



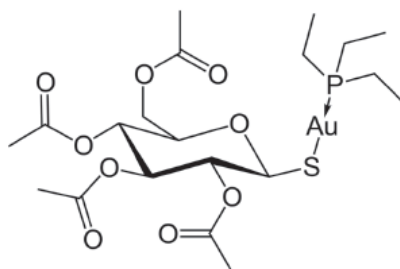
# Nanogold's chemical revolution

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From a chemist's point of view, gold used to be a relatively unimportant element. A few compounds were known, and some had healing properties, but that was as far as it went. Today nanogold is a hot topic in laboratories around the world and is having an impact on the chemical industry. It is part of the movement to "green" the industry thanks to its remarkable catalytic ability. And it began in a rather low key way in a Japanese government laboratory 25 years ago.

For centuries, gold was seen as the never-changing metal of adornment and wealth. Chemists viewed it as the least reactive of the metals but some gold compounds were made and some even came to be used in the treatment of rheumatism.<sup>†</sup> In the modern era, gold therapy began in 1927 when gold sodium thiomalate (known as myocrisin) was discovered to relieve the symptoms of arthritis. Originally this had to be injected, but today there is an oral version, with fewer side effects, called auranofin (trade name Ridaura) (Scheme 1) which was approved by the US Government's Food and Drugs Administration in 1985. The dose is 6 mg per day and this delivers 2 mg of gold, with around 0.5 mg being absorbed by the patient.



Scheme 1. The chemical formula of auranofin.

Admirable as this use of gold is, it pales in comparison to the way that nanogold is transforming academic and industrial chemistry around the world. As a catalyst, nanogold is

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<sup>†</sup> Note that Paracelsus describes the preparation and therapeutic use (e.g., against leprosy) of colloidal gold (aurum potable). See, *inter alia*, T. Paracelsus, *Philosophiae et medicinae utriusque universae*, pp. 36, 47. Basel: Peter Perna (1568).

greening the world's chemical industry, by making it possible to reduce energy input and increase product output. An example is the manufacture of vinyl acetate monomer (VAM), the precursor to the polyvinyls used as adhesives, fibres and paints. The chemical company INEOS has a plant at Hull, England, which produces 300,000 tonnes of VAM a year and it relies on a gold-based catalyst developed by Johnson Matthey.

Nanogold is not new. It has been used for centuries to colour glass and decorate ceramics. It was made by dissolving gold in *aqua regia* ("King of Waters") which is a mixture of concentrated nitric and hydrochloric acids. When tin foil was added to such a solution, a brilliant purple precipitate slowly formed and became known as Purple of Cassius, named after Andreas Cassius of Potsdam in Germany who revealed the method of making it in 1685. But what exactly was it? In the 1800s, chemists were puzzled because analysis proved it was just pure gold. It fell to the Viennese chemist and Nobel prizewinner, Richard Zsigmondy, to come up with the answer as he researched colloids. He showed how differently sized particles produce a range of colours by their selective interaction with visible light. Interesting, but of little use as far as chemists were concerned.

### Golden dawn

And then things suddenly changed in 1985, triggered by the remarkable discovery of Masatake Haruta, of Japan's Government Industrial Research Institute in Osaka. At a conference in the USA he revealed that nanogold would catalyse the conversion of CO to CO<sub>2</sub>.<sup>1</sup> In 1987 he wrote a full paper on his ground-breaking work, and that work has been cited more than a thousand times.<sup>2</sup> Haruta, now a professor at Tokyo Metropolitan University, is seen as the father of modern nanogold chemistry.

Nanogold will convert CO to CO<sub>2</sub> at temperatures down to -70 °C and as such it is incorporated into safety masks where exposure to the toxic monoxide is a threat. It may one day even be part of vehicle catalytic converters to effect the same transformation. A Californian company, Nanostellar, has a product called NS Gold, which might well join the traditional metals of platinum and palladium used for this purpose.

Other commercial nanogold catalysts are being produced. 3M has developed NanAucat which is nanogold on a carbon substrate, and Strem Chemicals Inc. has AUROLite, which consists of 1% gold on titanium dioxide.

Haruta showed that the catalytic activity of nanogold depends on cluster size, method of preparation and support material.<sup>3</sup> His various methods of making nanogold, using wet or dry processes, are widely used. In some cases they produce clusters with fewer than 20 atoms but 200-atom clusters are the norm. He tested various particle sizes, some as large as 30 nm, but it was only the smaller ones that caused the predissociation of O<sub>2</sub> to O that was necessary for the CO reaction.

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<sup>1</sup> M. Haruta and H. Sano, "Composite oxide catalysis containing silver or gold for the low-temperature oxidation of hydrogen and carbon-monoxide". *Abstracts of Papers of the American Chemical Society* **189** (1985) 171.

<sup>2</sup> M. Haruta et al., "Novel gold catalysts for the oxidation of carbon monoxide at a temperature far below 0 degrees C". *Chemistry Letters* **2** (1987) 405-408.

<sup>3</sup> M. Haruta, "Size- and support-dependency in the catalysis of gold". *Catalysis Today* **36** (1997) 153-166.

One of the world's leading, and most cited, gold chemists is Graham Hutchings of the Catalysis Centre of Cardiff University, Wales.<sup>4</sup> Hutchings has greatly extended the range of reactions catalysed by gold. In 2002 he demonstrated gold's capability with the rapid synthesis of hydrogen peroxide, H<sub>2</sub>O<sub>2</sub>, from hydrogen and oxygen, and without the formation of water as a by-product. A more recent paper of his has been on the oxidation of cyclo-octene by means of a nanogold catalyst supported on graphite and he has proved this can be used and re-used many times. Moreover, the process does not require a solvent.<sup>5</sup>

More recently, the Cardiff group has looked into the issue of removal of the ligands attached to nanogold, which are necessary to stabilize it during its formation. After the nanoparticles have been deposited on a substrate these ligands are no longer required and in effect they reduce the catalytic activity. Removing them has been done by crude methods such as heating, which reduced the catalytic ability. Hutchings has shown that the ligands can be extracted by aqueous means and without affecting the morphology of the nanoparticles.<sup>6</sup>

### Hydrogen economy

One curious feature of nanogold is its ability to generate hydrogen gas. A group headed by Hermenegildo Garcia of the University of Valencia, Spain, reports that nanogold particles on a titanium dioxide support can decompose water to its elements when exposed to visible light.<sup>7</sup> The most active catalyst contained 0.2% w/w gold and gave yields of 7.5% H<sub>2</sub> and 5.0% O<sub>2</sub> when exposed to light of wavelength 560 nm (green). Further work by Garcia's group has shown that gold will perform the Sonogashira coupling reaction just as well as the metal catalysts normally used.<sup>8</sup> This reaction forms carbon-carbon bonds under mild conditions and has proved particularly useful in the synthesis of new pharmaceuticals.

Generating hydrogen from ethanol can also be catalysed by nanogold on titanium dioxide, and that has been the focus of research at the University of Aberdeen by Russell Howe. He asked what size of nanogold particles and which form of titanium dioxide would perform best. The answer was that those gold particles in the range 3–30 nm were most active, and that the much rarer mineral form of titanium dioxide known as anatase was a hundred times better than the rutile form.<sup>9</sup>

Gold/palladium nanoparticles, trapped in a metal-organic framework known as MIL-101 (MIL refers to materials from the Institut Lavoisier) have been found to be highly active for the conversion of formic acid to hydrogen of a quality convenient for hydrogen storage. Moreover,

<sup>4</sup> A.S.K. Hashmi and G.J. Hutchings, "Gold catalysis". *Angewandte Chemie International Edition* **45** (2006) 7896–7936.

<sup>5</sup> S. Bawaket et al., "Solvent-free selective epoxidation of cyclooctene using catalysts: an investigation of catalyst re-use". *Green Chemistry* **13** (2010) 127–134.

<sup>6</sup> J.A. Lopez-Sanchez et al., "Facile removal of stabilizer ligands from supported gold nanoparticles". *Nature Chemistry* **3** (2011) 551–556.

<sup>7</sup> C.G. Silva et al., "Influence of excitation wavelength (UV or visible light) on the photocatalytic activity of titania containing gold nanoparticles for the generation of hydrogen or oxygen from water". *J. Am. Chem. Soc.* **133** (2011) 595–602.

<sup>8</sup> A. Corma et al., "Gold catalyzes the Sonogashira coupling reaction without the requirement of palladium". *Chem. Commun.* **47** (2011) 1446–448.

<sup>9</sup> M. Murdoch et al., "The effect of gold loading and particle size on photocatalytic hydrogen production from ethanol over Au/TiO<sub>2</sub> nanoparticles". *Nature Chemistry* **3** (2011) 489–492.

the gold–palladium nanoparticles were able to tolerate CO without their catalytic activity being compromised as tends to happen with other noble metals.<sup>10</sup>

### Golden reactions

A combination of gold+silver nanoparticles also make good catalysts as shown by the work of Qiang Xu of the National Institute of Advanced Industrial Science and Technology (AIST) at Osaka, Japan. He refers to the catalyst as Au@Ag core–shell and these are immobilized on a metal–organic framework produced by a sequence of deposition and reduction methods. The resulting material can be fine-tuned to achieve catalytic abilities exceeding those of other types of catalyst.<sup>11</sup>

Gold catalysts for greening the chemical industry are extolled in the paper by Shu Kobayashi of the University of Tokyo. He reports the synthesis of commercially important amides from alcohols and amines and using oxygen as an oxidant.<sup>12</sup> The paper not only deals with gold as the catalyst, but also its combinations with iron, nickel and cobalt. Recently, Kobayashi has published a similar paper reporting the formation of imines from alcohols and amines, with oxygen as an oxidant.<sup>13</sup> In this case the catalyst was gold and palladium and it was embedded in a polymer with carbon black added to act as a stabilizer—and it was reusable, a feature that might one day be of commercial significance.

Avelino Corma of the Instituto de Tecnología Química at Valencia, Spain, reports that nanogold, when supported on a substrate of titanium oxide or iron(III) oxide, will boost the reaction of nitroarenes with hydrogen gas.<sup>14</sup> For example, 3-nitrostyrene undergoes 99% conversion and 96% selectivity to 3-vinylaniline and without the formation of the hydroxylamine styrene as a by-product. This could have commercial significance.

### Health-giving gold

In 1998, Professor Chad Mirkin of Northwestern University, Evanston, Illinois, showed it was possible using nanogold to identify the DNA of disease pathogens at extremely low concentrations, thereby aiding rapid diagnosis.<sup>15</sup> His method is based on completing an electrical circuit between two electrodes 20 micrometres apart, which can only be done by a particular strand of DNA interacting with a so-called capture strand. The capture strand is

<sup>10</sup> X. Gu et al., “Synergistic catalysis of metal-organic framework-immobilized Au-Pd nanoparticles in dehydrogenation of formic acid for chemical hydrogen storage”. *J. Am. Chem. Soc.* **133** (2011) 11822–11825.

<sup>11</sup> H.-L. Jiang et al., “Synergistic catalysis of Au@Ag core-shell nanoparticles stabilized on metal-organic framework”, *J. Am. Chem. Soc.* **133** (2011) 1304–1306.

<sup>12</sup> J.-F. Soulé et al., “Powerful amide synthesis from alcohols and amines under aerobic conditions catalysed by gold or gold/iron, -nickel or -cobalt nanoparticles”. *J. Am. Chem. Soc.* **133** (2011) 18550–18553.

<sup>13</sup> J.-F. Soulé et al., “Selective imine formation from alcohols and amines catalyzed by polymer incarcerated gold/platinum alloy nanoparticles with molecular oxygen as an oxidant”. *Chemical Commun.* **49** (2013) 355–357.

<sup>14</sup> G. Abdessamad et al., “Gold-catalyzed synthesis of aromatic azo compounds from anilines and nitoraromatics”. *Science* **332** (2008) 1661–1664.

<sup>15</sup> J.J. Storhoff et al., “One-pot colorimetric differentiations of polynucleotides with single base imperfections using gold nanoparticle probes”. *J. Am. Chem. Soc.* **120** (1998) 1959–1964.

designed to have just the right sequence of bases to attract DNA from the disease microbe. 3'- and 5'-alkanethiololignucleotides are attached to gold nanoparticles of around 13 nm diameter and these are used to hybridize with the unknown DNA target resulting in the formation of extended polymeric aggregates and producing a colour change in solution. TLC can then identify the disease DNA, or it can be done by means of the aggregates completing a circuit between two electrodes.

The Mirkin method offers a means of analysis that is a hundred times quicker than conventional DNA analysis techniques, which rely on the polymerase chain reaction (PCR) to replicate the DNA to a level at which it can be identified. Such is the interest in Mirkin's work that some of his systems have already been commercialized and are being evaluated at major US hospitals. This technique may one day prolong millions of lives, and the kit is already available from the Illinois-based company Nanosphere, whose diagnostic system is called Verigene.

Gold can also be used in other kinds of medical screening. Professor Mostafa El-Sayed at the Laser Dynamics Laboratory of the Georgia Institute of Technology, Atlanta, in collaboration with his son Ivan El-Sayed of the University of California at San Francisco, has developed simple and unique techniques for cancer imaging and photothermal therapy based on gold nanorods as contrast agents.<sup>16</sup>

Other gold-based therapies are showing promise as cancer treatments, in which the disease is attacked with gold-encrusted particles in the shapes of spheres (nanoshells) and bullets (nanorods), the former already approved by the FDA in the USA. The nanoshells are built round a core of silica, and are produced commercially as Aurolase. They are injected into the patient and penetrate and accumulate in tumours by virtue of the fact that cancer cells have much weaker walls than healthy cells and are more easily penetrated. When the tumour is then exposed to near infrared radiation (NIR), directed along an optic fibre probe, the nano-shells absorb so much energy the gold melts and the tumour is cooked to destruction.

Alternatively, gold nanorods can be grown from a dilute solution of  $\text{HAuCl}_4$  after seeding the solution with gold nanoparticles. These are incorporated into certain monoclonal antibodies that bind preferentially to the surface of cancer cells. When blasted with NIR, the nanorods eject their atoms at high velocity into the cancer cell and kill it.

Pregnancy kits contain nanogold. They rely on the detection of a hormone called human chorionic gonadotropin (hCG) that a woman's body releases when she becomes pregnant and which is excreted via her urine. In the test, a sample of urine is put on the end of an immunoassay strip along which it will move by capillary action until it encounters monoclonal antibodies specifically designed to interact with hCG, and which have been attached to gold nanoparticles. When that happens, the particles cluster together to create much larger units. They now move along the strip until they come up against a filter that stops them and turns the traditional red of colloidal gold. If there is no hCG present in the urine then the gold nanoparticles don't coagulate and so can pass through the first filter only to be caught on a second barrier. This now shows red, indicating a successful test but a negative result. It will also show red even if the pregnancy indicator strip has turned red, because some nanogold particles don't pick up the hCG and so can pass through the first barrier.

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<sup>16</sup> X. Huang et al., "Cancer cell imaging and photothermal therapy in the near-infrared regions by using gold nanorods". *J. Am. Chem. Soc.* **128** (2006) 2115–2120.

## **Gold prospects**

The future of gold as a catalyst could hardly have been foreseen when Haruta began his research more than 25 years ago. Today there are new avenues opening up that will see gold become a part of everyday life. Nanogold particles display antimicrobial action and treatments based on them will begin to appear in the battle against bacteria that have become resistant to conventional drugs. Gold-based anti-cancer technology is being developed by start-up companies. The greening of the chemical industry by the use of nanogold catalysts is already under way and improved catalytic converters for vehicles will see this use as part of the struggle to reduce urban air pollution. It might also play a part in fuel cells and solar cells. Furthermore, water pollution will be reduced by using nanogold to break down harmful organochlorines and pesticide traces in water supplies. Indeed by the end of this century gold will have vital roles in many areas of life and its use as bullion and for jewellery may well be very much a fringe activity.