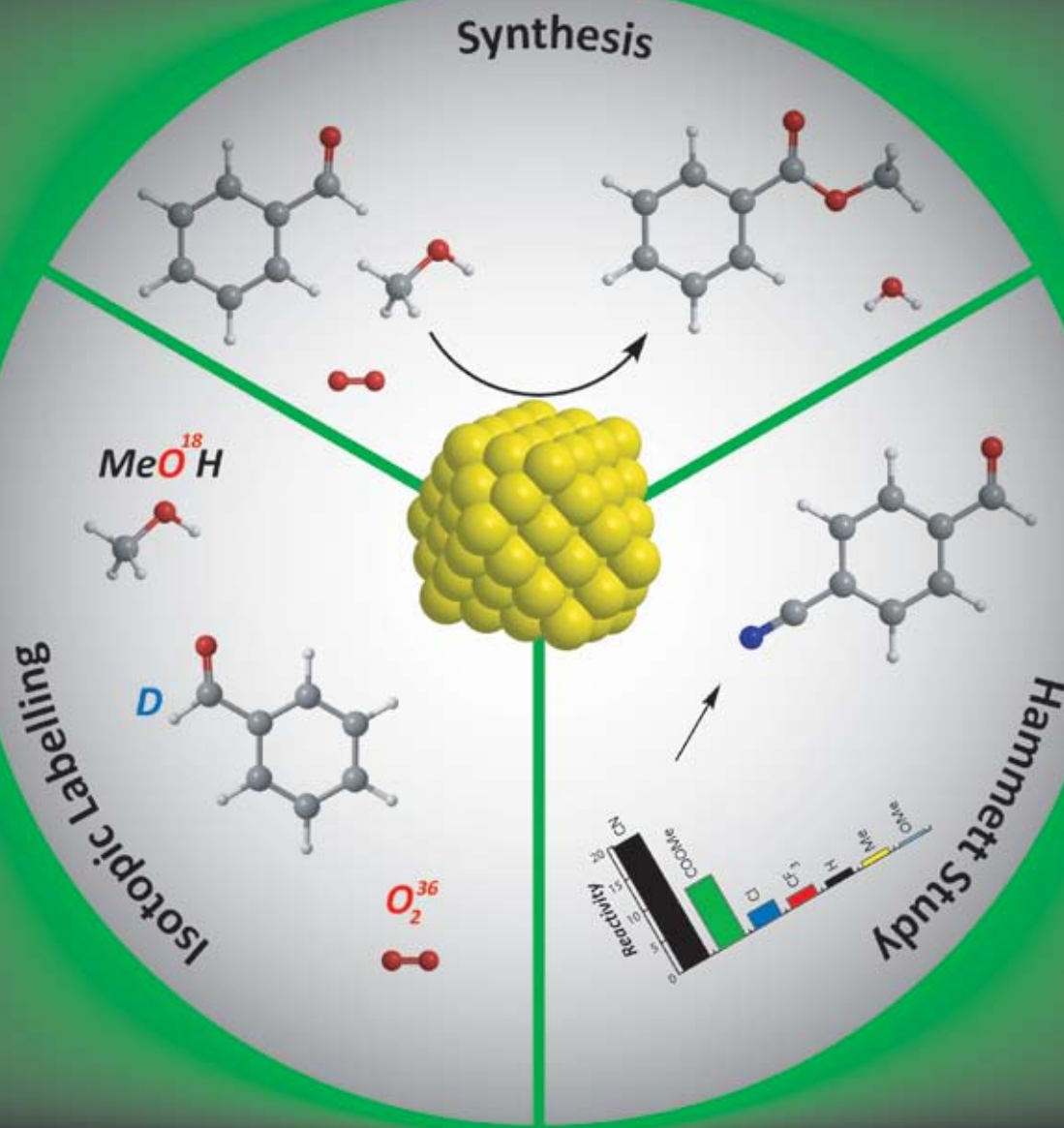


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Mechanistic investigation of the gold-catalyzed aerobic oxidation of aldehydes: added insight from Hammett studies and isotopic labelling experiments†

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The gold-catalyzed aerobic oxidation of aldehydes proceeds through development of a partial negative charge and has a significant kinetic isotope effect ($k_{\text{H}}/k_{\text{D}} = 2.8\text{--}2.9$), which illustrates that activation of the C–H bond takes place in the rate-determining step.

Since the pioneering discovery by Haruta and coworkers that nano-particulate gold catalyzes the oxidation of CO effectively at low temperatures,¹ the scope of gold-catalyzed oxidation reactions has expanded tremendously.² In particular, the oxidation of alcohols has received significant attention,³ and rightfully so since the reaction satisfies most of the demands for a modern, sustainable, and “green” reaction. The high activity of the supported gold nanoparticles allows the use of air as the stoichiometric oxidant, thus ensuring optimal atom economy. Furthermore, the reaction has the potential to play an important role in the synthesis of both commodity and fine chemicals,⁴ where the use of a heterogeneous catalyst allows the isolation of product(s) by a simple separation. This represents a major improvement compared to more “traditional” oxidation technologies in the speciality chemicals field, which often rely on stoichiometric amounts of heavy metals and/or halogens.

The mechanism for the oxidation of CO to CO₂ has been studied in great detail,⁵ but the mechanism(s) for oxidation of more complex substrates have only recently received attention.⁶ We have previously studied the oxidation of benzyl alcohol to benzaldehyde using both Hammett methodology and isotope studies.⁷ These investigations clearly identified the important step in this reaction to involve the abstraction of a hydride in the β -position with concomitant build-up of positive charge in the benzylic position. Depending on the reaction conditions, the aldehyde can either be isolated or oxidized further to the acid,⁸ or ester⁹ (in the presence of a suitable alcohol), and in the current work we investigate the mechanism for this oxidation of aldehydes.

This reaction is important in itself as the produced methyl esters are valuable chemicals (*e.g.* as solvents, extractants, diluents and ingredients in perfumes), and can in addition

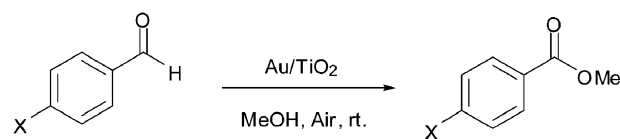
serve as a key step in the transformation of renewable resources into commodity chemicals.¹⁰

Interestingly, aldehyde oxidation only takes place in the presence of water (yielding the acid) or an alcohol (yielding the ester), thus strongly suggesting the intermediacy of a hydrate or hemiacetal, respectively. However, when the necessary condition of having either water or alcohol present is satisfied, the reaction takes place much more readily than alcohol oxidation (even significantly below room temperature¹¹), thus making it impossible to investigate when the reaction is started from the alcohol.

To study the influence of electronic effects in the substrate on the rate of the reaction, we invoked the well-known Hammett methodology, and focused our attention on a range of selected *para*-substituted benzaldehydes (Scheme 1).¹² A series of competition experiments were performed in methanol, which allowed a direct conversion into methyl esters suitable for GC analysis. In all cases, the disappearance of both benzaldehydes followed first order kinetics, which facilitated construction of plots where the relative reactivity could be easily determined as the slope of the line (Fig. 1).

The inherent approximations (first order reaction in both of the benzaldehydes, and equal reaction order for other components) are justified by the good correlation coefficients, see Table 1.

With the relative reactivities for the six *para*-substituted benzaldehydes in hand, the Hammett plot could be constructed using σ -values from the literature (Fig. 2).^{13,14} When examining the kinetic data it immediately became clear to us that no single set of σ -values was valid over the entire span of reactivity from the very electron-donating substituent (OMe) to the very electron-accepting substituent (COOMe). With the regular σ -values the slope is positive (black dots), indicating that a partial negative charge is built up in the rate-determining step, but the CF₃-substituted aldehyde has a significantly lower reactivity than expected. Instead, we attempted to fit Creary's σ^{\bullet} -values (blue dots), and now obtained a good correlation for the substrates with electron-withdrawing



X=H, Me, Cl, OMe, CF₃, CN, COOMe

Scheme 1 The set of *para*-substituted benzaldehydes which was subjected to gold-catalyzed oxidation in the presence of methanol.

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† Electronic supplementary information (ESI) available: Detailed experimental procedures for the competition experiments and for the GC analysis (column type, temperature program and retention times). See DOI: 10.1039/b803270j

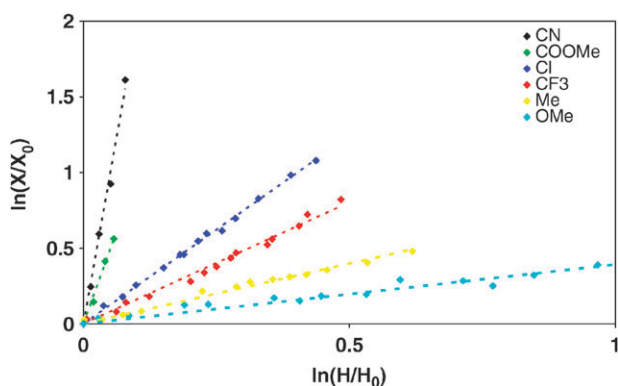


Fig. 1 The kinetic plots illustrating the relative reactivity of the six different *para*-substituted benzaldehydes relative to benzaldehyde itself.

substituents ($X = \text{Cl}, \text{CF}_3, \text{CN},$ and COOMe) indicating that a radical mechanism is operating. For the substrates with an electron-donating substituent the observed low reactivity is expected from several of the possible σ -values ($\sigma, \sigma^+,$ or σ^-) and it is clear that a radical mechanism is not operating.

Determination of kinetic isotope effects (KIE) is one of the most effective ways to gain insight into the nature of the rate-determining step in a complex reaction. In the current study we decided to employ deuterated benzaldehyde, and investigate its reactivity in comparison to the non-labelled compound. If addition of a nucleophile (*e.g.* MeOH or MeO^-) took place in the rate-determining step the KIE should be less than unity (“inverse”, $k_{\text{H}}/k_{\text{D}} < 1$), due to a loosening of the in-plane vibration modes in the transition state. On the other hand, if a weakening of the C–H(D) bond occurred in the transition state for oxidation, the KIE should be larger than unity (“normal”, $k_{\text{H}}/k_{\text{D}} > 1$) with a theoretical maximum value of 7 when the bond is fully broken in TS (298 K).¹⁵ The KIE was first determined indirectly, by comparing the reactivities of benzaldehyde and *d*-benzaldehyde to that of *p*- CH_3 -benzaldehyde in two separate experiments. The resultant KIE was 2.83, which clearly indicates that the bond to H (or D) is partially broken in the rate-determining transition state. Using a GC-MS it was also possible to perform the competition experiment in a direct fashion using selected ion monitoring (SIM) for the molecular ions of both compounds ($M = 106$ and 107 for the normal and deuterated substrate, respectively). This experiment resulted in a KIE of 2.88 in excellent agreement with the result from the indirect determination, thus also adding further support to the validity of the competition experiments.

The combination of a relatively large primary KIE and simultaneous development of a partial negative charge sug-

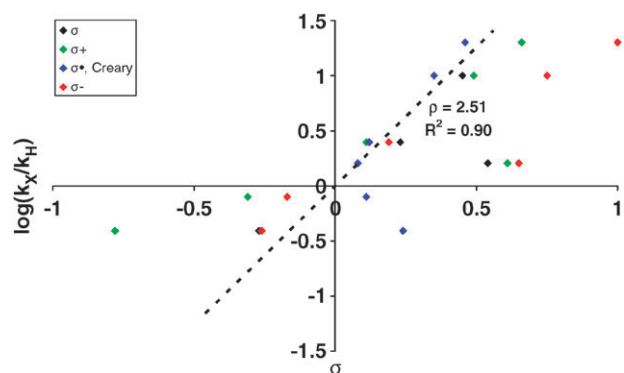


Fig. 2 Hammett plots obtained using four different sets of σ -values. The positive slope indicates build up of a partial negative charge in the rate-determining step.

gests that proton abstraction is the rate-determining step. For the more electron-withdrawing substituents the superior fit to Creary’s σ^* -values strongly suggests that the radical anion of the aldehyde is formed. In this case the reaction could be abstraction of H^\bullet with *e.g.* an Au-O-O^\bullet species in a radical recombination.¹⁶ The relative energies for these two pathways (H^+ vs. H^\bullet abstraction) is likely to be heavily influenced by the inherent electronic properties of the substrate. In the current study the transferred proton is abstracted from a benzylic position, allowing for a stabilizing delocalization of the developed negative charge. In the more general case of alcohol oxidation (*e.g.* with ethanol) it is not *a priori* clear which of the two paths are favourable, however the build up of negative charge in the transition state documented in the current study should still be valid.

It is generally accepted that in gold-catalyzed oxidations the transferred hydrogen is accepted by an oxygen species residing on the gold surface. Several different oxygen species have been suggested, including oxo, peroxy and superoxy.¹⁷ In the gas-phase oxidation of CO to CO_2 the additional oxygen clearly originates from dioxygen, however, it is less clear from which source the oxygen originates in liquid phase oxidations. The formal addition of the MeO moiety from methanol seems to be a reasonable suggestion, which could arise *via* prior formation of the hemiacetal, and to investigate this point in detail we acquired O^{18} -labelled oxygen and methanol. The oxidation reaction was then conducted as usual, while monitoring the reaction mixture by GC-MS using SIM. In the experiment with labelled oxygen we did not observe significant incorporation of O^{18} , only 1%, indicating that oxygen originating from dioxygen is practically never incorporated into the ester product. On the other hand, when labelled methanol (95% isotopic purity) was used as a solvent, the molecular ion of the

Table 1 Characteristics for the competition experiments

<i>para</i> -Substituent X	Relative reactivity $k_{\text{X}}/k_{\text{H}}$	Correlation coefficient R^2	Final conversion PhCHO	Final conversion <i>p</i> -X-PhCHO
CN	19.8	0.992	12%	95%
COOMe	9.82	0.991	15%	95%
Cl	2.49	0.998	35%	66%
CF_3	1.61	0.989	38%	56%
Me	0.80	0.988	46%	38%
OMe	0.39	0.944	68%	35%

O¹⁸-labelled methyl ester was, not surprisingly, significantly larger than that of the un-labelled ester (92 : 8), indicating that nearly complete incorporation of the labelled oxygen-atom had taken place. Thus, it is clear that in the present study dioxygen functions as the stoichiometric oxidant by providing reactive oxo functionalities, and that the methoxy moiety always originates from methanol. This suggests that reversible formation of the hemiacetal takes place prior to reaction with the gold-oxo functionality.¹⁸

In the present study we have investigated the mechanism for the gold-catalyzed, aerobic direct oxidation of aldehydes to methyl esters in methanol, and found that a significant partial negative charge is developed. The determined kinetic isotope effect (k_H/k_D) was found to be 2.8–2.9, clearly indicating that breakage of the bond to the neighbouring hydrogen atom takes place in the rate-determining step. In addition, experiments which involved either O¹⁸-labelling of oxygen or methanol clearly indicated that the additional oxygen functionality present in the product ester originates from methanol rather than dioxygen, which is compatible with reversible formation of the hemiacetal prior to the actual proton abstraction.

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