

Mechanistic Investigation of the Gold-catalyzed Aerobic Oxidation of Alcohols

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Abstract The mechanism for the gold-catalyzed aerobic oxidation of alcohols was studied using a series of *para*-substituted benzyl alcohols (Hammett methodology). The competition experiments clearly show that the rate-determining step of the reaction involves the generation of a partial positive charge in the benzylic position (i.e. hydride abstraction). This was further substantiated by the determination of a significant kinetic isotope effect ($k_H/k_D = 1.41$), when employing an alcohol substrate deuterated in this position.

Keywords Heterogeneous catalysis · Oxidations · Gold · Mechanism · Hammett

1 Introduction

Only during the last few decades, gold catalysis has emerged as one of the new promising research areas within chemistry, with novel reactions being frequently discovered within both homogeneous and heterogeneous catalysis. The fact that this special reactivity of gold nanoparticles was only discovered very recently is conspicuous since nano-sized gold particles have been known for long and they play an important role in the early history of modern chemistry [1]. However, gold has historically been considered a noble and quite unreactive metal [2], and

as a result thereof deemed unable to participate to any significant extent in chemical reactions. This view changed dramatically, when it was discovered by Haruta and coworkers that gold nanoparticles can be extremely active catalysts for low-temperature CO oxidation [3]. Around the same time, Hutchings and coworkers similarly found gold to be an efficient catalyst for the hydrochlorination of alkynes [4], but still today the exact mechanisms for these transformations remains a subject of considerable debate.

Building on the pioneering discoveries within CO oxidation and hydrochlorination, the field of gold catalysis has expanded tremendously, and now also includes, for example; direct synthesis of hydrogen peroxide [5]. In addition to these heterogeneous reactions, a multitude of homogeneous reactions have similarly been discovered, in which the typical role of gold is to activate π -systems (e.g. alkenes or alkynes), thus effecting ring-closing reactions [6]. Recently, gold-catalyzed oxidations have also been suggested as a viable pathway for transforming biomass (e.g. glycerol, carbohydrates) into useful chemical building blocks [7].

The mechanism for these gold-catalyzed processes remains largely unknown, thus it would be interesting to investigate whether it follows a mechanism similar to other noble metal oxidation catalysts [8], or if a hitherto unknown mechanism is operating. In any case, it appears clear that special active sites present only in gold nanoparticles are responsible for the observed reactivity. So far, most attention has been devoted to explaining the reasons for the remarkable catalytic activity in the oxidation of CO with dioxygen. Obviously, in this reaction the activation of dioxygen is a key step and numerous theoretical and experimental approaches have been used to provide more detailed mechanistic insight into this particular reaction [9]. The selective oxidation of CO to CO₂ by gold catalysts might find practical use in the removal of undesired trace

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amounts of CO e.g. in reformat gases for fuel cells. However from the perspective of developing new synthesis methodologies, the selective oxidation of alcohols to ketones, aldehydes and carboxylic acids as well as carboxylic acid derivatives appears even more promising [10]. Initially, Rossi, Prati and coworkers developed this field using a number of different substrate alcohols including 1,2-diols [11, 12], aminoalcohols [11], and even carbohydrates [11, 13], which could be selectively oxidized in the presence of base.

Recently, a wide range of alcohols, including allylic alcohols were shown to be selectively oxidized in high yields at moderate reaction conditions using CeO₂-supported gold nanoparticles [14]. If methanol is used as the solvent alkylic, allylic and benzylic alcohols can be oxidized directly to the corresponding methyl esters in high yields [15]. This is obviously only possible because the primary alcohols are oxidized much faster than methanol. At the same time, it became clear that the various alcohols were oxidized at different rates and this prompted us to investigate how the nature of the substrate influences its reactivity. In the presence of acid or base the oxidation proceeds to the carboxylic acid, but in the current study no acid/base is added, to allow an investigation of the initial reaction from alcohol to the corresponding aldehydes. Here, this is done by performing competition experiments rather than establishing absolute kinetics. There are several reasons for this approach. First of all, a competition experiment is more robust towards small variations in temperature, concentration, catalyst concentration/activity etc. than determination of absolute rates, and in addition it allows a reaction to be followed to as much as 90% conversion without deviation from linearity. Secondly, and more importantly, a competition experiment can be designed to probe a different step than the overall rate-determining step. In the current study, we are interested in the elementary step of the reaction that directly involves activation of the substrate alcohol and therefore it is desirable to be able to neglect any influence from step(s) involving activation of dioxygen.

2 Experimental Section

The competition experiments were run in 15 g of anisole, and for each experiment 7.8 mmol (5 mol% compared to anisole) benzyl alcohol was oxidized in competition with 7.8 mmol (5 mol% compared to anisole) of the *para*-substituted benzyl alcohol under investigation. Naphthalene was used as internal standard (1 mol% compared to anisole) and the reactions were conducted using a 500 mg of a 1% Au/TiO₂ as catalyst with oxygen supplied at atmospheric pressure. The reaction mixture was heated in

an oil-bath, which was kept at a temperature of 130 °C. Samples of 0.10 mL each were withdrawn from the reaction mixture after 0, 0.5, 1, 2, 4, 6, and 24 h reaction time, filtered, diluted with 1 mL dichloromethane and analyzed by GC. The gold catalyst (1% Au/TiO₂) was acquired from the World Gold Council (Gold reference catalyst #02–06, Sued-Chemie Catalysts Japan) and used as supplied. GC analysis was performed with a Agilent Technologies 6890N Network GC System equipped with a flame ionization detector (FID) and an Agilent HP-5 column (30 m × 0.32 mm × 0.25 μm). The temperature program was: 80 °C (1 min), then a ramp (10 °C/min) until 280 °C.

For each compound the response factor was determined by dissolving approx. 100 mg of the compound along with 100 mg of int. standard in dichloromethane, followed by a simple comparison of the respective areas obtained using GC. The determination of kinetic isotope effect was performed on smaller scale (1/5 compared to the other competition experiments), while still keeping the amount of anisole constant (15 g). To achieve an easy chromatographic separation the competition experiments were performed by reacting *p*-methyl benzyl alcohol with either benzyl alcohol or benzyl alcohol- α,α -d₂, respectively. Samples were withdrawn at the intervals stated earlier, diluted and analyzed on a Shimadzu GC-2010 system using a Supelco Equity-1 column (30 m × 0.25 mm × 0.25 μm).

3 Results

Table 1 collects retention times and response factors (relative to int. standard, naphthalene) for all compounds detected in the current study.

Tables 2–6 and Figs. 1–4 summarize the results obtained from the competition experiments. To eliminate the possibility of “cross-over” from *para*-chloro benzyl alcohol to benzyl alcohol due to dechlorination, we chose to perform the competition experiment with *para*-methyl benzyl alcohol instead. The resulting relative reactivity was then corrected for the difference in reactivity between *para*-methyl benzyl alcohol and benzyl alcohol (Table 7).

4 Discussion

To study the influence of electronic effects in the substrate on the rate of the reaction, we invoked the well-known Hammett methodology [16], and employed a range of selected *para*-substituted benzyl alcohols (Scheme 1).

The competition experiments were performed using anisole as a solvent, and for each experiment 5 mol%

Table 1 Retention times and response factors for all compounds in this study

#	Compound	Retention time (min)	Response factor
1	Anisol (solvent)	1.7	Not determined
2	Benzaldehyde	2.0	0.69
3	Benzyl alcohol	2.7	0.70
4	4-(Trifluoromethyl)benzaldehyde	3.0	0.49
5	4-Methylbenzaldehyde	3.2	0.73
6	4-(Trifluoromethyl)benzyl alcohol	3.4	0.51
7	4-Chlorbenzaldehyde	3.5	0.53
8	4-Methylbenzyl alcohol	3.7	0.75
9	Naphthalene (int. std.)	4.3	1.00
10	4-Chlorbenzyl alcohol	4.8	0.42
11	4-Cyanobenzaldehyde	5.2	0.63
12	4-Methoxybenzaldehyde	5.3	0.56
13	4-Methoxybenzyl alcohol	5.7	0.57
14	4-(Hydroxymethyl)benzoesnitril	7.4	0.62

benzyl alcohol was oxidized in competition with 5 mol% of the *para*-substituted benzyl alcohol under investigation [17]. In all cases, the disappearance of both alcohols followed first order kinetics, which allowed the construction of plots where the relative reactivity could be determined as the slope of the line [18]. Such “kinetic plots” are shown in Fig. 5, and the inherent approximations (first order reaction in both of the benzyl alcohols) are justified by the good correlation coefficients ($R^2 > 0.96$ in all cases).

With the relative reactivities of the four different *para*-substituted benzyl alcohols at hand, the Hammett plot could be constructed (Fig. 6) [19]. A linear correlation of $\log(k_X/k_H)$ was only possible with σ^+ -values ($R^2 = 0.976$), resulting in a line with a relatively small negative slope ($\rho = -1.10$). This clearly demonstrates that a build-up of positive charge takes place in the step involving substrate activation. There is no correlation with Creary's σ^* -values [20], which rules out the involvement of a benzyl radical in this reaction.

Thus, the Hammett study strongly suggests that the reaction proceeds via generation of a cation in the benzylic

Table 2 Data for the competition experiment involving benzyl alcohol and *para*-methyl benzyl alcohol. In the sample withdrawn after 24 h, no *para*-methyl benzyl alcohol was detected so this sample was omitted in the kinetic plot

Time (h)	Conversion (benzyl alcohol)	Conversion (pMe-benzy alcohol)	GC yield (benzaldehyde)	GC-yield (pMe-benzaldehyde)
0.5	0.16	0.24	0.06	0.09
1	0.23	0.35	0.13	0.22
2	0.41	0.59	0.29	0.47
4	0.59	0.77	0.47	0.67
6	0.71	0.87	0.58	0.76
24	0.99	1.00	0.94	1.00

Table 3 Data for the competition experiment involving benzyl alcohol and *para*-(trifluoromethyl) benzyl alcohol

Time (h)	Conversion (benzyl alcohol)	Conversion (pCF ₃ -benzy alcohol)	GC yield (benzaldehyde)	GC-yield (pCF ₃ -benzaldehyde)
0.5	0.21	0.05	0.18	0.03
1	0.32	0.06	0.30	0.04
2	0.45	0.10	0.40	0.05
4	0.54	0.13	0.47	0.06
6	0.57	0.12	0.51	0.07
24	0.67	0.17	0.57	0.11

Table 4 Data for the competition experiment involving benzyl alcohol and *para*-methoxy benzyl alcohol. In the samples withdrawn after 6 and 24 hrs, no *para*-methoxy benzyl alcohol was detected, so these samples were omitted in the kinetic plot

Time (h)	Conversion (benzyl alcohol)	Conversion (pOMe-benzy alcohol)	GC yield (benzaldehyde)	GC-yield (pOMe-benzaldehyde)
0.5	0.00	0.11	0.03	0.07
1	0.02	0.14	0.04	0.13
2	0.12	0.56	0.12	0.39
4	0.43	0.98	0.38	0.74
6	0.60	1.00	0.53	0.75
24	0.97	1.00	0.91	0.86

Table 5 Data for the competition experiment involving *para*-chloro benzyl alcohol and *para*-methyl benzyl alcohol

Time (h)	Conversion (pMe-benzyl alcohol)	Conversion (pCl-benzyl alcohol)	GC yield (pMe-benzaldehyde)	GC-yield (pCl-benzaldehyde)
0.5	0.19	0.20	0.14	0.04
1	0.30	0.31	0.24	0.07
2	0.43	0.39	0.38	0.12
4	0.57	0.41	0.54	0.20
6	0.65	0.52	0.63	0.24
24	0.75	0.56	0.75	0.35

Table 6 Data for the competition experiment involving *para*-methyl benzyl alcohol and benzyl alcohol (reduced concentrations)

Time (h)	Conversion (pMe-benzyl alcohol)	Conversion (benzyl alcohol)
0.5	0.19	0.13
1	0.23	0.17
2	0.28	0.20
4	0.34	0.25
6	0.38	0.28
24	0.57	0.43

position (i.e. a β -hydride elimination). A recent Hammett study performed on a heterogeneous, Ru-catalyzed oxidation of alcohols also resulted in a negative ρ -value albeit with significantly smaller slope (-0.54) [21]. This suggests that a similar mechanism is operating on Ru, despite that fact that there oxygen coverage is very high on Ru, but very low on Au [9]. One way to probe if hydride abstraction indeed is involved in the activation of the substrate is by deuterium incorporation in the α -position. The deuterated substrate should then react significantly slower due to differences in zero-point energy (ZPE) for the two isotopes. Benzyl alcohol- α,α -d₂ was acquired, and subsequently subjected to the standard oxidation procedure in competition with *p*-methylbenzyl alcohol, which allowed a

straight-forward analysis using GC. After correcting for the reactivity of the *p*-methylbenzyl alcohol compared to the parent benzylalcohol, the relative reactivity was found to be 1.82 (the double deuteration leads to a statistical correction of the KIE by a factor of two, $k_H/k_D = 1.41$).

A fully broken C-H(D) bond in the transition state (TS) would result in a KIE of 4.2 at 130 °C ($T = 403$ K) based solely on the differences in stretching frequencies (C–H: 2900 cm⁻¹, C–D: 2100 cm⁻¹) [22]. The significantly lower value determined here indicates that the bond is not fully broken in the TS, which could be due to neighbouring Au-oxo species which stabilizes the hydride transfer. In this study, we have not attempted to determine the exact nature of this “auxiliary” gold species, but it should be mentioned that a dual-site mechanism involving both Au⁰ and Au⁺ have been suggested by Guzman and Gates [23]. Obviously, the nature of the accepting oxygen-species also influences the kinetics of the reaction, and here both peroxide and superoxide species have been suggested [24], but further studies are needed to elucidate this in detail. The dual-site mechanism readily explains the superior activity of catalysts featuring alloyed nano-particles, most clearly observed with a Au-Pd catalyst [25], since one metal may be superior in hosting the substrate, whereas the other metal can be superior in O₂-activation, or hosting the reactive oxo-moiety. From the results in the present study it

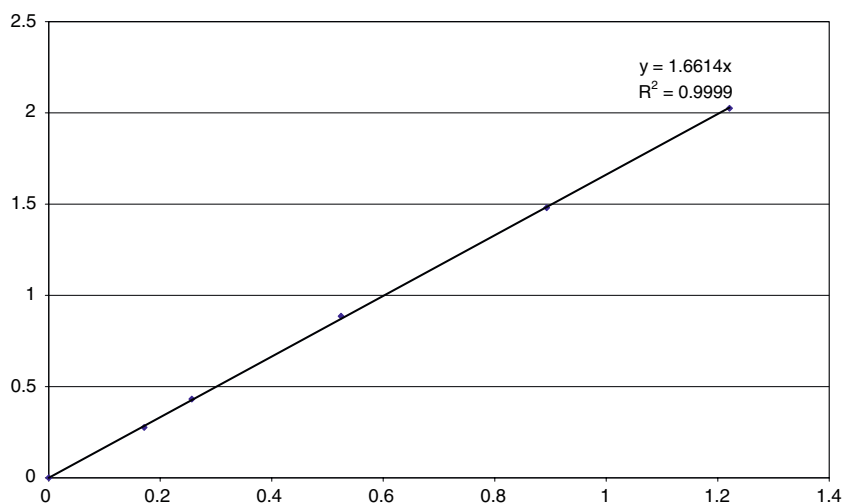
Fig. 1 Kinetic plot for the competition experiment with benzyl alcohol and *para*-methyl benzyl alcohol. The slope represent the reactivity of *para*-methyl benzyl alcohol relative to benzyl alcohol

Fig. 2 Kinetic plot for the competition experiment with benzyl alcohol and *para*-(trifluoromethyl) benzyl alcohol. The slope represent the reactivity of *para*-(trifluoromethyl) benzyl alcohol relative to benzyl alcohol

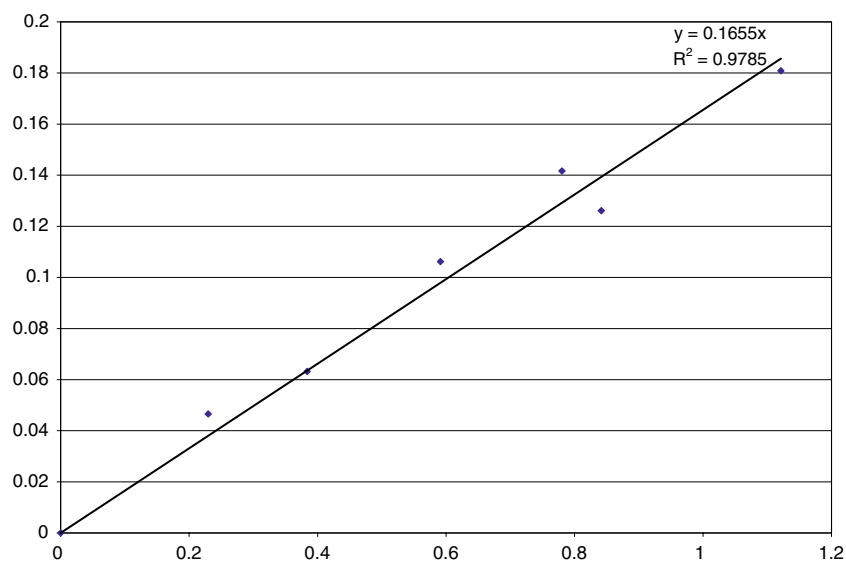


Fig. 3 Kinetic plot for the competition experiment with benzyl alcohol and *para*-methoxy benzyl alcohol. The slope represent the reactivity of *para*-methoxy benzyl alcohol relative to benzyl alcohol

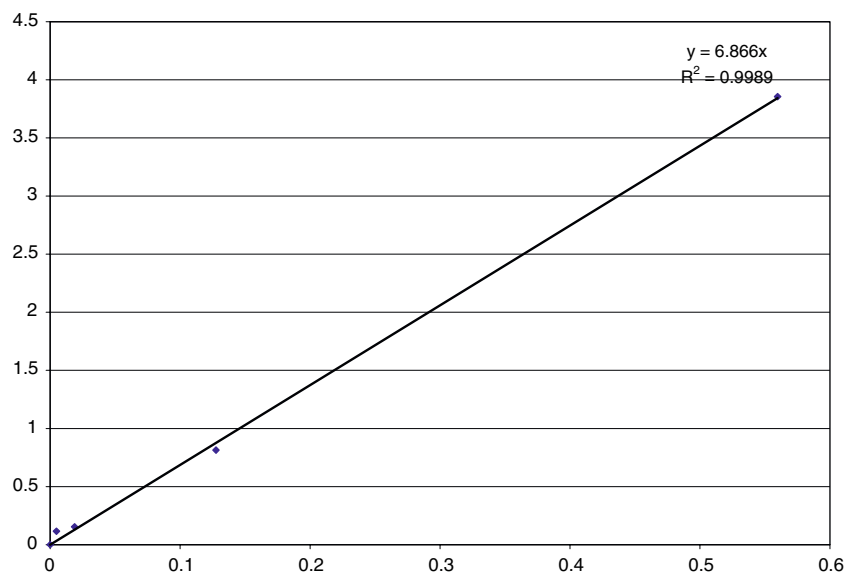


Fig. 4 Kinetic plot for the competition experiment with *para*-chloro benzyl alcohol and *para*-methyl benzyl alcohol. The slope represent the reactivity of *para*-chloro benzyl alcohol relative to *para*-methyl benzyl alcohol

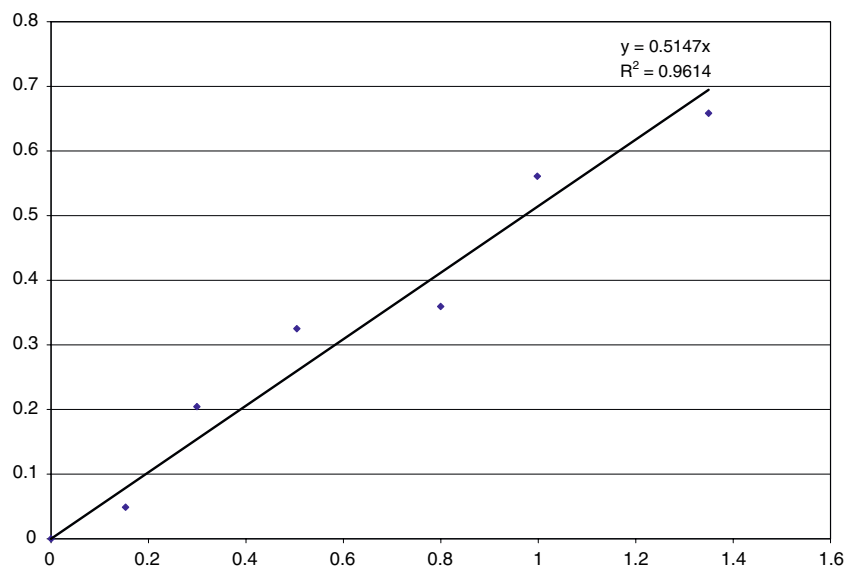
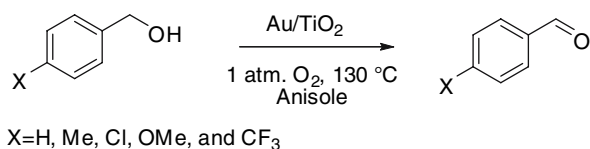


Table 7 Data for the competition experiment involving *para*-methyl benzyl alcohol and α,α -d₂-benzyl alcohol

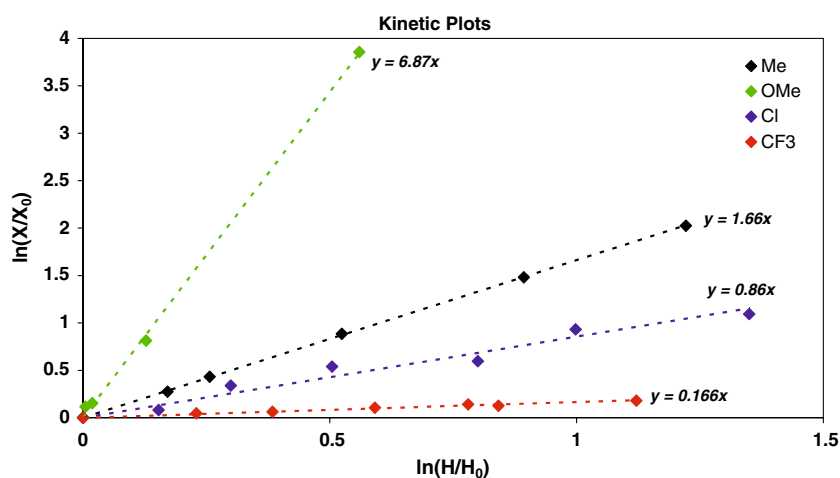
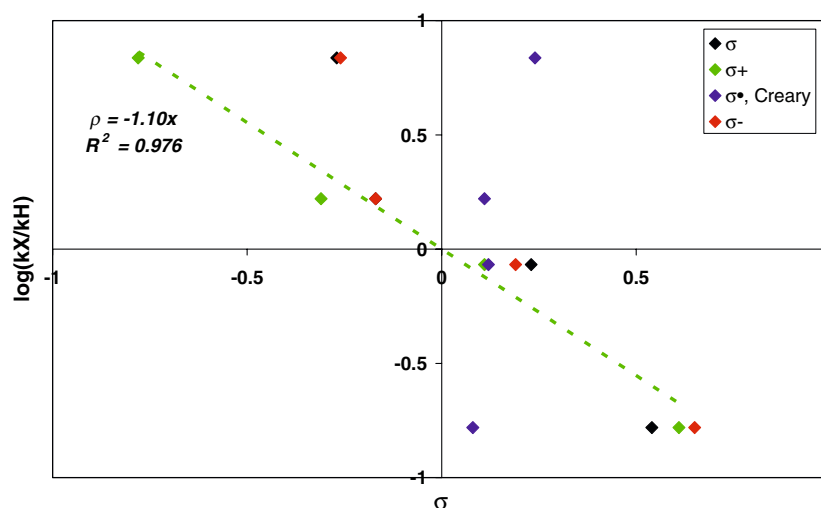
Time (h)	Conversion (pMe-benzyl alcohol)	Conversion (α,α -d ₂ -benzyl alcohol)
0.5	0.31	0.14
1	0.36	0.17
2	0.42	0.19
4	0.49	0.23
6	0.53	0.25
24	0.67	0.33

**Scheme 1** The set of *para*-substituted benzyl alcohols which was subjected to gold-catalyzed oxidation

appears that gold catalysis does not proceed through a mechanism, which is fundamentally different from the reaction catalyzed by other platinum-group metals [8]. On the contrary, the unique catalytic oxidation properties seem to be a result of the nano-sized gold particles (<5 nm) [9].

5 Conclusions

In conclusion, we propose one special gold site, which stabilizes the formation of a cation, and a neighbouring gold site to be responsible for “hosting” the reactive oxo-moiety. The KIE determined here strongly indicates that the activation of the alcohol indeed involves breakage of the C–H(D) bond in the benzylic position, thus leaving behind a partial positive charge as also suggested by the Hammett study. We are confident that the improved understanding of the intimate mechanism in the gold-catalyzed oxidation of alcohols presented here will be useful

Fig. 5 Kinetic plots illustrating the relative reactivity of the four different *para*-substituted benzyl alcohols relative to unsubstituted benzyl alcohol**Fig. 6** Hammett plot obtained from relative reactivities. A linear correlation can only be obtained using σ^+ -values

for further expanding the scope and utility of this important reaction. One may envision that the dependence on the electronic nature of the alcohol documented here can be useful in the development of new reactions which are more selective towards a specific alcohol moiety in a polyhydroxylated substrate.

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