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A Generalized Two-Point H-Bonding Model for Catalytic Stereoselective Hydrogenation of Activated Ketones on Chirally Modified Platinum

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Abstract: The asymmetric hydrogenation of α-ketoesters on cinchona-modified supported platinum particles is a prototype reaction in heterogeneous chiral catalysis. The catalysis literature shows that the reaction is highly metal-specific, that it displays rate-enhancement with respect to the racemic reaction on the nonmodified surface, and that the observed stereoselectivity is a sensitive function of substrate and modifier structure. This set of observations has proven difficult to rationalize within the context of existing models for the mechanism of the Orito reaction. The most widely discussed mechanistic models are based on the formation of chemisorbed 1:1 complexes through H-bonding between the quinuclidine function of the cinchona modifier and the prochiral, keto-carbonyl, function of the substrate. Recent surface science studies, as well as advances in the area of C−H···O hydrogen bonding, suggest that chemisorption-induced polarization may lead to an aromatic-carbonyl H-bonding interaction between the aromatic anchor of the modifier and the coadsorbed substrate. By specifying that the aromatic C−H···O interaction is to the prochiral carbonyl and that it is accompanied by a H-bonding interaction between the ester carbonyl and the quinuclidine function, we show that it is possible to rationalize essentially all of the catalysis literature for the Orito reaction in terms of a single molecular mechanism. The generality of the proposed mechanistic model is demonstrated by addressing data from the literature for a representative range of substrates, modifiers, solvents, and metals. Results of catalytic tests on an asymmetric diketone substrate are presented in support of the model.

Introduction

The continually increasing need for enantiomerically pure chemicals has driven numerous major advances in the area of homogeneous chiral catalysis.[1] There is a parallel need for heterogeneous chiral catalysts, systems that may offer many advantages.[2] The asymmetric hydrogenation of prochiral ketocarbonyls may be performed using chirally modified supported platinum catalysts. This reaction, first reported by Orito et al.[3] selectively converts methyl pyruvate to (*R*)-methyl lactate on cinchonidine modified Pt (Scheme 1). The reaction is typically carried out at room temperature and at low surface coverages of the modifier, using toluene or acetic acid as a solvent. Three decades of investigation of the Orito reaction have revealed a set of complex, and sometimes apparently contradictory, data that are difficult to rationalize in terms of a single molecular-level mechanism.[4−12] This complexity arises from the multiple intramolecular, intermolecular, and chemisorption interactions inherent to catalytic stereoselective synthesis on metal surfaces. It manifests itself in several intriguing phenomena such as extreme metal specificity, substituent-dependent stereochemical inversion,[13] significant rate acceleration with respect to the racemic reaction on nonmodified platinum, and pronounced changes in the enantioselective excess arising from minor modifications in the structure of the activated ketone.[6,7] We show that a comprehensive range of phenomena reported in the

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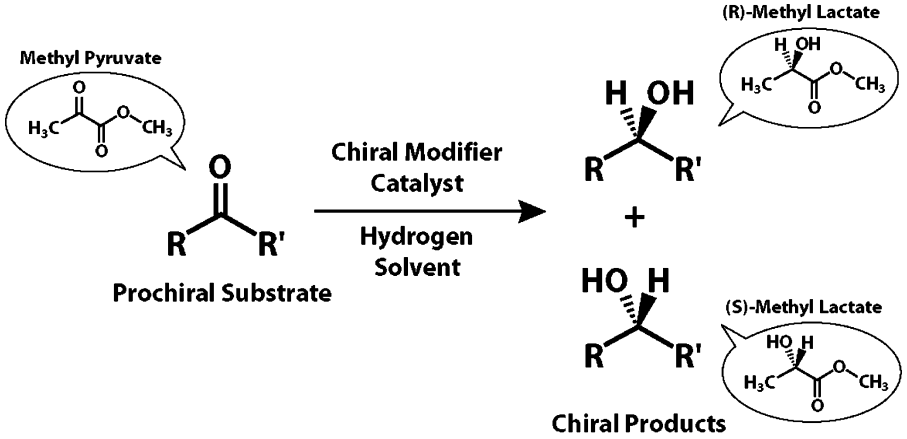
Scheme 1. Heterogeneous Enantioselective Hydrogenation of Methyl Pyruvate on Chirally Modified Pt



catalysis literature on the Orito reaction may be explained in the context of a simple two-point attractive interaction between coadsorbed chiral-modifiers and prochiral substrates.

Experimental Section

Measurements on the hydrogenation of an asymmetric diketone were carried out using the following materials: 1% Pt/Al_2O_3 (Aldrich), 2,3-pentanedione (Aldrich, 97%), acetic acid (Fisher Scientific ≥99.7%) and cinchonidine (Fluka, ≥98%). The hydrogenations were carried out in a mechanically stirred reactor (Parr 3911) using 77 mg of the Pt catalyst, 3.0 mg of the modifier, 40 mmol of 2,3-pentanedione, and 200 mL of the solvent, acetic acid, at 2.1 bar and 23−25 °C for 6 h. The enantiomeric excess was determined by gas chromatography in CH_2Cl_2 at a constant temperature of 80 °C using a beta-cyclodextrin dimethyl (B-DM type; 30 m × 0.25 mm) column. The products were identified by GC/MS (5890 Series II Gas Chromatograph/ HP 5989A Mass Spectrometer) and by NMR. The observed ee values were 17% (*R*)-2-hydroxy-3-pentanone, and 9% (*R*)-3-hydroxy-2-pentanone.

Discussion

A representative range of substrates for the Orito reaction may be divided (Chart 1) into three categories displaying high ee, medium ee, and low ee, respectively.[6,7] The categories high, medium, and low represent optimal values in the ranges ≥65%, 31−64%, and ≤30%, respectively. Since enantioselectivity is very dependent on reaction conditions, Chart 1 is organized on the basis of the maximum reported enantioselectivity. Effective substrates include aliphatic and cyclic α-ketoesters, α-dicarbonyls, and certain *β*-ketoesters. In each case, the prochiral ketone group (p-CO), shown in red in Chart 1, is activated by a group in the α-position. In addition to (p-CO), all effective substrates contain a group (R′) that is capable of forming H-bonds. With the exception of *β*-ketoesters, (R′) also serves to activate (p-CO). For example, (R′) can be an ester, ether, keto, or CF_3 group.

Three representative chiral modifiers, cinchonidine (CD), napthylethylamine (NEA),[14] and naphthylethanediol (NED),[15] are illustrated in Chart 2. CD and its diastereomer cinchonine (CN), the most commonly used modifiers, induce right-handed and left-handed hydrogenation, respectively, on platinum catalysts.[6,7] Baiker and co-workers have shown that NEA and NED, as well as secondary amine derivatives of NEA, are effective modifiers for the Orito reaction.[14,15] An ee of 56% in favour of the (R)-product was reported for the hydrogenation of ketopantolactone on platinum modified using the primary amine, NEA.[14] All effective modifiers for the Orito reaction possess the three molecular features labelled as (A), (B), and (*) in Chart 2. (A) is a group capable of conventional hydrogen bonding,[12a,16]

Chart 1. Substrates for the Orito Reaction Divided into Three Categories According to the Highest Enantioselectivities Reported in the Literature

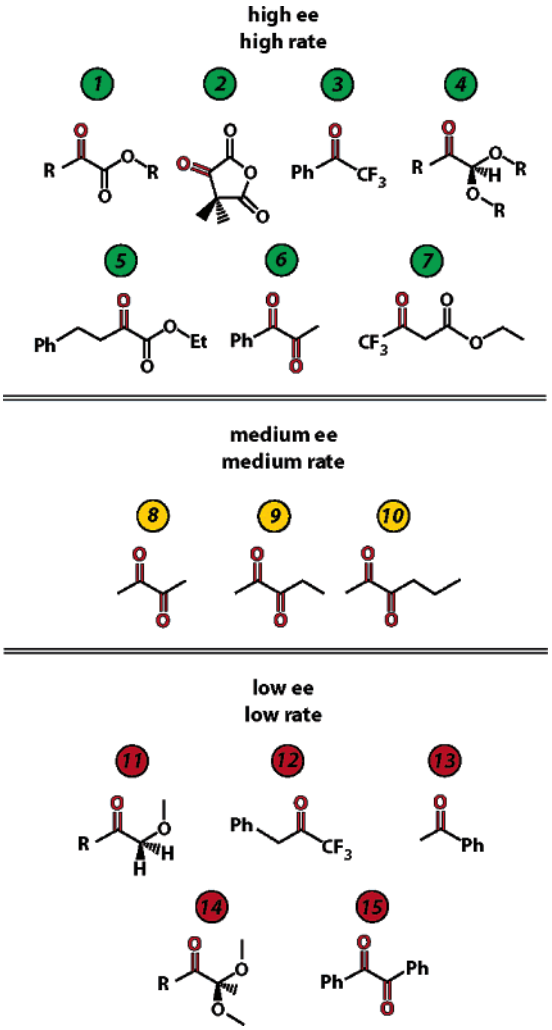


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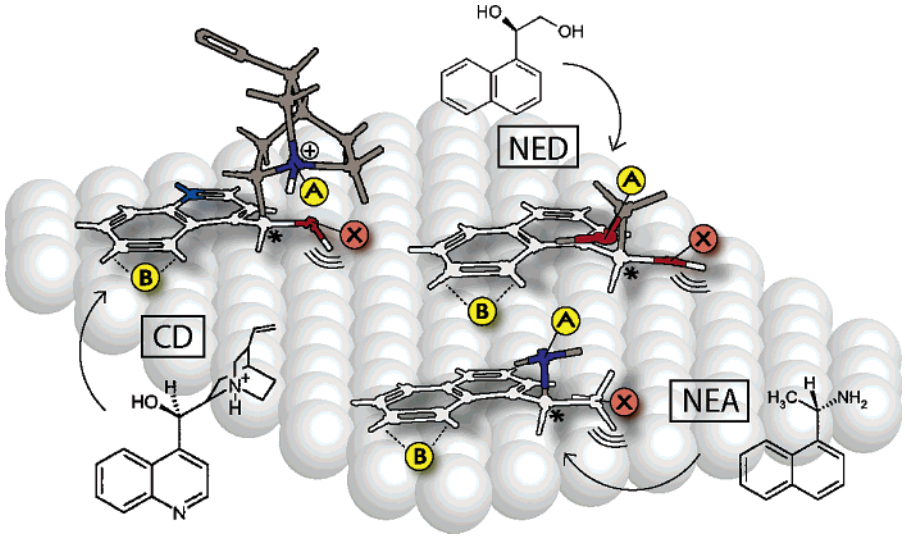
Chart 2. Representative Chiral Modifiers for the Orito Reaction[a]



[a] Cinchonidine (CD), naphthylethylamine (NEA), and naphthylethanediol (NED) are shown. Three molecular features common to all efficient modifiers are labeled as (A), (B), and (*). (A) is a conventional H-bond donor, (B) is an extended aromatic group, and (*) is a stereogenic centre located between (A) and (B). (X) is the substituent at (*).

such as a hydroxyl or a primary, secondary, or protonated tertiary amine function. The tertiary amine group of the quinuclidine ring of CD is assumed to be protonated in protic solvents.[6,7] Recent work shows that protonation can also occur in aprotic solvents, presumably through interaction of the tertiary amine group with surface hydrogen.[17] (B) is a double, or triple, aromatic ring that serves, in part, to anchor the modifier to the surface. Several groups have provided evidence, including in situ spectroscopic data, showing that the aromatic anchor is oriented roughly parallel to the surface.[18,19] In particular, an in situ infrared and Raman study concluded that there is a strong π-type interaction between the aromatic ring of CD and the platinum surface at the low coverages typical of reaction conditions.[19c] Finally, there is, in every case, a stereogenic center, (*), positioned between (A) and (B).

A number of mechanisms have been proposed for the Orito reaction.[4−12] The widely discussed 1:1 hydrogen-bonded modifier−substrate model developed by Baiker et al.[4] and Wells et al.[8] assumes that H-bonding occurs between (p-CO) and (A). This interaction combined with steric repulsion between (R′) and (B) is suggested as the origin of stereoselection. Rate enhancement with respect to the racemic reaction is attributed[4] to a combination of chemisorption and H-bonding activation of (p-CO) by (A). The latter two interactions are, however, optimized at separate positions in space, the former at the surface and the latter above the surface. A weakly constrained chiral pocket, defined mostly by steric repulsion between (B) and (R'), makes it difficult to explain the sensitive dependence on the substrate molecular structure. Effects such as stereoinversion[13] resulting from substitution at (*), and the regioselectivity observed for asymmetric α-diketones,[20] are very difficult to rationalize using the (p-CO)−(A) H-bonding model. While there is a general consensus[4−12] that a 1:1 substrate−modifier prochiral adsorbed complex forms, there is no experimental evidence for a (p-CO)−(A) as opposed to an (R′)−(A) H-bonding interaction. The ester carbonyl of an α-ketoester is predicted[21] to have a higher proton affinity than the (p-CO) function; hence (R′)−(A) H-bonding is the expected interaction in solution. Since the (R′)−(A) pair is located above the surface in the chemisorbed complex, the interaction may be similar to that for the solution phase.

Recent surface science studies indicate that a second H-bonding interaction may occur in the adsorbed 1:1 modifier−substrate complex. Specifically, aromatics chemisorbed on Pt(111) form C−H···O interactions with carbonyl groups of coadsorbed molecules.[12c] Such an interaction is in line with recent reports on C−H···O bonding in tetrafluorobenzene/oxygenate clusters[22] and in benzene/oxyanion complexes,[23] as well as chemisorption-induced C−H···O bonding between C_2H_4 and O_2 on Ag(111).[24] The H-bonding observed for coadsorbed aromatics and carbonyls on platinum is attributed[12c] to the fact that the redistribution of electrons involved in chemisorption bond formation[25] renders the aromatic hydrogens more acidic. Hydrogen bonding may be used to induce asymmetric reactions[26] and it has recently been shown that C−H···O bonding can induce stereoselection in an intermolecular Pauson−Khand

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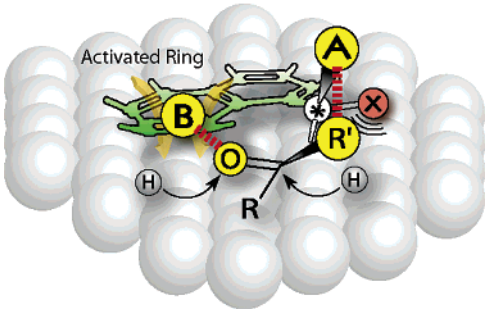
Chart 3. A Generic Prochiral Complex[a]

Generic Complex



[a] Taking the example of methyl pyruvate and cinchonidine coadsorbed on platinum, (A) is the protonated tertiary amine group, (B) is the activated aromatic anchor, (X) is an OH group, and (R′) is the $COOCH_3$ moiety of methyl pyruvate. The chemisorption interaction between (B) and platinum activates the ring towards H-bond formation. The ester carbonyl in (R′) forms a H-bond to (A), and the keto-carbonyl, (p-CO), forms O···HC bonds to (B). The substituent (X) imposes a unique directionality on the (p-CO)−(B), (R′)−(A) two-point interaction, thereby defining the chiral pocket.

reaction.[27] By taking into account a chemisorption-induced C−H···O attractive interaction between (B) and (p-CO), we propose a two-point H-bonding mechanism for the Orito reaction and successfully test it against a comprehensive range of literature data which were measured under catalytic conditions. The proposed mechanism specifies that the requirement for efficient asymmetric induction is that the prochiral complex, as shown in Chart 3, forms by pairing (R′) to (A) and (p-CO) to (B).

Several examples of two-point bonding prochiral complexes are illustrated in Chart 4 and discussed below. Taking CD as an example, it can be seen that steric hindrance due to the substituent (X) at (*) imposes a unique directionality to the two-point modifier−substrate interaction, thereby preventing the formation of a pro-(S) complex. The (p-CO)−(B) interaction depopulates intrinsic adsorption states of α-ketoesters, such as the enediolate or *trans*-states of methyl pyruvate on nonmodified Pt(111),[12a] leading to adsorption geometries in which (p-CO) is oriented towards the aromatic anchor (B) close to the metal surface.[12c] The metal surface is a key activating and directing agent in the reaction. Along with (R′), it serves to activate (p-CO) towards hydrogenation, it serves to activate function (B) towards H-bonding to (p-CO), it permits an adsorption geometry that could form the two-point contact, and it furnishes atomic hydrogen at the enantioface determined by the resulting substrate−modifier complex. We assume that hydrogenation does not require a strongly chemisorbed prochiral carbonyl, since the formation of a relatively immobile η^2-(p-CO) state would inhibit the (p-CO)−(B) interaction required to form the two-point complex. The surface science data for aromatic−carbonyl complexes are more consistent with a π-type interaction with the surface.[12c] Interestingly, Loffreda et al.[28] calculated that the hydrogenation of the carbonyl group of acrolein on Pt(111) involves a precursor state in which the carbonyl group is not strongly chemisorbed.

The importance of the (p-CO)−(B) interaction for stereoselection is directly manifested in experiments performed by Diezi et al.[13a,b] using a range of CD modifiers substituted at (*). Hydrogenation to yield (R)-products is observed for (X) = OH, OCH_3, and OCH_2CH_3 substituents, whereas (S)-products are formed for O-phenyl substitution. The stereochemical inversion can be explained by noting (Chart 4a) that a competing (p-CO)−(B′) interaction may be formed to the phenyl (B′) substituent. The highest stereoinversion is observed for cyclic substrates, whereas the more flexible aliphatic ketoesters give essentially racemic products due to the small difference in the competing (p-CO)−(B) and (p-CO)−(B′) interactions.[13a] The above analysis can also be used to interpret the stereoinversion observed in a recent study, by Cserenyi et al.[13c] of the effect of various substituents (X) at the stereogenic center, (*).

Representative substrate−CD complexes are illustrated in Chart 4b. For each pair, the two-point model can be used to rationalize the ee range indicated in Chart 1. The adsorption geometry of the substrate is evidently a key factor in facilitating the two-point interaction. As illustrated next, small changes in substrate structure can lead to large changes in adsorption geometry and hence large changes in the observed enantioselectivity. The arguments are made on the basis of plausible adsorption geometries, as experimental data are not available for most of the substrates under discussion. Substrate **13** is a trivial example in that it does not possess an (R′) group and, hence, cannot form two-point bonding to the modifier. The small ee observed may then be attributed to the difference in steric repulsion of the phenyl and alkyl substituents in the chiral pocket. In contrast, substrates **3** and **12** possess two functions capable of H-bonding. Flat-lying chemisorption of the phenyl group of **3** places (p-CO) close to the surface, at (B). H-bonding of the CF_3 group to (A) completes the two-point attachment to form a pro-(R) complex. The simple addition of a methylene spacer between (p-CO) and the phenyl group, as in substrate **12**, removes the constraint forcing (p-CO) close and parallel to the surface. As a result, a competing geometry in which the phenyl group bonds to the surface and the (p-CO) bonds to (A) is facilitated. The resulting lack of a strongly preferred (p-CO)−(B) interaction leads to a reduction in enantioselectivity. In contrast, replacing the CF_3 group with an ester group in a substrate with a similar alkyl spacer, **5**, re-establishes a strong (R′)−(A) interaction and leads to high stereoselectivity. The fact that substrate **15** displays zero ee[20] may be explained by the interaction of both PhCO groups with the surface, thereby preventing (R′)−(A) bonding. The poor stereoselectivity observed for **11** is due to bonding of the ether group to the surface in competition with the formation of an (R′)−(A) interaction. Substrate **4**, in contrast, possesses two ether groups, one of which is free to form an (R′)−(A) interaction. Steric repulsion, as by the methyl group in substrate **14**, can hinder the formation of an effective (R′)−(A) contact. Asymmetric hydrogenation of the β-ketoester **7** can be performed since the CF_3 group activates (p-CO) and the ester carbonyl forms an (R′)−(A) bond.

The two-point bonding model predicts that symmetric α-diketones such as **8** will give a single product, the (R)-enantiomer, on CD-modified Pt. In contrast, asymmetric α-diketones will give two different products, each of which will be right-handed. This prediction was confirmed by experiments performed in our laboratory on substrate **9** under typical reaction conditions, as well as by literature data[20] for substrates **6** and **10**. The combination of regioselectivity and enantioselectivity observed

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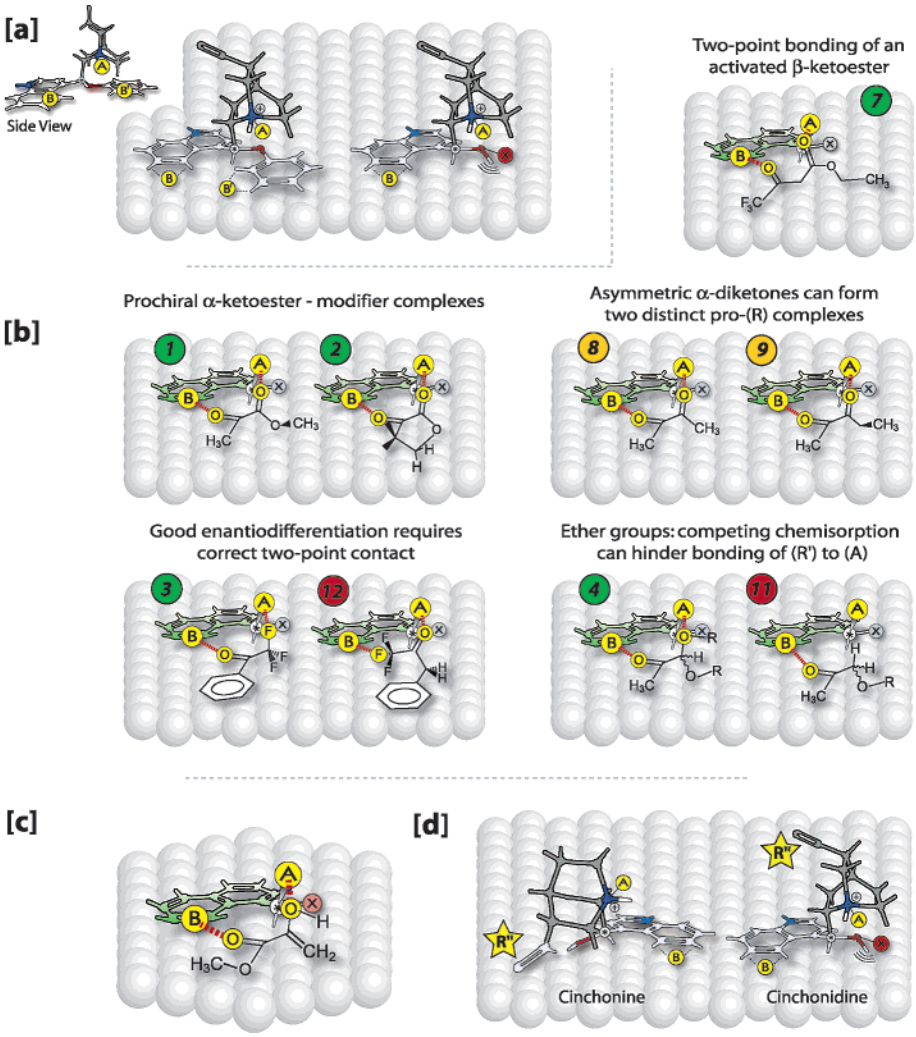
Chart 4.[a]



[a] (a) Cinchonidine (CD) and phenyl-substituted CD. (b and c) Representative prochiral complexes. (d) Possible role of the vinyl group (R″) in cinchonine (CN) adsorption.

for the hydrogenation of asymmetric α-diketones is a key test for the validity of the proposed two-point contact model. The two-point model predicts that hydrogenation of α-diketones will occur at a slower rate at the (R′)−(A) pair because it is not in optimal contact with the surface. Hence hydrogenation of a pro-(R) active complex is expected to display a lower activation energy than that for the racemic reaction on the nonmodified surface, while the opposite is expected to hold for a pro-(S) complex. For example, the hydrogenation of substrate **6** occurs with increased regioselectivity to the phenyl-substituted (p-CO) group on the CD-modified surface.[20] Chemisorption of the phenyl substituent forces a preferential (p-CO)−(B) interaction. Indeed, kinetics studies on **6** by Toukoniitty et al.[20] show that stereoselection derives from an increased rate of the (R)-reactions and a decreased rate of the (S)-reactions. This phenomenon may be further illustrated by considering data for the Orito reaction on CD-modified Pd catalysts. In contrast to the chemistry of alkyl pyruvates observed on platinum, keto-enol tautomerisation occurs on palladium even in the presence of hydrogen.[29] The enol group will bond to (A) rather than to (B), thereby forming a pro-(S) complex (Chart 4c). Indeed, the (S)-product is formed in excess on palladium.[8a,29] Furthermore, the rate of the reaction is lower than that for the racemic reaction on the nonmodified surface, presumably because the enol−(A) interaction tilts the prochiral CC double bond away from the surface.

Although it is known that the Orito reaction can take place in the absence of solvent,[30] the nature of the solvent is an important parameter under typical reaction conditions.[4−7,31] The use of solvent polarity is exploited in heterogeneous diastereoselective synthesis to turn a specific face of the prochiral group towards the solution phase.[32] In the context of the two-point model, the polarity of the solvent will play a role in determining the dihedral angle between (R')−(A) and (p-CO)−(B) pairs. Toluene is the optimal solvent for cyclic α-ketoesters such as **2**, whereas acetic acid is the optimal solvent for aliphatic ketoesters such as **1**.[6] Acetic acid is a polar solvent and can solvate (A) and hence draw it away from the surface. The

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resulting large dihedral angle is energetically favourable for **1** in that it minimizes carbonyl−carbonyl dipole repulsion. In contrast, **2** is less flexible, and the optimal conditions require that (A) be located closer to the surface. This will occur in toluene, since as an apolar solvent it will not compete as strongly as acetic acid with the adsorption forces on the modifier. A further example of the importance of the distance of the quinuclidine group from the surface is given by comparing the ee yields obtained using the diastereomeric pair CD and CN. While the vinyl, R″ substituent of CD is held away from the surface through flat-lying adsorption of (B), the same substituent in CN can interact with the metal (Chart 4d) thereby forcing (A) away from the surface. This effect possibly contributes to the lower ees obtained using CN and rigid modifiers.[6] In support of this proposal, we note that identical stereoselectivities are observed for CD and CN when R″ is a hydrogen atom.[5a]

Conclusion

The proposed mechanistic model may be used as a guide to understanding a comprehensive range of reported studies of the Orito reaction. The model permits a consistent analysis of a complex, and sometimes apparently contradictory, set of data for a wide range of substrate−modifier pairs. In common with the majority of previous models, the proposed model is based on the formation of coadsorbed 1:1 modifier−substrate H-bonded complexes. It differs from previous models in three respects, which may be illustrated, as follows, by considering a 1:1 cinchonidine−methyl pyruvate complex. The prochiral complex is formed by two separate H-bonding interactions; the prochiral carbonyl forms a C−H···O bond, at the surface, to the chemisorption activated aromatic anchor of the modifier; the ester carbonyl forms a conventional H-bond, above the surface, to the protonated tertiary amine function of the modifier. The formation of the C−H···O interaction is entirely consistent with recent advances in the understanding of H-bonding[22,23] and in the chemisorption-induced formation of H-bonded coadsorption complexes.[24] The specific case of aromatic−carbonyl H-bonded complexes on platinum is supported by surface science data.[12c] The extreme metal specificity displayed by the Orito reaction is attributed, in part, to the ability of platinum to activate the aromatic anchor towards H-bonding.

It is shown, by addressing a comprehensive range of literature data, that the model may be extended to a full range of effective modifier−substrate pairs, by specifying, in all cases, an aromatic−prochiral carbonyl C−H···O interaction at the surface and a substrate−modifier H-bonding interaction above the surface. The latter interaction could involve, for example, a CF_3 group of the substrate and OH, NH, NH_2, or NH^+ functions of the modifier. The substrate must be sufficiently flexible to permit both H-bonding interactions simultaneously. The adsorption geometry of the substrate is then a key factor in facilitating the two-point interaction. Small changes in substrate structure can lead to large changes in adsorption geometry and hence large changes in the observed enantioselectivity. Competing modifier−substrate interactions can induce stereoinversion, as in the case of phenyl substitution at the stereogenic center or in enol formation in the Orito reaction on palladium surfaces.

For the case of α-diketones, substrates which possess two prochiral carbonyls, the rate of hydrogenation of the carbonyl at the surface is expected to be accelerated with respect to the racemic reaction on the nonmodified surface, whereas the reverse is expected to hold for the carbonyl located above the surface. That is, the (p-CO) group in interaction with both the aromatic anchor and the surface is further activated towards hydrogenation. In contrast, the second (p-CO) group, the pro-(S) carbonyl, is tilted away from the surface to make contact with (A), for example, with the quinuclidine group of cinchonidine. The consequent distancing of the pro-(S) carbonyl from the surface results in a higher activation energy than that for reaction on the nonmodified surface. This effect, which follows directly from the proposed model, is clearly shown by the study of Toukonitty et al.[20] of the hydrogenation of substrate **6**.

The two-point H-bonding model also provides an appealingly simple stereodynamical description of the formation of prochiral complexes. The combination of the (R′)−(A) interaction and the preferential chemisorption of the keto-carbonyl[4] captures the substrate into the chiral pocket defined by the stereogenic center (*). The second modifier−substrate interaction, at (B), orients and further activates (p-CO) providing rate acceleration with respect to the racemic reaction on nonmodified areas of the surface. The model may find application in the asymmetric hydrogenation of olefin and CN functions in substrates capable of forming two-point contacts to modifiers.

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