The Catalytic Resting State of Asymmetric Homogeneous Hydrogenation. Exchange Processes delineated by Nuclear Magnetic Resonance Saturation-transfer (DANTE) Techniques

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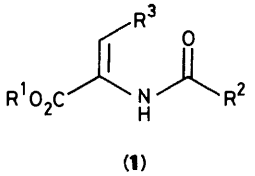
The DANTE magnetisation transfer technique has been employed to demonstrate site exchange in the ^{31}P n.m.r. spectra of dehydroamino acid and ester rhodium diphosphine complexes. When the ligand is bis-(1,2-diphenylphosphino)ethane, this occurs by dissociation of the enamide followed by recombination from the solute pool. The reaction is quite general but its rate is dependent on the nature of the enamide, with a pivalamide forming the least readily dissociated complex, and a t-butyl ester the most readily dissociated. Rate constants span the range 0.15—10 s^{-1} at 300 K. Similar observations were made for rhodium enamide complexes derived from *RR*-1,2-bis-(*o*-methoxyphenylphenylphosphino)ethane (dipamp) which dissociate more slowly so that experiments were carried out at 325 rather than 300 K. A further intramolecular reaction whereby two diastereoisomeric enamide complexes were interconnected by olefin dissociation and recombination was observed; the amide group remains co-ordinated throughout this process.

In the asymmetric hydrogenation of dehydroamino acid derivatives catalysed by rhodium biphosphine complexes, an enamide complex provides the normal resting state of the catalytic cycle.[1] There are two diasteroisomeric forms of this complex[2] and usually,[3] although not invariably,[4] the one present at lower concentration carries the flux of catalysis. Since the rate-determining stage of reaction involves H_2 addition to the enamide, rapid exchange between the two diastereoisomers is indicated. The purpose of the present work is to clarify the mechanism of that exchange process and determine the consequences of structural variation in both the ligand and dehydroamino acid derivative. This has been achieved by the application of the DANTE pulse sequence[5] to define rates of magnetisation transfer in ^{31}P n.m.r. spectra.

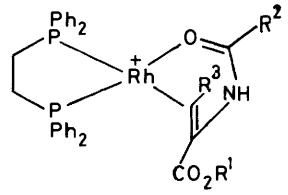
Complexes derived from Bis(diphenylphosphino)ethane.—It is well appreciated[6] that *Z*-dehydroamino acids and esters bind strongly to five-membered ring rhodium biphosphine chelates in methanol solution (K 10^4—$10^5 M^{-1}$) so that complexation is essentially complete in the 10—50 mmol range, particularly when the olefinic component is present in excess. The ^{31}P n.m.r. spectrum of complex (**1b**) at 300 K in MeOH obtained from *Z*-methyl α-benzamidocinnamate (**1a**) consists of two sharp double doublets centred at δ 72.9 and 60.9 p.p.m.[2] (J_{PRh} 162, J_{PRh} 157, J_{PP} 40 Hz). Trial experiments conducted on a sample sealed under argon and containing excess of olefin demonstrated that it was possible to invert one *P*-coupled doublet by means of a DANTE pulse sequence (see Experimental section) without affecting other lines in the spectrum. By conducting a series of spectral accumulations with varying delay times,[5] chemical exchange between P_a and P_b was substantiated (Figure 1). The application of standard procedures[5] provided a rate constant k_{ex} of 1.36 s^{-1} at 300 K.

Similar experiments were carried out for a range of dehydroamino acid derivatives, the results being gathered in the Table. In all cases studied under standard conditions with the olefinic compound present in excess, the enamide complex was the only species observed by ^{31}P n.m.r. The rate of site exchange is very dependent on the substitution pattern in the dehydroamino acid derivative. Thus it is about twice as fast in the *Z*-benzamidocinnamic acid complex (**2b**) as in complex (**2a**).



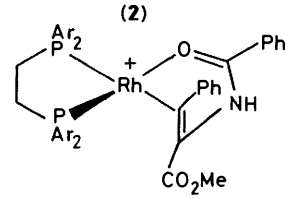
(**1**)

	R^1	R^2	R^3
a;	CH_3	Ph	Ph
b;	H	Ph	Ph
c;	CH_3	CH_3	Ph
d;	H	CH_3	Ph
e;	CH_3	CH_3	Pr^i
f;	Bu^t	CH_3	Ph
g;	CH_3	Bu^t	Ph

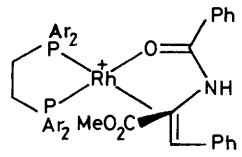


(**2**)

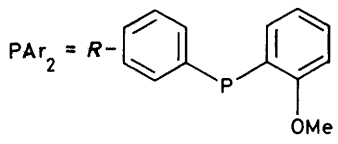
a-g as above
counterion BF_4^-



(**3a**)



(**4a**)



Changing the amide group from benzamide to acetamide enhances magnetisation transfer rates by a factor of three; this holds good for both methyl ester (**1c**) and acid (**1d**). The t-butyl ester (**1f**) resembles its parent acid in reactivity. Replacing the

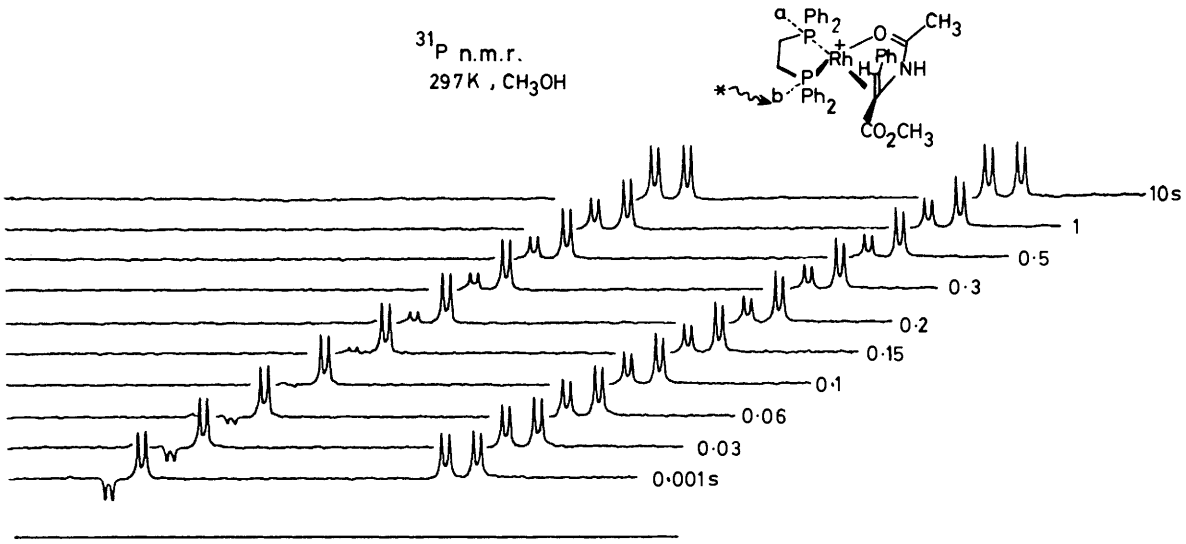


Figure 1. DANTE Pulse sequence applied to the ^{31}P n.m.r. spectrum of rhodium enamide complex (**1b**) in methanol solution, irradiating the low-field doublet of P_a

Table. ^{31}P Site-exchange experiments for 1,2-bis(diphenylphosphino) ethane derivatives

Entry	Dehydroamino acid or ester	Concentrations M[a] $[Rh^+]$/[substrate]	$k_{exch}(s^{-1})$/T(K)	T_1[b]
1	(**1a**)	0.037/0.18.	1.36/298	1.49
2[c]	(**1a**)	0.026/0.052	2.6/300	{12.5 (bound)} {28.5 (free)}
3[d]	(**1b**)	0.037/0.19	2.85/300	1.26
4	(**1c**)	0.037/0.068	3.75/300	1.70
5	(**1d**)	0.037/0.06	9.7/300	1.48
6	(**1d**)	0.037/0.24	8.2/300	1.55
7[e]	(**1d**)	0.037/0.22	6.6/300	2.0
8	(**1e**)	0.037/0.27	2.2/300	1.0
9	(**1f**)	0.037/0.19	8.3/301	1.55
10[f]	(**1c**)	0.018/0.14	1.75/300	1.73
11	(**1g**)	0.037/0.19	0.14/300	1.44
12	(**1g**)	0.037/0.19	0.25/310	1.79
13	(**1g**)	0.037/0.19	0.55/320	2.10

[a] These relate to the initial concentrations of norbornadiene-biphosphinerhodium complex and substrate at the commencement of the experiment. [b] The spin–lattice relaxation time, arranged for the two nuclei; unless otherwise stated. [c] The result of a ^{13}C DANTE experiment employing substrate enriched at the amide carbonyl group; results are computer analysed. [d] In this case three determinations were carried out with irradiation at different sites, with essentially identical results. [e] With a deficiency of substrate the Rh solvate is prominent. This experiment involved excitation of the low-field signal of the enamide complex and was analysed by computer. The time evolution of *all* signals (P_a and P_b of complex and P_c of solvate) was simulated with a dissociative exchange rate of 6.6 s^{-1} for both P_a and P_b and an intramolecular exchange rate of 0, *i.e.* all exchanges involve the solvate. [f] The phosphine here is *SS*-2,3-bis-(diphenylphosphino)butane (chiraphos).

olefinic group of the substrate by isopropyl as in (**1e**) results in a minor diminution of site exchange reactivity. Only the pivalamidocinnamate (**1g**) is appreciably different. Here the measured rate of site exchange is 0.14 s^{-1} at 300 K, close to the lower limit of measurement. It increased modestly with increasing temperature.

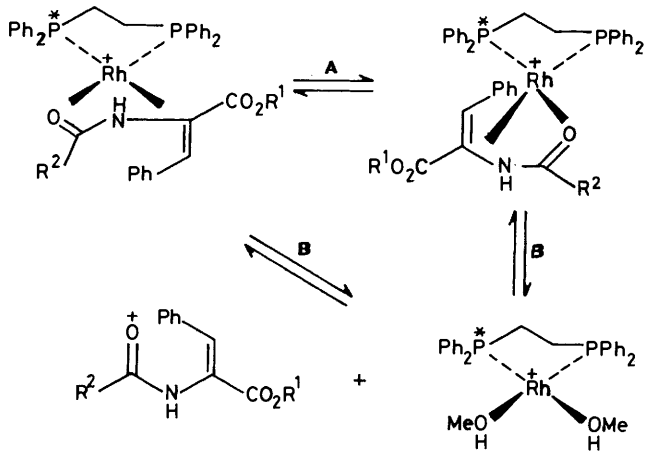


Figure 2. Possible mechanisms for site exchange in enamide complexes based on the experimental observations

In one set of experiments, the chiraphos [7] complex of methyl *Z*-α-acetamidocinnamate was examined. The observed rate constant for magnetisation transfer between P_a and P_b was 1.85 s^{-1}, slower than for the diphos analogue but still rapid on the time-scale of catalytic turnover in asymmetric hydrogenation under ambient conditions.[1]

The Mechanism of Site Exchange.—Variation of the concentration of *Z*-α-acetamidocinnamic acid (**1d**) at constant concentration of the rhodium bisphosphine complex (3.7×10^{-2}M) was carried out. Over a fourfold range (0.24—0.06M) the influence on the rate of magnetisation transfer was minimal (Table). If anything, the reaction is slower at the higher concentration.

Two possible explanations are then consistent with the experimental data. First, an intramolecular process **A** involving the rotation of the enamide moiety with respect to the PRhP plane so that P_a and P_b exchange environments could be occurring. Secondly, dissociation of the enamide ligand could prevail, **B**. In the latter case, magnetisation transfer proceeds through reversible generation of the solvate complex and its trapping by a dehydroamino acid or ester from the solute pool (Figure 2).

The dissociative process **B** requires that only half the events cause magnetisation transfer; if P_a (*trans* to amide) is excited by the DANTE sequence and dissociation occurs then only those recombinations which place P_b *trans* to amide can be observed. Two experiments which discriminate between the intramolecular and dissociative mechanisms were devised. In the first of these, complex (**2a**) carrying ^{13}C-labelling at the amide carbon[2] was subjected to a DANTE pulse sequence in which the ^{13}C signal of the bound amide at δ 182.7 p.p.m. was excited, and magnetisation transfer to the free substrate, present in excess, at δ 169.8 p.p.m. observed. A rate constant k_c 2.8 s^{-1} was determined for the exchange process, this being twice the value observed for the corresponding ^{31}P DANTE experiment. This result encourages the belief that dissociation of enamide is occurring in the site exchange process, and implicates the corresponding solvate complex. Consequently a sample was prepared in which the substrate (**1d**) was present in deficiency so that ^{31}P resonances due to the enamide complex at δ 72.7 and 52.8 p.p.m. and due to the solvate complex at δ 81.2 p.p.m. were both clearly visible. DANTE Experiments were carried out in which either one line of the solvate complex, or one *P*-coupled doublet of P_b in the enamide complex, was inverted. The results (Table) indicate that the methanol complex is indeed involved in the exchange process.

In summary, these experiments show that the enamide complex observed to be the resting state in asymmetric homogeneous hydrogenation is in rapid equilibrium with the methanol solvate complex by dissociation. The equilibrium constant has been measured in several cases,[1,6] and a value of 4.4 s^{-1} (298 K) obtained for the site exchange process in complex (**2a**),[8] based on the extent of line-broadening in ^{31}P n.m.r. and assuming the extreme narrowing simplification of the modified Bloch equations ($k = \pi\Delta\omega$).[9] This compares with the value of 3.7 s^{-1} observed in the present work.

In all cases save that of (**2g**) the dissociation process is much faster than the turnover of hydrogenation under ambient conditions (*ca.* 0.1—0.3 s^{-1}).[10] We were interested to observe that the pivalamide (**1g**) is anomalously unreactive in catalysis. Reduction in MeOH as previously described, employing the rhodium complex of dipamp, was very slow and gave a product of 62% e.e., far less than the 92—96% e.e. normally obtained[11] in the hydrogenation of *Z*-dehydroamino acid derivatives with this ligand.

Complexes derived from RR-*Bis*-(o-*methoxyphenylphenylphosphino*)*ethane*.[12]—With optically active biphosphines, two enamide complexes can be formed which differ in whether the C_α–*re* or C_α–*si* face of the olefin is bound to rhodium.[1] When chiraphos is the ligand only one of these is observable under ambient conditions; it has the opposite configuration to the product of asymmetric hydrogenation, assuming *cis*-delivery of H_2. When dipamp is the ligand, both diastereoisomeric complexes can be observed and it is the one present at lower concentration which is reactive towards H_2 at −60 °C.[3c]

Samples of the *Z*-methyl α-benzamidocinnamate complex were prepared for ^{31}P n.m.r. It was discovered that irradiation of one of the P_a doublets of the major diastereoisomer (**3a**) through a DANTE pulse sequence at 300 K caused no detectable magnetisation transfer to the corresponding doublet of P_b, and hence subsequent determinations were carried out at 320 or 325 K. At this temperature, magnetisation transfer competes with relaxation (Figure 3) and the diminution of the appropriate signal in P_b is observed at intermediate delay times. Concomitant with this, additional changes occur consistent

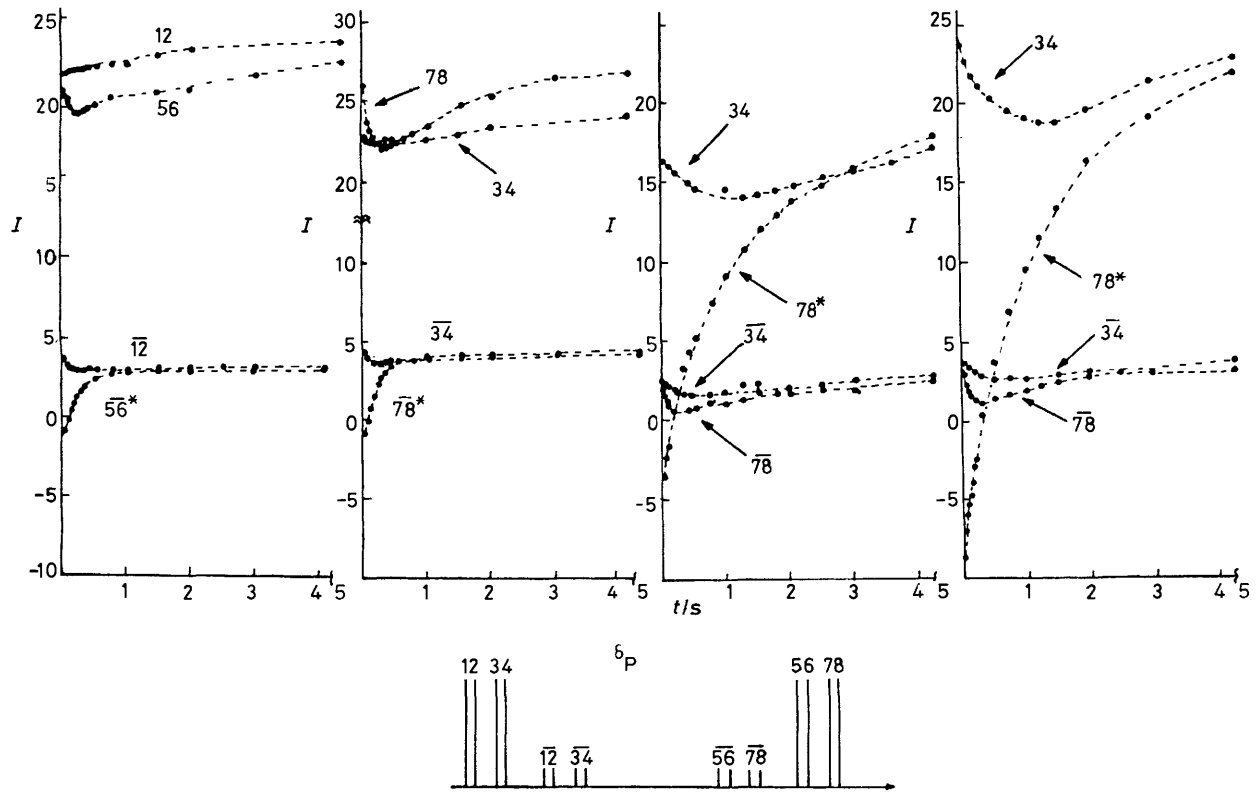


Figure 3. Evolution of magnetisation following DANTE excitation of one *P*-coupled doublet in the ^{31}P n.m.r. spectrum of the enamide complex derived from dipampRh$^+$ and dehydroamino ester (**1a**)

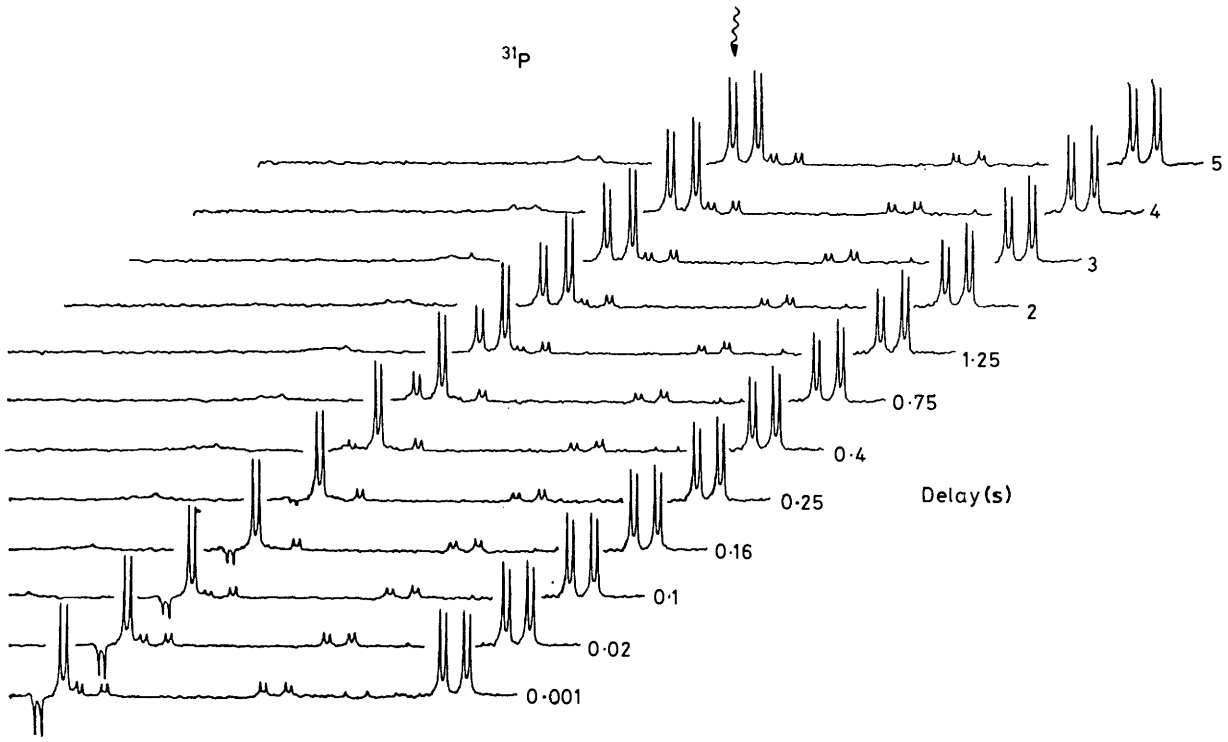


Figure 4. The intramolecular exchange process in dipampRh$^+$ complexes (**3a**) $\rightleftharpoons$ (**4a**), by ^{31}P n.m.r.

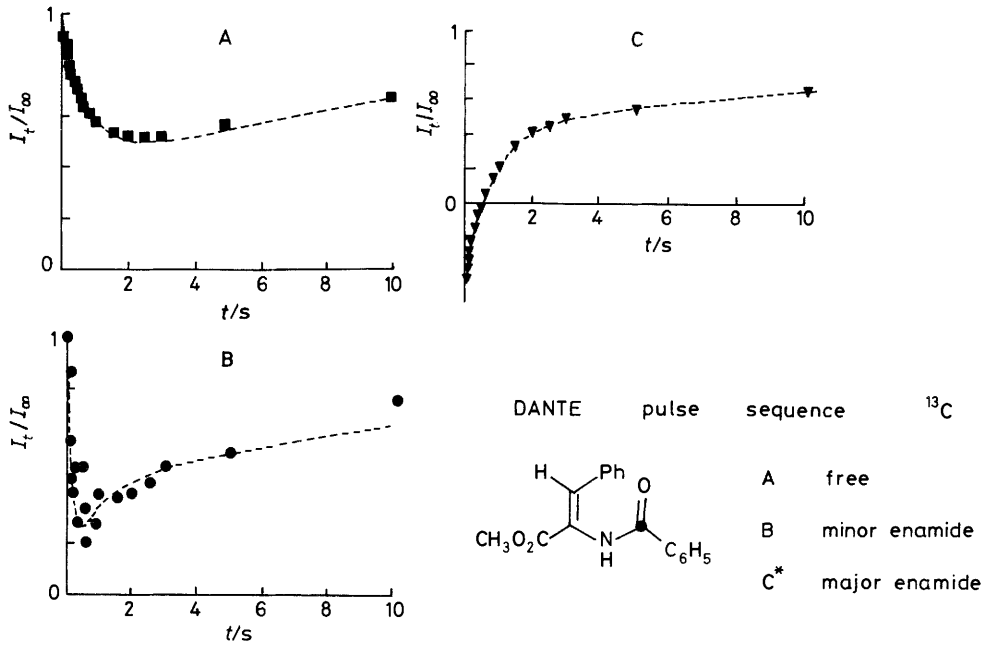


Figure 5. Consequences of a DANTE pulse sequence applied to the ^{13}C n.m.r. spectrum of ^{13}C-labelled complex (**3a**) $\rightleftharpoons$ (**4a**) demonstrating the intramolecular major $\rightleftharpoons$ minor enamide equilibrium

with the direct exchange of magnetisation between P_a in the major diastereoisomer (**3a**) and P_a in the minor diastereoisomer (**4a**) as indicated. This unexpected observation implies an intramolecular process, most economically explained as a dissociation–recombination of the olefin, with rotation about the N–vinyl bond in the dissociated state. It is reinforced by experiments in which a *P*-coupled doublet arising from either P_a or P_b of the minor diastereoisomer was irradiated through a DANTE sequence (Figure 4). These illustrate very clearly that an unsymmetrical exchange process is occurring, with the bulk of magnetisation transfer between P_a and P_a in the one case, or between P_b and P_b in the other. It was further confirmed that exchange between the major and minor diastereoisomers takes place, by simultaneous DANTE inversion of P_a and P_b (by

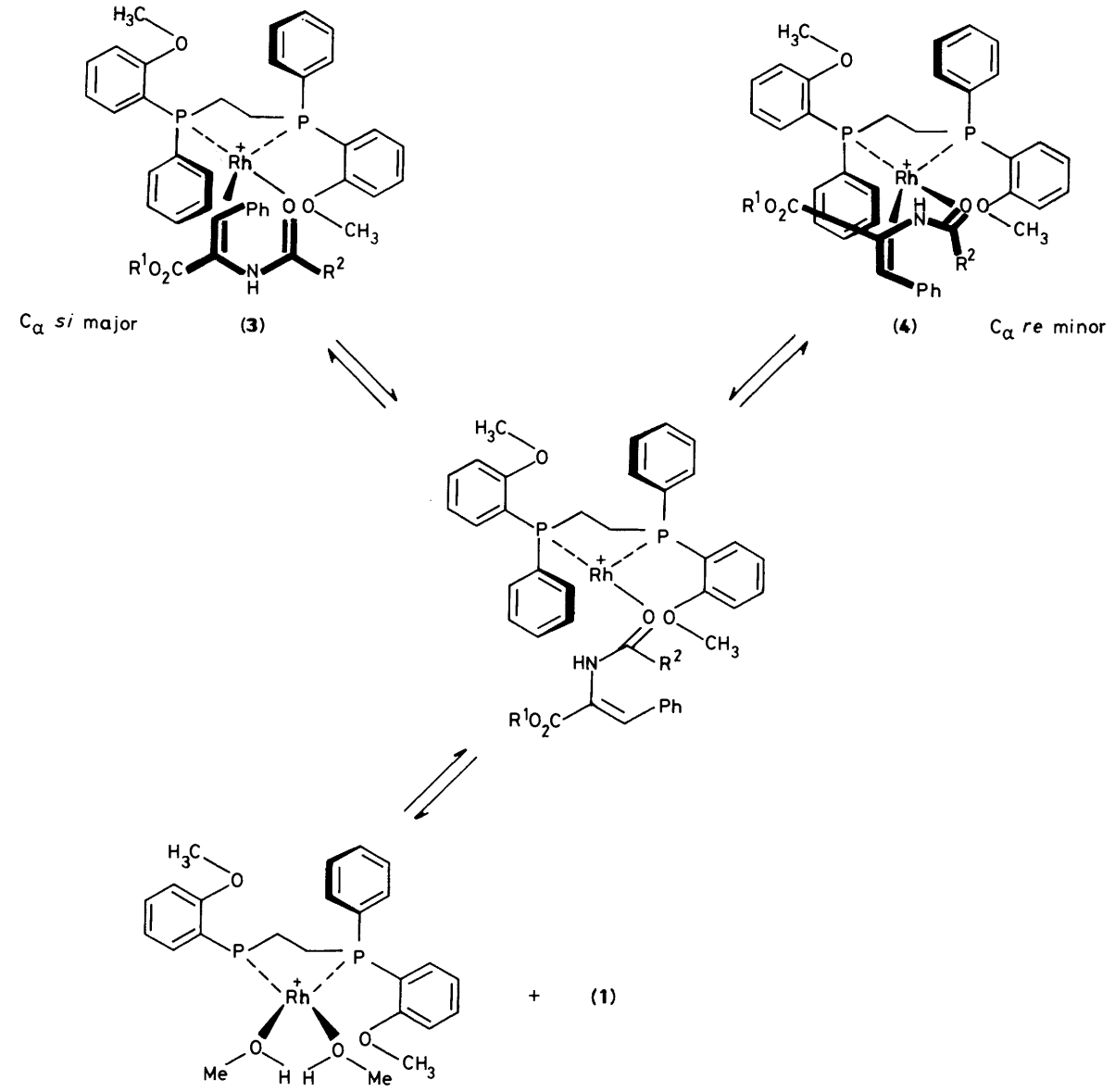


Figure 6. The mechanism for intramolecular equilibration of enamide diastereoisomers

judicious choice of pulse timing and oscillator frequency) and observing exchange with P_a and P_b.

The system is kinetically complex, with up to six independent rate constants and four spin–lattice relaxation times involved in the magnetisation transfer, and so accurate and unambiguous analysis is impossible. Further insight was obtained from ^{13}C n.m.r., employing amide-labelled (**1a**). The complex was prepared in the normal manner and in the presence of excess of substrate the ^{13}C spectrum exhibited signals at δ 181.0 and 182.0 p.p.m. due to the major and minor diastereoisomers (**3a**) and (**4a**) respectively together with the resonance of free (**1a**) at δ 169.8 p.p.m. Inversion of the signal due to the major diastereoisomer through a DANTE sequence and following recovery in the normal manner (Figure 5) indicated that the major *initial* flux was from major to minor diastereoisomer rather than to free enamide. The data were subjected to computer simulation showing that for the intramolecular process $k_1 = 0.65\ s^{-1}$ at 325, and for dissociation $k_1 = 0.45\ s^{-1}$ at 325 K.

These results demonstrate an intramolecular process for interconversion of the diastereoisomers, but what of their relevance to asymmetric hydrogenation? Halpern and Landis have made a detailed study of the kinetics of hydrogenation of *Z*-methyl α-acetamidocinnamate (**1c**) catalysed by Rhdipamp$^+$, and analysed their results in terms of competing H_2 addition to diastereoisomeric enamide complexes in the rate-determining stage.[1,13] On the basis of observation of the reaction of rhodium enamide with H_2, in the temperature range −40 to −25 °C, and a full kinetic analysis of asymmetric hydrogenation between 0 and 37 °C, they conclude that the enamide interconversion process corresponding to (**3c**) ⇌ (**4c**) is entirely dissociative. In the absence of a more direct evaluation using, for example, a set of DANTE experiments along the lines reported here for (**3a**) ⇌ (**4a**) we are sceptical of this conclusion. Analysis of the original Monsanto data[14] on the pressure dependence of asymmetric hydrogenation of *Z*-α-benzamidocinnamic acid[14] suggest that the e.e can be simulated using reasonable values for the rate constants of individual steps[13] without recourse to an intramolecular exchange pathway. It is critically dependent on the value of k_1 taken for

the dissociative enamide exchange, and an intramolecular component could be subsumed.

Experimental

Samples for n.m.r. study were made up as described previously,[2] sealed under argon in 8.4 mm tubes; ^{31}P spectra were normally run with an external CD_3OD lock maintained in a 10 mm tube; ^{13}C samples were made up in deuteriated solvent.

All spectra were recorded on a Bruker WH300 whose probe temperature had been calibrated by the standard CH_3OH method, adapted with a radiofrequency attenuator appropriate for DANTE experiments.

Spectra were measured using the DANTE pulse sequence for selective inversion according to relationship (i) where P_1 has a

$$T_w\text{–}(P_1 - \tau)_n\text{–}T_v\text{–}P_z\text{–measure f.i.d.} \qquad \text{(i)}$$

flip angle of $\pi/2n$ radians; the value of n was in the range 10—20, most commonly 12. P_z Is a $\pi/2$ pulse, T_w a delay sufficient for complete relaxation, and T_v a variable delay. All pulses were applied on resonance for the signal of interest; the parameters n were chosen so that sideband excitation did not interfere with other resonances, τ being in the range 0.8—1.1 ms (sideband spacing 909—1 250 Hz). When the variable delay T_v is very short, the inverted resonance A appears in emission and all other signals in absorption; as T_v is lengthened any chemical exchange leads to the inverted magnetisation being partially transferred to other sites. At the same time spin–lattice relaxation is taking place, so that a biexponential recovery from the perturbation is normally observed; in the case of the inverted signal A the two exponentials have the same sign, while for signals which enjoy chemical exchange with site A the two signs are opposite.

For simple two-site exchanges graphical analysis was carried out as in the original work. This involved plotting $\ln(\Sigma_0 - \Sigma_t)$ as ordinate *versus* T as abscissa, where Σ_0 is the summed equilibrium intensity of the irradiated resonance and its exchange partner and Σ_t their summed intensity at time T. At relaxation time T_1 is then derived as the inverse of the slope of the line. Similarly, a plot of $\ln \Delta$ as ordinate *versus* T as abscissa, where Δ is the difference between the intensities of the resonances at time T, has a slope of $(2k + 1/T)$ and the rate constant for exchange may be derived. The procedure assumes that the spin–lattice relaxation time is identical at the two sites, and experimental measurement indicates that this is reasonable in the present case.

More accurate two-site exchange data, and all three-site exchange data, were obtained by comparison of computer-simulated intensity–delay time curves with experimental data. The appropriate kinetic expressions were obtained by numerical integration using a fourth-order Runge–Kutta routine written for a Hewlett–Packard HP85 microcomputer. Copies of the programs are available on request from the authors.

Substrates, including ^{13}C-labelled compounds and complexes, were prepared by methods reported earlier.[2,4]

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