Asymmetric Hydrogenation on Chirally Modified Pt: Origin of Hydrogen in the N−H−O Interaction between Cinchonidine and Ketone

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S *Supporting Information*

ABSTRACT: An understanding of the chiral site−substrate interaction is a necessary prerequisite for the rational design and development of efficient heterogeneous asymmetric catalysts. For the enantioselective hydrogenation of α-ketoesters on cinchona-modified platinum, it has earlier been proposed that the crucial interaction is an N−H−O type hydrogen bonding between the quinuclidine N atom of cinchonidine and the α-carbonyl O atom of the substrate. The involved hydrogen atom has been proposed to originate either from protonation (in protic solvent) or from dissociatively adsorbed hydrogen (in aprotic solvent), but experimental evidence for the latter was lacking so far. In this study, in situ attenuated total reflection infrared spectroscopy combined with modulation excitation spectroscopy and phase sensitive detection provides clear evidence that in aprotic media, hydrogen dissociated on Pt is involved in the N−H−O interaction between the chiral modifier, cinchonidine, and the ketone. In the absence of Pt (pure alumina support), no such interaction occurs, indicating the crucial role of dissociated hydrogen in the formation of the diastereomeric transition complex.

The synthesis of optically pure compounds is one of the most challenging tasks in chemical industry, particularly in the areas of pharmaceuticals, agrochemicals, flavors, and fragrances.[1a] Among the various methods[1b] applied for the production of pure enantiomers, successful heterogeneous asymmetric catalysis has so far mainly been confined to hydrogenation of activated ketones using cinchona alkaloid-modified noble metal catalysts or tartaric acid modified nickel. Since the original discovery of the Pt−cinchona system by Orito et al,[2] the asymmetric hydrogenation of activated ketones, particularly α-ketoesters, over cinchonidine (CD)-modified supported Pt was studied extensively by several groups, and considerable insight into the reaction mechanism was gained, as covered in several recent reviews.[3] Among other aspects of this fascinating catalytic system, the reaction mechanism and particularly the origin of the enantiodifferentiation, that is, the interaction between adsorbed CD and substrate, are subject of an ongoing debate. Different types of interactions between the cinchona modifier and the substrate were proposed by various groups, including: (i) H-bond between protonated quinuclidine N of CD and keto-carbonyl O atom, i.e., N−H−O type H-bonding;[4] (ii) nucleophilic attack of the

quinuclidine N atom on the keto-C atom, i.e., N−C type attractive interaction;[5] and (iii) the two-point H-bonding model assuming N−H−O bonding between the quinuclidine N of CD and the ester carbonyl O and a bifurcated H-bond involving two aromatic H atoms of CD at 5′- and 6′-positions and the O atom of the keto-carbonyl group.[6]

Among these interactions, only N−H−O type H-bonding was demonstrated by in situ IR spectroscopic analysis in the liquid phase, that is, under similar conditions as encountered during asymmetric hydrogenation.[7] However, the origin of H in this N−H−O bond that results in a diastereomeric complex consisting of CD and the ketoester still remained unclear because the study utilized CH_2Cl_2 as a solvent, which decomposes on Pt producing hydrochloric acid, which can protonate the quinuclidine N atom,[8] and thus, these experiments did not allow the unambiguous conclusion that the hydrogen involved in the N−H−O bond originates from adsorbed hydrogen.

Here, we provide evidence that in aprotic solvents, the hydrogen in the N−H−O bond originates exclusively from dissociated hydrogen adsorbed on the platinum.

For this purpose, we have investigated the transient adsorption−desorption behavior of methyl benzoylformate (MBF) on CD-modified Pt/Al_2O_3 in a H_2- or D_2-saturated aprotic solvent, toluene, by means of in situ attenuated total reflection infrared (ATR-IR) spectroscopy combined with modulation excitation spectroscopy (MES) and phase sensitive detection (PSD).[9] The key advantages of this technique are that interactions at complex catalytic solid−liquid interfaces can be detected with much higher sensitivity (enhanced signal-to-noise ratio) due to the PSD of periodically varying signals and the high selectivity for species, which are affected by the stimulation. Here, we applied the cycling between two different solutions; 0.1 mM of CD in toluene was first admitted to a flow-through reactor for 75 s, followed by 1.0 mM of MBF and 0.1 mM of CD in toluene for 75 s. This cycle was continuously repeated nine times to obtain a stable response. The spectra of the last six cycles were averaged to remove the spectral noise for sensitive detection of the trace amounts of reaction intermediates, which cannot be detected by any conventional FT-IR spectroscopic techniques. The averaged response $A(t)$ obtained by MES was mathematically processed to extract the kinetic information, i.e., phase-domain spectra, by means of the PSD method according to the
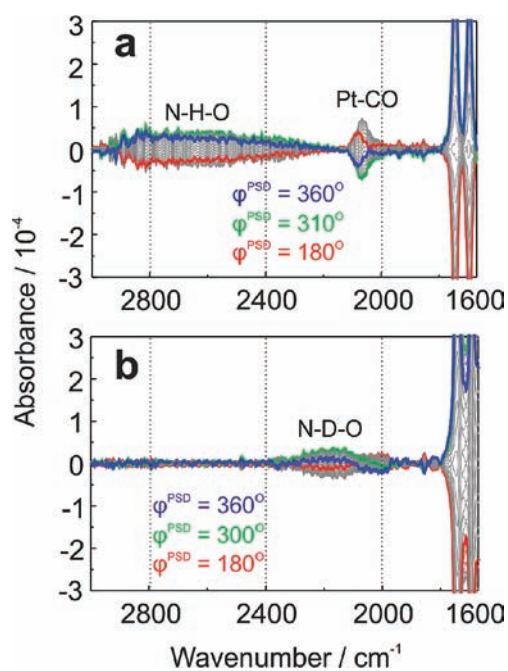
Figure 1. Phase-domain ATR-IR spectra during MBF adsorption−desorption induced by periodically changing between 1 mM solution of MBF in (a) H_2- or (b) D_2-saturated toluene and pure toluene over CD-modified Pt/Al_2O_3 at 283 K.

following eq 1:

$$A_k(\phi_k^{PSD}) = \frac{2}{T}\int_0^T A(t)\sin(k\omega t + \phi_k^{PSD})\,dt \qquad (1)$$

where T is the length of one period, ω is the modulation frequency, k is the demodulation index, ϕ is the demodulation phase angle for $k\omega$ demodulation, and $A(t)$ and A_k are the active species response in time- and phase-domain, respectively. Analysis of the phase angle ($0° \rightarrow 360°$), i.e., time-delay of reaction intermediates, provides kinetic information of chemical species involved in the surface processes.

Figure 1a shows phase-domain ATR-IR spectra during MBF adsorption−desorption on CD-modified Pt/Al_2O_3 in H_2-saturated toluene. Upon admission of MBF (two intense absorption bands at $1700-1750\ cm^{-1}$) to CD-modified Pt/Al_2O_3, a broad band at around $2600\ cm^{-1}$ emerged with the same kinetics, i.e., $\varphi = 310, 360°$. This broad signal is characteristic of N−H−O type H-bonding between the protonated quinuclidine N and O atom of the α-carbonyl of the substrate,[7] MBF in this study.

Adsorbed CO on Pt was also observed because of some decomposition of MBF. When the solutions were saturated with D_2, the broad band shifted toward $2200\ cm^{-1}$ because of the isotope effect, indicating the formation of N−D−O bonding (see Figure 1b). This is clear evidence that the hydrogen atom in N−H−O bonding originates from H_2 molecules to form the CD−MBF diastereomeric complex. This bonding has been found to be crucial for enantiodifferentiation. Blocking of the quinuclidine nitrogen and thus preventing H-bond formation resulted in a complete loss of enantioselectivity.[10] Similar experiments without Pt, that is, with CD-modified Al_2O_3, showed no evidence for the N−H−O bonding even though CD was present on the Al_2O_3 surface (see Figures S1 and S2, Supporting Information). This behavior demonstrates that the chiral
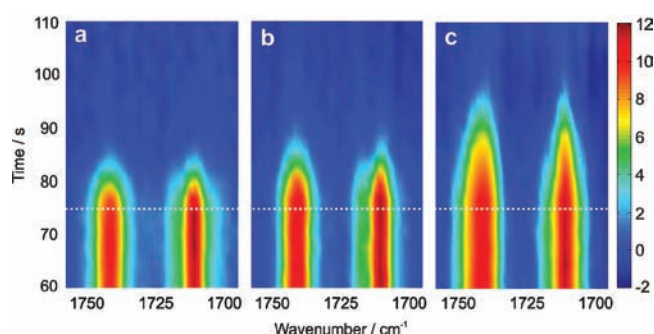

Figure 2. Time-domain ATR-IR spectra of MBF adsorption−desorption induced by periodically changing between a 1 mM solution of MBF in H_2-saturated toluene and pure toluene over CD-modified (a) ZnSe window (blank test), (b) Al_2O_3, and (c) Pt/Al_2O_3 at 283 K. The white dotted line (75 s) marks the time when the solution was switched from MBF in toluene to pure toluene to start the MBF desorption. The unit of absorbance (color bar) is 10^{-4}.

Scheme 1. Adsorption Modes of CD[a] Proposed Based on Previous Detailed ATR-IR Studies[12]
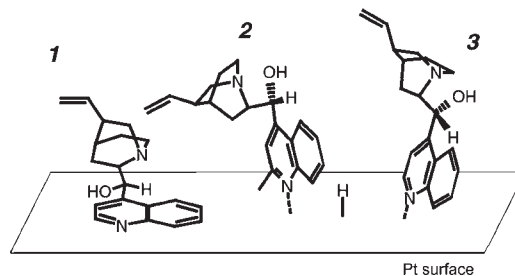
[a] The orientation of the quinoline moiety with respect to the surface was determined from the orientation of the dynamic dipole moment associated with several vibrations of the molecule; **1** = π-bonded, **2** = α-H abstracted, and **3** = N-lone pair bonded.

modifier−substrate diastereomeric complex cannot be formed without H_2 dissociation on the metal surfaces. As seen in Figure 2, this interaction is strong enough to slow down the MBF desorption or the decomposition of the "CD−MBF diastereomeric complex". The MBF desorption spectra from Al_2O_3 is almost identical to that of the blank test (ZnSe window), whereas desorption was significantly delayed by 20 s on Pt/Al_2O_3. Taking these results into account, we propose the following mechanism for the formation of the diastereomeric transition complex and the enantioselective hydrogenation of α-ketoesters in aprotic media: (i) H_2 is dissociatively adsorbed on the Pt surface; (ii) dissociated hydrogen is transferred from the Pt surface to the quinuclidine N atom and forms a diastereomeric surface complex consisting of CD and the ketoester via N−H−O bond; and finally, (iii) the diastereomeric complex is hydrogenated, producing the specific enantiomer of the hydroxyester, in the present case, (R)-methyl mandelate, and releasing the CD in its original adsorbed state. The feasibility of this hydrogen transfer from the platinum surface (step ii) was recently proposed on the basis of ab initio calculations but never proven experimentally so far.[11] Therefore, this in situ ATR-IR study combined with MES and PSD techniques provides the first experimental proof of the hydrogen transfer from the platinum surface to the quinuclidine N atom in aprotic media. Note that in protic solvents, such as,
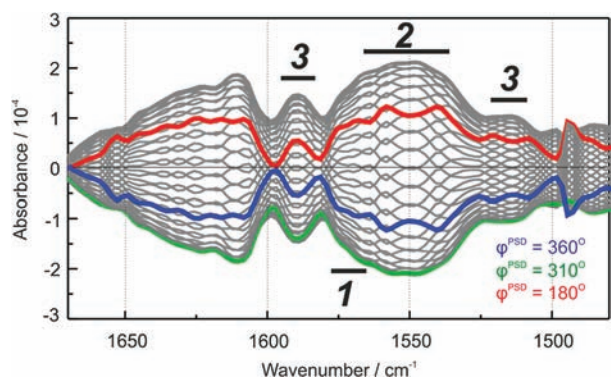
Figure 3. Phase-domain ATR-IR spectra during MBF adsorption—desorption on CD-modified Pt/Al$_2$O$_3$ at 283 K in the wavenumber range of ring-stretching modes of quinoline in CD. The numbers **1**, **2**, and **3** correspond to CD structures in Scheme 1.

e.g., acetic acid, step (ii) is likely to occur mainly by proton transfer, but some contribution from surface hydrogen cannot be excluded.

Close inspection of the ring stretching modes of quinoline (1500—1600 cm^{-1}) of CD provided further interesting information concerning the adsorption sites of MBF. As reported previously,[12] CD adsorbs on the Pt surface in three different adsorption modes **1—3** (Scheme 1); π-bonded, α-H abstracted, and N-lone pair bonded CD. These species can be well-distinguished in the infrared spectra because of changes in dynamic dipole moment of quinoline rings[12] (see Figures 3 and S2, Supporting Information). Among the three adsorption modes, the α-H abstracted CD (a broad band at ca. 1550 cm^{-1}), species **2**, responded most significantly upon the MBF admission (as seen in Figure 3); at a phase angle $\varphi^{PSD} = 310°$, MBF bands showed the highest intensity while the signal of α-H abstracted CD (**2**) was negative in the phase-domain spectra (compare Figures 1a and 3). We assume that MBF adsorbs on Pt sites competitively with α-H abstracted CD and forms the surface diastereomeric complex preferentially with π-bonded species **1**, but the involvement of N-lone pair bonded CD, species **3**, cannot be ruled out. Our in situ ATR-IR study combined with MES and PSD proves that in aprotic solvents, hydrogen dissociated on Pt is involved in the N—H—O type H bonding between CD and the α-ketoester, MBF. This interaction involves π-bonded or N-lone pair bonded CD on Pt, whereas α-H abstracted CD on Pt and CD on Al$_2$O$_3$ are merely spectators.

Finally, it should be noted that the heterogeneously catalyzed asymmetric hydrogenation over chirally modified platinum is rather complex, and subtle changes of the structure of the cinchona modifier or the activated ketone can cause changes in the stereochemical outcome of the reaction. Therefore, the type of the chiral modifier—substrate interaction might be different in other combinations of modifiers and substrates. However, the present study clearly shows that the use of a protic solvent is not a prerequisite for the formation of an N—H—O bond between CD and the α-ketoester. In an aprotic medium, such as toluene, the hydrogen is provided from dissociatively adsorbed hydrogen from the platinum surface. The N—H—O, originating from H$_2$ molecule, plays a critical role by "triggering" the enantiodifferentiation at the metal surface.

■ ASSOCIATED CONTENT

ⓢ Supporting Information. Experimental section and results: detailed procedure of MES experiments. Figure S1, IR

spectra of CD adsorbed on Pt/Al$_2$O$_3$ and Al$_2$O$_3$. Properties of Pt/Al$_2$O$_3$ and Al$_2$O$_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

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