DOE/ER/14532--T1

MECHANISMS AND DESIGN IN HOMOGENEOUS CATALYSIS

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FEB 05 1999
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Final Report

for Period April 15, 1995 - April 14, 1998

Clark R. Landis

Department of Chemistry
University of Wisconsin
1101 University Avenue
Madison, WI 53705

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Jan 26, 1999
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Prepared for

The U.S. Department of Energy
Grant No. DE-FG02-95ER14532

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Report Section

Mechanisms and Design in Homogeneous Catalysis

DOE Grant #DE-FG02-95ER14532

Clark Landis, Department of Chemistry, University of Wisconsin, 1101 University Ave., Madison, WI 53705, (608)262-0362, landis@chem.wisc.edu

Department of Energy support has been used to address fundamental mechanistic questions concerning metal-catalyzed transformations, to design, synthesize, characterize, and apply new ligands for use in asymmetric catalysis, to apply NMR methods to the determination of three-dimensional solution structures of small molecules (including homogeneous catalysts), and to promote the development of new computational modeling methods. This section describes our results for the first three years of our DOE supported work. All of the described work has either been published or accepted for publication.

Secondary Interactions: New Ligand Designs for Asymmetric Catalysis

In an effort to develop new strategies for controlling the selectivity of metal catalyzed transformations, ligands utilizing "secondary interactions", a term first coined by Ito¹, have been designed and synthesized. Secondary interactions involve attractive substrate-catalyst interactions that lie outside the first coordination sphere of the metal; these may include rapidly reversible covalent bonds, hydrogen bonds, electrostatic interactions, and Lewis acid-base dative bonds. Based on crystallographic and molecular mechanics modeling we have focused on two ligand templates: chiral ferrocenyl-based diphosphines and functionalized DuPhos ligands.

A variety of borate and crown-ether modified diphosphines with a chiral ferrocene backbone have been synthesized and characterized²⁻⁴. Examples are shown below.

The design of these ligands which contain aminophenol moieties (**1,3-5**) was based on the prediction that coordination of the diphosphine to a square planar transition metal complex will lead to a structure in which the N and O atoms of the aminophenol group are projected about 3 Å above the empty coordination sites. Such a preorganized structure should promote the formation of secondary interactions: For the borate functionalized ligands the secondary interaction would comprise covalent binding of an unsaturated alcohol and for the crown ether functionalized ligand the secondary interaction would comprise, e. g., hydrogen bonding to an ammonium group of and unsaturated ammonium salt.

The design of these ligands is based on the premise that such secondary interactions can be used to control regio, chemi, and stereoselectivity in metal catalyzed reactions.

Crystallographic analysis⁴ reveals that the predicted structural motif for aminophenol-functionalized ferrocenyl diphosphines is found: the plane of the aminophenol is nearly coplanar with the coordination plane of the metal and the N and O atoms of the aminophenol are positioned 3.1 Å above the proximal coordination site. Thus, this is a good platform design for

secondary interactions.

Metal complexes containing borate and crown ether functionalized ferrocenyldiphosphines are active catalysts for hydrogenation and hydroformylation reactions³⁻⁵. Via a double control experimental design we have shown that borate functionalized diphosphines yield higher enantioselectivities than can be accounted for by simple increments of steric interactions; these results may be an indication that secondary interactions of the type envisioned are taking place.

The synthesis of resolved C_2 symmetric, crown ether functionalized phosphines and phosphites based on the DuPhos motif has created new opportunities for control of reaction selectivity and for catalyst separations^{6,7}. The phosphites **8a-c** ligate rhodium carbonyl precursors to form

very active hydroformylation catalysts for simple alkenes and for allylic ammonium salts. Because the crown ethers are attached to the 3 and 4 positions of the dioxaphoshacyclopentane rings, they are not well positioned for secondary interactions. Nevertheless catalytic hydroformylations of methylallylammonium triflate with comprehensive controls reveal a small (6-fold) rate increase for ligand **8a** relative to closely related phosphites lacking the crown ether functionality⁶. Interestingly, these catalysts derived from these phosphites phase separate from organic solvents when exposed to ammonium salts. Deprotonation of the ammonium groups restores homogeneous solutions.

These results suggest interesting possibilities for catalysts separations from high boiling aldehydes - a critical requirement for the extension of high activity homogeneous hydroformylation catalysts to higher aldehydes.

Significant progress to the crown ether functionalized DuPhos ligand, **11**, has been made. The thesis work of Darren MacFarland⁶ has demonstrated the synthesis of the key

intermediate, the resolved, chiral bis(azacrown ether)diol (**10**) starting from malic acid as shown below.

Further completion of this synthesis has been delayed due to an impending postdoctoral fellows last minute decision to accept a permanent job in industry.

Mechanisms and Asymmetric Catalysis

Despite significant efforts the most critical mechanistic detail of catalytic asymmetric hydrogenation of prochiral enamides, the nature of the rate- and

enantio-controlling H_2 activation step, is still a subject of active discussion. We have taken a combined mechanistic/computational approach to this important problem^{8,9}. In overview our results indicate: (1) dihydrides can be minima on the reaction surface but that diastereomeric dihydride stabilities do not reflect the transition state stabilities, (2) of the four possible diastereomers that can be generated from the addition of H_2 to complexes of the form $[Rh(\text{diphosphine})(\text{enamide})]^+$, two apparently are inaccessible due to high (> 20 kcal/mol) barriers according to computations on simple achiral model systems (3) that H:D regioselectivities for addition of HD to prochiral enamides in the α vs. β positions are not the result of relative H:D site preferences in the formation of dihydrides with two cis, chelating ligands, (4) under catalytic conditions the alkyl hydrides formed by insertion of the enamide C=C into the M-H bond cannot revert back to H_2 + $[Rh(\text{diphosphine})(\text{enamide})]^+$ (5) experimental kinetic isotope effects are consistent with a rate controlling oxidative addition but not a concerted transition state in which activation of the H-H bond occurs simultaneously with the formation of C-H and M-H bonds to generate an alkyl hydride directly, and (6) we have established by NOE solution structure determination methods the structure (including absolute stereochemistry) of the preferred diastereomer of the model dihydride, $[Ir(\text{Me-DuPhos})(\text{COD})H_2]^+$, as well as the kinetic and thermodynamic diastereoselectivities for its formation and the mechanism of diastereomer interconversion.

Kinetic Isotope Investigations of Prochiral Enamide Hydrogenation. Kinetic isotope effects in

enamide hydrogenation, specifically the rate for H_2 vs. D_2 and the partitioning of HD between α and β positions, provides insight into the mechanism of hydrogenation. We sought⁹ to distinguish among the mechanistic alternatives shown below.

First, it was necessary to determine if the formation of the known alkyl hydride intermediate was reversible or not. Using the enamide without β substitution, careful analysis of the product formed under a D_2 atmosphere revealed no scrambling, hence no reversibility in the formation of the alkyl hydride.

Kinetic isotope measurements for H_2 vs. D_2 by direct competition methods reveal little kinetic isotope effect ($KIE = 1.04 \pm 0.04$). In contrast, hydrogenation with HD reveals a significant preference for D to occupy the

α position (Partitioning Ratios 1.21-1.34 depending on the enamide).

The partitioning of D between α and β positions could reflect a kinetic or thermodynamic preference for D to occupy a site trans to one of the P ligands rather than cis to both P centers. Model studies of the oxidative addition of HD to $[Ir(\text{diphosphine})(\text{COD})]^+$ complexes suggest that there is no intrinsic kinetic or thermodynamically selectivity of this type. At low temperatures the reaction of HD with $[Ir(\text{DIPHOS})(\text{COD})]^+$ yields both deuterohydrides in equal

concentrations ($H_t/H_i=1.02\pm0.04$). This is a kinetically determined ratio as demonstrated by the selective

production of a single isomer by independent synthesis as shown below. At low temperatures the interconversion between isomers is quite slow (half-life > 12 hours), thus, there is no kinetic selectivity. Upon warming the other isomer appears, yielding an equilibrium ratio between isomers of 1:1. Thus, there is no equilibrium isotope effect.

Of the mechanisms shown for catalytic hydrogenation illustrated in the reaction coordinates from above, two mechanisms may be excluded from our data. For both pathway 1 and pathway 3, the partitioning of HD addition and

the H_2/D_2 kinetic isotope effect are controlled by the same transition state. This would require that the value of the regioselectivity partitioning ratio lie between 1.0 and the H_2/D_2 KIE (1.04). Because the partitioning ratio is 1.2-1.3, we can eliminate pathways 1 and 3. Only mechanisms 2a and 2b are viable. We favor 2a from more detailed analysis of the data but require that the intermediate 2a be fluxional to accommodate the observed partitioning of D into the α vs. β positions. A concern here is the overinterpretation of data, so we turned to computational modeling of reaction mechanism.

Ab Initio Modeling of the Mechanism of Asymmetric Hydrogenation. Our empirical results favored mechanism 2a shown above. To complement this work we performed⁸ detailed ab initio modeling of the asymmetric hydrogenation mechanism employing a simple model system (the $[Rh(PH_3)_2(\alpha\text{-formamidoacrylonitrile})]^+$ complex). In the process of this strenuous modeling exercise we identified some 26 stable intermediates (not all of which are shown below) and 16 transition states. All computations were at the DFT(B3LYP) level using the Stuttgart group's^{10,11} high-quality effective core potentials and basis sets.

Some of the major conclusions from this study are:

1. Dihydrogen complexes have been found to be stable intermediates. First, dihydrogen coordination to the square planar $[Rh(PH_3)_2(\alpha\text{-acetamidoacrylonitrile})]^+$ complex occurs with formation of three different dihydrogen complexes. All stable structures exhibit a site preference for the carbonyl oxygen in an axial position of a trigonal bipyramidal geometry. On the other side, geometries with the double bond of the enamide moiety in axial position do not represent stable intermediates. Another outcome of our investigation is that for dihydrogen coordination to the square planar educt along the axis carrying the double bond (A, C) results in two different isomers with relative small

nuclear changes and small activation barriers whereas dihydrogen coordination along the axis with the carbonyl oxygen (B, D) leads to the same intermediate with a larger change in geometry and significantly higher activation barriers. 2. Isomerization of the dihydrogen complexes has a

high energy barrier. Isomerization pathways of A2 or C2 to B2,D2 proceed via the same transition states as for dihydrogen complex formation. 3. Oxidative addition of the dihydrogen ligand to the rhodium center leads to four stable dihydrides. The activation barriers for oxidative addition and dihydrides are grouped in two pairs, the lower energy pathways leading to the thermodynamically disfavored dihydrides (A,C) and vice versa. Considering the high barrier for dihydrogen coordination for B and D and the fact that isomerization of the dihydrogen complexes can be excluded, just the two dihydrides A3, C3 are directly accessible. 4. Isomerization of the kinetically favored dihydrides to the thermodynamically favored pair is possible via a three step mechanism including decooordination and recoordination of the olefin. Despite exhaustive efforts we could not locate Bailar Twist transition state structures for isomerization. Isomerization via decooordination and recoordination of PH_3 was excluded on the basis of the high energy of a decoordinated PH_3 and the five coordinated structure (for A3 decooordination of PH_3 trans to H yields a combined energy of +27 kcal/mol). 5. The most stable dihydride B3 is kinetically disfavored and accessible via an isomerization mechanism (TS(A3-B3) for B3) and has the lowest energy barrier for insertion. It inserts without any significant barrier via an intermediate alkyl hydride with agostic interaction. The second thermodynamically favored but kinetically disfavored dihydride D3 inserts in α -position with formation of a β -alkyl hydride with a low barrier. Insertion in the β -position with formation of a α -alkyl hydride reveals a significantly higher barrier. The lowest energy pathway connecting a kinetically favored dihydride A3 leads directly to the most stable alkylhydride A4. No competitive pathway for insertion starting from C3 could be determined. 6. Reductive elimination shows a significant energy barrier with ca. 15 kcal/mol. This result is in perfect agreement (even under the presumption that cancellation occurs) with the previous experimental observations that the alkylhydride accumulates at lower temperatures and that the reductive elimination has an enthalpy of activation of about 16 kcal/mol.

Clearly, the mechanism of enamide hydrogenation is complicated even in the absence of chiral ligands. To provide a better foothold, we have turned to experimental and computational modeling of a simpler system: the addition of H_2 to complexes chiral complexes of the type $[Ir(\text{chiral diphosphine})(\text{COD})]^+$.

Diastereoselective Addition of H_2 to $[Ir(\text{chiral diphosphine})(\text{COD})]^+$ Complexes This model oxidative addition reaction can produce two diastereomers if the chiral diphosphine is C_2 -symmetric and four diastereomers if the diphosphine is asymmetric. We have investigated⁵ the kinetic and thermodynamic selectivities for this reaction with a variety of diphosphines. Interestingly there is no direct correlation for diastereoselectivity in H_2 addition to these compounds with enantioselectivity for enamide hydrogenation. For example, DIOP generally yields <70% ee's whereas CHIRAPHOS generally yields >90% ee's for enamide hydrogenation; these trends

Table 1. Selectivity of Oxidative Addition of H_2 to $[Ir(\text{bisphosphine})(\text{COD})]BF_4$

complex	$[IrH_2(P-P)(COD)]BF_4$ P-P =	product ratio at $-80^\circ C^a$	product ratio after warming at $-45^\circ C^a$
6	(S,S)-DIOP	26.8 : 1.0	18 : 1 ^d
7	(S,S)-CHIRAPHOS	1.8 : 1.0	1.0 : 6.1
8	(R)-BINAP	>50 : 1	>50 : 1.0 ^e
9	(R)-Tol-BINAP	>50 : 1	>50 : 1.0 ^e

10	(R,R)-Me-DuPHOS	47.4 : 1.0	5.8 : 1.0
14	(R,R)-NORPHOS ^c	26.0 : 23.0 : 3.0 : 1.0	15.0 : 6.1 : 1.0 : 1.2
15	(S,R)-BPPFA ^c	25 : 18 : 28 : 1 ^b	7.1 : 1.6 : 1.0 : 1.0 ^d
16	(S,R)-BPPFAc ^c	1.3 : 1.0	1 : 19 ^d

^aProduct ratio determined by ¹H NMR, unless otherwise indicated. ^bProduct ratio determined by ³¹P NMR due to overlap in the ¹H NMR. ^cUp to four products can be seen in solution for asymmetric chiral ligands. ^dDihydride ratio changes but decomposition occurs; thermodynamic equilibrium cannot be determined. ^eDecomposition of the major dihydride occurs and a second dihydride isomer cannot be characterized.

are reversed for the diastereoselectivities shown above. These data also show that kinetic and thermodynamic diastereoselectivities are different in magnitude and, for CHIRAPHOS and BPPFAc, different in the preferred sense of stereochemistry.

We have examined the DuPHOS system in detail. Two-dimensional COSY, NOESY, and HMQC NMR studies analyzed with the 2DCPA program (developed by this research group) yielded the solution structure with the absolute stereochemistry depicted below for the kinetically preferred diastereomer.

Upon warming to -45°C, a portion of the kinetic diastereomer converts to the other diastereomer to yield an equilibrium distribution. We have followed the kinetics for this process under a variety of conditions. Interestingly, the rate of diastereomer interconversion is independent of the metal complex concentration and the concentration of H₂ or D₂ in the solution. When the dideuteride is initially formed, approximately half of the Ir-D resonances are lost with a rate identical to the diastereomer interconversion rate. We have been able to show, through detailed NMR measurements, that D is scrambled into both the COD and DuPHOS ligands with exquisite

selectivity: only the H1 and H25 protons exchange with the metal deuterides. If the dideuteride is placed under an atmosphere of H₂, the deuterium is washed out completely at the same rate as diastereomer interconversion. We have accounted for these data with the following mechanism (for simplicity the D exchange with the DuPHOS ligand is not shown but proceeds analogously to the D exchange with COD).

It is interesting to note that this mechanism differs significantly from that proposed by Eisenberg for isomer exchange in the related $\text{Ir}(\text{diphosphine})(\text{CO})\text{H}_2\text{Cl}$ complexes. In our studies, isomer exchange occurs without the loss of H_2 (this mechanism would give slower rates for diastereomer interconversion than for isotope exchange). These results underscore the often complex isomer exchange processes that can occur at metal dihydrides that are closely related to catalytic intermediates in asymmetric hydrogenation reactions.

The observed kinetic diastereoselectivities are rationalized by least nuclear motions arguments based on crystallographic analysis. For illustrative purposes, consider the crystallographic structure of $[\text{Ir}(\text{DuPHOS})(\text{COD})]^+$ shown below. The plane defined by the two phosphorous atoms and the Ir is twisted relative to the plane of the Ir and the two C=C centroids. The kinetically preferred diastereomer formed upon addition of dihydrogen is always that which corresponds to further twisting of these planes in the same direction.

Structures of Alkene Polymerization Catalysts

Recently we have initiated an examination mechanistic aspects of metal-catalyzed alkene polymerization (see the proposal section). Our entry into this area of intense ongoing research was the application of sophisticated NMR methods to the solution structure characterization of model polymerization catalysts¹²⁻¹⁴. Two collaborations, one with Prof. Chuck Casey of this Department and one with Dr. Andrew Horton and Dr. Marianne Ros of the Shell Research Labs in Amsterdam, have resulted in two publications and one submission. The Casey collaboration^{12,14} concerned the characterization of the putative first d^0 -metal alkyl alkene complex (**18**) shown below. Chemical

shift changes suggested coordination of the alkene to the Y center, but further evidence was required to conclusively demonstrate that the major species was not the simple alkyl complex, **17**. We employed quantitative low temperature (-100°C) 2D NOESY measurements at several mixing times and

analysis of that data through the use of our 2DCPA program and structures generated by molecular mechanics force fields. These studies led to the conclusions that (1) the dominant

structure is **18** and (2) the chair conformation of the chelate shown below is most likely. In addition, these studies represent a significant milestone in the multiconformational analysis of solution structures of small molecules due to the difficulties of the experimental analysis (low temperatures and quantitative cross relaxation analysis in a system with 30 equivalent methyl protons) and the need to include fast time-scale dynamical motions in the structural analysis.

Our second collaboration¹³ concerned the verification of η^6 coordination of the benzylic arene ring and analysis of rotamers distributions generated by rotation about the Zr-arene centroid axis. The observed R-factors for computed vs. observed are quite sensitive to the rotamer distributions as seen by comparing the R-factors for the bottom- and top-most rotamer distributions shown below. This work demonstrates that (1) quantitative NOE data for small molecule transition metal catalysts can be determined (2) consideration of multiconformational and dynamical aspects of solution structure is critical to modeling NOE data and (3) computational programs have been developed (in this group) that account for multiple, fast converting populations.

Extending Valence Bond Theory to Metals

A small amount of DOE funding was used to support basic research on the nature of metal ligand bonding. A result of this support was the publication of a new Valence Bond Theory of metal complex shapes and its verification by molecular mechanics^{15,16}. Our extension of Pauling's Valence Bond concepts to transition metal compounds dominated by covalent bonding leads to simple prescriptions for determining bond hybridizations and molecular shapes. As a result, transition metal structures can be discussed in the familiar terminology of Lewis structures, lone pairs, hybrid orbitals, hypervalence, and resonance. A primary feature of these prescriptions is the relative impotence of valence p-orbitals in the formation of covalent bonds at transition metals: sd^n hybridization dominates. This feature is consistent with detailed analyses of high level quantum mechanical computations. Unlike Pauling's original treatments of hypervalency, this work shows that rationalization of empirical structures and high level electronic structure computational results requires consideration of multiple resonance structures. Also resulting from this work are insights into the nature of Bent's rule and its extension to transition metals, a new paradigm for understanding the *trans* influence, and effective molecular mechanics algorithms for describing metal hydrides and alkyls.

Publications Resulting from DOE Support

1. 'Synthesis and Characterization of Novel Ligands Designed for Secondary Interactions', Darren K. MacFarland and Clark R. Landis, *Organometallics* **1996**, *15*, 483-485.
2. 'Synthesis and Characterization of Boron-Containing Ferrocenyl Ligands for Asymmetric Catalysis' Barbara F. Kimmich, Clark R. Landis, and Douglas R. Powell, *Organometallics* **1996**, *15*, 4141-4146.
- 3*. "Formation and Spectroscopic Characterization of Chelated d⁰ Yttrium(III)-Alkyl-Alkene Complexes", Charles P. Casey, Susan L. Hallenbeck, J. Monty Wright, and Clark R. Landis, *J. Am. Chem. Soc.* **1997**, *119*, 9680-9690.
- 4*. 'Using Valence Bond Concepts to Model Transition Metal Complexes and Bond-Making and Breaking Processes' by Clark R. Landis for the NATO Advance Workshop on "Molecular Modeling and Dynamics of Biological Molecules Containing Metal Ions"; Pisa, Italy March 16-21, 1997, Kluwer, pages 49-76.
- 5*. 'Valence Bond Concepts Applied to the Molecular Mechanics Description of Molecular Shapes. 3. Applications to Transition Metal Alkyls and Hydrides', Tom Cleveland, Tim Firman, and Clark R. Landis, *J. Am. Chem. Soc.* **1998**, *120*, 2641-2649.
6. 'Further Mechanistic Aspects of Catalytic Asymmetric Hydrogenation' by Clark R. Landis and Tom W. Brauch, for *Inorganica Chimica Acta* Special Issue Honoring Professor Jack Halpern, **1998**, *270*, 285-297.
6. 'Oxidative Addition of Dihydrogen to [IrH₂(bisphosphine)(1,5-cyclooctadiene)]BF₄ Complexes: Kinetic and Thermodynamic Selectivity', Clark R. Landis, Barbara F. M. Kimmich, and Ekasith Somsook, accepted in JACS with minor revision.
7. 'An Ab Initio Model of Catalytic, Asymmetric Enamide Hydrogenation', Clark R. Landis and Peter Hilfenhaus, manuscript to be submitted to JACS 6/98.
8. 'Synthesis and Characterization of Crown Ether Modified Ferrocenyl Ligands for Asymmetric Catalysis', Clark R. Landis, Rachel Sawyer, and Ekasith Somsook, manuscript to be submitted to *Organometallics* 6/98.