Asymmetric Synthesis. Asymmetric Catalytic Hydrogenation Using Chiral Chelating Six-Membered Ring Diphosphines

Patricia A. MacNeil, Nicholas K. Roberts, and B. Bosnich*

Contribution from the Lash Miller Chemistry Laboratories, University of Toronto, Toronto, Ontario, Canada, M5S 1A1. *Received August 18, 1980*

Abstract: Rhodium(I) catalysts formed by the two chiral chelating six-membered ring diphosphines, 2,4-bis(diphenylphosphino)pentane (skewphos) and 1,3-bis(diphenylphosphino)butane (chairphos), are efficient catalysts for the hydrogenation of amino acid precursors. The two chiral phosphines differ in that skewphos probably adopts a chiral conformation whereas chairphos probably adopts an achiral conformation. As a consequence the former generally gives high optical yields whereas the latter is ineffective as a chiral catalyst. This comparison evidences the importance of ring conformations in determining optical yields. The mechanism of asymmetric hydrogenation is discussed, and a number of particular and general conclusions are drawn which may prove useful in predicting optical yields from asymmetric synthesis.

The amino acid precursors, (*Z*)-(*N*-acylamido)acrylic acids, are reduced catalytically by soluble cationic rhodium(I) species. When such species incorporate chiral bidentate phosphine ligands, remarkably high optical yields are observed.[1-3] In two recent papers, we proposed a rational approach to the design of chiral chelating phosphine ligands for the catalytic asymmetric reduction of the amino acid precursors.[4,5] We reported the results of incorporating the bidentate diphosphines, (*S*,*S*)-chiraphos and (*R*)-prophos, which chelate to the rhodium atom in preferred chiral conformations[6] that are stabilized by chiral centers at the ring backbone. The chiral discrimination, it was asserted, was due to the chiral array of quasi-axial and quasi-equatorial phenyl groups bonded to the phosphorus atoms (Figure 1). We showed that the catalysts formed by these two ligands gave similar optical yields but of opposite chirality as would be predicted because of the enantiomeric configurations of the chelate rings.

This paper provides an incisive test of this hypothesis. It describes our results with two analogous ligands, (*S*,*S*)-skewphos (2,4-bis(diphenylphosphino)pentane)) and (*S*)-chairphos (1,3-bis(diphenylphosphino)butane)). These two ligands form six-membered chelate rings containing two- and one-chiral centers, respectively, but unlike the (*S*,*S*)-chiraphos and (*R*)-prophos analogues give spectacularly different results.

Stereochemistry

In principle six-membered chelate rings may adopt many ring conformations, but for the present purposes only two are important, the chiral skew and the achiral chair conformations. And of these two, the chair conformation is intrinsically more stable.[7,8] When chiral centers are incorporated at the 2- and 4-carbon atoms of the ring, one or other of these two conformations may be stabilized by the requirement that the substituents be equatorially disposed.[7-11]

In Figure 2 we show some of the ring conformations of (*S*,*S*)-skewphos, two skew and two chair conformations. Both chair conformations have one destabilizing[7,8] axially disposed methyl group, one of the skew conformations has two axial methyl groups, and the remaining skew conformation has both methyl groups in the preferred[7,8] equatorial dispositions. Given a choice between these conformations, experiment suggests[9-11] and theory supports[7,8] the conclusion that the skew conformation having two equatorial methyl groups is preferred. The difference in energy between the all-equatorial skew and the one-axial–one-equatorial chair conformations, however, may not be large, and steric effects associated with the whole complex may tip the balance in either direction.

The corresponding conformations for (*S*)-chairphos are shown in Figure 3. It will be noted that both a chair and a skew conformation exist which have equatorially disposed methyl groups. Because the unsubstituted chair conformation is intrinsically more stable, we would expect that this conformation would be the more stable for (*S*)-chairphos. This has been experimentally confirmed and theoretically supported for the corresponding diamine complexes.[11]

In discussing asymmetric hydrogenation using rhodium catalysts formed by chiraphos and prophos, we asserted that the major source of discriminatory interaction was the chiral array of phenyl groups, held so by the fixed chiral ring conformations (Figure 1). If this be so, then it follows that skewphos, in its chiral skew conformation, should give comparable optical yields to chiraphos and prophos, because the skew conformation fixes the phenyl groups in a similar chiral array. The chair conformation itself is achiral, and hence the phenyl groups are not in a chiral array. Thus we expect that chairphos catalysts, although chiral, will give low or negligible optical yields if the ligand adopts the chair conformation.

Ligand Synthesis

The synthesis of (*S*,*S*)-skewphos (and (*R*,*R*)-skewphos) is outlined in Figure 4. Racemic 2,4-pentanediol is separated from the meso form by fractional distillation of the sulfite esters.[12] The racemic diol was converted to the bis(*d*-10-camphorsulfonate ester), giving two internal diastereomers which are readily separated by crystallization. About 70% of each diastereomer is obtained. Either of these two diastereomers was reacted with lithium diphenylphosphide to give optically active skewphos in about 40% yield. A notable feature of this strategy is that the sulfonic ester is used both as a resolving agent and a leaving group. The skewphos ligand was isolated from the reaction mixture as the [Ni(skewphos)$(NCS)_2$] complex which was purified by

(1) Dang, T. P.; Kagan, H. B. *J. Am. Chem. Soc.* **1972**, *94*, 6429.
(2) Knowles, W. S.; Vineyard, B. D.; Sabacky, M. J.; Backman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.
(3) Cullen, W. R.; Yeh, E. S. *J. Organomet. Chem.* **1977**, *139*, C13. Yamamoto, K.; Tomita, A.; Tsuji, *J. Chem. Lett.* **1978**, 3. Achiwa, K. *J. Am. Chem. Soc.* **1976**, *98*, 8265. Beck, W.; Menzel, H. *J. Organomet. Chem.* **1977**, *133*, 307. Pracejus, G.; Pracejus, H. *Tetrahedron Lett.* **1977**, 3497. Tanaka, M.; Ogata, I. *Chem. Commun.* **1975**, 735. Hayashi, T.; Tanaka, M.; Ogata, I. *Tetrahedron Lett.* **1977**, 295. Cullen, W. R.; Sugi, Y. *Ibid.* **1978**, 1635. Tanao, K.; Yamamoto, H.; Matsumoto, H.; Miyake, N.; Hayashi, T.; Kumada, M. *Ibid.* **1977**, 1389. Grubbs, R. H.; DeVries, R. A. *Ibid.* **1977**, 1879. Hayahsi, T.; Mise, T.; Mitachi, S.; Yamamoto, K.; Kumada, M. *Ibid.* **1976**, 1133. Lauer, M.; Samuel, O.; Kagan, H. B. *J. Organomet. Chem.* **1979**, *177*, 309. Bruner, H.; Pieroncyzk, W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 620.
(4) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262.
(5) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1979**, *101*, 3043.
(6) Ball, R. G.; Payne, N. C. *Inorg. Chem.* **1977**, *16*, 1187.
(7) DeHayes, L. J.; Busch, D. H. *Inorg. Chem.* **1973**, *12*, 1505.
(8) Nicketic, S. R.; Woldbye, F. *Acta Chem. Scand.* **1973**, *27*, 621.
(9) Boucher, H.; Bosnich, B. *Inorg. Chem.* **1976**, *15*, 1471.
(10) Kojima, M.; Fujita, M.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 898.
(11) Kojima, M.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3237.
(12) Pritchard, J.; Vollmer, R. *J. Am. Chem. Soc.* **1963**, *85*, 1545.

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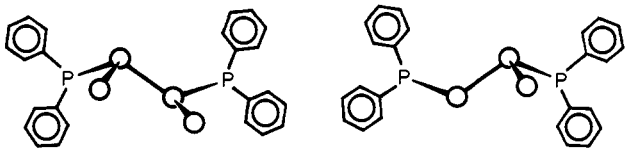


Figure 1. The preferred chiral conformation of (*S*,*S*)-chiraphos and (*R*)-prophos.

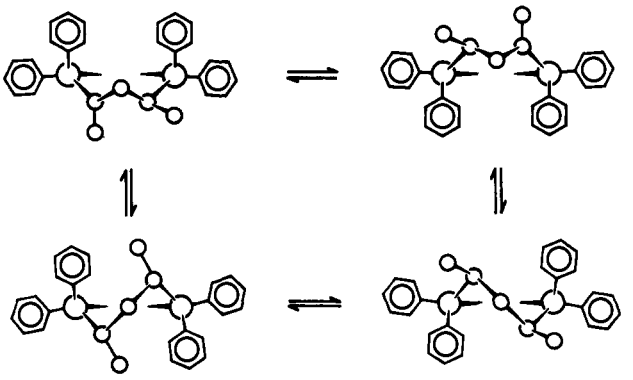


Figure 2. A selection of possible conformations of (*S*,*S*)-skewphos.

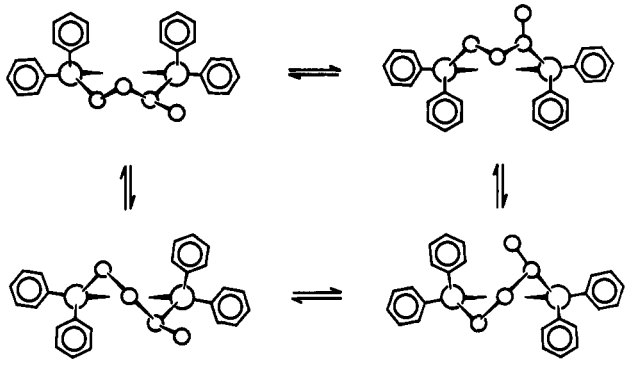


Figure 3. A selection of possible conformations of (*S*)-chairphos.

crystallization from methylene chloride/trifluoroacetic acid by the addition of ethanol. The purification at this stage is important because, after removal of the ligand from the nickel complex with cyanide ions, we were unable to induce the ligand to crystallize or to distill it. The methyl bis(quaternary salts) of the two antipodes are highly crystalline solids and have equal but opposite rotations, and the catalytic precursors (vide infra) give excellent crystals. There seems little doubt that the catalytic precursors are optically pure.

For the synthesis of chairphos, we were less concerned with synthetic efficiency than with ensuring that it was optically pure, because the low optical yields we predict should be clearly traceable to the nature of the ligand rather than to questions of optical purity. The synthesis is outlined in Figure 5. Optically pure malic acid was esterified in chloroform/methanol solution by using an ion-exchange catalyst (H^+ form), and the resulting dimethyl ester was reduced with lithium aluminum hydride.

The problem of selectively protecting the 1,3-disposed diols was solved by forming the cyclic acetal of formaldehyde. Experience suggests that cyclic formaldehyde acetals prefer to form six-membered rings. In the event, a 77:23 mixture of the six- and five-membered ring acetals, respectively, was obtained, and, after the methanesulfonic esters were formed, the desired pure six-membered ring system was isolated as crystals in 85% yield. The other steps in the sequence to form the optically pure 1,3-butanediol proceeded without incident.

Reaction of the bis(methanesulfonic ester) of 1,3-butanediol with lithium diphenylphosphide gave (*S*)-chairphos in 70% yield. The ligand was isolated and purified as its [Ni(chairphos)$(NCS)_2$] complex and set free from the complex with cyanide ions. As in the case of optically active skewphos, we were unable to obtain

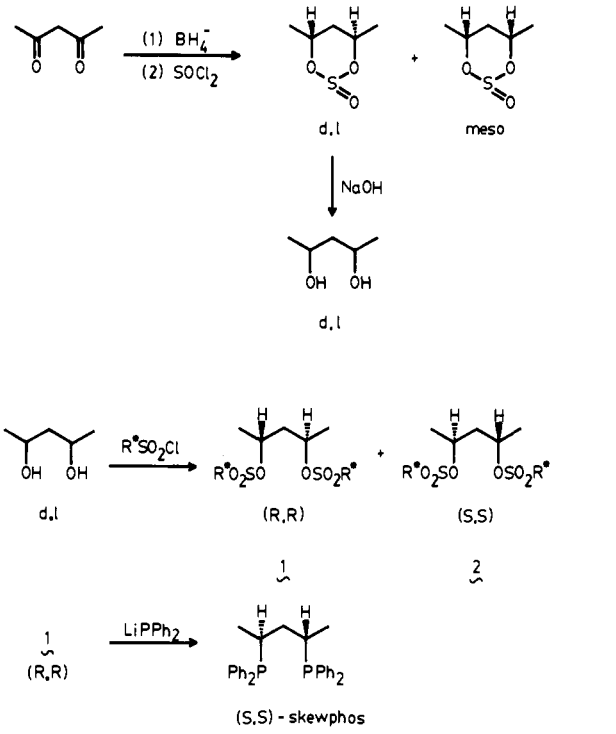


Figure 4. An outline of the synthesis of (*S*,*S*)-skewphos.

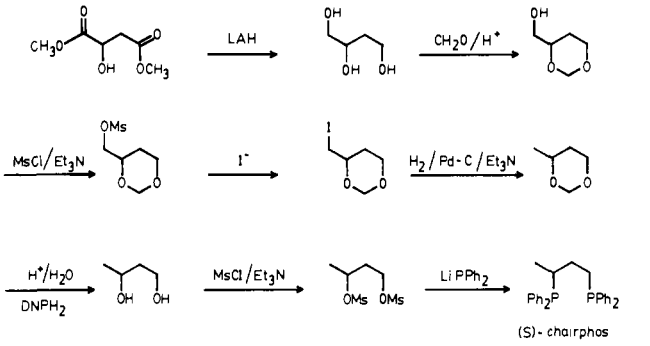


Figure 5. An outline of the synthesis of (*S*)-chairphos.

(*S*)-chairphos crystalline, but it was characterized as its methyl bis(quaternary salt) and as its rhodium(I) complexes.

Catalytic Precursors

The catalytic precursors, [Rh((*S*,*S*)-skewphos)NBD]ClO_4, [Rh((*S*,*S*)-skewphos)COD]ClO_4, [Rh((*S*)-chairphos)NBD]ClO_4, and [Rh((*S*)-chairphos)COD]ClO_4, were isolated as highly crystalline materials (NBD = norbornadiene, COD = cycloocta-1,5-diene). All were prepared from the [Rh(diolefin)$_2$]ClO_4 complexes and may be stored under N_2 at 0 °C for months without appreciable loss of catalytic activity.

Crystal structures[13] of [Rh((*S*,*S*)-skewphos)NBD]ClO_4 and [Rh((*S*,*S*)-skewphos)COD]ClO_4 confirm the absolute configuration of the ligand and also provide an insight into the stability of the ring conformation. The NBD complex has the ligand in a chair conformation whereas the COD complex has the chelate ring in a skew conformation with di-equatorial methyl groups. We presume that this difference is due to the exigencies of crystal packing and, perhaps, is related to the different "bite" angles of the diolefin ligands.[14] Whatever the precise reasons for this

(13) Payne, N. C. personal communication.

(14) It is generally found that skew rings have a smaller bite angle than chair rings. NBD has a smaller bite angle than COD. It is assumed that as the bite angle decreases, the angle opposite in the plane will increase. Hence, NBD and COD being fairly rigid in their bite angles will tend to stabilize the wider angle chair and smaller angle skew conformations, respectively. This in essence is the bite angle theory although we view it with some circumspection.

Table I

(S,S) - skewphos

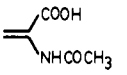
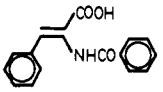
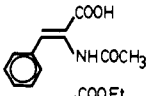
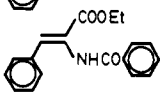
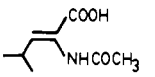
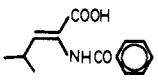
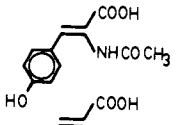
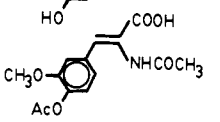
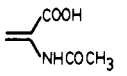
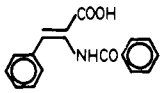
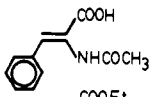
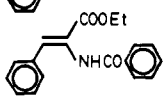
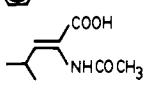
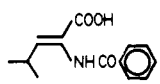
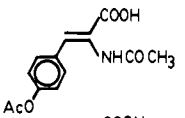
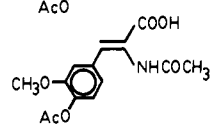
Amino acid	Substrate	Optical Yield (%) THF	EtOH (95%)	MeOH
alanine		95 (R)	98 (R)	96 (R)
phenylalanine		90 (R)	80 (R)	
		93 (R)	92 (R)	
		76 (R)	60 (R)	
leucine		17 (R)	23 (R)	
		8 (S)	14 (S)	23 (S)
tyrosine		90 (R)	84 (R)	
DOPA		93 (R)	92 (R)	

Table II[a]

(S) - chairphos

Amino acid	Substrate	Optical Yield (%) THF	EtOH (95%)	MeOH
alanine		9 (R)	5 (R)	4 (R)
phenylalanine		12 (R)	10 (S)	
		1 (S)	20 (S)	
		4 (R)	10 (S)	
leucine		5 (S)	3 (S)	
		11 (S)	16 (S)	24 (S)
tyrosine		5 (R)	12 (S)	
DOPA		1 (R)	9 (S)	

[a] A similar catalyst containing (*R*)-chairphos has recently been prepared (Kagan, H. B.; Fiand, J. C.; Hoornaert, C.; Meyer, D.; Poulin, J. C. *Bull. Soc. Chim. Belg.* **1979**, *88*, 923). The results obtained for the *N*-acetylalanine and -phenylalanine substrates are similar to ours.

change in conformation, it does suggest that the difference in energy for these two conformations may not be large.

In methylene chloride solution at 30 °C, the [Rh((*S*,*S*)-skewphos)NBD]$^+$ ion shows a two-line (proton-decoupled) phosphorus NMR spectrum (δ 27.3 (H_3PO_4, J_{Rh-P} = 149.4 Hz). The spectrum remains essentially unchanged when the temperature is lowered to the freezing point of the solvent. This establishes that the phosphorus atoms are equivalent on an NMR time scale; the question of whether the ring is in a static symmetrical skew conformation or is conformationally fluxional (see Figure 2) is not resolved by this experiment. We shall show presently, however, that a comparison of the circular dichroism spectra of skewphos and chairphos complexes indicates that the skew ring is preferred for skewphos complexes.

Optical Yields

All catalytic hydrogenations were carried out under ambient conditions. The rates of hydrogenation with these six-membered ring chelates is somewhat faster than those observed for the five-membered ring analogues, and either the COD or NBD catalytic precursors could be used under our conditions. The ratio of catalyst to substrate was generally 1:200; higher ratios could be used but more rigorous exclusion of oxygen was required. All of the chemical yields were quantitative. The two antipodes of the skewphos catalyst gave equal but opposite optical yields. The methods for determining these optical yields followed procedures described by us elsewhere[4] and were reproducible to ±2%.

The results for the (*S*,*S*)-skewphos and (*S*)-chairphos catalysts are given in Tables I and II, respectively. Taken as a whole, the optical yields contained in these two tables are in accord with expectation. Thus the skewphos catalyst gives high optical yields, if we ignore the leucine result; in fact these yields are comparable to and in some cases better than those obtained with the chiraphos and prophos catalysts.[4,5] The generally high optical yields are expected if the ring is in the skew conformation during the catalytic cycle. As predicted, the chairphos catalyst gives poor optical yields and, moreover, the sense of induction can depend on both the solvent and the substrate. The low and incoherent induction of the chairphos catalyst is expected if the ring is in a *chair* conformation and, as a consequence, the phenyl groups are in an achiral array.

For the leucine substrates, both the skewphos and chairphos catalysts give low optical yields; and, because the behavior is so similar for the two catalysts, it is tempting to suggest that, for both catalysts, the rings are in chair conformations. We have attempted to resolve this problem by the use of circular dichroism.

Circular Dichroism Spectra

The absorption and circular dichroism spectra for the indicated rhodium(I)–(*S*,*S*)-skewphos complexes are shown in Figure 6, and the corresponding spectra for the (*S*)-chairphos complexes are shown in Figure 7. The dimethanolo complexes were prepared by adding 2 equiv of hydrogen to the [Rh(diphosphine)NBD]ClO_4 complexes in methanol solutions, and, thereafter, the substrate adducts were generated by the addition of 12 equiv of the substrates.[15-18] Without dwelling on some of the complications of these spectra or their electronic provenance, it seems sufficient to point out that the circular dichroism spectra for the (*S*,*S*)-skewphos complexes are about five times larger than the corresponding circular dichroism spectra exhibited by the equivalent

(15) Brown, J. M.; Chaloner, P. A. *J. Am. Chem. Soc.* **1978**, *100*, 4321.
(16) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *Inorg. Chim. Acta* **1979**, *37*, L477.
(17) Chan, A. S. C.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 838.
(18) Brown, J. M.; Chaloner, P. A. *J. Chem. Soc. Chem. Commun.* **1980**, 344.

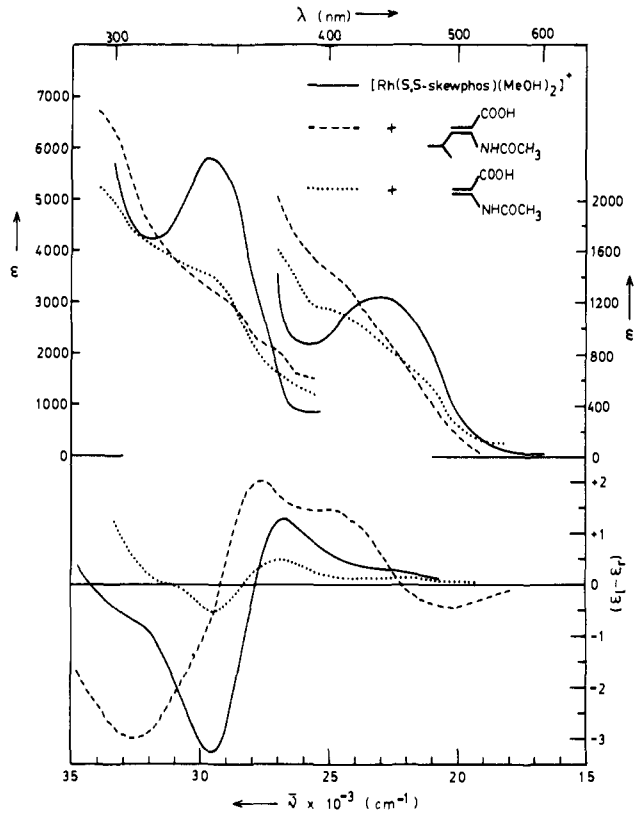


Figure 6. Absorption and circular dichroism spectra of the rhodium-(I)-(*S*,*S*)-skewphos species shown in methanol solutions.

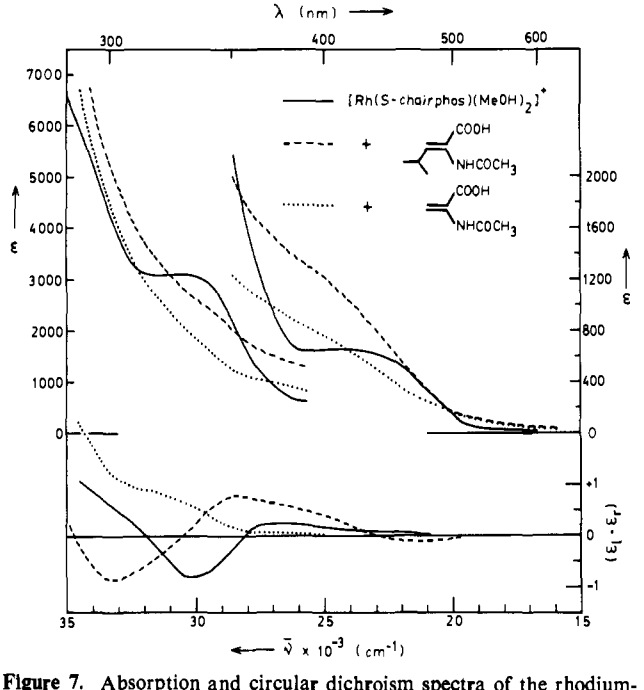


Figure 7. Absorption and circular dichroism spectra of the rhodium-(I)-(*S*)-chairphos species shown in methanol solutions.

spectroscopic transitions of the (*S*)-chairphos species.

The chair chelate ring formed with optically active 1,3-diaminobutane (chairphos analogue) induces circular dichroism for its cobalt(III) complexes which is about ten times weaker than the induction generated by the chelate ring formed by optically active 2,4-diaminopentane[9-11] (skewphos analogue). Thus the circular dichroism spectra in Figures 6 and 7 suggest that the predominant conformation of the chelate ring in the skewphos complexes is skew. This conclusion, however, is not meant to imply that the chelate ring of skewphos is not chair in a crucial step of the catalytic cycle (vide infra); it only refers to the species involved in the diastereomeric equilibrium.

Discussion

The optical yields generated by the chiraphos, prophos, skewphos, and chairphos catalysts present a pattern which we believe is most readily explained by the conformational arguments we have presented here and elsewhere.[4,5] Thus the presence of either one or two methyl groups on the rings of prophos and chiraphos does not cause significant changes in the magnitudes of the optical yields, but a similar change for the six-membered ring systems causes spectacular changes. We see no structural feature, other than the conformations which these ligands may adopt, to explain these results. It is therefore not difficult to envisage other chiral chelating phosphines which will prove effective (as well as those that will be ineffective) for the asymmetric hydrogenation of amino acid precursors. A large number of efficient catalysts incorporating chiral chelating diphosphines have been reported,[1-3] and we believe that the high optical yields observed can be understood in terms of the conformations these ligands adopt.

The conformational arguments, as we have presented them, are in essence only an effective prescription for phosphine design and, as such, do not fully explain how and where in the catalytic cycle the chiral induction occurs. Neither can they be rationally extended to predict which other substrates may give high optical yields with a given chiral phosphine. These central questions cannot be discussed without a fairly precise knowledge of the thermodynamic and kinetic factors which control the asymmetric hydrogenation. Two recent studies[17-19] on the mechanism of asymmetric hydrogenation of amino acid precursors, however, have defined the steps in the catalytic cycle with some clarity, and we are now in a position to discuss the origins of the chiral discrimination with greater precision than has hitherto been possible.

Figure 8 outlines the mechanism taking the (*S*,*S*)-chiraphos catalyst as an example; the other chiral catalysts appear to behave in the same way. The very rapidly attained diastereomer equilibrium, K_d, has been measured for a number of systems[15,17-19] by ^{31}P NMR. In the case of (*S*,*S*)-chiraphos, K_d is large for ethyl (*Z*)-α-acetamidocinnamate (EAC) and the minor diastereomer has not been detected. X-ray structure determinations of [Rh(diphos)(EAC)]$^+$[16] and [Rh((*S*,*S*)-chiraphos)(EAC)]$^+$[19] show that the amino acid substrate acts as a bidentate chelate involving the *N*-acyl oxygen atom and the olefin. This chelation is probably crucial in obtaining high optical yields, for it imparts rigidity to the system. It is generally found, for reasons discussed elsewhere,[20] that a fixed orientation of the substrate and the chiral-inducing ligand gives the highest dissymmetric discrimination. This is evidenced by the large value of K_d for chiraphos. Were the corresponding velocity constants shown in the two columns in Figure 8 the same, that is, $k_1 = k_1'$, $k_2 = k_2'$, and $k_3 = k_3'$, then the optical yields would be determined solely by the value of K_d. Given the excellent correlation between the *magnitudes* of K_d and the corresponding optical yields,[15] it has commonly been assumed that the asymmetric hydrogenation is largely determined by the value of K_d and that the prevailing chirality of the product is traceable to the *major* four-coordinate diastereomer. Mirabile dictu this is not the case at ambient hydrogen pressures; the predominant chiral product originates from the *minor* four-coordinate diastereomer. Thus, the velocity constant for hydrogenation of the minor diastereomer is more than 3 orders of magnitude greater than that of the major diastereomer.

Above −40 °C in methanol solutions, the rate-determining step is believed to be the oxidative addition of hydrogen (k_1, k_1'); the hydride addition step (k_2, k_2') is assumed to be fast. Below −40 °C, the rate-determining step is the hydride insertion (k_3, k_3') and, as a result, the monohydrido-σ-alkyl intermediate has been detected and its structure has been deduced by NMR.[17,18] That the α-carbon and the *N*-acyl oxygen atoms are coordinated was inferred with confidence, but the coordination of the carboxyl group

(19) Chan, A. C. S.; Pluth, J. J.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 5952 and personal communication.
(20) Boucher, H. A.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6253.

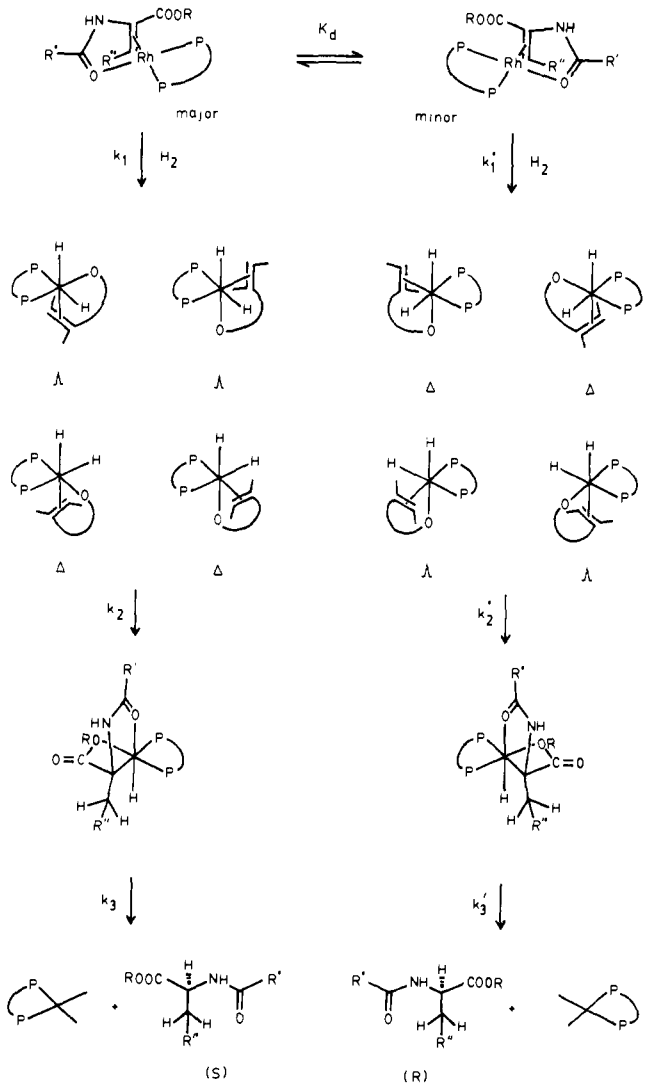


Figure 8. The probable mechanism of asymmetric catalytic hydrogenation of (*Z*)-(*N*-acylamino)acrylic acids using cationic chiral bidentate diphosphine rhodium(I) species.

is in dispute, although this may depend on whether a carboxylic acid[17] or ester[18] is involved. The dihydrido octahedral intermediates were not detected and nor was any reversibility of hydrogen uptake observed. Similarly, no β-elimination, that is, the reverse of k_2, k_2', was detected.

Provided the attainment of the K_d equilibrium is fast at ambient conditions, which it is, the value of K_d is kinetically irrelevant in deciding the optical yield. The optical yield is decided by the different *rates* of reaction of the two four-coordinate diasteromers, and these rates are determined by the *relative* energies of the two diasteromeric transition states and are not dependent on the initial reactant energies[21] (Curtin–Hammett principle). The only way in which K_d could affect the optical yields would be if the attainment of K_d were slow relative to the rate of hydrogenation or if, when the equilibration is fast, the stabilities of the two four-coordinate diastereomers were reflected in the two corresponding diastereomeric transition states. Neither is the case for

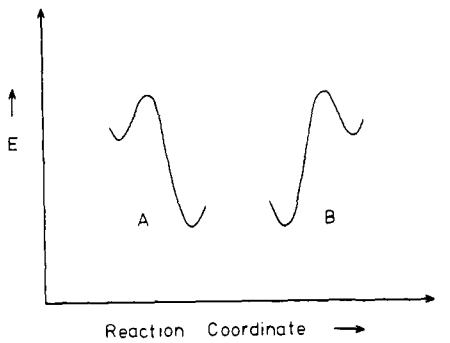


Figure 9. Two reaction profiles representing the first irreversible step in asymmetric synthesis.

the present systems. Optical yields are determined by the first irreversible step of reaction which, in the present case, is believed to be the oxidative addition of hydrogen (k_1, k_1'). The origins of the dissymmetric rate differentiation must reside in the different dissymmetric interactions of the chiral phosphine ligand and the prochiral substrate in the diastereomeric transition states of the reaction.

Dihydrido metal complexes generally prefer to adopt a *cis*-dihydrido geometry. If this obtains for the present system, the major and minor four-coordinate rhodium(I) diastereomers, in principle, can generate eight *cis*-dihydrido bis-bidentate octahedral isomers, four for each planar diastereomer (Figure 8). Each of these isomers is chiral about the metal atom (designated, Δ and Λ), but because both the phosphine and (complexed) substrate are also chiral, the interligand interactions will tend to select a preferred absolute configuration about the metal atom. This, so-called, stereospecificity is a thoroughly explored phenomenon and its origin is well understood[8,22,23] in terms of the interactive forces between ligands. Moreover, the quasi-empirical calculations[8,22,24] which have been performed on such systems are, in most cases, in excellent agreement with experiment.[24]

We assume an asymmetric variation of the Hammond hypothesis,[25] namely, that, for the presumably endothermic hydrogen addition, the structure of the transition state and that of the corresponding octahedral *cis*-dihydrido intermediate will resemble one another. With this assumption we may conclude that the more stable the *cis*-dihydrido intermediate the lower will be the corresponding transition state and hence the rate of hydrogenation will be fastest via the most stable intermediate. Molecular models are inconclusive to us in deciding which of the putative intermediates is the most stable, but what is clear is that the dissymmetric array of phenyl groups of the chiral phosphine is the major source of discriminatory interaction which gives rise to the stereospecificity. It is also clear that the symmetrical array of phenyl groups of chairphos will not induce strong stereospecificity in the intermediates. Thus it could be argued plausibly that if skewphos were to flip to a quasi-symmetrical chair conformation in arriving at the octahedral intermediates when the leucine substrates are bound, the optical yield would be low as is observed.

This description of the asymmetric synthesis, if correct, provides more than a prescription for matching the inducing chiral ligand and the prochiral substrate for asymmetric hydrogenation. Thus it may be possible to calculate the stabilities of the octahedral intermediates and thereby, to some extent, predict optical yields for these and other substrates. In general, we expect that chelation of the substrate will be important.

We should caution, however, that specifying the oxidative addition of hydrogen as the rate-determining step is an assumption. It is possible, though we think unlikely, that the first hydride-

(21) Lest this statement be misconstrued, the following is a proof.

$$\xleftarrow{k_a} A \underset{}{\overset{k_d}{\rightleftharpoons}} B \xrightarrow{k_b}$$

$$\frac{R_b}{R_a} = \frac{k_b[B]}{k_a[A]} = \frac{k_b}{k_a}K_d = e^{(-\Delta G^{\ddagger}_b + \Delta G^{\ddagger}_a - \Delta G_d)/RT}$$

The quantity $(-\Delta G^{\ddagger}_b + \Delta G^{\ddagger}_a - \Delta G_d)$ is equal to the difference in transition-state energies (not activation energies) for the reactants A and B. See Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962; Chapter 8.

(22) Corey, E. J.; Bailar, J. C. *J. Am. Chem. Soc.* **1959**, *81*, 2620.
(23) Hawkins, C. J. "Absolute Configuration of Metal Complexes"; Cotton, F. A.; Wilkinson, G., Eds.; Wiley-Interscience: New York, 1971; Chapter 3.
(24) Sargeson, A. "Transition Metal Chemistry"; Carlin, R. L., Ed.; Marcel Dekker: New York, 1966; Vol. 3, p 303.
(25) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

transfer step (k_2, k_2') is rate determining. In this event, by using the same assumptions and depending on the rate profile, an indication of optical yields might be obtained by determining the stabilities of the monohydrido-σ-alkyl intermediates. Matters could become intractably complicated if the hydrogen addition step were partially reversible.

Finally, some general conclusions may be drawn from the above discussion. Figure 9 shows two reaction profiles (A and B) which refer to the first irreversible step, the step where the die is cast for asymmetric synthesis. The endothermic profile, B, will have a transition-state structure which resembles the product, whereas the exothermic profile, A, will have a transition state resembling the reactant structure. Profile B probably corresponds to the present hydrogenation system, and so it can be understood why the magnitude of K_d, the reactant equilibrium constant, is largely irrelevant to the observed optical yields. For other systems where profile A obtains, however, the diastereomer preequilibrium may be a useful guide in assessing potential optical yields. Thus one of the important considerations in any rational approach to asymmetric synthesis is to decide whether the first irreversible step is under reactant, profile A, or product, profile B, control.

Experimental Section

The free phosphines and the catalytic precursors were manipulated under nitrogen. Substrates for hydrogenation were prepared, hydrogenations were performed, and the products were analyzed by methods described elsewhere.[4]

(a) Skewphos. (*R,R*)- and (*S,S*)-2,4-Pentanediol Bis(*d*-10-camphorsulfonate). To a stirred solution of *freshly recrystallized d*-10-camphorsulfonyl chloride[26] (55 g) in dry pyridine (50 mL) at 0 °C was added slowly racemic 2,4-pentanediol[12] (10.4 g) in dry pyridine (15 mL). The mixture was stirred at 0 °C for 4 h and then at 25 °C for a further 12 h. Crushed ice was added to the reaction mixture until the product, a colorless oil, was fully formed. This mixture was poured into a stirred mixture of HCl (12 N, 70 mL) in crushed ice (~600 g). The product was extracted from the neutralized mixture with ether (2 × 200 mL); the combined ether extracts were washed with water (2 × 100 mL) and then with brine (100 mL) and were dried over $MgSO_4$. The ether was removed under reduced pressure at 40 °C leaving a colorless oil (52 g).

(*R,R*)-2,4-Pentanediol Bis(*d*-camphorsulfonate). The oil (52 g), from above, was dissolved in diethyl ether (52 mL); the solution was stoppered and allowed to stand at room temperature for 4 days. The fine white crystals which formed were filtered and washed with ether. The filtrate was set aside, and the solid (18 g) was recrystallized from CH_2Cl_2 (50 mL) and ether (100 mL) to which hexane (200 mL) was gradually added. The well-formed cyrstals (plates) of the pure *R,R* diastereomer were filtered and were washed with ether and then with hexane: 17 g, 67%; mp 118–120 °C; $[\alpha]^{25}_D$ + 6.8° (1.4, $CHCl_3$). Anal. Calcd for $C_{25}H_{40}S_2O_8$: C, 56.4; H, 7.6; O, 24.0; S, 12.0. Found: C, 56.2; H, 8.2; O, 23.6; S, 11.8.

(*S,S*)-2,4-Pentanediol Bis(*d*-camphorsulfonate). The solvent from the filtrate of the first crystallization was removed under reduced pressure to give an oil. This was dissolved in CH_2Cl_2 (32 mL), and then cyclohexane (480 mL) was added. After 2 days the resultant white solid (20 g) was collected and washed with cyclohexane. It was recrystallized from CH_2Cl_2 (20 mL) and ether (100 mL) by the slow addition of hexane (80 mL). The colorless rod-shaped crystals of the pure *S,S* diastereomer were collected and were washed with 1:1 ether/hexane and then with hexane: 18 g, 70%; mp 103–105 °C; $[\alpha]^{25}_D$ + 75.6° (1.4, $CHCl_3$). Anal. Calcd for $C_{25}H_{40}S_2O_8$: C, 56.4; H, 7.6; O, 24.0; S, 12.0. Found: C, 56.3; H, 7.9; O, 23.7; S, 11.8.

(*S,S*)-Skewphos. To a magnetically stirred solution of freshly recrystallized triphenylphosphine (26.2 g) in dry THF (75 mL) at 25 °C was added thin, finely cut strips of lithium (1.4 g). The mixture was stirred for 2 h during which time the solution turned orange, the lithium was consumed, and the temperature initially rose to 55 °C and at the end was at 25 °C. Freshly distilled *tert*-butyl chloride (9.25 g) was then added dropwise to the reaction. The solution became hot, and after it was stirred for 30 min, the reaction vessel was immersed in an ice bath. (*R,R*)-2,4-Pentanediol bis(*d*-camphorsulfonate) (10.6 g) in dry THF (35 mL) was then added dropwise to the stirred, cold phosphide solution. The reaction mixture was then stirred for 30 min. Water (100 mL) was slowly added and, upon completion, most of the THF was removed under reduced pressure. The residue was extracted with ether (2 × 100 mL) and added slowly to a stirred solution of $Ni(ClO_4)_2 \cdot 6H_2O$ (5 g) and NaNCS (5 g) in ethanol (100 mL). Yellow crystals formed at once, and after the slurry was stirred for 10 h, the yellow solid [Ni((*S,S*)-skewphos)$(NCS)_2$] was collected and was washed with ethanol and then with ether (8.8 g).

[Ni((*S,S*)-skewphos)$(NCS)_2$]. Recrystallization of this complex was carried out by suspending the solid (8.8 g) in CH_2Cl_2 (170 mL). To this mixture was added slowly trifluoroacetic acid (9 mL) whereupon the complex dissolved. It was filtered and ethanol (170 mL) was slowly added to the now clear orange-brown filtrate. The solution was allowed to stand for 2 h during which time more ethanol (150 mL) was added. The bronze-colored plates were collected and washed first with ethanol and then with ether. (The [Nidiphos$(NCS)_2$] (diphos = bidentate diphosphine) complexes are generally very insoluble in all common solvents. Addition of trifluoroacetic acid to a CH_2Cl_2 suspension of these species, we believe, serves to protonate the sulfur of the coordinated thiocyanate and as a consequence leads to dissolution. Addition of ethanol deprotonates the sulfur and results in precipitation.) The nickel complex was recrystallized a second time by the same procedure; 4.9 g, 40%. Anal. Calcd for $NiC_{31}H_{30}N_2P_2S_2$: C, 60.5; H, 4.9; N, 4.6; P, 10.1; S, 10.4. Found: C, 60.6; H, 4.8; N, 4.3; P, 9.6; S, 11.1.

Free (*S,S*)-Skewphos. The complex [Ni((*S,S*)-skewphos)$(NCS)_2$] (4.5 g) was suspended in ethanol (20 mL) and THF (20 mL). The mixture was stirred and brought to 80 °C, and then NaCN (1.5 g) in water (10 mL) was rapidly added. A deep red solution formed which rapidly faded to a pale yellow color. The ethanol and THF were removed under reduced pressure, water (50 mL) was added to the residue, and the phosphine was extracted with ether (2 × 50 mL). The combined ether extracts were washed with water (2 × 50 mL) and then with brine (50 mL) and then were dried over Na_2SO_4. The ether was removed under reduced pressure to leave (*S,S*)-skewphos as an oil; 3.3 g, 95%. The phosphine was stored under N_2 at 0 °C. It is not very air sensitive, however.

(*R,R*)-Skewphos. This was prepared by the same method just described for the enantiomer by using (*S,S*)-2,4-pentanediol bis(*d*-camphorsulfonate). The yields were the same.

(*S,S*)-2,4-Bis(diphenylmethylphosphonium)pentane Iodide. To a solution of (*S,S*)-skewphos (0.3 g) in absolute ethanol (20 mL) was added methyl iodide (2 mL). The solution was allowed to stand at 25 °C for 12 h and upon the careful addition of ether (100 mL), a fine white precipitate formed. This was collected and washed with ether. The solid was recrystallized from acetone (10 mL) and ethanol (5 mL) by the gradual addition of ether (50 mL). Fine white needles of the bis(quaternary salt) formed and were collected and washed with ether: 0.31 g, 60%; $[\alpha]^{25}_D$ −81° (1.3, $CHCl_3$). Anal. Calcd for $C_{31}H_{36}P_2I_2$: C, 51.4; H, 5.0; P, 8.6; I, 35.0. Found: C, 51.5; H, 5.0; P, 8.8; I, 34.6.

The bis(quaternary salt) of (*R,R*)-skewphos was prepared similarly and gave an equal but opposite optical rotation.

[Rh((*S,S*)-skewphos)(NBD)]ClO_4. A solution of (*S,S*)-skewphos (0.36 g) in CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of $[Rh(NBD)_2]ClO_4$[27] (0.32 g) in CH_2Cl_2 (3 mL). A red solution resulted to which was added freshly distilled (LAH) THF (5 mL). The solution was filtered and to the filtrate was added sufficient freshly distilled (LAH) ether (~3 mL) to begin crystallization. After this mixture was allowed to stand at 25 °C for 3 h, it was kept at 5 °C for 12 h. The orange prisms were collected, were washed with THF (3 × 1 mL), and were stored under N_2 at 5 °C; 0.39 g, 64%. Anal. Calcd for $RhC_{36}H_{38}P_2ClO_4$: C, 58.8; H, 5.2; P, 8.4. Found: C, 58.5; H, 5.1; P, 8.6.

[Rh((*S,S*)-skewphos)(COD)]$ClO_4 \cdot$THF$\cdot 0.25CH_2Cl_2$. A solution of (*S,S*)-skewphos (0.39 g) in CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of $[Rh(COD)_2]ClO_4$[27] (0.35 g) in CH_2Cl_2 (2.5 mL). Freshly distilled THF (3 mL) was added and the solution was allowed to deposit crystals at 24 °C for 3 h. More THF (5 mL) was then added, and the mixture was allowed to stand at 5 °C for 12 h. The yellow-orange crystals were collected and were washed with THF (3 × 2 mL), and the complex was stored under N_2 at 5 °C; 0.66 g, 96%. The solvents of crystallization were confirmed by NMR. Anal. Calcd for $RhC_{27}H_{42}P_2ClO_4 \cdot (C_4H_8O) \cdot 0.25CH_2Cl_2$: C, 58.7, H, 6.0; P, 7.3; Cl, 6.3. Found: C, 58.8; H, 6.0; P, 7.4; Cl, 6.2.

(b) Chairphos. (*S*)-Malic Acid Dimethyl Ester. A mixture of L-(−)-malic acid (100 g; $[\alpha]^{20}_D$ −28.6° (5.5, pyridine)) and Dowex 50W-X8 H^+ ion-exchange resin (7 g) in methanol (110 mL) and $CHCl_3$ (160 mL) was heated under reflux through a Soxhlet thimble containing anhydrous $MgSO_4$ (~80 g). The drying agent was replaced twice during the reflux period of 14 h. The solution was filtered, the solvents were removed, and the residue was distilled to give a colorless oily liquid: 111 g, bp 60–65 °C (0.1 mm); $\alpha^{24.5}_D$ −29° (neat, l = 1 dm); ^1H NMR ($CDCl_3$) δ 2.80

(26) Bartlett, P.; Know, L. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 196.

(27) Fryzuk, M. D. Ph.D. Thesis, University of Toronto, 1978.

(d, 2 H, $^3J_{H-H}$ = 5.2 Hz, CH_2), 3.70 (s, 3 H, CO_2CH_3), 3.80 (s, 3 H, CO_2CH_3), 4.49 (t, 1 H, $^3J_{H-H}$ = 5.2 Hz, CH).

(*S*)-(−)-Butane-1,2,4-triol. A solution of the dimethyl ester (110 g) in dry ether (300 mL) was added dropwise to a stirred suspension of LAH (52 g) in ether (600 mL) at such a rate as to maintain gentle reflux. After the addition, the mixture was stirred for 12 h. It was then cooled in an ice bath as water (26 mL) was cautiously added to the stirred mixture. This was followed by the cautious addition of sulfuric acid (400 mL, 10%). The ether layer was decanted and discarded, leaving a gray granular solid. Ethanol (800 mL) was added and the mixture was refluxed for 4 h. The mixture was filtered and the solid was washed with ethanol (300 mL). This procedure was repeated two more times and the combined ethanol extracts were reduced to an orange oil. Distillation of the residue gave the product as a pale yellow oil with an evanescent aroma of sweet apples: 47 g, 65%; bp 120–130 °C (0.1 mm). A distilled sample had $\alpha^{24.5}_D$ −29° (neat, *l* = 1 dm). ^{1}H NMR (D_2O): δ 1.67 (m, 2 H, CH_2), 3.60 (m, 5 H, OCH_2 and OCH).

(*S*)-4-(Hydroxymethyl)-1,3-dioxan and (*S*)-4-(2-Hydroxyethyl)-1,3-dioxolan. A mixture of the triol (23 g) and paraformaldehyde (6.5 g) in benzene (400 mL) was treated with methanesulfonic acid (16 drops). The mixture was stirred under reflux for 0.75 h. A Dean–Stark apparatus was then attached to the flask, and the water was slowly collected. The now clear reaction mixture was cooled and then was stirred with anhydrous Na_2CO_3 (5 g) for 0.5 h. After filtration and the removal of the benzene, the residue was distilled to give a colorless oil consisting of a mixture of the two methylene acetals: 19.8 g, 77%; bp 80–90 °C (20 mm). ^{1}H NMR in $CDCl_3$ of the O_2CH_2 signals showed this to be a 77:23 mixture of the dioxan and dioxolan, respectively.

(*S*)-(+)-4-(Hydroxymethyl)-1,3-dioxan Methanesulfonate. A solution of the methylene acetals (19.8 g) and dry triethylamine (27.7 mL) in CH_2Cl_2 (400 mL) was cooled to −20 °C and stirred while a solution of methanesulfonyl chloride (14.4 mL) in CH_2Cl_2 (100 mL) was added dropwise. The mixture was allowed to attain room temperature and then was extracted with HCl (3 mL, 12 M) in water (200 mL). The separated CH_2Cl_2 layer was washed with water (2 × 100 mL) and was dried over $MgSO_4$. The solvent was removed under reduced pressure, and the last traces of CH_2Cl_2 were removed by adding THF (50 mL) and again removing the solvent. A pale yellow oil resulted. This was taken up in THF (30 mL), and sufficient dry ether was added until the solution became cloudy. The crystals were allowed to form for 1 h, and then more ether (500 mL) was slowly added. It was now held at 5 °C for 12 h. The crystals (as needles) were collected and washed with ether. A second crop of the pure dioxan was obtained by reworking the filtrate. The total yield was 21.6 g, 85%: mp 73.5–74.5 °C; $[\alpha]^{25}_D$ +13.3° (1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.2–2.2 (br m, 2 H, CH_2), 3.08 (s, 3 H, SO_3CH_3), 3.5–4.4 (br m, 5 H, OCH and OCH_2), 4.88 (AB_q, J_{AB} = 6.6 Hz, 2 H, O_2CH_2). Anal. Calcd for $C_6H_{12}O_5S$: C, 36.7; H, 6.2; S, 16.3. Found: C, 36.9; H, 6.3; S, 16.4.

(*S*)-4-(Iodomethyl)-1,3-dioxan. Finely ground KI (32.5 g) and the above mesylate (19.1 g) were added to dry DMF (70 mL) under N_2. The mixture was stirred and heated at 100–120 °C for 2.5 h. The solution was cooled and was then poured into water (500 mL) containing sodium thiosulfate (2 g), and the product was extracted with benzene (4 × 100 mL). The combined extracts were washed with water (2 × 300 mL) and were dried over $MgSO_4$, and then most of the benzene was removed under reduced pressure. The remaining pale yellow liquid consisted of 17.6 g of the (iodomethyl)dioxan. This is a somewhat unstable material which crystallizes at 5 °C and should be stored at this temperature. It is a liquid at 25 °C: ^{1}H NMR ($CDCl_3$) δ 1.73 (m, 2 H, CH_2), 3.18 (d, 2 H, CH_2I), 3.4–4.4 (br m, 3 H, OCH and OCH_2), 4.87 (AB_q, J_{AB} = 6.4 Hz, 2 H, O_2CH_2).

(*R*)-4-Methyl-1,3-dioxan. Palladium on charcoal (4 g, 10%) was suspended in dry ether (250 mL) under argon; then dry triethylamine (24 mL) and the (iodomethyl)dioxan (15.5 g) were successively added. The mixture was hydrogenated and stirred for 22 h under ambient conditions. The mixture was then filtered through Celite, and the clear filtrate and ether washings (3 × 50 mL) were bubbled with dry HCl to remove excess triethylamine. Again the mixture was filtered. Fractional distillation through a 10 in. column of the ether solvent left an oil containing the desired product and 20% of the starting iodo compound. This oil was dissolved in dry ether (100 mL), hydrogenated for 5 h in the presence of Pd/C (1.6 g, 10%) and triethylamine (9.5 mL), and worked up as before. The reaction was complete. Fractional distillation gave the pure (*R*)-4-methyl-1,3-dioxan as a colorless liquid: 6.8 g, 98%; bp 100–110 °C (760 mm); ^{1}H NMR ($CDCl_3$) δ 1.08 (d, J_{H-H} = 6.6 Hz, 3 H, CH_3), 1.4–2.2 (br m, 2 H, CH_2), 3.4–4.3 (br m, 3 H, OCH and OCH_2), 4.85 (AB_q, J_{AB} = 6.0 Hz, 2 H, O_2CH_2).

(*R*)-(−)-Butane-1,3-diol. To a hot stirred solution of 2,4-dinitrophenylhydrazine (13.2 g) in HCl (200 mL, 5 M) was added the methyldioxan (6.8 g). A thick yellow paste of the hydrazone formed at once. The mixture was stirred and allowed to cool. After 12 h, it was filtered and the yellow solid was washed with water (100 mL). The combined aqueous filtrates were extracted with benzene (4 × 100 mL) and were then pumped down under reduced pressure to leave a yellow oily residue. This was diluted with water (100 mL), filtered, and neutralized with $NaHCO_3$. The neutralized solution was extracted with benzene (2 × 100 mL) and then with CH_2Cl_2 (2 × 20 mL). The aqueous solution was reduced to an oil under vacuum, and the last traces of water were azeotroped with a mixture of benzene and ethanol. The dry residue was twice distilled to give the pure diol as a colorless viscous liquid: 4.5 g, 75%; bp 45–46 °C (0.1 mm); $\alpha^{23.3}_D$ −30.8° (neat, *l* = 1 dm) (lit.[28] α^{23}_D −27°). The ^{1}H NMR ($CDCl_3$) was identical with that of a pure sample of the racemic diol (Aldrich).

(*R*)-(−)-Butane-1,3-diol Bis(methanesulfonate). To a stirred solution of (*R*)-(−)-butane-1,3-diol (4.5 g) and dry triethylamine (16.5 mL) in CH_2Cl_2 (200 mL) at −20 °C was added dropwise a solution of methanesulfonyl chloride (8.6 mL) in CH_2Cl_2 (50 mL). The mixture was stirred at −20 °C for 15 min after the addition and then was allowed to rise to 25 °C. The mixture was extracted with water (150 mL) containing HCl (8 mL, 12 M) and then with water (2 × 100 mL). The CH_2Cl_2 extract was dried ($MgSO_4$) and the solvent removed to leave an oil from which the last traces of CH_2Cl_2 were removed by adding THF (5 mL) and removing the solvent. The oily residue was dissolved in THF (10 mL), and ether was added until the solution became cloudy (~15 mL). When the mixture was left standing at 25 °C, fine white crystals of the product began to form. The mixture was then cooled slowly to −10 °C whereupon more crystals began to deposit. More cold ether (200 mL) was gradually added to the cold mixture. After it was left standing at −10 °C for 1 h, the supernatant liquor was quickly decanted and the crystals of the product were washed with cold ether (2 × 30 mL). The crystals were dried in vacuo at 25 °C: 11.2 g, 91%; mp 28.5–29 °C; $[\alpha]^{25}_D$ −37° (1.03, CH_2Cl_2). Anal. Calcd for $C_6H_{14}O_6S_2$: C, 29.3; H, 5.7; S, 26.0. Found: C, 29.3; H, 5.5; S, 26.3.

[Ni((*S*)-chairphos)(NCS)$_2$]. A solution of $LiPPh_2$ was prepared by reacting lithium (1.12 g) with triphenylphosphine (21 g) in dry THF (100 mL), followed by the addition of *t*-BuCl (7.4 g) according to the procedure described for skewphos. To this stirred solution at 0 °C was added dropwise the dimesylate (7 g) in THF (50 mL). The mixture was stirred at 25 °C for 1 h and hydrolyzed with a 50% aqueous solution of acetic acid (30 mL). Ethanol (50 mL) was then added and the mixture was added *slowly*, dropwise to a warm vigorously stirred solution of Ni($C_3H_3CO_2)_2$·4H_2O (10 g) and NaNCS (10 g) in water (50 mL) and ethanol (150 mL). The yellow crystalline product was filtered and was washed with ethanol and water and dried. The solid was taken up in a solution of CH_2Cl_2 (50 mL) and trifluoroacetic acid (13 mL) and was then filtered. Gradual addition of ethanol (250 mL) to the brown filtrate caused the deposition of the product as yellow-brown rosettes of needles: 12 g, 70%; mp 221–222 °C. Anal. Calcd for $C_{30}H_{28}N_2P_2S_2Ni$: C, 59.9; H, 4.7; N, 4.7; P, 10.3; S, 10.7. Found: C, 60.0; H, 4.7; N, 4.6; P, 10.4; S, 10.4.

(*S*)-Chairphos. To a hot stirred suspension of [Ni((*S*)-chairphos)(NCS)$_2$] (2 g) in 95% ethanol (20 mL) was added NaCN (1 g) in water (3 mL). The complex slowly dissolved and then ethanol (10 mL) followed by water (10 mL) was added. The now clear solution was diluted with water (300 mL) and extracted with ether (50 mL), and the ether layer was then washed with water (3 × 50 mL). After the solution was dried ($MgSO_4$), the ether was removed under reduced pressure to give the phosphine as a viscous colorless oil, 1.4 g, 98%. No method was found for crystallizing the product; it was stored under N_2 at −10 °C.

(*S*)-(−)-1,3-Bis(methyldiphenylphosphonium)butane Hexafluorophosphate. To a solution of (*S*)-chairphos (0.43 g) in ethanol (2.5 mL) was added iodomethane (0.55 g), and the solution was allowed to stand at 25 °C for 12 h. More ethanol (10 mL) was then added, followed by dry ether (100 mL). The dimethiodide deposited as a gum. The supernatant liquor was decanted; the gum was dried and was then taken up in methanol (10 mL) to which was added a concentrated solution of NH_4PF_6 (0.5 g). Water (~1 mL) was added until the mixture became cloudy. White crystals began to deposit and the crystallization was completed by slowly adding more water. The solid was collected and dried and was recrystallized from hot methanol to give colorless octahedral crystals which became opaque upon filtration: 0.38 g, 72%; mp 105–107 °C; $[\alpha]^{25}_D$ −8.7° (1.2, acetone). Anal. Calcd for $C_{30}H_{34}F_{12}P_4$: C, 48.3; H, 4.6; P, 16.6. Found: C, 48.0; H, 4.8; P, 16.3.

[Rh((*S*)-chairphos)(COD)]ClO$_4$. A solution of (*S*)-chairphos (0.102 g) in CH_2Cl_2 (1 mL) was added dropwise to a stirred solution of [Rh$(COD)_2$]ClO_4 (0.10 g) in CH_2Cl_2 (0.5 mL). The bright orange solution was filtered under gravity, and the filter paper was washed with CH_2Cl_2 (0.5 mL). The filtrate was diluted with dry THF (2 mL) and ether (1.5

(28) Serck-Hansen, K. *Ark. Kemi* **1955**, *8*, 401.

mL). After 3 h at 25 °C, the suspension of crystals was allowed to stand at 5 °C for 12 h. The orange needles of the product were collected and were washed with THF (2 × 1 mL) and dried under a stream of N_2; 0.16 g, 91%. Anal. Calcd for $C_{36}H_{50}ClO_4P_2Rh$: C, 58.7; H, 5.5; Cl, 4.8; P, 8.4. Found: C, 58.7; H, 5.8; Cl, 4.5; P, 8.1.

[Rh((*S*)-chairphos)(NBD)]ClO_4·$^3/_8CH_2Cl_2$. A solution of (*S*)-chairphos (0.37 g) in CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of [Rh(NBD)$_2$]ClO_4 (0.33 g) in CH_2Cl_2 (4 mL). The orange solution was filtered and then was gradually diluted with THF (~2 mL) until crystallization began. After 2 h at 25 °C, more THF (2 mL) was added, and 2 h later the mixture was held at 5 °C for 12 h. The red-orange prisms of the product were collected and were washed with THF (2 × 2 mL) and were dried under N_2; 0.62 g, 98%. The CH_2Cl_2 of crystallization was quantitatively confirmed by ^1H NMR. Anal. Calcd for $C_{35}H_{36}ClO_4P_2Rh·^3/_8CH_2Cl_2$: C, 56.4; H, 4.9; Cl, 8.2; P, 8.2. Found: C, 56.3; H, 5.1; Cl, 7.9; P, 8.4.

(c) Circular Dichroism Spectra. [Rh((*S*,*S*)-skewphos)Y]ClO_4, Y = $(CH_3OH)_2$, Leucine Precursors. A suspension of [Rh(*S*,*S*)-skewphos)(NBD)]ClO_4 (2.61 mg) in methanol (3.0 mL) was stirred under argon until all of the solid had dissolved. Hydrogen gas (1.7 mL) was then injected, and the sample was shaken (~5 min) until the 472-nm absorption peak, characteristic of coordinated NBD, had disappeared to give the dimethanolo adduct. An aliquot of this solution (0.34 mL) was transferred to a 1-mm cell under argon, and the circular dichroism spectrum was measured with a JASCO J-41A spectropolarimeter. The same sample was then injected with 5.4 μL of a 0.76 M solution of the leucine precursor, β-isopropyl-α-benzamidoacrylic acid in methanol solution, and the spectrum was recorded. A second aliquot of the stock methanolo complex solution (0.34 mL) was injected with 20 μL of a 0.203 M solution of the alanine precursor, α-acetamidoacrylic acid in methanol solution, and the spectrum was recorded.

[Rh((*S*)-chairphos)Y]ClO_4. A stock solution of the dimethanolo complex was prepared in the manner described for the skewphos analogue. Thus [Rh((*S*)-chairphos)(NBD)]ClO_4·$^3/_8CH_3Cl_2$ (2.8 mg) in methanol (3 mL) was reduced with hydrogen gas (1.7 mL). The circular dichroism spectra were obtained with the same substrate to complex ratios as for skewphos.

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Intramolecular Electron Transfer and Dehalogenation of Anion Radicals. 4. Haloacetophenones and Related Compounds[1]

D. Behar*[2] and P. Neta*

Contribution from the Radiation Laboratory and Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556. *Received November 13, 1980*

Abstract: Halogen-substituted acetophenones and several other carbonyls and carboxyl derivatives were reduced with e_{aq}^- in irradiated aqueous solutions to produce the anion radicals. In certain cases, reduction by $(CH_3)_2\dot{C}O^-$ was also used. The anion radicals undergo intramolecular electron transfer and dehalogenation to yield inorganic halide ions. The rates of these reactions varied over a wide range (10^1–10^7 s^{-1}) and were strongly dependent on the nature of the halogen and the other substituent and their relative positions in the molecule. The results obtained here are discussed along with previous measurements on cyano and nitro derivatives. The rate of dehalogenation is found to be dependent on the electron affinity of the other substituent on the ring. Hammett's substituent constants do not correlate with the observed rates. However, spin density distribution in the anion radicals, as derived from ESR parameters, yields a good qualitative correlation. Increased spin density on the ring carbon bearing the halogen is accompanied by an increase in the rate of C–X bond scission. The spin density represents in this case the negative charge density, since protonation of the anion radicals results in minor changes in spin densities but causes a dramatic decrease of the rate of dehalogenation.

One-electron reduction of organic halides leads in most cases to the immediate release of a halide ion with formation of an alkyl or aryl radical.[3]

$$RX + e^- \rightarrow \dot{R} + X^- \quad (1)$$

However, when the molecule contains an electron affinic substituent such as NO_2 or CN, the initial electron adducts were shown to have finite lifetimes before releasing the halide,[4-6] e.g.

$$XCH_2C_6H_4NO_2 + e^- \rightarrow XCH_2C_6H_4N\dot{O}_2^- \rightarrow X^- + \dot{C}H_2C_6H_4NO_2 \quad (2)$$

In these cases the dehalogenation reactions have been viewed as intramolecular electron-transfer processes, where an electron is transferred from the $N\dot{O}_2^-$ or $\dot{C}N^-$ groups, and the conjugated π system, to the halogen atom to cause the C–X bond scission. The rates of these processes were found to depend on the nature of the halogen (I > Br > Cl) and its relative position to the other subsitutent on the ring ($o > p > m$).[4-6] For example, the anion radicals of nitrobenzyl halides undergo dehalogenation with rates ranging from <5 s^{-1} for m-$(ClCH_2)C_6H_4N\dot{O}_2^-$ to 5.7×10^5 s^{-1} for p-$(ICH_2)C_6H_4N\dot{O}_2^-$.[4] The variations in the rates were rationalized by the differences in C–X bond dissociation energies and by the spin density distribution at the various positions. Contrary to the case of nitrobenzyl halides, the anion radicals of halonitrobenzenes did not undergo dehalogenation,[5] because the aromatic C–X bonds are much stronger than the benzylic analogues. Replacement of NO_2 by CN allows greater electron density to reach the halogen and thus increases the rates of dehalogenation considerably.[6] In order to further examine the effect of the substituent on the rate of dehalogenation, a study of haloacetophenones and related compounds has been undertaken. The

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(2) On leave of absence from the Soreq Nuclear Research Center, Yavne, Israel.

(3) Anbar, M. *Adv. Phys. Org. Chem.* **1969**, *7*, 115.

(4) Neta, P.; Behar, D. *J. Am. Chem. Soc.* **1980**, *102*, 4798.

(5) Behar, D.; Neta, P. *J. Phys. Chem.*, in press.

(6) Neta, P.; Behar, D. *J. Am. Chem. Soc.* **1981**, *103*, 103.

0002-7863/81/1503-2280$01.25/0