Influence of adsorption geometry in the heterogeneous enantioselective catalytic hydrogenation of a prototypical enone

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ABSTRACT

Asymmetric catalysis is of paramount importance in organic synthesis and in current practice is achieved by means of homogeneous catalysts. The ability to catalyze such reactions heterogeneously would have a major impact both in the research laboratory and in the production of fine chemicals and pharmaceuticals, yet heterogeneous asymmetric hydrogenation of C=C bonds remains hardly explored. Very recently, we demonstrated how chiral ligands that anchor robustly to the surface of Pd nanoparticles promote asymmetric catalytic hydrogenation: ligand rigidity and stereochemistry emerged as key factors. Here, we address a complementary question: how does the enone reactant adsorb on the metal surface, and what implications does this have for the enantiodifferentiating interaction with the surface tethered chiral modifiers? A reaction model is proposed which correctly predicts the identity of the enantiomer experimentally observed in excess.

KEYWORDS Enantioselective Catalysis; Isophorone; Hydrogenation; NEXAFS; Alkene.

Introduction

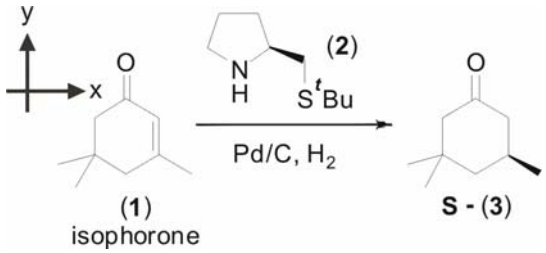
The development of homogenous chiral transition metal catalysts created a major new field of chemistry: the synthesis of pure enantiomers from achiral precursors. The academic and technical consequences of this advance transformed synthetic chemistry as acknowledged by the award of the 2001 Nobel Prize for chemistry.[1,2,3] By comparison, effective *heterogeneously* catalyzed enantioselective reactions are rarities,[4,5] despite their huge potential importance which derives from the major operational advantages offered by heterogeneous over homogeneous catalysis. Thus although homogeneously-catalyzed asymmetric hydrogenation of C=C bonds is often a critical step in an overall synthetic scheme (e.g. the synthesis of L-dopa) no effective heterogeneously catalysed analogues exist.

The ability to catalyze such reactions *heterogeneously* would have a major impact both in the research laboratory and in the production of fine chemicals and pharmaceuticals. The Pd-catalyzed proline-directed asymmetric hydrogenation of isophorone was thought to be an example of such a process, in which the proline acted as a chiral auxiliary.[6] However, we showed that in this case the metal surface merely carries out a racemic hydrogenation,[7] the observed enantiomeric excess in the product being simply due to subsequent kinetic resolution that takes place in solution as a result of one enantiomer of the product reacting with the chiral agent much faster than the other. In other cases,[8,9] it has been claimed/reported that the enantiodifferentiating step is both heterogeneous and catalytic, although the alkaloid modifiers used are themselves known to undergo hydrogenation,[8] necessitating replenishment during the course of the reaction.[10]

In order to achieve true *heterogeneous* enantioselective C=C hydrogenation it is necessary to force the crucial enantiodifferentiating step to take place *at the metal surface*. Recently, we demonstrated how purposefully-synthesized chiral ligands that anchor robustly to the surfaces of Pd nanoparticles and resist displacement do enable true heterogeneous asymmetric catalytic hydrogenation.[11] Ligand rigidity and stereochemistry emerged as key factors affecting the degree of asymmetric induction achieved, thus providing valuable insight into the reaction mechanism.

By experimentally determining the adsorption geometry of isophorone on an extended palladium surface, fundamental insight into possible reaction steps is obtained allowing a plausible mechanism to be put forward for the origin of enantioselectivity in this system. This mechanism correctly predicts the identity of the enantiomer that is actually produced in excess (Scheme 1).

Scheme 1. Pd-catalyzed hydrogenation of 3,5,5-trimethylcyclohex-2-enone (**1**) directed by (*S*)-2-(tert-butylthiomethyl)pyrrolidine (**2**) to produce 3,3,5-trimethylcyclohexanone (**3**) ((*S*)-**3** is the enantiomer produced in excess).



Experimental Methods

Isophorone was purchased from Sigma Aldrich. The preparation, mounting, heating, cooling and manipulation of the Pd(111) single crystal are described in the Supporting information, likewise the methodology used for the synchrotron radiation measurements. X-ray photoelectron spectroscopy (XPS) control experiments showed that there was no detectable beam damage of the adsorbed layer during the acquisition of near edge X-ray absorption fine structure (NEXAFS) and XPS data. Quoted coverages are based on estimation of the monolayer point (one monolayer = 1 ML) from the associated shift in C 1s binding energy that is apparent in the temperature programmed XP spectra. High resolution fast XPS and NEXAFS measurements were carried out on the SuperESCA beamline at the ELETTRA synchrotron radiation facility in Trieste, Italy.

Results and Discussion

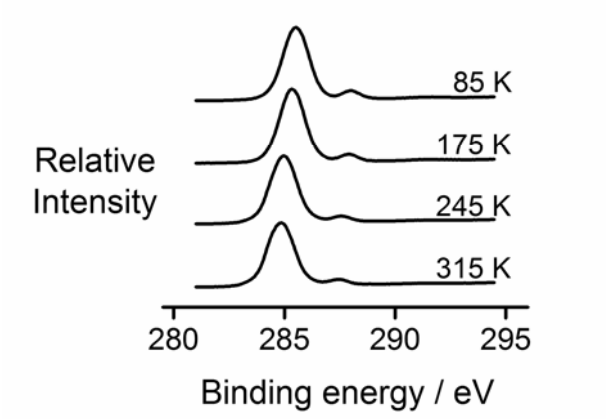


Figure 1. The surface chemistry of isophorone on Pd(111). Subset of carbon 1s temperature programmed XPS for isophorone (**1**) on Pd(111) showing key changes with temperature (for full dataset see Supporting information), obtained with an incident photon energy of 350 eV.

High resolution fast XP and NEXAFS spectra of isophorone (**1)** adsorbed on a Pd(111) single crystal surface were acquired under a variety of conditions. The (111) surface was chosen because it should be the dominant crystal plane at the surfaces of the ~ 8 nm nanoparticles used in the catalysis experiments reported in our previous work.[11] Figure 1 shows a partial set of temperature programmed carbon 1s XP spectra acquired over the range 85 K to 315 K at 6 K intervals, after deposition of ~ 3 ML of isophorone (**1**) on the clean metal surface. (The full dataset is presented in the Supporting information). Initially, at 85 K, two C 1s signals are evident at 285.2 eV and 288.0 eV due to the non-carbonyl carbon atoms[12] and the carbonyl carbon,[13,14] respectively. Their intensity ratio is 8:1, as expected for a molecular multilayer consisting of intact molecules. Between 175 K and 315 K, the spectra undergo a significant shift of ~ 0.4 eV to lower binding energy and a small decrease in intensity, the latter reflecting the high surface sensitivity of the measurement (C 1s photoelectron kinetic energy 65 eV) as explained in the Supporting Information. These changes are attributable to desorption of the multilayer, with the molecules remaining in the contact layer continuing to exhibit the 8:1 intensity ratio characteristic of

isophorone. The important point is that the 315 K spectrum is consistent with chemisorbed isophorone molecules having retained their integrity at the temperature pertinent to the catalysis experiments. This conclusion that adsorption is non-dissociative is strongly confirmed by the NEXAFS data presented in Figure 2.

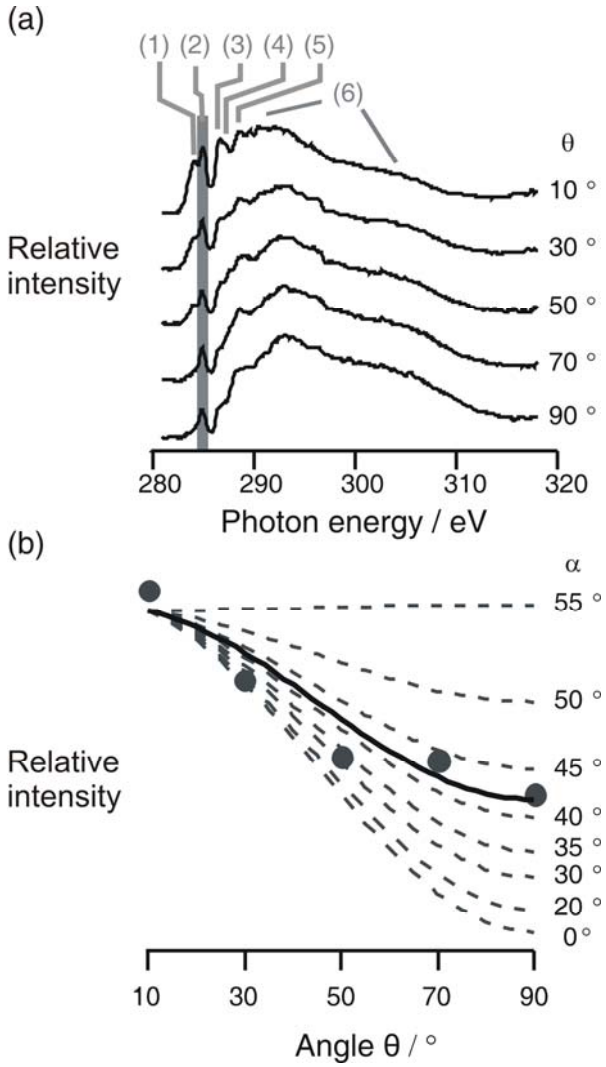


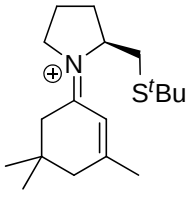
Figure 2. The adsorption geometry of isophorone on Pd(111). (**a**) C K-edge NEXAFS of 0.4 ML isophorone (**1**) adsorbed on Pd(111) at 200 K. (**b**) Fitting of observed normalized π* resonance intensities (resonance 2) to calculated values as a function of photon-incidence angle, θ. Molecular tilt angles with respect to the surface are indicated.

Representative step edge-normalized C K-edge NEXAFS spectra for a submonolayer coverage (0.4

ML) of isophorone adsorbed on Pd(111) as a function of photon incident angle acquired at ~~and~~ 200 K are shown in Figure 2a. Detailed assignment of the various spectral features is provided in the Supporting information. Figure 2b shows the angular dependence of the most important resonance (denoted resonance 2 in Figure 2a - the C 1s → π_1* of Isophorone (C=C)), overlaid on theoretical curves[15] calculated as a function of molecular tilt angle (α) with respect to the surface, best fit being achieved for α = 42° corresponding to strong tilting of the C=C-C=O framework with respect to the palladium surface. (Resonance 3 exhibits a broadly similar angular dependence, as expected, but the presence of other features in this spectral region make it less reliable for use in determining molecular orientation.) The technique does not allow a distinction to be made between tilt about the x or y molecular axes, or some combination of the two (Scheme 1). However, as shown below, this does not affect the conclusions that may be drawn.

In our earlier work[11] we proposed a mechanism for the asymmetric hydrogenation of isophorone (**1**) which involved interaction between the secondary amine of the chiral modifier **2** and the ketone functionality of the enone to yield an iminium species (**4**) (or enamine) as the reaction intermediate (Scheme 2). In keeping with this we found that, when used as the chiral agent, a tertiary amine analogue of **2** which prevents formation of such an intermediate gave only racemic product.

Scheme 2. Intermediate iminium species (**4**) resulting from condensation of **1** and **2**, which yields H_2O as a co-product.



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Taking these findings into account, we now offer a plausible mechanistic hypothesis based on steric and geometric effects that arise during asymmetric heterogeneous hydrogenation of isophorone when both reactant and chiral modifier are *confined to the metal surface*. It is important to note that our model correctly predicts the identity of the enantiomer that is produced in excess, as shown below, a key point in its favor. The first step postulates formation of an iminium intermediate resulting from reaction of the enone with the chiral modifier, by analogy with the well known *un-catalyzed* homogeneous reaction between secondary amines and carbonyl compounds in solution which results from a nucleophilic attack by the amine of the pyrrolidine ring on the isophorone carbonyl. However, it is important to recognize that in the present case we are dealing with a *catalyzed* process comprising a quasi two-dimensional system whose behavior is determined by the collective properties of the delocalized valence electrons present in the metal and the strongly perturbed valence orbitals of the adsorbed reactants: a very different situation. Accordingly, one cannot speak of adsorbed species bearing or transferring formal charges in the sense that is well founded and developed in organic and organometallic chemistry. Nor can it be assumed that the reaction coordinates of a constrained, strongly-interacting two-dimensional system bear any resemblance to those of the same molecules approaching each other in a three-dimensional framework. Thus when catalytic reactions take place between molecules chemisorbed on a metal surface it is not generally possible to make straightforward analogies with formal mechanisms based on the homogeneous chemistry of free molecules. We draw attention to these points so as to alert the reader to the fact that the stereochemistry of our proposed mechanism is very different from the generally accepted Bürgi-Dunitz mechanism for the homogeneous un-catalyzed attack of carbonyls by nucleophilic species. Substantiation or refutation of our proposal awaits further work that, either way, should advance the subject.

Figure 3a depicts the two possible configurations of iminium intermediate **4** resulting from interaction of the prochiral substrate **1** and the chiral modifier **2** assumed to adsorb to the metal surface as shown: it is clear that different degrees of steric encumbrance arise. The conformation shown in the left panel

should be sterically disfavored relative to that shown in the right panel, the geminal dimethyl group on **1** (Me*) interfering more strongly with the *tert*-butyl group on the chiral modifier **2**. *Accordingly, the (S)-enantiomer of the product (S)-**3** should predominate, in agreement with experiment.*

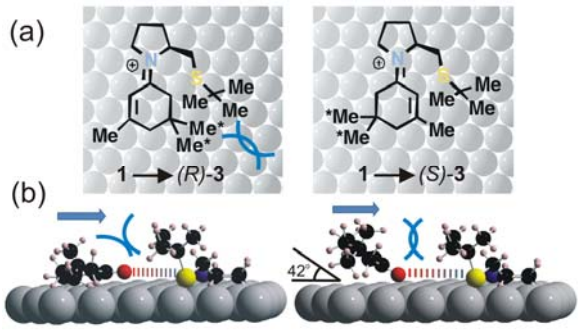

Figure 3. The asymmetric heterogeneous hydrogenation of isophorone. (a) The difference in steric inhibition for reactant (**1**) – modifier (**2**) configurations of iminium intermediate **4** that lead to (*R*) and (*S*)-**3**. (b) Enhanced steric interaction between the geminal dimethyl group (Me*) of isophorone and the *tert*-butyl group of the chiral modifier upon tilting isophorone (**1**) from flat to ~ 42°. At 42° it is clear that these two groups would sterically interfere in the orientations depicted when following direction of approach indicated by blue arrows.

Consider now Figure 3b which illustrates the *disfavored* reactant/modifier configuration corresponding to formation of the iminium intermediate that leads to the (*R*)-**3** product. The chiral modifier **2** is shown with the pyrrolidine ring approximately parallel to the surface in accord with the known behavior[16] of functionalized pyrrolidines. An encounter involving a flat-lying isophorone molecule (**1**) is illustrated on the left. However, NEXAFS shows that adsorbed isophorone (**1**) is actually *strongly tilted* as illustrated on the right. This tilting would increase the degree of steric hindrance, further disfavoring formation of the iminium species that leads to (*R*)-**3**, hence acting to further enhance enantioselectivity towards the (*S*)-**3** product. Note that tilting about the molecular x or y axes (Scheme 1) or, more likely, a combination of the two, would lead to the same outcome: steric inhibition of (*R*)-**3** product formation.

Conclusions

The enantioselective heterogeneous hydrogenation behavior of isophorone is understandable in terms of steric effects, which are amplified by strong tilting of the molecule with respect to the metal surface. Specifically, in the substrate/ligand configuration that leads to the (*R*)-**3** product, the already unfavourable interaction between the geminal dimethyl group of **1** and the *tert*-butyl group of the chiral ligand is exacerbated by tilting, thus favouring the formation of (*S*)-**3** product. The mechanistic insight uncovered here by considering the adsorption geometry of the reactant on the surface crucially correctly predicts the sense of the observed enantioselectivity and signposts approaches to the rational design of improved catalytic systems.

ACKNOWLEDGMENTS

S.K.B. acknowledges financial support from Cambridge University, Trinity Hall, Cambridge, the UK Society of the Chemical Industry and the International Precious Metals Institute. G.K., D.J.W., and A.C.P. acknowledge financial support from the UK Engineering and Physical Sciences Research Council. O.P.H.V. acknowledges financial support from King's College, Cambridge. The authors are grateful to Silvano Lizzit for his assistance during the synchrotron experiments.

SUPPORTING INFORMATION PARAGRAPH

Supporting information includes additional experimental details, complete dataset of temperature programmed XP spectra for isophorone, and detailed assignment of the NEXAFS spectra. This information is available free of charge via the Internet at http://pubs.acs.org.

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