Catalysis Letters 34 (1995) 1–9

Enantioselective hydrogenation of ethyl pyruvate in supercritical fluids

B. Minder [a], T. Mallat [a], K.H. Pickel [b], K. Steiner [b] and A. Baiker [a]

[a] *Department of Chemical Engineering and Industrial Chemistry, ETH Zentrum, CH-8092 Zurich, Switzerland*

[b] *Research Laboratories, Hoffmann La Roche AG, CH-4303 Kaiseraugst, Switzerland*

Received 22 February 1995; accepted 25 April 1995

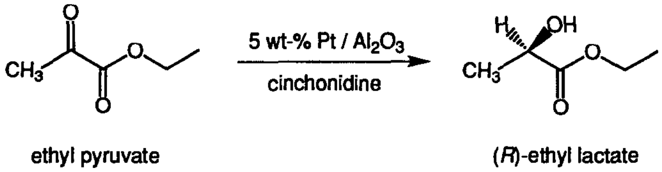
The enantioselective hydrogenation of ethyl pyruvate to (R)-ethyl lactate has been studied using gases under supercritical conditions as solvents. The catalyst was a 5 wt% Pt/alumina modified with cinchonidine. In supercritical ethane the reaction time could be reduced by a factor of 3.5 compared to toluene under similar conditions, without any loss in enantioselectivity. A further advantage of ethane is that the enantioselectivity remains high even at high catalyst/reactant ratio, which is interesting in view of a possible application of a continuous fixed-bed reactor for this reaction. A strong catalyst deactivation was observed in supercritical CO_2, which is due to the reduction of CO_2 on Pt as indicated by FTIR.

Keywords: enantioselective hydrogenation; supercritical fluids; ethyl pyruvate; cinchonidine; Pt/alumina; CO-poisoning

1. Introduction

The enantioselective hydrogenation of ethyl pyruvate to (R)-ethyl lactate is one of the most studied heterogeneously catalyzed asymmetric reactions (scheme 1) [1–3]. The chiral information is transferred by the "modifier" (usually cinchona alkaloids or their simple derivatives), which is adsorbed on the surface of supported Pt.

The influence of solvents on enantio-differentiation and reaction rate has been extensively investigated, but the interaction of the solvent with the reactant, the



Scheme 1.

modifier and the surface Pt^0 active sites is still not fully elucidated [4–7]. Both the initial rate and enantiomeric excess (ee) decrease with ascending solvent polarity (characterized by the empirical solvent parameter E_T^N [8]). In the range of polar solvents, such as acetic acid, primary alcohols and water, the influence of solvent polarity is ambiguous due to chemical interactions with the modifier or the reactant (protonation of the N-base modifier, hemiketal and geminal glycol formation from the α-ketoester, respectively) [6]. It has been found recently that using new chiral N-base modifiers instead of the cinchona alkaloids, the effect of common solvents is even more complex [9].

Supercritical fluids represent another class of solvents with their unique property of pressure-dependent density [10]. Moreover, the presence of a single homogeneous phase can eliminate mass transfer limitations. Several examples can be found in the literature on the application of these properties in a wide variety of chemical transformations [11–14], but there are no data available to our knowledge on catalytic hydrogenation. This prompted us to study the enantioselective hydrogenation of ethyl pyruvate in supercritical fluids, such as CO_2 and ethane. These solvents are strongly apolar which seems to be advantageous for obtaining good enantioselectivity in the title reaction.

2. Experimental

2.1. HYDROGENATION REACTION

A commercial 5 wt% Pt/Al_2O_3 catalyst (Engelhard, 4759) with a dispersion of 22% [17] was prereduced at 673 K for 2 h in 30 ml min^{-1} flowing hydrogen. The pretreated catalyst was transferred under argon to the hydrogenation reactor. Ethyl pyruvate (Fluka) was freshly distilled before each reaction. The cinchonidine modifier was used as received from Fluka. The purities of the gases were: H_2 – 99.995%, CO_2 – 99.99% and C_2H_6 – 99.4%. The critical pressures and temperatures of CO_2 and C_2H_6 are 73 bar / 304 K and 48 bar / 305 K, respectively. Under standard conditions (see below) the ethane–hydrogen and CO_2–H_2 mixtures are in the supercritical regions [15,16].

The hydrogenation reaction was carried out in a thermostated 500 ml MEDIMEX SS stirred autoclave. Under *standard conditions*, 20 ml ethyl pyruvate, 0.45 g catalyst (transferred to the reactor as a slurry with a part of the reactant), 0.088 g cinchonidine and 121 g ethane or CO_2 (measured with a Rheonik flow controller) were used. This amount of solvent provides a partial pressure of approximately 60 and 80 bar for ethane and CO_2 at 323 and 313 K, respectively. The initial hydrogen pressure was 70 bar. In order to facilitate the comparison to reactions performed in common liquid solvents, the molality (mol reactant / kg solvent) was always kept at a constant value of 1.5 mol kg^{-1}. These standard conditions were used if not otherwise stated. It was proved that under these conditions the reactor worked in the kinetic regime.

Enantiomeric excess (ee) and conversion were determined on a HP 5890A gas chromatograph using a WCOT fused silica capillary column with a CP-Cyclodextrin-β-2,3,6-M-19 chiral phase. ee (in %) is expressed as the absolute value of $([R] - [S])/([R] + [S]) \times 100$.

2.2. FTIR MEASUREMENTS

The in situ diffuse reflectance FTIR studies were carried out on a Perkin Elmer (model 2000) instrument. A diffuse reflection unit (Spectra-Tech, type 0030-033, DRIFT) including a reaction chamber (Spectra-Tech, type 0030-102) was used for all the experiments. The catalyst temperature was measured with a thermoelement (type K, accuracy ±2 K) and controlled by a Tecon 580. The constant gas streams, flowing through the reaction chamber, were controlled by mass flow controllers (Brooks, 5850E). The catalyst was put onto an alumina sample holder. The gases (H_2 – 99.999 vol%; N_2 – 99.995 vol% and CO_2 – 99.99 vol%) were used without further purification.

The catalyst was first pretreated at 673 K for 1.5 h in flowing H_2 of 30 ml min^{-1}. The background (100 scans, 8 cm^{-1}) was measured after cooling the catalyst to 313 K in nitrogen. The cell was flushed with H_2 at 1 bar for 2 min (spectrum 1 in fig. 6) before increasing the pressure to 10 bar (spectrum 2). Hydrogen was substituted by a mixture of CO_2 and H_2 in a 1 : 4 ratio, using a total flow of 100 ml min^{-1}, and the pressure was increased continuously to 20 bar (12 bar after 15 s, spectrum 3, 15 bar after 2 min, spectrum 4). All spectra, shown in fig. 6 in the reflection mode (R (%)), were recorded with 25 scans and 8 cm^{-1}.

3. Results and discussion

3.1. INFLUENCE OF REACTION PARAMETERS

Fig. 1 shows a *comparison* between supercritical ethane and the two solvents used most frequently for this reaction: ethanol and toluene. It can be seen that, under otherwise identical conditions, the reaction is much faster (by a factor of more than 3) in supercritical ethane. The high average reaction rate (or low reaction time necessary to achieve full conversion) is attributed to the higher solubility of hydrogen in ethane. The ee's are almost equal in the two apolar solvents, toluene and ethane. In ethanol both reaction rate and enantioselectivity are lower, as expected [4].

The enantiomeric excess as a function of the reaction *temperature* is shown in fig. 2. There is hardly any difference between the two apolar solvents ethane and toluene. In both cases ee drops significantly at temperatures higher than 340 K. In ethanol the influence of increasing temperature on the enantio-differentiation is qualitatively similar.

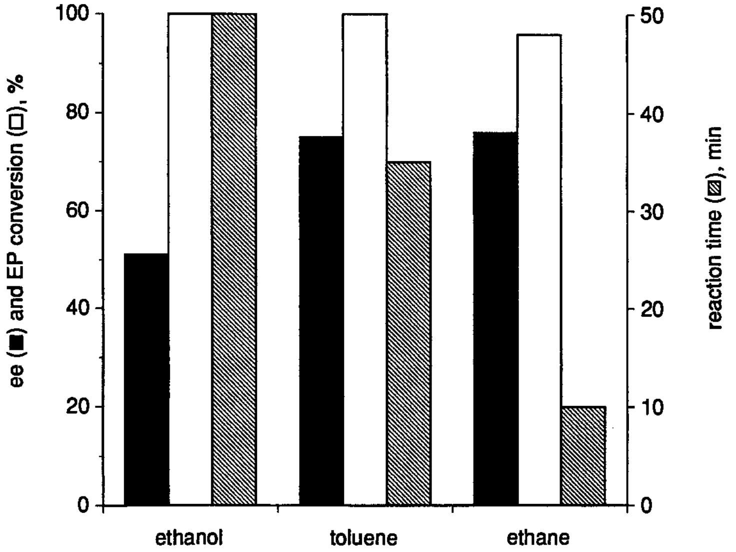


Fig. 1. Enantiomeric excess, ethyl pyruvate (EP) conversion and reaction time measured in ethanol, toluene and supercritical ethane; standard conditions, see experimental section.

Unfortunately, the choice of solvents, applicable under supercritical conditions in the enantioselective hydrogenation of ethyl pyruvate, is rather limited. Ambient temperature or even lower is advantageous for obtaining high enantioselectivity, but the critical temperature of the majority of solvents is above 350 K. For example, propane was also tested (T_c = 370 K [18]), but the ee was very poor at the required higher temperature. The difficulties emerging when using supercritical CO_2 will be discussed later.

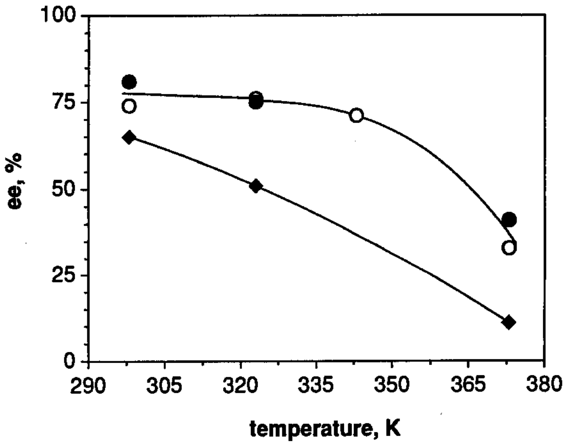


Fig. 2. Influence of reaction temperature on the enantiomeric excess measured in ethanol (◆), toluene (●) and supercritical ethane (○); standard conditions.

The increase of *catalyst/reactant weight ratio* in ethane has a small positive effect on the enantioselectivity, as indicated in fig. 3. Interestingly, in ethanol under similar conditions ee decreased significantly with increasing catalyst loading [19]. The striking difference is likely due to the influence of transport processes. Kinetic analysis of the results obtained in ethanol [19] indicates that at low catalyst/reactant ratio the reaction is kinetically controlled, but at higher ratios (above 15 mg g^{-1}) it is limited by mass transfer. On the contrary, in supercritical ethane the solubility of hydrogen is high and there was no sign of transport limitations. Note that other (yet not clarified) factors may also be responsible for the change of ee with increasing catalyst loading, as has been reported recently [7].

The fact that good ee can be obtained even at very high catalyst/reactant ratio, renders the supercritical ethane a promising candidate as a solvent for application in continuous fixed-bed reactors, where the catalyst/reactant ratio is high and the mixing efficiency is far below that characteristic of slurry reactors.

Fig. 4 shows the enantiomeric excess as a function of hydrogen pressure. These findings are similar to those observed in ethanol [20]. The pressure dependence of ee in this reaction is not fully understood. A possible explanation is the partial, competitive hydrogenation of the modifier [21,22]. The saturation of the vinyl group results in the formation of 10,11-dihydrocinchonidine, which is a more efficient modifier than cinchonidine itself. On the contrary, the partial saturation of one of the quinoline rings under more severe conditions lowers the enantio-differentiation significantly [21,22].

3.2. CATALYST POISONING IN SUPERCRITICAL CO_2

Supercritical CO_2 is widely used in various hydrogenation reactions [23] as a solvent due to its moderate critical parameters ($T_c = 304$ K; $P_c = 73$ bar) and low

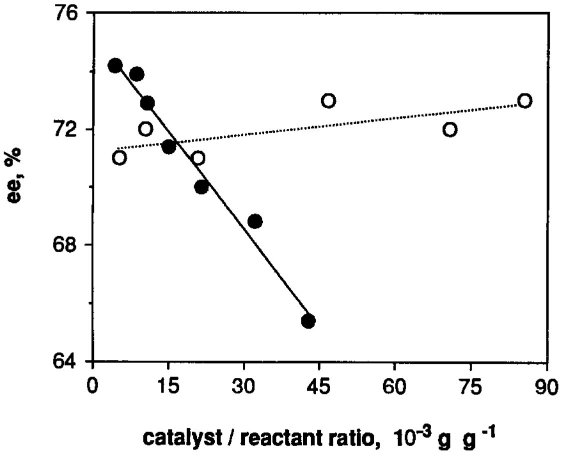


Fig. 3. Enantiomeric excess measured in ethanol (●) and supercritical ethane (○) as a function of the catalyst/reactant weight ratio (standard conditions for ethane; 295 K for ethanol [19]).

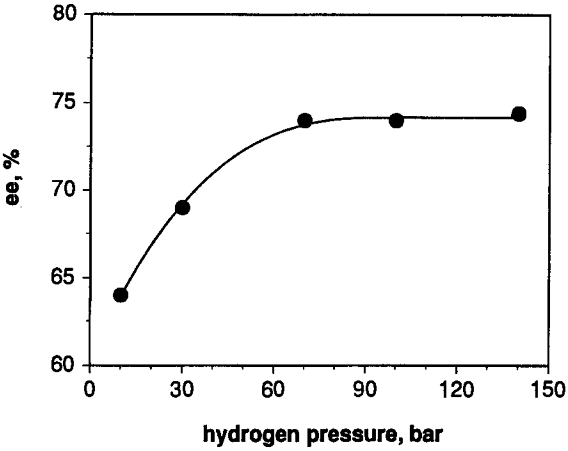


Fig. 4. Enantiomeric excess in supercritical ethane as a function of the hydrogen partial pressure (standard conditions).

polarity. Surprisingly, a strong catalyst deactivation was observed in the enantioselective hydrogenation of ethyl pyruvate in CO_2. The poisoning effect of CO_2 is illustrated in fig. 5. The hydrogenation of ethyl pyruvate was performed in ethanol. At about 40% conversion, CO_2 (80 bar) was added which immediately terminated the hydrogen consumption. When the hydrogenation reaction in ethane was performed after stirring the catalyst and reactant for 5 min in a CO_2–H_2 mixture, the activity was almost zero. A similar catalyst deactivation in the presence of CO_2 was observed when the activated keto group of ethyl benzoylformate was attempted to reduce.

Based on these observations it is likely that the reason for catalyst deactivation is the reduction of CO_2 on the Pt surface. There exists considerable evidence on the

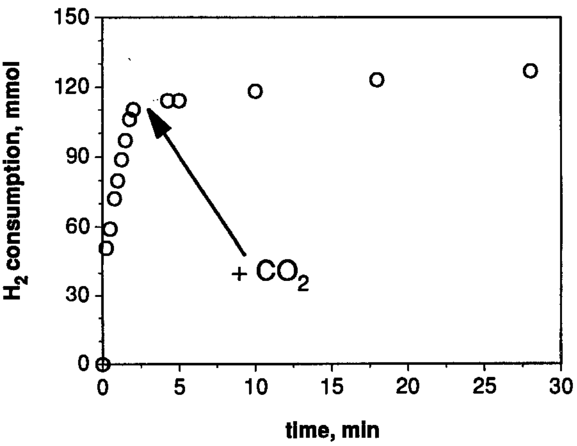


Fig. 5. The influence of CO_2 addition on the hydrogen consumption during the reduction of ethyl pyruvate in ethanol (34.5 ml EP, 265 ml ethanol, 0.85 g catalyst, 0.15 g cinchonidine, 308 K and P_{CO_2} = 80 bar).

formation of CO from CO_2 over Pt at temperatures above 470 K [24], and at room temperature in aqueous acidic and basic solutions [25,26]. It is also known that CO poisons Pt in the reduction of a carbonyl group [26,27].

The presence of CO on Pt/alumina after contacting it with CO_2 was proven by FTIR experiments. The catalyst was pretreated in a hydrogen atmosphere at 673 K in the reaction chamber, according to the standard procedure described in the experimental part. Fig. 6 shows the spectra of the catalyst prereduced in H_2 at 1 and 10 bar (curves 1 and 2). The bands at 2067 and 1877 cm^{-1} indicate the partial coverage of Pt by CO [28,29]. During storage of the catalyst in air, CO_2 can adsorb on alumina (likely as carbonate), as indicated by the three typical absorption bands at 1660, 1443 and 1235 cm^{-1} [30,31]. Note that the adsorption of CO_2 on Pt is weak and non-dissociative [32]. A more detailed analysis of CO formation during catalyst prereduction is discussed elsewhere [31].

After flushing the reaction chamber of the spectrometer with a CO_2/H_2 mixture,

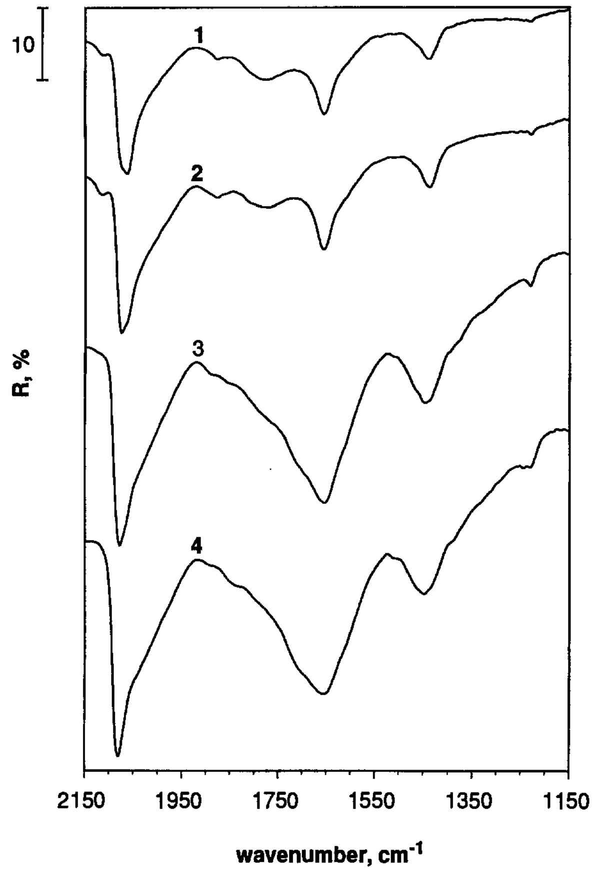


Fig. 6. FTIR spectra of the 5 wt% Pt/alumina catalyst measured after catalyst prereduction at 673 K and cooling to 313 K; atmosphere: 1 bar H_2 (1), 10 bar H_2 (2), 2.4 bar CO_2 + 9.6 bar H_2 (3), and 3 bar CO_2 + 12 bar H_2 (4).

the bands characteristic of CO_2 and CO increase (spectra 3 and 4). Comparing the CO bands before and after the introduction of gaseous CO_2, we can conclude that the moderate increase in CO-coverage of Pt (by a factor of ca. 2) cannot be the only reason for the drop in the rate of ethyl pyruvate hydrogenation (by almost two orders of magnitude). It seems that the reduction of CO_2 on Pt is more complex and the catalyst poisoning is also due to the formation of other type of species, to the presence of which the IR analysis is less sensitive. This assumption is supported by in situ FTIR analysis of single crystal and polycrystalline Pt in aqueous solutions, indicating the formation of –COOH and triple-bonded COH (beside linearly and bridge-bonded CO) [25].

4. Conclusions

Substituting toluene by supercritical ethane in the enantioselective hydrogenation of ethyl pyruvate to (R)-ethyl lactate results in considerably higher reaction rates (by a factor of 3.5) without any loss in enantioselectivity. A further advantage of supercritical ethane is the high degree of enantio-differentiation even at high catalyst/α-ketoester ratio. This is an important characteristic in view of a possible application of a continuous fixed-bed reactor for this reaction.

Supercritical CO_2 was found to be a poor solvent for the carbonyl reduction due to catalyst deactivation probably caused by the formation of poisoning species by CO_2 reduction on Pt. This effect may be used in other type of hydrogenation reactions, when the reduction of a carbonyl functional group is undesired. A further interesting consequence of our observation is that during hydrogenation in supercritical CO_2 over Pt (and possibly over other Pt metals), the solvent can be contaminated by CO.

Acknowledgement

Financial support of this work by F. Hoffmann La Roche AG, Switzerland and the "Kommission zur Förderung der wissenschaftlichen Forschung" (project No. 2413.2) is gratefully acknowledged. Thanks are also due to Ch. Fröhlich for the FTIR measurements and to Professor G. Brunner (TU Hamburg, Germany) for valuable discussions.

References

[1] Y. Orito, S. Imai and S. Niwa, J. Chem. Soc. Japan (1980) 670.
[2] H.U. Blaser, Chem. Rev. 92 (1992) 935.
[3] A. Baiker, DGMK Tagungsber. 9305 (ISBN 3-928164-61-9) 119 (1992).

[4] J.T. Wehrli, A. Baiker, D.M. Monti, H.U. Blaser and H.P. Jalett, J. Mol. Catal. 57 (1989) 245.
[5] H.U. Blaser, H.P. Jalett and J. Wiehl, J. Mol. Catal. 68 (1991) 215.
[6] B. Minder, T. Mallat, P. Skrabal and A. Baiker, Catal. Lett. 29 (1994) 115.
[7] B. Minder, T. Mallat, A. Baiker, G. Wang, T. Heinz and A. Pfaltz, J. Catal., in press.
[8] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry* (VCH, Weinheim, 1988) p. 359.
[9] B. Minder, M. Schürch, T. Mallat and A. Baiker, Catal. Lett. 31 (1995) 143.
[10] V. Krukonis, G. Brunner, M. Perrut, *Proc. 3rd Int. Symp. on Supercritical Fluids*, Strasbourg 1994.
[11] B. Subramaniam and A. McHugh, Ind. Eng. Chem. Process Des. Dev. 25 (1986) 1.
[12] L. Book, B. Wu, C. LaMarca, M. Klein and S. Paspek, CHEMTECH 12 (1992) 719.
[13] P.G. Jessop, T. Ikariya and R. Noyori, Nature 368 (1994) 231.
[14] G. Kaupp, Angew. Chem. 106 (1994) 1519.
[15] A. Heintz and W.B. Streett, J. Chem. Eng. Data 27 (1982) 465.
[16] C.Y. Tsang and W.B. Streett, Chem. Eng. Sci. 36 (1981) 993.
[17] J.T. Wehrli, A. Baiker, D.M. Monti and H.U. Blaser, J. Mol. Catal. 61 (1990) 207.
[18] T.E. Daubert and R.P. Danner, eds., *Physical and Thermodynamic Properties of Pure Chemicals: Data Compilation* (Taylor and Francis, Washington, 1993).
[19] J.T. Wehrli, PhD Thesis, ETH-Zürich, No. 8833 (1989).
[20] H.U. Blaser, H.P. Jalett, D.M. Monti, J.F. Reber and J.T. Wehrli, Stud. Surf. Sci. Catal. 41 (1988) 153.
[21] H.U. Blaser, H.P. Jalett, D.M. Monti, A. Baiker and J. T. Wehrli, Stud. Surf. Sci. Catal. 67 (1991) 147.
[22] E. Talas, L. Botz, J. Margitfalvi, O. Sticher and A. Baiker, J. Planar Chrom. 5 (1992) 28.
[23] K. Steiner and K.H. Pickel, unpublished.
[24] T. Inoue and T. Iizuka, J. Chem. Soc. Faraday Trans. 82 (1986) 1681.
[25] S. Taguchi and A. Aramata, Electrochim. Acta 39 (1994) 2533.
[26] E. Morallòn, J.L. Vàzquez, J.M. Pèrez and A. Aldaz, J. Electroanal. Chem. 380 (1995) 47.
[27] M. Freifelder, in: *Practical Catalytic Hydrogenation* (Wiley–Interscience, New York, 1971).
[28] A.W. Frahm, *Methoden der Organischen Chemie* (Thieme, Stuttgart, 1980).
[29] M. Primet, J.M. Basset, M.V. Mathieu and M. Prettre, J. Catal. 29 (1973) 213.
[30] N.D. Parkyns, J. Chem. Soc. A (1967) 1910.
[31] B. Minder, M. Schürch, T. Mallat, A. Baiker, T. Heinz and A. Pfaltz, J. Catal., submitted.
[32] Z.M. Liu, Y. Zhou, F. Solymosi and J.M. White, Surf. Sci. 245 (1991) 289.