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STRUCTURAL REQUIREMENTS IN CHIRAL DIPHOSPHINE-RHODIUM COMPLEXES. VI[1]. INHIBITION OF THE ASYMMETRIC HYDROGENATION OF Z-METHYL-α-ACETAMIDOCINNAMATE CATALYZED BY DIOP-RHODIUM CATALYST IN THE PRESENCE OF Z-ADAMANTYL OR BORNYL-α-ACETAMIDOCINNAMATE.

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Summary: The half-life period (6.6 min.) for the hydrogenation of Z-methyl-α-acetamidocinnamate (catalyzed by a neutral DIOP·Rh complex) was found to be the same when the Me ester reduction was performed in the presence of equimolar quantities of the corresponding i-Pr or t-Bu ester unsaturated substrates. Neither the Me nor the i-Pr or t-Bu esters underwent appreciable Z,E-isomerization. The formation of N-acetylphenylalanine methyl ester product suffered inhibition when the hydrogenation reaction was performed in the presence of the corresponding bornyl or 1-adamantyl unsaturated esters (half-life period of the Me ester: 27 & 40 min., respectively). The greater the inhibition of the Me ester unsaturated substrate, the more the bulky inhibitor itself underwent Z,E-isomerization. In the presence of inhibitors, the Me unsaturated substrate did not undergo appreciable Z,E-isomerization.

(+) or (-)-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP)[2] has been used as a chiral ligand in rhodium-catalyzed asymmetric hydrogenation reactions of Z-α-acetamidocinnamate esters to yield the corresponding N-acetylphenylalanine esters.[1] In a series of achiral Z-α-acetamidocinnamate esters the following optical yields were reported: Me [69 % enantiomeric excess (R) for (-)-(2R,3R)-DIOP]; Et [72 % ee (R)]; i-Pr [76 % ee (R)]; t-Bu [77 % ee (R)]; and 1-adamantyl [71 % ee (R)].[1a] Z-(-)-(1S,2R,4S)-bornyl-α-acetamidocinnamate similarly gave 64 % diastereomeric excess (R,2R) with (-)-DIOP and 50 % d.e. (S,2R) with (+)-DIOP.[1b] These neutral Rh·DIOP complexes[3] appear not to be very sensitive to steric bulk in the alcohol moiety of the unsaturated esters (judging from the fairly tight compression of the increasing percent enantiomeric excess within the ester series up to and including t-Bu). However, when the alcohol moiety becomes larger than t-Bu, the stereospecificity observed in the reaction product decreases as shown with 1-adamantyl and bornyl.[4,5]

The half-life period[4] for the reduction[5] of Z-methyl-α-acetamidocinnamate was found to be 6.6 min.[6] Fig. 1 represents the production of saturated Me ester product as a function of reaction time.[6] When the reaction was performed with an equimolar quantity of the corresponding i-Pr or t-Bu unsaturated ester in the presence of the Me ester substrate, the same hyperbolic type curve was obtained for the formation of saturated Me ester product (see fig. 1). However, when the corresponding (1S,2R,4S)-bornyl or 1-Ada unsaturated esters are now reduced in the presence of

the Me substrate, it is seen from fig. 1 that these relatively more bulky substrates have caused inhibition of the formation of saturated Me ester product (half-life period of Me ester now 27 & 40 min., respectively). The formation of saturated Me ester product in the competition experiments with the more bulky alcohol substrates also does not show the normal initial fast rate of product formation which later tapers off. Z,E-isomerization prior to hydrogenation was found to be very small for the Me unsaturated ester (alone and in all competition experiments discussed in this paper). The same small degree of isomerization was found for the i-Pr and t-Bu analogues [alone or in the presence of the Me ester].

Thus, the co-substrates [in the competition reactions] fall into two groups in their behavior towards the Me ester. In the first group [the smaller ester analogues: i-Pr & t-Bu] the co-substrates do not act as inhibitors. In the second group [the larger ester analogues: 1-Ada & Bornyl] the co-substrates now do act as inhibitors. Fig. 2 is representative of the first group of co-substrates [graph shows t-Bu reacted in the presence of the Me ester].

Fig. 3 & 4 portray the second group of co-substrates [graphs show reactions in presence of Me ester]. The co-substrates in this group are characterized by a larger extent of Z,E-isomerization. Note that this isomerization occurs in the initial period while the rate of product formation is slow. The group 2 co-substrate (1-Ada) which caused the most inhibition of the Me ester competitor was also shown to undergo the most Z,E-isomerization itself [alone or in the presence of the Me ester]. It should be remembered that the optical yield of the 1-Ada ester reduction product suffered a decrease compared to that of t-Bu [71 % ee vs. 77 % ee] and this may now be attributed to Z,E-isomerization prior to hydrogenation.

A preliminary interpretation of these competition experiments may be given in terms of a build-up of one or more intermediate species containing the relatively more bulky substrate in the catalytic complex. The longer-lived intermediate(s) now may undergo Z,E-isomerization more effectively than complete reduction to product. The inhibition of the methyl substrate in these competition experiments with the relatively more bulky bornyl and 1-Ada analogues may then be interpreted as arising from a decrease in the amount of available free catalytic species. Additional work is in progress to determine the nature of this inhibition.

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3. prepared in-situ by reaction of chloro(1,5-cyclooctadiene)rhodium(I) dimer with DIOP.
4. determined by gas-liquid chromatography on a 6 % Carbowax 20M column, 1 m long.
5. [Rh] = 3.0 mmol l^{-1}; [DIOP]/[Rh] = 1.1; [Me substrate]/[Rh] = 25; [abs. ethanol]/[benzene] = 2.3; total volume 10 ml; 1 atm. H_2 and 25°C.
6. In figures 1-4, "total area" refers to the sum total of the areas of all the three peaks: Z-substrate, E-substrate, and saturated product found in the gas chromatogram.