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Molecular graphics and asymmetric catalysis

B. Bosnich

Department of Chemistry, The University of Chicago, 5735 S. Ellis Avenue, Chicago Illinois, 60637 U.S.A.

Abstract - Molecular graphics and Van der Waals minimizations are used to analyze the steric interactions of the enantioselective step of asymmetric catalytic hydrogenation of amino acid precursors using chiral bidentate phosphine rhodium (I) complexes. It is concluded that, of the eight possible hydrogenation paths, only two, one for each diastereomer, are allowed because of severe steric interactions in the other six paths.

INTRODUCTION

Asymmetric catalysis is perhaps the most refined synthetic method, because it embodies two of the most desirable synthetic characteristics, hyperreactivity and hyperselectivity provided by small amounts of regenerated material. Although there exist many efficient catalysts, the problem of modifying these systems into highly selective reagents remains a major challenge. Effective asymmetric catalysts are usually discovered through a mixture of luck, intuition and a great amount of perseverance (ref. 1). It would, therefore be a matter of considerable importance if a technique were developed which could provide a rational and systematic approach to the design of effective asymmetric catalysts. We describe here a method which may provide such a guide provided the catalytic mechanism is understood and due circumspection is exercised. The method is computer driven molecular graphics coupled with a calculation of minimized non-bonded interactive energies.

MOLECULAR GRAPHICS

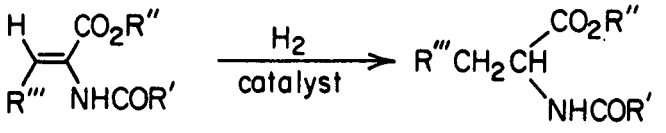
Although there are a number of approaches that may be adopted in using molecular graphics for the design of asymmetric catalysts, the one described here is what may be called formal molecular model building. In essence the method formalizes the intuitive considerations that are used when assessing steric interactions by means of mechanical molecular models. Thus, mechanical molecular model building begins by the construction of scale molecular models which have standard bond lengths, bond angles and atoms of proportional radii, which, depending on the model set, are some fraction of the Van der Waals (VDW) radii (e.g., CPK = 0.67 VDW). The steric interactions are then assessed by allowing rotation about all requisite acylic single bonds; bend, angle and torsional strain are generally neglected. Thus, for example, it is asserted that certain parts of the molecule are more "crowded" or the interaction is greater for certain molecular arrangements and so on. Despite its intuitive nature, model building has proved effective in approximately assessing steric interactions. Molecular graphics allows us to assess steric interactions systematically and quantitatively and allows us to identify the major atom-atom contacts.

In order to begin one needs access to: (a) a reasonably fast computer, (b) a graphics terminal preferably with 3-D motion capability and (c) sophisticated software. We used a Micro-Vax II, a Sigmex 6268M graphics terminal and the Chem-X software (ref. 2). Structures can be drawn on the screen either by employing standard bond lengths and angles or by imputing crystal structure coordinates. The molecule can then be manipulated either

with respect to its internal or external coordinates or with respect to another molecule. The minimum energy structure can, in principle, be obtained by use of an empirical force field calculation but this cannot be done accurately as yet for organometallic catalysts. The best that can be done is to obtain the minimum (VDW) conformation with respect to rotation about acylic single bonds. Chem-X embodies a VDW minimizing bond rotation algorithm which employs the Buckingham equation and empirically derived VDW parameters (ref. 3). The algorithm fixes all bond lengths, bond angles and torsional angles and only allows rotation about specified acylic single bonds. It gives the VDW minimized rotameric conformation. The major atom-atom interactions of any rotameric conformation can be identified by a process called "bump checking" which simply counts the number of atom-atom VDW contacts. One can determine which of these contacts is "hard" or "soft" by reducing atomic radii by an arbitrary amount. As the radii are reduced, so the number of atom-atom contacts is reduced. In this way one can identify the hard and soft contacts. Thus the VDW minimization gives the stable rotamertic conformation and bump checking identifies the regions of greatest interaction. This process is essentially what is done when molecular models are used but differs from the intuitive method in that it is systematic, formal and quantitative. We now outline how this method was applied to analyzing the steric interactions in asymmetric catalytic hydrogenation of amino acid precursors.

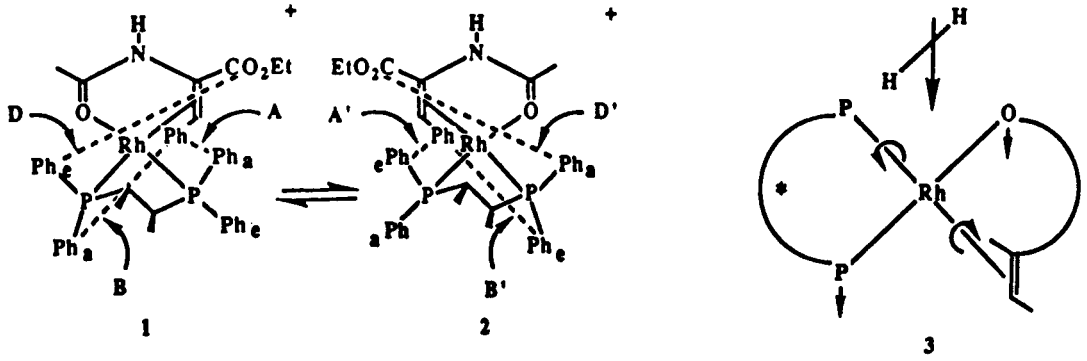
ASYMMETRIC CATALYTIC HYDROGENATION

Asymmetric catalytic hydrogenation of amino acid precursors (eq. 1) by chiral bidentate phosphine rhodium (I) complexes can give the products in almost quantitative ee (ref. 4).



(1)

The mechanism of this catalysis is understood in great detail (ref. 5) but the structural origins of the enantioselection is a matter of speculation. It is known that the reduction of N-acetyl-α-aminocinnamate (see **1** and **2**) by the $[Rh(S,S\text{-chiraphos})]^+$ catalyst (ref. 6) (S,S-chiraphos = $Ph_2PCH(CH_3)CH(CH_3)PPh_2$) leads to the initial formation of the major (**1**) and minor (**2**) diastereomers where the substrate is bound to the rhodium by both the acyl oxygen and the olefin (ref. 7). The chelated chiraphos exists in the conformation shown



(**1** and **2**) where the P-phenyl groups are disposed in axial (a) and equatorial (e) dispositions. The two diastereomers (**1** and **2**) add H_2 (endothermically) to form (undetected) 6-coordinate dihydrido intermediates, which by successive hydride transfer steps produce the product. The prevailing enantiomer of the product can be traced to the minor diastereomer because of its greater kinetic reactivity (see ref. 8 for a possible explanation). Since the oxidative addition of H_2 to **1** and **2** is the first irreversible step involving diastereomeric transition states, it is the enantioselective step and the structural

origins of the enantioselection are completely defined by this step (ref. 1). Thus the molecular graphics calculations need only consider this step.

Oxidative addition of H_2 to **1** and **2** can, in principle, lead to eight diastereomeric dihydrido intermediates, four each from **1** and **2** depending on the trajectory of the H_2 addition (ref. 9, Fig. 1). The object is to try to calculate, approximately, the steric interactions during the addition of H_2 to **1** and **2**. It is clear that (at least) two major problems are involved in attempting to track the steric interactions during the reaction trajectory. First, we require to be able to define the molecular coordinates during H_2 addition (ref. 10). Second, there are stereoelectronic differences between H_2 addition along the P-Rh-olefin and P-Rh-oxygen axes (ref. 9). In the spirit of model building, however, we shall ignore the stereoelectronic effect and ignore the presence of the H_2 molecule. With these two assumptions, the reader may be inclined to flip to the next article, but the utilitarian prospects are not as bleak as they may appear. The trajectory coordinates were constructed by the method implicit in **3** where the P-Rh-O angle is contracted in 5° intervals by rigid rotation about P-Rh and olefin-Rh bonds. A similar process was applied for the other H_2 additions (Fig. 1). At each 5° interval the system was VDW minimized by allowing rotation about the P-phenyl, olefin-phenyl and all of the requisite single bonds of the carboethoxy group. The minimized VDW energy was noted and the minimized configuration was bump checked.

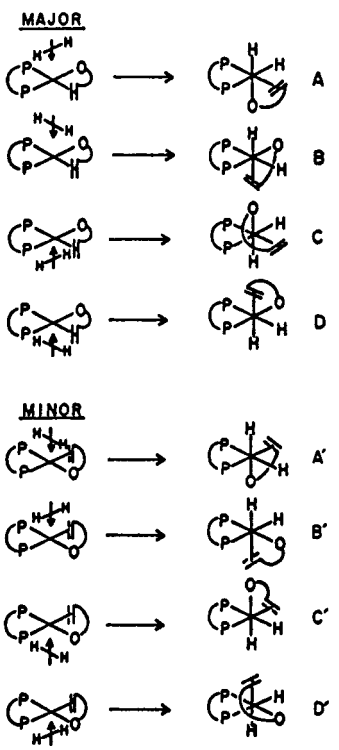


Figure 1: A schematic representation of the dihydrido products formed by concerted H_2 addition to the major and minor isomers.

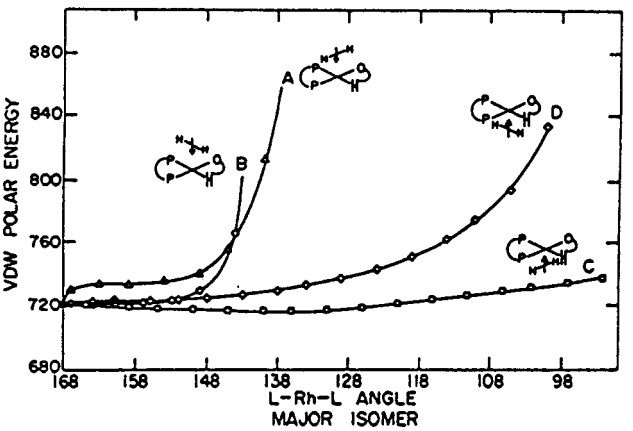


Figure 2: The Van der Waals (polar) energy (in kcal/mol) profiles for H_2 addition to the major isomer (1,3-interactions are included).

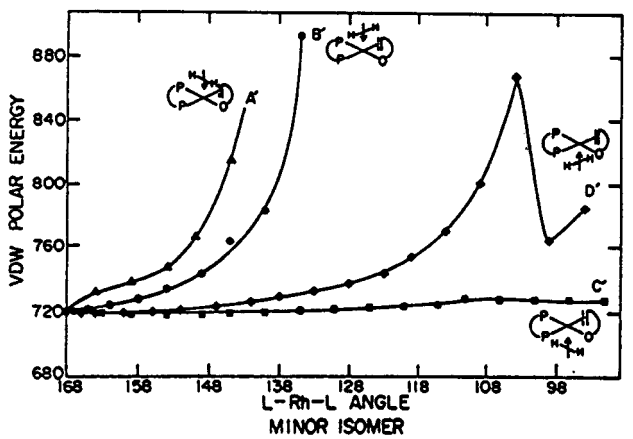


Figure 3: The Van der Waals (polar) energy (in kcal/mol) profiles for H_2 addition to the minor isomer (1,3-interactions are included).

We show in Figs. 2 and 3 the results of the trajectory calculations for the eight paths. Of the eight possible paths only two, the corresponding paths C and C' of **1** and **2**, are devoid of impossibly large atom-atom interactions. The major interactions in these forbidden paths arise from interactions between the olefin substituents and the P-phenyl groups of chiraphos. These interactions are indicated by the dotted lines in **1** and **2**. Because of the magnitude of the interactions in the forbidden paths, it seems unlikely that the results would be affected by the initial assumptions we made or by a more sophisticated calculation. Further confirmation that C and C' are the preferred paths is provided by the observation that the β-olefin carbon atom and a hydride are aligned for C and C' so that a tertiary carbon-rhodium bond is formed for one of the catalytic intermediates. This is an experimental observation (ref. 5).

We find that the trajectory C' from the minor isomer is preferred over C from the major isomer late in the trajectory. Although this is consistent with observation, the highly approximate nature of these calculations does not permit us to attach any significance to this results. The origins of the enantioselection appears to arise from a series of subtle effects which are distributed among many atoms of the molecule. It is clear, however, that the formation of the substrate chelate ring is crucial to the overall results, for without the ring the major interactions in the six forbidden paths could be avoided by olefin-metal rotation.

DISCUSSION

It is clear from the brief outline given that the conclusions drawn from molecular graphics in assessing steric interactions have to be treated with caution. There are many aspects of the total energy which are not taken into account and it is easy to drift into unreality by the charms of computer graphics. If the process is treated as a guide rather than as a firm theoretical directive, the technique can provide useful stereochemical insight. Molecular graphics is still in a rudimentary state and it is sure to develop as a more formal procedure. We have given one possible approach here. A similar although less sophisticated approach has recently been published for the conformations of metal acyl complexes (ref. 11). A more detailed description of this work is presented elsewhere (ref. 12).

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