cyclooctane. Proton NMR analysis indicates the presence of ca. 0.3 molecule of lattice acetone/$(Ph_3P)_2Ir$ unit. Additional characterization data, including elemental analyses, NMR, and X-ray powder diffraction results, are given in ref 6. Compound 1 often contains small amounts, ca. 5%, of an impurity having $\delta(^{31}P)$ −7.5 (d, J_{HP} = 21 Hz) and $\delta(^{1}H)$ −27.4 (t, 21) (in dmf). This we attribute to a decomposition product of $(Ph_3P)_2IrH_2^+$ for it is present in reactions carried out at elevated temperatures and is a major product formed when 1 is heated at 180 °C in a sealed tube.

Registry No. 1, 115794-94-0; 2, 115777-39-4; 3, 115805-05-5; 4, 120410-53-9; 5, 120410-55-1; 6, 115805-07-7; 7, 120410-57-3; 8, 120410-59-5; 9, 120410-61-9; 10, 115731-73-2; 11, 115777-38-3; 12, 115777-37-2; 13, 120410-63-1; 14, 120410-65-3; 15, 120410-67-5; 16, 120410-69-7; 17, 115777-41-8; 18, 115805-09-9; 19, 120410-71-1; 20, 120410-73-3; 21, 120410-75-5; 22, 120410-78-8; CO, 630-08-0; PF_3, 7783-55-3; C_2H_4, 74-85-1; C_2H_2, 74-86-2; C_3H_6, 115-07-1; C_6H_6, 71-43-2; $CH_3C_6H_5$, 108-88-3; $CH_2{=}C(CH_3)C(CH_3){=}CH_2$, 513-81-5; $CH_2{=}CHC(CH_3){=}CH_2$, 78-79-5; $CH_2{=}CHCH{=}CH_2$, 106-99-0; Me_3SiH, 993-07-7; C_2F_4, 116-14-3; C_3F_6, 116-15-4; $CF_2{=}CFCl$, 79-38-9; $CH_3C(O)H$, 75-07-0; CH_3OH, 67-56-1; $CH_2{=}CH(CH_2)_3CH_3$, 592-41-6; $CH{\equiv}C(CH_2)_3CH_3$, 693-02-7; $[(Ph_3P)_2Ir(C_8H_{12})]PF_6$, 61817-47-8; $(H_3O)_3PW_{12}O_{40}$, 1343-93-7; $[(Ph_3P)_2Ir(C_8H_{12})]_3PW_{12}O_{40}$, 115731-66-3; $(Ph_3P)_2IrD_2(dmf)_2^+$, 115731-71-0; $(Ph_3P)_2IrHD(dmf)_2^+$, 115731-70-9; $(Ph_3P)_2IrH_2(dmf)_2^+$, 115731-69-6; $(Ph_3P\text{-}2\text{-}d_1)(Ph_3P)IrH_2(dmf)_2^+$, 120410-76-6; C_6D_6, 1076-43-3; cyclopentene, 142-29-0; ethylene oxide, 75-21-8.

Asymmetric Synthesis. Molecular Graphics and Enantioselection in Asymmetric Catalytic Hydrogenation

Paula L. Bogdan, John J. Irwin, and B. Bosnich*,[†]

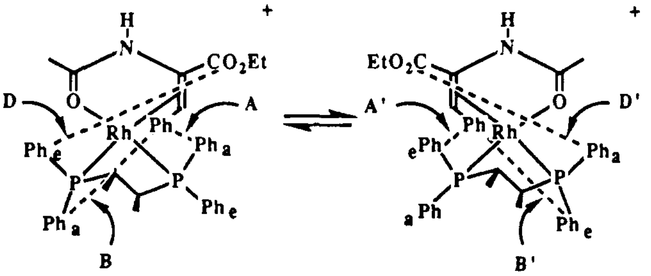
Lash Miller Chemical Laboratories, The University of Toronto, Toronto, Ontario, Canada

Received October 5, 1988

Molecular graphics and associated energy calculations are used to analyze the addition of H_2 to the major and minor diastereomer precursors for asymmetric catalytic hydrogenation of ethyl *N*-acetyl-α-aminocinnamate with $[Rh((S,S)\text{-chiraphos})]^+$. It is found that, of the eight possible modes of H_2 addition, six paths generate impossibly large atom–atom interactions between the substrate and the *P*-phenyl groups suggesting that it is improbable that these paths engage in asymmetric hydrogenation. The two remaining paths, one for each isomer, appear to be devoid of strong atom–atom interactions. The details of the molecular graphics analysis are presented, and it is suggested that the approach provides a systematic, formal method of molecular model building which may prove superior to the current intuitive use of molecule models for assessing steric interactions. Molecular graphics may be helpful in designing asymmetric catalysts.

Introduction

Asymmetric catalytic hydrogenation of amino acid precursors by chiral bidentate (phosphine)rhodium(I) catalysts is one of the most efficient synthetic methods of generating amino acids.[1,2] The mechanism of catalysis is understood in great detail[3-5] but the precise structural origins of the enantioselection remains a matter of speculation. The following features are established for the reduction of ethyl *N*-acetyl-α-aminocinnamate (see 1 and 2) by the $[Rh((S,S)\text{-chiraphos})]^+$ catalyst ((*S*,*S*)-chiraphos = $Ph_2PCH(CH_3)CH(CH_3)PPh_2$). First, the ee is >95%. Second, chelated (*S*,*S*)-chiraphos exists in the conformation shown in 1 and 2[6,7] where the *P*-phenyl groups are arranged in axial (a) and equatorial (e) dispositions. Third, the substrate is bound to the metal as a bidentate chelate via the olefin and the acyl oxygen atom, 1 and 2.[3] Fourth, the major diastereomer is in rapid equilibrium with the minor isomer 2 and the equilibrium is displaced strongly to 1. Fifth, the minor isomer 2 is the more reactive isomer so that the prevailing enantiomer of the product originates from the minor isomer. Sixth, the addition of H_2 to these two isomers is both the turnover limiting as well as the enantioselective step at 25 °C and 1 atm of H_2. Since the addition of H_2 is the first irreversible step involving diastereomeric transition states, the structural origins of the enantioselectivity are completely defined by this step.[8]



1 2

This note describes a highly approximate method for analyzing the steric interactions of the enantioselective step. The method employs computer-driven molecular graphics and van der Waals (VDW) energy minimization for identifying these interactions. The process we describe amounts to a sophisticated method of model building

---

[†] Present Address: Department of Chemistry, The University of Chicago, 5735 S. Ellis Avenue, Chicago, IL 60637

(1) Koenig, K. E. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, p 71.

(2) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106.

(3) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 5952.

(4) Halpern, J. *Asymmetric Synthesis*; Morrison, J. D., Ed. Academic Press: New York, 1985; Vol. 5, p 41.

(5) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746 and references cited therein.

(6) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262.

(7) Bosnich, B.; Roberts, N. K. *Catalytic Aspects of Metal Phosphine Complexes*; Alyea, E. C., Meek, D. W., Eds.; ACS Publication, Washington, D.C., 1982; p 337.

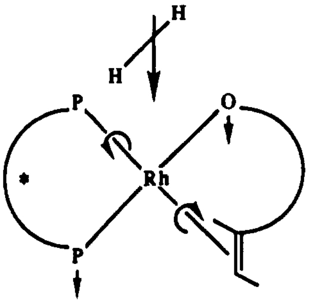
(8) *Asymmetric Catalysis*; Bosnich, B., Ed.; Martinus Nijhoff Publishers: Boston, 1986.

0276-7333/89/2308-1450$01.50/0

whereby, instead of intuitively assessing steric interactions by the use of hand-manipulated mechanical models, we employ computer driven molecular graphics to determine the number of atom–atom interactions ("bump checking") and the net VDW (polar) energy after the energy has been minimized by allowing rotation about all acylic single bonds. It should be made clear that these calculations are not molecular mechanics optimizations because they exclude terms associated with stretching, bending and torsional strain of bonds. Thus, in the absence of reliable force field constants for metal complexes, the present method can only point to major atom–atom interactions and suggest that certain molecular configurations are improbable when the VDW energy becomes very large.

Molecular Graphics

The initial input structure for these calculations was the crystal structure of the major diastereomer 1.[3] The minor isomer 2 was generated from this structure by a series of routines[9] that led to a structure of 2 that was a diastereomeric copy of 1 (see Molecular Graphics Details). The oxidative addition of H_2[10] to 1 and 2 can, in principle, lead to eight isomerically different octahedral *cis*-dihydrido species, four each from 1 and 2. These arise from addition of H_2 along the ligand–metal–ligand axes of the square-planar diastereomers, two from the "top" and two from the "bottom" (Figure 1). We assume, first that the H_2 addition is a concerted process involving the displacement of the trans disposed donor atoms in the manner illustrated by 3 for the production of A. The process shown represents the "downward" displacement of the trans P and O ligands by simultaneous rigid rotation of the two chelate rings about the P-Rh and olefin-Rh bonds. The second assumption is that the presence of the H_2 molecule can be ignored for assessing the major interligand interactions. Third, we ignore the stereoelectronic distinction[11] between H_2 addition to the P-Rh-O and P-Rh-olefin axes. It is clear, therefore, that with these assumptions the results cannot be definitive. Only when very large interactions are involved, can they suggest probable results. Fortunately, we find very large atom–atom interactions for some of the H_2 addition paths.



3

The calculations were performed by using the two input structures as follows. For each path the trans L-Rh-L angle was contracted by increments of 5°. At each angle increment the structure was VDW minimized by allowing all of the acylic single bonds to rotate (except chiraphos methyl groups) to a minimum rotameric conformation. The energy and the number of atom–atom contacts were noted. The results of these calculations for the eight reaction trajectories are shown in Figures 2 and 3.

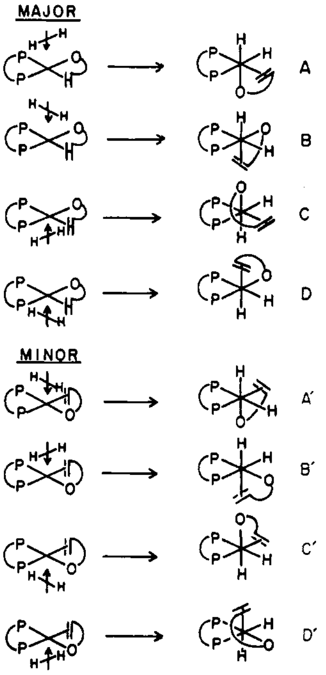


Figure 1. A schematic representation of the dihydrido products formed by concerted H_2 addition to the major and minor isomers.

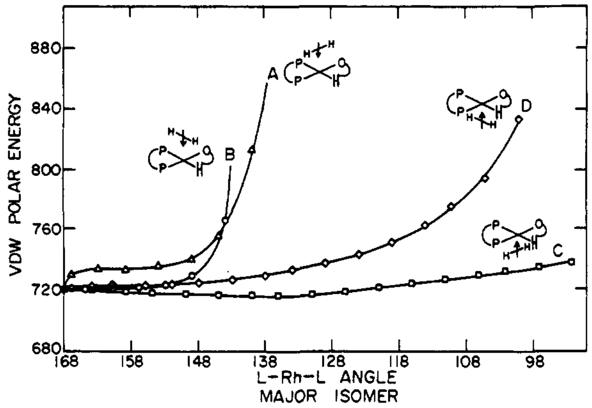


Figure 2. The van der Waals (polar) energy (in kcal/mol) profiles for H_2 addition to the major isomer (1,3-interactions are included).

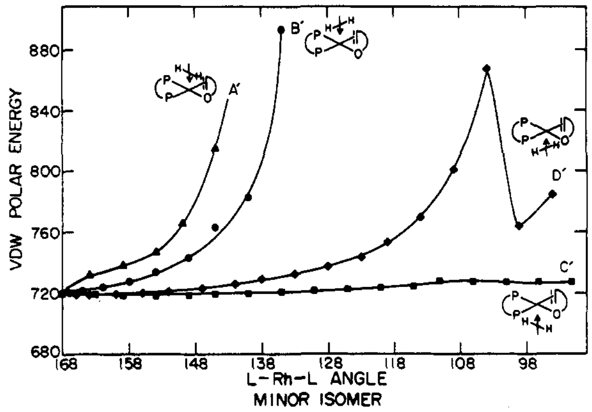


Figure 3. The van der Waals (polar) energy (in kcal/mol) profiles for H_2 addition to the minor isomer (1,3-interactions are included).

It will be noted that, of the eight possible trajectories, only two appear to be devoid of impossibly large VDW interactions. These allowed trajectories, C. and C′, involve the approach of H_2 from the "bottom" along the P-Rh-O axes of the major and minor isomers, respectively. Al-

---

[9] These are embodied in the program Chem-X, developed and distributed by Chemical Design, Ltd, Oxford, England.

[10] Daniel, C.; Koga, N.; Han, J.; Fu, X. Y.; Morokuma, K. *J. Am. Chem. Soc.* **1988**, *110*, 3773 and references cited therein.

[11] Johnson, C. E.; Eisenberg, R. *J. Am. Chem. Soc.* **1985**, *107*, 3148. Kunin, A. J.; Farid, R.; Johnson, C. E.; Eisenberg, R. *J. Am. Chem. Soc.* **1985**, *107*, 5315.

though the C′ trajectory of the minor isomer appears to be favored over the corresponding trajectory for the major isomer (C) late in the H_2 addition process, consistent with experiment, we place no significance on this observation because of the gross approximations involved. It is significant, however, that the C and C′ paths lead to *cis*-dihydrido isomers which have a M–H bond and the M–olefin bond aligned correctly for hydride transfer to the β–olefin carbon atom leading to a tertiary carbon–metal bonded intermediate. This is the intermediate detected at low temperatures for this system.[3-5]

Given the large atom–atom interactions calculated for six of the paths and the fact that the allowed paths lead to *cis*-dihydrido intermediates for which the M–H and olefin bonds are properly aligned, it seems reasonable to conclude that asymmetric catalytic hydrogenation of the present substrate proceeds via paths C and C′. Moreover, if the reaction trajectories chosen are a reasonable approximation to the actual trajectories, then the severe steric interactions observed for the six paths are likely to be sustained even after an accurate molecule mechanics force field calculation.

We find that the major interactions for the six excluded paths are as follows. Path A leads to strong interaction between the substrate phenyl group and an axial *P*-phenyl group that was originally cis to the olefin; path A′ involves the same interaction but with the corresponding cis equatorial *P*-phenyl group. For path B, severe interaction occurs between the substrate phenyl group and the axial *P*-phenyl group originally trans to the olefin; for path B′ the same interaction occurs but with the corresponding trans equatorial *P*-phenyl group. Path D generates strong interactions between the carbethoxy group and the originally trans equatorial *P*-phenyl group whereas, for D′, this same interaction involves the corresponding trans axial *P*-phenyl group. These interactions are shown in **1** and **2** by the dotted lines. The "kink" in D′ at ≈100° occurs because the carbethoxy group and the trans axial *P*-phenyl group become increasingly "locked" as the "kink" angle is approached. As the trajectory continues, the two locked groups suddenly become unlocked and rotate to minimize the energy. There are no major interactions along either path C or path C′, although we find that these paths require considerable rotation of the carbethoxy group to avoid *P*-phenyl interactions. The chiral discrimination appears to arise from the accumulation of a number of subtle interactions which are impossible to define by the present method since at most, they amount to a difference of about ≈3 kcal/mol. We note that the formation of the substrate chelate ring is crucial in excluding the six forbidden paths for, without the ring, the strong atom–atom interactions could be avoided by (coordinated) olefin rotation. Furthermore, the large *P*-phenyl groups are necessary to ensure that the six paths are blocked. Finally, the severity of the interactions for the six forbidden paths suggests that our exclusion of the H_2 molecule and the stereoelectronic effect were not critical to the result.

Discussion

Although there have been some notable achievements, there exists no systematic method for designing effective asymmetric catalysts and reagents. The current methods of employing molecular models for assessing steric interactions before, but usually after, the event is largely intuitive and prone to considerable ambiguity. Although a similar criticism can be leveled at the use of molecular graphics, it, nonetheless, provides a formal method of molecular model building that may prove more effective than the current intuitive mechanical methods. The molecular graphics method provides a facile method for identifying atom–atom interactions, can generate a minimized rotameric structure, and can calculate the VDW energy of the minimized structure. As such, it removes many of the intuitive aspects of molecular model building, and if adequate caution is exercised, it potentially provides a guide for the design of asymmetric catalysts and for assessing steric interactions in general. Ultimately the method will be judged by its ability to guide experiments.

Molecular Graphics Details

Graphics manipulations and energy calculations were carried out with a MicroVAX-II and an IBM-AT compatible computer. For structure building, structure manipulation, and VDW minimizations the program Chem-X was used. For molecular mechanics calculations the program MODEL-MMX was used.[12]

The major **1** and minor **2** isomers were constructed as follows. The crystal structure of the major isomer was used as the initial input structure.[13] The minor isomer was generated from this structure by first inverting the major isomer to its mirror image, and then the inverted structure was rigid fitted[14,15] to the original major isomer. From the superimposed structures was removed graphically the generated (*R*,*R*)-chiraphos, the original (univerted) substrate fragment, and one rhodium atom, to leave the minor isomer consisting of (*S*,*S*)-chiraphos, rhodium, and the inverted substrate.

For minimization with respect to VDW polar energies, $V(P)$, the Buckingham formulation was used

$$V(P) = \frac{A\exp(-Br)}{r^D} - \frac{C}{r^6}$$

where r is the atom–atom distance. Literature values[16] of A, B, C, and D were used for all of the atoms except rhodium, for which the parameters are not known. The rhodium was treated as a parameterless dummy atom. The quadratic gradient method minimizer embodied in Chem X[17] was used for minimizing the VDW energy. Minimizations were carried out with respect to rotation about all P–phenyl bonds, the olefin–phenyl bond, and the requisite single bonds of the carbethoxy group.

The VDW radii were calculated by setting the Buckingham VDW energy equation to zero energy for like atoms. These computed radii are somewhat different from the empirical values used in Chem-X. The computed radii were used in "bump checking" (the number of atom–atom contacts). Using VDW radii, however, can be misleading because this form of bump checking does not distinguish between "hard" or "soft" contacts, all types of atom–atom contacts are counted. In order to determine the number of "hard" contacts, all of the radii can be reduced by an arbitrary amount (for example, CPK = 0.67 VDW radii) and these "hard" or reduced contacts can be counted to

---

(12) We used the prerelease version (2.9) of MODEL-MMX. The graphics front end of this program was a modified version of the MODEL program of Clark Still. It was modified by K. Steliou (University of Montreal). The backend consisted of the MMX force field developed by K. Gilbert and J. J. Gajewski (Indiana University) who sell the program through Serena Software.

(13) The coordinates were provided by J. Halpern. In this structure the phenyl groups were refined as rigid bodies.

(14) Kabsch, W. *Acta Crystallogr., Sect. A.* **1976**, *A32*, 922; **1978**, *A34*, 827.

(15) Yuen, P. S.; Nyburg, S. C. *J. Appl. Cryst.* **1979**, *12*, 258.

(16) DelRe, G.; Gavuzzo, E.; Giglio, E.; Lelj, F.; Mazza, F.; Zappia, V. *Acta Crystallogr., Sect. B* **1977**, *B33*, 3289.

(17) The algorithm for this minimization is described in: Davies, E. K.; Murrall, N. W. *Comput. Chem.* **1988**, *00*, 000.

assess the major contact terms. We found that using 0.85 VDW radii contacts were most useful for focusing on the number of "hard" contacts in the minimized structures and hence identifying the major interactions. (The result does not depend on the value of the radii used.) Using "hard" contact numbers, we find that plots of "hard" contacts versus angle give similar results to those shown in Figures 2 and 3. The description of the major interactions given in section 1 was derived from the use of these "hard" contacts.

The error in the VDW energies based on uncertainties of the crystallographically determined atomic positions was determined by the following *correlated* stochastic procedure. The x, y, z coordinates of each atom were altered by a normally distributed random number between −1 and +1 multiplied by 3 times the standard deviations of the crystallographically determined atomic positions of the major isomer. This randomly distorted structure was graphically converted into the minor isomer by the procedure just described. The two distorted diastereomers were then VDW minimized. The difference in energy was noted for all interactions except those involving 1,3-interactions. This whole procedure was repeated 82 times, and from the distribution of the energy differences it was determined that the error in the *difference* in the VDW energy of the two isomers was between 1 and 2 kcal/mol. The assumption behind this stochastic correlated procedure is that the diastereomers will have essentially the same corresponding bond lengths, angles, and torsional angles and that only rotations about bonds will vary. This, of course, is the assumption we have used in this paper.

The calculations described here depend to some extent on having the correct input structures for the major and minor isomers. In principle, these structures could be obtained from a molecular mechanics optimization.[18] We attempted to obtain these with MMX. The best representation of the crystal structure was obtained by inputing the P atoms as both "bonded" *and* "coordinated", the acyl oxygen atoms as "coordinated", and the olefin as a "bonded" metallocyclopropane. No "lone pairs" were added to the rhodium atom, the radius of which was inputed as 1.30 Å. All other parameters were those provided by version 2.9 of MODEL-MMX. Search for the global energy optimum[19] was carried out by randomly displacing the atomic coordinates by amounts varying between 0.1 and 0.3 Å and inputing the "shaken" structures for MMX optimization. The final optimized structure for the major isomer obtained in this way was in good agreement with that of the crystal structure. In particular, torsional and rotameric conformations of chiraphos were in excellent agreement, as were the rotameric conformations of the carbethoxy and phenyl group of the bound olefin. The C–C bond of the olefin was too long because of the metallocyclopropane input, but the rhodium–carbon bond lengths were in excellent agreement with the crystal structure. Moreover, the trans P–Rh–α-olefin–carbon angle was reproduced ($\approx$168°). Slight puckering of the substrate chelate ring, which is not observed in the crystal structure, was obtained due to the long olefin C–C bond. The C–P–C angles were compressed by $\approx$10% compared to the crystal structure, but this difference can be accounted for by crystal packing effects. Overall, the optimization procedure gave what appeared to be a reasonable structure for the major isomer, leaving a degree of confidence that the optimized structure of the minor diastereomer was a good representation of the structure. Furthermore, the same structures were obtained either by inputing the crystal structure of the major isomer and the graphically derived minor isomer structure or by "drawing" these two isomers from scratch. The energies of the optimized major and minor isomers were essentially the same which occasioned no surprise because of the approximate force field and because solvent effects were ignored. The MMX procedure, although approximate, does provide a systematic method of varying the structures of the two isomers to give coordinates somewhat different from those used in the trajectory calculations. This provides a method of testing the sensitivity of the trajectory profiles to variations of initial input structures. When the MMX optimized structures were used for the trajectory calculations, essentially the same results as those shown in Figures 2 and 3 were obtained.

The force field embodied in MMX did not produce a good structure for the dihydrido intermediates derived from the preferred paths C and C′. The P–Rh bond lengths were too long leading to gross distortions of the two intermediates.

Acknowledgment. This work was supported by grants from the Natural Sciences and Engineering Research Council of Canada. We thank S. Whittington, R. Kapral, D. Farrar, and J. Sawyer for helpful discussions.

Registry No. 1, 2, 74858-55-2.

---

[18] We use "minimize" for finding the lowest van der Waals energy and "optimize" is used in searching for the lowest molecular mechanics energy that includes VDW interactions.

[19] Saunders, M. *J. Am. Chem. Soc.* 1987, *109*, 3150.