

Advances in  
Organic Chemistry  
*Methods and Results*

VOLUME 8

*Edited by*  
EDWARD C. TAYLOR

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## Preface

When this series was inaugurated eleven years ago, we felt it necessary to offer some special justification for the addition of still another treatise to the popular sphere of organic chemistry, which exercises such a perennial fascination for the scientific publisher. The stated goal was to provide a critical appraisal and evaluation of new discoveries in organic chemistry ripe for further development and of novel extensions to well-established methods. We aimed at bridging the time gap that inevitably intervenes between the evolution of new ideas, techniques, and methodologies and their appreciation and general use by organic chemists. It was recognized that, ideally, the authors of such articles should be either the originators of the methods described or practitioners expert in their use.

I hope that this volume, the eighth in this series, successfully fulfills these exacting objectives. The Birch reduction is finally reviewed, in collaboration with Subba Rao, by the master himself; this is the definitive treatment of this now classical synthetic method. The chapter by Story and Busch on new synthetic routes to macrocyclic compounds presents, for the first time, full details on their versatile ketone peroxide fragmentation procedure, which promises to be a very significant contribution (both scientifically and economically) to this field. Synthetic organic chemists should welcome the definitive, exhaustive, and critical discussion of silylation by Klebe, who has personally contributed so much to the development of this important technique. Comprehensive reviews by McOmie and by Boissonnas on the design and use of protecting groups in organic synthesis were published in Volume 3 of the series. In this volume, a complementary exposition of the latent functionality concept of protecting groups is given by Lednicer; not only has there been no previous review of this intriguing and widely applicable concept, but also the concept itself is formalized for the first time. Wiesner gives us a masterful presentation of a great achievement in the art of structure elucidation, the unraveling of the molecular intricacies of the alkaloid ryanodine. The volume concludes with the chapter by Jones and Bartle on the use of N.M.R. in structure identification of polycyclic hydrocarbons; as a comprehensive review of applications of a now broadly used

physical technique to this specific field, it represents a unique and useful contribution.

I hope that these essays on the development and applications of synthetic and physical methodologies, complete with experimental details, will be of broad interest and utility to organic chemists. Opinions, criticisms, and suggestions for incorporation into future volumes are welcomed.

Dr. Johann F. Klebe died suddenly on September 22, 1971. His tragic death represents a profound loss to his family and friends, to General Electric, and to science. His chapter on silylation is his final contribution to organic chemistry.

EDWARD C. TAYLOR

*Princeton, New Jersey*  
*December 1971*

*Publisher's Note.* The composition used for this book is a departure from that in the earlier volumes in the series. The change was made in the interest of continuing the series in the face of steadily rising costs. We hope the reader will accept this new format. There will be no change in the high quality of the articles already established for the series.

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# REDUCTIONS BY METAL-AMMONIA SOLUTIONS AND RELATED REAGENTS

By A. J. BIRCH and G. SUBBA RAO, *Research School of Chemistry, Australian National University, Canberra, Australia*

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### I. Introduction

The aim of this chapter is to summarize those aspects of the organic reactions of solutions of metals in liquid ammonia, amines, or appropriate dipolar solvents that render them uniquely or outstandingly useful from a synthetic point of view. Reactions, where they are not greatly or usefully different from those of other dissolving metal reagents, are mentioned only for the understanding of theoretical points. Understanding of theory in this field is more important than in most, even from the angle of relatively routine experimental employment; experimental conditions frequently have a drastic effect on the reaction products, and a close control over products requires a good understanding of the reactions involved. It is now becoming increasingly possible to predict appropriate experimental conditions for achieving a given objective, to control degrees of reduction, and to isolate intermediates. It is not unusual to find reported in the literature the failure of a reaction, when this was carried out under obviously inappropriate conditions for the desired objective.

This chapter cannot cover all of the papers published in this field; we believe, however, that it covers the majority of those which contribute to a fundamental understanding of the reactions and their practical utility, and provides essential points of entry to the general literature. Organometallic compounds are not covered.



## II. Historical

The alkali and alkaline-earth metals dissolve in liquid ammonia and in hexamethylphosphoramide to give solutions which behave as if they contained metal cations and "solvated electrons." Discussions as to the type of interaction implied by the last term are still inconclusive (1), but the solutions, particularly in ammonia, provide the organic chemist with a source of highly reactive electrons which can be used to carry out a number of difficult reduction reactions.

Reactions of the solutions with aromatic substances first drew attention to their unique character: in many cases saltlike substances were formed containing mesomeric carbanions; see, for example, Ref. 2. Several notable events in the development of their use were the demonstration of the reduction of naphthalene to 1,4-dihydronaphthalene (2), the reduction with calcium hexammoniate of benzene to 1,4-dihydrobenzene, and under different conditions, of benzene or substituted benzenes to cyclohexenes (3), of the production of 1,4-dihydrobenzene from benzene by the joint action of sodium and ethanol in liquid ammonia (4), and of 2,5-dihydroanisole from anisole (5). Synthetic use of these findings led to one of the two present major fields of utility: the partial reduction of aromatic systems. The other major utility lies in the frequent stereospecificity of the reductions first observed in the reduction of acetylenes (6), noted as a possibility in other cases (7), and generalized (8) with modifications (9,10). Theoretical ideas on distinctions between the products of reactions controlled by rates and by equilibria which arose from the reduction work (11) and which were later elaborated (12,13) had much wider applications.

On the experimental side, highlights include the completion of the total synthesis from estrone of 19-nortestosterone, the first potent synthetic hormone other than an estrogen (14). This type of reduction, with experimental modifications, is employed industrially on a large scale (15,16). Another noteworthy example is a stereospecific synthesis of steroids (17) with the efficient production of a number of centers of correct configurations. Ether fission reactions have enabled the structures and configurations of the bisbenzylisoquinoline alkaloids to be determined (18) and there have been other applications in structure work. In recent years such reductions have largely rendered unnecessary the catalytic hydrogenation of an aromatic compound as a step in synthesis.

## III. The Solutions

### A. THE METALS; PURITY OF THE AMMONIA

As already noted, alkali and alkaline-earth metals dissolve at the boiling point of ammonia ( $-33^{\circ}\text{C}$ ), but the solutions most frequently employed in practice are of lithium, which is very soluble and can form a concentrated solution of composition  $\text{Li}(\text{NH}_3)_4$  with almost no vapor pressure even at room temperature or of sodium, or occasionally of calcium. Evaporation of solvent ammonia

usually regenerates the metal, although "ammoniates," for example,  $\text{Ca}(\text{NH}_3)_6$  (19), may be formed as intermediates. Lithium, which is very soluble in ammonia, dissolves in some primary amines, for example, ethylamine (20) or ethylenediamine (21), but other metals are little soluble in such solvents with the occasional exception of the sodium-potassium alloy. There is some evidence that the electrons in amine solutions may be more chemically reactive than in ammonia, possibly because of a smaller degree of solvation stabilization.

Calcium solutions are usually employed when relatively low basicity is required, for example, in reduction of  $\alpha$ -acetoxyketones (22). More extensive investigations of the uses of other metals might be profitable; for example, the production of insoluble salts may protect intermediates in some cases, a possible contributing factor to the utility of calcium. Europium and ytterbium have been used in ammonia at  $60^\circ\text{C}$  to reduce benzene to cyclohexa-1,3- and 1,4-diene, and cesium (2 atoms) adds to ethylene (23). Magnesium and alcohols in ammonia have been used to reduce benzoic esters or amides and some polycyclic hydrocarbons (24).

The solutions often form two immiscible phases (1), a tendency enhanced by the presence of salts or of organic solvents, globules of a concentrated "metallic" phase appearing. Phase separation is more marked with the alkaline earths than with the alkali metals. However, organic solvents can usually be admixed, particularly with lithium solutions (16,25). In fairly dilute solutions reactions of the metals with alcohols to evolve hydrogen gas are quite slow, after an initial fairly rapid reaction; the base formed in the reaction acts as an inhibitor (26). The rate of gas evolution increases with the acidity of an added proton source: ammonium salts react very rapidly, water and methanol quite rapidly, and *t*-butanol very slowly. This reaction, like that with pure ammonia itself which is normally very slow, is greatly subject to catalytic acceleration, particularly by traces of transition metals (5,16). Pure ammonia is therefore greatly superior as a solvent and this superiority manifests itself particularly for slow and difficult reductions in the presence of alcohols, such as that of some substituted benzenes to dihydrobenzenes (16). The deliberate addition of ferric chloride has been used to limit the extent of reductions; anthracene and phenanthrene, for example, react very readily in the 9,10 positions, and this reduction step is not notably inhibited by the presence of iron, although further reduction is prevented (27). Clean partial reduction can therefore be achieved.

If pure ammonia is used, the choice of the metal does not seem to be crucial (16) and in most cases where reduction proceeds with ease sodium can be efficiently used. With more difficult cases lithium still seems to have an advantage, probably because of a mixture of factors, including the effect of the cation. Ion-pair formation may be involved, since the addition of lithium bromide to sodium reductions was found to be favorable (28). The lower basicity of lithium salts, including the amide, results in fewer secondary processes; the greater solubility of the metal in mixed solvent systems helps in cases of difficult solubility, and lithium is less sensitive to catalysis in the competing reaction of the metal with ammonia or an alcohol. This last factor is

possibly the main reason why lithium seemed to be outstanding before it became customary to use pure redistilled ammonia.

#### B. OTHER AMINES

The use of solutions of metals in other amines is limited to primary aliphatic amines of low molecular weight, such as methylamine or ethylamine (20) or anhydrous ethylenediamine (21), and to metallic lithium. The chemical nature of the blue solutions of alkali or alkaline earth metals in hexamethylphosphoramide is not clear; these solutions are rather unstable but can also be used for many reduction processes (29). However, the use of mixtures of solvents (30) could be further explored. For example, lithium dissolves readily in small volumes of ammonia; the resulting solution can then be added to ethylamine to give a solution or dispersion which is very reactive. In ethylamine alone the metal dissolves slowly; continuous shaking or stirring during the reaction is required.

Lithium can be used with mixed amines, including secondary plus primary amines (31). A solution of sodium, lithium, or barium in trimesitylborane has recently been used to reduce the conjugated octalone-2 to *cis*- and *trans*-decalone-2, the proportion of *cis* being much higher than with ammonia as solvent (32).

#### C. SOLUBILITY OF ORGANIC COMPOUNDS; MIXED SOLVENTS

Although many organic compounds, particularly those containing polar or hydrogen-bonding groups, are soluble to a useful extent in ammonia, solubility usually decreases in the presence of inorganic ions. Admixed solvents such as polar ethers (tetrahydrofuran, ethylene glycol dimethyl ether, and dioxane) or alcohols [ethanol, *t*-butanol, and *t*-amyl alcohol (5,33)] up to about 30% by volume and occasionally more can be helpful to solubility, if their presence is compatible with the desired process. Such admixture is usually not necessary for readily soluble compounds unless alcohols must be present for chemical reasons. Many substances which are rather insoluble can frequently be reduced in a sufficiently dispersed form; such dispersion can usually be achieved by adding them in solution in another compatible solvent which dissolves in ammonia. Reduction products of aromatic compounds are frequently more soluble in ammonia than the starting materials, so that insoluble compounds often dissolve as the reaction proceeds.

Many organic compounds are more soluble in amines such as methylamine, ethylamine, and particularly anhydrous ethylenediamine than in ammonia. Hexamethylphosphoramide is also a good solvent for many organic substances.

### IV. The Reduction Process

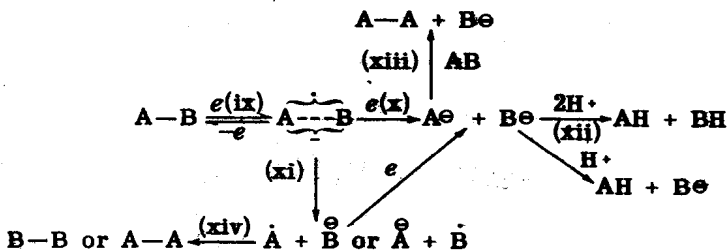
Two basically different final consequences become apparent in reductions. A molecule can give rise to initial addition products with the metal, which then

### A. ADDITION REACTIONS

[illegible]

### Schönitz 1

The possible processes involving A—B are shown in Scheme 2.



### Scheme 2

The electron addition stage is usually a reversible equilibrium, and the electron can often be removed completely in various ways from the adduct (34). The position of the equilibrium should be affected by the solvation of both ions involved, a probable reason for the favorable effect of ammonia as a dipolar molecule in encouraging the production of ions. The rate of the overall reduction can be affected by the rate of addition of the electron, or by the equilibrium position which determines the concentration of anion radical. The rate should be first order in metal and substrate if their concentrations are involved in this way. This has been claimed (28) but disputed (35) in the case of reduction of benzene with sodium and ethanol in ammonia. However, the original conclusions may well be correct so far as this stage of the process is concerned.

The position of the equilibrium is related to the structure of the substrate in predictable ways. The greater the extent of the unsaturation, the higher the electron affinity of the system, and the greater the ground-state strain, the more the equilibrium will tend toward addition. Conversely, the greater the stabilization of the ground state, as in aromatic compounds, the further the equilibrium will be towards dissociation. Since rate of reduction is dependent, as one factor at least, on the equilibrium concentration of anion radical, it can be qualitatively related to these factors. As examples of compounds of greater electron affinity, both naphthalene and pyridine are more readily reduced than benzene; as an example of stabilization of the substrate, benzene is less readily reduced than cyclohexa-1,3-diene. The effects of substituents are largely predictable. Isolated double bonds are difficult to reduce at all, and the rate of reduction depends on the degree of alkyl substitution in the order  $\text{CH}=\text{CH}_2 > \text{C}=\text{CH}_2 > \text{RCH}=\text{CHR}' > \text{RCH}=\text{CR}'\text{R}'' > \text{RR}''\text{C}=\text{CR}'\text{R}''$  (36). Only the first two types are reducible in ammonia, but the others can be slowly reduced in amines (37), possibly because of the greater activity of the electron in these solvents. The order of reduction rates may be determined by the inductive effects of the attached groups and by their effects on solvation and the situation of the adjacent metal cation; all of these influences would retard reduction of more highly alkylated double bonds.

### 2. Stage ii

A second electron is added only slowly because of the negative charge already present. Solvation can be critical in formation of the dianion if the electron addition is reversible. This factor is clearly illustrated by the distinction between polar ethers and ammonia in the addition of sodium to naphthalene (38). In the ethers, one atom of sodium is added reversibly to give a green salt of an anion radical, and in ammonia two atoms give the red salt of a dianion, also reversibly. Whether two electrons can be added depends on the structure of the molecule; the addition is favored by extended unsaturation and by appropriate positioning of atoms such as nitrogen or oxygen, of higher electron affinities than carbon, so that they can stabilize the negative charge. Polycyclic aromatic compounds, in contrast to monobenzenoid ones, form dianions readily, and differences in the nature of products formed by reduction using two processes: (1) sodium and an alcohol; and (2) sodium alone followed by ammonium chloride or other proton source have been interpreted (13,39) as being due in the first case to protonation of an intermediate anion radical and in the second case to protonation of a dianion.

### 3. Stage iii

This reaction is often irreversible. Whether it is depends on the acidity of the proton source, that is, on the basicity of its conjugate base. The effect of alkoxide ion in slowing the reduction of benzene (26) is clear evidence that the protonation step is reversible under these conditions. Owing to electronic stabilization an anion radical is far less basic than a similar monoanion, and,

experimentally, protonation of anion radicals derived from aromatic compounds is very slow and incomplete unless "acids" more acidic than ammonia ( $pK_a \sim 34$ ), such as alcohols ( $pK_a = 16-18$ ), are present. This explains the necessity for the presence of alcohols in the standard reduction of monobenzenoid compounds in ammonia; in their absence the low concentration of anion radical is not further transformed. With amine solvents the very slow reduction of monobenzenoid compounds may be due to the higher reaction temperatures (0-100°C), with slow protonation becoming possible; this view is supported by the occurrence of similar reductions in ammonia itself at higher temperatures than the boiling point under pressure (40). An alternative possibility in such cases is the production of small amounts of the more basic dianion, particularly in amines, where the electrons are probably more reactive. In amines the use of an added alcohol greatly speeds the reductions (41), and the combined reagent has more powerful reducing properties than the ammonia-lithium-alcohol system and can accomplish the efficient reduction of a tetrasubstituted ring in a hydrophenanthrene (42), a process which is very slow and difficult with lithium and *t*-butanol in ammonia (43). So far such solutions have been virtually unused for synthetic purposes.

#### 4. Stage iv

Reduction of a radical would be expected to be very rapid in a medium which is an electrical conductor containing excess of reducing agent. Dimerization of such radicals is therefore likely to be a minor process.

#### 5. Stage v

Protonation of a monoanion is likely to be rapid and complete for carbon systems because of the very high basicity of such anions. The mesomeric cyclohexadienyl anion, for reasons noted below, is experimentally found to be comparable in basicity to an amide anion, and clearly should undergo equilibrium protonation by solvent ammonia, and should be rapidly protonated by more acidic sources, with the equilibrium well towards the product.

#### 6. Stage vi

The dianion should be very highly basic. Experimental evidence shows, for example, that the naphthalene dianion is rapidly protonated at the boiling point of ammonia by the solvent, although more slowly at -80°C (2). Protonation presumably occurs in two stages with the formation of an intermediate mesomeric monoanion, analogous to but not necessarily identical with that considered under Section IV.B.5, depending on the position taken up in the mesomeric system.

#### 7. Stage vii

Anion radicals are unlikely to dimerize because of their charge; the protonated species can do so, but are unlikely to do this in competition with reduction.

#### 8. Stage viii

As discussed below, there is a strong possibility with some monobenzenoid systems that expulsion of a hydride ion may occur to some extent, with regeneration of the aromatic system. The result is catalysis of hydrogen gas evolution.

#### 9. Stages ix, x, and xi

The effects of substitution of the system in, for example, the fission of allyl alcohols, are in accord with expectation on the basis of the production of intermediate mesomeric anions as the rate-determining step. The products also usually correspond to the formation of two anions. It is not clear, however, whether this implies that the rate-determining step involves two electrons. The effect of substituents on a transition state involving the addition of one electron could well be that experimentally observed (see below), and any radical formed by fission in this way would clearly be rapidly converted into an anion in a subsequent process. An investigation of a number of cleavage reactions leads to the conclusion that probably a two-electron addition is in fact involved with allylic systems, and that in some cases at least dimeric products do not result from radicals, but by attack of an anion on the original molecule (44). The question still, however, seems open. The reaction normally occurs readily only when one of the resulting anions is the conjugate base of a fairly acidic acid: acetates, for example, cleave much more readily than alcohols.

#### 10. Stages xii, xiii, and xiv

These represent possible alternative explanations for the dimeric products sometimes encountered. There is clear evidence for Stage xiii in some cases (44). Since one or both  $A^-$  and  $B^-$  are usually mesomeric if organic, the protonated products AH and BH (Stage xii) may be mixtures of isomers.

### V. Reductions of Unsaturated Systems

Some characteristics in which the reagents differ from other systems in ways which render them useful are as follows:

1. Experimentally the stages of electron addition and of protonation can often be separated. This has consequences both in theoretical interpretations and in the arrest of reductions at intermediate stages.

2. The acidity of an added proton source can be varied widely and conveniently from ammonia or the amine solvent to alcohols and strong "acids" such as ammonium salts. Consequently the nature of intermediates can be altered in a number of instances, in the presence of reducing metal, leading to different final products.

3. Temperatures can be controlled and the lifetimes of unstable intermediates can be extended in some cases until work-up.

4. Control of the basicity of the reagent (buffering) can induce or inhibit conjugation of unsaturation in intermediates and alter the degree of reduction of final products.

5. Steric control can be exercised frequently, in the sense that predominantly a predictable isomer is obtained.

6. Selectivity in reduction of unsaturation, or in fission reactions, particularly of ethers, is frequently high and may differ from that observed with other reagents.

7. The reagents are the most powerful chemical reducing agents known, and correctly used can result in the specific partial reductions of monobenzenoid systems.

In order to achieve a desired result the experimental conditions must be very carefully chosen using two types of procedure:

1. Reaction with a metal under conditions where the anion radicals or anions resulting are not protonated until work-up.

2. Reaction with a metal in the presence of a proton source where the resulting anion radicals or anions are (a) irreversibly, or (b) reversibly, protonated according to the acidity of the proton source and the basicity of the anions.

Quite different products may result, for a variety of reasons, from these different procedures, and it is necessary to consider some fundamental questions before proceeding to detailed considerations of cases.

#### A. METAL ADDITION FOLLOWED BY PROTONATION

A mesomeric anion formed by electron addition is inhibited from further electron addition by its negative charge. Whether only one, or two, electrons can be added depends on the structure of the compound as discussed below. Monobenzenoid compounds, for example, are in equilibrium with anion radicals; many polycyclic compounds form dianions readily. There is no evidence that an intermediate carrying more than two electrons in the same system is ever involved. The earlier reductions of polycyclic aromatic compounds by Hückel and Bretschneider (2) were carried out by this method.

Because of survival of the intermediate, implying its inability to abstract a proton from solvents such as ammonia, the reduction products are those resulting from the addition of only one or two electrons. The protonation of some anion radicals on work-up leads to the formation of aromatic starting material and a dihydro product, apparently by disproportionation.



Examples are quoted below, but two illustrations can be given. The reduction of  $\alpha\beta$ -unsaturated ketones with lithium in ammonia leads to saturated ketones (45)



In this case the mesomeric carbanion probably is basic enough to abstract a proton from ammonia; the enolate anion is not ketonized until work-up and is therefore not reducible. Another example of a protective negative charge in directing the course of reaction is the reduction of *o*- and *p*-hydroxyacetophenones (46). These yield the pinacols, rather than the carbinols; presumably the formation of a dianion is inhibited by the *ortho* or *para* charges on the ring and the protonated anion radical dimerizes. In contrast, *m*-hydroxyacetophenone gives the carbinol.

The practical result of this general type of process is that, provided the electron-addition equilibrium lies towards a product, and provided the resulting anions are not protonated under the conditions of the reaction but only on work-up, it is possible to obtain final partially hydrogenated products even when such products are themselves reducible. Among compounds appropriate to the method are aromatic acids, amides, and polycyclic compounds.

Other effects of anion formation including inhibitions of cleavage reactions are noted later.

Theoretically, as discussed below, the products obtainable from protonation of an anion radical intermediate *in situ* or from a dianion by subsequent protonation could differ, as has been pointed out by Hückel (1).

In order to avoid reduction of protonated products by excess metal during work-up it is often advisable to destroy the latter. This frequently may be accomplished by addition of ammonium chloride or water; hydrogen gas is produced at a rapid rate, but this is without effect on the reduction product. However, the addition of benzoic acid, which is very rapidly reduced, is useful provided the product is not acidic. The addition of traces of ferric salts, or of sodium nitrite, also results in removal of metal.

## B. METAL ADDITION IN THE PRESENCE OF A PROTON SOURCE

### 1. Effects on Primary Reduction Stages

The presence and acidity of a proton source other than ammonia or an amine can have profound effects on whether reductions occur at all and on the structures of the products.

As has been explained above (Section IV.C), the reduction of monobenzenoid compounds, other than carboxylic acids and amides, does not occur in the absence of a proton source such as ethanol. The observation of Wooster (4) that the joint action of sodium and ethanol in ammonia or benzene gives