On the Role of Noncovalent Ligand-Substrate Interactions in Au(I) Catalysis: An Experimental and Computational Study of Protodeauration

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ABSTRACT: A systematic study of protodeauration, a crucial step often found in gold catalysis, was performed using isolated vinyl gold(I) complexes. By varying substituents on gold complexes, we explore how their properties influence protodeauration. Phenols were employed as the proton source, and their substituents were also varied, providing insight through variation of their acidity. A linear Hammett correlation is identified for the series of substituted vinyl gold(I) complexes, while a nonlinear trend is found for the series of substituted phenols. Computationally, we reproduce our experimental observations and identify significant noncovalent interactions (NCIs) between the proton donor and vinyl gold(I) complexes. This finding is of particular importance for gold-catalyzed reactions as they often employ linear two-coordinate complexes where the site of the reaction is spatially remote from the ligand bound to gold. The NCIs between substrates and intermediates lead to a significant acceleration of the protodeauration step in this work, opening the door to alternative strategies in the field of gold catalysis.

KEYWORDS: protodeauration, gold catalysis, vinyl gold(I) complexes, noncovalent interactions (NCIs), DFT calculations

Introduction

Transformations catalyzed by gold and involving substrates containing unsaturated C-C bonds (e.g., alkynes, allenes, and alkenes) have been extensively studied over the last few decades.1 These types of reactions often follow a similar pathway (Scheme 1), where two key steps may be highlighted.1e,i,2 Frequently, a gold catalyst will interact with a substrate, leading to a vinyl gold complex as an intermediate which results from the activation of π-bonds present in the substrate.3 Notably, only a limited number of vinyl gold(I) complexes have been reported to date, which could be characterized or even isolated.4 The second crucial step is the subsequent reaction of the said vinyl gold(I) intermediate, which, in the presence of a proton source (or, more generally, an electrophile), undergoes protodeauration to release the final product—thereby completing the catalytic cycle.5 Due to the fundamental relevance of these steps to the field of gold catalysis, several efforts have been made to gain detailed mechanistic insight. However, gaining insight into the whole catalytic cycle might be challenging because the two key steps highlighted above generally have opposing requirements. For example, electron-withdrawing groups (EWGs) on the spectator ligands promote reaction rates, likely resulting from the acceleration of the first step (formation of the vinyl gold complex).6 Therefore, a systematic study of protodeauration is crucial for a better understanding of gold-catalyzed reactions.
complex). On the other hand, protodeauration tends to be accelerated by electron-donating groups (EDGs) on the spectator ligands. For example, Wang et al. reported systematic studies on ligand effects in the gold-catalyzed activation of alkynes. In their systems, EDGs increase the reaction rates by promoting the (rate-limiting) protodeauration step. Even though these reports propose catalytic cycles that fall into the same general scheme, they have opposing electronic requirements since the rate-determining step is either the formation of the vinyl complex or protodeauration. Therefore, obtaining a detailed understanding of these systems during catalysis becomes generally difficult.

In a previous study, we reported the preparation of vinyl gold(I) complexes based on earlier reports (Scheme 2) and found that these complexes are indeed rather easily handled. In this communication, we decided to design a study with the intent of probing the protodeauration step in an isolated fashion, where our result would not be complicated by the surrounding steps taking place in gold-catalyzed reactions.

We prepared vinyl Au(I) complexes with different substituents placed on the benzofuran unit following our previously reported procedure (Scheme 2). The resulting complexes were isolated in good yields (72–81%). With these well-characterized and isolated vinyl gold(I) complexes in hand, we conducted systematic kinetic studies focusing on the protodeauration step. We first focused on the effect of placing substituents on the benzofuran units in the vinyl gold(I) complexes and then exposing these complexes to 4-bromophenol as an acid (Figure 1).

The reaction rates were recorded by 1H NMR spectroscopy (Tables S1–S6). A clear trend was observed, as expected; EDGs accelerate the rates of reaction (up to ca. 100×), and vice versa, EWGs result in reduced rates (Figure 1b). For these complexes, a linear Hammett correlation between σ values and log(k/k0) was found (ρexp = −2.19), which indicates the build-up of positive charge in the vinyl gold(I) complexes during protonation. This observation is, in principle, not surprising. This did, however, change once we explored density functional theory (DFT) calculations. Reaction paths for the protodeauration were optimized at the PBEh-3c/cPCM(CHCl3) level of theory (which includes the D3 model for dispersion effects and gCP corrections for the basis set superposition error), and electronic energies were refined using the PW6B95-D3(BJ)/def2-TZVPP/cPCM//PBEh-3c/cPCM (anti-conformation: red dashed line and squares and syn-conformation: blue dashed line and squares). (c) Simplified TS structures based on the conformation.

For the F-substituted vinyl complex (1F), we determined the free energy of activation experimentally for the protodeauration. Upon addition of different amounts of 4-bromophenol (50, 75, 100, and 125 equiv) to 1F, a second-order rate constant for this reaction was obtained (k2 = 1.48 × 10−1 M−1 s−1) (Figure S16), which corresponds to a barrier of ΔG‡ = 18.5 kcal mol−1. Therefore, we conclude that the most relevant conformers for the TS are the computed syn-conformers because: (i) The syn-conformers are consistently calculated to be energetically favorable by ca. 6 kcal mol−1 and (ii) the experimentally obtained free energy of activation of protodeauration for the F-substituted complex 1F is in good agreement with our findings for the syn-conformer.
Figure 2. Computed activation energies of $k_2$ (R = OMe, Me, H, F, CF$_3$) in the anti (red) and syn (blue) conformations regarding the orientation of 4-bromophenol. The experimentally obtained free energy of activation for $k_2$ is plotted (black) for comparison.

$(\Delta G_{298.2}^{\#}(\text{syn, anti}) = (19.4, 25.2)$ kcal mol$^{-1}$). The energetic preference for the syn-conformation is remarkable, as one may expect no significant interactions between the phenol and gold-phosphine moieties since these are oriented trans to the vinyl gold moiety. If any interaction is to be expected, it might be an unfavorable steric clash, resulting in a preference for the anti-conformation. We thus began to explore the origin of this difference in barrier heights, $\Delta \Delta G_{\text{anti-syn}}^{\#}$. Since the key structural difference between the conformations is the proximity of the phenol’s aromatic system to the gold-phosphine moiety (Figure 1c), we suspected favorable noncovalent interactions (NCIs) between these sites might be playing a crucial role. Such interactions have been well studied in other fields and have been found to significantly affect reaction barriers. 14 Although these studies clearly show the variation of NCIs upon the change of substituents, the observed $\Delta \Delta G_{\text{anti-syn}}^{\#}$ remains almost constant regardless of the substituents on the vinyl substituent. $R^2$ is rather far removed from the interacting sites, resulting in a negligible change of NCIs due to substitution. The electronic effects from substitution are, therefore, solely responsible for the observed linear Hammett correlation. How might we experimentally probe the role of NCIs leading to a preferential syn-conformation? If NCIs between the phenol and gold-phosphine moieties are playing a significant role in the reaction, we should expect them to depend on the nature of the substituent present in the phenol. As the Hammett correlation identified for the substitution at the vinyl moiety indicates a linear correlation resulting from substitution effects, we may anticipate that substitution at the phenol would also result in a linear correlation in the absence of relevant NCIs. However, should the NCIs become relevant, as in the syn-conformation, a perturbation of this linear correlation may be observed, as has been indicated before for linear free energy relationships. 15 We accordingly introduced substituents at the para position of the phenol, which will probe the significance of the aforementioned NCIs.

The protodeauration of 1$_{\text{OMe}}$ with para-substituted phenols was monitored by $^1$H NMR spectroscopy to observe the reaction rate ($k_{\text{calc}}$) when varying the phenol substituents. In contrast to the previous series (1 and 2$_{\text{Me}}$), EWGs accelerated the reaction in this series (1$_{\text{OMe}}$) and para-substituted phenols (2) (Figure 3, see black squares). The result indicates a build-up of negative charge at the phenols during the reaction, forming a phenolate anion stabilized by the EWGs, i.e., the phenol acts as an acid. Although log($k_{\text{calc}}$/ $k_{\text{OMe}}$) generally increases with $\sigma_{\text{para}}$, we did not obtain a reasonably linear correlation, unlike in the previous case (Figure 1). This nonlinearity indicates that the expected acidity effects (accounted for in the Hammett $\sigma_{\text{para}}$ values) do not adequately explain the trend. To further probe these experimental results, we optimized all syn and anti pathways and calculated log($k_{\text{calc}}$/ $k_{\text{OMe}}$) (Figure 3, see red and blue squares). The computed data also exhibit a trend similar to the experimentally observed one. It appears that the interaction between the phenol unit and the complex (TS$_{\text{syn}}$) perturbs the slope in the Hammett plot, similar to the experimental data. These results are noticeably different from the previous ones (Figure 1), where a linear correlation was found regardless of conformation. Furthermore, $\Delta \Delta G_{\text{syn-anti}}^{\#}$ shows a more significant variability (5.2–8.2 kcal mol$^{-1}$), leading us to conclude that the magnitude of the NCIs varies considerably in this series $R^2 = (\text{NMe}_2, \text{OMe}, \text{H}, \text{F}, \text{Cl}, \text{Br})$.

To quantify the effect of the dispersion interaction on the observed kinetic trends, we performed a series of calculations with the B3LYP$^{16}$-D3(BJ)$^{10a}$ functional at the (PBEh-3c) optimized geometries. The intrinsic parameterization of the B3LYP functional is well known to poorly describe dispersion effects, 17,18 allowing us to mostly separate the dispersion energy (Table S23) between the phenol and the vinyl gold(1) complex, $E_{\text{disp}}$, from the electronic barrier height, $\Delta E^\ddagger$. The anti-syn difference in barrier height ($\Delta \Delta E_{\text{anti-syn}}^{\ddagger}$) generally increases with the anti-syn difference in the dispersion energies.

Figure 3. (a) Reaction scheme of the protodeauration of 1$_{\text{OMe}}$ with para-substituted phenols. (b) Experimentally obtained Hammett correlations of $\sigma_{\text{para}}$, the para-Hammett substituent parameter, vs. log($k_{\text{calc}}$/ $k_{\text{OMe}}$) (black squares). The data for 4-dimethylaminophenol (2$_{\text{OMe}}$) are represented as an empty box as the reaction was not followed completely due to the slow rate. Computationally obtained Hammett correlations with PW6B95-D3(BJ)/de2-TZVPP/cPCM//PBEh-3c/cPCM (anti-conformation: red squares and syn-conformation: blue squares). (c) Qualitative depictions of TS structures for the anti- and syn-conformation.
of the transition states \(\Delta E(\text{disp})_{\text{anti-syn}}\) (Figure 4). The reduction in barrier height (when going from \textit{anti} to \textit{syn}) is more than accounted for by the dispersion interaction between the phenol and the vinyl gold(I) complex. We note that the difference in dispersion energy does not directly translate into a reduction in barrier height due to some minor destabilizing effects, e.g., steric clashes.

To further probe the role and spatial distribution of the NCIs, we employed the reduced density gradient (RDG) method from Johnson et al.,\textsuperscript{19} using the freely available MultiWFN code\textsuperscript{20} with VMD\textsuperscript{21} for visualization via all-electron single point calculations at the B3LYP-ZORA\textsuperscript{22}-def2-TZVPP//PBEh-3c level in ORCA 4.2.1.\textsuperscript{23} Examination of the RDG isosurfaces reveals a pronounced increase in favorable NCIs in the region between the phenol and gold-phosphine moieties of the TS\textsubscript{syn-H} structure, as compared to TS\textsubscript{anti-H} (Figure 5). This analysis, therefore, further substantiates the origin of the energetic preference for the \textit{syn}-conformation, seen experimentally and computationally across this series of substituents.

The kinetics of the protodeauration step were investigated in detail for a series of isolated vinyl gold(I) complexes employing phenols as proton sources. Our findings shed light on broader questions in gold catalysis, as controlling the reactivity in linear gold(I) complexes is sometimes considered to be challenging due to the 180° bond angle between the metal center and the (often) several Ångstroms of separation between the spectator ligand and the substrate.\textsuperscript{24} Indeed, this argument is often used to motivate work in enantioselective gold(III) catalysis.\textsuperscript{25} In this work, however, we highlight a strategy to fine-tune the reactivity in gold(I) complexes, namely, the modulation of noncovalent interactions (NCIs) between the spectator ligand and the substrate. This was achieved via substitution, which, in our case, resulted in more than three orders of magnitude rate enhancement based on our computational analysis. The substitution on the proton source, or more broadly speaking electrophile, seven bonds away from the gold center, challenges the perception that ligand effects in two-coordinate linear gold(I) complexes are mostly confined to electronic effects and that no special control may be realized. As indicated in the introduction, the key steps in many catalytic cycles for gold-catalyzed transformations of unsaturated compounds involve an initial formation of a vinyl gold intermediate followed by protodeauration. These steps have inherently different requirements with respect to the choice of the (spectator) ligand, where EWGs promote the initial formation of a vinyl gold intermediate, and EDGs promote protodeauration, or, more generally, the reaction with an electrophile. This leads to an inevitable tradeoff when matching requirements in designing efficient catalysts. Our results presented within this work, however, indicate that this tradeoff may, in fact, not be as significant as chemical intuition might make us believe. If the formation of the initial vinyl gold moiety required a more electron-withdrawing ligand, this may, in fact, be compensated through the NCIs identified here. This stems from the fact that the addition of a nucleophile to a gold-activated alkyne occurs opposite to the gold and its (spectator) ligands. Here, NCIs may, in fact, not play such a dominant role. Hence, the significant rate enhancement based on NCIs identified here may, in fact, compensate sufficiently and lead to more efficient catalytic systems.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.2c03384.

Experimental details, characterization data, full computational details, and Cartesian coordinates (PDF)

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**ACKNOWLEDGMENTS**

We thank the Center for Information Technology of the University of Groningen for their support and for providing access to the Peregrine high-performance computing cluster. J.E.M.N.K. acknowledges funding from the Netherlands Organisation for Scientific Research (NWO START-UP grant). S.T. is grateful for a Ph.D. scholarship from the German Academic Exchange Service (DAAD). I.F.L. thanks the Dutch Ministry of Education, Culture, and Science (OCW) for funding his Ph.D. scholarship. C.B. is grateful for support through the Erasmus exchange program.

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