Homogeneous Gold Catalysis through Relativistic Effects: Addition of Water to Propyne. *

Matthias Lein, A. Stephen K. Hashmi and Peter Schwerdtfeger†

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†Dr. Matthias Lein, Prof. Dr. Peter Schwerdtfeger, Center for Theoretical Chemistry and Physics, The New Zealand Institute for Advanced Study, Massey University Auckland, Private Bag 102904, North Shore City, 0745 Auckland, New Zealand; Prof. Dr. Stephen K. Hashmi, Organisch-Chemisches Institut, Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany.
For a long time, gold was considered to be catalytically rather inactive due to its "chemical inertness", but recent work has demonstrated that gold shows some unexpected and quite novel catalytic activities in both heterogeneous [1] and homogeneous systems [2–5, 7], with a number of potential commercial applications [8]. This has led to an immense increase in research activity in gold catalysis and has been termed the catalytic gold rush [9].

It has been speculated that the unusual catalytic activity in homogeneous gold catalysis is due to relativistic effects [10]. It is now well known and accepted that gold exhibits unusually large relativistic effects compared to its neighboring atoms in the periodic table, termed the gold maximum of relativistic effects [11, 12], which originates mainly from a very large direct relativistic valence 6s-shell contraction [13, 14]. This gives gold rather unique chemical and physical properties within the Group 11 elements of the periodic table. Reviews on this subject were recently given by Pyykkö [15] as well as our research group [14]. In this context we note that relativistic effects substantially stabilize the higher oxidation states +III and +V of gold [12, 16, 17], e.g. for the corresponding copper and silver compounds only the fluorides are known in the +III oxidation state. Nevertheless, beside this important fact it remains to be shown if the unusual catalytic activity of Au(III) is indeed due to relativistic effects.

In order to solve this important question, we investigated the intermolecular addition of oxygen-nucleophiles to alkynes (see Fig. 1), which is known for more than fifteen years now, [18, 19] and is part of the standard toolkit of organic synthesis [20–23]. This class of reactions has several advantages which makes it appealing for consideration in a theoretical study (see computational section). Firstly, the high yield under mild conditions indicates a clear thermodynamical preference for the products which enables a discussion solely on the basis of the energy differences on the potential energy hypersurface. Secondly, the high turnover numbers and turnover frequencies with a low catalyst loading of only 2 mol% indicates that the reaction is likely to
be catalyzed by a single catalyst molecule, which makes the search for the activated complexes feasible. Third, in the presence of water in the reaction mixture, the reaction yields the thermodynamically stable ketone, i.e. the addition product of water. In order to obtain the product of the addition of methanol solvent-molecules, i.e. the acetal, one has to work water-free. Markovnikov’s rule also applies in this case. Finally, one question that is often raised in the context of homogeneous gold catalysis concerns the speed of the reaction. In many cases where reactions can in principle be catalyzed by a number of transition metals, gold reacts much faster than its alternatives [5].

The addition of water to propyne is catalyzed by \( \text{AuCl}_3 \) and takes place in several steps as the overall calculated energy profile in Fig. 2 shows. Schröder and Schwarz showed that in the strictly bimolecular regime of the gas-phase ”kinetic and entropic restrictions are too large” for the reaction to proceed [6]. Here we show that solvent molecules dramatically change the catalytic cycle and, for the first time explain the mechanistic background of this important mainstay of organic synthesis.

In the first step of the catalytic cycle the gold moiety coordinates to the triple bond of the alkyne, thus occupying the last available coordination site of the Au(III) atom, leading to the well known square planar motif common for Au(III) complexes. The bonding situation of the alkyne changes dramatically upon coordination. The bond length of the formal triple bond lengthens from 1.21 Å in the free propyne to 1.32 Å. This change is a clear indication of the activation of the \( \equiv C \) bond through the gold catalyst. Furthermore, the linear structure of the free propyne is not retained in the \( \text{AuCl}_3 \) adduct. The terminal hydrogen atom is bent by 125.7° away from the coordinating gold compound (Au-C-H angle), and the methyl group is bent even stronger with a C-C-C angle of 138.9°. The planar arrangement of the carbon backbone is retained. This first step of the catalytic cycle is energetically favorable by -32.3 kcal/mol.

In the second step the other reactant enters the scene. A water molecule attaches itself to the activated complex, forming two hydrogen bonds. One relatively long hydrogen bond (2.41 Å) between a chlorine atom of the catalyst and the water molecule holds the reactant in place from one side while the second hydrogen bond between the terminal hydrogen of the alkyne and the water molecule clamps the reactant from the other side. The attachment of the water molecule to the activated complex is energetically favourable by -2.9 kcal/mol.

A second water molecule comes into play in the next step. This is a necessary requirement in order to bring the activation barriers down. The same mechanism, without the help of a second water molecule, suffers from activation energies more than 20 kcal/mol higher than shown in this investi-
gation. In the case of the second water molecule too, a network of hydrogen bonds to hold the reactants in place is formed. The formerly long hydrogen bond between a chlorine atom of the catalyst and the first molecule is now shortened to only 2.29 Å and a hydrogen bond between the two water molecules is formed. The length of this hydrogen bond is in the typical range for water-water hydrogen bonds with 1.81 Å. Because of the second water molecule’s steric needs no hydrogen bond can be formed with the terminal hydrogen atom of the alkyne. Instead a new hydrogen bond is formed with one of the hydrogen atoms of the terminal methyl group at the other end of the substrate molecule. This hydrogen bond is 2.15 Å long. The formation of this network of relatively weak interactions due to the introduction of a second water molecule leads to a stabilization by -5.0 kcal/mol.

The next step leads to the first transition state of this catalytic path. Surprisingly, most bond lengths do not change considerably. The hydrogen bonds that were present in the preceding step and which hold the two water molecules in place are basically the same. The hydrogen bond between the catalyst’s chlorine atom and the first water molecule is with 2.29 Å exactly the same length as it was before and the water-water hydrogen bond is only slightly elongated from 1.81 Å to 1.83 Å. The hydrogen bond between the second water molecule and the methyl group however is lengthened from 2.15 Å to 2.27 Å in the transition state. This is accompanied by a turning of the catalyst along the C-Au-Cl axis by 20°. This can be viewed as a relatively stiff hydrogen bonding network that is being directed along the reaction coordinate by the catalyst molecule. This stresses the fact that the catalyst does not only activate the triple-bond electronically, but acts as a directing agent that guides the necessary reactant molecules into the right position for reaction. This transition state is a mere 0.2 kcal/mol energetically above the preceding minimum.

Following the intrinsic reaction channel towards the product leads energetically downwards by -8.5 kcal/mol. The resulting structure shows the lead-in to the migration of the hydrogen atom from the oxygen atom of the second water molecule to the terminal carbon atom. In this minimum structure this hydrogen is clearly starting to dissociate - the distance to the oxygen atom of the second water molecule is 1.55 Å, while the distance to the oxygen atom of the first water molecule is only 1.01 Å. In this step the role of the first water molecule is redefined. In the beginning of the reaction it served as scaffolding to put the second water molecule in place through formation of a network of hydrogen bonds that connect the catalyst with the substrate through the reactant. In this later stage of the reaction the second water molecule also plays the role of the mediator, guiding the migration of the hydrogen atom from the oxygen atom of the enol to the terminal carbon atom.
to which the catalyst is attached. With the onset of the migration of the hydrogen atom come several subtle changes in the structure of the hydrogen bonding network that holds the mediating water molecule in place. Firstly, the hydrogen bond between the chlorine atom of the catalyst and the mediating water molecule shortens dramatically from 2.29 Å in the transition state to 1.71 Å in this structure, indicating a stronger association with the catalyst molecule. Furthermore, the corresponding bond between this hydrogen atom and the oxygen atom of the mediating water molecule is lengthened to 1.14 Å. This is, in fact, longer than the distance of the oxygen atom to the migrating hydrogen atom (1.01 Å). The distance between the gold atom of the catalyst and the terminal carbon atom of the substrate molecule is also shortened by 0.26 Å to 2.03 Å.

The following transition state is again very educt like, but the structural changes between the transition state and the preceding minimum are noticeable and subtle. First of all, the migrating hydrogen atom is completely abstracted from the enol-oxygen atom. The distance grows from 1.55 Å to 2.09 Å in the transition structure. At the same time, the bond between the enol-oxygen atom and the carbon atom of the now alkyl chain consolidates and the bond length is shortened slightly from 1.45 Å to 1.41 Å. The distance between the migrating hydrogen atom and the oxygen atom of the mediating water molecule shortens slightly to 0.99 Å, while at the same time the hydrogen bond to the chlorine atom of the catalyst contracts even further to 1.52 Å. This transition state is 1.3 kcal/mol higher in energy than the preceding minimum.

The intrinsic reaction channel leads energetically steeply downwards by -24.7 kcal/mol into the product valley. After the migration of the hydrogen atom is completed, the mediating water molecule looks for a suitable place, and the terminal methyl group seems to be a more favourable target than the terminal hydrogen atoms on the opposite side of the alkyl chain which the water molecule preferred in the beginning stages of the reaction mechanism. The water molecule forms two hydrogen bonds - one short hydrogen bond to the same chlorine atom which guided the water molecule through the catalytic cycle (1.29 Å), and a longer hydrogen bond with one of the hydrogen atoms of the terminal methyl group (2.23 Å). The product of this catalytic cycle is now obvious in this structure and the enol-form of acetone can easily be seen along with the catalyst and one water molecule in this minimum structure.

The last two steps of the catalytic cycle are endothermic by 4.2 kcal/mol and 25.1 kcal/mol respectively. These amounts of energy are needed to remove the remaining water molecule first and then the catalyst second. Note that the relatively high energetic cost for removing the catalyst molecule is
mitigated by the fact that the catalyst can immediately coordinate with another substrate molecule which brings it back to the start of the catalytic cycle. The total energetic balance of the reaction is $\Delta E = -42.7 \text{ kcal/mol}$ in the gas phase and $\Delta E = -36.5 \text{ kcal/mol}$ if the effects of a methanol solution are taken into account. Vibrational and thermal corrections to the energy of the solvated system lead to a free energy balance of $\Delta G = -25.3 \text{ kcal/mol}$ for the complete catalytic cycle.

We also note that the mechanism of a cis-addition proposed by Teles and co-workers [20] for the analogue Au(I) system is not reproduced in this study of the Au(III) catalytic cycle. It is indeed sterically impossible for the water molecule to attack the substrate in this fashion as the mediating water molecule acts as a spacer group which pushes the second water molecule into a $\text{trans}$ approach. It remains to be seen if our results represent a peculiarity of the water addition in the Au(III) case, or if our results can be generalized to Au(I) and Au(III) systems with a variety of oxygen-nucleophiles.

Another reaction that has to be considered in this context is the deactivation of the catalyst by a competing reagent in the reaction mixture. Water comes to mind since we already know that there are at least trace amounts of water present. This reaction is also shown in Fig [2]. Fortunately, we compute the deactivation of the catalyst through a water molecule to be only energetically favourable by $-23.1 \text{ kcal/mol}$ as opposed to $-28.4 \text{ kcal/mol}$ in the competing reaction of the catalyst with the substrate molecule (Table [1], reactions 2 and 3). Hence, a poisoning of the catalyst by water, which is not observed in the experiment, is also not predicted by theoretical consideration.

| Reaction | $\Delta E$ | $\Delta G$ |
|----------|------------|------------|
| 1 CH$_3$C≡CH + H$_2$O $\rightarrow$ CH$_3$COCH$_3$ | -36.5 | -25.3 |
| 2 a AuCl$_3$ + CH$_3$C≡CH $\rightarrow$ AuCl$_3$-H≡CCCH$_3$ | -28.4 | -14.3 (rel) |
| b AuCl$_3$ + CH$_3$C≡CH $\rightarrow$ AuCl$_3$-H≡CCCH$_3$ | -18.5 | -5.7 (non-rel) |
| 3 a AuCl$_3$ + H$_2$O $\rightarrow$ AuCl$_3$-H$_2$O | -23.1 | -10.1 (rel) |
| b AuCl$_3$ + H$_2$O $\rightarrow$ AuCl$_3$-H$_2$O | -13.7 | -2.2 (non-rel) |
| 4 a AuCl$_3$-HC≡CCH$_3$ $\rightarrow$ AuCl-H≡CCCH$_3$ + Cl$_2$ | 22.2 | 9.5 (rel) |
| b AuCl$_3$-HC≡CCH$_3$ $\rightarrow$ AuCl-H≡CCCH$_3$ + Cl$_2$ | 9.3 | -3.7 (non-rel) |
| 5 a AuCl$_3$-H$_2$O $\rightarrow$ AuCl-H$_2$O + Cl$_2$ | 30.4 | 19.2 (rel) |
| b AuCl$_3$-H$_2$O $\rightarrow$ AuCl-H$_2$O + Cl$_2$ | 5.3 | -6.0 (non-rel) |

Table 1: Reaction energies and free energies of all computed reactions including solvent effects. All values in kcal/mol.

An interesting question that we would like to address is the effect that relativity has on this catalytic cycle. In order to compare the relativistic and the non-relativistic case all computations were repeated with a non-relativistic gold atom and the results are shown in Fig[2] as well. The non-relativistic cycle is computed to be much shallower than its relativistic counterpart. This
indicates a weaker interaction of the non-relativistic gold atom with the substrate molecule but it does not change the nature of the path or the height of the reaction barriers significantly. However, a different picture emerges if one considers the dissociation of the activated complex into the corresponding Au(I) compound. It has been known that relativistic effects stabilise higher oxidation states in gold [16] and so this reaction lends itself for consideration in this study. In order to ascertain whether the Au(III) adducts are stable with respect to relativistic effects, the fragmentation reaction into the respective Au(I) compounds and dichlorine have been calculated (Fig 2 and Tab 1, reactions 4 and 5). The results of both calculations show, that the relativistic molecules are held together much more strongly than the non-relativistic molecules. The AuCl₃ adducts are less stable by roughly 10 kcal/mol in the non-relativistic case. But more importantly, if one adds the vibrational and thermal corrections to the energy in order to obtain the free energy of the dissociation reaction, one can see that in the relativistic case thermodynamics actually prefers to form dichlorine and the Au(I) compound. The dissociation reactions are favourable by -3.7 kcal/mol and -6.0 kcal/mol respectively. Relativistically this does not happen. Here, the AuCl₃ adducts are favoured by 9.5 kcal/mol and 19.2 kcal/mol respectively. This shows that in a non-relativistic world even the first step of the catalytic cycle is not feasible because the propyne-AuCl₃ adduct would decompose into the Au(I) compound and Cl₂. Hence, in this respect the catalytic activity of Au(III) compounds is indeed a relativistic effect.

1 Computational Details

All elementary steps of the nucleophilic addition of water to propyne catalyzed by AuCl₃ have been calculated and characterized by using density functional theory (DFT) with the Becke-Perdew (BP86) density functional. Correlation consistent triple-ζ basis sets (aug-cc-pVTZ/aug-cc-pVTZ-PP) were used for H [24], C, O [25], Cl [26] and Au [27]. For Au we used a scalar relativistic energy-consistent small-core pseudopotential of the Stuttgart group. To estimate the influence of relativistic effects, a non-relativistic pseudopotential [28] with the accompanying basis set by Schwerdtfeger and Wesendrup was used [29]. Solvent effects were taken into account by calculating self-consistent polarizable continuum model (PCM) single points at the previously obtained structures with methanol as a solvent [30, 31]. Gibbs free energies were obtained by adding vibrational and thermal corrections to the result of the PCM single point calculations. The nature of all stationary points was examined through the calculation of the second derivative ma-
trix. The Gaussian suite of programs was used for all calculations [32].

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Figure 2: Reaction energy profile of the catalytic gold process for the $\text{H}_3\text{C}-\text{C}≡\text{CH} + \text{H}_2\text{O} \rightarrow \text{H}_3\text{C}-\text{CO}-\text{CH}_3$ reaction. All energies in kcal/mol, all distances in Å. Structures shown are from relativistic gas-phase calculations. For the overall reaction we find: $\Delta E = -42.7$ kcal/mol (gas-phase); $\Delta E = -36.5$ kcal/mol (solvated); $\Delta G = -25.3$ kcal/mol (solvated).
In the catalytic addition of water to propyne the Au(III) catalyst is not stable under non-relativistic conditions and dissociates into a Au(I) compound and Cl₂. This implies that one link in the chain of events in the catalytic cycle is broken and relativity may well be seen as the reason why Au(III) compounds are effective catalysts.