

# Detailed Contents

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# **Catalysts, Reactors, and Reaction Parameters**

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## **1.1. Introduction**

Catalytic hydrogenation is one of the most powerful weapons in the arsenal of the synthetic organic chemist. Most functional groups can be readily reduced, often under mild conditions, and frequently in high chemo-, regio-, and stereoselectivity. At the conclusion of the reduction, hydrogen is allowed to escape, and the heterogeneous catalyst is filtered from the mixture, to leave a solution free of contaminating reagents. Homogeneous hydrogenation catalysts need to be removed otherwise, a major disadvantage of using this type of catalyst.

In the minds of many, especially those who have not had the opportunity to use it, catalytic hydrogenation has acquired an aura of mystery; the choice of catalyst seems capricious, operating conditions arbitrary, catalyst preparation secret, and the working of the catalyst unfathomable. It is the purpose of this work to meet these objections; to provide rationale for choice of catalyst and conditions; to acquaint the reader with catalysts, equipment, and procedure; and to impart the conviction that hydrogenation is a powerful, readily handled, broad-scoped procedure of general utility for synthesis in both laboratory and industrial plant.

## **1.2. Hydrogenation Catalysts**

Hydrogenation catalysts are of two types, heterogeneous and homogeneous. Heterogeneous catalysts are solids that form a distinct phase in the gas or liquid environment. The great majority of hydrogenations are done with this type of catalyst. Homogeneous catalysts dissolve in the liquid environment, forming only a single phase. Catalysts of this type are of relatively recent

origin; the first example was reported by Calvin in 1939 (27), but the area remained dormant until interest was spurred by the classic papers of Wilkinson on chlorotris(triphenylphosphine)rhodium(I), a catalyst that bears his name. Considerable effort has been expended in recent years in "anchoring" homogeneous catalysts to a solid, insoluble support in an effort to capture the best features of both types of catalysts (9,10,11,23,44).

Heterogeneous catalysts can be divided into two types; those for use in fixed-bed processing wherein the catalyst is stationary and the reactants pass upward (flooded-bed) or downward (trickle-bed) over it, and those for use in slurry or fluidized-bed processing. Fixed-bed catalysts are relatively large particles, 1/32 to 1/4 inch, in the form of cylinders, spheres, or granules. Slurry or fluidized-bed catalysts are fine powders, which can be suspended readily in a liquid or gas, respectively. Fixed-bed processing is especially suited to large-scale production, and many important bulk chemicals are made in this mode.

However, the vast majority of catalytic hydrogenations are done in a slurry process. Fixed-bed processing demands a dedicated unit, continuous production, invariant feed, large capital investment, and lengthy development to establish optimum conditions and adequate catalyst life. Slurry processes permit variations in the substrate as in hydrogenation of unsaturated triglycerides from a variety of sources, multiuse equipment, easily changed reaction conditions, intermittent operation, and relatively quick development time. Laboratory experiments are scaled up easily to industrial productions.

### 1.3. Choosing a Catalyst

The gross physical form of a catalyst is chosen to conform to the type of process to be used. The chemical and catalytic characteristics are chosen to achieve the desired reaction and, as an important corollary, to avoid undesired reactions.

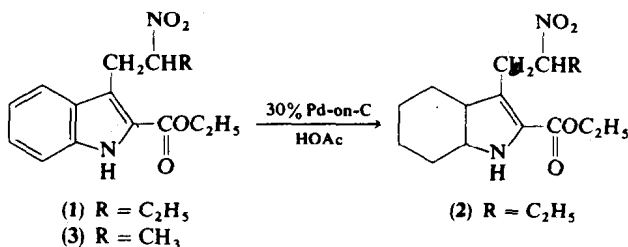
The literature on catalytic hydrogenation is very extensive, and it is tempting to think that after all this effort there must now exist some sort of cosmic concept that would allow one to select an appropriate catalyst from fundamentals or from detailed knowledge of catalyst functioning. For the synthetic chemist, this approach to catalyst selection bears little fruit. A more reliable, quick, and useful approach to catalyst selection is to treat the catalyst simply as if it were an organic reagent showing characteristic properties in its catalytic behavior toward each functionality. For this purpose, the catalyst is considered to be only the primary catalytic metal present. Support and



catalyst preparation usually have but secondary influences compared to the metal.\* Viewed this way, selection of a catalyst is no different than selection of any other reagent. One simply checks the literature to find what type of metal has proved active and selective previously. Many guides to catalyst selection are given throughout this work. Theoretically oriented scientists are apt to feel dissatisfied with this purely empirical approach to catalyst selection, but with the present state of the art no surer means exists short of a catalyst development program.

There is a complication in choosing a catalyst for selective reductions of bifunctional molecules. For a function to be reduced, it must undergo an activated adsorption on a catalytic site, and to be reduced selectively it must occupy preferentially most of the active catalyst sites. The rate at which a function is reduced is a product of the rate constant and the fraction of active sites occupied by the adsorbed function. Regardless of how easily a function can be reduced, no reduction of that function will occur if all of the sites are occupied by something else (a poison, solvent, or other function).

Adsorbability is influenced strongly by steric hindrance, and because of this almost any function can be reduced in the presence of almost any other function in suitably constructed molecules. A case in point is the reduction of the aromatic ring in **1** in preference to reduction of the nitro function, producing **2**. However, when  $R = \text{CH}_3$  (**3**) the nitro group was reduced instead, a fact attributed to a less sterically crowded environment (109).



The simplest guide for choosing a catalyst to achieve a selective reduction in a bifunctional molecule is from among those catalysts that are effective for what is to be achieved, avoiding those that are also effective for what is to be avoided. Guides for such a selection may be obtained from the chapters devoted to the chemistry of the functions in question. Selectivity can be influenced further by the reaction environment, solvent, and modifiers; these are discussed in other sections.

\* There are, of course, many preparations, some good, some poor, and the statement applies only to preparations yielding good, i.e., active, catalysts.

### 1.4. Choosing a Catalyst Support

Base metals frequently are used in nonsupported form, but noble metals rarely are, except in laboratory preparations. Supporting the noble metals makes a more efficient catalyst on a weight of metal basis and aids in recovery of the metal. Neither of these factors is of much importance in experimental work, but in industrial processing both have significant impact on economics.

A great many materials have been used as catalyst supports in hydrogenation, but most of these catalyst have been in a quest for an improved system. The majority of catalyst supports are some form of carbon, alumina, or silica-alumina. Supports such as calcium carbonate or barium sulfate may give better yields of B in reactions of the type  $A \rightarrow B \rightarrow C$ , exemplified by acetylenes  $\rightarrow$  cis-olefins, apparently owing to a weaker adsorption of the intermediate B. Large-pore supports that allow ready escape of B may give better selectivities than smaller-pore supports, but other factors may influence selectivity as well.

Materials, such as activated carbons, that are derived from natural products differ greatly in their effectiveness when used as catalyst supports, but it is difficult to delimit the factors present in the carbon that influence performance. Certain broad statements, such as that carbons with excessive sulfur or ash content tend to make inferior catalysts, only begin to touch on the problem. One of the advantages of buying commercial catalysts, instead of using laboratory preparations, is that commercial suppliers have solved this problem already by empirical testing of many carbons. They provide catalysts that are best by test.

### 1.5. Choosing a Metal Concentration

Metal concentration in hydrogenation catalysts varies from 100% metal to a small fraction of 1%. In laboratory experiments where economics is not a factor, noble-metal blacks (finely divided metal) or metal oxides are sometimes used, but these catalysts are seldom seen in industrial practice. More commonly, noble metals are supported, usually on a high surface material such as carbon or alumina, to facilitate metal dispersion and to aid in metal recovery. The lower the metal concentration the higher the specific rate (rate per unit weight of metal) (Table 1)(48). Offsetting the gains in metal efficiency, brought about by low metal concentrations, is the increased cost of making the catalyst. To maintain a certain metal level in the system, increasing amounts of catalysts are required as metal concentration is decreased. Supported noble metal catalysts are most commonly used in the 3-5% metal

TABLE 1  
Effect of Platinum Content on  
Cyclohexene Hydrogenation

% Pt-on- $\text{Al}_2\text{O}_3$	Specific rate
1.11	76
0.72	96
0.52	113
0.39	121

concentration range, a range apt to give maximum economy when all factors are considered.

More concentrated metals are sometimes used despite declining metal efficiency. These catalysts are used to decrease loss of valuable products by absorption on the carrier, to minimize the amount of catalyst to be filtered, to aid in settling of the catalyst, and to facilitate difficult reductions.

Base metals are much less active and are generally used in much higher metal concentration ranges up to 100%.

## 1.6. Choosing Conditions

Some hydrogenations require exacting conditions for optimal results but most do not. There is often a wide range of conditions under which satisfactory results can be obtained, which is one of the great assets of hydrogenation as a synthetic tool. The quickest way to success is simply to choose conditions that experience and literature deem reasonable and proceed. Satisfactory results will be obtained very likely. If satisfactory results are not achieved, the most fruitful approach is to ascertain what went wrong, e.g., poisoning, interaction with the solvent, coupling, poor selectivity, or overhydrogenation. It is very much easier to correct a problem if it can be identified. Frequently, potential problems can be identified in advance and corrective measures incorporated in the initial experiments.

## 1.7. Effect of Temperature

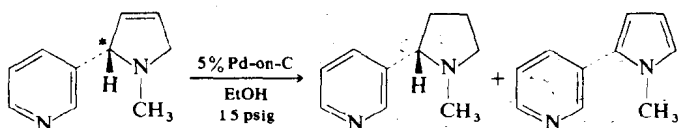
Temperature can have an important influence on rate, selectivity, and catalyst life. In general, the rate of hydrogenation rises with increasing temperature; the rate increase will be much larger when the reaction is

kinetically controlled than when diffusion limited. Catalyst life is often affected adversely by an increased temperature. A 2% palladium-on-carbon catalyst could be reused repeatedly at 69°C without loss in activity in reduction of *o*-nitroaniline to *o*-phenylenediamine in methanol, but at 90°C much activity was lost after one use (52).

Most hydrogenations can be achieved satisfactorily near ambient temperature, but in industrial practice the temperature is usually elevated to obtain more economical use of the catalyst and increase the space-time yield of the equipment. In laboratory work, a convenient procedure is to begin at ambient temperature, if reasonable, and raise the temperature gradually within bounds, should the reaction fail to go or if it is proceeding too slowly.

### 1.8. Prereduction

Prereduction of a catalyst is frequently practiced, that is, the catalyst, solvent, and hydrogen are shaken together before the substrate is added. One purpose of this procedure is to ensure that the measured hydrogen consumption arises only from uptake by the substrate. Another purpose is to activate the catalyst, and another is to eliminate induction periods. At times, selectivity of reduction may be changed by this procedure. For instance, more of the *cis*- $\beta$ -decalone was formed from hydrogenation of  $\Delta^{1,9}$ -octal-2-one over palladium when the catalyst was not presaturated than when it was (8). See also Ref. 34 for a further example of the hydrogenation of bisenones. Prereductions have been used to suppress unwanted dehydrogenation. Prereduction of 5% Pd-on-C was necessary in the hydrogenation of dehydronicotine to nicotine if formation of the aromatized nicotyrine were to be avoided (29).



Prereductions are usually not necessary and may even be detrimental (85,86). They are always time-consuming. As a practical matter, prereductions can usually be omitted and reserved only for those catalysts known to require it. Activation by prereduction of a catalyst is more likely to be required if the catalyst is to be used under mild conditions. It is a technique worth resorting to when a system, which literature and experience suggests should work, fails.

## 1.9. Measurement of Selectivity

There appears now and then in the literature a statement to the effect that the hydrogenation was not selective because there was no break in the hydrogenation rate curve or that the hydrogenation was not selective because absorption did not cease at a discreet number of moles of hydrogen. Statements of this sort arise from a misunderstanding. Neither the rate curve nor the moles absorbed at cessation have necessarily anything to do with selectivity. The only sure way of measuring selectivity is by analysis of the product at or near the theoretical absorption of hydrogen, where usually, but not always, maximal selectivity will occur. Reliance on rate curves as the criterion of selectivity may result in satisfactory reductions being discarded.

## 1.10. Catalyst Reuse

In commercial hydrogenations, a catalyst should be used as many times as possible consistent with adequate rates and selectivities. Each reuse lowers the cost of operation. Intervening regenerations may or may not be required between reuses. However, in experimental laboratory work the small savings are not worth the uncertainty introduced by reuse.

## 1.11. Synergism

Two catalysts together sometimes give better results than either separately. The effect may occur when the two catalytic elements are made into a single catalyst and also when two separate catalysts are used together. In the latter case, synergism can be accounted for by the assumption that the reaction involves two or more stages with neither catalyst being optimal for both stages. One could also assume that the second catalyst functions by its superior ability to remove an inhibitor that may form in the reaction. In either case, if one can guess the sequence of steps or the likely inhibitors, one can guess a reasonable second catalyst that, when mixed with the first, will produce synergism (82).

## 1.12. Solvents

Solvents are often used in catalytic hydrogenation (81). Solvents may be one of the best means available for markedly altering the selectivity, a fact not sufficiently appreciated. Solvents also help to moderate the heat of hydrogenation, to aid in catalyst handling and recovery, and to permit the use of solid substrates. A convenient solvent may be the product itself or the solvent used in a prior or subsequent step.

Solvents influence rate as well as selectivity. The effect on rate can be very great, and a number of factors contribute to it. In closely related solvents, the rate may be directly proportional to the solubility of hydrogen in the solvent, as was shown to be the case for the hydrogenation of cyclohexene over platinum-on-alumina in cyclohexane, methylcyclohexane, and octane (48). Solvents can compete for catalyst sites with the reacting substrates, change viscosity and surface tension (108), and alter hydrogen availability at the catalyst surface.

The amount of solvent relative to the amount of total catalyst is usually large, and the amount of solvent relative to the number of active catalyst sites larger still; very small amounts of inhibitors or poisons can have, therefore, large adverse influences on the rate of reduction. Solvent purity per se is of little regard in this connection, for gross amounts of innocuous impurities can be present without untoward effect.

Most workers in exploratory experiments use high grade solvents for it helps avoid complicating factors. Results thus obtained cannot necessarily be extrapolated safely to technical, reused, or reclaimed solvents, and serious errors have been made by doing so. If, in commercial practice, a lower grade solvent is to be used, its effect on the catalyst should be ascertained beforehand.

### 1.12.1. Influence of Solvent on Selectivity

At times, selectivity changes drastically with a change in solvent, providing one of the best means available for controlling selectivity. The powerful influence of solvent is insufficiently appreciated and its efficacy often overlooked. There are many examples, so many that it is difficult to make encompassing generalities.

One very useful, although fallible, generality is that in a series of solvents the extremes of selectivity will be found at the extremes of the dielectric constant with two provisos; (a) alcohols sometimes should be considered separately,

and (b) the charge on the species undergoing hydrogenation should not change. Selected data of Augustine (7) on the hydrogenation of  $\beta$ -octalone illustrates appreciable selectivity changes with solvent and the first proviso. The differences in results between methanol and *t*-butanol is particularly striking since these are closely related compounds. Note that in this case selectivity moves with dielectric constant in opposite directions in protic and aprotic solvents. Reasons for these results are discussed by Augustine (7).

Solvent	% <i>cis</i> -2-Decalone	Dielectric constant
Methanol	41	33.6
<i>t</i> -Butanol	91	10.9
Dimethylformamide	79	38.0
<i>n</i> -Hexane	48	1.89

*cis*-2-Decalone is obtained in 99.5% yield by palladium-catalyzed hydrogenation of the octalone in tetrahydrofuran containing hydrogen bromide, a solvent system used with much success in the hydrogenation of 3-oxo-4-ene steroids to the 5 $\beta$  compounds (101).

Selected data of Wuesthoff and Richborn (112) on the hydrogenation of the vinylcyclopropane **4** further illustrates the effect of solvent on selectivity as well as the reason for the second proviso.

Solvent	% <b>5</b>	% <b>6</b>
50 % Aq ethanol	23	77
Hexane	68	32
85% Aq ethanol, 0.1N NaOH	84	16

The basic solution, which now contains the enolate ion, gives much different results than those obtained in neutral media. More of the hydrogenolysis product (**6**) is obtained in polar 50% aqueous ethanol than is obtained in the

nonpolar hexane. This latter single bit of data can be used to illustrate a good working generality. One of the most common of competing systems is some sort of hydrogenation versus some sort of hydrogenolysis. The generality is that the hydrogenation product is favored by the less polar solvent, the hydrogenolysis product by the more polar solvent, as illustrated above. The generality applies to a variety of competing reactions including saturation of vinylic, allylic, benzylic, and ring-substituted molecules versus loss of function by hydrogenolysis.

### 1.12.2. Effect of Acidity

In general, the hydrogenolysis product is also favored by an acidic medium, as illustrated in the hydrogenation over 5% palladium-on-carbon of acetophenone to the hydrogenation product phenylethanol and to the hydrogenolysis product ethylbenzene, with various additives present (83).

Moles of additive per mole of acetophenone	Maximum % phenylethanol
None	90
0.20 Acetic acid	60
0.014 Hydrochloric acid	76
0.008 Sodium hydroxide	100

Other workers have obtained higher yields of phenylethanol in absolute methanol; the 90% yield reported above was probably due to traces of residual acid remaining from the catalyst preparation. Note that hydrogenolysis with this catalyst can be prevented completely by traces of base; addition of base is often a useful means of preventing or minimizing unwanted hydrogenolysis in a variety of systems.

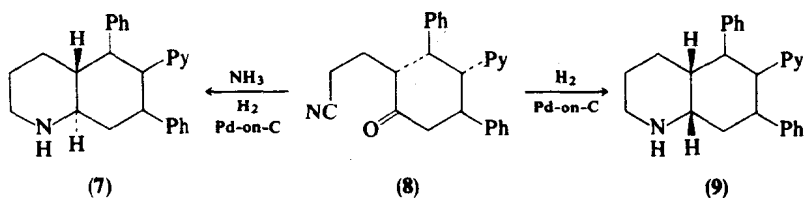
Unrecognized traces of residual acids or bases in catalysts is one reason investigators have failed to duplicate the work of others (or their own). On the other hand, this variable often has little or no influence. Acidity of a catalyst can be readily checked by slurring it in water and measuring the pH.

### 1.12.3. Reactive Solvents

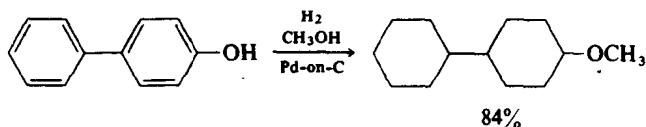
Solvents may enter into the reaction sequence transiently or permanently. Well-known examples of the transient participation of solvent are the use of



ammonia to prevent secondary and tertiary amine formation in the hydrogenation of nitriles, oximes, or anilines. Ammonia enters the product permanently in other reactions such as reductive alkylations with aldehydes or ketones. Ammonia has been used to change stereochemistry as in reduction of 8 to either 7 or 9 (77). In the absence of ammonia, the nitrile is reduced to an amine, which undergoes intramolecular reductive alkylation with the carbonyl group; in the presence of ammonia reductive alkylation at the carbonyl group occurs to give the equatorial cyclohexylamine, which in turn reacts with the intermediate aldimine, followed by hydrogenolysis to 7.



Solvents sometimes participate in the reduction unexpectedly. For example



This ether formation arises from conversion of the phenol to a cyclohexanone, and ketal formation catalyzed by Pd-H<sub>2</sub> and hydrogenolysis. With Ru-on-C, the alcohol is formed solely (84).

### 1.13. Safety

There are several sources of potential danger in catalytic hydrogenations; these are failure of equipment because of excessive pressures, solvent fires, explosions and fires from mixtures of hydrogen in air, and, with finely divided carbon supports, dust explosions. None of these should cause concern, for all may be avoided easily.

Unlike reactions such as certain oxidations and polymerizations, hydrogenations will not detonate unless the substrate or solvent itself is explosive or undergoes extensive decomposition. Excessive pressures can only come from overpressuring the reaction vessels and from pressures generated by large