A kinetic treatment of heterogeneous enantioselective catalysis

Mark A. Keane[†]

Department of Chemical Engineering, University of Leeds, Leeds, UK LS2 9JT

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Kinetic data are reported for the liquid phase racemic hydrogenation and enantioselective hydrogenation of methyl acetoacetate (MAA) over Ni/SiO₂ and tartaric acid (TA)-treated Ni/SiO₂, respectively, conducted in a slurry-type reactor. The contribution of mass transport to the overall reaction rate was considered by studying the effects of varying a number of process variables, such as catalyst particle size, catalyst weight, stirring speed and reaction temperature. Reaction conditions are identified wherein contributions due to mass transfer are slight and the hydrogenation proceeds under surface kinetic control. Reaction orders with respect to MAA, hydrogen and the product, methyl 3-hydroxybutyrate (MHB), were determined and activation energies over the temperature range $318 \le T \le 383$ for the bare and TA-modified supported nickel are presented. The reaction rates were observed to pass through maxima as the MAA concentration was increased. The rate data are fitted to a Langmuir–Hinshelwood model where both reactants adsorb competitively on the surface; the experimentally determined rates agree to $\pm 15\%$ with the values predicted by the kinetic model. Modification of the catalyst with TA not only induced enantioselectivity but also promoted the rate of hydrogenation and this effect is discussed in terms of surface interactions and the proposed kinetic model. The ratio of MAA concentration in bulk solution to that at the catalyst surface under reaction conditions is examined and the dependence of enantioselectivity, in the case of the TA-treated sample, on MAA concentration is presented.

The surge in the worldwide market for single-enantiomer forms of chiral drugs has stimulated a flurry of activity as drug companies, fine-chemical/chirotechnology firms and academic research groups explore new ways to make singleisomer compounds.¹ Biocatalysis employing enzymes has emerged as a possible route for chiral molecule synthesis²⁻⁴ but the use of enzymes in environments differing significantly from physiological conditions, as is the case in industrial processes, has limited the commercial applications.^{5,6} The viability of heterogeneous enantioselective catalysis, employing inorganic materials, has not yet been fully explored and research⁷⁻⁹ has largely focused on two systems, namely the asymmetric hydrogenation of ethyl pyruvate and methyl acetoacetate (MAA) using cinchonidine-modified platinum and tartaric acid (TA)-modified nickel catalysts, respectively. The latter reaction involves an asymmetric addition of hydrogen to generate methyl 3-hydroxybutyrate (MHB), the (R)-(-)form of which is an important intermediate in the synthesis of the carbonic anhydrase inhibitor MK-0507 used in the treatment of glaucoma.¹⁰ Conventional nickel catalysts possess no inherent chirality and the bare nickel metal generates a racemic product.^{11–15} A chiral environment is achieved by treating the activated catalysts with an optically pure reagent or catalyst modifier.^{14–19} Such a modification has been shown not only to induce enantioselectivity but also to increase the overall reaction rate generated by the nickel^{17,18} and platinum²⁰⁻²² systems. Variations in reaction conditions have been related to the ultimate enantioselectivity and the effects of such changes on the reaction rate have, to a great extent, remained unreported. The concentration of MHB produced in a batch liquid phase system has, however, been shown to increase with an increase in reaction time7,23 and temperature^{7,10} and to inhibit the progress of the reaction at high concentrations.²⁴⁻²⁶ The effect of increasing the substrate concentration, the presence of metal poisons and the role of the reaction solvent have also been considered.²⁶⁻³¹ Reactions over a range of supported and unsupported nickel catalysts at temperatures in the range $313 \leq T/K \leq 423$ have been reported to yield a zero or near zero dependence on

hydrogen concentration,^{32,33} a first order³² or partial³³ (0.3) dependence on MAA concentration and apparent activation energies^{12,32,33} in the range 44-66 kJ mol⁻¹. Although the hydrogenation of MAA and ethyl acetoacetate (EAA) have now been reported for a range of unsupported nickel systems,^{7–9,14,34,35} and nickel supported on amorphous^{14-19,33,34,36-38} and crystalline¹¹⁻¹³ carriers, the reaction mechanism is still not fully understood. In this paper a kinetic model is proposed that accounts for the observed rate dependence on MAA concentration in the absence of strong mass transport limitations for both an unmodified and TA-modified Ni/SiO₂ catalyst.

Experimental

An 11.6 wt.% Ni/SiO₂ catalyst was prepared by the impregnation of a non-porous microspheroidal Cab-O-Sil 5 M silica with nickel nitrate to incipient wetness as described in detail previously.39 The nickel loading was determined by atomic absorption (Perkin-Elmer 360 AA spectrophotometer) using the experimental procedure outlined elsewhere^{15,17} and the water content of the catalyst precursor was measured by thermogravimetry.⁴⁰ The hydrated supported precursor was reduced, without a precalcination step, by heating in a 150 cm³ min⁻¹ stream of dry hydrogen at a fixed rate of 5 K min⁻¹ to a final temperature of 723 ± 2 K which was maintained for 18 h. The temperature-programmed reduction profile was obtained as discussed previously.¹⁷ The reduced catalyst was then flushed in a purified stream of nitrogen at 200 cm³ min⁻¹, cooled to room temperature and used directly in the 'unmodified' state to promote the hydrogenation of MAA, adopting the procedure outlined below. Alternatively, the cooled, activated sample was 'modified' by contacting with a 0.01 mol dm⁻³ aqueous solution of R-(+)-TA (TA/Ni molar ratio = 0.8). The pH of the aqueous modifier was preadjusted to the isoelectric point for TA (pH = 5.1) with 1 and 0.01 mol dm⁻³ NaOH and the resultant solution was thoroughly purged with helium to remove any entrapped air bubbles. The solid catalyst/aqueous modifier suspension was kept under constant agitation at 600 rev min⁻¹ (Stuart Scientific SM26 Ceramic Magnetic Digital Stirrer/Hotplate) for 2 h

[†] E-mail address: chemaak@leeds.ac.uk

HPLC. After modification, the catalyst was decanted and washed with deionized water $(1 \times 25 \text{ cm}^3)$, methanol $(2 \times 25 \text{ cm}^3)$ cm³) and *n*-butanol (2×25 cm³); the reagents used in the washing step were thoroughly degassed in helium. Both the modified and unmodified samples were stored in n-butanol prior to use. The nickel content of the post-modifier solution, resulting from acid leaching of the catalyst, was determined by AA spectrophotometry.^{15,17} Nickel metal dispersions, before and after modification, were determined by carbon monoxide chemisorption^{15,17} at 273 K, assuming a nickel surface atom to adsorbed carbon monoxide stoichiometry of 2:1.41 The amount of TA adsorbed was determined by analysing the preand post-modification solutions by HPLC (Spectra-Physics) as outlined elsewhere.15,17,19 The liquid phase hydrogenation of MAA in n-butanol was conducted over the temperature range $318 \leq T/K \leq 383$

(± 2). The apparatus and procedure have been described in some detail previously.^{15,17,18} The MAA/*n*-butanol molar ratio was varied (in the range 4×10^{-3} -2.0) but the total volume was maintained at 50 cm³ and a 60 cm³ min⁻¹ stream of dry hydrogen was bubbled through the suspension. The possible contribution of mass transport to the overall reaction rate was monitored by (a) varying the weight of catalyst to give MAA/Ni molar ratios in the range 20–400, (b) using six separate batches of catalysts with particle diameters in the overall range 50–1680 µm and (c) varying the stirring speed in the range 100–1000 rev min⁻¹. The extent of hydrogenation was determined by HPLC using a Pirkle type 1A 5 µ reversible column (250 × 4.6 mm) with a 10% IPA–90% hexane mixture as the mobile phase. Optical yields (O.Y.) were determined from measurements of optical rotation (AA-10 Automatic Digital Polarimeter) using the equation,

at 298 ± 1 K. The tartaric acid was of AnalaR grade and the

prepared solutions were found to be better than 99% pure by

$$O.Y. = \frac{\left[\alpha\right]_{D}^{T}}{\left[\alpha\right]_{0}^{T}} = \frac{100\alpha}{\left[\alpha\right]_{0}^{T}lc}$$
(1)

where $[\alpha]_D^T$ is the specific rotation of the product solution measured at the sodium D-line and temperature $T = 293 \pm 3$ K, $[\alpha]_D^T$ is the specific rotation of the pure enantiomer under the same conditions $[-22.95^\circ$ for R-(-)-MHB], α is the measured optical rotation, l is the path length (20 cm) of the cell and c is the solute concentration. In this paper, optical selectivity is expressed in terms of enantiomeric excess (e.e.) or percent optical purity which, in the case of an excess of R-(-)-MHB, is given by,

%e.e. =
$$100 \frac{([R-(-)-MHB] - [S-(+)-MHB])}{([R-(-)-MHB] + [S-(+)-MHB])}$$
 (2)

In many cases the reaction was repeated under identical conditions and all the rate and enantioselectivity data are plotted to illustrate reproducibility.

Results and Discussion

Catalyst characterization

The results reported in this paper refer to the treatment of an 11.6 wt.% Ni/SiO₂ catalyst with R-(+)-TA which yielded R-(-)-MHB as the predominant product. Replacement of the modifier by its antipode has been shown^{15,17,19} to generate identical values of enantiomeric excess but with a reversal of the sign while modification with optically inactive meso-TA yielded virtually racemic (e.e. < 2%) product mixtures. The pertinent physical characteristics of the catalyst precursor, the activated unmodified and activated modified material are given in Table 1. The temperature-programmed reduction profile¹⁷ is characterized by four peaks: a small ill-defined peak at $T_{\text{max}} = 528$ K which has been ascribed⁴² to an endothermic phase transition from rhombohedral to cubic NiO which occurs simultaneously with reduction; a minor (573 K) and a major (610 K) peak due to the reduction of weakly and strongly support-interacting NiO to $Ni^0 + H_2O$; a broad peak with $T_{\text{max}} = 693$ K due to the more difficult reduction of a surface nickel silicate species. The total hydrogen consumption in the activation step exceeded the theoretical value for a complete reduction of the nickel content and the excess may be attributed to a spillover of hydrogen from the nickel metal which is held on the silica carrier. The nickel metal dispersion unmodified reduced catalyst, expressed of the as $(Ni_{surface}/Ni_{total}) \times 100\%$, equals 17%. The supported nickel particle size is estimated to equal 5.9 nm from the relationship⁴³ d = 101/D, where D is dispersion and d represents the surface-weighted-average crystalline diameter assuming (spherical) particles ≤ 1 nm to be 100% dispersed. Transition electron microscopic analysis has revealed a broad particle size distribution with supported particles of up to 20 nm in diameter detected.¹⁷ The dispersion or dimension of the supported nickel crystallites in the unmodified catalyst remained unchanged after repeated catalysis cycles. It has been demonstrated elsewhere^{14,15,17–19,34} that the generation of enantioselective sites is a corrosive process and results in the extraction of nickel atoms from the metal lattice. Under the stated modification conditions 29% of the initial nickel content was leached into solution. In TA treatment the smaller nickel particles were preferentially removed.^{15,17} with a consequent shift in the average supported crystallite diameter to the higher value of 8.4 nm. It is evident that the composition of the modified catalyst differs appreciably from that of the freshly reduced catalyst. In this kinetic study, the reaction rates are quoted per gram of supported nickel which takes into account the loss of nickel during the modification step. The treated Ni/SiO₂ sample retained 1.3×10^{19} TA molecules per gram of catalyst which represents a fractional coverage (θ_{TA}) of 0.32 of the available surface nickel metal.

 Table 1
 Physical characteristics of the catalyst precursor and the activated unmodified and TA-modified material

precursor	support Ni (wt.%) H ₂ O (wt.%)	Cab-O-Sil 5M SiO ₂ (194 m ² g ⁻¹) 11.6 8.0
activated unmodified catalyst	$\begin{array}{c} T_{\rm red}{}^{a}\!/{\rm K} \\ {\rm H_2\ consumption}/10^{-2}\ {\rm dm^3\ g^{-1}} \\ {\rm Ni^0\ dispersion\ (\%)} \\ d^{b}/{\rm nm} \end{array}$	528, 573, 610, 693 5.7 17 5.9
activated TA-modified catalyst	Ni leached (%) Ni ^o dispersion (%) $d^{b/\text{nm}}$ $N_{\text{TA}}^{c}_{d}$ θ_{TA}^{d}	$29 \\ 12 \\ 8.4 \\ 1.3 \times 10^{19} \\ 0.32$

^{*a*} Temperature corresponding to a maximum in hydrogen consumption. ^{*b*} Average nickel particle diameter. ^{*c*} Number of TA molecules retained per gram of catalyst. ^{*d*} Fractional surface coverage by TA.

Mass transport limitations

The rate of a number of liquid phase reactions has been shown to be controlled by the transport of reactants and products in the bulk solution to and from the solid catalyst surface.44,45 Indeed, a number of workers29,33,37 have noted that MAA hydrogenation is limited, to varying degrees, by mass transport constraints and the observed reaction rate is a combination of reactant transport and catalytic activity. As part of a thorough kinetic study it is essential to ascertain the extent to which such physical processes control the rate of the overall reaction and to establish the reaction conditions wherein such rate limitations are negligible and the reactor is operating in the 'reaction-limited' regime. In this particular reactor configuration, hydrogen is bubbled through the MAA/ n-butanol solution which contains suspended solid catalyst particles and the gaseous reactant must overcome the following resistances which are viewed as acting in series: (i) H_2 must cross the gas film to reach the gas/liquid interface; (ii) H_2 must cross the liquid film to reach the main body of liquid; (iii) H₂ must cross the liquid film surrounding the catalyst particle to reach the solid surface; (iv) H₂ then reacts with MAA on the surface of the catalyst particle. Since pure hydrogen is used the gas phase resistance can be ignored but the relative resistance at the gas/liquid interface or at the surface of the catalyst particles must be determined.

In this study three established diagnostic criteria,44-48 stirring speed, catalyst particle size and catalyst weight, are used to gauge the contribution of mass transport resistance. A more effective agitation of the solution around the solid catalyst does not affect chemically controlled or surface-controlled processes but markedly increases diffusion rates in the bulk liquid.44,46 The influence of stirring speed on the observed reaction rate is illustrated in Fig. 1. The hydrogenation rate clearly responds to increased agitation of the MAA/n-butanol/ catalyst suspension which serves to extend the gas/liquid/solid interface and minimize the distance that a hydrogen molecule has to diffuse through the liquid phase in order to reach the catalyst surface. The rate is, however, essentially independent of stirring speed at values in excess of 600 rev min⁻¹. Singh et al.49 have examined the effect of bulk diffusion limitations in the enantioselective hydrogenation of ethyl pyruvate over dihydrocinchonidine-modified platinum and likewise observed a marked increase in rate on raising the agitation speed from 200 to 600 rev min⁻¹ but little dependence at higher stirring speeds. In a catalytic reaction where external mass transfer resistance is high, the reaction rate has been shown to be dependent on the catalyst particle shape and size.44,47,48,50,51



Fig. 1 The effect of stirring speed on the rate of MAA hydrogenation over the TA-modified (\blacktriangle) and unmodified (\blacksquare) Ni/SiO₂; T = 343 K; particle diameter = 75–125 µm; MAA/Ni molar ratio = 47–66. Inset: the variation of hydrogenation rate with the unmodified catalyst particle size; stirring speed = 800 rev min⁻¹.

The observed influence of catalyst particle diameter on reaction rate is shown in the inset to Fig. 1. In the size range 150-1680 µm the rate is proportional to particle diameter and mass transport limitations inhibit the progress of the reaction. As the particle size was decreased from 150 to 50 μ m the rate was largely unaffected which is indicative of a reaction operating within the kinetic control regime. Catalytic rate is directly proportional to the weight of catalyst for reactions controlled by the surface kinetics.^{44,48,50} Such a relationship, using the criteria set down by Roberts,⁴⁸ is illustrated in Fig. 2 where the variation in catalyst weight spans the MAA/Ni molar ratio range 20-400. It may be noted that the rates of hydrogenation are appreciably higher for the modified samples, an observation that is in direct conflict with earlier reports^{24,52,53} where the adsorption of TA on Raney nickel was viewed as inhibiting hydrogenation activity by occluding part of the metal surface. In recent studies, rate increases due to modification have, however, been reported for a number of asymmetric systems 17,18,20-22 and a possible source of such an enhancement is proposed in the kinetic model discussed below.

Kinetic model

The hydrogenation of MAA to MHB may be represented by the power equation

$$R = k[H_2]^a[MAA]^b[MHB]^c$$
(3)

where R represents the reaction rate, k the rate constant and a, b and c the orders of the reaction with respect to the concentration of H₂, MAA and MHB, respectively. The inclusion of increasing MHB concentrations $(9.3 \times 10^{-3} - 4.5 \times 10^{-2})$ mol dm^{-3}) in the reactant mixture was observed to have a negligible effect on the overall rate and the reaction can be considered to be zero order with respect to [MHB]. A small dependence (<0.1) of rate on the partial pressure of hydrogen (in the range 0.3-1 atm) was observed at 343 K which compares with the zero³² and 0.2 order⁵⁴ dependences that have been quoted elsewhere. The slopes of the logarithmic plots that relate reaction rate to MAA concentration are shown in Fig. 3 and yield a reaction order with respect to [MAA] of 0.4 for both the modified and the unmodified system. Taking the reaction to be zero order in terms of $[H_2]$ and [MHB] and assuming that the observed partial order with respect to [MAA] holds over the temperature range $318 \leq T/K \leq 383$, the rate constant was calculated from the experimentally determined rates and the resultant Arrhenius relationships for the unmodified and modified samples are illustrated in Fig. 4. The apparent rate was increased in both cases by a factor of



Fig. 2 The influence of TA-modified (\blacktriangle) and unmodified (\blacksquare) Ni/SiO₂ catalyst weight on the hydrogenation rate; T = 343 K; particle diameter = 75–125 µm; stirring speed = 800 rev min⁻¹; MAA/Ni molar ratio = 20–400



Fig. 3 Rate of MAA hydrogenation as a function of MAA concentration over TA-modified (\blacktriangle) and unmodified (\blacksquare) Ni/SiO₂; T = 343 K; particle diameter = 75–125 µm; stirring speed = 800 rev min⁻¹

up to 75 in going from 318 to 383 K, which is certainly diagnostic of a surface reaction proceeding with minimal mass transport constraints. The author could find no available experimental data on diffusion of MAA in *n*-butanol but the diffusion coefficient (cm³ s⁻¹) may be calculated using the Wilke–Chang estimation which is represented by⁵⁵

$$D_{\rm AB} = \frac{7.4 \times 10^{-8} (\phi M_{\rm B})^{0.5} T}{\mu_{\rm B} V_{\rm A}^{0.6}} \tag{4}$$

where A corresponds to the solute (MAA), B the solvent (nbutanol), ϕ an association factor, $M_{\rm B}$ the solvent molecular mass (g mol⁻¹), T the absolute temperature (K), $\mu_{\rm B}$ the solvent viscosity (cp) and V_A the critical molar volume of solute A. The temperature dependence of D_{AB} reduces to a constant multiplied by the ratio of reaction temperature to n-butanol viscosity. Solvent viscosities at 318 K and 383 K were estimated using the temperature related constants provided by Yaws *et al.*⁵⁶ and the diffusion coefficient is calculated to be four times greater at the higher temperature. Gerrard⁵⁷ has reported that the solubility of hydrogen in alcohols is also raised with increasing temperature. Nevertheless, the observed hydrogenation rate increase is considerably greater than the relative improvement in the transport of reactants to the catalyst surface and can be attributed predominantly to kinetic phenomena. The Arrhenius relationships yield apparent activation energy values (with 95% confidence limits) of $59 \pm 4 \text{ kJ}$ mol^{-1} and $49 \pm 5 \text{ kJ} \text{ mol}^{-1}$ for the unmodified and modified systems, respectively. These values of E_{app} are considerably



Fig. 4 Arrhenius plots for the hydrogenation of MAA over TAmodified (\blacktriangle) and unmodified (\blacksquare) Ni/SiO₂; particle diameter = 75– 125 µm; stirring speed = 800 rev min⁻¹; Ni/MAA molar ratio = 47–66

larger than the 10-16 kJ mol⁻¹ activation barrier that is characteristic of purely diffusion-controlled processes^{44,46,48,52} and lie within the range of values provided elsewhere.^{12,32,33} Hydrogenation of MAA over the TA-modified catalyst therefore proceeds at a higher rate and with a lower associated energy barrier.

The relationship between reaction rate and MAA concentration is shown in Fig. 5. It can be seen that the rate passes through a maximum (in the range 0.1–0.2 mol dm⁻³ MAA) for both the modified and unmodified catalysts as [MAA] is increased which is typical of a Langmuir dependence of rate on concentration. According to the Langmuir-Hinshelwood model, MAA and hydrogen react in the adsorbed state on the catalyst surface and the associated rate expression assumes different forms depending on whether the adsorption is competitive or not.46,47 The surface conditions which prevail during hydrogenation were probed by considering the following three pretreatments: (a) pre-contacting the activated catalyst/*n*-butanol suspension with a 60 cm³ min⁻¹ purge of hydrogen for 1 h prior to the introduction of MAA $(9.3 \times 10^{-2} \text{ mol dm}^{-3})$ where the activated catalyst had been swept with helium (400 cm³ min⁻¹) for 24 h at 723 K; (b) pre-contacting the helium-flushed activated catalyst with a MAA/*n*-butanol mixture (mole fraction of MAA = 0.02) for 1 h prior to the introduction of hydrogen; (c) simultaneous introduction of MAA (9.3×10^{-2} mol dm⁻³) and hydrogen to the helium-flushed activated catalyst/n-butanol suspension without any pretreatment. Pre-contacting the catalyst with hydrogen or MAA resulted in a lower reaction rate (by a factor of up to 1.2) than that observed for the simultaneous addition of both reactants. Such an observation suggests that there is competition for adsorption sites between MAA and hydrogen which suppresses the reaction rate when one of the reactants is pre-adsorbed on the surface. Taking the adsorption of hydrogen, MAA and n-butanol to be reversible and competitive, ratios of the fractional coverages of MAA (θ_{MAA}) and *n*-butanol (θ_{n-but}) to that of hydrogen (θ_{H_2}) are given by

$$\frac{\theta_{\text{MAA}}}{\theta_{\text{H}_2}} = \left(\frac{[\text{MAA}]}{[\text{H}_2]}\right) \exp\left(\frac{-\delta\Delta G_{\text{MAA}}}{RT}\right)$$
(5)

$$\frac{\theta_{n-\text{but}}}{\theta_{\text{H}_2}} = \left(\frac{[n-\text{but}]}{[\text{H}_2]}\right) \exp\left(\frac{-\delta\Delta G_{n-\text{but}}}{RT}\right) \tag{6}$$

where $\delta\Delta G_{MAA}$ (or $\delta\Delta G_{n-but}$) is the difference of the Gibbs energies of adsorption between MAA (or *n*-butanol) and hydrogen. The reaction was conducted at a constant pressure of hydrogen and assuming that the solubility of hydrogen is indepen-



Fig. 5 Plot of MAA hydrogenation rate vs. [MAA] for the TAmodified (\blacktriangle) and unmodified (\blacksquare) Ni/SiO₂; T = 343 K; particle diameter = 75–125 µm; stirring speed = 800 rev min⁻¹. Note: the solid line represents the rate expression R = 2.85[MAA]/ (1 + 8.39[MAA])² and the dashed line the expression R = 1.47[MAA]/(1 + 7.67[MAA])².

dent of the mole fractions of MAA and n-butanol the liquid phase concentration of hydrogen can be considered constant and

$$\frac{\theta_{MAA}}{\theta_{H_2}} = \gamma_{MAA} [MAA]$$
(7)

$$\frac{\theta_{n-\text{but}}}{\theta_{\text{H}_2}} = \gamma_{n-\text{but}}[n-\text{but}]$$
(8)

where $\gamma_{MAA} = (1/[H_2]) \exp(-\delta\Delta G_{MAA}/RT)$ and $\gamma_{n-but} = (1/[H_2])\exp(-\delta\Delta G_{n-but}/RT)$. In the absence of strong diffusional limitations, the rate-determining step is the surface reaction between adsorbed MAA and hydrogen where the rate is proportional to the fractional surface coverage,

$$R = k\theta_{\rm MAA}\,\theta_{\rm H_2} \tag{9}$$

and assuming that the catalyst has at least a monolayer coverage

$$\theta_{\text{MAA}} + \theta_{\text{H}_2} + \theta_{n\text{-but}} = 1 \tag{10}$$

The fractional coverage by each component will depend on differences in adsorption strength. Substituting eqn. (7) and (8) into eqn. (10) yields

$$\theta_{\rm H_2} = \frac{1}{(1 + \gamma_{\rm MAA}[{\rm MAA}] + \gamma_{n-\rm but}[n-\rm but])}$$
(11)

and substitution of eqn. (11) into eqn. (9) gives a Langmuirtype expression of the form

$$R = \frac{k\gamma_{\text{MAA}} [\text{MAA}]}{(1 + \gamma_{\text{MAA}} [\text{MAA}] + \gamma_{n-\text{but}} [n-\text{but}])^2}$$
(12)

Contacting the activated catalyst with *n*-butanol [*n*-butanol: Ni molar ratio = $(2.6-6.5) \times 10^2$] for extended periods (up to 24 h) prior to the introduction of MAA and/or hydrogen had no observable effect on rate which suggests that the solvent interacts weakly with the catalyst and the term $\gamma_{n-but}[n-but]$ can be ignored in the denominator of eqn. (12). Eqn. (12) predicts a linear relationship between ([MAA]/R)^{0.5} and [MAA] where

$$\left(\frac{[MAA]}{R}\right)^{0.5} = \left(\frac{1}{k\gamma_{MAA}}\right)^{0.5} + \left(\frac{\gamma_{MAA}}{k}\right)^{0.5} [MAA] \quad (13)$$

and the straight line plots are shown in Fig. 6. The graphically evaluated values of k and γ_{MAA} were used to calculate reaction rate over the [MAA] range using the expression

$$R = \frac{k\gamma_{\text{MAA}}[\text{MAA}]}{(1 + \gamma_{\text{MAA}}[\text{MAA}])^2}$$
(14)

and the calculated R vs. [MAA] relationship is compared with the experimental values in Fig. 5. The experimentally deter-

З

2

0

0

([MAA]/R)^{0.5}/h^{0.5} g_{Ni}^{0.5} dm^{-1.5}



[MAA]/10⁻² mol dm⁻³

20

30

10

mined rates agree to $\pm 15\%$ with the values predicted by the kinetic model and both experimental and calculated rates exhibit maxima in the [MAA] range 0.1–0.2 mol dm⁻³.

There is strong spectroscopic evidence² to suggest that TA is adsorbed on the nickel metal surface as a carboxylate and the active centres in the modified system may then be considered to be composed of both zero-valent nickel metal which serves to dissociate the adsorbed hydrogen and the nickel ions in the surface nickel/modifier 'complex' where the latter environment is essential to promote enantioselectivity. The MAA reactant is adsorbed on a bare nickel site as an Obonded chelate⁵⁸ but on the modified surface MAA can also interact with adsorbed TA via hydrogen bonding between the OH group of the hydroxy acid and the methoxy oxygen atom of MAA. In the batch liquid phase reaction, the free reactants as well as the site attached reactants are assumed to be in equilibrium. The term γ_{MAA} given in the rate expression in eqn. (14) can be considered to be a measure of the driving force or displacement from this equilibrium. The values of γ_{MAA} evaluated from the data plotted in Fig. 6 are 8.4 dm³ mol⁻¹ and 7.7 dm³ mol⁻¹ for the TA-modified and unmodified samples, respectively. The product MHB once formed is not converted. under the stated reaction conditions, back to MAA and the parameter γ_{MAA} refers to the equilibrium formation of the active site/MAA complex shown below for the unmodified system

$$Ni + MAA \rightleftharpoons Ni - MAA$$
 (15)

where the greater the value of γ_{MAA} the greater is the equilibrium shift to the right. The additional interaction of MAA with the nickel-supported TA is proposed as the source of the higher γ_{MAA} values. Moreover, this interaction must induce a further polarization of the carbonyl function, thereby rendering it more susceptible to attack by hydrogen with a consequent enhancement of the hydrogenation rate where the value of k, the kinetic term, evaluated from Fig. 6 is greater for the modified system, *i.e.* $0.34 > 0.19 \text{ mol } h^{-1} (g_{Ni})^{-1}$. The TA modifier may also serve as a template through which activated hydrogen is transferred to the substrate as distinct from hydrogen transfer from the bare metal surface or spillover hydrogen from the silica carrier. This supply of hydrogen may be more effective than that provided by the unmodified catalyst or it may merely serve as an additional source of reducing agent with the result that the overall conversion rate is increased. The effect of varying [MAA] on the enantiomeric excess generated by the TA-treated sample is illustrated in Fig. 7. Enantioselectivity can be seen to increase with reactant concentration, tending towards a limiting value of $22 \pm 2\%$ which is independent of concentration over the [MAA]/Ni



Fig. 7 The variation of enantiomeric excess with increasing [MAA]; T = 343 K; particle diameter = 75–125 µm; stirring speed = 800 rev min⁻¹

(22)



Fig. 8 Relationship between stirring speed and the dimensionless parameter x (=[MAA]*/[MAA]) for the TA-modified (\blacktriangle) and unmodified (\blacksquare) Ni/SiO₂; T = 343 K; particle diameter = 75–125 µm; MAA/Ni molar ratio = 47–66

range 1–65 mol_{MAA} $(g_{Ni})^{-1}$. In contrast, Lipgart *et al.*³¹ observed distinct concentration related maxima in the asymmetric hydrogenation of ethyl acetoacetate while Nitta *et al.*⁵⁹ reported an increase in selectivity as the mole fraction of MAA in ethyl acetate was raised to one. On the other hand, optical yields have been reported^{27,60,61} to be independent of reactant to catalyst ratios in the range 70–170 mmol_{MAA} $(g_{Ni})^{-1}$. The extent of nickel leaching was not addressed in the other studies with the result that the quoted reactant/metal stoichiometry may not in fact prevail during catalysis.

The influence of mass transfer on the overall reaction rate is often represented by use of the effectiveness factor, η , which is defined physically as

$$\eta = \frac{\text{observed reaction rate}}{\text{rate obtained with no mass transfer resistance}}$$
(16)

At steady state the rate of MAA supply by mass transfer is counterbalanced by the rate of MAA consumption in the reaction at the catalyst surface. The effectiveness factor equals unity where the surface reactant concentration ([MAA]*) equals the bulk solution concentration ([MAA]) and the observed reaction kinetics is the same as the true, intrinsic kinetics at the liquid/gas/solid interface. In terms of the proposed rate expression

$$\eta = \frac{\frac{k\gamma_{\text{MAA}}[\text{MAA}]^*}{(1 + \gamma_{\text{MAA}}[\text{MAA}]^*)^2}}{\frac{k\gamma_{\text{MAA}}[\text{MAA}]}{(1 + \gamma_{\text{MAA}}[\text{MAA}])^2}}$$
(17)

which reduces to

$$\eta = \frac{[\text{MAA}]^*(1 + \gamma_{\text{MAA}}[\text{MAA}])^2}{[\text{MAA}](1 + \gamma_{\text{MAA}}[\text{MAA}]^*)^2}$$
(18)

Introducing the dimensionless variables

$$\kappa = \gamma_{[MAA]}[MAA] \tag{19}$$

and

$$x = \frac{[MAA]^*}{[MAA]} \tag{20}$$

eqn. (17) takes the form

$$\eta = \frac{x(1+\kappa)^2}{(1+\kappa x)^2}$$
(21)

Algebraic manipulation of eqn. (21) gives a quadratic for x, so that an analytical solution is available

 $x = \frac{\beta}{2\eta\kappa^2} \pm \frac{1}{2\eta\kappa^2} \sqrt{(\beta^2 - 4\eta^2\kappa^2)}$

where

$$\beta = 2\kappa\eta - \kappa^2 - 2\kappa - 1 \tag{23}$$

Taking the effectiveness factor at the highest recorded reaction rate for both systems to be equivalent to unity, the apparent ratio of surface to bulk [MAA] under the reaction conditions was calculated and is plotted as a function of stirring speed in Fig. 8. The value of x is clearly a function of the stirring speed and it is immediately evident that a vigorous agitation of the catalyst/reactant suspension is required to ensure that the rate of supply of the [MAA] reactant approaches the rate of consumption. The unmodified and modified systems exhibit the same dependence of [MAA] diffusion on agitation where mass transfer contributions are minor at stirring speeds in excess of 600 rev min⁻¹.

Conclusions

The liquid phase hydrogenation of MAA catalysed by Ni/SiO₂ in a slurry-type reactor is characterized by an appreciable mass transport retardation of reaction rates (i) at stirring speeds < 600 rev min⁻¹, (ii) when using catalyst particles $>150 \ \mu m$ in diameter and (iii) at MAA/Ni molar ratios >400. The reaction is essential zero order with respect to [MHB] and [H₂] but exhibits a partial (0.4) dependence on [MAA]. Modification of the surface with TA not only increases the reaction rate but lowers the apparent activation energy from 59 to 49 kJ mol⁻¹. Such an effect is attributed primarily to the additional polarization of the carbonyl function due to TA/MAA hydrogen bonding which renders the C=O bond more susceptible to attack. The catalytic data are consistent with a Langmuir-Hinshelwood model in which both hydrogen and MAA adsorb competitively on the surface to generate [MAA] related activity maxima and the rate-determining step is the surface reaction between the two adsorbed species. The dependence of rate on MAA concentration over the TAmodified and unmodified surface can be represented by the rate expressions $R = 2.85[MAA]/(1 + 8.39[MAA])^2$ and $R = 1.47[MAA]/(1 + 7.67[MAA])^2$, respectively. Enantioselectivity, on the other hand, increases with an increase in [MAA]/Ni to attain a plateau value over the range 1-6.5 $\operatorname{mol}_{MAA}(g_{Ni})^{-1}$.

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