REDUCTION OF HETEROCYCLIC COMPOUNDS BY METAL-AMMONIA SOLUTIONS AND RELATED REAGENTS

Arthur J. Birch* and Jacob Slobbe

Research School of Chemistry, The Australian National University, P.O. Box 4, Canberra, A.C.T. 2600, AUSTRALIA.

The theoretical and practical bases of the metal-ammonia and related reductions of heterocyclic compounds are reviewed. No attempt to summarise all extant results has been made, but rather a critical evaluation of possible procedures is illustrated by pertinent examples. The headings in order are:

Introduction, structure and reducibility
The addition of the first electron
Further reactions: (i) Protonation of $A^{\pm}$
(ii) Dianion formation (iii) Dimerisation
Cleavage reactions
Oxygen heterocycles
Sulphur heterocycles
Results of different proton availabilities
Uniquely available compounds

Introduction

Useful practical variants of reduction reactions by alkali metals in ammonia or related solvents continue to evolve. However, a close appreciation of the theoretical background is needed in order

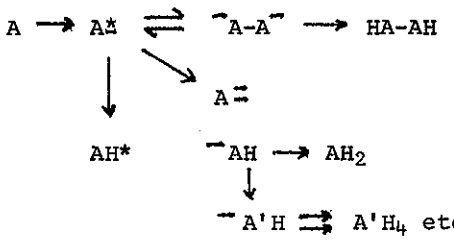
to choose the correct conditions for a given substance and a desired result. While a theoretical basis has been discussed for carbocyclic aromatic substances, no systematic examination has been made of heterocyclic compounds. Some aspects have been reviewed in more general articles[1,2,3].

The aim of the present review is to survey results in key instances, and to relate the theoretical aspects to the experimental conditions needed to achieve defined objectives. It is possible a number of failures in the past can be attributed to the use of unsuitable conditions.

For convenience, this survey can be related to two aspects: an initial addition of one or of two electrons and how this is affected by structure and conditions, and the subsequent fates of the radical anions or dianions so generated.

The decisive step in a reduction is addition of the first electron. Reducibility may be defined in terms of whether this happens to an extent which makes possible further steps. These can include overall hydrogenation, involving another electron and two protons; hydrogenative dimerisation, involving two protons, and possible further steps of electron and proton addition; isomerisation, cleavage, and so forth. The results are critically dependent on the nature of the initial substrate, and the reaction conditions. An understanding of the mechanisms of the processes is required in order to suggest appropriate conditions for a given substrate and a required result.

The summary of the major possible reactions is shown below, where A' represents an isomerised product



The first electron

The first, and usually rate-limiting stage, is the reversible addition of a solvated electron in what amounts to an internal electrolytic reduction[4]. For a substrate A, the equation may be written

$$M^{+}_{solv_1}\cdots e_{solv_2} + A_{solv_3} \rightleftharpoons A^{\ddagger}_{solv_4}\cdots M^{+}_{solv_5}$$

To study the position of such an equilibrium, which is probably a slow reaction compared with most subsequent stages, and the concentration [A‡] which probably defines the overall rate, the structural and solvation factors must be at least qualitatively elucidated.

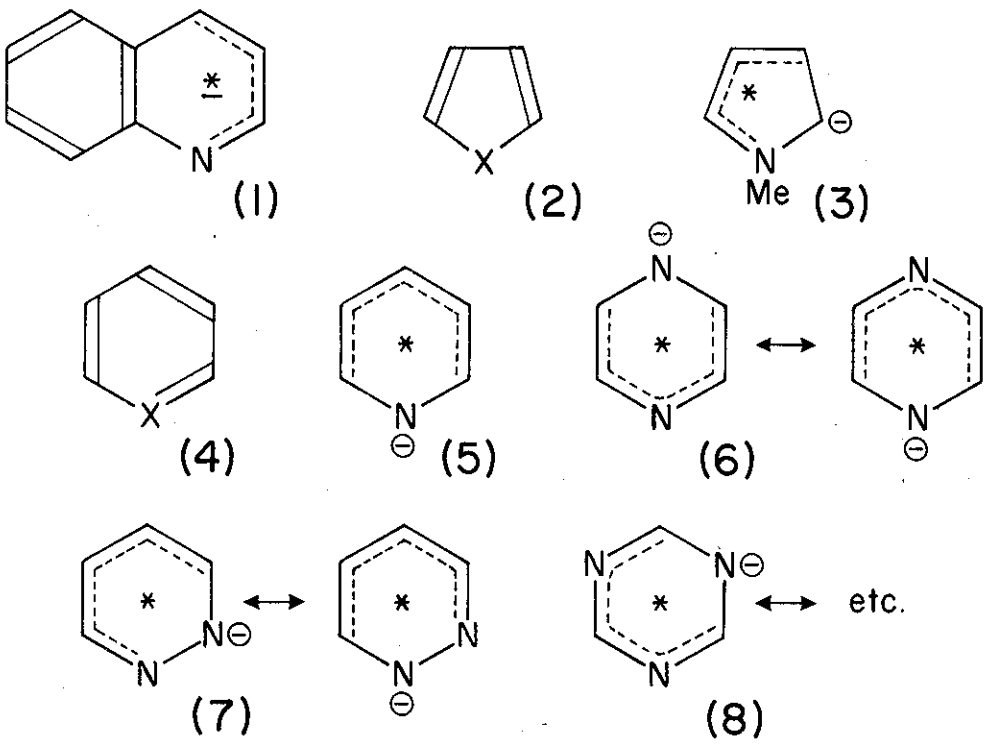
The reversibility of the addition can be shown in a number of instances by subsequent electron transfer to another substrate of lower reduction potential, or by electrochemistry (see below). Subsequent fast processes may obscure the reversibility under some conditions.

(i) The solvent

$Solv_1$ and $solv_5$ are probably not very different, depending on the other ionic interactions represented; certainly solvation of the cation is very important. $Solv_3$ is probably not energetically very important, but it does define the solubility of A. $Solv_2$ and

$solv_4$ are very important; the extent and nature of the first determines the solubility of the metal in ways still not entirely clear. There may be two opposing effects with $solv_2$; the greater it is the more soluble the metal is likely to be, on the other hand the greater also will be the energy required to desolvate the electron in forming $A^{\pm}$. Ammonia appears to be a particularly good solvating agent for the highly mobile electrons, which probably associate with the positive, hydrogen ends of the dipoles[5]. There is evidence from general aromatic reductions that electrons in amines are more 'active' than in ammonia, possibly because of temperature differences, but also probably because of the lower $solv_2$ to be expected. $Solv_4$ is important in stabilising the radical anion. These considerations add up to a rationalisation of the superiority of polar solvents, and the particular importance of amines.

The macroscopic dielectric constant of the solvent is not necessarily meaningful for the small mobile electron but may be for ions. The extent of dimerisation of the quinoline radical anion (1) can be related to it. In THF (ε 7.6) this radical dimerises to a dianion, but remains monomeric in the more highly solvating HMPA (ε 46)[6]. Electrochemically generated (1) in liquid ammonia appears from cyclic voltammetry[7] to be dimeric, although no dimer was formed in ammonia by the chemical reduction of quinoline[8]. The pyridine radical anion dimerises rapidly even in HMPA[6], a situation also reflected in the products of reduction by $Li-NH_3$.[9] In many cases an equilibrium probably exists between radical anion and dimeric anion.



Choice of solvent depends on a number of factors to be assessed in a given case. Many heterocyclic compounds are fairly or completely soluble in ammonia. Anhydrous ethylenediamine is a good solvent, and admixed ethers can be used, such as dioxan, THF or particularly dimethoxyethane. With insoluble compounds it is good practice to dissolve, even by heating, in a solvent such as DME, then to add to liquid ammonia in a regulated manner to precipitate finely divided solid.

Of the metals, Li is the most soluble in all of the range of amines. Na or K are little soluble, except in ammonia, although the liquid Na-K alloy is observably soluble in a solvent such as

ethylenediamine. For many purposes Na in pure redistilled NH_3 is satisfactory[10]. Organic solvents in ammonia usually decrease metal solubility; crown ethers might be expected to increase it, but have not been examined.

In relation to possible base-catalysed processes, which are often desirably avoided, $LiNH_2$ is less soluble and less basic than $NaNH_2$ or KNH_2. The last amide is particularly soluble and basic and K may be preferable if intermediate salts are required to persist until work-up.

The solvent is important in connection with the possible range of temperatures of reactions which are frequently, though not invariably, carried out at the b.p. and can be carried out below the m.p. of pure solvent by using mixtures, for example of ammonia with methylamine. Ranges are ammonia -80° to -33°, ethylamine -81° to 17° and ethylenediamine 8° to 116°. Although higher temperatures promote both solubilities and the primary reductions, loss of metal by secondary reaction with the solvent is also marked, and further reductions may result. Selective reductions are best carried out at the lowest possible temperature.

(ii) The structural factors

Some general factors apply to all organic compounds. Stabilisation of A by special features such as aromatic character will tend to inhibit reduction. Any special characters which stabilise $A^{\pm}$ for example, polarisability or relief of steric strain, will favour reduction. In the last connection the geometry of $A^{\pm}$ seems[11] to be similar to A, although it is rather more mobile. This contrasts with $A^{=}$ which exhibits complete conformational mobility[12].

Structural factors as discussed in the literature for organic compounds in general of course apply. C=C has a low electron affinity,

whereas C=N has a relatively high electron affinity. Initial discussions below are concerned chiefly with aromatic heterocycles since the non-aromatic ones behave as would be expected from known general chemistry[1,2]. A few rather special illustrative cases may be noted, particularly in connection with fission processes (below).

An example of C=N to CH-NH is the conversion of imidazolines into imidazolidines[13], a step in a synthesis of aldehydes. This reduction is totally selective in relation to a benzene ring in the same molecule.

The structure of A determines its electron affinity, which, in the gas phase, can be defined by the level of the lowest unoccupied molecular orbital (*LUMO*): *the lower this is, the more rapid is* reduction. Since these levels can in principle be calculated, this term provides a base against which other perturbing factors such as solvation can be set[14,15]. In a series of similar molecules, under similar experimental conditions, the LUMO can be related to the ease of reduction in the series. *Ab initio* molecular orbital calculations[16] on the energies of the LUMO indicate pyridine < benzene < furan < pyrrole which is the experimentally observed order of decreasing rates. A related series[17] gives thiophene < furan. The only direct consideration in the literature of these kind of calculations in relation to heterocyclic reductivity[18] gives quinoline < naphthalene < N-methylindole < benzene, which also agrees with experimental results and the more qualitative structural factors discussed below. Since this kind of calculation ignores special factors in A±, such as polarisability due, for example to atoms like S, the calculations cannot be taken too seriously for comparisons outside a related series.

In discussing the influence of structures the most meaningful measurement of reducibility in solution would be a rate, but such measurements hardly exist. The reaction rates of $e_{ammon.}$ with the series NH_4^+ > imidazole >> pyridine > thiophene > pyrrole[19] is probably a measure with the first two of reaction with solvated H^+, (i.e. NH_4^+) due to high acidity, rather than to reduction of the ring of imidazole.

A more extensive series of relevant measurements involves polarographic studies of reduction potentials[14]. The half-wave potentials of heterocyclic compounds[20] are quantitative indications of reducibility under the experimental conditions used. Of particular interest is the examination[21,22] of azines by polarography and cyclic voltammetry in DMF or acetonitrile. The trend of ease of the first electron addition is pyridine < biphenyl < naphthalene < pyrimidine < isoquinoline < quinoline < acridine. Agreement is usually found when the series of half-wave potentials is compared with energies of the LUMO's. An earlier paper[23] sets out similar conclusions, and shows a small negative shift for an extra alkyl group. This could be interpreted as due to the normal inductive effect of such groups, but since an alkyl group is more polarisable than hydrogen, steric interference with solvation of A‡ is a likely factor.

For many simple aromatic heterocycles the half-wave potentials cannot be determined in the usual solvent systems since it lies above the solvent or supporting electrolyte limit. Few data are available for liquid ammonia as a solvent. However, the single value of -1.56V for quinoline[7] closely resembles the -1.60V found in DMF[21], and trends of results are likely to be similar.

The formation of A‡ could possibly be examined by e.s.r. measurements, but the simple heterocyclic systems often do not form observable primary radical anions[24]. None has been observed with thiophene, although evidence from derivatives suggests that it is of higher energy than that from benzene[25]. The pyrrole[26], indole[26], furan[27] and oxazole[27] radical anions are observable only under very special conditions. Their instability to cleavage or other secondary processes[26,27] is reflected in the products of reactions as discussed below.

In practical situations intuitive inspections of formulae help in the assessment of reducibility. In five-membered heterocycles (2,X O,NR,S) the nature of X seems to affect electron-addition in relation to the predictable participation of the X lone pair in the aromaticity. The order of basicity of X, NR > O is also the reverse order of reducibility. Since NR,O,S are all more basic than C=C, reducibility would be expected to occur with more difficulty than the corresponding benzene. However, the nature of the intermediate A‡ is also pertinent, and it may well be stabilised by more polarisable atoms such as S, and may explain why thiophenes are reducible.

Nitrogen poses a particular problem because of the acidity of NH in pyrrole or imidazole or similar structures, which usually results in alteration of the substrate under the experimental conditions from the neutral molecule to the anion. The charge on this anion will protect the ring from further electron addition. To have any chance of reduction at highly basic pH (which normally exists in these reductions) the group must be N-alkyl or a more acidic buffer must be added. In base interchanges the rate of reaction of NH_2^- with an acid is very much greater than that of an electron; sodamide for

instance generates a salt from indole very much faster than does sodium metal, so that appropriate buffering may permit reductions even of acidic systems.

Experimentally, simple thiophene derivatives are reducible[28], but furans only under forcing conditions[29] unless an anion-stabilising group such as CO_2H is present[30]. Pyrroles have not been reduced and even N-alkyl pyrrole carboxylic acids can be reduced only very slowly[31]. This order of reducibility is as predicted by the calculated electron affinities. N-Methylpyrrole's resistance to reduction may in part be rationalised by the fact that a negative charge α to nitrogen, as in the radical anion (3), is especially unfavoured[32].

Six-membered rings such as (4) require the presence of a trivalent atom such as N to exist as a neutral molecule. Cations such as oxonium salts would be expected to be readily reducible, and they are.

Qualitatively, reductions can be also considered in terms of probable effects of hetero-atoms on A‡. One outstanding effect is due to the higher electron-affinity of N in relation to C, so that when N can provide a site for a negative charge in A‡ reduction is facilitated. That pyridine is more readily reducible than benzene can be rationalised in terms of an intermediate of type (5). For pyrazine (6), pyridazine (7) and s-triazine (8) the anionic intermediates have structures which accord on these grounds with the experimentally determined[21] order of half-wave potentials pyridine > pyrimidine > pyridazine > pyrazine > s-triazine. Other examples are complicated frequently by ring-cleavages, which may occur totally and irreversibly even if the concentration of A‡ is very low. High nuclear charge (S) might be expected to stabilise A‡, as

noted, charge concentrated next to N is somewhat unfavourable [compare pyrazine (6) more reducible than pyridazine (7)].

Extension of saturation, permitting further delocalisation of charge in A‡ would be expected to favour reduction. This delocalisation is notably assisted by aromatic annelation (e.g. quinoline, isoquinoline, indole) or by carboxyl substitution[33]. For example, furan is not reducible by Li-NH_3, but 2-furoic acid can be readily reduced[30]. The expected positive shift in half-wave potential for several aromatic acids has been observed in our laboratory[31] using a cell similar to Bard's preliminary cell[34].

Quaternisation is an extreme case of facilitation by structural change; for example pyridinium salts show a much lowered $E_{\frac{1}{2}}$[21].

A further factor in considering reducibility is the frequent occurrence of $2A^{\ddagger} \rightleftharpoons A^{-}-A^{-}$; clearly the more stable the latter, the more the initial electron addition takes place. Because of reversibility, products can correspond either to further reactions of A‡ or of $^{-}A-A^{-}$.

Further reactions

(i) Protonation of A‡ Two further reactions of A‡ can occur: addition of another electron to form $A^{=}$, or protonation to *AH. The last reaction can occur if a sufficiently acidic proton source is present, which may not include the ammonia or amine solvent, addition of an alcohol or other 'acid' being necessary. A proton can be acquired only during work-up in some instances. The expected low basicities of mesomeric radical anions in relation to similar anions was noted many years ago[35], requiring more acidic proton sources for reaction.

In determining the nature of the product from A‡ the first question concerns the position of addition of a proton to a mesomeric system.

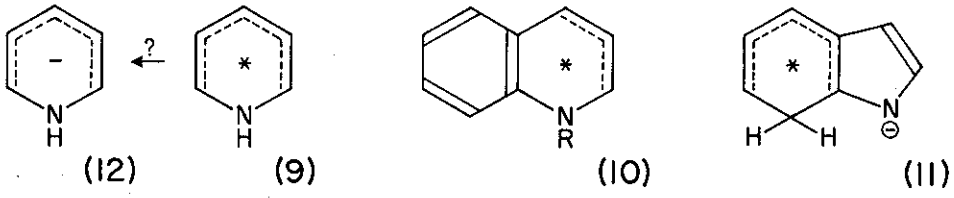
The π-electron densities in carbocyclic radical anions seem to be useful guides to the situations of protonation[36,37], but the validity of the concept for heterocycles has not been demonstrated. Also, the initial protonation for carbocycles is irreversible[38], but this may not be so for protonation, particularly on a heteroatom such as N.

E.s.r. studies in conjunction with MO calculations enables examinations of *electron spin densities*. The suggestion[37] that protonation occurs at the position of highest spin density correlates products of reduction of *polycyclic aromatic carbocyclic compounds*, despite neglect of steric, solvation, and counter-ion factors[36].

Experimental data are available[24] for *heterocyclic compounds*, mainly six-membered nitrogen-containing aromatics, including pyridine, quinoline, acridine[6], and pyridines with alkyl, OMe, CO_2H substituents[39] and relations between calculated and experimental spin-densities are usually good. However, in protonation reactions N has a special situation. Although in pyridine and quinoline radical anions the 4-position has the highest π-electron density, and the N only the second highest, e.s.r. studies of the pyridine radical generated by $Na-NH_3$ in the presence of EtOH suggests the structure (9)[39].

Similarly alkylation of the electrochemically generated quinoline radical anion in NH_3 leads to structure (10). The process of protonation or alkylation requires localisation of a pair of electrons, and the availability of the nitrogen *p*-electrons may well play a special part in the process.

Radicals resulting from monoprotonation can dimerise, or can add another electron to produce a mesomeric monoanion (e.g. 12) which may or may not be identical with that formed by monoprotonation of a dianion. This question is discussed later.

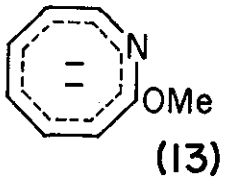


(12) (9) (10) (11)

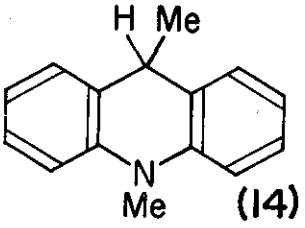
(ii) Dianion formation Despite the negative charge on a radical anion, the addition of a second electron into the same orbital, to give a dianion, can occur. The resulting salts exist presumably as ion-pairs. Liquid ammonia, as a dipolar hydrogen-bonded solvent, seems particularly effective in stabilising dianions[18]. Direct evidence of their existence comes from electrochemical studies in NH_3, where dianions have been observed, in contrast to some other polar solvents[34,40]. With a few exceptions such as noted below, the radical anion is more difficult to reduce than the starting material, so the possibility of dianion formation is controlled by the reduction potential of A$^{\pm}$ and by the reduction potential and proportion of metal used. However, products in some cases may correspond to dianion, even if this is present in low concentrations in an equilibrium. Because of its high basicity, further reactions, particularly protonation by the solvent, can lead irreversibly to complete conversion to a monoprotonated monoanion (see below). Some dianions are relatively stable to ammonia, for example acridine forms with just 2 Li a dianion which can be methylated to (14)[41,42].

Particular factors such as an electronic configuration conferring classical aromaticity, result in stable dianions. One class of examples is a series of 2-methoxyazocines[43] which readily give the type (13) best using K-NH_3. These salts contain an aromatic

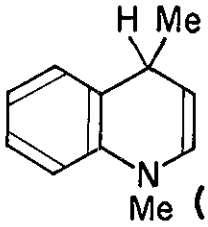
10π-electron system, attested by a ring current to be associated with a planar fully delocalised structure[43]. The two electrons are added at the same potential[44] in THF or DMF, suggesting that the second is at least as readily added as the first. The effects of annelation or alkylation to (13) have been examined in detail[43,45].



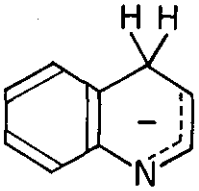
(13)



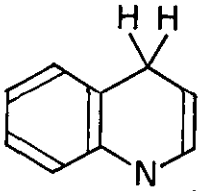
(14)



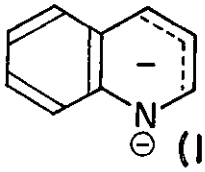
(18)



(15)



(16)



(17)

Evidence is available of formation of unstable dianions which rapidly undergo further reactions, notably removal of a proton from the solvent. The evidence indicates that the most basic centre of mesomeric dianion, for example the 4-position of the quinoline dianion, is at least comparable in strength to NH_2^- (pK_a ammonia about 34-35). Quinoline reacts rapidly with about 2.5 Li in NH_3 to give the anion (15) as the observable product which can be protonated[46] or alkylated[8] to (16, R=H or alkyl respectively). Intermediate production of the dianion (17)[8] and proton-abstraction from the solvent NH_3, is supported by the incorporation of D at C-4 when the reaction occurs in ND_3. Further evidence is that the 1,4-dimethyl product (18) results from addition of excess Me_2SO_4 together

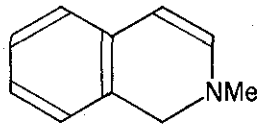
with quinoline to Li-NH_3 at -70°, when methylation competes favourably with protonation[8]. Without examination of kinetics it is not possible to be absolutely certain that such a process does not involve successive processes, beginning with methylation of a radical anion. However, examination of substituted quinolines fits the dianion picture. The reductive methylation of 4-phenylquinoline in which the group would be expected to stabilise a 4-anion, gives rise to 1,4-dihydro-1,4-dimethyl-4-phenylquinoline in 100% yield[42], and in 67% yield even using a subsequent addition of Me_2SO_4. 4-Methylquinoline gives >90% yield of the 1,4,4-trimethylquinoline derivative and only a trace of the 1,4-dimethylquinoline[42].

The rule for reductions appears to be that the more basic negative charge in a dianion which can be readily localised is probably most rapidly protonated. A thermodynamic rather than kinetic view of the same process leads to the suggestion that a monoprotonated anion formed corresponds to the most acidic of the possible 'acids'. The remaining charge is to be found on nitrogen in the quinoline series. Both approaches lead to the same predictions in this series.

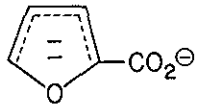
A close examination of quinoline derivatives[8,42] has served to demonstrate the necessity for stringent control of experimental conditions; this aspect is discussed later.

A single experiment[47], points to the possibility of reductive methylation of isoquinolines by reporting formation of (19), a result which has been confirmed[42]. The production of an intermediate dianion in this type of ring is supported by the observation that 1-phenylisoquinoline gives a substantial yield of the 1,2-dimethyl derivative together with some of the 2-methyl derivative[42]. The greater extent of protonation in the isoquinoline compared with the

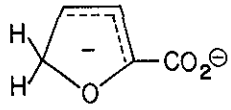
corresponding quinoline may be correlated with the lower stability (higher basicity) of the dianion. The slightly higher $E_{\frac{1}{2}}$ of isoquinoline[21-23] compared with quinoline is an index of higher energy and more reactive intermediates.



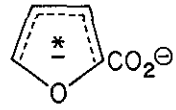
(19)



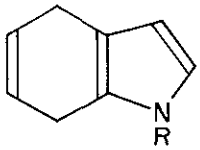
(20)



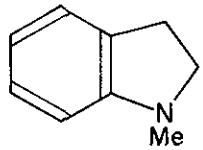
(21)



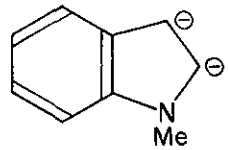
(22)



(23)



(24)



(25)

In some other cases indirect evidence exists for the production of dicarbanions, where the heteroatom is not directly involved. By analogy with benzoic acid[48], 2-furoic acid is readily reduced with $Li-NH_3$ and the dicarbanion carboxylate salt (20) may be an intermediate to the observed initial product (21)[30]. However, in view of the stoichiometric availability of H^+ from $CO_2H(NH_4^+)$ the radical anion (22) may be protonated and then further reduced to (21). Electrochemical investigations of this problem are in progress[31].

Alternative products in some instances may be due to alternative reactions involving radical anions or dianions. The reduction of benzene rings in presence of alcohols is made possible by protonation of an initial radical anion[2]. It seems probable that the reduction of the benzene ring of indole, or of N-methylindole[18], to the 4,7-dihydro derivatives (23), (R=H or Me) is due to such a process, which is a rapid one. It may be facilitated in the case of indole itself by internal transfer of a proton, since a radical anion (11) can be detected under special isolated circumstances in a matrix[26]. A very

much slower reduction, in absence of any added proton source, of N-methylindole produces the 2,3-dihydro derivative (24) which might go through the dianion (25)[18]. This is not a very attractive proposal, because of the necessity of the unfavourable[32] localisation of the charge at C-2. Another possibility is the base-catalysed isomerisation of (23), initially obtained, to produce (24). Further work seems required.

(iii) Dimerisation An important further reaction, particularly with pyridine derivatives[6,9], is dimerisation to yield in the first instance a dimeric dihydro-derivative. The ratio of hydrogenation to reductive dimerisation is dependent on experimental conditions, particularly on the solvent and the presence or absence of a proton source. Quinolines are less prone to dimerisation than pyridines[7].

Two mechanisms could operate. Electrochemical studies of quinoline in NH_3[7] suggest a pairing of radical anions, despite the negative charge on each. Charge repulsion may be compensated by ion pairing.

$$2A^{\pm} \rightleftharpoons {}^{-}A\text{-}A^{-}$$

Coulometric studies of pyrazine or pyridazine in DMF,[21] by contrast suggest a reaction of radical anion with the starting-material, a type of process related to the well known additions of anions to such systems:

$$A^{\pm} + A \longrightarrow {}^{-}A\text{-}A^{*}$$

E.s.r. examinations of a number of pyridine derivatives[39] indicate rapid formations of anion radicals corresponding to dimeric products, although the 4-methylpyridine products decay rapidly to diamagnetic compounds of unknown nature.

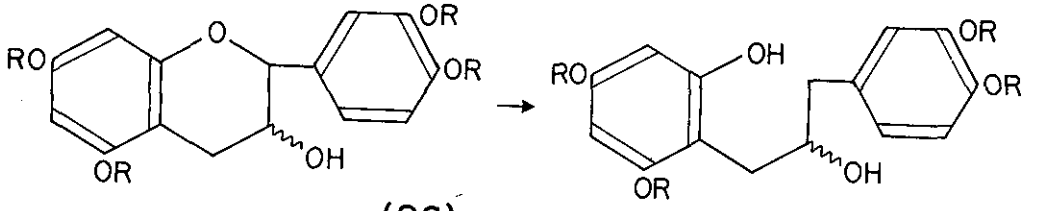
Cleavage reactions

Because of the higher electron-affinities of hetero atoms such as O,N,S, compared with carbon atoms, a widespread reaction, not found with carbocycles, is ring cleavage. This may be desirable, or may require to be avoided if possible, according to circumstances.

With most non-aromatic compounds the same kind of rules hold as with acyclic structures[1,2], so that only a brief summary is needed. There are two major processes, direct cleavage and base-catalysed elimination.

(i) Direct cleavage This occurs with diaryl ethers, some allyl ethers and most benzyl ethers. The corresponding nitrogen compounds are usually unaffected, while similar sulphur derivatives are more readily cleaved. Some indication of the likelihood of the process can be obtained by considering the effects of structure on a transition state of type $^{-}C\text{---}X^{*} \leftrightarrow {}^{*}C\text{---}X^{-}$. Any factors which stabilise negative charge on either C or X facilitate fission. The order of rates S > O >> N fits this picture, related to the order of acidities SH > OH >> NH. A lactone, for example, reacts much more readily than a corresponding ether.

A few examples are the tetrahydrofuranoid lignans[49] and catechins (26)[50] which are benzylic ethers. An example in the S series is 2,5-dihydrothiophene (below).

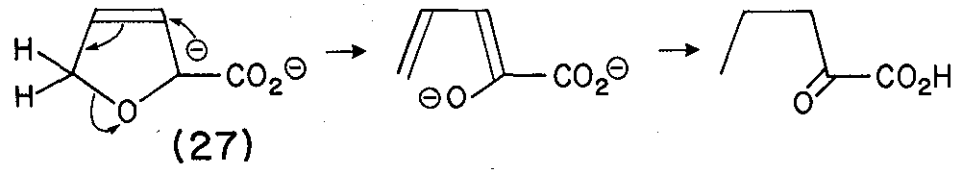


(26)

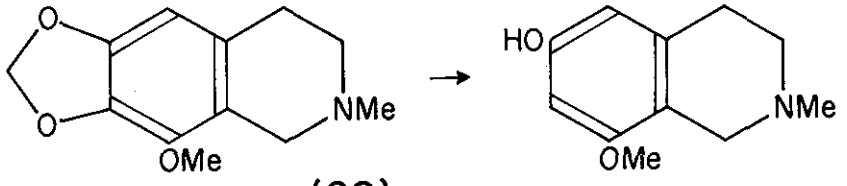
More subtle effects due to ring size or other structures have not been investigated. A point of interest with cyclic allyl derivatives is that because of location of the double bond in a ring, fission products are *cis*-olefins[51] (see also configurations of the aromatic products below). Cleavages of quaternary ammonium salts by $Na-NH_3$ afford an alternative procedure to the classical Emde reduction, usually free of base-catalysed side reactions[52].

(ii) Base-catalysed fission This usually results from an elimination of the type $\overset{\curvearrowright}{C}-C-\overset{\curvearrowright}{X} \longrightarrow C{=}C + X^{-}$. It can result from an anion produced by reduction, or from deprotonation due to the basic conditions, such as the presence of NH_2^{-}. The first situation may be unavoidable, or desirable. The second, may be in some cases avoided by buffering, or, if desirable, deliberately induced by providing the basic conditions. In any case the possibility has to be carefully considered in relation to the nature of the starting-material and the circumstances.

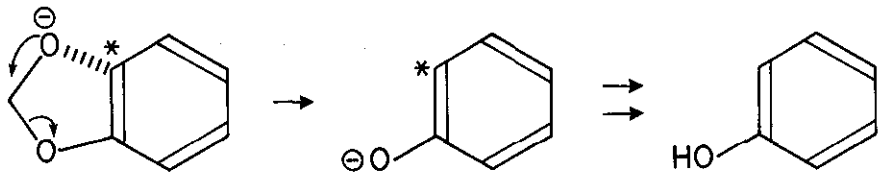
One example[30] is the fission of (27) which occurs under some conditions in the reduction of 2-furoic acid.



(27)



(28)



A particularly interesting cleavage of a non-aromatic heterocycle is that of methylenedioxy (or related ketal) structures, with loss of an oxygen from an aromatic ring. An example is cotarnine (28)[53a]. The mechanism is not entirely clear, but may be something like that shown, which agrees with observed substituent effects[53b].

Compounds of some of the types mentioned could be formed to intermediates in reduction of aromatic structures, as discussed below.

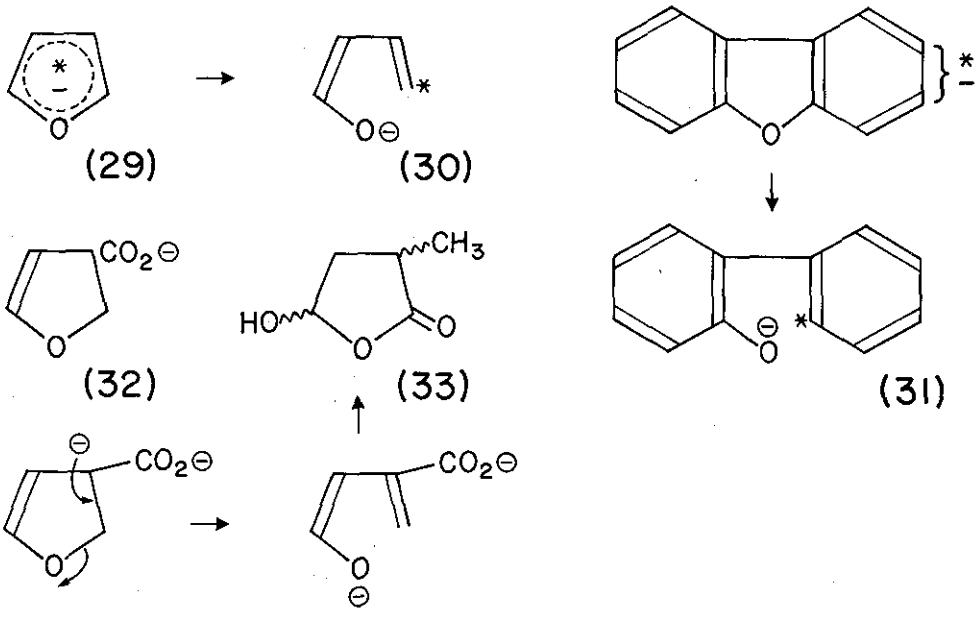
Aromatic Oxygen Heterocycles

(i) Cleavages of furans Furan and 2-methylfuran are reducible only under forcing conditions using Li-$MeNH_2$[29]. The products all result from ring-fission, probably due initially to conversion of (29) into (30), which is observable (e.s.r. at 4°K)[27]. This then undergoes rational conversions into observed products.

More stable anions may survive without fission. 2-Furoic acid in NH_3, with Li under a variety of conditions, and with other metals such as Na together with a proton source, does not cleave, the product being 2,5-dihydrofuroic acid. However, Na or K in NH_3 at either -33° or -78°, form predominantly cleaved products[31]. Whether cleavage occurs in a radical anion of type (22) or a carbanion (27) is not certain. We originally favoured (27)[30] since evidence of its formation can be obtained by alkylation under the appropriate conditions.

Dibenzofuran also cleaves in THF, and rate-studies suggest the direct process shown through (31)[54]. The order of effects of counter ion Li > Na > K > Cs accord with the assumption that the process is assisted by proximity effects, with the smaller ion (Li^+) adjacent to oxygen in the cleavage product contributing to the cleavage process. If this is general, it is a useful point to consider if reductions other than cleavage (e.g. of the benzene ring in dibenzofuran)

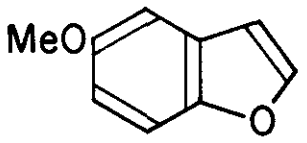
is to be encouraged. The reported product from dibenzofuran with Na in liq.NH_3 results from reduction of a benzene ring[55].



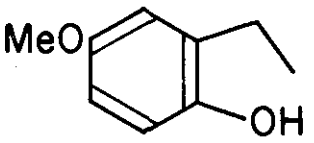
3-Furoic acid products are also sensitive to conditions, and cleavage seems to depend on whether or not a proton source is present. With Na and a range of proton sources the product is (32) or rational derivatives of it[56], but with Li or Na in pure NH_3 the product is (33) presumably due to the type of cleavage shown, followed by further reductions, and conversions on work-up[57]. However, no decision can be made to differentiate a radical anion or a monoprotonated dianion as an intermediate. It is clear in this case as in other similar ones, that whatever is the intermediate it must survive long enough to undergo cleavage, and that the presence of a proton source usually adds very rapidly protons to remove such ionic intermediates, often directing the course of the process in alternative directions.

This is very obvious with some benzofurans[58] where the benzene ring acts as a charge-stabilising structure. For example, Li-NH_3

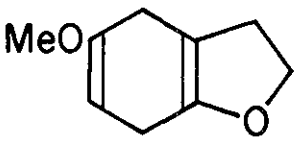
on (34) gives (35) whereas with 15% ethanol in the ammonia the rings-reduced product (36) is obtained in excellent yield. The radical anion may cleave (*cf.* 29 → 30), and there is no ammonium ion present to complicate the issue, as there is with the acids above.



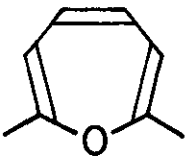
(34)



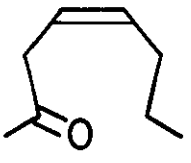
(35)



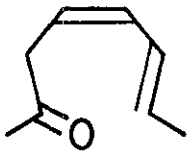
(36)



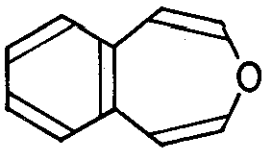
(37)



(38)



(39)



(40)

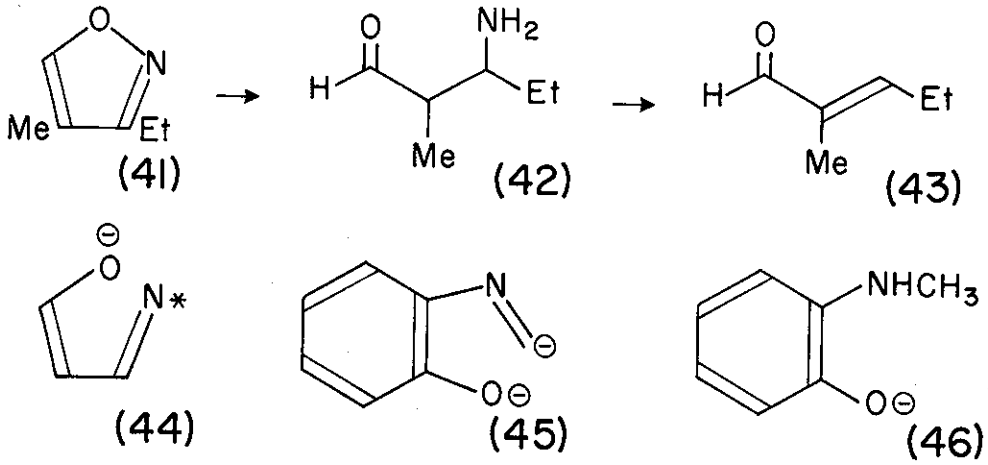
(ii) Oxepines These non-aromatic ethers behave as might be expected from addition of electrons to the unsaturated system. 2,7-Dimethyloxepine (37) with K-NH_3 at -70° produces a mixture of (38) and (39)[59]. The mechanism suggested by the authors seems valid, the unsaturated system surviving as the enolate anion. The production of (38) may be due to remaining metal during the work-up procedure. The benzoxepin (40) behaves similarly[59]. In the mechanistically analogous case of 1-methoxycyclohexa-1,3-dienes, cleavage occurs in absence of ethanol, reduction of the olefinic system in its presence[60]. The effects of a proton source have not

been examined here.

(iii) Oxazoles and Isoxazoles and related compounds. Since N-O bonds are known to cleave with great ease, it is not surprising that this occurs with isoxazoles, e.g. (41) even in presence of t-BuOH[61]. That the expected product (42) was formed was shown by the isolation after pyrolysis of (43) in 72% yield. This overall process has been used as part of a structural reversal of an α,β-unsaturated ketone system and was devised for this purpose[61]. E.s.r. studies[27] show that observable radical anions from isoxazole have the structure (44).

Oxazoles do not seem to have been examined. Benzoxazole is cleaved[62]; in the absence of a proton source the stable salt (45) is generated, and this can, for example, be alkylated on carbon. In presence of ammonium bromide which causes protonation of (45), further reduction occurs to (46).

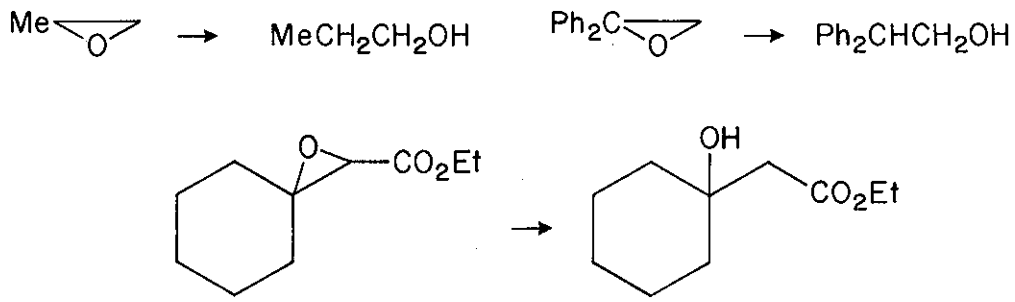
In benzimidazole, the acid NH results in salt formation[63]; reduction of the N-alkylated derivatives does not seem to have been examined, but would be expected to present greater difficulty than the corresponding benzoxazole.



(iv) Epoxides and Aziridines. These illustrate the effects of ring-strain, since ethers are not cleaved. Metal-ammonia solutions yield alcohols from epoxides[64a], although whether the rate determining step involves one or two electrons is not known. That C-O bond is cleaved which would leave a negative charge on the situation which can most effectively stabilise it, as shown below.

Cleavage in some steroidal epoxides with Li-$EtNH_2$ is sterically directed, yielding mostly axial alcohols[64b].

Aziridines are also reducible[64a].



Some Sulphur Heterocycles

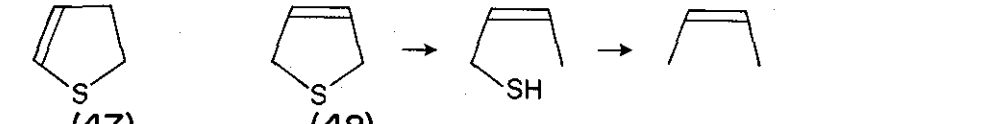
The C-S bond is more labile to cleavage than the corresponding C-O. E.s.r. studies suggest that S delocalises an unpaired electron more readily than does O, although d-orbital participation seems unlikely[24]. Radical anions of undefined structures have been postulated as intermediates in the cleavage of dialkyl sulphides[65].

For unsymmetrical sulphides, competition between the two directions of cleavage is qualitatively observed[66] to relate to formation of the most stable intermediates. Choice between alternative transition states or reductive cleavages of R-X-R' which may be written

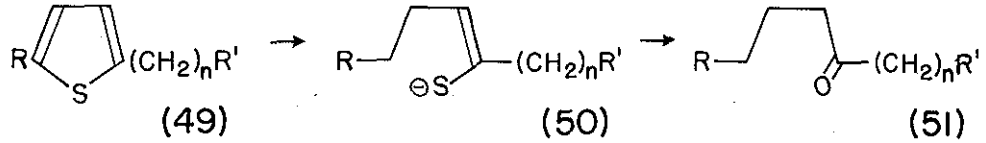
as $R\overset{*-}{---}X\text{-}R'$ or $R\text{-}X\overset{*-}{---}R'$ seems to be defined by the ability of R or R' to stabilise the negative charge, taking into account solvation factors as well as the structures of R and R'. The nature of X relates to the ease of fission in the order S > O >> N, which is the same order of acidity as RXH.[67]

(i) Thiophenes. Although reduction of thiophenes occurs in the absence of a proton source, formation of hydrogenation products requires the presence of such a source, only fission products being formed in its absence. A range of products is obtained[28,68,69] resulting from different procedures, including those which could have been produced by allylic cleavage of (48) which with (47) is a major product in presence of MeOH. In the 2-butene finally produced the double bond is *cis*.

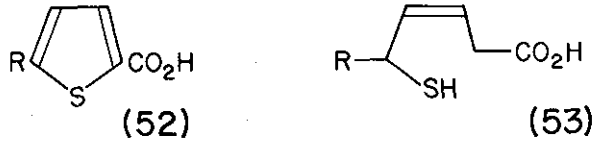
Alkylthiophenes are reported to give solely cleavage products either with $Na\text{-}NH_3$[70] or with $Li\text{-}NH_3$[71]. The general type (49, R=H or Me; R'=Me or CO_2H) leads to the thioenolate type (50), converted into ketone (51) on work-up. These workers report the production from thiophene itself of butyraldehyde, which could arise by cleavage of (47), but more likely from the thioenolate (50, n=0, R=R'=H) formed from cleavage of the initial radical anion followed by further reduction.



(47) (48)



(49) (50) (51)



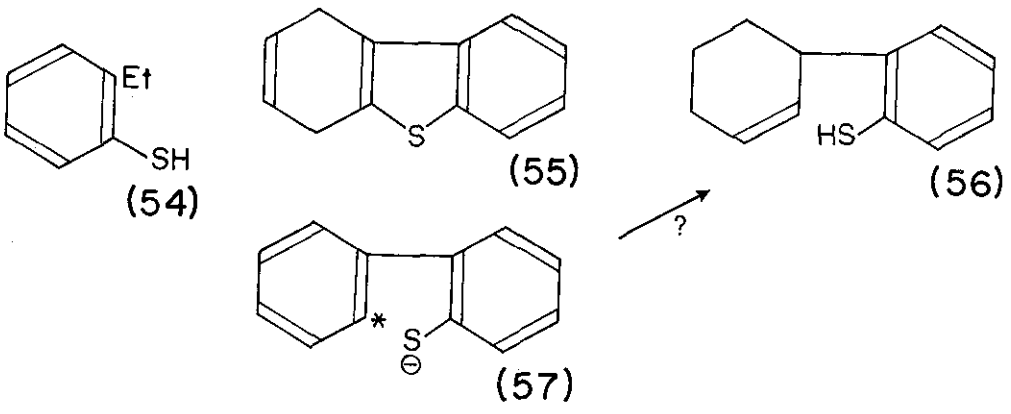
(52) (53)

The direction of cleavage in unsymmetrically substituted thiophenes is between S and the least alkylated (or the CO_2H substituted) carbon atom. Mechanistically this may be similar to the sulphide fission above. The fission of thiophene-2-carboxylic acids, briefly investigated[31], occurs between S and CCO_2H as expected. Under optimal conditions (5Li-NH_3-MeOH at -33°) acids of type (52) (R=H or Me) give (53) (R=H or Me) almost quantitatively. The double bond geometry has not been investigated but is expected to be that shown.

Electrochemical examination of thiophene-2-carboxylic acid suggests a rapid fragmentation of a radical anion[31], since, unlike benzoic acids, electron addition is irreversible on the time-scale of cyclic voltammetry.

Thionaphthenes are reported[69] to cleave with Na-NH_3 under all conditions giving the thiphenol type (54). Early work[69] on dibenzothiophenes indicated (55) as the product, but later work[72] indicated cleavage to a thiophenol of type (56) (double bond position undefined). A re-examination[73] suggests that the mode of mixing may be critical; the 2,5-dihydro-derivative arises if a solution of dibenzothiophene in ethanol and ether is added to sodium in ammonia, whereas thiophenol is produced if the metal is added last. Cleavage to (56) could proceed through (57). The result might be due to dianion formation by excess metal, but further systematic examination is needed.

Some evidence is provided by e.s.r. spectra[24] for production of a rather stable dibenzothiophene radical anion.

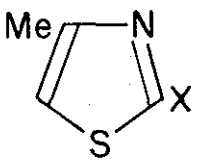


(ii) Thiazole itself does not appear to have been examined, but 4-methylthiazoles (58) with R=SH, OH or NH_2 have been reacted with $Na-NH_3$[74]. Salt formation with R=OH inhibits reaction, but with $R=NH_2$ (58) is partially converted into (60), probably through (61). Despite salt formation, (58) (R=SH) is rapidly cleaved in the same position to (59).

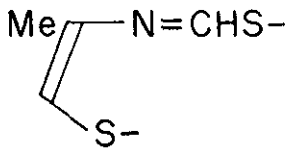
Thiazole-4-carboxylic acid, and some derivatives, have been investigated[75] on a micro-scale, and the products of $Na-NH_3$ reaction examined by hydrolysis. No selectivity of C-S fission was discernible.

Benzothiazole has long been known[62] to react with $Na-NH_3$, a process recently repeated[76]. The ring-opened products have not been thoroughly investigated, but are probably analogous to those from benzoxazole (45) and (46).

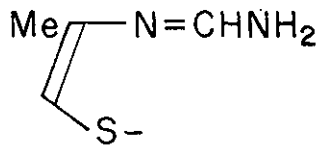
Partially unsaturated ring systems such as (62)[76] and (63)[77] behave as expected from the general theory, through the stabilised anions, and there seems no need to discuss specific cases. Similarly, 1,3-dithianes[78] are reducible as expected from work on simple thioethers.



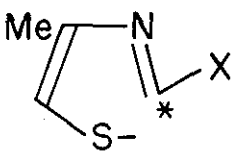
(58)



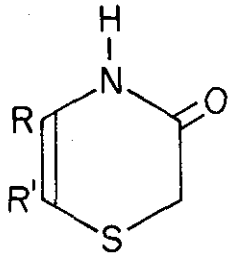
(59)



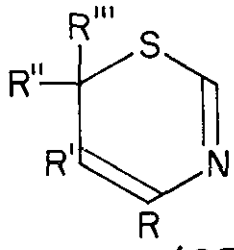
(60)



(61)



(62)



(63)

More complex heterocycles, such as purines, pteridines and pyrimidines have been little investigated, but under appropriate conditions groups such as $-CON\lesssim$ are reducible as for amides (below) and the reduced products are cleaved by acids to expected fragments. This can sometimes be used for structure determinations.

Effects of Proton Sources

Some general effects of changed conditions have been noted, but it is worthwhile to note more systematically the four most important ways in which added proton sources such as ROH or NH_4^+ can intervene.

(i) For difficult reductions, that is when $A^{\pm}$ is formed only to a minor extent in the electron-addition equilibrium, hydrogenation occurs only when a proton source such as ROH is present. This induces an irreversible through-put to products by protonation of $A^{\pm}$ to *AH a process for which ammonia itself is usually not sufficiently acidic. Such reductions, when they occur, are usually very rapid.

A different, but related, aspect is that if $A^{\pm}$ is formed, but is slowly transformed by ring-fission or dimerisation, a competing hydrogenation process can be encouraged by adding a proton source. Pyridines, for example, tend to hydrogenate rather than to dimerise under these conditions.

(ii) When the starting material is acidic, the addition of a sufficiently acidic buffer, such as MeOH for indole reduction[18], prevents total formation of salt, and therefore permits reduction of the neutral molecule.

(iii) When an anionic product is formed by cleavage or dimerisation, the charge inhibits further electron-addition, and a partially reduced product may result on work-up. If further reduction is desired, such anions require to be protonated *in situ*. One example among many is benzoxazole[62].

To obtain partially reduced products, it is often advisable to remove any excess metal before protonation during work-up. This can be done catalytically by adding a little ferric nitrate, or, conveniently if the product is not acidic, by the addition of benzoic acid. Sodium nitrite is efficient, providing the solution does not subsequently require to be acidified. Some results reported in the literature may be due to further reduction during the work-up procedure.

(iv) Protonation of mesomeric anions under kinetically controlled conditions often gives thermodynamically unstable isomers[79,80]. Since these frequently contain isolated C=C, the products are usually stable to further reduction. However, reversible protonation, linked to the degree of buffering of the solution, can lead to more stable isomers, containing C=C-C=C, or C=N, or C=O. These can then undergo further reduction if metal is still present.

There are two possible desirable situations to obtain uniform products. Preservation of enolate anions can be achieved until work-up by omitting a proton source. Alternatively, with highly basic carbanions in particular, it may be desirable to buffer the solution with ROH or NH_4^+ to ensure that once kinetically protonated the hydrocarbon 'acid' cannot equilibrate, through re-formation of its anion, with a more stable isomer which is further reducible.

The time involved in the reaction may in some cases be critical, since equilibration through acid-base exchange is often slow compared to the initial reduction step.

Even the proton source for quenching an anion may be important. With biphenyl[81], Li-NH_3 quenched with NH_4Cl gives cleanly 1,4-dihydrobiphenyl, while alcohols kinetically yield some proportion of conjugated isomer leading to further reduction products. NH_4^+ shows little or no steric hindrance effects in protonation; on the other hand it reacts much more rapidly than do alcohols with metal to produce hydrogen gas, and thus to divert reducing agent unless the substrate is very readily reducible.

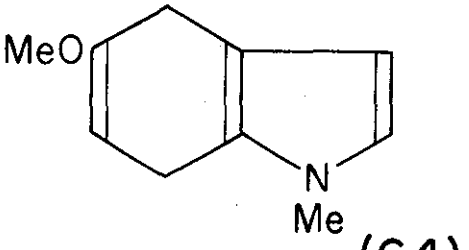
As usual, it is necessary to consider carefully each individual case in relation to a given objective. Some examples may be quoted to indicate the operations of some of these factors.

Even the most powerful technique of Li-NH_3-tert.BuOH, which is successful with benzene produces no reduction of some systems. These include pyrroles, even N-methylpyrrole, and simple furans[29], which however might be further investigated. N-Phenylpyrrole is reduced solely in the benzene ring[82].

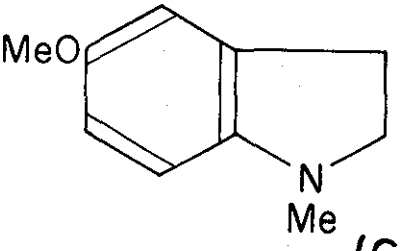
Indole requires the presence of MeOH(pKa 16) to maintain the presence of the ring NH(pKa about 17)[18]; carbazole similarly needs EtOH. Only the benzene ring of indole reacts.

5-Methoxy-N-methylindole can be converted by Li-NH_3-MeOH into (64) (60%) and (65) (5%). Without MeOH reaction is much slower and eventually gives (65) (70%) as the sole recognisable product[18]. N-Methylindole behaves similarly, but the ratio of reduction in the two rings is more nearly equal; from the benzene series it is known that OMe facilitates reduction of a ring to which it is attached.

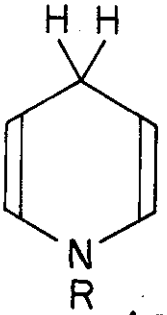
The dimerisation of pyridine with Li-NH_3 has been noted. In the presence of EtOH (2 equivalents) and Li (3 equivalents) pyridine yields (66, R=H or alkyl)[9] on work-up with NH_4Cl or RX respectively. The third equivalent of metal seems desirable to maintain the intermediate anion until work-up. Earlier work[83] had deduced the formation of such dihydro-derivatives from the products of acid hydrolysis.



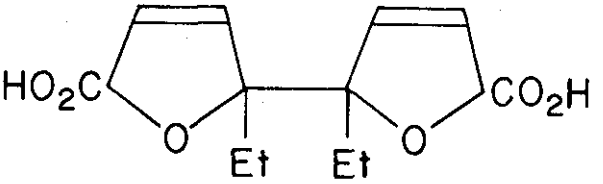
(64)



(65)



(66)



(67)

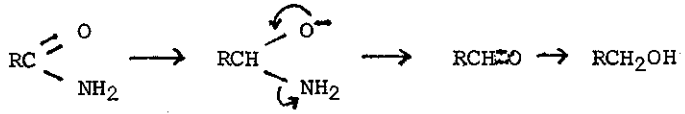
Quinolines have been studied fairly systematically in ammonia under different conditions[8,42]. The use of Li (2.5 equivalents) on quinoline and quenching with either NH_4Cl or RX results in 1,4-dihydro- or 1-alkyl-1,4-dihydroquinoline in good yields. The result contrasts with earlier ones[18] where MeOH was used *in situ* or for quenching, when a rather undefined product resulted, containing some 5,8-dihydroquinoline and further reduction products. The differences may be due to dianion formation in absence of MeOH, and protonation of a radical anion in its presence.

With Li-NH_3 acridine yields a stable dianion as demonstrated by alkylation to (14)[41,42]. In the presence of ethanol 1,4,5,8-tetrahydroacridine is formed but with NH_4OAc the 9,10-dihydro product is observed[41]. An explanation for this effect has been advanced[41] though the reasons are far from clear.

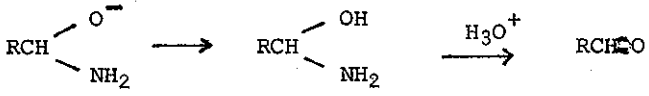
5-Ethyl-2-furoic acid yields the dimer (67) (50%) with Na (3 equivalents) in NH_3, followed by MeOH after 20 minutes[84]. This contrasts with clean formation of the 2,5-dihydrofuroic acids under conditions where NH_4Cl is used as a rapid quench or with MeOH *in situ*[30]. The reason for the contrast is not clear; possibly under the first conditions dianion may react with starting material, or more likely a slow dimerisation of radical anion may occur.

In absence of alcohol, benzofurans are cleaved, as already noted, but in its presence the benzene ring is hydrogenated[58]. Protonation probably removes the radical anion before it has a chance to undergo fission. The reduction of amides[13] provides a model for the numerous biologically important heterocycles containing CONH. In the absence of any proton source, the usual main reaction is salt formation without reduction, although some reduction may occur through protons supplied by the CONH itself. In presence of an alcohol such as ethanol, the course

of reaction is



In the presence of the much more acidic NH_4^+ the aldehyde-ammonia is protonated and remains until work-up, giving the aldehyde instead of the alcohol.



In recording reductions for publication exact procedures should be noted.

Uniquely available compounds

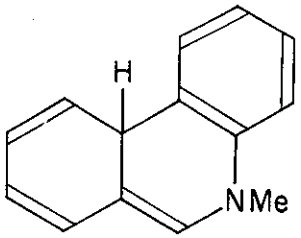
Using the appropriate procedure, the methods are characterised by a combination of great power and great specificity. The otherwise mild conditions, particularly low temperatures, and easy and rapid work-up procedures, often by mere addition of water, also permit isolations of unstable products.

The specificity of reduction is usually quite different to other processes, which depend on hydride addition or catalytic addition of hydrogen atoms. In this case reducibility is defined by electron-affinity, so that C=C in isolation is normally not reducible, in contrast to catalytic hydrogenation. Partially hydrogenated systems may therefore be uniquely available. Some of the cleavage products, such as thioenols, are not available by other routes. Anions generated can also be used as intermediates in other processes. The method is potentially useful in cases where hydrogenation catalysts are normally poisoned, such as sulphur derivatives and some amines.

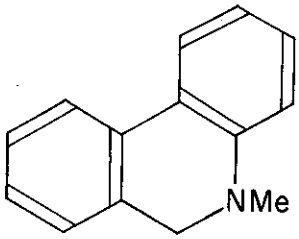
Many examples have been touched upon, and we note here several further characteristic examples.

Phenanthridine may be regarded as either a benzoquinoline or a benzoisoquinoline. Reductive methylation with Li-NH_3 yields (68) corresponding to quinoline reduction[42]. This contrasts with (69) obtained from the quaternary metho-salt and lithium aluminium hydride[42].

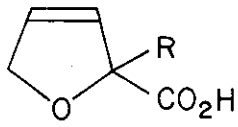
Reductive alkylation of 2-furoic acid yields (70, R=alkyl). Oxidative decarboxylation then provides a synthesis of 2-alkylfurans, including some natural terpene derivatives[85].



(68)



(69)



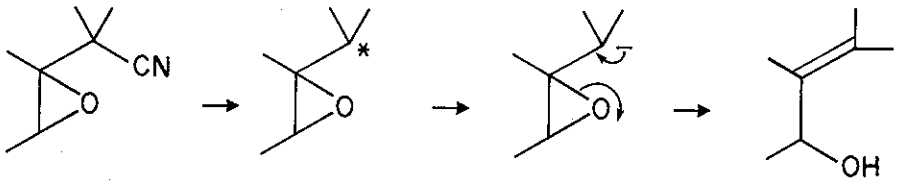
(70)

1,4-Dihydropyridines are readily available by reduction of pyridines. The products are reactive enamines, which can be hydrolysed to 1,5-dicarbonyl compounds, cyclisable to cyclohexenones[86]. This type of process has been used in steroid total synthesis[83].

The partially unsaturated compounds (62)[76] or (63)[77] on reduction give specific dianions which may be protonated or alkylated and further reacted to give systems not readily available by other methods. Thus readily available heterocycles may be simply transformed into less accessible products by this method.

The ring openings of certain types of epoxides are synthetically useful. Allylic epoxides[87], α-ketoepoxides[88], αβ-unsaturated γδ-epoxy

esters[89] and others can be opened in a regiospecific manner, and sometimes stereospecific manner, often differing from other methods. Uses have been made in synthesis[88,89], including the preparation of specific ketone enolate anions[90]. Unusual reactions include the production of allylic alcohols[91] readily rationalised as below.



Acknowledgment. We are indebted to Dr P.G. Lehman for unpublished information.

References

1 H. Smith, 'Organic Reactions in Liquid Ammonia', Vieweg, Braunschweig, 1963.

2 A.J. Birch and G. Subba Rao, 'Advances in Organic Chemistry - Methods and Results', e.d. E.C. Taylor, Wiley-Interscience, Vol. 8, 1972, pp. 1-65.

3 H.O. House, 'Modern Synthetic Reactions', Benjamin, Menlo Park, 1972, Chap. 3.

4 Reference 3, p. 146.

5 A.J. Birch and D.K.C. MacDonald, *Oxford Science*, 1948, 1.

6 J. Chaudhuri, S. Kume, J. Jagur-Grodzinski and M. Szwarc, *J. Am. Chem. Soc.*, 1968, 90, 6421.

7 W.H. Smith and A.J. Bard, *J. Am. Chem. Soc.*, 1975, 97, 6491.

8 A.J. Birch and P.G. Lehman, *J. Chem. Soc., Perkin Trans. I*, 1973, 2754.

9 A.J. Birch and E.A. Karakhanov, *Chem. Commun.*, 1975, 480.

10 H.L. Dryden, G.M. Webber, R.R. Burtner and J. Cella, *J. Org. Chem.*, 1961, 26, 3237.

11 C.S. Johnson, Jr. and R. Chang, *J. Chem. Phys.*, 1965, 43, 3183.

12 J.F. Garst, J.G. Pacifici and E.R. Zabolotny, *J. Am. Chem. Soc.*, 1966, 88, 3872.

13 A.J. Birch, J. Cymerman-Craig and M. Slaytor, *Aust. J. Chem.*, 1955, 8, 512.

14 M. Szwarc and J. Jagur-Grodzinski, 'Ions and Ion Pairs in Organic Reactions', ed. M. Szwarc, Wiley-Interscience, New York, Vol. 2, 1974, pp. 1-150.

15 M.J.S. Dewar and R.C. Dougherty, 'The PMO Theory of Organic Chemistry', Plenum Press, New York, 1975, pp. 504-509.

16 L. Radom, personal communication.

17 W. von Niessen, W.P. Kraemer and L.S. Cederbaum, *J. Electron Spectrosc. Relat. Phenom.*, 1976, 8, 179.

18 W.A. Remers, G.J. Gibs, C. Pidacks and M.J. Wiess, *J. Org. Chem.*, 1971, 36, 279.

19 R.R. Dewald, R.L. Jones and H. Boll, 'Electrons in Fluids - The Nature of Metal-Ammonia Solutions', ed. J. Jortner and N.R. Kestner, Springer-Verlag, Berlin, 1973, pp. 473-478.

20 For a general discussion of polarographic data and a compilation of $E_{\frac{1}{2}}$ for a variety of aromatic heterocycles see: C.K. Mann and K.K. Barnes, 'Electrochemical Reactions in Nonaqueous Systems', Dekker, New York, 1970, Chap. 10.

21 K.B. Wiberg and T.P. Lewis, *J. Am. Chem. Soc.*, 1970, 92, 7154.

22 S. Millefiori, *J. Heterocycl. Chem.*, 1970, 7, 145.

23 B.J. Tabner and J.R. Yandle, *J. Chem. Soc.(A)*, 1968, 381.

24 For a review on e.s.r. of heteroaromatic anion radicals see: B.C. Gilbert and M. Trenwith, 'Physical Methods in Heterocyclic Chemistry', e.d. A.R. Katritzky, Academic Press, New York, Vol. VI, 1974, pp. 115-129.

25 L. Lunazzi, G. Placucci, M. Tiecco and G. Martelli, *J. Chem. Soc.(B)*, 1971, 1820.

26 P.H. Kasai and D. McLeod, Jr., *J. Am. Chem. Soc.*, 1973, 95, 27.

27 P.H. Kasai and D. McLeod, Jr., *J. Am. Chem. Soc.*, 1973, 95, 4801.

28 S.F. Birch and D.T. McAllan, *J. Chem. Soc.*, 1951, 2556.

29 A.O. Bedenbaugh, J.H. Bedenbaugh, J.D. Adkins and W.A. Bergin, *J. Org. Chem.*, 1970, 35, 543.

30 A.J. Birch and J. Slobbe, *Tetrahedron Lett.*, 1975, 627.

31 J. Slobbe, unpublished results.

32 For a general discussion see: D. Seebach and D. Enders, *Angew. Chem., Int. Ed. Engl.*, 1975, 14, 15.

33 A.P. Krapcho and A.A. Bothner-By, *J. Am. Chem. Soc.*, 1959, 81, 3658.

34 A. Demortier and A.J. Bard, *J. Am. Chem. Soc.*, 1973, 95, 3495.

35 A.J. Birch, *Q. Rev., Chem. Soc.*, 1950, 4, 69.

36 R.G. Harvey, *Synthesis*, 1970, 161.

37 H.E. Zimmerman, *Tetrahedron*, 1961, 16, 169.

38 A.J. Birch and W.M.P. Johnson, *Aust. J. Chem.*, 1976, 29, 1631.

39 A.R. Buick, T.J. Kemp, G.T. Neal and T.J. Stone, *J. Chem. Soc.(A)*, 1969, 1609.

40 W.H. Smith and A.J. Bard, *J. Am. Chem. Soc.*, 1975, 97, 5203.

41 A.J. Birch and H.H. Mantsch, *Aust. J. Chem.*, 1969, 22, 1103.

42 P.G. Lehman, unpublished results.

43 L.A. Paquette, J.F. Hansen and T. Kakihana, *J. Am. Chem. Soc.*, 1971, 93, 168.

44 L.B. Anderson, J.F. Hansen, T. Kakihana and L.A. Paquette, *J. Am. Chem. Soc.*, 1971, 93, 161.

45 L.A. Paquette, L.B. Anderson, J.F. Hansen, S.A. Lang, Jr. and H. Berk, *J. Am. Chem. Soc.*, 1972, 94, 4907.

46 A.J. Birch and P.G. Lehman, *Tetrahedron Lett.*, 1974, 2395.

47 W. Hückel and G. Graner, *Chem. Ber.*, 1957, 90, 2017.

48 H. van Bekkum, C.B. van den Bosch, G. van Minnen-Pathuis, J.C. de Mos and A.M. van Wijk, *Recl. Trav. Chim. Pays-Bas*, 1971, 90, 137.

49 A.J. Birch, B. Milligan, E. Smith and R.N. Speake, *J. Chem. Soc.*, 1958, 4471.

50 A.J. Birch, J.W. Clark-Lewis and A.V. Robertson, *J. Chem. Soc.*, 1957, 3586.

51 A.J. Birch and B. McKague, *Aust. J. Chem.*, 1970, 23, 813.

52 S.C. Bhattacharji, A.J. Birch, A. Brack, A. Hofmann, H. Kobel, D.C.C. Smith, H. Smith and J. Winter, *J. Chem. Soc.*, 1962, 421.

53a D.B. Clayson, *J. Chem. Soc.*, 1949, 2016.

53b A.J. Birch, *J. Chem. Soc.*, 1947, 102.

54 A.G. Evans, P.B. Roberts and B.J. Tabner, *J. Chem. Soc.(B)*, 1966, 269.

55 H. Gilman and C.W. Bradley, *J. Am. Chem. Soc.*, 1938, 60, 2333.

56 T. Kinoshita, K. Miyano and T. Miwa, *Bull. Chem. Soc. Jpn.*, 1975, 48, 1865.

57 J. Slobbe, *Aust. J. Chem.*, in press.

58 S.D. Darling and K.D. Wills, *J. Org. Chem.*, 1967, 32, 2794.

59 L.A. Paquette and T. McCreadie, *J. Org. Chem.*, 1971, 36, 1402.

60 A.J. Birch and G.S.R. Subba Rao, *Aust. J. Chem.*, 1970, 23, 1641.

61 G. Büchi and J.C. Vederas, *J. Am. Chem. Soc.*, 1972, 94, 9128.

62 C.M. Knowles and G.W. Watt, *J. Org. Chem.*, 1942, 7, 56.

63 D. Wood, Jr., and F.W. Bergstrom, *J. Am. Chem. Soc.*, 1933, 55, 3314.

64a E.M. Kaiser, C.G. Edmonds, S.D. Grubb J.W. Smith, and D. Tramp, *J. Org. Chem.*, 1971, 36, 330.

64b A.S. Hallsworth and H.B. Henbest, *J. Chem. Soc.*, 1960, 3571.

65 Reference 3, pp. 215-216.

66 L. Brandsma, *Recl. Trav. Chim. Pays-Bas*, 1970, 89, 593.

67 Reference 1, p. 191.

68 R.C. Krug and S. Tocker, *J. Org. Chem.*, 1955, 20, 1.

69 W. Hückel and I. Nabih, *Chem. Ber.*, 1956, 89, 2115.

70 Ya. L. Gol'dfarb and E.P. Zakharov, *Zh. Org. Khim.*, 1970, 6, 1765.

71 Ya. L. Gol'dfarb and E.P. Zakharov, *Khim. Geterotsikl. Soedin. Sb.* 1971, 7, 1633; *Chem. Abstr.*, 1972, 76, 139896j.

72 A.J. Birch and D. Nasipuri, *Tetrahedron*, 1959, 6, 148.

73 W. Hückel, S. Gupté and M. Wartini, *Chem. Ber.*, 1966, 99, 1388.

74 S. Hoff and A.P. Blok, *Recl. Trav. Chim. Pays-Bas*, 1974, 93, 18.

75 P. Brookes, R.J. Clark, B. Majhofer, M.P.V. Mijović and J. Walker, *J. Chem. Soc.*, 1960, 925.

76 S. Hoff, A.P. Blok and E. Zwanenburg, *Recl. Trav. Chim. Pays-Bas*, 1973, 92, 879.

77 S. Hoff and A.P. Blok, *Recl. Trav. Chim. Pays-Bas*, 1974, 93, 78.

78 For references see: B.C. Newman and E.L. Eliel, *J. Org. Chem.*, 1970, 35, 3641.

79 A.J. Birch, *Discuss. Faraday Soc.*, No.2, 1947, 246.

80 Reference 3, pp. 193-196.

81 A.J. Birch and G. Nadamuni, *J. Chem. Soc. Perkin Trans. I*, 1974, 545.

82 A.J. Birch, R.W. Rickards, and K.J.S. Stapleford, *Aust. J. Chem.*, 1969, 22, 1321.

83 S. Danishefsky, P. Cain and A. Nagel, *J. Am. Chem. Soc.*, 1975, 97, 380.

84 T. Masamure, M. Ono and H. Matsue, *Bull. Chem. Soc. Jpn.* 1975, 48, 491.

85 A.J. Birch and J. Slobbe, *Tetrahedron Lett.*, 1976, 2079.

86 S. Danishefsky and P. Cain, *J. Org. Chem.*, 1975, 40, 3606.

87 R.S. Lenox and J.A. Katzenellenbogen, *J. Am. Chem. Soc.*, 1973, 95, 957.

88 P.A. Grieco, M. Nishizawa, S.D. Burke and N. Marinovic, *J. Am. Chem. Soc.*, 1976, 98, 1612.

89 R.E. Ireland, R.H. Mueller and A.K. Willard, *J. Org. Chem.*, 1976, 41, 986.

90 J.D. McChesney and A.F. Wycpalek, *Chem. Commun.*, 1971, 542.

91 J.A. Marshall and G.M. Cohen, *J. Org. Chem.*, 1971, 36, 877; J.A. Marshall, C.P. Hagan and G.A. Flynn, *J. Org. Chem.*, 1975, 40, 1162.

Received, 21st September, 1976