$$\lambda_1,\lambda_2 = \tfrac{1}{2}\{(a + d) \pm \sqrt{(a + d)^2 - 4(ad - bc)}\} \quad (31)$$

The kinetic behavior of $S_R(t)$ and $S_S(t)$ is highly dependent on whether λ is a real or imaginary number and positive or negative. In the dynamic kinetic resolution of Scheme II both λ^1 and λ^2 are proved to be negative real numbers by a simple mathematical treatment of eqs 30 and 31 on the premise k_R, k_S, and $k_{inv} > 0$.

C_1, C_2, C_3, and C_4 can be expressed by

$$C_3 = \alpha C_1 \quad (32)$$

$$C_4 = \beta C_2 \quad (33)$$

where α and β are solutions of the equation

$$bx^2 + (a - d)x - c = 0$$

Initial concentrations of the substrates are formulated by substitution of $t = 0$ into eqs 4 and 5 to be $S_R(0) = C_1 + C_2$ and $S_S(0) = C_3 + C_4$. Combining these equations and eqs 32 and 33 yields, on the assumption that the reaction starts from 2 mol of racemic mixture ($S_R(0) = S_S(0) = 1$ at time $t = 0$),

$$C_1 = \frac{\beta - 1}{\beta - \alpha} \quad (34)$$

$$C_2 = \frac{1 - \alpha}{\beta - \alpha} \quad (35)$$

$$C_3 = \frac{\alpha(\beta - 1)}{\beta - \alpha} \quad (36)$$

$$C_4 = \frac{\beta(1 - \alpha)}{\beta - \alpha} \quad (37)$$

Substitution of a, b, c, and d, which are correlated with k_R, k_S, and k_{inv} by eq 30, into eq 31 and eqs 34-37 affords eqs 8-13.

Mechanistic Aspects of the Rhodium-Catalyzed Enantioselective Transfer Hydrogenation of α,β-Unsaturated Carboxylic Acids Using Formic Acid/Triethylamine (5:2) as the Hydrogen Source[1]

Walter Leitner,*,†,‡,§ John M. Brown,*,† and Henri Brunner*,‡

Contribution from the Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, U.K., and Universität Regensburg, Institut für Anorganische Chemie, Universitätstrasse 31, 8400 Regensburg, FRG. *Received April 20, 1992. Revised Manuscript Received August 27, 1992*

Abstract: The mechanism of the rhodium-catalyzed enantioselective transfer hydrogenation of methylenebutanedioic acid (itaconic acid) (**1**) and related α,β-unsaturated carboxylic acids using formic acid/triethylamine (5:2) as the hydrogen source is investigated. Kinetic studies using ^1H NMR spectroscopy are presented. Formic acid decomposition is shown to be the rate-limiting step with **1** as the substrate, while hydrogen transfer turns out to be rate determining in the case of (*E*)-(phenylmethylene)butanedioic acid ((*E*)-phenylitaconic acid) (**3**). Furthermore, extensive use is made of deuterium labeling and the analysis of part-deuterated products by ^1H and $^{13}C\{^1H,^2H\}$ NMR spectroscopy. Firstly it is demonstrated that transfer deuteration of (*E*)-phenylitaconic acid (**3**) using DCO_2D as the deuterium source leads to (2*R**,1′*S**)-2-deuterio-2-(1′-deuteriophenylmethyl)butanedioic acid (**9d**) as the only isotopomer. The same isotopomer is obtained using gaseous D_2 under otherwise identical conditions. Use of HCO_2D or DCO_2H leads to a mixture of d_0, d_1, and d_2 isotopomers **9a–d**. Further information is obtained from the transfer hydrogenation of (*RS*)-, (*R*)-, and (*S*)-2-methylene-3-methylbutanedioic acid (β-methylitaconic acid) (**4a**) with the asymmetric in-situ catalyst **8** consisting of $[Rh(norbornadiene)Cl]_2$ and (2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-((diphenylphosphino)methyl)pyrrolidine (bppm). The pure enantiomers react at rates differing only by a factor of 2, but kinetic resolution of the racemate is efficient with a selectivity factor of 18. Additionally, the reaction of HCO_2NH_4 or HCO_2K with intermediates $[Rh(dppe)L_n]^+$ (dppe = 1,2-bis(diphenylphosphino)ethane; L = MeOH, $n = 2$, **11**; L = methyl α-acetamidocinnamate, $n = 1$, **12**) of the catalytic cycle of hydrogenation using gaseous hydrogen is followed by ^{31}P NMR spectroscopy at variable temperature. No indication of a formate coordination to rhodium is observed in these experiments. Taken together, these results indicate that the mechanism of rhodium-catalyzed transfer hydrogenation with formic acid/triethylamine as the hydrogen source most likely involves decarboxylation of a transient formate species to form hydridic complexes of rhodium, in which the Rh–H entity has a long lifetime relative to hydrogen transfer to the substrate.

Introduction

Asymmetric hydrogenation of C=C double bonds is a major application of homogeneous catalysis by chiral transition metal complexes.[2] A wide range of substrates can be reduced with excellent enantioselectivity employing optically pure phosphine complexes of rhodium or ruthenium.[2,3] We reported recently that use of potentially hazardous gaseous hydrogen can be avoided by hydrogen transfer from a mixture of formic acid and an amine in the approximate molar ratio of 5:2 using similar catalysts.[4] The enantioselectivities achieved by this new and simple methodology

† University of Oxford.
‡ Universität Regensburg.
§ Current address: Arbeitsgruppe für CO_2-Chemie der Max-Planck-Gesellschaft an der Friedrich-Schiller-Universität Jena, Lessingstrasse 12, O-6900 Jena, FRG.

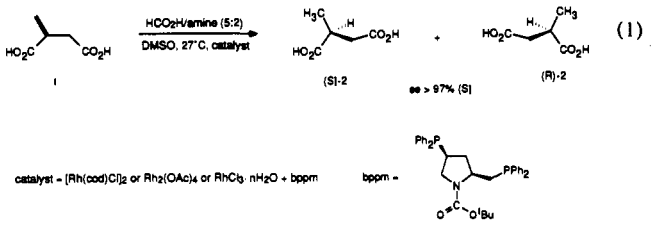
(1) Asymmetric Catalysis. 80. Part 79: Brunner, H.; Forster, S. *Monatsh. Chem.* **1992**, *123*, 659.

(2) (a) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1985; Vol. 5. (b) Noyori, R. *Science* **1990**, *248*, 1194. (c) Noyori, R.; Kitamura, M. *Mod. Synth. Methods* **1989**, *5*, 115. (d) Brunner, H. *Top. Stereochem.* **1988**, *18*, 129. (e) Brunner, H. *Synthesis* **1988**, 645. (f) Brown, J. M.; Davies, S. G. *Nature* **1989**, *342*, 631. (g) Brown, J. M. *Nature* **1991**, *350*, 191.

(3) (a) Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, R.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174. (b) Ohta, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 7189. (c) Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922. (d) Kawano, H.; Ikariya, T.; Ishii, Y.; Saburi, M.; Yoshikawa, S.; Uchida, Y.; Kumobayashi, H. *J. Chem. Soc., Perkin Trans. I* **1989**, 1571.

0002-7863/93/1515-152$04.00/0

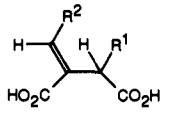
are often comparable to and sometimes even higher than those obtained with gaseous hydrogen under similar conditions. Transfer hydrogenation of methylenebutanedioic acid (itaconic acid) (**1**) using a catalyst formed in situ from a rhodium precursor and the chiral phosphine bppm[5] yields for example (*S*)-methylsuccinic acid (**2**) of >97% optical purity (eq 1).[4b] Hydrogenation with gaseous



(1)

hydrogen in the presence of a cationic rhodium complex of the same ligand yields 94% ee.[6] Likewise, 93% (*R*) enantioselectivity can be achieved by transfer hydrogenation of substrate **1** in tetrahydrofuran using the ruthenium complex $[Rn(\eta^3\text{-}C_3H_5)(acac\text{-}F_6)\{(S)\text{-BINAP}\}]$[7] as a catalyst,[4e] whereas hydrogenation employing $[Ru_2\{(R)\text{-BINAP}\}_2Cl_4(NEt_3)]$ in methanol yields (*S*)-**2** with only 88% optical induction at 2 atm H_2.[3d]

Whilst the catalytic cycle of enantioselective hydrogenation with chiral rhodium phosphine complexes has been thoroughly investigated,[8] very little is known about the mechanism of transfer hydrogenation reactions.[9] We wanted to elucidate the mechanism of enantioselective rhodium-catalyzed transfer hydrogenation of itaconic acid (**1**) with HCO_2H/NEt_3 (5:2) as the hydrogen source and compare it to the catalytic cycle of hydrogenation using gaseous hydrogen. Transfer hydrogenation may provide additional mechanistic information, because two distinct hydrogen atoms are delivered.



1 $R^1 = R^2 = H$
3 $R^1 = H, R^2 = Ph$
4a $R^1 = Me, R^2 = H$

5 [Rh(cod)Cl]2 + dppb (ligand : metal = 1.2 : 1)
6 [Rh(nbd)(dppb)]CF3SO3
7 [Rh(cod)Cl]2 + bppm (ligand : metal = 1.2 : 1)
8 [Rh(nbd)Cl]2 + bppm (ligand : metal = 1.2 : 1)

The itaconic acid derivatives **1**, **3**, and **4a** and the catalysts **5**–**8** were used throughout the study.[10] The short induction period[4a] observed in kinetic measurements using the in-situ systems **5**, **7**, and **8** is absent in experiments with the preformed phosphine complex **6**, but earlier results indicate that the same catalytically active rhodium phosphine complex is formed from different precursors.[4d] Unless otherwise stated, substrate concentration was in the range 0.50–0.65 M and the ratio substrate:triethylamine:formic acid was 1:2:5 (vide infra). Dimethyl sulfoxide was used as a solvent, and the temperature was controlled by an external thermostat.

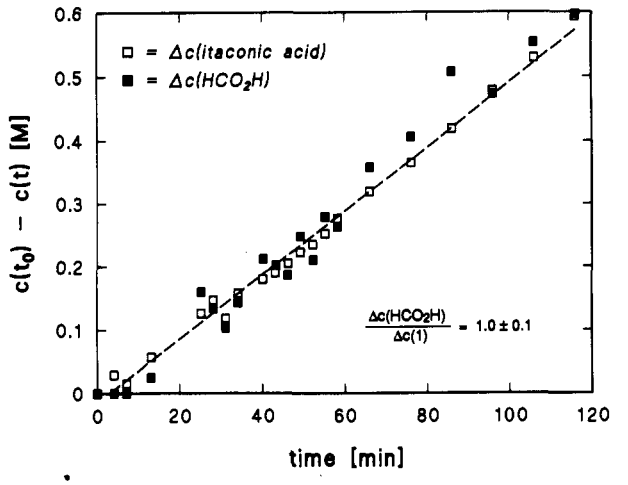


Figure 1. Change of concentration of itaconic acid (**1**) (□) and formic acid (■) during transfer hydrogenation of **1** (0.64 M) in DMSO-d_6 at 297 K using HCO_2H (3.34 M) in the presence of NEt_3 (1.29 M) as the hydrogen source and $[Rh(cod)Cl]_2$ (3.28×10^{-3} M Rh) in the presence of dppb (3.77×10^{-3} M) as catalyst.

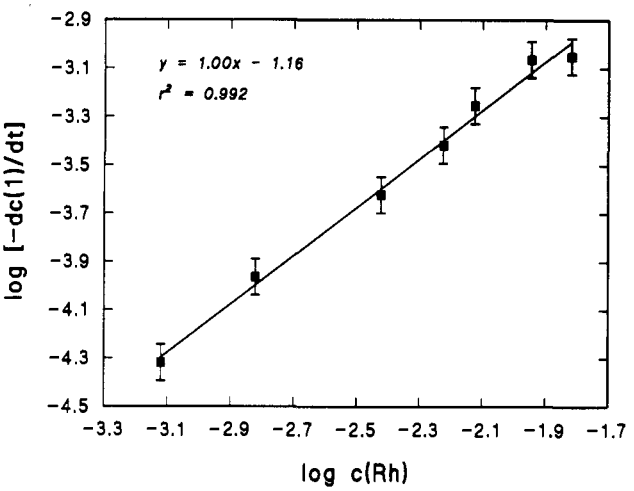


Figure 2. Influence of rhodium concentration on the rate of transfer hydrogenation of itaconic acid (**1**) (0.50 M) in DMSO-d_6 at 305 K using HCO_2H (2.50 M) in the presence of NEt_3 (1.00 M) as the hydrogen source and catalyst **5**.

Results

Kinetic Studies. The kinetics of the transfer hydrogenation of itaconic acid (**1**) were followed by measuring the areas of the olefinic proton peaks of compound **1** and the formyl hydrogen peak of formic acid in the ^1H NMR spectrum relative to those of the internal standard mesitylene.[4a] Figure 1 shows the change of the concentration of both itaconic and formic acid during transfer hydrogenation employing catalyst **5** (3.28×10^{-3} M in rhodium) at 297 K. The concentration of substrate decreases linearly with time, indicating that the reaction is zero order in the concentration of substrate **1** under turnover conditions. Since formic acid is always present in 5-fold or greater excess, as in preparative scale reactions,[4] its concentrations is essentially constant during the course of the reaction. A primary kinetic isotope effect for DCO_2H/HCO_2D (vide infra) indicates direct involvement of formate, however. The reaction was found to be first order in

(4) (a) Brunner, H.; Leitner, W. *Angew. Chem.* **1988**, *100*, 1231; *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1180. (b) Brunner, H.; Graf, E.; Leitner, W.; Wutz, K. *Synthesis* **1989**, 743. (c) Brunner, H.; Leitner, W. *J. Organomet. Chem.* **1990**, *387*, 209. (d) Leitner, W. Ph.D. Thesis, Universität Regensburg, Germany, 1989. (e) Brown, J. M.; Brunner, H.; Leitner, W.; Rose, M. *Tetrahedron: Asymmetry* **1991**, *2*, 331. (f) For a recent review on enantioselective transfer hydrogenation, see: Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051.

(5) bppm is (2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-((diphenylphosphino)methyl)pyrrolidine: Achiwa, K. *J. Am. Chem. Soc.* **1976**, *98*, 8265.

(6) Ojima, I.; Kogure, T.; Yoda, N. *J. Org. Chem.* **1980**, *45*, 23.

(7) Alcock, N. W.; Brown, J. M.; Rose, M.; Wienand, A. *Tetrahedron: Asymmetry* **1991**, *2*, 47. BINAP is 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.[3a]

(8) (a) Halpern, J. In ref 2a, pp 41–69. (b) Brown, J. M.; Chaloner, P. A. In *Homogeneous Catalysis with Metal Phosphine Complexes*; Pignolet, L. H., Ed.; Plenum Press: New York, 1983, pp 137–165. (c) Halpern, J.; Riley, D. P.; Chan, A. S. C.; Pluth, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 8055. (d) Brown, J. M.; Chaloner, P. A. *Tetrahedron Lett.* **1978**, *21*, 1877. (e) Chan, A. S. C.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 838. (f) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746. (g) Brown, J. M.; Chaloner, P. A. *J. Am. Chem. Soc.* **1980**, *102*, 3040. (h) Brown, J. M.; Chaloner, P. A.; Morris, G. A. *J. Chem. Soc., Perkin Trans. II* **1987**, 1583.

(9) Recent examples for mechanistic investigation of rhodium-catalyzed transfer hydrogenation using 2-propanol as the hydrogen source: Brune, H. A.; Unsin, J.; Hemmer, R.; Reichhardt, M. *J. Organomet. Chem.* **1989**, *369*, 335. Esteruelas, M. A.; Garcia, M. P.; López, A. M.; Oro, L. A. *Organometallics* **1992**, *11*, 702.

(10) The following abbreviations are used: cod = 1,5-cyclooctadiene; dppb = 1,4-bis(diphenylphosphino)butane; nbd = 2,5-bicyclo[2.2.1]heptadiene (norbornadiene).

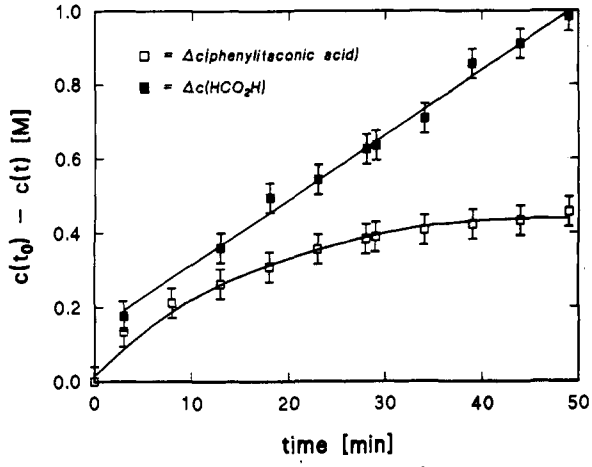


Figure 3. Change of concentration of (*E*)-phenylitaconic acid (**3**) (□) and formic acid (■) during transfer hydrogenation of **3** (0.51 M) in DMSO-d_6 at 318 K using HCO_2H (2.89 M) in the presence of NEt_3 (0.93 M) as the hydrogen source and catalyst **6** (1.31×10^{-2} M).

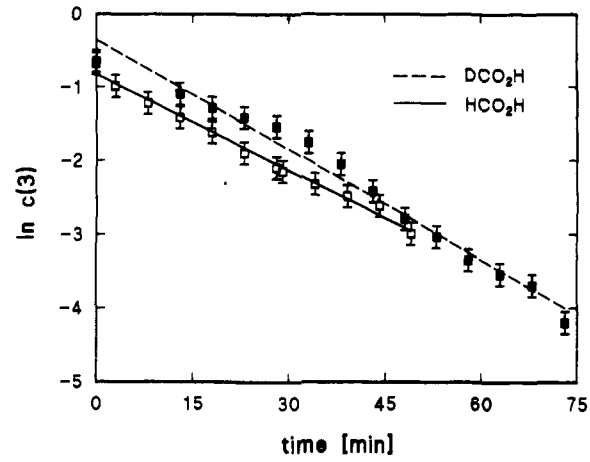


Figure 4. First-order plots for transfer hydrogenation of (*E*)-phenylitaconic acid (**3**): □, reaction of **3** (0.51 M) in DMSO-d_6 at 318 K with HCO_2H (2.89 M) in the presence of NEt_3 (0.93 M) and catalyst **6** (1.31×10^{-2} M); ■, reaction with DCO_2H and 1.81×10^{-2} M catalyst under otherwise identical conditions.

the initial concentration of rhodium (Figure 2), and the rate constant k_{obs} defined by eq 2 was determined for the in-situ catalyst

$$-dc(1)/dt = k_{obs}c(Rh) \quad (2)$$

5 as $(6.7 \pm 0.6) \times 10^{-2}$ s^{-1} at 305 K and an initial formic acid concentration of 2.50 M. Catalytic activity was still observed at an initial rhodium concentration of 7.5×10^{-4} M, corresponding to a substrate to catalyst ratio of 670:1.

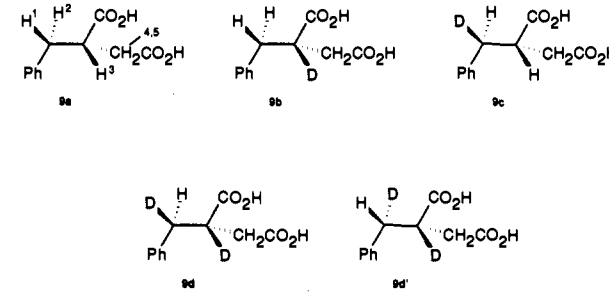
Figure 1 also indicates that exactly 1 mol of formic acid is consumed per mol of itaconic acid (Δc(formic acid)/Δc(**1**) = 1.0 ± 0.1). Nevertheless a 5-fold excess of formic acid was used throughout the study in order to mimic the conditions used in preparative scale reactions[4] as closely as possible. The decomposition of formic acid continues after all the olefin has been consumed at approximately the same rate.

Compound **1** was also successfully hydrogenated using gaseous hydrogen instead of formic acid under otherwise identical reaction conditions. The rate of reaction measured by hydrogen uptake was, however, an order of magnitude slower using the same catalyst **7** in both reactions. If transfer hydrogenation of **1** was carried out under a hydrogen atmosphere employing only 0.5 molar equiv of formic acid, hydrogen uptake started immediately after carbon dioxide evolution had stopped. The hydrogenation rate was identical to the one observed in the absence of formic acid.

When the formyl H of formic acid was replaced by deuterium, a primary kinetic isotope effect $k_H/k_D = 3.1 \pm 0.1$ was observed at 305 K using catalyst **5** (1.5×10^{-2} M Rh). If only the carboxylate bears deuterium, k_H/k_D is close to unity.[4b] Interestingly, when DCO_2H was employed for the transfer hydrogenation of itaconic acid (**1**), a very slow exchange of deuterium by hydrogen in the formyl position was observed in the ^1H NMR spectrum. The decomposition of formic acid must therefore be a reversible process.[11] The exchange is, however, very slow compared to hydrogen transfer. Less than 10% of DCO_2H was converted into HCO_2H or HCO_2D at 100% conversion of acid **1**.

(*E*)-(Phenylmethylene)butanedioic acid ((*E*)-phenylitaconic acid, **3**) is obtained by Stobbe condensation of benzaldehyde and sodium diethyl succinate.[12] The stereochemistry was verified by a nuclear Overhauser enhancement of 3.3% between the aromatic protons of the phenyl ring (δ 7.43–7.39) and the two methylene protons (δ 3.39) in the ^1H NMR spectrum (500 MHz, DMSO-d_6). No enhancement occurs between the olefinic proton (δ 7.76) and the methylene group. Figure 3 shows the change of concentration of both substrate and formic acid during the transfer hydrogenation of (*E*)-phenylitaconic acid (**3**). Although the conditions are significantly different for the sets of experiments with compounds **1** and **3**, the indication is that the rate of formic acid decomposition is similar, correcting for the different rhodium concentrations. Whereas the rate of formic acid decomposition remains constant during the investigated period, the rate of hydrogen transfer now depends strongly on the concentration of substrate **3**. The gap between formic acid decomposition and product formation shows that the capture of released hydrogen through transfer hydrogenation is incomplete in this case. Measuring the decrease of concentration of substrate **3**, the experimental data may be fitted by a first-order rate dependence on substrate as shown in Figure 4 for the transfer hydrogenation of **3** using HCO_2H and DCO_2H. The pseudo-first-order rate constants for the reactions shown in Figure 4 are $k_{obs} = 7.3 \times 10^{-4}$ s^{-1} with HCO_2H and 8.3×10^{-4} s^{-1} with DCO_2H, indicating as expected that the kinetic isotope effect is in this case close to unity ($k_H/k_D = 1.2$, correcting for the different catalyst concentrations). As in the case of substrate **1**, a very slow internal H–D exchange is observed using DCO_2H as the hydrogen source, leading to 4% hydrogen incorporation at the formyl position at 100% conversion of compound **3**.

Labeling Studies. The two diastereotopic benzylic protons H^1 and H^2 of benzylsuccinic acid (**9a**), the hydrogenation product of (*E*)-phenylitaconic acid (**3**), show a chemical shift difference of 0.16 ppm in the ^1H NMR spectrum (500 MHz, DMSO-d_6).



One resonance appears as part of an ABM spin system at δ 2.74 ppm ($^2J_{H^1H^2}$ = 15.6 Hz, $^3J_{HH}$ = 9.9 Hz); the other one is centered at $\delta \approx 2.9$ ppm and coincides with the multiplet arising from methine proton H^3. The remaining diastereotopic protons H^4 and H^5 give rise to the AB part of an ABX system at δ 2.42 ppm ($^2J_{H^4H^5}$ = 16.8 Hz, $^3J_{HH}$ = 8.9 Hz) and δ 2.24 ppm ($^2J_{H^4H^5}$ = 16.8 Hz, $^3J_{HH}$ = 4.4 Hz), respectively. This connectivity was proved by the $^1H,^1H$-COSY NMR spectrum. The two diastereomers **9d** and **9d'**, arising from cis- or trans-addition of deuterium to **3**, are therefore easily distinguished by ^1H NMR. Rhodium-catalyzed hydrogention with gaseous hydrogen is known to proceed via cis-addition.[13] Accordingly, deuteration of (*E*)-phenylitaconic

(11) The reversibility of formic acid decomposition may be utilized for the direct formation of HCO_2H from H_2 and CO_2 at elevated pressure: Graf, E.; Leitner, W. *J. Chem. Soc., Chem. Commun.* **1992**, 623.

(12) Horning, E. C.; Walker, G. N. *J. Am. Chem. Soc.* **1952**, *74*, 5147.

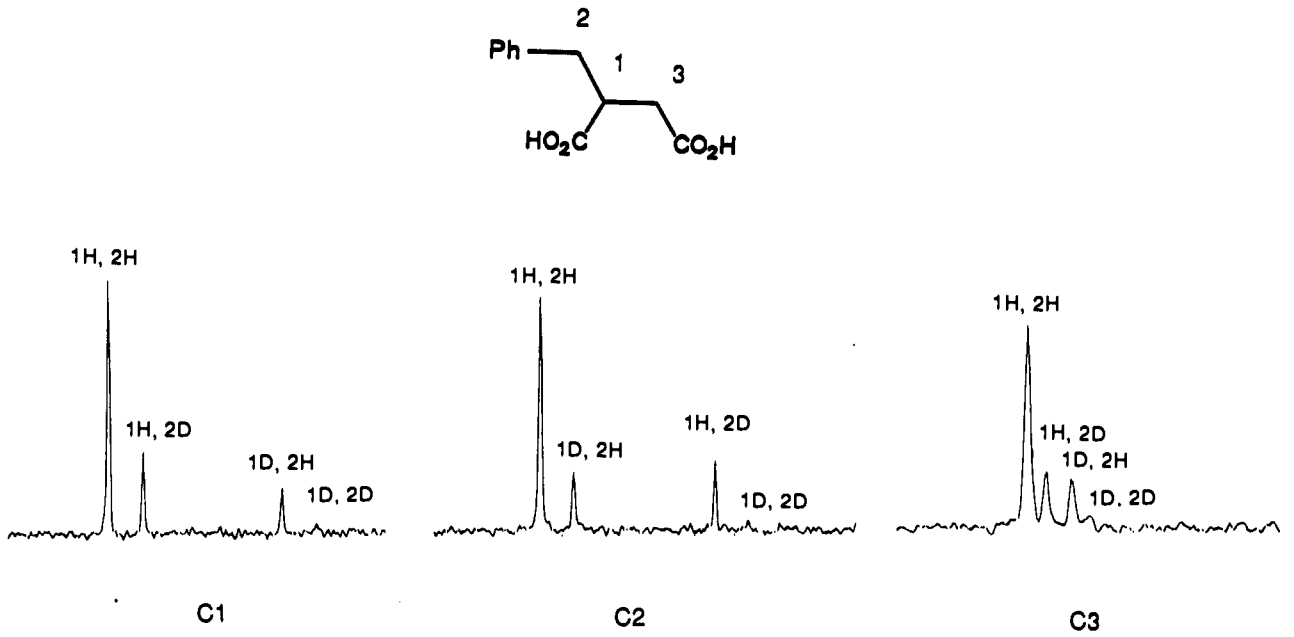


Figure 5. The three high-field signals C1–C3 in the $^{13}C\{^1H,^2H\}$ NMR spectrum (125.7 MHz, methanol-d_4) of the product obtained by transfer hydrogenation of **3** with DCO_2H/NEt_3 at about 25% conversion.

acid, pretreated with MeOD to exchange the carboxylate hydrogens with deuterium (**3**-d_2), using gaseous D_2 in the presence of catalyst **6** (6.5×10^{-3} M) and 2 equiv of NEt_3 in either MeOD or DMSO-d_6 gave the (2*R**,1′*S**) isomer **9d**. As expected, its ^1H NMR spectrum consists of a singlet at δ 2.71 ppm and an AB system (δ_A 2.41 ppm, δ_B 2.24 ppm, $^2J_{HH}$ = 16.8 Hz) with all signals slightly broadened owing to coupling to deuterium. The same diastereomer was formed exclusively by transfer deuteration of **3**-d_2 with DCO_2D in DMSO-d_6 under otherwise identical conditions. No deuterium incorporation into the CH_2–CO_2H group was observed in either reaction, indicating that double-bond migration does not occur as a side reaction.[14]

If monodeuterated formic acid is employed as the hydrogen source, the formation of isotopomers **9b** and **9c** would be expected from transfer hydrogenation of (*E*)-phenylitaconic acid (**3**). The ratio of these two isotopomers might give information on the sequence of addition of the formyl and the carboxylate hydrogen atom during the course of reduction. Therefore transfer hydrogenation of compound **3** was carried out using HCO_2D (DCO_2H) in the presence of triethylamine as the hydrogen source with catalyst **6** (5.0×10^{-3} M) at 308 K. After 7 min (33 min), an aliquot of the reaction mixture was taken out by syringe and quenched by addition of aqueous NaOH. This reaction time corresponds to less than 30% conversion under these reaction conditions as shown by independent kinetic measurements on a small scale and by the weight balance of the isolated product and unreacted starting material (ca. 80% combined yield). The remaining reaction mixture was worked up after a total reaction time of 20 h.

The ratio of **9b** and **9c** is readily obtained from concurrent analysis of the signals of C1, C2, and C3 in the $^{13}C\{^1H,^2H\}$ NMR spectrum[15] (Figure 5) at δ 44.3, δ 38.6, and δ 35.9 ppm, respectively (values for the undeuterated isotopomer **9a** in methanol-d_4). They are also easily distinguished from isotopomers **9a** and **9d** by this methodology, as each sp^3-carbon shows a distinct singlet for any of the four isotopomers if coupling to both hydrogen and deuterium is eliminated (see Experimental Section). The assignments of the signals in Figure 5 are based on the fact that replacement of a hydrogen atom by deuterium shifts the resonances of adjacent carbon nuclei to higher field.[16] If several hydrogen atoms are replaced, the total shift is the sum of the individual shifts.[16] For compounds **9a–d** the deuterium isotopic shifts are respectively α 0.34 ppm, β 0.07 ppm, and γ 0.027 ppm. The ratios of isotopomers given in Table I were calculated from the relative areas of the separate C3 peaks, assuming that their relaxation times are identical. This was further checked by combining the data for C1 and C2 with the additional information that the sum of the four isotopomers must be 100%. Values obtained from different calculations were identical within experimental error.

Table I. Ratio (%) of Isotopomers **9a-d** Formed during Transfer Hydrogenation and Hydrogenation of (*E*)-Phenylitaconic Acid (**3** and **3**-d_2)[a]

substrate (conc, M)	hydrogen source (conc, M)[b]	conversion (%)	**9a**	**9b**	**9c**	**9d**
3 (0.51)	DCO_2H (2.07)	≤30	60	17	18	5
3 (0.51)	DCO_2H (2.07)	100	57	20	17	6
3-d_2 (0.51)	HCO_2D (2.19)	≤30	6	17	19	58
3-d_2 (0.51)	HCO_2D (2.19)	100	13	24	19	44
3-d_2 (0.51)	H_2 (saturated)	100	63	16	16	5

[a] Reaction conditions: **3** (826.1 mg, 4.0 mmol) was reacted with DCO_2H/NEt_3 (3.6:2,[17] 1.80 mL) in DMSO (6.0 mL) at 308 K using catalyst **6** (5.0×10^{-3} M). **3**-d_2 in DMSO-d_6 was treated in the same way with HCO_2D/NEt_3 (3.8:2[17]) or 1 atm of H_2 in the presence of NEt_3 (1.30 M), respectively. [b] Concentrations were calculated assuming a density $d \approx 1.0$ for the formic acid/triethylamine azeotropes.

All four possible isotopomers were formed in the transfer hydrogenation of compound **3** with DCO_2H. The monodeuterated products **9b** and **9c** were present in almost equal amounts. The main product was the isotopomer arising from transfer of two hydrogen atoms. The amount of double incorporation of deuterium was very small, but still detectable. The isotopomeric ratio remained constant over the whole course of the reaction. Interestingly, a similar distribution of isotopomers was found in the hydrogenation of **3**-d_2 using gaseous hydrogen. Exchange of the

(13) (a) Kirby, G. W.; Michael, J. *J. Chem. Soc., Perkin Trans. I* **1973**, 115. (b) Detellier, C.; Gelbard, G.; Kagan, H. B. *J. Am. Chem. Soc.* **1978**, *100*, 7556.

(14) Transfer deuteration of **1** also gave 1,2-addition of the two deuterium atoms exclusively, as revealed by ^1H and ^{13}C-DEPT NMR spectroscopy. The dimethyl ester of **1**, however, was reduced by DCO_2D to yield solely the 1,3-addition product. This suggests that there is a change of mechanism in hydrogen transfer going from acids to esters, which probably accounts for the in general much lower optical induction observed in enantioselective transfer hydrogenation of esters compared to their corresponding acids.[4c]

(15) Brown, J. M.; Derome, A. E.; Hughes, G. D.; Monaghan, P. K. *Aust. J. Chem.* **1992**, *45*, 143.

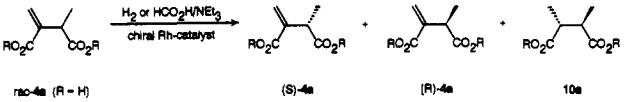
(16) Hansen, P.-E. *Annu. Rep. NMR Spectrosc.* **1984**, *15*, 105.

(17) The different composition of the azeotropes formed from NEt_3 and HCO_2H, DCO_2H, or HCO_2D may be explained in terms of the different densities of the pure acids.

hydrogen atoms at the carboxylate of acid **3** with deuterium by treatment with MeOD (**3**-d_2) and subsequent transfer hydrogenation using HCO_2D lead to an exactly reversed ratio of **9a** and **9d** at low conversion. In this case however, the amount of double incorporation of the formyl hydrogen increases with time.

Kinetic Resolution of β-Methylitaconic Acid (4a). The acid **4a** is readily available through hydrolysis of the corresponding dimethylester **4b**. Racemic dimethyl β-methylitaconate (*rac*-**4b**) was prepared by a one-pot modification of the method of Brown and Conn (see Experimental Section).[18] The single enantiomers (*R*)-**4b** and (*S*)-**4b** were obtained via kinetic resolution of *rac*-**4b** by hydrogenation in the presence of [Rh(nbd)[(*R*)-BINAP]]-[CF_3SO_3] and the equivalent catalyst derived from (*S*)-BINAP, respectively, similarly to a previously described procedure (see Experimental Section).[19b]

The two enantiomers of compound **4a** showed a kinetic behavior identical to that of unsubstituted itaconic acid (**1**) when treated separately with HCO_2H/NEt_3 reagent in the presence of the chiral catalyst **8** at 308 K. Transfer hydrogenation of (*S*)-**4a** was somewhat faster than that of (*R*)-**4a**, by a factor of about 2. In order to determine the actual selectivity factor[20] of kinetic resolution of *rac*-**4a** (eq 3), transfer hydrogenation of *rac*-**4a** was



(3)

quenched at 54% and 70% conversion according to ^1H NMR analysis of the isolated material. The crude mixture of **4a** and its hydrogenation product **10a** was esterified with diazomethane, distilled, and then reacted with [Pt[(*S*,*S*)-DIOP](C$_2$H$_4$)] in tetrahydrofuran at room temperature. Coordination of the Pt(*S*,*S*)-DIOP fragment to either the *si*- or the *re*-face of (*S*)- and (*R*)-**4b**, respectively, leads to a mixture of four diastereomeric complexes, in which no preference for the binding of either enantiomer of **4b** is observed.[18] Thus, quantitative analysis of the $^{31}P\{^1H\}$ NMR spectrum of this mixture at 202 MHz allows the determination of the enantiomeric excess of unreacted starting material **4a**.[18,21] Enantiomerically pure (*R*)-**4a** was obtained at 70% conversion. From the enantiomeric excess of 86% ee (*R*) at 54% conversion, a selectivity factor of 18 for the (*S*) isomer was calculated.[20] In all cases, the (*R**,*R**) isomer **10a** of methylsuccinic acid was identified as the major product in the transfer hydrogenation of β-methylitaconic acid (**4a**) by ^1H NMR spectroscopy.

^{31}P NMR Investigations. In addition to the indirect methods of investigating the mechanism of the rhodium-catalyzed transfer hydrogenation using formic acid as the hydrogen source, the reaction of model rhodium complexes with HCO_2NH_4 and HCO_2K in methanol was followed by ^{31}P NMR spectroscopy to search for possible intermediates. The complexes [Rh(dppe)-(MeOH)$_2$]$^+$ (**11**)[8c,d] and [Rh(dppe)(mac)]$^+$ (**12**)[8c,g] (dppe = 1,2-bis(diphenylphosphino)ethane, mac = methyl α-acetamidocinnamate) are both intermediates of the catalytic cycle of hydrogenation using gaseous hydrogen[8] and were therefore used in these investigations. The dppe ligand was chosen for the relatively low catalytic activity of its rhodium complexes in transfer hydrogenation,[4a] thus making it more likely to observe highly reactive intermediates. Addition of 3 equiv of HCO_2K to a methanol solution of complex **11** at −40 °C resulted in a considerable broadening of the phosphorus signal (δ 81 ppm, J_{RhP} = 206 Hz[8d]), and upon warming, a new doublet centered at δ 75 ppm (J_{RhP} = 204 Hz) appeared which became the only observable signal above 0 °C. This signal may be assigned to the trinuclear cluster [Rh$_3$(dppe)$_3$(OMe)$_2$]$^+$, obtained on base addition to a methanol solution of compound **11**, by comparison to literature values (δ 72 ppm, J_{RhP} = 201 Hz[8c]). When complex **11** was reacted with 3 equiv of HCO_2NH_4 at 233 K, however, a different phosphorus signal was observed at δ 76 ppm with a coupling constant J_{RhP} = 176 Hz. In the latter case, catalytic decomposition of formate occurred upon warming, as seen by gas evolution and a slow pressure buildup in the NMR tube. Due to this pressure buildup, the tubes must not be flame-sealed. They were closed with a rubber septum and the NMR spectra taken as quickly as possible. Immediately after measurement, the tubes were vented to an argon line. Two reasonable possibilities for the newly formed rhodium complex are [Rh(dppe)(NH$_3$)$_2$]$^+$ (**13**)[22] and [Rh(dppe)(η^2-O$_2$CH)] (**14**). Formula **13** seems much more likely, as reaction of **11** with KO_2CH does not produce detectable amounts of **14** and the coupling constant J_{RhH} in **14** would be expected to be considerably larger than the observed 176 Hz.[23] If complex **12** is treated with 6 equiv of NH_4HCO_2 at room temperature in methanol, the two characteristic double doublets[8c,g] immediately disappear and the doublet assigned to **13** is observed. In order to search for intermediates during the formation of **13**, the ^{31}P NMR spectra of a mixture of complex **12** and 2 equiv of NH_4HCO_2 in methanol were recorded over a temperature range 193–293 K. No change was observed in the spectrum up to 278 K. Then, very slowly the doublet assigned to **13** appeared. After 2 h at 293 K, a mixture of **12** and **13** was obtained without any intermediate being observable. It is noteworthy, that a substantial amount of intensity of the phosphorus signals is lost at temperatures less than 278 K, possibly due to a fast exchange process between coordinated mac and formate. Unfortunately, complex **13** proved to be very unstable, and after evaporation of the solvent, a complex mixture of rhodium compounds containing mainly [Rh$_2$(dppe)$_2$]$^{2+}$ [8c] was obtained, according to FD mass spectroscopy. Attempts to define the species present under the conditions of catalytic turnover using catalysts **6** and **7** were hampered by consistent appearance of significant amounts of phosphine oxide after consumption of the substrate.

Discussion

Overall, there are striking similarities between reduction with gaseous hydrogen and transfer hydrogenation in the present context of itaconate reduction. The two systems yield similar optical inductions,[4] diastereoselective reduction of **4a** yields mainly **10a**,[19] no *E*–*Z* isomerization is observed,[13b] and the two hydrogen atoms are delivered via cis-addition.[13] These findings, together with the easy "switch" from transfer hydrogenation to hydrogenation, suggest a common intermediate for the two reactions. It was already postulated earlier[4b] that oxidative addition of hydrogen could be bypassed in transfer hydrogenation via oxidative addition of formic acid and subsequent decarboxylation, yielding the key intermediate [Rh(diphosphine)(substrate)(H)H]$^+$ according to route **B** in eq 4. The present results confirm this very tempting proposal to a certain extent, but nevertheless some modifications are necessary in order to explain all experimental data.

The first question to be answered about the mechanism of any transfer hydrogenation reaction is whether it proceeds via direct hydrogen transfer or via intermediate evolution of free molecular hydrogen. Both possibilities are described in the literature for transfer hydrogenations using formic acid.[24] The decomposi-

(18) Alcock, N. W.; Brown, J. M.; Conn, A. D.; Taylor, R. J. Publication in preparation.

(19) (a) Brown, J. M. *Angew. Chem.* **1987**, *99*, 169; *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190. (b) Brown, J. M.; Cutting, I.; James, A. P. *Bull. Soc. Chim. Fr.* **1988**, 211.

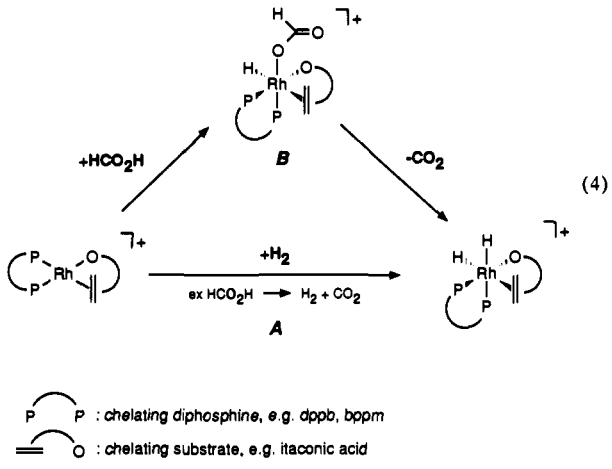
(20) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(21) (a) Parker, D.; Taylor, R. J. *Tetrahedron* **1988**, *44*, 2241. (b) Fulwood, R.; Parker, D.; Ferguson, G.; Kaltner, B. *J. Organomet. Chem.* **1991**, *419*, 269.

(22) Similar amine complexes were recently reported: Inoue, S.; Takaya, H.; Tani, K.; Otsuka, S.; Sato, T.; Noyori, R. *J. Am. Chem. Soc.* **1990**, *112*, 4897.

(23) Oxygen, *trans* to phosphorus induces in general coupling constants J_{RhP} between 190 and 220 Hz. For related examples with an η^2-carboxylate moiety see: (a) Korgsrud, S.; Komiya, S.; Ito, T.; Ibers, J. A.; Yamamoto, A. *Inorg. Chem.* **1976**, *15*, 2798. (b) Schäfer, M.; Wolf, J.; Werner, H. *J. Chem. Soc., Chem. Commun.* **1991**, 341.

(24) For direct transfer see: (a) Bar, R.; Sasson, Y.; Blum, J. *J. Mol. Catal.* **1984**, *26*, 327. For free H_2 see: (b) Watanabe, Y.; Ohta, T.; Tsuji, Y. *Bull. Chem. Soc. Soc. Jpn.* **1982**, *55*, 2441. (c) Khai, B. T.; Arcelli, A. *J. Organomet. Chem.* **1986**, *309*, C63.



(4)

tion/hydrogenation pathway (route A in eq 4) seems not unlikely for the rhodium-catalyzed transfer hydrogenation with formic acid, as the decomposition of HCO_2H to H_2 and CO_2 is known to be catalyzed by rhodium complexes.[25] However, this mechanism appears not to be operating in the rhodium-catalyzed transfer hydrogenation of itaconic acid (**1**) with HCO_2H/NEt_3. The cleavage of the C–H bond of formic acid is clearly demonstrated to be the rate-limiting step in this reaction by a primary kinetic isotope effect $k_H/k_D = 3.1$ on replacing this hydrogen atom by deuterium. This value is in excellent agreement with the isotope effects found in enzymatic decarboxylation of formic acid[26] and other reactions where C–H bond cleavage of formic acid is rate determining.[27] Hydrogen transfer must therefore be a fast process compared to formic acid decomposition. Hydrogenation with gaseous hydrogen is, however, much slower than transfer hydrogenation under identical reaction conditions. Furthermore, hydrogen uptake does not start before carbon dioxide evolution has ceased, if transfer hydrogenation of substrate **1** is carried out with less than 1 equiv of formic acid under a hydrogen atmosphere. The participation of free molecular hydrogen may be ruled out for the transfer hydrogenation of substrate **1** on the basis of these results. Additional evidence comes from the fact that only chiral phosphines forming six- or seven-membered chelate rings around the metal are suitable ligands for transfer hydrogenation,[4a-d] whereas five-ring ligands are very effective in asymmetric hydrogenation with H_2.[2] One of several possible explanations for this finding is the assumption that formation of an intermediate [Rh(diphosphine)(substrate)(H)H]$^+$ via decarboxylation of a formate species is blocked in transfer hydrogenation if the chelate ring around the rhodium is too rigid.

The kinetics of transfer hydrogenation of (*E*)-phenylitaconic acid (**3**) differ considerably from those observed with **1**, as might be expected for reduction of a weakly binding trisubstituted olefinic bond.[2] The first-order rate dependence in substrate and the absence of an isotope effect indicate that C–H cleavage is no longer rate limiting with substrate **3** and, therefore, more decomposition of formic acid takes place than would be necessary for reduction. Subsequently an appreciable amount of free molecular hydrogen must be present in solution at advanced stages of reaction and it cannot be ruled out completely that it will participate in the reduction. Nevertheless, this seems rather unlikely in light of the results obtained with substrate **1**.

It is seen from these results that oxidative addition of molecular hydrogen to a rhodium complex of type [Rh(phosphine)(substrate)]$^+$ (route A in eq 4) does not play a key role in transfer hydrogenation of itaconates. This is further emphasized by the results of kinetic resolution experiments using β-methylitaconic acid (**4a**). The single enantiomers of β-methylitaconic acid (**4a**) show a kinetic behavior identical to that of **1**, and participation of free molecular hydrogen may be ruled out following the above arguments. Furthermore, if the hydrogen addition would be identical in hydrogenation and transfer hydrogenation, kinetic resolution of racemic β-substituted itaconic acid derivatives *rac*-**4** should also proceed in an identical or at least closely related fashion. There are, however, clearly some differences between the two cases, as delineated below.

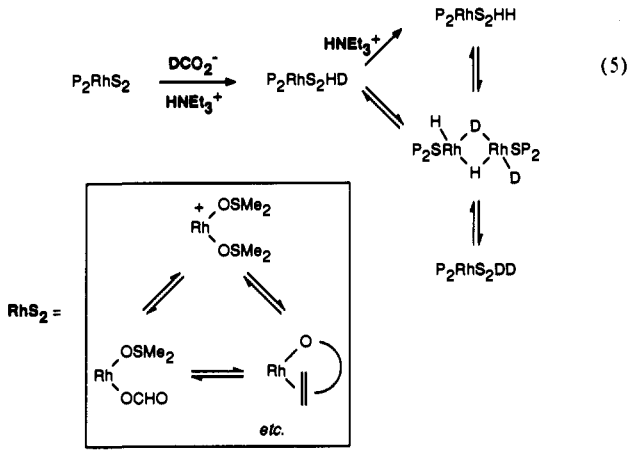
The hydrogenation of *rac*-**4a** or its dimethyl ester *rac*-**4b** with gaseous hydrogen in the presence of a chiral rhodium catalyst leads to kinetic resolution; i.e., one enantiomer of the racemic starting material reacts preferentially, the other one being enriched during the course of reaction.[18,19] The overall selectivity in kinetic resolution of *rac*-**4b** is determined by two independent factors: (a) the difference in binding constant of the two enantiomers to the chiral catalyst and (b) the difference in reactivity of the resulting diastereomeric complexes.

In the kinetic resolution of **4b** in methanol with [Rh(DIPAMP[28])]$^+$ complexes using gaseous hydrogen, the two factors work in opposite directions: a 10-fold unfavourable difference in binding constant is counteracted by a 100-fold difference in rate.[18,19] Thus the overall selectivity factor *S* of ca. 10 is mainly determined by the difference in reaction rates of the two diastereomeric complexes [Rh(DIPAMP)(olefin)]$^+$ toward H_2, according to parallels with the mechanism of hydrogenation of dehydroamino acids with the same catalyst.[8,18]

Kinetic resolution during the transfer hydrogenation of acid *rac*-**4a** with HCO_2H/NEt_3 and the catalyst **8** manifests distinct behavior, however. Since this substrate reacts rapidly, resembling itaconic acid (**1**) in its kinetic behavior, formate decomposition is involved in the rate-determining step. The rate of this step is little influenced by reactant binding, since the (*R*)- and (*S*)-enantiomers of **4a** react at rates within a factor of 2. At the same time, there is a substantial discrimination between these enantiomers during transfer hydrogenation of the racemate, since the overall selectivity of catalytic turnover favors the (*S*) enantiomer by a factor of 18. This requires that discrimination occurs *between* the formation of a rhodium hydride species and the transfer of hydride to coordinated olefin to form a rhodium alkyl; reversibility of substrate binding to the intermediate rhodium hydride complex is permissible.

Further mechanistic information comes from the reduction of (*E*)-phenylitaconic acid (**3**) carried out with monodeuterated formic acids DCO_2H and HCO_2D (Table I). Extensive isotopic exchange is observed; in the former case, product with a total deuterium content of 0.45–0.49 atoms is formed, and in the latter, it possesses 1.31–1.52 atoms of deuterium. Within experimental error there is no discrimination between C_α and C_β of the olefin as the site for deuterium transfer. Since the activation of formic acid occurs early in the catalytic cycle, these results require that a complex with a [Rh(H)D] entity is formed from either isotopomer in which the hydrogen and deuterium can site exchange faster than their transfer to coordinated substrate. Exchange with external hydrogen (DCO_2H) or deuterium (HCO_2D) is in competition with this isomerization, but the H-transfer step of reduction occurs before there is complete equilibration with the external pool, as otherwise the isotopomers **9a** and **9d** should be formed almost exclusively from DCO_2H and HCO_2D, respectively. In addition, a second intermolecular exchange mechanism is necessary to explain the double exchange (i.e. the formation of **9d** starting with DCO_2H and **9a** starting with HCO_2D), which consistently occurs even at a very early stage of the reaction (<30% conversion). Internal scrambling of formic acid, which could also lead to double exchange, was shown to be much too slow to account for the observed amounts of **9a** and **9d**. A possible pathway for the observed exchange processes is shown in eq 5. Dimeric hydride-bridged rhodium phosphine complexes and their deuterium-exchange reactions as postulated in eq 5 are well described

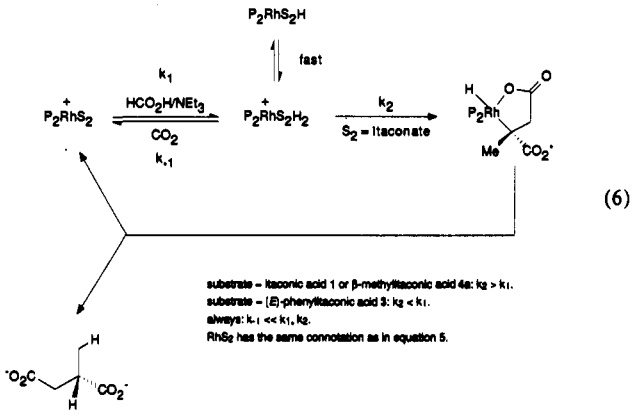
(25) Strauss, S. H.; Whitmire, K. H.; Shriver, D. F. *J. Organomet. Chem.* **1979**, *174*, C59.
(26) O'Leary, M. H. *Acc. Chem. Res.* **1988**, *21*, 450.
(27) Ruppert, R.; Herrmann, S.; Steckhan, E. *J. Chem. Soc., Chem. Commun.* **1988**, 1150.
(28) DIPAMP is 1,2-bis((*o*-anisylphenyl)phosphino)ethane: Knowles, W. S.; Sabacky, M. A.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567.



(5)

in the literature.[29] Alternatively, the formation of rhodium polyhydride species from further reaction of rhodium hydrides with formate cannot be ruled out completely as a possible source of double exchange.[30] It seems, however, rather unlikely, as the participation of polyhydrides has never been observed in rhodium-catalyzed hydrogenation. The similarity of hydrogenation with H_2 and HCO_2H in DMSO is emphasized by the extent of exchange observed when reduction of **3**-d_2 with H_2 was carried out in the presence of NEt_3. In this case an additional scrambling due to equilibration of H_2 with D^+ to form H_2, HD, and D_2 must be considered.[31]

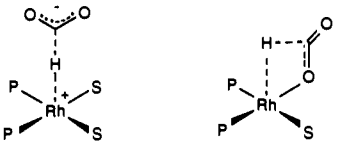
Taken together, these results are most consistent with the catalytic cycle outlined in eq 6. In the first step, activation of formic acid occurs to produce a rapidly equilibrating dihydride in proton–proton exchange with the reactant pool. The additional



(6)

ligands on rhodium are the diphosphine, assumed to be fixed, and solvent or reactant molecules, probably in dynamic equilibrium (eq 5). Coordination of NEt_3 seems rather unlikely, as it should be present almost exclusively in its protonated form under the reaction conditions. Hydride transfer occurs subsequently and is presumed to give a transient rhodium alkyl hydride which rapidly eliminates product by analogy with the mechanism of hydrogenation.[8] The dihydride intermediate [Rh(diphosphine)(substrate)(H)H]$^+$ required in the present case of transfer hydrogenation has been widely inferred in asymmetric hydrogenation with H_2 but was never observed there, despite much effort.[8]

An appraisal of the mechanism of activation of formic acid by rhodium remains to be considered. In the ^{31}P NMR studies reported here, evidence for coordination of formate to possible intermediates of the catalytic cycle was sought unsuccessfully, although a hitherto unknown species derived from HCO_2NH_4 and [Rh(dppe)(MeOH)$_2$]$^+$ was observed. It is thus not possible to decide whether hydride transfer from formate to rhodium occurs within the coordination sphere or externally as schematically represented below.



Possible pathways of hydride transfer from formate to rhodium

In both cases stereoelectronic considerations must be important. The intermolecular pathway should occur by a linear or near-linear hydride transfer orthogonal to the square plane by analogy with hydride transfer processes whose energy surfaces have been investigated by ab initio MO calculations.[32] The intracomplex route involves hydride transfer from an η^1-formate moiety to give a transiently coordinated CO_2 molecule. Both this and the reverse reaction have been extensively studied theoretically[33] and experimentally.[25,30,34] Alternatively, intramolecular hydride transfer may occur via decarboxylation of a formato bridge to yield a dimeric hydrido-bridged rhodium complex similar to the one postulated in eq 5. The reverse reaction, insertion of CO_2 into a rhodium hydride bridge, is documented.[35]

Conclusion

The results presented in this study strongly suggest that transfer hydrogenation using HCO_2H/NEt_3 (5:2) in the presence of rhodium catalysts proceeds via an intermediate [Rh(substrate)(P$_2$)(H)H]$^+$, which is identical or at least very similar to the key intermediate in hydrogenation using gaseous hydrogen and similar catalysts. The findings rule out the formation of this intermediate through oxidative addition of free molecular hydrogen. The results are, however, in agreement with an alternative two-step pathway (eq 6). A rhodium hydride species is formed via hydride transfer from formate to rhodium without the necessity for direct substrate involvement. This rhodium hydride intermediate has—at least for the weakly binding substrate (*E*)-phenylitaconic acid (**3**)—a lifetime sufficiently long for extensive scrambling with the proton pool and intermolecular proton exchange before hydride transfer to substrate occurs and the product is eliminated to regenerate the rhodium species catalytically active in formate decomposition.

The most significant feature of these results is that the same stereochemical discrimination is observed in hydrogenation and transfer hydrogenation of itaconic acid (**1**) and its β-methyl analogue **4a**, although the H-addition step is rate limiting with H_2 but occurs subsequent to the rate-determining step in transfer hydrogenation. This finding emphasises a simple factor often neglected in discussions of rhodium-catalyzed asymmetric hydrogenation. Enantioselectivity arises because the relative transition state energies for the step which fixes the stereochemistry of the H_2 addition are different. *It is not necessary for the H-transfer step to be rate determining.* The fact that the two

(29) (a) Yoshida, T.; Okano, T.; Thorn, D. L.; Tulip, T. H.; Otsuka, S.; Ibers, J. A. *J. Organomet. Chem.* **1979**, *181*, 183. (b) Fryzuk, M. D. *Can. J. Chem.* **1983**, *61*, 1347. (c) Fryzuk, M. D.; Piers, W. E.; Einstein, F. W. B.; Jones, T. *Can. J. Chem.* **1989**, *67*, 883. (d) Fryzuk, M. D.; Jones, T.; Einstein, F. W. B. *Organometallics* **1984**, *3*, 185.

(30) Yoshida, T.; Thorn, D. L.; Okano, T.; Ibers, J. A.; Otsuka, S. *J. Am. Chem. Soc.* **1979**, *101*, 4212.

(31) (a) Ahmad, N.; Robinson, S. D.; Uttley, M. F. *J. Chem. Soc., Dalton Trans.* **1972**, 843. (b) Ashby, M. T.; Halpern, J. *J. Am. Chem. Soc.* **1991**, *113*, 589.

(32) For ab initio 6-31+G calculations on hydride transfer between HCO_2^- and CO_2, where the C–H–C angle is 180°, see: Jones, J. P.; Urbaner, J. L. *J. Comput. Chem.* **1991**, *12*, 1134. Hillier, I. H.; Smith, S.; Mason, S. C.; Whittleton, S. N.; Watt, C. I. F.; Willis, J. *J. Chem. Soc., Perkin Trans. II* **1988**, 1345. Other calculations on H-transfer between C-atoms: Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 906 and 2226.

(33) (a) Dedieu, A.; Bo, C.; Ingold, F. In *Enzymatic and Model Carboxylation and Reduction Reactions for Carbon Dioxide Utilization*; Aresta, M., Schloss, J. V., Eds.; NATO *ASI Series C, Vol. 314*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1990, pp 23–42. (b) Bo, C.; Dedieu, A. *Inorg. Chem.* **1989**, *28*, 304.

(34) (a) Slater, S.; Wagenknecht, J. H. *J. Am. Chem. Soc.* **1984**, *106*, 5367. (b) Darensbourg, D. J. In ref 33a, pp 43–64. (c) Burgemeister, T.; Kastner, F.; Leitner, W. Submitted for publication.

(35) (a) Kubiak, C. P.; Woodcock, C.; Eisenberg, R. *Inorg. Chem.* **1982**, *21*, 2119. (b) Bulch, A. L.; Talyathan, B. *Inorg. Chem.* **1977**, *16*, 2840.

diastereomeric substrate complexes have the energetic preference opposite to that of the two transition states in rhodium-catalyzed asymmetric hydrogenation—a widely discussed factor—is interesting, but accidental.

Experimental Section

General Remarks. All manipulations involving organometallic compounds were done under an argon or nitrogen atmosphere using standard Schlenk techniques. DMSO, DMSO-d_6, and NEt_3 were dried by distillation from 3-Å molecular sieves and stored under argon. Formic acid (96%, Aldrich) was distilled from anhydrous $CuSO_4$.[36] The following commercial products were used without further purification: itaconic acid (**1**) (Fluka), DCO_2D (>99.5% D, Merck), MeOD (>99.5% D, Aldrich), dppb, dppe (Strem Chemicals), and (*R*)- and (*S*)-BINAP (APIN Chemicals). The compounds (*E*)-phenylitaconic acid (**3**),[12] bppm,[37] $[Rh(cod)Cl]_2$,[38] $[Rh(nbd)Cl]_2$,[39] and $[Pt(C_2H_4)\{(S,S)\text{-DIOP}\}]$[21a] and complexes $[Rh(nbd)(diphosphine)][CF_3SO_3]$[39] were prepared according to literature procedures. Transfer hydrogenations and hydrogenations were carried out as described elsewhere.[4,39] FT-NMR spectra were recorded on Varian Gemini 200 (^1H NMR), Bruker WM250 (^1H and ^{31}P NMR), and Bruker WM500 (^1H, ^{13}C, and ^{31}P NMR) spectrometers.

Kinetic Studies. The samples for kinetic measurements were prepared as previously described.[4a] NMR spectra (250 or 500 MHz) were automatically recorded at constant time intervals.

Labeling Studies. The following precautions were taken to exclude traces of moisture during transfer hydrogenations of **3** and **3**-d_2 using deuterated formic acid derivatives: All glassware was thoroughly dried by treatment with chlorotrimethylsilane and removal of the volatiles at 10^{-3} Torr. Freshly distilled reagents and solvents were used, and **3** was dried for 1 day at 10^{-3} Torr. **3**-d_2 was obtained by stirring **3** (825 mg, 4.0 mmol) in MeOD (5 mL) for 5 h, evaporating the solvent, and repeating the procedure three times. HCO_2D/NEt_3 was prepared by mixing a solution of HCO_2H (4 mL) in D_2O (5 mL) with a mixture of NEt_3 (6 mL) and D_2O (5 mL). The water was distilled off at atmospheric pressure over a short Vigreux column, D_2O (10 mL) was added to the residue, and the procedure was repeated three times. The last time, the residue was fractionalized at 12 Torr. The ratio of HCO_2D to NEt_3 in the fraction boiling at 98–100 °C was 3.8:2 by ^1H NMR. DCO_2H/NEt_3 (3.6:2) was prepared in a similar way starting from DCO_2D and H_2O.[17]

Simultaneously deuterium- and proton-decoupled $^{13}C\{^1H,^2H\}$ NMR spectra were recorded unlocked at 125.7 MHz. Deuterium decoupling was achieved by supplying the appropriate frequency through the lock channel of the probe head using a home-built device.[15]

Preparation of *rac*-Dimethyl β-Methylitaconate (*rac*-4b). In a 1-L three-necked round-bottom flask equipped with a nitrogen inlet, a dropping funnel, and an overhead stirrer, a solution of methyl (diethylphosphono)acetate (40.0 g, 0.19 mol) in dry tetrahydrofuran (100 mL) was added dropwise to a slurry of NaH (8.00 g, 60% in mineral oil, 0.20 mol) in 300 mL of the same solvent over a period of 1 h at room temperature. The mixture was stirred for 1.5 h, and a slightly yellow, almost clear solution was obtained. A solution of methyl D,L-bromopropionate (32.0 g, 0.19 mol) in tetrahydrofuran (50 mL) was added dropwise over a period of 30 min and the mixture stirred overnight. The NaBr precipitate was removed by filtration over Celite, and NaH (6.50 g, 60% in mineral oil, 0.16 mol) was added as a solid in small portions under nitrogen. After the reaction mixture was stirred for 1 h, a slurry of paraformaldehyde (4.50 g, 0.15 mol) in tetrahydrofuran (50 mL) was added in small portions using a Pasteur pipet. After the addition was complete, the mixture was stirred for another 1.5 h and the solvent was then removed under reduced pressure. The residue was taken up in Et_2O (300 mL) and water (300 mL). The layers were separated, and the organic layer was washed with two 200-mL portions of water. The combined water layers were extracted three times with diethyl ether (200 mL). After the ether extracts were dried over $MgSO_4$, the solvent was removed under reduced pressure. Fractionalized high-vacuum distillation over a short Vigreux column gave 17.2 g of a colorless liquid of boiling point 50–53 °C at 0.05 Torr. The material was 90% pure *rac*-dimethyl β-methylitaconate and contained 6% of dimethyl maleate and 4% of a second unknown impurity, according to GLC and ^1H NMR analysis. It was used without further purification in the following experiments. The yield was 60% of the theoretical amount and 45% based on the phosphono acetate. ^1H NMR (200 MHz, $CDCl_3$) δ 6.33 (s, 1 H), 5.71 (s, 1 H), 3.76 (s, 3 H), 3.68 (s, 3 H), 3.61 (q, 1 H, $^3J_{HH}$ = 7.2 Hz), 1.37 (d, 3 H, $^3J_{HH}$ = 7.2 Hz).

Preparation of *rac*-β-Methylitaconic Acid (*rac*-4a). The acid was obtained in 80% yield from **6** by treatment with 20% aqueous HCl for 6 h at 70 °C. Any contaminations of the crude product with dimethylmaleic anhydride were removed by washing with $CHCl_3$. ^1H NMR (200 MHz, acetone-d_6) δ 6.20 (s, 1 H), 5.70 (s, 1 H), 3.58 (q, 1 H, $^3J_{HH}$ = 7.4 Hz), 1.33 (d, 3 H, $^3J_{HH}$ = 7.4 Hz).

Preparation of Optically Pure (*R*)- and (*S*)-β-Methylitaconic Acid ((*R*)- and (*S*)-4a). *rac*-**4b** (2.03 g, 0.12 mol) in MeOH (10.0 mL) was hydrogenated in the presence of $[Rh(nbd)\{(R)\text{-BINAP}\}][CF_3SO_3]$ (52.0 mg, 53.8 μmol) as described in ref 39. Hydrogenation was stopped at a hydrogen uptake corresponding to 65–70% conversion by switching off the stirrer. The amount of hydrogenation was quickly cross checked by GLC (Carbowax 20m, 10%, 5′, 160 °C, retention times 282 s for **10b** and 366 s for **4b**), hydrogen and methanol were removed in vacuo, and the residue was distilled at 0.05 Torr in a Kugelrohr apparatus at 75 °C. The quantitatively obtained mixture of starting material and hydrogenation product was dissolved in diethyl ether (ca. 2 mL) and separated by preparative GLC (PEG 20m, 15%, 30′, 190 °C, 250 μL each run, retention times 21 min for **10b** and 25 min for **4b**). Thus (*S*)-**4b** (385 mg, 19%) was isolated with an optical rotation of $[\alpha]^{20}_D$ = +15.3° (*c* 1.87 Et_2O).[40] The (*R*) enantiomer {344 mg, 16%, $[\alpha]^{20}_D$ = −16.7° (*c* 2.05, Et_2O)} was prepared identically using the (*S*)-BINAP-derived catalyst. The acids were obtained from these samples as described for *rac*-**4a**. The optical rotations were $[\alpha]^{20}_D$ = +18.1° (*c* 0.97, H_2O) and $[\alpha]^{20}_D$ = −19.1° (*c* 0.97, H_2O) for (*S*)- and (*R*)-**4a**, respectively.[40]

Kinetic Resolution of *rac*-β-Methylitaconic Acid (*rac*-4a) by Transfer Hydrogenation. *rac*-**4a** (432 mg, 3.00 mmol), $[Rh(nbd)Cl]_2$ (5.70 mg, 12.4 μmol), and bppm (16.5 mg, 29.8 μmol) were dissolved in DMSO (8.20 mL) and stirred for 10 min at 35 °C. Triethylamine (1.00 mL, 7.15 mmol) was added followed by formic acid (0.60 mL, 15.9 mmol). The reaction was quenched after 21 min by addition of 10% aqueous HCl (10 mL) and filtered through Celite. The Celite was washed with water (5 mL), and the combined filtrates were extracted for 12 h in a liquid/liquid extractor with diethyl ether. ^1H NMR spectroscopic analysis of the crude product revealed a conversion of 70%. An identical experiment quenched after 15 min lead to 54% hydrogenation.

Determination of the Optical Purity of β-Methylitaconic Acid (4a). DMSO impurities were removed from the crude product described above at 10^{-3} Torr and 40 °C. The mixture was then esterified with diazomethane and the product distilled at 10^{-3} Torr in a Kugelrohr apparatus at 75 °C. A sample of the obtained mixture of **4b** and **10b** (40 μL for 70% hydrogenation, 30 μL for 54%) was injected by syringe into a solution of $[Pt\{(S,S)\text{-DIOP}\}(C_2H_4)]$[21] (12.7 mg, 18.3 μmol) in tetrahydrofuran (1.00 mL). The solution was stirred for 10 min at ambient temperature before the solvent was evaporated. The residue was taken up in C_6D_6 for ^{31}P NMR spectroscopic analysis according to ref 21. Detailed analysis of the ^{31}P NMR spectrum will be reported elsewhere.[18]

Acknowledgment. We wish to thank the Stiftung Volkswagenwerk and the SERC for financial support and Johnson-Matthey Ltd. for a generous loan of $RhCl_3 \cdot nH_2O$. W.L. wishes to thank the Stiftung Volkswagenwerk for an exchange scholarship. Thanks are due to Dr. Susan Armstrong and Dr. Patrick Guiry for a critical reading of the manuscript. We are indebted to one of the reviewers for very helpful comments and for sharpening the tenor of discussion. Many of the NMR experiments presented in this paper would not have been possible without the dedicated help of the late Dr. Andrew E. Derome. His help and the support of the staff of the NMR facilities at Oxford and Regensburg are gratefully acknowledged.

(36) It is interesting to note that the azeotrope HCO_2H/NEt_3 (5:2), obtained by mixing the two components or purchased from Merck, cannot be dried by this method, as it reduces Cu^{2+} to metallic Cu.

(37) Baker, G. L.; Fritschel, S. J.; Stille, J. R.; Stille, J. K. *J. Org. Chem.* **1981**, *46*, 2954.

(38) Fehlhammer, W. P.; Herrmann, W. A.; Öfele, K. In *Metallorganische Komplexverbindungen*; Brauer, G., Ed.; Enke Verlag: Stuttgart, Germany, 1981, Vol. III, p 1799.

(39) Brown, J. M.; Evans, P. L.; James, A. P. *Org. Synth.* **1989**, *68*, 63.

(40) These values replace those quoted in ref 18b.