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STRUCTURAL REQUIREMENTS IN CHIRAL DIPHOSPHINE-RHODIUM COMPLEXES. VIII[1]. ASYMMETRIC HYDROGENATION OF N-ACETYLDEHYDROAMINO ACIDS WITH RHODIUM(I) COMPLEXES CONTAINING CHIRAL CARBOCYCLIC ANALOGUES OF DIOP.

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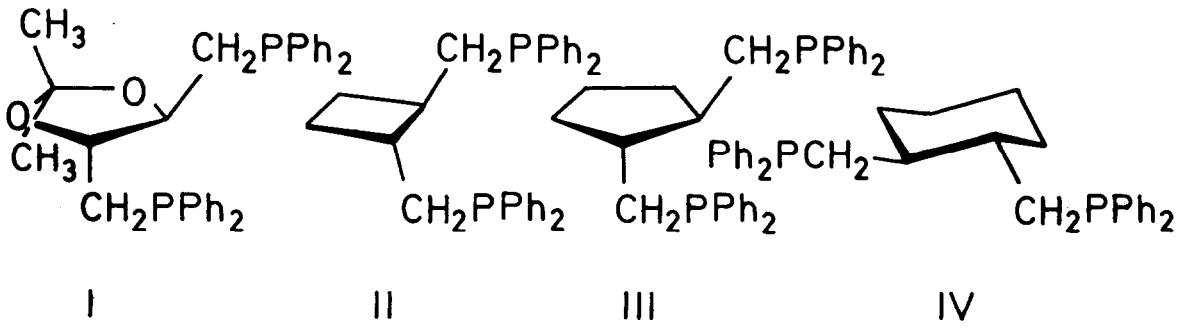
Summary: Z-α-acetamidocinnamic acid was hydrogenated with neutral diphosphine-rhodium(I) complexes containing trans-1,2-bis(diphenylphosphinomethyl)cycloalkanes to give N-acetylphenylalanine: 86 % e.e.-(R) [(1R,2R)-cyclobutane]; 63 % e.e.-(R) [(1R,2R)-cyclopentane]; 35 % e.e.-(S) [(1S,2S)-cyclohexane]; and 82 % e.e.-(R) [(2R,3R)-DIOP]. Similarly, α-acetamidoacrylic acid was hydrogenated to give N-acetylalanine: 72 % e.e.-(R) [(1R,2R)-cyclobutane]; 72 % e.e.-(R) [(1R,2R)-cyclopentane]; 40 % e.e.-(S) [(1S,2S)-cyclohexane]; and 73 % e.e.-(R) [(2R,3R)-DIOP].

2,3-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP)[2a,b] (I) has been successfully utilized as a chiral ligand in rhodium(I) complexes for the asymmetric hydrogenation of dehydroamino acid derivatives.[1a,b,d,2-6] The high degree of enantioface selectivity exhibited by these DIOP·Rh(I) complexes in the hydrogenation of the prochiral dehydroamino acid derivatives may be likened in some respects to the intimate relationship found between a "lock" and a "key". In this particular case, the DIOP·Rh(I) complex may be considered to be the "lock" while the prochiral substrate [the dehydroamino acid derivative] is designated as the "key". We have been interested in investigating these types of interactions in which the polar and steric factors may be metaphorically thought of as the "tumblers of the lock" or the "indentations of the key". Some systematic investigations of structural parameters in the "key" (such as changes in the carboxyl[1a] and amido[1d] moieties as well as in the β-substituent[7]) have been recently undertaken.

Concurrently with these systematic investigations of the "key", it was decided to undertake similar studies of the "lock". More specifically, it was decided to prepare chiral carbocyclic analogues of DIOP in which the torsional angle would be systematically varied between the two diphenylphosphinomethyl [Ph_2PCH_2] ring substituents. While this work was in progress, some reports of carbocyclic analogues of DIOP appeared.[2c,d,6] However, these analogues were neither extensively nor systematically investigated.

The (1R,2R)-trans-1,2-bis(diphenylphosphinomethyl)cyclobutane (II) analogue was first prepared by Rhone Poulenc S.A.[6] and later in our laboratories.[7] The (1R,2R)-trans-1,2-bis(diphenylphosphinomethyl)cyclopentane (III) analogue was prepared by Kagan et.al.[2c] Finally, the (1S,2S)-trans-1,2-bis(diphenylphosphinomethyl)cyclohexane (IV) analogue has been recently synthesized.[7] The cyclopropane analogue is currently being synthesized.

Neutral Rh(I) catalysts were prepared in-situ from chloro(1,5-cyclooctadiene)rhodium(I) dimer



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(V) and the corresponding chiral diphosphines (I-IV) in benzene. The homogeneous catalysts were used in the asymmetric hydrogenation of α-acetamidoacrylic acid (VI) and α-acetamidocinnamic acid (VII) to yield N-acetylalanine (VIII) and N-acetylphenylalanine (IX), respectively. The results of these investigations (performed in [abs. EtOH]/[benzene] = 2.3) are reported in the table. Thus, in the series of chiral C-4, C-5, and C-6 carbocyclic diphosphines and the heterocycle (DIOP) the optical purity of the N-acetylphenylalanine (IX) reduction products were found to be 86, 63, 35 and 82 % enantiomeric excess (% e.e.), respectively. Similarly, the optical purity of the N-acetylalanine (VIII) reduction products were found to be 72, 72, 40 and 73 % e.e., respectively.

The optical purity of the N-acetylphenylalanine (IX) product produced by the chiral carbocyclic C-4, C-5, and C-6 diphosphines (II-IV) appears to change in the same direction as the increasing torsional angle PCH_2C-C-CCH_2P and concomitant conformational rigidity within the seven-membered chelating ring with rhodium. It must be cautioned that this does not imply that there is a linear relationship between reduction product optical purity and the torsional angle or conformational rigidity in the chelating ring. Also, the change in conformational rigidity in the chelate ring [as a function of the size of the trans-fused carbocycle of the diphosphine] may increase at a different rate than the increase in the torsional angle. The result from the heterocyclic diphosphine (I) [82 % e.e.] appears to fall between that of the C-5 [63 % e.e.] and the C-4 diphosphine [86 % e.e.]. We may speculate whether or not this result may be due to the torsional angle and degree of chelate ring conformational rigidity in the heterocyclic DIOP falling between those of the C-5 and C-4 analogues. Perhaps it is due to the presence of the ring oxygen atoms and the gem-dimethyl group in the heterocycle?

The optical purity of the N-acetylalanine (VIII) products produced under the same circumstances seems to provide a clue. The optical yields for the C-4, C-5, and the heterocyclic diphosphine (DIOP) are all the <u>same</u> (72-73 % e.e.). This appears to be a very significant finding which has important structural implications, and is not the result of a mere casual sequence of events. It is clear that the alanine precursor (VI) [in which all β-substituents = H] is not sensitive to the PCH_2C-C-CCH_2P torsional angle in the chelating ring for the C-4 and C-5 analogues. However, it is also not sensitive to the presence of the gem-dimethyl group nor to the oxygen atoms in the heterocyclic moiety. This was indicated by Kagan[2d] in regard to the reduction of α-acetamidoacrylic acid (VI) with the C-5 analogue of DIOP. Thus, a special interaction between the alanine precursor (VI) and the oxygen atoms or the gem-dimethyl group in DIOP does not appear to be crucial for the relatively high degree of optical purity found in the reduction product (VIII).

It is not unreasonable that a similar situation also exists with the phenylalanine precursor

Table. Asymmetric hydrogenation of N-acetyldehydroalanine [CH_2=C(NHCOCH_3)COOH] and Z-N-acetyldehydrophenylalanine [C_6H_5CH=C(NHCOCH_3)COOH] catalyzed by neutral chlororhodium(I)/chiral diphosphine complexes.[a]

chiral diphosphine	CH_2=C(NHCOCH_3)COOH $[\alpha]_D^{25}$[b]	% opt. purity[c]	abs. config.	C_6H_5CH=C(NHCOCH_3)COOH $[\alpha]_D^{25}$[b]	% opt. purity[c]	abs. config.
(1R,2R)-II	+47.9[d]	72[e]	R	-40.0[f,g]	86[h,i]	R
(1R,2R)-III	-	72[j]	R[j]	-	63[j]	R[j]
(1S,2S)-IV	-26.7[d]	40[e]	S	+16.4[f]	35[h]	S
(2R,3R)-DIOP	[+46.8][d,k,l]	73[k]	R[k]	-38.1[f,h]	82[j,m]	R

[a][Rh] = 3.0 mmol l^{-1}; [diphosphine]/[Rh] = 1.1; [substrate]/[Rh] = 50; [abs. ethanol]/[benzene] = 2.3; total volume 10 ml; 1 atm. H_2; 25° C; and ~100 % conversion. (1R,2R)-trans-1,2-bis(diphenylphosphinomethyl)cyclobutane: $[\alpha]_D^{20}$ -17.0° (C 1.0, benzene); mp 107°; lit.[6] $[\alpha]_D^{25}$ -18.6° (C 1.0, benzene) and mp 107°. (1S,2S)-trans-1,2-bis(diphenylphosphinomethyl)cyclohexane: $[\alpha]_D$ +52.7° (C 1.0, benzene); mp 55-56°. [b] 10^{-1} x [α] = degree g^{-1} cm^2. [c] % enantiomeric excess, ±1 %. [d] (C 2.0, H_2O). [e] based upon N-acetyl-(R)-alanine: $[\alpha]_D^{25}$ +66.5° (C 2.0, H_2O), ref. 11.[6] [f] (C 1.0, 95 % EtOH). [g] $[\alpha]_D^{25}$ -39.5° for reaction performed in [abs. EtOH]/[benzene] = 2.0 lit.[22] $[\alpha]_D^{25}$ -36.3°. [h] based upon N-acetyl-(S)-phenylalanine: $[\alpha]_D^{25}$ +46.5° (C 1.0, 95 % EtOH) lit.[2e] $[\alpha]_{D_6}^{25}$ +46.8° (C 1.06, 95 % EtOH). [i] 85 % e.e. for reaction performed in [abs. EtOH]/[benzene] = 2.0 lit. 78 % e.e. [j] data taken from ref. 2d. [k] data taken from ref. 2b. [l] +46.8° value corresponds to only 70 % e.e. [a +48.6° value would correspond to 73 % e.e.]. [m] data taken from ref. 1a.

(VII). Thus, the presence of the β-phenyl ring in the prochiral substrate appears to be the factor which senses the differences in the torsional angle and the concomitant flexibility of the chelate ring [for the diphosphines I-IV]. The alanine precursor (VI) just seems to sense the difference between a more rigid catalytic hydrogenation complex [those containing diphosphines I-III] and a more flexible one[7] [that containing the C-6 diphosphine (IV)].

As a first approximation for this PCH_2C-⬡-CCH_2P torsional angle, one may utilize data for the COC-⬡-CCO torsional angle in the following compounds: trans-1,2-cyclohexane dicarboxylic acid,[8a] trans-1,2-cyclopentane dicarboxylic acid mono N-methyl amide,[9] and trans-1,2-cyclobutane dicarboxylic acid.[8b] From the x-ray crystallographic data it is seen that in this series of decreasing ring-size carbocycles, the torsional angle varies from 69°, 79°, to 99°, respectively. The x-ray structure of the heterocyclic diphosphine (I) within a cationic iridium complex has been determined,[10] and the PCH_2C-⬡-CCH_2P torsional angle therein has been found to be 87°. If the chosen model compounds are really "good" models, then the hypothesis seems reasonable that the torsional angle for the heterocyclic DIOP appears to fall between that for the carbocyclic four and five-membered rings. A better comparison would obviously be to compare the x-ray data of rhodium chelate complexes with all the diphosphines (I-IV).

Attainment of a rigid chiral conformation of the chelate ring in the catalytic complex will effect the local geometrical requisites of the phenyl rings attached to phosphorous. Kagan et.al.[2c] have demonstrated the importance of the conformation and degree of phenyl ring substitution in DIOP·Rh(I) catalyzed hydrogenation reactions. Further experiments are now in progress to ascertain the manner in which these factors influence the "lock and key"-type interactions within rhodium/chiral diphosphine complexes.

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