Palladium-Mediated Heterogeneous Catalytic Hydrogenations

SELECTIVITY OF LIQUID-PHASE REACTIONS FOR THE FINE CHEMICALS INDUSTRY

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The fine chemicals industry, particularly the pharmaceutical industry, is the most developed of the chemical industries in Hungary, and for this reason our catalytic research work has been focused on liquid-phase hydrogenation and oxidation reactions. In a small country, such as Hungary, the chances of developing large catalytic technologies is minimal, so we have targeted our work on small scale processes, concentrating on investigating and developing hydrogenation processes and their catalysts for the synthesis of fine chemicals.

When developing catalysts, the most important properties are their activity, stability and selectivity. In liquid-phase batch processes, selectivity is of crucial importance, especially in the production of drugs, where the permissible amount of impurities allowed in the product has decreased dramatically in the last decades. This paper describes the various types of selectivity and looks at methods for their optimisation, using liquid-phase hydrogenation reactions as illustrations.

Types of Selectivity
Chemoselectivity
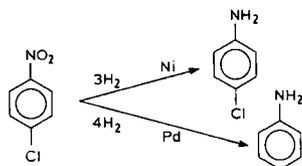
The hydrogenation of 4-chloronitrobenzene in methanol using a catalyst of palladium supported on active carbon at room temperature and atmospheric pressure gives aniline as the product together with hydrochloric acid.

With a catalyst of skeletal nickel under the same conditions the process consumes one mole less of hydrogen and the product is 4-chloroaniline. This demonstrates that the Raney-nickel catalyst is chemoselective in the hydrogenation of halogen-containing aromatic nitro compounds, as it does not cleave the halogen from the aromatic ring.

Regioselectivity

Regioselectivity can be demonstrated by the palladium-catalysed hydrogenation of β-naphthol, which contains two similar aromatic rings to be saturated.
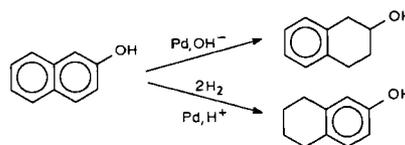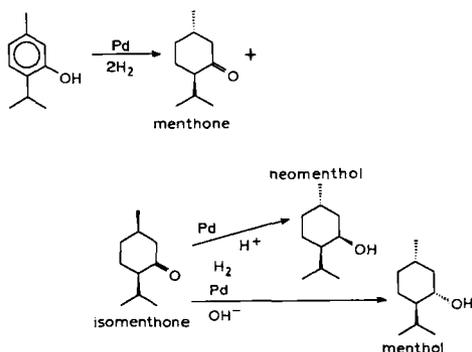

Under basic conditions the hydroxyl-substituted ring is hydrogenated, while in the presence of acids the unsubstituted ring is reduced producing aromatic tetralol in excess.

Stereoselectivity

If the product molecule contains stereoisomers then the hydrogenation reaction can be characterised by its stereoselectivity. Palladium catalysts can be used to produce stereochemically-enriched products. The hydrogenation

of thymol in water at 383 K and 6 bars of pressure results in an equilibrium mixture of menthone isomers (60 per cent menthone, 40 per cent isomenthone), which are themselves hydrogenated after the thymol is almost completely converted.

menthone

neomenthol

isomenthone

menthol

Under acidic conditions neomenthol is formed in excess, while under basic conditions menthol is formed with 75 per cent stereoselectivity as the main product (1, 2). In menthol the hydroxy group is in the equatorial position.
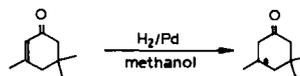
Enantioselectivity

The most sophisticated type of selectivity is enantioselectivity, where a prochiral compound is converted into a chiral product, and the enantiomers are not produced in a 1:1 ratio:
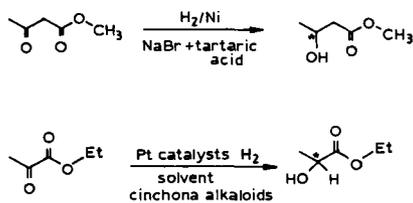
Two well-known enantioselective heterogeneous hydrogenation reactions, which are carried out using Raney-nickel and platinum catalysts modified, respectively, with the chiral compounds tartaric acid and cinchonidine, are shown above. Under optimised conditions the enantioselectivity in both systems reaches 95 to 98 per cent (3).

In our laboratory, methods were developed for the asymmetric hydrogenation of isophorone

using palladium-based catalysts. (S)-proline was used as the chiral auxiliary in one case and (−)-dihydro apovincaminic acid ethyl ester was used as the chiral modifier in the other:


In the presence of a stoichiometric amount of (S)-proline the highest enantiomeric excess was 80 per cent. However, when catalytic amounts of the vinca-alkaloid were used as the chiral modifier, the enantioselectivity reached 55 per cent (4, 5).

Factors Affecting Chemoselectivity

In developing industrial hydrogenation processes one important question is how the selectivity of a reaction can be increased. Ways in which this can be achieved are suggested in the next section.

Change of Solvent

When 4-chloronitrobenzene is hydrogenated in methanol at room temperature and atmospheric pressure using a palladium catalyst, the main products are aniline and hydrochloric acid. However, if the solvent is ethyl acetate, and an 0.2 per cent palladium/carbon catalyst is used with respect to the substrate, then chemoselectivity to 4-chloroaniline increases to over 90 per cent.
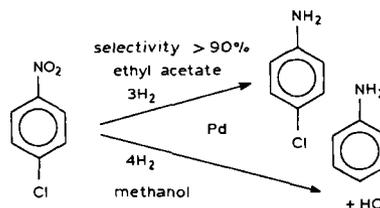

In the less polar, aprotic, ethyl acetate solvent the solvation changes, affecting the adsorption strength of the substrate and the products. Thus the hydrogenation of chloroaniline to aniline becomes a very slow process.

Another example of solvent effects is shown by the selective ring saturation of pyrrole derivatives which can be performed using a catalyst of palladium/carbon, but only in a solvent

mixture; however, in methanol the reaction proceeds easily, if rhodium or ruthenium catalysts are used (6–9).

Change of Catalyst

In the reduction of benzoic acid derivatives, containing similar functional groups, using a palladium catalyst, a simple change of solvent is not sufficient to preserve the chloro substituent.
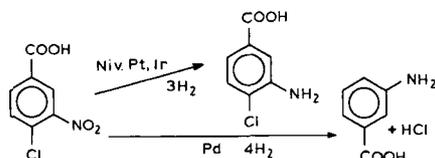

To retain the chloro substituent on the benzoic acid, the palladium catalyst has to be substituted for platinum, iridium or nickel (10). The reactions were carried out at room temperature and atmospheric pressure.

Catalyst Modification

Palladium is an especially selective metal for several hydrogenation reactions; for example, it can be used for the selective reduction of a C=C double bond next to an aliphatic carbonyl. A classic example where the selectivity of palladium has been increased is the Lindlar catalyst. This is a lead-poisoned palladium catalyst which can selectively saturate a triple bond to a double bond. Another example is the catalyst for the Rosenmund reaction, where after poisoning the activity of the palladium decreases, and only the selectivity is enhanced. Here palladium is applied to a low surface area BaSO$_4$ support and poisoned with a sulfur-containing compound. This catalyst is effective for the selective hydrogenation of aromatic acid chlorides to the corresponding aldehydes.

Although this method of catalyst modification is applicable for many reactions, it is not sufficiently reproducible for industrial use. Therefore we have developed a preparation method for catalysts used in the Rosenmund reaction (11). **Alloying the Active Metal:** According to our method the hydrogenation of acid chlorides is carried out at elevated temperature using a

catalyst of palladium-copper alloy supported on active carbon, with aromatic hydrocarbons as solvents (11). The selectivities achieved for aldehyde production are between 70 and 90 per cent.
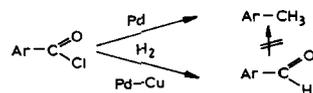

The alloying can be carried out during the preparation of the palladium catalyst or by metal adsorption at controlled potential onto the ready made palladium catalyst.

The following aromatic aldehydes were prepared by the hydrogenation of the corresponding acid chlorides using Pd-Cu/C catalyst:
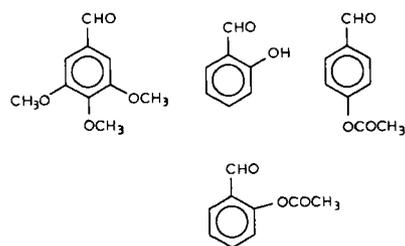

Poisoning the Catalyst: In addition to their use in alloying, anions and cations can also increase catalyst selectivity by poisoning. Sometimes they work by causing a reduction in catalyst activity. However, when used in small controlled quantities they can improve the selectivity of palladium catalysts, such as in the hydrogenation of nitroso lupetidine:
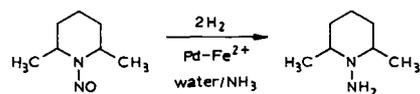
Additional advantages of this process are that water can be used as the solvent and that the reaction takes place at low pressure and temperature.

In the next example, Cl⁻ anions were used to increase the selectivity of the palladium catalyst. The reaction was first carried out in hydrochloric acid solution, but the reaction rates were slow. Then it was found that much higher reaction rates could be achieved in sulfuric acid
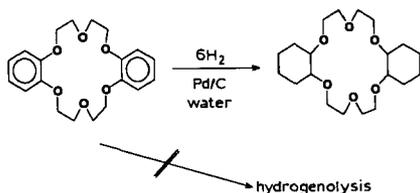
solution containing small amounts of chloride ions, without any loss in the 95 per cent selectivity obtained with hydrochloric acid solution.
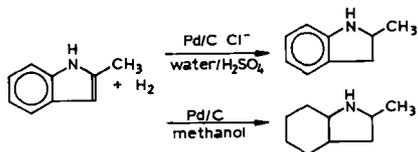
The reactions were carried out at 323 K and under 3 bars of pressure.

Optimised Reaction Conditions

Last, but not least, the optimisation of the reaction conditions is a good method to increase the selectivity:


In the palladium-mediated hydrogenation of dibenzo-18-crown-6 carried out at 423 K and under 10 bars of pressure, the proportion of products produced by hydrogenolysis was too high. By determining the optimal temperature, pressure, catalyst and substrate concentration, the selectivity was able to be increased from 40 to 65 per cent.

## Factors Affecting Regioselectivity
Optimised Catalyst Preparation

A new method of preparation was developed for palladium catalysts used in liquid-phase hydrogenations, in which a tetraalkyl ammonium palladate precursor is formed (12).
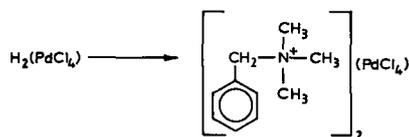
The resulting amine-containing catalyst has a dispersion > 50 per cent and gives higher selectivity (80 per cent) and activity for the

hydrogenation of naphthol to aromatic tetralol:
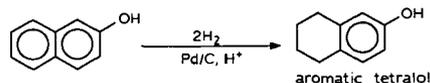
The Role of pH in the Stereochemistry

It is known that the pH of a reaction can influence product distribution; for example, when cyclic ketones are reduced, the pH affects the ratio of the product stereoisomeric alcohols, demonstrated by the hydrogenation of thymol and menthone. This experience has been used to develop the stereoselective hydrogenation of 4-acetyl-amino phenol.

Using water as the solvent and a basic buffer, the stereoselectivity towards trans-4-acetyl-amino cyclohexanol was 80 per cent in the palladium-mediated hydrogenation of 4-acetyl-amino phenol. However, when the same reaction was performed with Adams' platinum catalyst the stereoselectivity was only 40 per cent to the trans-4-acetyl-amino cyclohexanol. The trans product has two forms: the equatorial-equatorial and the axial-axial, with respect to the position of the two substituents. The form of the ketone containing the acetylamino substituent in the equatorial position can be adsorbed on the catalyst surface more easily. If the reduction of this form results in the equatorial alcohol, which is preferred in basic solution, the product will be an excess of the trans stereoisomer.
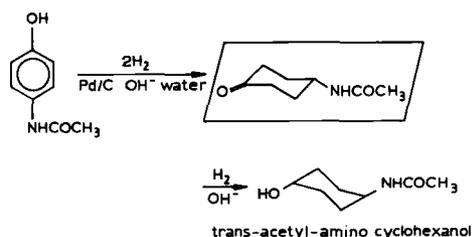
## Factors Affecting Diastereoselectivity

The most important factors, which influence diastereoselectivity, are:
• the properties of the molecule to be hydrogenated – the substituents of the unsaturated atoms
• the catalytically active metal, the support

that is used and its dispersion
- the solvent (protic-aprotic, polar-apolar)
- the preliminary reduction of the catalyst surface and its saturation with hydrogen
- the pH of the reaction mixture.

The hydrogenation of the Schiff-base prepared by the condensation of acetophenone and optically active 1-phenyl-ethyl amine is a good example for demonstrating these factors (13):
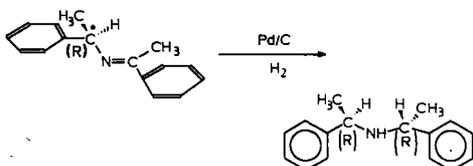
Here, in an apolar solvent, such as benzene, the diastereoselectivity is over 90 per cent when a palladium catalyst of small dispersion is used. This is determined mainly by the substrate itself, where the bulky phenyl group substituents tend to take up positions as far from each other as possible and are attached to the catalyst surface by anchoring with their π electrons. Therefore the most favourable substrate conformation on the surface is fixed, and if the direction of attack of the entering hydrogen is determined, it results in high diastereoselectivity.

(S)-Proline as a Chiral Auxiliary

(S)-Proline has proved to be an excellent homogeneous chiral catalyst, for example, for the Robinson-type condensation of α,β-unsaturated ketones. We investigated whether this could also be applied to heterogeneous hydrogenations (14).
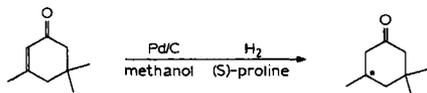
The hydrogenation of isophorone with a palladium catalyst, in the presence of stoichiometric amounts of (S)-proline and methanol as solvent at room temperature, resulted in the production of dihydroisophorone with enantiomeric excesses up to 80 per cent. However, after the uptake of more than one equivalent of hydrogen the chemical yield of dihydroisophorone

decreased significantly, giving the alkylated proline as the major product (15).

In the hydrogenation of acetophenone, with palladium and stoichiometric amounts of (S)-proline and methanol as solvent, the enantiomeric excess was around 20 per cent (16).
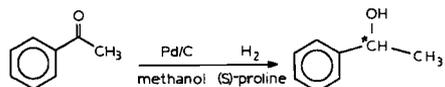
Kinetic investigations of the reactions above, using circular dichroism spectroscopic studies of the methanol solution of isophorone and proline, and the characterisation of the side-product alkylated proline led us to conclude that these reactions, while appearing to be enantioselective, are in fact diastereoselective, see Scheme I (14–19).

Enantioselective Hydrogenations

The scope of enantioselective heterogeneous catalytic hydrogenations using chirally modified catalysts is rather limited; they can only be used for the reduction of α-keto esters and β-diketones or β-keto esters. The use of chiral auxiliaries for similar purposes is no more successful, as was demonstrated using (S)-proline, where the enantioselectivity was remarkable, but the chemical yield was low. In order to find new chiral modifiers and auxiliaries a screening was performed and α,α-dihydro apovincaminic acid ethyl ester, a vinca-type alkaloid, proved to be an effective chiral modifier (20–22):
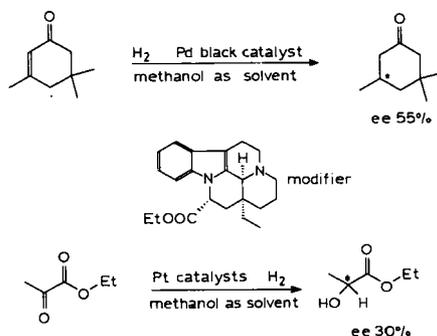
This modifier is effective in the palladium-mediated hydrogenation of isophorone and in

Scheme I

diastereoselective

carbinol amine

−H$_2$O

2H$_2$

chemo- and diastereoselective
Pd/C catalyst

H$_2$
+H$_2$O

enamine

Z E
iminium salts

2R,4S and 2S,4S
oxazolidinones

Scheme I
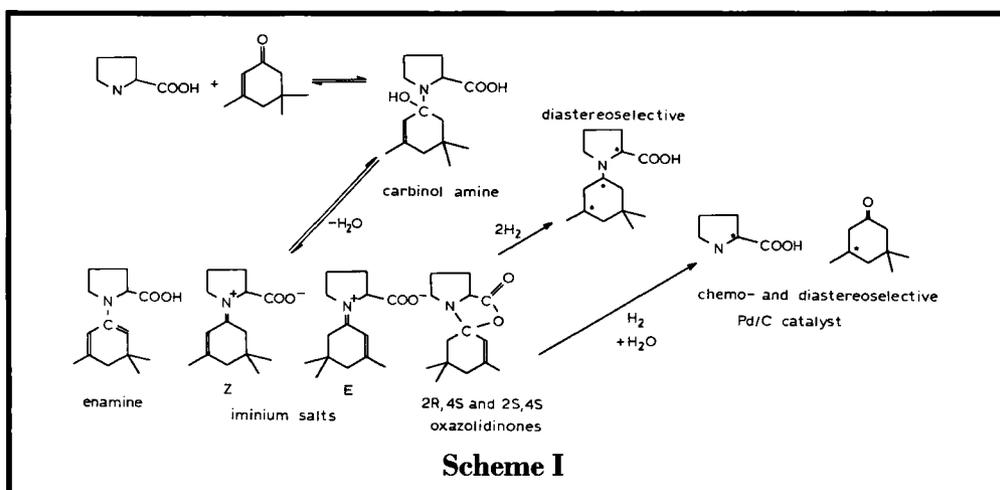
the platinum-mediated hydrogenation of ethyl pyruvate. According to circular dichroism spectroscopic investigations and studies of the enantioselective hydrogenations, the probable processes of enantiodifferentiation could be as shown in Scheme II.
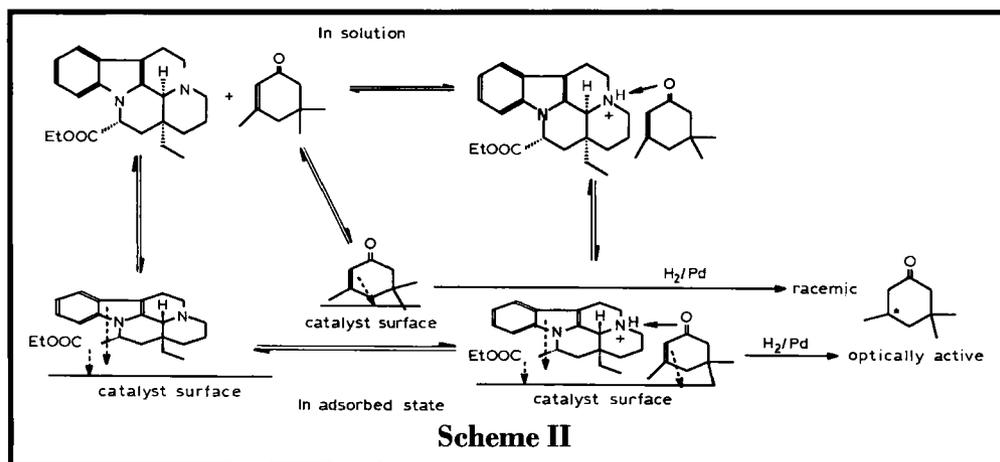
Similar processes may take place in platinum-cinchona and nickel-tartaric acid mediated reactions. The enantiomeric excess of the product depends, in each case, on the equilibrium constants of adduct formation and adsorption reactions and the relative rates of chiral and racemic reactions, which are competing hydrogenations.

This new modifier is somewhat broader in scope than previously used systems, but the enantioselectivities are only moderate. However, its study has contributed to improving the understanding of the enantioselective reaction mechanisms.

Conclusions

Liquid-phase hydrogenation has been demonstrated to be a versatile method in organic syntheses. It can offer – even for asymmetric reactions – good catalytic systems which, in some cases, afford chiral products with high stereoselectivity. The scope of the reactions involving mostly palladium-mediated hydrogenations shows the usefulness of these type of reductions among organic synthetic methods. Studying

In solution

EtOOC

EtOOC

catalyst surface

catalyst surface

In adsorbed state

catalyst surface

H$_2$/Pd → racemic

H$_2$/Pd → optically active

Scheme II

Production of Enantiomerically Pure Products by Heterogeneous Catalytic Hydrogenations			
Methods of enantioselective hydrogenation	Chiral modification of the catalyst	Use of chiral auxiliaries in the reaction mixture	Forming a new chiral compound with a chiral reactant for diastereoselective hydrogenation
Catalyst examples	Pt/cinchonidine/ ethyl pyruvate	Pd/(S)-proline/ isophorone	Schiff-bases from a chiral amine and a prochiral ketone
Optical purity	Good ⇒ excellent	Good	Poor ⇒ excellent
Chemical yield	Good	Poor	Acceptable
Scope	Narrow	Narrow	Broad
Possible industrial applications	Limited	None	Hopeful

asymmetric hydrogenations has a double impact: chiral compounds can be produced by such processes, in addition to giving detailed information about the elementary steps of surface reactions, for example about the processes involved in enantiodifferentiation.

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Small Compact and Portable Fuel Cell Systems

Fuel cells which transform the chemical energy in a hydrocarbon fuel and air directly into electrical energy have been an aim of electrochemists for nearly 70 years. Such a fuel cell conveniently fuelled by alcohols, principally methanol, would ideally have a high specific energy and be environmentally friendly, compared to the more traditional batteries presently available, in terms of recycling the materials of construction.

The major drive in fuel cell research has been towards producing mobile units that can power vehicles and towards static power supplies for local facilities, sometimes in remote locations. However these are generally fuel cells of 50 kW to MW size. There is a market for smaller, portable fuel cells for use in small-scale electrical equipment. These will have to operate at modest temperatures, be mechanically robust and show a high energy and power density for compactness.

For a small and cost effective direct methanol fuel cell showing high energy and power density there is a requirement for better electrocatalysts, and for the prevention of methanol crossover, which is the diffusion of methanol to the cathode. This results in a degraded performance through fuel loss and depolarisation of the air electrode. To overcome this an ultra-thin pore-free electrode – or barrier – made from transition element metals, such as palladium, which is permeable to hydrogen ions but excludes water and hydrocarbon fuels, has been developed. The metal membranes are formed by vacuum-deposition coating and plugging the pores of an etched nuclear particle track membrane. This membrane can be placed at either electrode or between them.

The use of a dielectric porous substrate onto which one or more fuel cells can be formed by vacuum deposition, has enabled multiple fuel cells and series connections to be made on the substrate, in a similar way to printed circuits (1, 2). These fuel cells, directly powered by methanol, and using small amounts of platinum as the electrocatalyst, could provide significant economic advantages when reduced to micro proportions. Together with advances in electrocatalysts (3) and with reduced methanol crossover, there are opportunities for using such small compact fuel cells as an effective alternative to current battery technology for powering a whole new range of portable electronic applications.   R. HOCKADAY

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Conference on the Chemistry of the Platinum Group Metals

The Seventh International Conference on the Chemistry of the Platinum Group Metals will be held at Nottingham University, England, from the 25th to 30th July 1999. Organised by the Dalton Division of the Royal Society of Chemistry, these conferences take place every three years, earlier ones having been held in Edinburgh, Sheffield, Cambridge, St. Andrews and York. Professor Martin Schröder is the convener.

Those who have accepted an invitation to speak in plenary and keynote lectures include: M. Abrams, G. S. Attard, C. Bianchini, D. G. Blackmond, H.-U. Blaser, B. Chaudret, R. H. Crabtree, N. Farrell, M. Fujita, R. H. Grubbs, B. F. G. Johnson, J. M. Kelly, G. van Koten, P. W. N. M. van Leeuwen, D. M. P. Mingos, K. Nozaki, L. A. Oro, P. G. Pringle, R. A. van Santen, J. P. Sauvage, M. D. Ward, V. W. W. Yan, L. J. Yellowlees, A. von Zelewsky and T. Ziegler.

Oral and poster contributions are welcomed. Persons wishing to submit either should send an Abstract, in the prescribed format, by 18th January 1999, to Dr John F. Gibson, 99PGM7, The Royal Society of Chemistry, Burlington House, London W1V 0BN; Fax: +44(0)171 734 1227; e-mail: Conferences@rsc.org.