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Comparative Mechanistic Study on [Au(NHC)]$^+$ Catalyzed Hydration of Alkynes, Alkenes and Allenes

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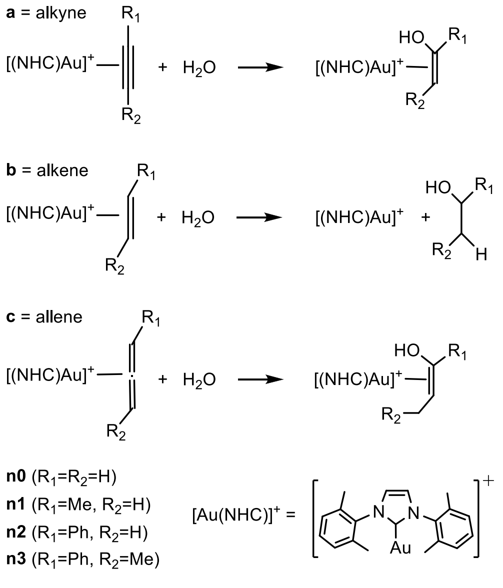
Supporting Information Placeholder

ABSTRACT: The addition of water molecules to unsaturated substrates is a highly desired process. Addition to alkynes are very common, whereas addition to allenes and specially alkenes are rather scarce. One of the main aims here is to perform a comparative analysis of their reaction mechanisms for the process catalyzed by Au(I); another objective is to analyze why alkenes are much less reactive than their alkynes or allenes counterparts. With this purpose the reaction mechanism for the addition of water to terminal and internal alkynes, alkenes and allenes catalyzed by an [Au(NHC)]$^+$complex (NHC= N-heterocyclic carbene) is analyzed by means of DFT calculations. The general catalytic cycle for the three kind of substrates can be described by three main steps: (i) reactant π-coordination to the Au(I) complex, (ii) water nucleophilic addition, and (iii) protodeauration, with subtle differences among the reactants. The comparative analysis, from the evolution of the centroids of Localized Molecular Orbitals (CLMO), of the electronic rearrangements taking place in the protodeauration step reveals different mechanisms for these three substrates, both regarding the electron pair that accepts the proton and the fate of the Au-C bond pair. Calculations show that for alkenes, despite the nucleophilic additions is relatively high but affordable, protodeauration step results in any case energetically prohibitive. The main reason is not the intrinsic barrier of the protodeauration step, just a few kcal·mol^{-1} higher than that of alkynes, but the high energy of the water-added intermediate. This issue is not related to the strength of the Au(I)-CC bond, but to that of the C-O bond.

INTRODUCTION

Carbon-carbon unsaturated bonds (alkynes, alkenes, allenes) are undoubtedly among the most important functional groups that allow the synthesis of new and more complex molecules. The addition of water molecules to these unsaturated species gives rise to the formation of alcohols or ketones.[1,2] These transformations are very desirable for their redox neutrality[3] and atom economy.[4] Among these unsaturated species, the hydration of alkynes is by far the most common one.[5,6,7] Hydration of alkenes[8,9] and allenes,[10,11] however, are much more scarce. The reactivity between a nonpolar reactant (unsaturated C-C bond) and a highly polar molecule (water) is not favorable, thus, the presence of a catalyst is required for these processes to proceed. There are several metals employed as catalysts (Rh,[12] Pd,[13] Pt,[14] Ru,[15] others[16]) but gold[17] occupies a prominent place due to its ability to activate C-C unsaturated bonds for addition reactions.[18,19] Hence, gold-catalyzed additions of O-based nucleophiles have been largely explored.[20] The use of the simplest O-based nucleophile, water, is commonly found for alkynes, but is much less common for alkenes and allenes.

Aimed to rationalize and guide the development of synthetic tools that employ simple and readily available starting materials to produce higher added value chemicals, our group has been involved in mechanistic analysis of gold(I)-catalyzed additions of simple reagents, as ammonia,[21,22] hydrazine,[23] and water[10, 24] to multiple CC bonds.



Scheme 1. Gold catalyzed hydration of alkynes (**an**), alkenes (**bn**) and allenes (**cn**) analyzed in the present paper. R$_1$ and R$_2$ may be H, Me or Ph alternatively (**n0-3**). A schematic representation of the [Au(NHC)]$^+$ catalyst is also shown.

Despite the success in the gold-catalyzed hydration of unactivated alkynes, its application to unactivated allenes, and particularly to alkenes is much more challenging. To help on its development, this article reports a comparative DFT study on the mechanism of the gold(I)-catalyzed hydration of different non-activated carbon-carbon unsaturated bonds. Scheme 1 summarizes the reactions studied in the present work. For comparative purposes our previous results on the hydration of allenes[24] will be also summarized and included here. As a ligand for the gold catalysts we selected the N-heterocyclic carbene ligand (NHC) [1,3-bis(2,6-dimethylphenyl)imidazole-2-ylidine] (Scheme 1) that was employed in our previous study on hydration of allenes.[24] Although dual activation by diaurated species has been a subject of debate in the literature of $[Au(NHC)]^+$-catalyzed phenoxylation and hydration of alkynes,[25] a recent thorough kinetic study clearly points towards a reaction mechanism involving only monoaurated intermediates,[26] and we have only considered monoaurated species. In addition, to compare alkyne, allene and alkene functionalities, regio- and stereoselectivity issues[5] have been also analyzed with the introduction of substituents in the π bond (Scheme 1).

COMPUTATIONAL DETAILS

DFT calculations were carried out using the M06 functional including an ultrafine integration grid, as implemented in Gaussian 09;[27] this functional was shown to properly describe this type of systems,[28] and was used in our previous studies.[23, 24] Basis set BS1 was used for the optimizations and general comparison of the different pathways. With BS1 the Au atom was described using the scalar-relativistic Stuttgart−Dresden SDD pseudopotential along with its associated double-ζ basis set; a set of *f* polarization functions[29] were also added. For H, C, O and N the 6-31G(d) basis set was employed. The reactants, intermediates, transition states, and products were optimized in solvent (THF; ε = 7.4257), by means of the SMD continuum model. The nucleophile (water) was modelled by including three explicit water molecules (see Figure S1); such a model performed properly in other hydration processes.[7] Considering that the protodeauration barrier may be influenced by the number and disposition of the water molecules employed, for sake of comparison the same model has been retained for each substrate and pathway.[7] The NHC ligand for gold catalyst was [1,3-bis(2,6-dimethylphenyl)imidazole-2-ylidine] (Scheme 1); it was employed in our previous study on hydration of allenes.[24] Frequency calculations were completed for all the optimized geometries to confirm the nature of the stationary points as either transition states or minima. Connection between transition states and intermediates was confirmed by usual intrinsic reaction coordinate (IRC) calculations and subsequent optimization to minima. Energies of the lowest energy pathways were refined by single point calculations on the optimized geometries, using the extended triple-ζ *def2*-TZVP for main group elements and quadruple-ζ *def2*-TQVP including def2 pseudopotential for Au (BS2).[30] All the energies given in the Schemes are Gibbs energies in solution (THF) at 298K and 1 atm[31] obtained adding the thermal and entropic corrections computed with BS1 to the electronic energy in THF computed with BS2. Species are named as **nx_y**, where **n** corresponds to the different unsaturated hydrocarbon (**a** alkyne**, b** alkene and **c** allene), **x** accounts for the substituent (H, Me or Ph) and **y** to the position within the reaction mechanism (Scheme 1). The cluster of fourteen H_2O molecules used for ΔG calculation for the deprotonation processes was taken from ref. 32 and is depicted in Figure S2.

RESULTS AND DISCUSSION

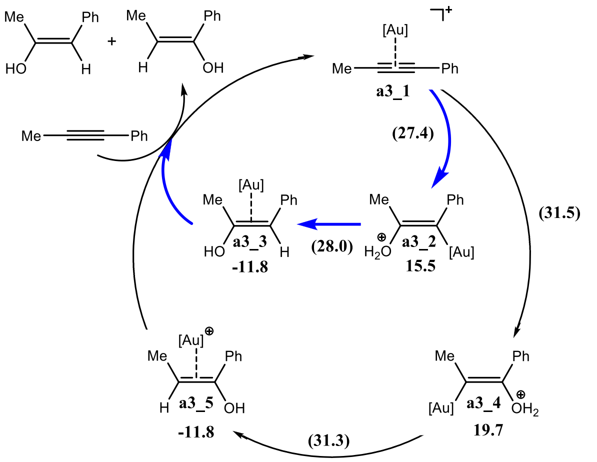
In this study we investigate the reaction mechanism for the hydration of terminal and internal alkynes (HC≡CMe, **a1** HC≡CPh, **a2**, MeC≡CPh, **a3**) and alkenes (H_2C=CHMe, **b1,** H_2C=CHPh, **b2**, MeHC=CHPh, **b3**) catalyzed by a $[Au(NHC)]^+$ complex. They were selected as representative examples of non-activated substrates and model catalyst. For the sake of completeness, the previous mechanistic analysis of allenes is also summarized and included. For comparative purposes we have also computed the reaction with the non-substituted unsaturated hydrocarbons (HC≡CH, **a0**; H_2C=CH_2, **b0** and H_2C=C=CH2, **c0**).

The general mechanism for the Au(I)-catalyzed hydration can be described by means of three fundamental steps: (i) π-coordination of the unsaturated substrate to the Au(I) catalyst, (ii) nucleophilic addition of water, and (iii) proton-transfer from water to the contiguous C atom of the substrate, commonly named protodeauration. The catalytic cycle of the general hydration reaction was completely explored for all the substrates. The water nucleophilic attack can take place from the gold side (*inner*) or from the opposite side (*outer*). In coherence with previous published reports,[33] the barriers for the nucleophilic addition step are very similar for both pathways, but the next step, proton-transfer, clearly favors the *inner* addition (otherwise indicated in the text). For clarity, energy profiles are described only for the lowest energy pathways. The other pathways are gathered in the Supporting Information, as well as a comparison of the different profiles. Regarding regioselectivity, the attack of the O-nucleophile can, in principle, take place on each of the coordinated carbon atoms of the substrate (Markovnikov and anti-Markovnikov addition in terminal substrates). Both possibilities have been also taken into account. The final product is the alcohol or enol, depending on the starting reactant. Results are presented in different subsections for alkynes, alkenes and as a summary for allenes.

A. Hydration of alkynes.

A.1 Internal alkynes.

With the substrate **a3** (MeC≡CPh), *inner* water nucleophilic attack as well as the formation of the product with Me and Ph substituents *cis* to each other, entails lower barrier and yields the most stable product (see Supporting Information). Regarding regioselectivity, the addition of water may take place on the Ph or Me substituted carbon atom. In Scheme 2 these two pathways for the hydration of alkyne **a3** are shown reporting the Gibbs energy values in $kcal\cdot mol^{-1}$ for intermediates and transition states. The computed pathways show that the formation of the 1-phenylprop-1-en-1-ol, coming from the water addition to Me-substituted carbon (**a3_5**), is favored, both in thermodynamic and kinetic grounds (Scheme 2). The catalytic cycle starts by coordination of alkyne **a3** to the gold(I) catalyst (**a3_1**). The addition of water to the Me substituted carbon, **a3_TS12**, and subsequent protodeauration, **a3_TS23**, step require relative activation Gibbs energies of 27.4 and 12.5 $kcal\cdot mol^{-1}$, respectively.



Scheme 2. Mechanistic alternatives for the gold-catalyzed hydration of internal alkyne **a3**. [Au]=[Au(NHC)]. For each intermediate and transition state two explicit water molecules (not shown for clarity) stabilize the nucleophilic water. Relative Gibbs energies with BS2 (kcal·mol^{-1}); transition state energies are shown in parenthesis. The Gibbs energy of the π-complex **a3_1** plus a cluster of three water molecules is taken as a zero energy.

The **a3_2** intermediate and subsequent enol product coordinated to the catalyst, **a3_3**, have relative Gibbs energies of 15.5 and -11.8 kcal·mol^{-1}, respectively.

As a general observation, the selectivity for the hydration of internal alkynes is low and is highly substrate dependent, often resulting in multiple regioisomeric products.[5] The nucleophilic addition of water on the Ph substituted carbon (generating intermediate **a3_4**, at 19.7 kcal·mol^{-1}) is more energy demanding with an associated Gibbs energy barrier of 31.5 kcal·mol^{-1}, **a3_TS14**. The last step, protodeauration, has the transition state at 31.3 kcal·mol^{-1}, **a3_TS45**, generating the coordinated enol product, **a3_5**, at -11.8 kcal·mol^{-1}.

Concerning the protodeauration step from intermediate **a3_2** to **a3_3**, or **a3_4** to **a3_5**, respectively, we invoked a transition state in which a water molecule is mediating a proton transfer between the nucleophilic water and the acceptor carbon (Figure 1 a and b.[7] However, there is also the possibility of direct proton diffusion in the bulk. This process cannot be rigorously evaluated by static DFT calculations; dynamic simulations would be needed to properly model the process, but this kind of analysis is out of the scope of this work.[34] Instead, we estimated the thermodynamics of the event computing the Gibbs energy of the reaction in which the proton is transferred from intermediates **a3_2** or **a3_4** to a cluster of 14 water molecules,[32] yielding the neutral intermediates generated after the proton release to the solution:

$$[Au(NHC)(MeCCPh(OH_2))]^{+}\cdot(H_2O)_2 + (H_2O)_{14} \rightarrow [Au(NHC)(MeCCPh(OH))]\cdot(H_2O)_2 + [(H(H_2O)_{14}]^{+} \tag{eq. 1}$$

These reactions are both markedly exergonic (with ΔG values of -19.2 and -22.4 kcal mol^{-1} for **a3_2** and **a3_4**, respectively), pointing out the thermodynamic feasibility of this acid-base pathway as a possible alternative to the proton-shuttle mechanism for the protodeauration step. Analogous conclusions were proposed by Hashmi[7a] and Wu and Zhao[7b] groups in their theoretical analyses of the hydration using Me-C≡CH as substrate and $[Au(PH_3)]^+$ as catalyst. They inferred that proton can travel to solvent instead of being involved in a cyclic mechanism through a direct and explicit motion from the added H_2O to the carbon atom, also suggesting that this mechanism might be feasible. The protodeauration step on Au(I)-catalyzed reactions was also evaluated by Ariafard and coworkers[35] assuming that the proton is already in the medium. On other side, Belanzoni and coworkers,[36] showed that the process can be accelerated by the presence of counterions. A similar conclusion for a related protodeauration step in the hydroamination of dienes was proposed by some of us.[37]

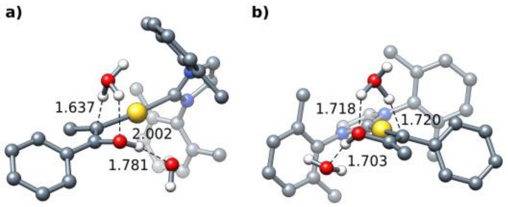
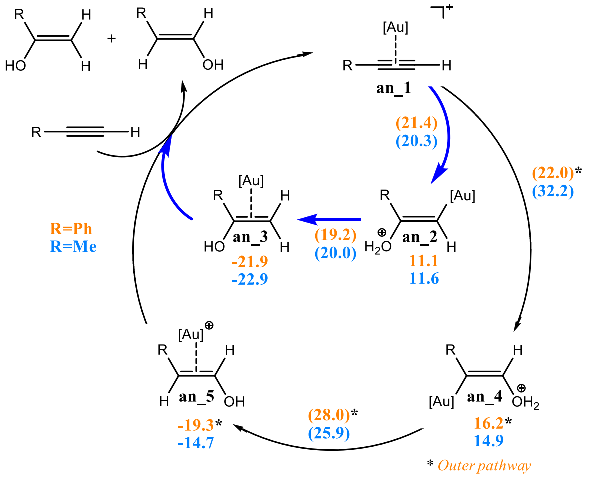


Figure 1. Protodeauration transition state for the isomerization of : a) **a3_2** to **a3_3**, and b) **a3_4** to **a3_5**. The relevant distances are also reported in Å.

A.2. Terminal alkynes

In order to study the hydration reaction of terminal alkynes catalyzed by $[Au(NHC)]^+$ we selected the HC≡CMe, **a1** and HC≡CPh, **a2** as representative non-activated substrates with aliphatic and aromatic substituents. For these two terminal alkynes analogous pathways to those for internal alkynes were theoretically characterized (see Scheme 3); analogous conclusions about the *inner* addition can be drawn (see Supporting Information). Usually, hydration of terminal alkynes proceeds with a high level of regioselectivity to furnish predominately the Markovnikov products.[5] We found the same regioselectivity in our study. The Markovnikov addition of water to the alkyne in **a1_1** has a Gibbs energy barrier of 20.3 kcal·mol^{-1}, **a1_TS12**, generating intermediate **a1_2** at 11.6 kcal·mol^{-1}.



Scheme 3. Mechanistic alternatives evaluated for the gold-catalyzed hydration of terminal alkynes **an** (**n= 1**, **2**). R=Me (**a1**, blue) and R=Ph (**a2**, orange). [Au]=[Au(NHC)]. For each intermediate and transition state two explicit water molecules (not shown for clarity) stabilize the nucleophilic water. Relative Gibbs energies with BS2 (kcal·mol^{-1}); transition state energies are shown in parenthesis. The Gibbs energy of the π-complexes **an_1** plus a cluster of three water molecules is taken as a zero energy.

The subsequent proton transfer, giving rise to intermediate **a1_3** (-22.9 kcal·mol^{-1}), requires 8.4 kcal·mol^{-1}, **a1_TS23**. The anti-Markovnikov nucleophilic addition to **a1_1** has a Gibbs energy barrier of 32.2 kcal·mol^{-1}, **a1_TS14**, giving rise to intermediate **a1_4**, at 14.9 kcal·mol^{-1}. The subsequent protodeauration generates **a1_5** species (-14.7 kcal·mol^{-1}), with transition state **a1_TS45** located at 25.9 kcal·mol^{-1}. Comparing the two possible nucleophilic additions on the coordinated alkyne **a1_1**, the one on the Me side (Markovnikov addition), as expected, is kinetically (20.3 vs 32.2 kcal·mol^{-1}), and thermodynamically (-22.9 vs -14.7 kcal·mol^{-1}) favored. For the case of alkyne with a Ph substituent **a2**, similar conclusions are obtained. Starting from **a2_1**, the addition of water on the Ph-substituted carbon atom (Markovnikov addition) has a lower Gibbs energy barrier, 21.4 kcal·mol^{-1}, **a2_TS12**, than the addition on the terminal carbon atom (22.0 kcal·mol^{-1}, **a2_TS14**).

Protodeauration by a proton-shuttle mechanism is also easier from the Markovnikov intermediate **a2_2** (at 11.1 kcal·mol^{-1}) than from the anti-Marovnikov intermediate **a2_4** (at 16.2 kcal·mol^{-1}). The respective Gibbs energy barriers are 8.1 and 11.8 kcal mol^{-1} (Scheme 3).

Concerning the protodeauration step by means of proton diffusion into the bulk, analogue thermodynamics considerations than for the internal alkyne were obtained. The ΔG values for the deprotonation reactions of intermediates **a1_2**, **a1_4**, **a2_2** and **a2_4**, calculated as in eq. 1,[32] are -18.0, -17.3, -16.2 and -21.3 kcal·mol^{-1}, respectively, suggesting that the neutral species with the proton in the bulk are thermodynamically accessible; thus, the acid-base mechanism cannot be discarded as a feasible pathway for the proton transfer.

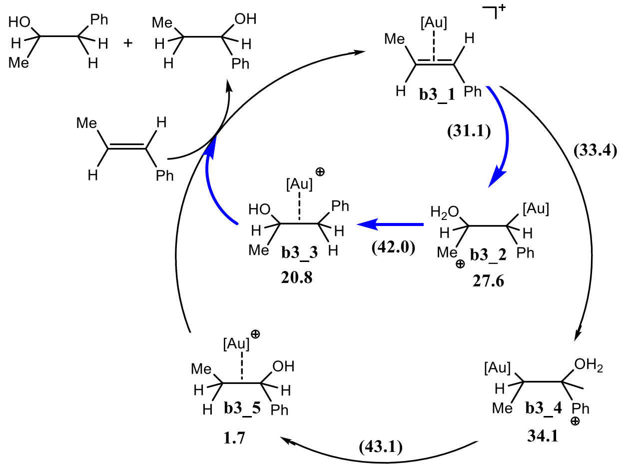
All terminal alkynes studied in this work share the same regioselectivity giving rise to the Markovnikov water addition. Terminal alkynes are more reactive than internal ones by kinetics (lower Gibbs energy barriers) and thermodynamic reasons (the relative stability of products is higher). Reaction with internal alkynes will require rather high temperatures as reported in the literature.[38]

B. Hydration of alkenes.

B.1. Internal alkenes

In coherence with the case of alkynes all the possible pathways were explored considering the nucleophilic attack to each of the coordinated carbon atoms, as well as the *inner* and *outer* additions.

As discussed above for the internal alkyne, the nucleophilic addition may take place on the Ph or Me substituted carbon of the internal alkene, **b3** (MeCH=CHPh; Scheme 4). The initial nucleophilic addition on the Me-substituted carbon of **b3_1** has a Gibbs energy barrier of 31.1 kcal·mol^{-1}, **b3_TS12**. The intermediate **b3_2** lies at 27.6 kcal·mol^{-1}. The final alcohol product coordinated to the catalyst, **b3_3**, has a relative Gibbs energy of 20.8 kcal·mol^{-1} and it is reached by overcoming **b3_TS23** at 42.0 kcal·mol^{-1} (Scheme 4). The nucleophilic addition on the Ph-substituted carbon atom over the intermediate **b3_1** is energetically more demanding with a Gibbs energy barrier of 33.4 kcal·mol^{-1}, **b3_TS14**. The intermediate lies at 34.1 kcal·mol-1, **b3_4** whereas the subsequent proton transfer has a barrier of 9.0 kcal·mol^{-1} (**b3_TS45** at 43.1 kcal·mol^{-1}).

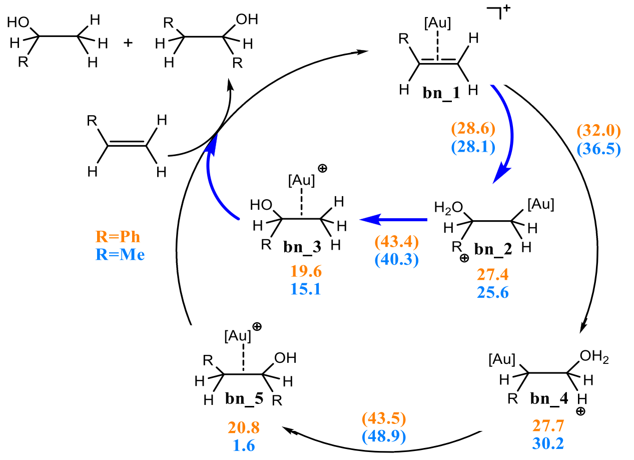


Scheme 4. Mechanistic alternatives evaluated for the gold-catalyzed hydration of internal alkene **b3**. [Au]=[Au(NHC)]. For each intermediate and transition state two explicit water molecules (not shown for clarity) stabilize the nucleophilic water. Relative Gibbs energies with BS2 (kcal·mol^{-1}); transition state energies are shown in parenthesis. The Gibbs energy of the π-complex **b3_1** plus a cluster of three water molecules is taken as a zero energy.

The final alcohol product coordinated to the catalyst, **b3_5**, has a relative Gibbs energy of 1.7 kcal·mol^{-1}. The computed pathways highlight that the formation of the 1-phenylprop-2-ol (addition on the Me side) results kinetically favored.

The protodeauration alternative going through a proton diffusion into the solvent was also considered, following the scheme devised in eq. 1.[32] The intermediates formed after the nucleophilic attack, **b3_2** and **b3_4**, lie very high in energy (at 27.6 and 34.1 kcal mol^{-1}, respectively) and, from eq. 1,[32] are greatly stabilized by deprotonation (ΔG values for the deprotonation reactions of intermediates **b3_2**, **b3_4** are -27.1 and -34.7 kcal·mol^{-1}, respectively). Thus, a priori this possibility could not be discarded. Nevertheless, the fact that hydration of alkenes is hardly observed experimentally suggest that this process cannot take place due to kinetic reasons.

Based on these results it can be concluded that the water nucleophilic attack to internal alkenes is quite difficult but an affordable step; moreover, the addition on the Me side is kinetically favored over the Ph side. In comparison with internal alkynes, nucleophilic additions to internal alkenes have a slightly higher Gibbs energy barrier (27.4 *vs.* 31.1 kcal mol^{-1}). The relative barriers for the protodeauration step from the intermediates resulting from the water addition (**a3_2** and **b3_2**) are similar (alkyne: 12.5 kcal mol^{-1}; alkene: 14.4 kcal mol^{-1}). The main difference is found in the relative energy of the intermediates with the added water: (**a3_2** lies at 15.5 kcal mol^{-1}, whereas **b3_2** is placed at 27.6 kcal mol^{-1} above the reactants. As a consequence, while the transition state for the protodeauration has a relative Gibbs energy of 28.0 kcal mol^{-1} for the internal alkyne, that for the internal alkene is 42.0 kcal mol^{-1}, preventing the hydration reaction to take place. This is a reason why hydration of alkenes is much more difficult than for alkynes or allenes (*vide infra*).



Scheme 5. Mechanistic alternatives evaluated for the gold-catalyzed hydration of terminal alkenes **bn** (**n= 1**, **2**). R=Me (**b1**, blue) and R=Ph (**b2,** orange). [Au]=[(NHC)Au]. For each intermediate and transition state two explicit water molecules (not shown for clarity) stabilize the nucleophilic water. Relative Gibbs energies with BS2 (kcal·mol^{-1}); transition state energies are shown in parenthesis. The Gibbs energy of the π-complexes **bn_1** plus a cluster of three water molecules is taken as a zero energy.

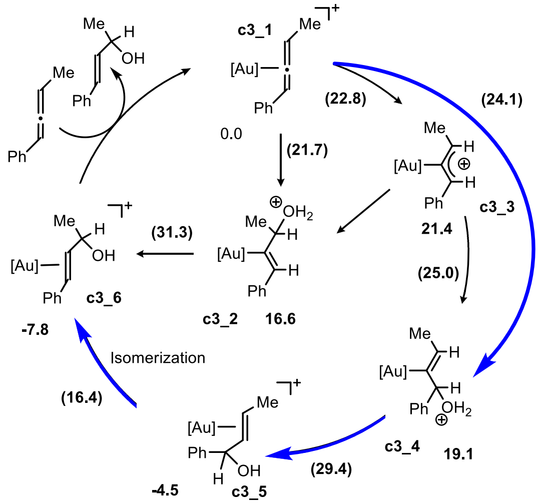
B.2. Terminal alkenes

Regarding the hydration of terminal alkenes**, b1** ($H_2C=CMe$) and **b2 (**$H_2C=CPh$), Scheme 5, the Gibbs energy barrier for the addition of water on the more substituted carbon atom (Markovnikov addition) are very similar, 28.1 and 28.6 kcal·mol^{-1}, for transition states, **b1_TS12** and **b2_TS12**, respectively. The formed intermediates, **b1_2**, and **b2_2** are at 25.6 and 27.4 kcal·mol^{-1}, respectively.

The subsequent protodeauration steps **b1_TS23** and **b2_TS23** have energy barriers of 14.7 and 16.0 kcal·mol^{-1} respectively. On the other side, addition on the terminal carbon atom (*anti*-Markovnikov addition) shows barriers of 36.5 and 32.0 kcal·mol^{-1} for **b1_TS14** and **b2_TS14**, respectively, whereas the intermediates are at 30.2 and 27.7 kcal·mol^{-1}, respectively. Protodeaurations display also similar barriers that place the corresponding transition states **b1_TS45** and **b2_TS45** at 48.9 and 43.5 kcal·mol^{-1}, respectively. None of the pathways evaluated show a feasible barrier for the hydration reaction to take place. In all cases the protodeauration step is high enough in energy to prevent the reaction to proceed.

The alternative pathway involving a proton diffusion to bulk (eq. 1) was also considered.[32] As found for the addition to the internal alkenes, the intermediates formed after the nucleophilic attack (**b1_2**, **b1_4**, **b2_1** and **b2_4**) lie very high in energy (at 25.6, 30.2, 27.4 and 27.7 kcal mol^{-1}, respectively) and are greatly stabilized by deprotonation (ΔG values for the proton release from intermediates **b1_2**, **b1_4**, **b2_2** and **b2_4** to the water cluster are -26.1, -30.5, -27.5 and -27.6 kcal·mol^{-1}, respectively). Thus, the species formed are thermodynamically accessible. Nevertheless, given the fact that these reactions are very scarce experimentally, one may expect that the barrier for the overall process should be also quite high.

In general, water nucleophilic attack to alkenes have relatively high energy barriers but still affordable steps; being the Markovnikov addition kinetically and thermodynamically favored. As for alkynes, nucleophilic additions over internal alkenes are slightly more demanding than for terminal ones. Nevertheless, the reaction is predicted to not proceed (at room temperature) due to the high energy of the transition states for the protodeauration process.

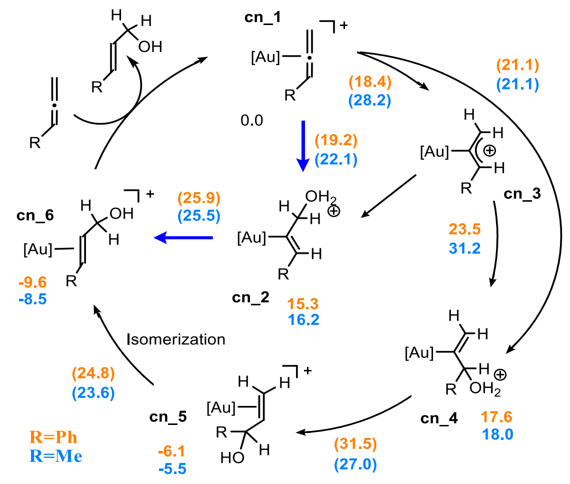


Scheme 6. Mechanistic alternatives for the gold-catalyzed hydration of internal allene **c3**. [Au]=[Au(NHC)]. For each intermediate and transition state two explicit water molecules (not shown for clarity) stabilize the nucleophilic water. Relative Gibbs energies with BS2 (kcal·mol^{-1}); transition state energies are shown in parenthesis. The Gibbs energy of the π-complex **c3_1** plus a cluster of three water molecules is taken as a zero energy.

C. Hydration of allenes

Allenes have diverse coordination chemistry due to the presence of both double bonds.[39] Gold-allene bond as well as the reactivity has been studied in detail in the literature,[40] including many computational studies.[41,42] The mechanistic study for the $[Au(NHC)]^+$ catalyzed hydration of terminal ($H_2C=C=CHMe$, **c1**, and $H_2C=C=CHPh$, **c2**) an internal allenes ($MeCH=C=CHPh$, **c3**) was recently published by us.[24] For the sake of completeness, a summary of those results is included here, updating Gibbs energy values with BS2 employed all along this work.

The pathways evaluated for the hydration of the internal allene $MeCH=C=CHPh$, **c3**, are shown in Scheme 6. The alternatives considered were the direct addition on the coordinated allene, or the nucleophilic addition of water on the σ-allyl cation intermediate that can be formed, **c3_3**. The Gibbs energies support a mechanism where the direct addition over the carbon bearing the Ph groups was the favored one. Then there is a protodeauration giving rise to intermediate **c3_5**. From this intermediate there is an isomerization process that produces the most stable product, that corresponds with the experimentally observed one.[10] The reaction mechanism for the hydration of terminal allenes $H_2C=C=CHR$ is shown in Scheme 7. For both allenes considered, R=Me, **c1**, and R=Ph, **c2**, the most stable product has the alcohol over the terminal carbon atom.



Scheme 7. Mechanistic alternatives for the hydration of terminal allenes **cn** (**n**= **1**, **2**). catalyzed by Au(I) reaction. R=Me (**c1**, blue), R=Ph (**c2**, orange). [Au]=[(NHC)Au]. For each intermediate and transition state two explicit water molecules (not shown for clarity) stabilize the nucleophilic water. Relative Gibbs energies with BS2 (kcal·mol^{-1}); transition state energies are shown in parenthesis. The Gibbs energy of the π-complexes **cn_1** plus a cluster of three water molecules is taken as a zero energy.

The mechanism is described by the same sequence of reaction steps: coordination, nucleophilic addition and protodeauration; for R=Ph an isomerization step may be also required to give the final product. The alternative route including the formation of a σ-allyl cation intermediate can be feasible for R=Ph but can be discarded as a general operative pathway.

D. Comparative analysis

The comparison of the reaction profiles computed for the hydration of unsaturated C-C bonds (non-activated alkynes, alkenes and allenes), shows a common mechanism that can be described in three main steps: (i) substrate π-coordination, (ii) nucleophilic addition and (iii) protodeauration; in the case of allenes an isomerization step may be required to complete the reaction depending on the substrate. The general mechanism is similar to that described for the Au(I) catalyzed hydroamination of the analogous C-C unsaturated functional groups.[23] The first step, π-coordination of the unsaturated CC bond to the gold(I) center, shows relatively similar ΔG_{coord} values for all reactants (binding Gibbs energies between 16-20 kcal mol^{-1}, Table 1, column 2).

Table 1. Binding Gibbs energy of reactants to Au(I) catalyst, relative Gibbs energies of TSs and intermediate **n_2** for the preferred Markovnikov pathway for the hydration of non-activated alkynes, alkenes and allenes and Gibbs energy for the product by reactant substitution (kcal mol^{-1}).

Species	ΔG_{coord} [a]	ΔG_{n_TS12} [b]	ΔG_{n_2} [c]	ΔG_{n_TS23} [d] ($\Delta\Delta G$)	ΔG_{subst} [e]
a0	-18.7	22.8	6.5	16.4 (9.9)	3.9
a1	-17.6	20.3	11.6	20.0 (8.4)	2.2
a2	-17.1	21.4	11.1	19.2 (8.1)	1.5
a3	-16.8	27.4	15.5	28.0 (12.5)	-3.5
b0	-19.8	29.8	24.8	40.4 (15.7)	-24.7
b1	-20.0	28.1	25.6	40.3 (14.7)	-23.2
b2	-17.9	28.6	27.4	43.4 (16.0)	-24.2
b3	-17.6	31.1	27.6	42.0 (14.5)	-24.5
c0	-17.9	23.4	16.8	29.6 (12.0)	-4.3
c1	-18.8	22.1	16.2	25.5 (9.2)	-3.4
c2	-16.4	19.2	15.3	25.9 (10.6)	-1.4
c3	-19.9	21.7	16.6	31.3 (14.7)	-3.3

[a] ΔG associated to: **nx_y** + $[Au(NHC)]^+$ → [Au(NHC)(π–**nx_y**)]$^+$. [b] Transition state corresponding to the Markovnikov nucleophilic attack. [c] Intermediate **n2** coming from water addition (**TS12**). [d] Transition state of the protodeauration step, in the case of allenes it corresponds to **TS26**. In parenthesis activation Gibbs energy from intermediate **n2**, associated to the protodeauration step. [e] ΔG associated to: [Au(NHC)(H**nx_y**–OH)]$^+$ + **nx_y** → [Au(NHC)(π–**nx_y**)]$^+$ + H**nx_y**–OH.

Thus, it does not introduce any clear differentiation among the reactants. The overall comparison between terminal and internal unsaturated functional groups shows that terminal ones are always more reactive; addition to internal groups are predicted in some case hardly affordable. The non-substituted alkyne (ethyne, **ao**) and alkene (ethene, **bo**) have somewhat higher barriers for the water addition than the terminal ones, proving the favorable impact of Me and Ph substituents in the Markovnikov addition.[43] Protodeauration barriers are less affected by the substitution.

Regarding regioselectivity the three π-bonds behave in a similar way: the addition on the most substituted carbon (Markovnikov addition) is always favorable for all the unsaturated functional groups evaluated. However, when comparing relative energies of transition states and intermediates for the preferred Markovnikov pathway striking differences appear (Table 1, ΔG_{n_TS12} and ΔG_{n_TS23}, Table 1, columns 3 and 5, respectively).

According to the results for alkynes, the Gibbs energies of the

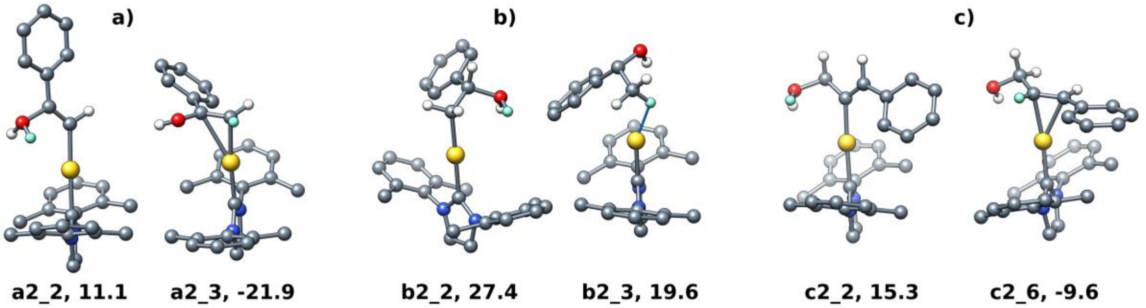


Figure 2. Optimized structures of the intermediates formed before and after the protodeauration step, for the three CC unsaturated CC bonds considered: **a)** alkyne **a2**; **b)** alkene **b2**; **c)** allene **c2** (R_1= Ph; R_2= H). In black, relative Gibbs energies with respect the corresponding π complexes, in kcal mol^{-1}. The two additional water molecules have been omitted for clarity.

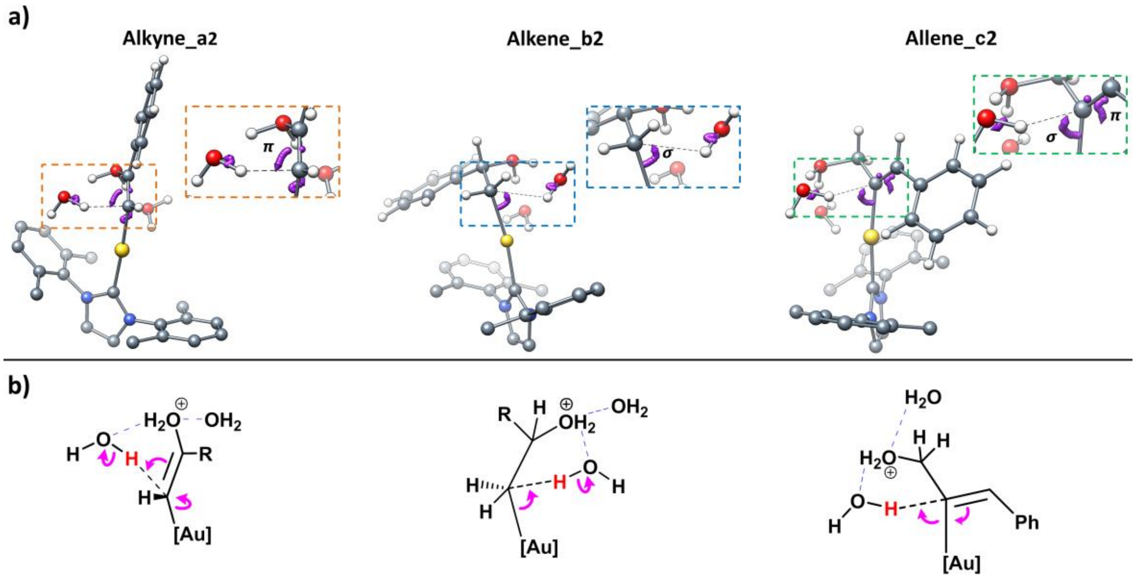


Figure 3. Superposition over the reactant structures of the localized orbital centroids (purple dots) along the IRC for the protodeauration process for: a) alkyne **a2**, alkene **b2** and allene **c3** and b) the corresponding arrow-pushing schemes.

transition states does not allow to clearly assign a rate determining step. Overall, for alkynes **a0**-**a2** the reaction takes place with relative low barriers (about 20 kcal mol^{-1}), except for the case of the internal **a3**.

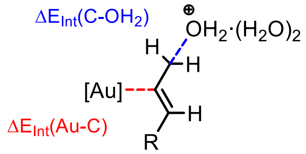
For the case of allenes, they behave in a similar way than alkynes regarding barriers, although in these cases the protodeauration can be clearly assigned as the rate determining step. The main difference is found in the stability of the intermediates formed after the water addition (**cn_2**), which are about 4 kcal mol^{-1} less stable than the corresponding to the alkynes (**an_2**) (Table 1, $\Delta\mathbf{G}_{\mathbf{n\_2}}$, column 4). Overall, the hydration reaction appears as feasible, except for the internal reactant, **c3**.

For the case of alkenes, the situation is quite different. Nucleophilic addition is significantly higher in terms of Gibbs energy barrier compared with alkynes and allenes, although affordable in harsher reaction conditions ($\Delta\mathbf{G}_{\mathbf{n\_TS12}}$ about 30 kcal mol^{-1}, Table 1**)**. However, the intermediates formed from the water addition (**bn_2**) are high energy species (Table 1, $\Delta\mathbf{G}_{\mathbf{n\_2}}$, column 5), around 15 kcal mol^{-1} above the related alkyne intermediates. The protodeauration barriers from these intermediates, although not much higher than those for alkynes (Table 1, **ΔΔG** at column 5), place the protodeauration transition states at energy levels (about 40 kcal·mol^{-1}) that make the process unaffordable even at drastic reaction conditions.

To shed light on the different behavior observed, we have performed a deeper analysis of the species involved in the so-called protodeauration step. That means the intermediate formed after the nucleophilic addition of water, that can be described as a protonated enol or alcohol, the transition state for the proton transfer from the protonated water to the carbon, and the resulting intermediate (addition product including the [Au(NHC]$^{+}$ complex)

The optimized structures of these two intermediates, **n2_y**, for the three kinds of CC multiple bonds with R_1=Ph and R_2=H are depicted in Figure 2, as well as their relative energies with respect the initial π complexes. Intermediates **n2_2**, formed by water addition to the CC multiple bond have a different nature both regarding the Au-C bond and the C-OH$_2$ moiety. Water addition to alkyne and allene CC bonds yield vinyl gold(I) intermediates (i.e. for R=Ph species **a2_2** and **c2_2**, respectively; Figure 2, a and c).

Table 2. Au-C and C-OH$_2$ interaction energies in intermediates **n0_2**.[a]



Species	$\Delta\mathbf{E}_{\mathbf{Int}}$ **(Au-C)** [b]	$\Delta\mathbf{E}_{\mathbf{Int}}$ **(C-OH$_2$)** [c]	$\Delta\mathbf{E}_{\mathbf{n0\_2}}$ [d]	$\Delta\mathbf{G}_{\mathbf{n0\_2}}$ [e]
a0_2	-75.6	-74.8	-13.3	6.5
b0_2	-80.4	-60.3	4.8	24.8
c0_2	-79.2	-75.9	-3.6	16.8

[a] Values in kcal·mol^{-1} computed with BS2. [b] Interaction energy between the two frozen fragments obtaining breaking heterolytically the Au-C bond and assigning the electron pair to the C containing fragment. [c] Interaction energy between the two frozen fragments breaking heterolytically the C-OH$_2$·(H$_2$O)$_2$ bond and assigning the electron pair to the O containing fragment. [d] Relative energy of intermediate **n0_2**. [e] Relative Gibbs energy of intermediate **n0_2**.

This kind of complexes, that contain a C$_{vinyl}$-Au σ-bond, have been characterized.[44] In the case of alkene, however, the addition of water generates an alkyl intermediate, with a C$_{alkyl}$-Au σ-bond, (i.e. for R=Ph intermediate **b2_2**, Figure 2b). Interestingly, these intermediates are around 10-15 kcal·mol^{-1} higher in energy (Table 1), than those for alkyne and allene counterparts.

To further analyze the origin of the energy difference among these intermediates, the interaction energy between two fragments involved in the Au-C bond (the one containing the Au(I) and the one containing the C-atom ligand) were calculated, $\Delta\mathbf{E}_{\mathbf{Int}}$ **(Au-C)**. The simplest reactants, ethyne, ethene and propa-1,2-diene (labelled as **a0_2**, **b0_2** and **c0_2**, respectively, were considered for analytical purposes (Table 2, column 2). The same analysis has been performed for intermediates **n2_2** (Table S1 in the Supporting Information). The difference in interaction energies between vinyl-Au(I) and alkyl-Au(I) fragments is lower than 5 kcal·mol^{-1} among the three species, with that for alkene species, **b0_2**, showing the largest value. Thus, the presence of a C_{alkyl}-Au bond is stabilizing more the intermediate than the C_{vinyl}-Au bond. These results indicate that the energy differences among the intermediates in the reaction profiles cannot be mainly due to the interaction between the vinyl- or alkyl- ligands and the Au(I) fragment.

Then, we turned our attention to the C-OH_2 interaction. The interaction energy between the fragments involved in the new formed C-O bond (water and the rest of the molecule) were also calculated, **ΔE_{Int} (C-OH_2)** (Table 2, column 3). The interaction energy between the fragments that contain the vinyl-Au(I) moiety (alkyne, **a0_2** and allene, **c0_2**) and water is about 15 kcal mol^{-1} higher than for the case of the alkene (**b0-2**). This energy difference matches the different stability of the intermediates. Thus, the high energy of the intermediates formed after addition of water to coordinated alkene is due to the less stability over the formation of this C-O bond compared to the case of alkyne or allene. This reveals an intrinsic difficulty for the hydration of alkene by this procedure. This issue might be related to the fact that in the intermediates coming from water addition to alkyne and allene there is a C=C π-bond that allows a better accommodation of the -O functionality (alkyne: protonated enol; allene: the C=C π-bond and the -O functionality are separated by a C-H group). Overall, the issue comes from the formation of the new C-O bond in the case of coordinated alkene compared to the coordinated alkyne or allene, not by the nature of the interaction of the ligand (alkyl vs vinyl) with the Au(I) metal center. Indeed, this feature is already apparent when computing the thermodynamics of the hydration reaction in the absence of the gold complex (Table S2 in the Supporting Information). ΔG values of -20.5, -10.6 and -8.5 kcal mol^{-1} are obtained for ethyne, propa-1,2-diene and ethene hydrations, respectively, displaying a more exergonic enol than primary alcohol formation (about 12 kcal mol^{-1}).

We then analyzed the protodeauration step. It has been often naively described as a simple exchange of and Au$^+$ by a proton, but recent deeper analyses of this step have disclosed a much more complex process. [35,36,45] Two kinds of intermediates are formed after the O- to C- proton transfer (formal protodeauration). In the alkyne and allene systems the formed intermediates correspond to η^2-CC complexes, there is a σ/π rearrangement in the nature of the electrons involved in the C-Au bond. The [Au(NHC)]$^+$ does not dissociate but remains π-coordinated to the C=C bond (Figure 2). Dissociation of C=C unit from the gold(I) takes place by ligand displacement for a better π-ligand (the reactant). For the alkyl-gold(I) intermediate, however, during the protodeauration the [Au(NHC)]$^+$ unit remains connected to the organic moiety only by a much weaker agostic interaction. The computed values for the substitution in the coordination sphere of gold(I) of the product by a new reactant molecule agree with this description. The reaction is almost thermoneutral in the case of π-bonded products enol and allyl alcohol, and highly exergonic for the weakly bonded products, primary and secondary alcohols (Table 1, ΔG_{subst}, column 6).

The nature of the σ/π rearrangement of the protodeauration step in vinyl Au species has been evinced by means of an intrinsic bond orbital analysis (IBO), based on localized molecular orbitals (LMO).[45] Some of us have devised a similar analysis from the evolution of the centroids of the localized molecular orbitals (CLMO).[46] In this approach, Kohn–Sham orbitals are transformed into maximally localized molecular orbitals (LMOs), and the centroids of these LMOs (CLMO) are computed for selected structures along the reaction path. The movement of the localized orbital centroids along the reaction path gives information about the electronic rearrangements of the bond-breaking and bond-forming processes. In this way a curly-arrow description of the process is obtained from the quantum mechanical calculations.[46]

Figure 3 shows the superposition over the reactant structure (intermediates coming from the water addition) of the localized orbital centroids for the IRC configurations coming from the transition states of the protodeauration transition states. The analysis enables a clear discrimination between the different mechanisms. For the case of alkynes, the electron pair of the coordinated double bond moves to form the new C-H bond, while a metal orbital is slightly moving its centroid to change from a σ-Au-C bond to a π-Au-C bond (Figure 3). Indeed, the well-known effect of strong electron donator ligands to accelerate the protodeauration[36,45] is explained by this simple model: putting π-donating substituents in the C=C bond will facilitate the attack of the π-electrons to the incoming proton. The same effect is caused by increasing the donor character of the gold ligand: electron-rich ligands such as PMe3 or PPh3 accelerate the reaction.[35]

For the allenes, is the electron pair of the σ-Au-C bond that moves to pick up the proton, meanwhile the π-electron pair coming from the neighbor unsaturated bond forms the new η^2-Au-alkene coordination. In this way the coordination of [Au(NHC)]$^+$ is preserved. Finally, the alkene protodeauration is characterized by a unique event involving the σ-Au-C bond electron pair that moves to form the new C-H bond. The Au-C interaction is lost, entailing a considerably higher energy cost. It must be pointed out that for a related process, Au(I)-catalyzed hydroamination of dienes,[47] the computational analysis displayed a favored protodeauration step that ends up with a η^2-CC complex coordinated to Au(I);[37] the presence of a π-coordinating unit makes the process much more feasible.

CONCLUSIONS

The comparative analysis of the gold(I)-catalyzed hydration of alkynes, alkenes and allenes reveals that, though these reactions share a common general mechanism, they take place with notably different reaction barriers. The nucleophilic attack step is not an issue for alkynes and allenes, whereas it is higher in energy, though affordable, for alkenes. The scarce reactivity of alkenes over the hydration reaction can be mainly attributed to the high energy intermediate formed after water addition along with the subsequent protodeauration step. The intrinsic nature of such intermediate makes it much more energy demanding. The high energy of this species, compared with those coming from the addition to alkynes and allenes is not related to the Au(I)-CC system interaction, but to the strength of the C-O bond in the presence of absence of a π-bond in the organic fragment.

Following the electronic rearrangements that take place in this apparently simple protodeauration step disclose different mechanisms for the three kind of substrates, both regarding the origin of the electron pair that will accept the proton and the fate of the Au-C bond electron pair. For alkynes the reaction is just the protonation of a π-bond (the electron pair involved in the protonation comes from the π-bond of a gold-vinyl intermediate) and is accompanied by a σ-π-rearrangement of the Au-C bond. In this way the reaction takes place with low barriers, always similar to those for the nucleophilic attack step. For allenes, although the electron pair that pick up the proton comes from the Au-C σ-bond, it remains another π-bond to which the gold can coordinate in a η^2-CC fashion. Overall, the protodeauration barriers in allenes are also low and relatively similar to those of alkynes. A remaining π-bond is absent in alkenes, the use of the Au-C σ-bond electron pair to accept the proton completely disrupts the Au-C interaction, giving rise to barriers about 5 kcal mol^{-1} higher. However, the very low stability of the water-added intermediates places the protodeauration transition states at values completely unaffordable.

EXPERIMENTAL SECTION

For description of the calculation performed see Computational Details section.

ASSOCIATED CONTENT

Supporting Information. Water clusters used in the calculations, thermodynamics of the hydration reactions in the absence of the gold complex, Au-C and C-OH_2 interaction energies in intermediates **n2_2** and energy profiles for all the *inner* and *outer* additions (PDF). Cartesian coordinates of all the optimized structures (XYZ).

Notes

The authors declare no competing financial interests.

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