide, P25 titania itself catalyzed the partial oxidation of aniline to soluble dark oligomers. Anyway, no long-chain polymer was produced without the presence of gold. Moreover, FT-IR, UV–vis and XRD analyses always identified PANI as emeraldine salt, the conductive form of polyaniline. Conductivity measurements performed with a standard conductivity cell (CON-H Material Mates) on PANI by 1%wt Au/TiO_2 catalysis registered the typical values around 1.5×10^{-1} S cm^{-1} obtained through other polymerization methods [30, 36]. Regarding the morphology, transmission electron microscopy (TEM) and scanning electron microscopy (SEM) showed the prevalence of PANI in nanospheres of 44-160 nm for both the catalysts.

5. Gold in biomedicine

5.1 Extra-small gold nanoparticles for breast cancer therapy

Among the most invasive and common types of cancer in women, breast tumor certainly holds the first position [74]. A burgeoning request for novel and efficient diagnostic medical tools stimulates scientists to find valid alternatives to the traditional ones often displaying adverse side-effects. Trastuzumab (Herceptin^{TM}) is currently the most effective drug in breast cancer therapy but its delivery requires urgent improvement. Engineered delivery systems based on gold nanoparticles (AuNPs) seem to be elective candidates to the scope. Gold in nanometric scale, in fact, is already successfully employed in biomedicine, including as contrast and photothermal agent for computed tomography (CT) and tumor photothermal ablation [75]. Furthermore, AuNPs display multifaceted chemico-physical properties spanning the broader visible to near-IR and are generally gifted with low toxicity, good stability, easy synthesis and facile conjugation with cancer-specific biomolecules [76]. Crucial factors in affecting physico-chemical properties in nanoparticles are size, shape, surface charge and surface coating. These could markedly change the way particles are recognized, processed and excreted by the body [76, 77]. Despite the widespread interest surrounding gold, some drawbacks still limit its clinical translation [78]. In order to overcome such limits, different biodegradable polymers were tested for assembling and coating gold nanoparticles clusters. In particular, linear polyamidoamines (PAAs) have recently emerged as promising tools for drugs due to their ease of formulation and biodegradability [79]. Among PAAs, the nicknamed AGMA1 can be used as a potential non-viral, non-toxic and efficient vector for the intracellular delivery of siRNA and DNA. Fascinated by this new frontier in gold applications, some of us recently established a network for developing more efficient AuNPs for therapeutic use. By conveying different areas of expertise, we developed a nanogold platform for the link with Trastuzumab monoclonal antibody for HER2-positive breast cancer targeting [80]. Accordingly AGMA1-SH, a biocompatible and biodegradable polyamidoamine bearing 20%mol SH pendants, served as a stabilizer for differently sized AuNPs (2.5, 3.5 and 5 nm in Au core) decorated with Trastuzumab (Scheme 5).



Scheme 5. Representation of AuNPs coated with AGMA1-SH and Trastuzumab

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The final hydrodynamic diameters were selected on the basis of cellular uptake feasibility. The AuNPs synthetic method followed an innovative 'green' protocol introducing significant advantages with respect to other routes currently adopted. First, the use of conventional stabilizers often cytotoxic could be avoided by tailoring thiol-functionalized biocompatible AGMA1 thanks to the renowned Au-S soft-soft interactions [31]. This guaranteed long-term stability of the hybrid nanomaterial. Worth noting, sulfur is even a component of Trastuzumab itself, thereby boosting the protective effect on gold-based composite. Second, the employment of an instant reducing reagent ($NaBH_4$) led to homogeneously sized and tailored 'on demand' gold nanoparticles by simply tuning $HAuCl_4$ concentration. Since AGMA1 was shown to be readily internalized in cells, one can expect an improvement in AuNPs cellular uptake as well [81]. In our work we systematically studied *in vitro* the impact of AuNPs size decorated with AGMA1-SH and Trastuzumab on the interactions with both breast cancer cells and healthy cells [80]. The cytotoxicity and cellular uptake of all nanoparticles were monitored by MTT and ICP-MS tests. Western blot analysis and cellular uptake studies by means of specific endocytosis inhibitors were further performed to evaluate the interaction with and mechanism of internalization of the nanogold scaffold by SKBR-3 target cells. The tests displayed a much higher cell internalization ability and cytotoxicity for the composite with the highest hydrodynamic diameter (5 nm in Au core) and positive charge than the smaller ones (2.5 and 3.5 nm in Au core). Moreover, the assays against Trastuzumab target cells (SKBR-3) demonstrated that the cytotoxicity of the largest scaffold was due to pro-apoptotic protein increase, anti-apoptotic

components decrease, survival-proliferation pathways downregulation and uptaking by cells via the activation of the typical receptor-mediated endocytosis [80]. Worthy to be underlined, these findings even suggest the fundamental role played by size control at the AuNPs when engineering molecular-cancer delivery systems. Once tested *in vivo*, the small Au core component (ranging from 2.5 to 5 nm) is expected to be solely extruded by the urinary system considering the AGMA1 biodegradability.

6. Conclusions

Discovering the versatile catalytic power of gold has signed a milestone in chemistry, thereby paving the way to novel eco-friendly routes towards strategic feedstocks. Moreover, gold has recently proven to be the ideal candidate in cancer therapy thus expanding its eclectic performances to biomedicine. The present mini-review is to commemorate prof. Renato Ugo introducing a brief overview of our research on gold conducted in the same department at Milan University where he worked as a beloved professor of Inorganic Chemistry and eminent scientist. The aim is to provide a short outline of our main contributions to gold-based heterogeneous catalysis with a look at biomedicine. Despite researchers are still focusing their efforts on the development of tomorrow's gold catalysts to tackle significant environmental and economic issues, the great versatility and effectiveness of gold clearly emerged in plenty of different applications as herein reported. The way from the discovery to the commercialization of gold-based catalysts has been difficult but the time has now finally arrived. In 2015, catalyst manufacturer Johnson Matthey officially released its novel developed gold catalyst with the brand name Pricat MFC for the manufacture of vinyl chloride monomer (VCM), the monomer for polyvinyl chloride (PVC, the world's third largest polymer) [82]. The once-believed inert metal has eventually found its first large-scale application in the chemical industry, thus showing that the chemistry of gold is more than a promise.

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