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MECHANISM AND STEREOCHEMISTRY OF ALKALI METAL REDUCTIONS OF CYCLIC SATURATED AND UNSATURATED KETONES IN PROTIC SOLVENTS

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CONTENTS

1. INTRODUCTION

Though abundant factual information appears to be available relating to the stereochemistry of reduction by alkali metals in protic solvents, crucial gaps remain which defy a full understanding of the subject.[1,2] What has attracted our group to this subject is its relevance to current thinking on through-bond orbital interactions[3] and stereochemistry of ketyl radical anions.[4] These concepts fill "the need for some sophistication in the application of stereoelectronic concepts" expressed by Stork[5] in 1964 in connection with the subject under review.

The article seeks to focus attention on those aspects where systematic work, using the latest practical and theoretical techniques, could prove rewarding. To make this task simpler a critical appraisal of the available data and possible solutions to the problems are presented below. Cognizance has been taken of recent studies on the subject but not of observations hidden in a mass of other data.

Pioneering work by Barton,[6] Stork[7] and House[8] has culminated in a text-book version[9] of the mechanism and stereochemistry of reductions where all the alkali metals are presumed to behave similarly in a variety of protic solvents. Modification has become overdue. It is hoped that this report will expedite the process.

A recent review,[2] restricted in scope, gives a useful survey of the earlier theories relating to alkali metal/NH_3 reductions of ketones. The article, however, fails to recognize the significance of some important recent findings.[10] That review concludes with the observation that the stereochemistry of reductions by alkali metal/NH_3 is dependent on very subtle variations in the structure of an assumed dimeric "quadrupole ion" intermediate. The implication is that rationalization, leave alone prediction, is out of the question.

We do not share this view. Careful sifting through the data, realization of the implications of

recent findings and judicious use of qualitative aspects of orbital interactions is all that is needed to go forward from where the pioneers left off.

To draw meaningful conclusions it is desirable to utilize data pertaining to well-defined sets of conditions. At first sight it appears that a relatively large number of reductions have been performed using Na/EtOH, Li/NH_3 and Na/NH_3. Closer examination reveals that both Li/NH_3 and Na/NH_3 reductions have generally been carried out in the presence of co-solvents. Wide variations are found in the amount of co-solvents added. The most frequently used ones are ether, dioxane and tetrahydrofuran (THF). Another additive is the "proton donor". Generally lower alcohols or ammonium salts are added in small amounts possibly because of the mistaken impression[11] that reduction does not take place in their absence. Systematic studies aimed at distinguishing between reactions with or without proton donors have often used ethanol for quenching.[12] It is now known that alcohols[13] and ammonium salts[14] are unsuitable for quenching of alkali metal/NH_3 reactions. Thus the above comparison has actually been made between reductions in which a proton donor is added at the beginning and one where the proton donor has been added after the reaction has proceeded to an unspecified extent. The mode of addition as well as the composition of the metal/ammonia combination, at least to the extent of a blue versus bronze[15] solution, can affect the mechanism. The failure to specify these invalidates the use of much data that could have been of value.

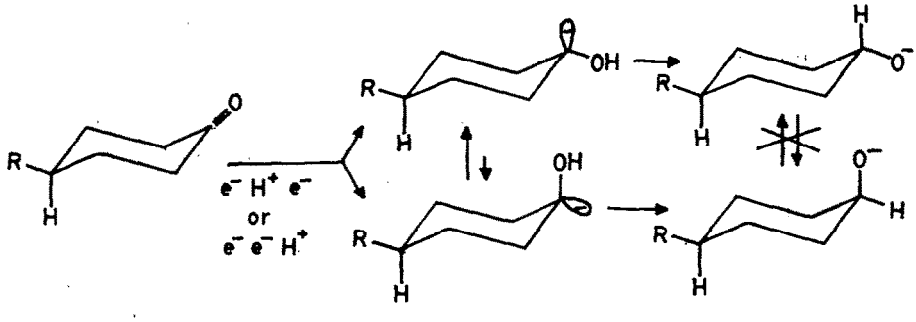
Thus, out of the above three, the Na/EtOH results are the only ones, where with a measure of confidence, a common mechanism can be assumed to apply. This consideration has dictated the order of presentation of the major topics. One topic which we could not include is the reduction in lower aliphatic amines, the Benkeser reaction[16] as opposed to the Bouveault-Blanc and the Birch reductions.[17]

2. MECHANISM AND STEREOCHEMISTRY OF REDUCTIONS OF SATURATED CYCLIC KETONES WITH Na/EtOH, Li/EtOH AND Na/*n*-PrOH

It is true that this mode of reduction is no longer in common usage though it happens to be the best method available for making some alcohols which cannot be obtained by hydride reductions.[18,19] The only recent study related to this reagent is by our group.[20] The previous one was by Kirk.[21]

The mechanism universally accepted for this reaction is the one proposed by House[8] wherein the e^-, H^+, e^-, H^+ path is followed.

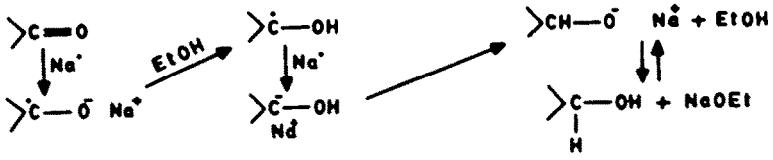
For these reductions it was possible at one time to predict the stereochemistry of the reaction simply by assuming that the more stable epimer would be the major, if not the exclusive, product.[6] Thus 2-, 3-, 4-, 6-, or 7-oxo-5α-cholestanes were expected to yield the more stable equatorial 2α-, 3β-, 4α-, 6α-, and 7β-hydroxy-5α-cholestanes respectively.[22] In the monocyclic case 4-*t*-butylcyclohexanone gives the diequatorial *trans*-4-*t*-butylcyclohexanol.[6] These products were obtained under conditions where the axial epimers were stable to isomerisation. The formation of the more stable product has been explained by assuming that the carbanion intermediate has a definite though easily inverted tetrahedral configuration and that the steric requirements of an electron pair are intermediate between those of a C—H bond and those of a C—O bond[23] leading to the following general picture for cyclohexanone reductions.[24,25]



An assumption inherent in this description is that protonation occurs with retention of configuration and that it proceeds at equal rates so that the transition state energy differences for protonation, correspond to ground state energy differences between the two carbanions. All proposals which rely on equilibration at the carbanion stage predict that camphor should give

endo-borneol and norcamphor should give *exo*-norborneol. The latter, however, gives the *endo*-norborneol.[26]

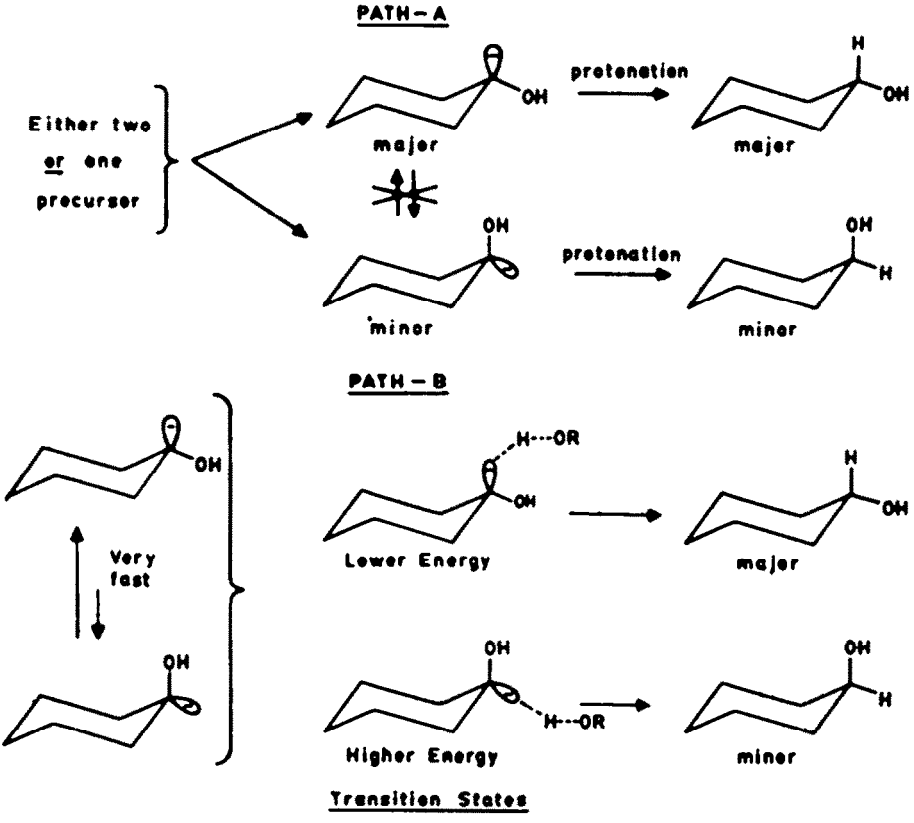
This exceptional behaviour giving the thermodynamically less stable epimer can, in principle, be due to a difference in mechanism. But this is very unlikely for Na/EtOH reductions. The House mechanism reproduced below can be assumed to apply.



If it is accepted that the mechanism is the same then the corollary to it is that *all products* are the results of *kinetic control* at the carbanion protonation or formation step and that accidentally or otherwise the major products in a fairly large number of reactions turn out to be the same as expected if thermodynamic control was operative.

An alternative possibility that protonation on carbon occurs at the radical anion stage has been proposed[27] and convincingly rejected.[28]

Rapidly inverting carbanions with differential rates of protonation have been suggested.[24] It is desirable that we examine this question for the Li/EtOH reductions since the evidence in favour of organolithium compounds undergoing protonation with retention of configuration is strong.[30] The formation of equatorial alcohols by protonation of carbanion must involve either Path A or Path B[31] (Scheme 1).

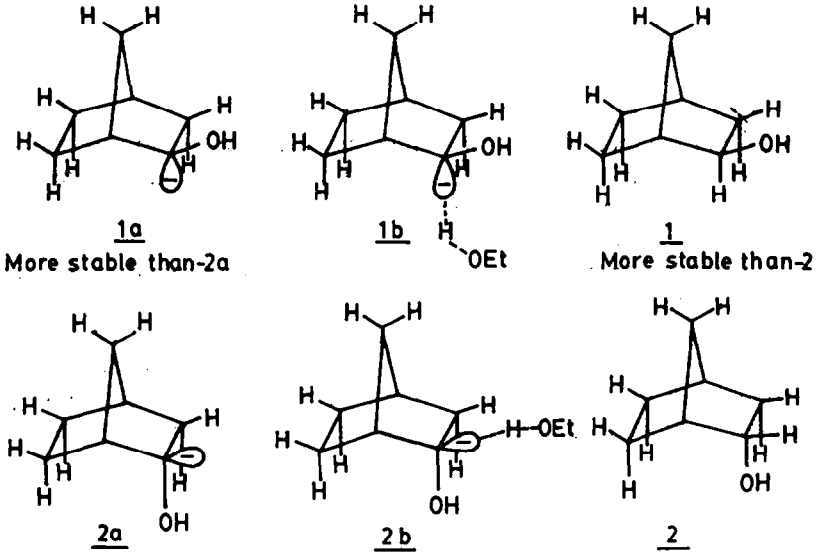


Scheme 1.

Path A represents an extreme situation where the carbanions[32] do not equilibrate and hence rate of protonation does not affect the stereochemistry. In the more likely event of slow interconversion the same result can be expected if protonation is much faster than interconversion.

Path B represents a situation where equilibrium is fast and the rate of protonation is slow. The

transition states shown in Scheme 1 are for the Li/EtOH reactions where protonation of the carbanion occurs with retention of configuration. Formation of the equatorial alcohol as the major product is then due to the energy of the transition state for axial protonation being less than that for equatorial protonation. Let us look at the analogous situation in the case of reduction of norcamphor. The *exo*-norborneol **1** is known to be more stable than the *endo*-norborneol **2**. The equilibrium composition is 91:9 for **1**:**2**. For the fully pyramidalized carbanions the relative



Scheme 2.

carbanion stability also works out to be as indicated in Scheme 2. Hence it is reasonable to conclude that the transition state **1b** would be lower in energy than the transition state **2b** and lead to formation of the *exo* alcohol **1** in larger amounts. Since the *endo* alcohol **2** is the major product Path B stands rejected.

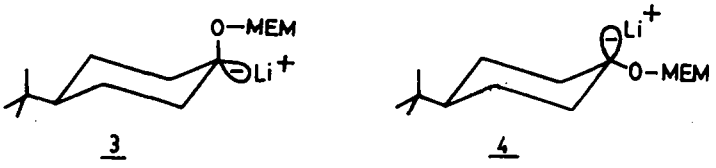
Rassat also has earlier rejected the mechanism embodied in Path B on the grounds that it cannot explain production of *endo* alcohols from both camphor and norcamphor. Methyl lithium in ether attacks camphor from the *endo* face to give an *exo* alcohol while it attacks norcamphor from the *exo* face to give the *endo* alcohol.[33] Path B has been regarded as unlikely by House[8] as well.

An additional factor which needs to be taken into consideration is that carbanions bearing an oxygen substituent on the same carbon do not interconvert at anywhere near the rates of the alkyl substituted carbanions. To cite a specific case the two organolithium compounds **3** and **4** have been shown to retain their stereochemistry and react with electrophilic agents with retention of configuration at low temperatures.[34]

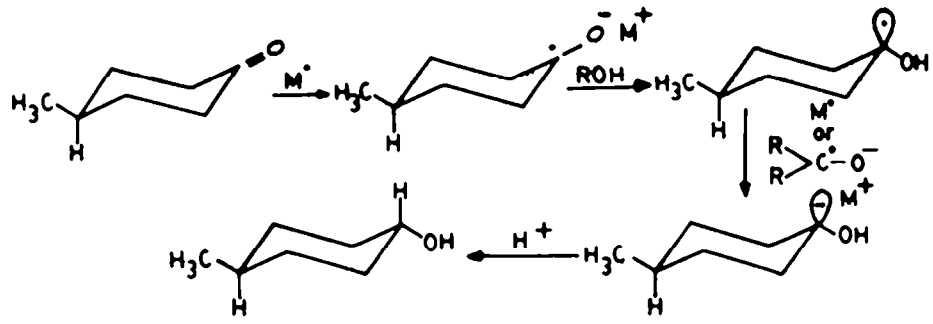
In EtOH the possibility of analogous carbanions being protonated faster than interconversion is that much greater.

Hence for Li/EtOH (and for Na/EtOH subject to the assumption that the carbanion associated with a Na^+ counterion also protonates with retention of configuration) the conclusion is inescapable that the product ratio reflects the ratio of hydroxy carbanion produced but not allowed to equilibrate prior to protonation.

So the scene shifts to the previous step in the House mechanism.[8] This is the addition of an electron to the ketyl radical i.e. to >Ċ—OH. According to House the ketone first adds an electron to give a ketyl radical anion. This is presumed to be planar. Protonation on oxygen is postulated to give a pyramidal ketyl.

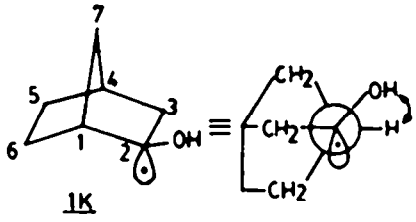


To account for the production of an equatorial alcohol the radical is considered to take up the more stable "configuration" before being reduced and protonated. The sequence as proposed by House is given in Scheme 3.



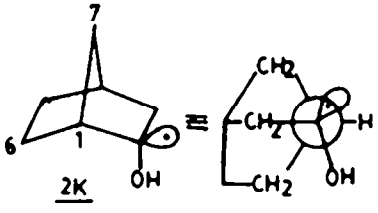
Scheme 3.

In order to explain the formation of *endo*-norborneol as the major product the torsional effect shown in Fig. 1 was invoked[8] as a destabilizing factor for *that* ketyl which could have led to *exo*-norborneol.



1K

Fig. 1.



2K

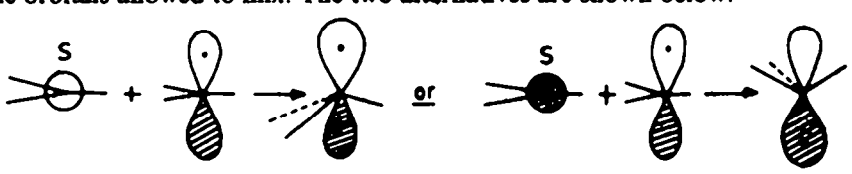
Fig. 2.

This explanation is not convincing for two reasons. The same torsional effect that makes the ketyl with the OH group bent in the *endo* direction more stable, should have made *endo*-norborneol (wherein the radical lobe is replaced by a C—H bond) more stable than *exo*-norborneol. The other objection is that replacement of OH by H should have removed the torsion and consequently the *exo* selectivity. Yet *exo* selectivity at radical sites persists for 2-norbornyl radicals and is well documented.[35]

It occurred to us that as ketyls are simply a special case of radicals in which a hydrogen or an alkyl group has been replaced by OH, the same *selectivity rules* may be applicable *to both*. Thus *exo* selectivity in reactions of bicyclo-[2.2.1]-heptan-2-yl radicals and the *axial* selectivity in the reactions of cyclohexyl radicals[36] could both be applicable to the corresponding ketyls. The advantage of pursuing this possibility was that *all reactions* including the *formation of equatorial alcohols* can be viewed as being under *kinetic* control.

The next step was to look for the most convincing explanation for the *exo* versus *endo* and *axial* versus *equatorial* selectivity in the reactions of bicycloheptanyl and the cyclohexyl radicals respectively. If the stabilization of *exo* radical[37] in the former is presumed to be a consequence of interaction with the antiperiplanar[38] C1—C6 bond (Fig. 2) then an equivalent interaction in the cyclohexyl case predicts stabilization of the *equatorial* radical lobe versus the *axial* one and is hence unacceptable. The orbital extension proposed by Fukui[39] has the advantage of explaining *both* the *exo* and the *axial* selectivity.

The essential feature of the concept is that an otherwise planar radical becomes somewhat pyramidalized due to a "neighbouring group effect". Under the influence of a vicinal σ bond and provided the said bond does not lie in the nodal plane of the p orbital, rehybridisation occurs. The direction of the orbital mixing of the s and the p orbital on the same carbon is determined by the phases of the orbitals allowed to mix. The two alternatives are shown below.



Which of the two alternatives is to be chosen in a specific case depends on the relative phases of the **s** and **p** orbitals and the particular σ orbital responsible for maximum perturbation. According to Fukui[39] the strained σ bond joining C1—C7 in bicyclo-[2.2.1]-heptan-2yl radical (H instead of OH in 2k, Fig. 2) ensures that the radical orbital is extended in the *exo* direction. Orbital extension in the *axial* direction in cyclohexyl radical requires the assumption that the ring is in the chair conformation. According to Fukui[39] the *axial* orbital extension is then due to the interaction with C2—C3 and C6—C5 σ bonds in the cyclohexan-1-yl radical.

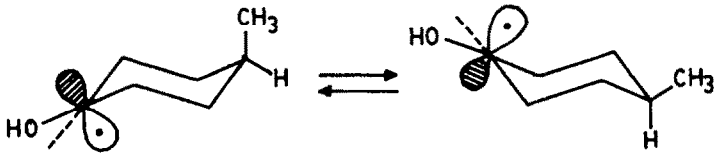
Orbital extension at a radical site and its utility in predicting stereoselectivity of fast and Frontier Molecular Orbital (FMO) controlled reactions[40] should not be bracketed with orbital extension of a π bond and the relative unimportance[41] of the latter in *slow* reactions such as Diels–Alder condensation.[42,43]

Yet because of the spotlight on the latter it is desirable to emphasize that **s** and **p** orbital mixing has been an accepted feature in interpretation of ESR spectra.[44] That it results in partial pyramidalization as envisaged by Fukui has been pointed out by Kawamura[45] who has not only provided experimental evidence but also referred to all the factors which contribute to pyramidalization. One of these is the presence of a lone pair of electrons on an attached atom. Whether carbon radicals are pyramidal or planar has been the subject of controversy over several years. Nonplanarity in the tertiary butyl radical has finally been accepted.[46] An attractive explanation by Dewar[47] invokes σ conjugation. According to him the radical hybridizes in order to get the benefit of conjugation with σ orbitals on the same carbon. This gives additional weightage to the concept of σ framework linked rehybridization including the Fukui concept.

The latter assigns stereoselectivity to orbital extension i.e. to a single species of minimum energy in the cyclohexyl and the 2-norbornyl radicals.

In the case of ketyls, ESR evidence supports the existence of a similar partially pyramidalized *single* species in unsymmetrical molecules.[48] Thus 2-norbonyl ketyl has been "assigned" a conformation in which the hydroxyl group is bent in the *endo* direction.[49] It is necessary to emphasize that the angle of bending relative to the plane containing C1, C2 and C3 is far short of the 54° required for a tetrahedral arrangement. Thus the "quasi-endo" hydroxyl in the ketyl does not encounter the same steric repulsion by the other three *endo* hydrogens that the hydroxy group of *endo*-norborneol does. In the fully pyramidalized alcohols on the other hand *endo*-norborneol is destabilized relative to *exo*-norborneol.

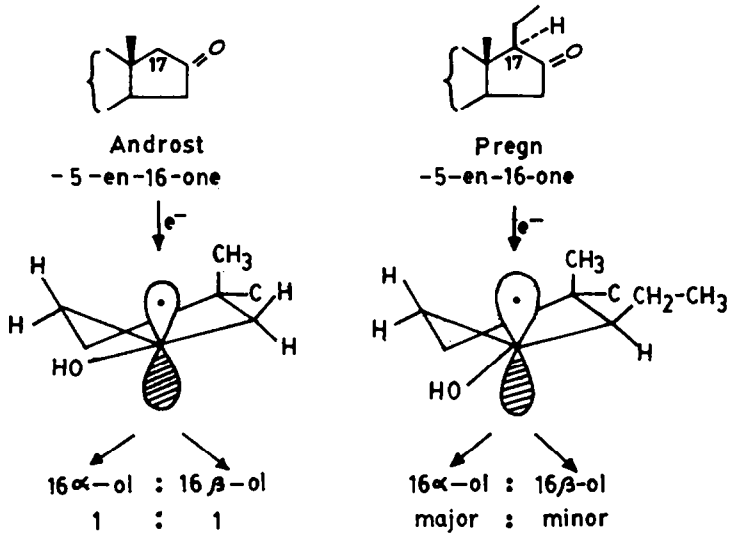
Recent work using variable temperature ESR studies confirm[4] that the ketyl from 4-*t*-butylcyclohexanone is also a single species with the ring "frozen" in a chair conformation and the hydroxyl in the "quasi-equatorial" position. With the less bulky methyl group in place of *t*-butyl, existence of the two conformers shown below is confirmed. An additional two species may not qualify to be described as such.



Note that the orbital containing the single electron (SOMO) is extended in the *axial* direction in both conformers.

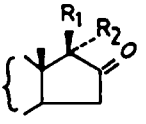
Orbital extension of the radical lobe in the *axial* direction in cyclohexyl ketyls[4] and in the *exo* direction in 2-bornyl ketyl[49] as well as 2-norbornyl ketyl,[49] has been linked empirically[20] with the stereochemistry of the major product of Na/EtOH reductions. The postulate[20] is "whenever the orbital extension is predominantly in one direction, a secondary alcohol is produced by attachment of hydrogen from the same direction provided the reaction is carried out in the presence of large excess of proton donors of sufficient acidity." We believed in the existence of such a relationship which forms a link between ESR data and reductions carried out under specified conditions. But sufficient examples of pyramidalized ketyl radicals, whose structures had been deduced using ESR, were not available. Hence we took up work using the Fukui concept as the basis for predicting orbital extension as well as incorporating reasonable assumptions to rationalize the empirical relationship.

This is best illustrated by reference to the actual work done on 16-oxo-steroids.[20] From CD evidence it was known that this cyclopentanone exists in a half-chair conformation.[50] In this conformation the ketyl derived from androst-5-en-16-one, **5**, can be expected to be planar.[51] The orbital extension in the α direction expected as a result of contribution by the C14—C15 σ bond and in the β direction due to the C13—C17 σ bond give a "resultant" with no extension in either side. The contribution by the C—H σ bonds at C15 and C17 is considered negligible because the energy separation between C—H HOMO and ketyl SOMO is sufficiently large as to minimize perturbation. The situation changes in going from androst-5-en-16-one to pregn-5-en-16-one, **6**. The latter differs from the former in having a 17β ethyl group i.e. a β carbon–carbon bond on a carbon adjacent to the ketyl. This should result in a pyramidalized orbital with orbital extension, due to Fukui effect, in the β direction with OH bent in the α direction below the plane containing the C15, C16 and C17 carbons. This is illustrated by partial formulae in Scheme 4.



Scheme 4.

The empirical relationship between orbital extension and stereochemistry of the secondary alcohol leads to the expectation that the androst-5-en-16-one would give almost equal amounts of the epimeric alcohols while in the alcohols obtained from pregn-5-en-16-one, the 16α ol would be the major product. Substituting the 17α hydrogen by a methyl group in the pregn-5-en-16-one should restore near planarity to the ketyl radical and result in a 16α : 16β alcohol ratio close to one. The results we obtained[20] were gratifying as can be seen from Table 1.



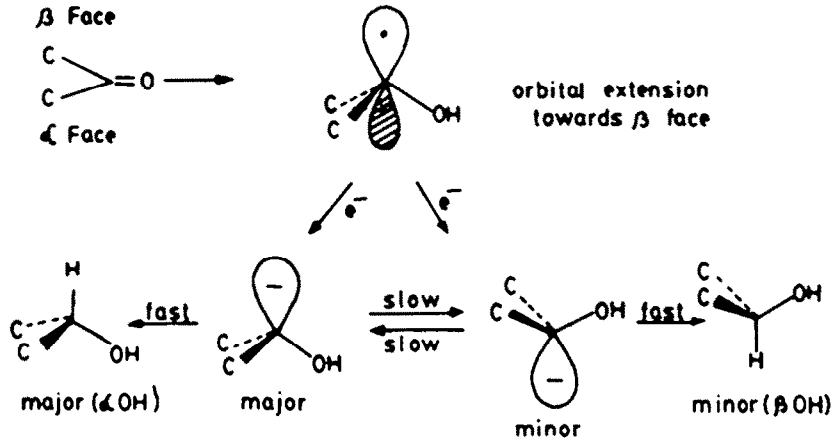
5 $R_1 = R_2 = H$

6 R_1 = Et, R_2 = H

Table 1. 16α : 16β-ols from alkylated androst-5-en-16-ones

Compound	$R_1 = R_2 = H$	R_1 = Et R_2 = H	R_1 = Et R_2 = Me
Na/EtOH	53:47	85:15	52:48
Equilibration	71:29	82:18	61:39

The absence of equality between Na/EtOH results and equilibration ratios confirm that the reaction is not under thermodynamic control. $LiAlH_4$ reduction of **6** gives mainly the 16β ol. CH_3Li also attacks **6** from the α side. Hence ease of approach of $H^\cdot$ or H^+ is unlikely to be the controlling factor in the Na/EtOH reduction. The empirical relationship has been explained[20] using Path A (Scheme 1) together with the assumption that the rate of formation of the carbanions is directly proportional to the coefficients of the lobes on the two sides of the plane containing the ketyl carbon and the adjacent carbons.[52] The consequence of this is best understood from Scheme 5 which refers to the reaction in which ethanol is the solvent.



Scheme 5.

Protonation of the two carbanions can be expected to be very fast in ethanol. It does not have to proceed at identical rates for the two carbanions. The result can be accounted for as long as interconversion between the carbanions is much slower or non-existent.

These examples of the applicability of the Fukui effect are in addition to those in the bicyclo-[2.2.1]-heptanyl series and to the numerous examples of production of equatorial alcohols as the major products in Na/EtOH reductions. It follows that formation of axial alcohols as the major product constitute exceptions. In steroids both 1-oxo-5-α-cholestane[53] and some 12-oxo-steroids[54,55] give predominantly axial alcohols. The Fukui effect like other orbital control phenomena can be expected to be in control only so far as strong steric effects do not come into play.[56] In the cases cited there are grounds for invoking steric effects and thus accounting for such anomalies.

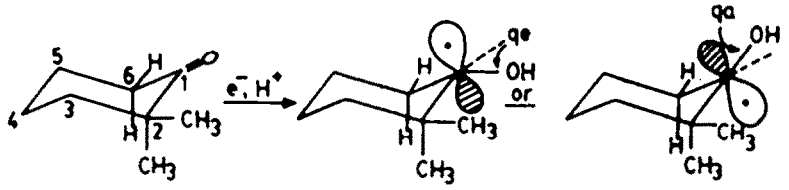
In order, however, to increase the predictive value of the concepts in case of saturated ketones in a variety of environments it is necessary to look into this matter in greater depth.

The first aspect to be considered is in relevance to Scheme 5 and the empirical relationship already referred to. It is claimed that orbital extension and hence pyramidalization governs the stereochemistry *irrespective of the factors responsible* for pyramidalization in a given direction. Thus in reduction of 5α-cholestan-1-one, **7a** wherein the axial 5α-cholestan-1α-ol, **7b**, is obtained (see Chart 1), the intermediate ketyl has to be pyramidalized in such a manner that the hydroxy group takes up a quasi-axial position and the orbital extension is in the *equatorial direction*. Steric compression due to C11 methylene can be considered as destabilizing the normal quasi-equatorial arrangement with the result that the latter is no longer the species of minimum energy. The *single species* of *minimum energy* in this case appears to be the one dictated by steric considerations *overriding* the Fukui effect.

But if one explains the axial alcohol formation from C1 ketyl as due to steric compression by C11 methylene then an equivalent steric compression of C11 ketyl by C1 methylene should result in formation of the axial 11β-ol as the major product. Contrary to this expectation the major product of Na/EtOH reduction of 11-oxo steroids, **8a**, is invariably the equatorial 11α-ol, **8b**.[57]

Such observations made us realize that a more detailed analysis of the stereoelectronic factors was necessary.

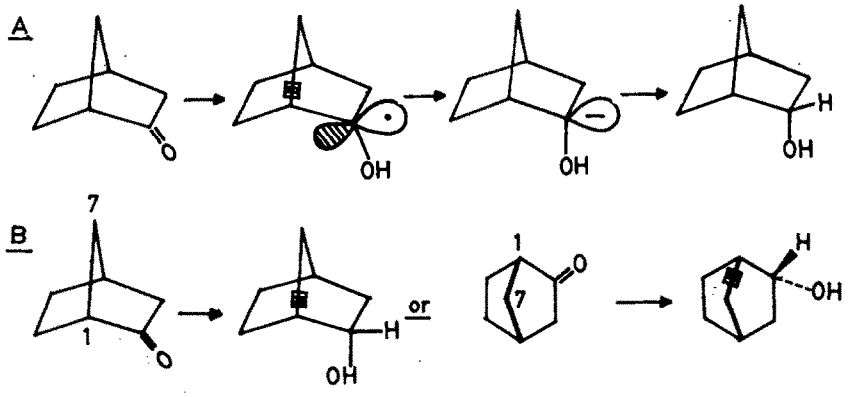
The orbital extension and hence pyramidalization can be expected to be influenced to different extents depending on the relative energy of the SOMO i.e. the singly occupied C—O π* orbital and the σ framework. Thus in the cases where no steric effect is operating the ketyl radical will take up that conformation which derives the greatest stabilization resulting from the strongest stereoelectronic contributor. This can be illustrated by considering the case of 2,2-dimethyl cyclohexanone.



Which one of these two will represent the ketyl radical? The σ orbitals which will stabilize the conformation in which the OH is quasi-equatorial ("qe" in the diagram) are C2—C3 and C5—C6. Those which stabilize the other conformation having a quasi-axial (qa) hydroxyl are the axial methyl and the axial hydrogen at C6. Contribution by the C—H bond can be neglected since the difference in energy between SOMO and C—H is much larger than the difference between SOMO and C—C. This is just an acceptance of the well known "C"-approximation.[3,58] The axial CH_3 represents a C—C bond which is not as near in energy to the SOMO as is the more highly substituted and more strained C2—C3 bond. Thus the latter dominates. If one adds the influence of the C5—C6 σ orbital then the lower energy species and to all practical purposes the *single* species will be the one with hydroxyl group quasi-equatorial.

The framework in 2,2-dimethyl-cyclohexanone ketyl includes all the other C—C bonds including the equatorial methyl. Contribution of the latter is expected to be small because it lies in the nodal plane of the "unpyramidalized" SOMO. The C1—C2 and C1—C6 bonds are expected to contribute significantly to the *pyramidalization* as visualized by Dewar[47] in the case of *t*-butyl radical. But they will not influence the *direction* of pyramidalization.

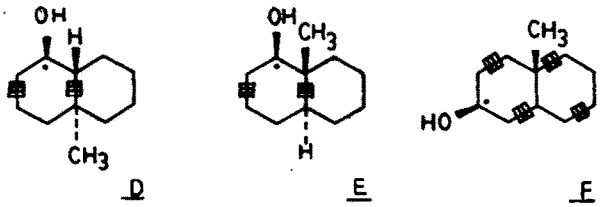
It is *incidental* that the conclusion arrived at using the Fukui effect places the C—O bond of the ketyl nearly antiperiplanar to the bonds which dictate the conformation.[59] This makes it easier to *represent* the consequences of the Fukui effect. We first introduce a symbol for picking out the particular σ bonds which are responsible for stereoelectronic stabilization of the specific ketyl conformation. In subsequent formulae, wherever relevant these bonds are shown as follows ⊞ . Such bonds will always be nearing antiperiplanarity to the C—O bond. This allows configuration to be assigned to the expected major epimer even if the orbital extension is not explicitly shown. Take the case of 2-norbornyl ketyl. Scheme 6 Path A indicates the steps in the reduction of 2-norbornanone with Na/EtOH. Path B is a shortened representation of the same in terms of starting ketone and major product.



Scheme 6.

It must be clearly understood that B is only an "abbreviation". It means that in the conversion of 2-norbornanone to *endo*-norborneol the intermediate ketyl radical has an endo bent OH because of the dominant effect of the C1—C7 σ bond.

The importance of the σ framework influencing the stabilization of the quasi-equatorial ketyl will be best understood by comparing D, E and F given below.



Stabilization and pyramidalization will be greater for D than for E because in the latter the angular methyl will contribute to orbital extension in the opposite direction. The stabilization and pyramidalization will be greater in F than in D. In F the contribution to pyramidalization and

stabilization is no longer of just two C—C σ orbitals contributing to the Fukui effect but of σ orbitals having higher HOMO energy as a result of through-bond interaction with the C—C σ orbitals which are antiperiplanar to them. The latter interaction highlighted by Hoffman[60] is maximized in the antiperiplanar arrangement of σ orbitals. The "trans bridges" of Weinhold,[61] the "trans rule" referred to by Paddon-Row[3] and σ conjugation by Dewar[47] all testify to the importance of this arrangement. Maximization of through-bond interactions in an "all trans" situation is manifest in the W-effect in NMR[62] and ESR[63] and in the usefulness of the "zig-zag" in interpretation of CD of cyclic ketones.[64]

We are now in a position to deal with 5α-cholestan-1-one,[53] 11-one[57] and 7-one.[65] See Chart 1. A double headed thick arrow is used for indicating the steric effect in the ketones. This effect will be perpetuated in the ketyl if the latter were planar. It will still be important for *partial* pyramidalization. Thus steric effect[66] is expected to disfavour the quasi-equatorial hydroxyl in ketyls from above ketones relative to quasi-axial hydroxyl.

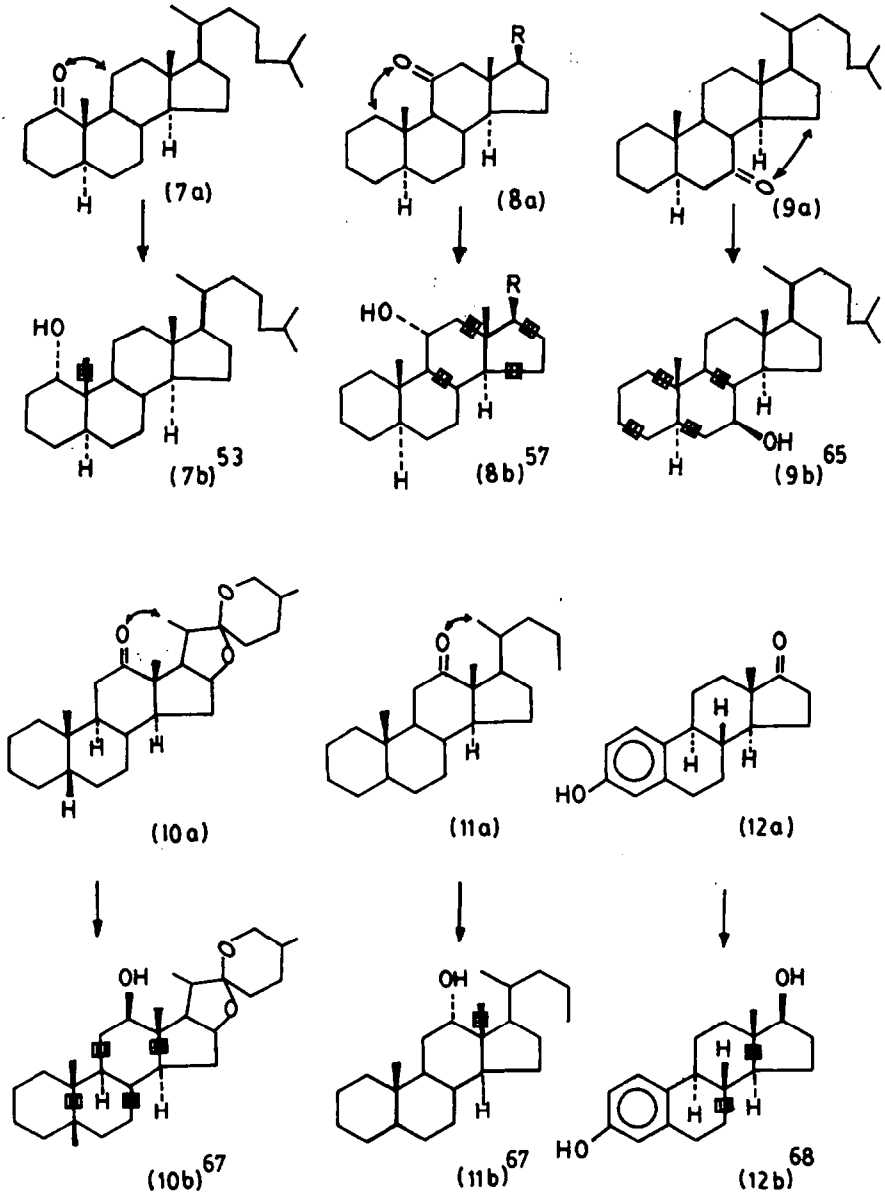


Chart 1.

The formation of the axial alcohol, **7b**, from 5α-cholestan-1-one, **7a**, can then be regarded as being due to (1) steric interaction between C11 methylene and the hydroxyl (or preferably the

hydrogen-bonded counterion associated "alkoxide" referred to at the end of this section) "pushing" the oxygen towards the quasi-axial direction; (2) the stereoelectronic contribution, of the adjacent angular methyl, supporting orbital extension in the equatorial direction. These two effects combine to overcome the stereoelectronic stabilization of orbital extension in axial direction discussed earlier and shown in D and E above.

An equivalent steric effect in the case of 5α-cholestan-11-one, **8a**, and 5α-cholestan-7-one, **9a**, does not lead to axial alcohol because there is no angular methyl on the next carbon to support it. More important is the strong stabilization of axial orbital extension as a result of the additional antiperiplanar contributions shown on **8b** and **9b**.

All the above considerations are called into play in order to understand the behaviour of the 12-oxo steroids, **10a**,[67] and **11a**[67] given in Chart 1. Many experiments on alkali metal/NH_3 have been reported. But these will be discussed later. Here we have the results of Na/EtOH reductions in which **10a** gives an equatorial alcohol **10b** whereas **11a** gives an axial alcohol **11b**. Stabilization shown in **10b** is strong enough to overcome the effect of the angular methyl as well as the steric effect of the substituent at C17. The steric effect is expected to be quite strong and possibly stronger than the one encountered in 5α-cholestan-1-one, **7a**. It is only because the "trans bridges" are quite "powerful" that axial orbital extension occurs.

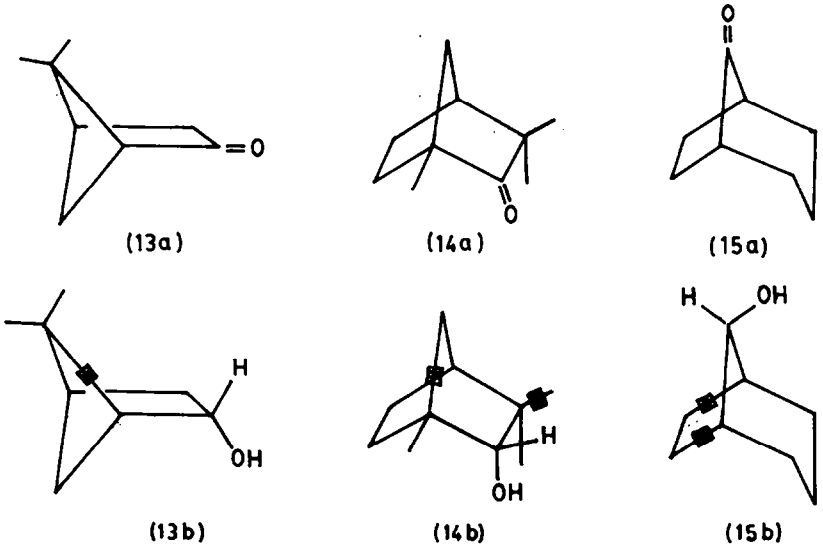
The freely rotating branched side chain, in **11a** can, however, be expected to exert a greater steric effect[66] than exerted by the "tied up" side chain. This tilts the balance in favour of a "take over" by the steric plus angular methyl stereoelectronic effect giving the axial alcohol. The delicate balance between opposing effects can be tilted the other way in favour of equatorial alcohol by putting an unbranched side chain i.e. a β-ethyl group at C17.

The question of steric hindrance does not come in as far as the reduction of estrone, **12a**, is concerned. The angular methyl is no match for the stereoelectronic effects favouring the 17β-ol, **12b**.[68]

Steric effects are considered to play only an insignificant role in the rest of the examples cited below except in so far as they may affect the conformation of the ketone.

Hence the above considerations make it possible to explain the stereochemistry of all Li/EtOH, Na/EtOH and Na/*n*-PrOH reductions of cyclic ketones. The only limitation is that in some cases knowledge of the preferred conformation of the *parent ketone* is essential. It is important to realize that steric effects which make one epimeric alcohol more stable than another refer to effects due to fully pyramidalized carbon. They are not relevant to the non-bonded interactions in the partially pyramidalized ketyls.

In Chart 2 are given examples of bicyclic ketones for which prediction is possible without any knowledge of the preferred conformation of the ketones. In the case of **13**[69] the dominant



(13a) (14a) (15a)

(13b) (14b) (15b)

Chart 2.

stereoelectronic effect is due to the more highly substituted single bond since its HOMO is higher in energy. In the case of the non-enolizable ketone, fenchone **14a**[70] no explanations are required. With the ketone **15a**[71] the C—C σ orbitals of higher energy are those belonging to the more strained ring system i.e. "5" vs "6". It does not matter whether the six membered ring exists as a chair or boat.

Conformation is important for compounds given in Chart 3. In case of isopinocamphone **16a** the conformation shown is preferred.[72] Thus the Fukui effect leads to orbital extension which results in the ketyl taking up the conformation which yields the **16b**.[73] It is immaterial whether **16b** once formed stays in this particular conformation or prefers another.

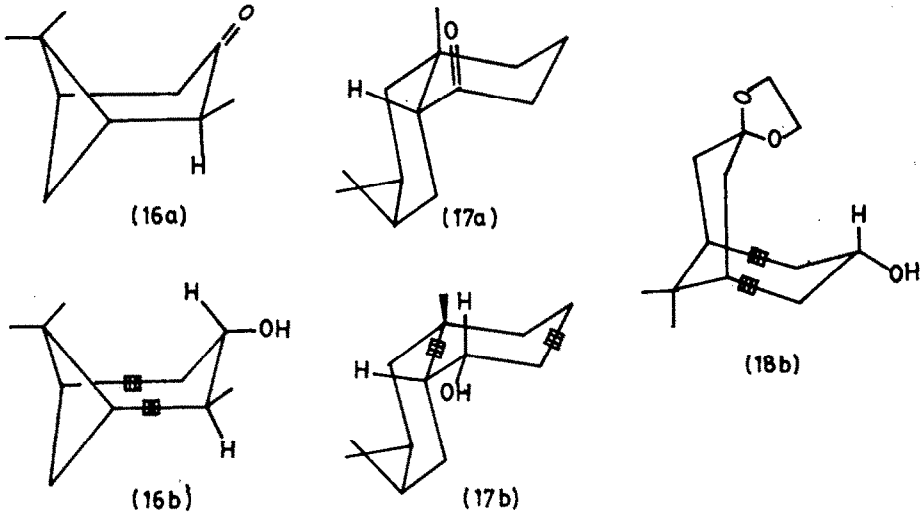
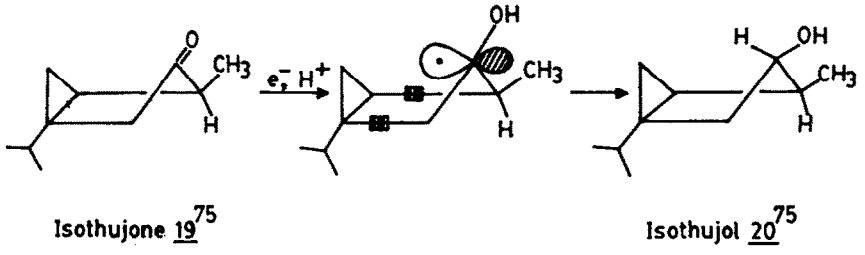


Chart 3.

Compounds **17b**[74] and **18b**[18] are both equatorial alcohols but their formation is predicted by an application of orbital extension which assumes that the ketone **17a** does not prefer the alternative *cis* conformation (with angular methyl in equatorial position) and that ketone corresponding to **18** does not prefer a boat conformation for the cyclohexanone ring.

Thus the orbital consideration in conjunction with results of Na/EtOH reductions can have a consequence of far-reaching significance in terms of stereochemistry of the ketones themselves.

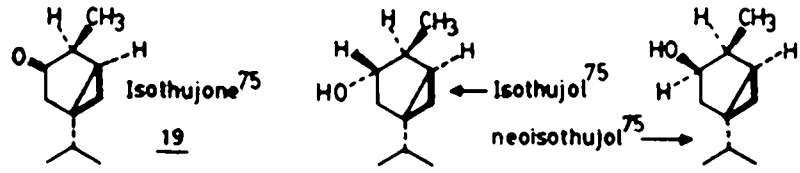
If the configuration of the major product obtained by Na/EtOH reduction is different from that expected on the basis of the above considerations it is likely that the conformation used for the latter is wrong. Thus if isothujone, **19**, is assumed to prefer a chair conformation in respect of the cyclohexanone ring the major product expected on these considerations would be neoisothujol. On the other hand a preferred boat conformation for the six membered ring, shown in Scheme 7, leads to the stabilization shown and acounts for the formation of isothujol **20**. Proportion of neoisothujol to isothujol produced in Na/EtOH reductions is 2 : 59.[75]



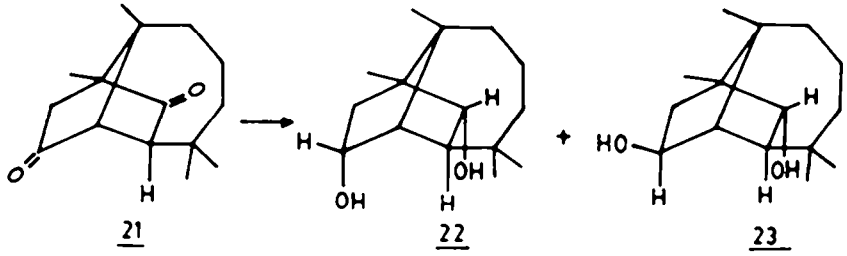
Scheme 7.

The conformation shown in Scheme 7 for isothujone is strongly supported by CD, NMR and MM-2 calculations.[76] These compounds have been named differently by different groups.[75,76] To

avoid confusion the configurations of the above compounds are given below.



An interesting case is the reduction by Na/*n*-PrOH of diketone **21**[77] to culmorin **22** and its isomer **23** in a 3 : 2 ratio shown in Scheme 8.



Scheme 8.

A close look at available stereoelectronic contributions enables one to understand this result in which one of the two ketones is reduced to endo alcohol in both **22** and **23**.

Hydride reduction of **21** does not give **22** but other epimers. Many of the compounds given in Charts 2 and 3 also give a different epimer on hydride reductions e.g. **8a**, **9a**, **12a**, **13a**, **17a** and **18a**.

Using the orbital extension concept supplemented where necessary with CD or ORD data it should be possible to predict the reduction product to be expected using Na/EtOH, Na/*n*-PrOH or Li/EtOH unless very strong steric effects intervene.

The above discussion did not differentiate between Li/EtOH and Na/EtOH.

In Table 2 some data which differentiates between the two is given along with results using *t*-BuOH as solvent.

Table 2. Ratios of major to minor alcohols obtained on reduction of various ketones. (Data in parentheses from Kirk[21])

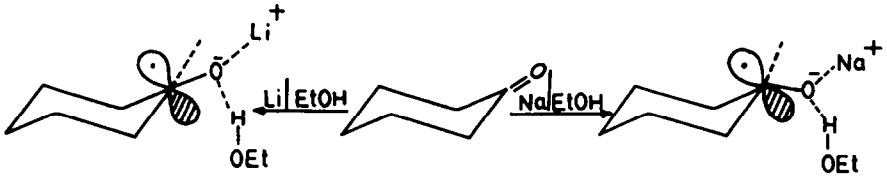
Compound \ Reducing Agent	Na/EtOH	Li/EtOH	Na/t-BuOH	Li/t-BuOH
Cholestan – 2 – one	— (3)	— (2)	— (3)	— (2·2)
Cholestan – 3 – one[78]	3·8	2·4	29 (37)	17 (12)
Cholestan – 6 – one[78]	11 (15)	6 (9)	25 (65)	15 (5)
Camphor	— (3)	— (2)	— (3)	— (2·2)
Pregn-5-en-16-one[79]	5·7	1·7	—	—
Androst-5-en-16-one[79]	1·8	1·8	—	—
Cholestan – 1 – one[78]	1·6	19	1·0	1·2

It is of interest that the amount of major alcohol is diminished in going from Na to Li in the same solvent with one exception. 5α-Cholestan-1-one, wherein strong steric effects are operating, gives a different result.

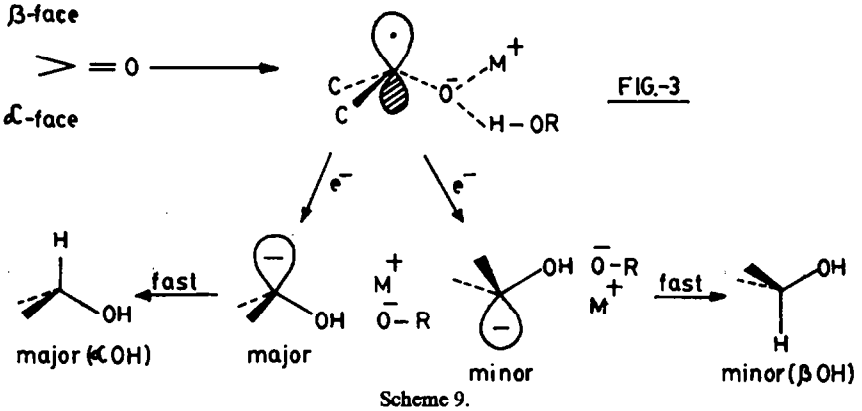
The data point to the need to modify an assumption that has been made (see Scheme 5) that the pyramidalized ketyl is the key intermediate which determines the stereochemistry of the reduction.

Two changes are required. Firstly, the House mechanism has to be modified by discarding the belief that the ketyl radical anion is planar. Secondly, a role has to be assigned to the cation at a crucial stage. The acceptance of a pyramidalized ketyl radical anion no longer poses any difficulty.[48,80] Greater carbanion character has been suggested for ketyl radical anion as compared to ketyl.[81] Taking into account the pyramidalization factors pointed out by Kawamura[63] leads one to the conclusion that the following order of decreasing pyramidalization would be observed.[82]

The role of solvent can also be incorporated by hydrogen bonding. Such a hydrogen bonded ketyl radical anion has been proposed in order to explain the ESR spectra of fluorenone ketyl radical anion in *n*-PrOH by Hirota.[83] Tentatively assuming association of a single molecule of solvent the difference between species produced in Li/EtOH and Na/EtOH is illustrated below.



A single species is postulated and Scheme 5 is modified to Scheme 9.



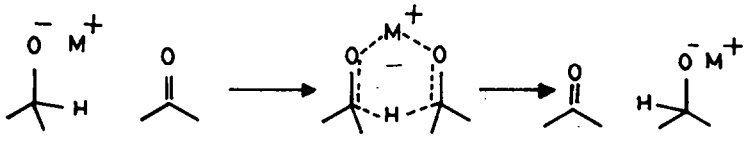
Scheme 9.

Since ketyl radical anions are weaker bases than alkoxide ions[84] hydrogen bonding with R—OH is to be expected rather than proton transfer. As electron (or alkali metal) addition to the carbon progresses, the basicity on oxygen should increase and proton transfer occur. Formation of a dianion is avoided when alcohols are used as solvents. The ratio of major to minor alcohols is *postulated* empirically as being dependent on the relative sizes of the two lobes on the different faces and hence by degree of pyramidalization. The postulate is rationalized by suggesting formation of intermediate hydroxy carbanions in different proportions and protonating them with retention of configuration without allowing them to interconvert.

3. COMMENTS ON USE OF OTHER COMBINATIONS OF ALKALI METAL/LOWER ALCOHOLS

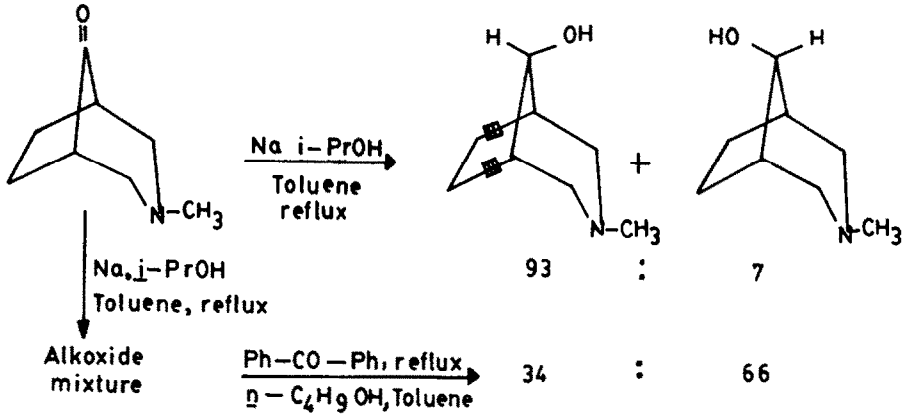
The need for this separate categorization is due to the realization that the final product obtained, using combinations other than those specified in the previous section, may not be the one that is initially formed. Equilibration by hydride transfer becomes a distinct possibility with higher temperature, prolonged reaction time and the use of secondary alcohols as solvent.

For sealed tube reactions even ethanol is not exempt in the sense that Windaus[85] converted 5α-cholestan-3β-ol to a mixture containing 10% 5α-cholestan-3α-ol by heating with NaOEt. For epimerization use of $NaOCH_3$ at high temperatures in the presence of a small amount of ketone is well known. A very interesting recent study by Warnoff[86] demonstrates that an intramolecular hydride transfer proceeds faster with R—O^- K^+ than with R—O^- Li^+ whereas the reverse is true for intermolecular hydride transfer which presumably occurs as follows.



Kirk[21] found that reduction of some 20-oxo steroids in Li/*i*-PrOH at refluxing temperatures[87] may not yield the kinetically controlled product unless it happens to be the same as the thermo-

dynamically controlled one. To ensure formation of the thermodynamically more stable alcohol by hydride transfer, non-enolizable ketones such as benzophenone have been deliberately added, after the alkali metal has reacted. The ketone acts as a catalyst. Given in Scheme 10 is an interesting case of this type.[88] The initially produced alcohol is an alcohol which is axial to the piperidine ring. The configuration shown was the one expected for this kinetically controlled product.



Scheme 10.

As far as hydride transfer from solvent is considered, it can be avoided by using *t*-BuOH. Hence results with *t*-BuOH have been compared with those with ethanol in Table 2. Scheme 9 in the previous section serves to explain the difference in product ratios observed with the *unhindered ketone*. Weaker hydrogen bonding by *t*-BuOH which is a weaker Lewis acid than EtOH and also the possibility of one *t*-BuOH molecule being associated with the ketyl radical anion against two molecules of EtOH, exists. Either of these can result in greater pyramidalization of ketyl radical anion in *t*-BuOH than in EtOH leading to increased amounts of the major alcohol in the former relative to the latter. More data are needed to confirm whether the above expectation is borne out.

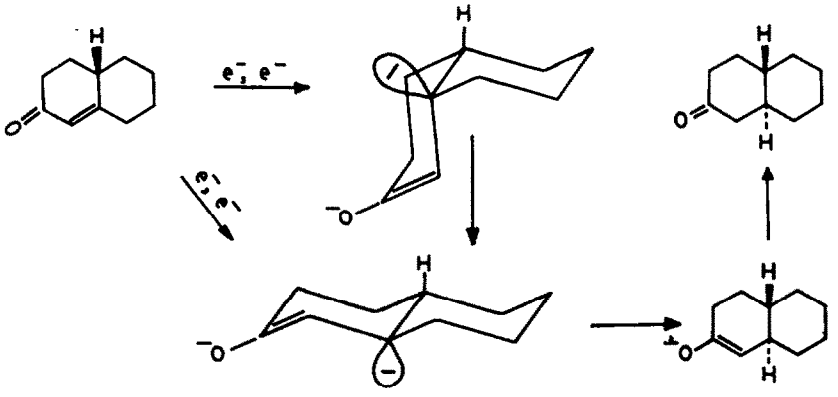
Most of the early work was synthetic and hence reliable data on product composition is not available.

We consider that no useful purpose will be served in listing the data here.

4. SOME ASPECTS OF STEREOCHEMISTRY AND MECHANISM OF REDUCTION OF α,β-UNSATURATED CYCLIC KETONES WITH Li/NH$_3$ AND Na/NH$_3$

Extensive literature survey by Caine[1] has made it possible for us to concentrate on those aspects which are relevant to mechanism and stereochemistry.

Barton and Robinson[6] proposed a dianion mechanism as part of one of the earliest studies on the stereochemistry of Li/NH$_3$ reductions of α,β-unsaturated ketones. As shown in Scheme 11 the carbanions were expected to take up the more stable configuration prior to protonation with retention of configuration.



Scheme 11.

Inherent in this proposal was the assumption that at the ring junction the stereochemistry of the more stable carbanion is the same as that of the compound obtained by making a C—H bond with retention of configuration.

This left some questions for which Stork sought answers. By carrying out the reaction under dry conditions and then quenching with D_2O it was possible for Stork[89] to establish that the hydrogen at the β position comes from NH_3 giving enolate ion prior to quenching. Djerassi[90] used Li/ND_3 and obtained **28** from **27** (Chart 4).

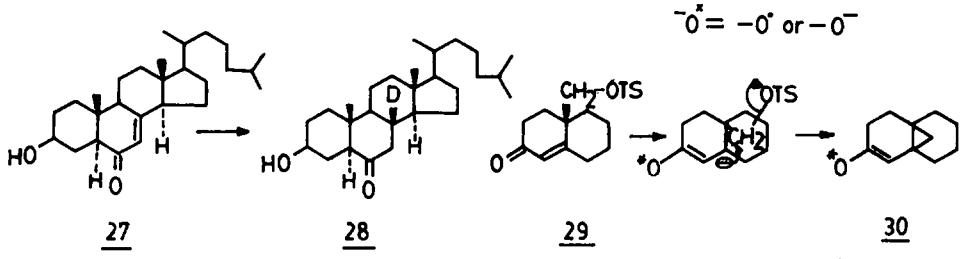
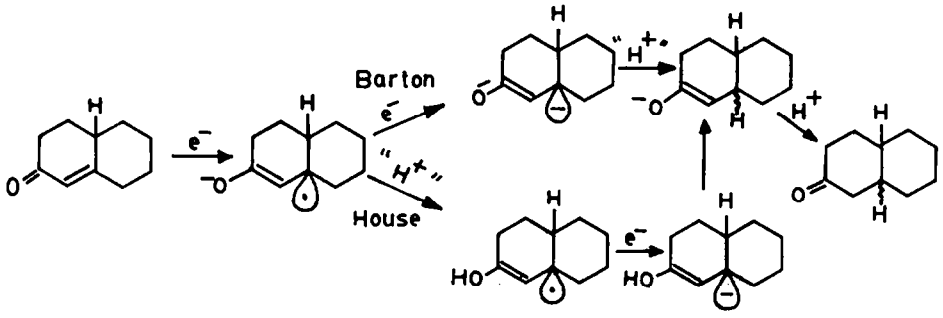


Chart 4.

Evidence of carbanion generation at β position was obtained when Li/NH_3 converted **29** to **30**.[91] The trapping experiments did not contribute to either proving or disproving the dianion mechanism. The alternative to the Barton mechanism was the House[92] mechanism. The first step is the addition of an electron to give a 1,4 radical anion.[92] The subsequent steps are expected to be fast leading to an enolate ion which does not protonate in NH_3.

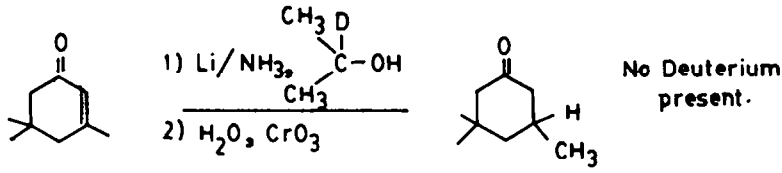


Scheme 12.

The third step consists of protonation of dianion by NH_3 in the Barton mechanism and the addition of an electron to the SOMO in the House mechanism. Both these are expected to be quite facile. A major objection to the House mechanism is the proposed protonation of a very weakly basic 1,4 radical anion by NH_3. Since the pKa value[84] of the radical anion is about 10 and that of NH_3 is[8] 35, then using the relationship proposed by Eigen[94] the rate of proton transfer is estimated to be about 10^{-24} M^{-1} sec^{-1}. According to House the enolizable α,β-unsaturated ketone itself would be a better proton donor. If this was correct then (1) no β deuteration should have been observed in the reduction of **27** with Li/ND_3; (2) an equivalent amount of enolate ion should have been produced. This enolate from starting unsaturated ketone is less basic than enolate from saturated ketone. The latter is known to survive ketonization[95] prior to work up particularly if the counterion is Li^+. Hence the starting material recovered on work up should have been close to 50%. There are no reports of such recovery. A typical case cited by Caine[96a] is of Li/NH_3 reduction of 3,5-dimethylcyclohex-2-en-1-one. Against 83% reduction only 13% starting material was recovered. The latter could be the result of proton abstraction by $LiNH_2$. By destroying the $LiNH_2$ using proton donors having high kinetic acidity recovery of starting material can be totally avoided. Normally lower alcohols or even water is added.

As an alternative to protonation, House[92] considered the possibility of hydrogen atom abstrac-

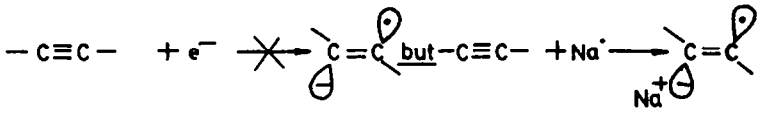
tion by the 1,4 radical anion at the β position. He was able to rule out this possibility on the basis of the following reaction:



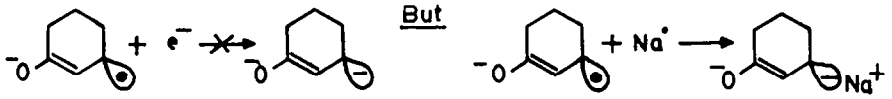
The absence of deuterium in the final product, in spite of addition of an efficient deuterium atom donor, provided convincing proof.

The dianion mechanism involving 1,4 dianions formed by successive addition of two electrons to the enones was strongly opposed by House[8] on the grounds that alkali metals in liquid ammonia should not be capable of reducing compounds which require a reduction potential more negative than -2.9 V (vs a saturated calomel electrode).[8] This allows dianion formation from benzophenone which exhibits two one-electron waves in aprotic or strongly alkaline media. In pyridine as solvent the waves are at -1.49 V and -1.72 V.[97] It does not allow a 1,4 radical anion from cyclic enones to be further reduced to 1,4 dianions.

There is, however, a fallacy in this argument which was located by House himself when he took up work on mechanism of alkali metal/NH_3 reductions of alkynes.[98] Disubstituted alkynes require for adding the *first* electron a reduction potential more negative than -3.0 V (vs. SCE) yet they are reduced by alkali metal in NH_3 in the absence of proton donors. The electrochemical arguments are relevant to addition of an electron *by itself* but not to the addition of an addition of an electron associated with a counterion. The difference can be represented as follows:



Applying the above rationalization by House to reduction of 1,4 radical anions leads to the following:



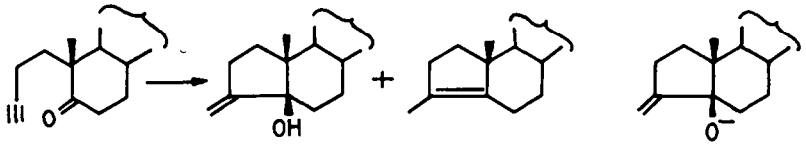
If the 1,4 radical anion is associated with a counterion then production of a 1,4 dianion associated with *two* counterions should be even more facile.

Having convinced ourselves that the dianion mechanism can no longer be rejected outright, the choice is between two mechanisms represented by e^-, e^-, H^+ and e^-, H^+, e^- respectively. Because he had rejected the former and demonstrated absence of hydrogen atom abstraction, House had to prefer the latter. The estimated rate of protonation of 1,4 radical anion by NH_3 has been given above and is so low that *proton transfer* can be ruled out unless the Eigen equation is questioned. Fessenden[99] used the Eigen[94] equation to calculate the rate of protonation of ketyl radical anions by water. The calculated value was very close to the experimentally determined one. Hence it is not surprising that recent publications take it for granted that the alkali metal/NH_3 reductions of enones proceed through 1,4 dianions.[100]

But the possibility has remained that instead of *proton transfer, hydrogen bonding* by the protic solvent might facilitate electron transfer to the 1,4 radical anion leading to the emergence of the *O*-protonated 1,4 dianion in one step. A somewhat analogous mechanism has been preferred for the alkali metal/EtOH reductions in this report. (See Fig. 3 in Scheme 9.)

In our opinion this possibility could not be totally discarded without the help of additional data bearing on the subject. Fortunately we had obtained[19] such data in our work on reductive cyclizations of γ ethynyl ketones. Because it has an important bearing on the subject of reductions of unsaturated as well as saturated ketones by alkali metals/NH_3, the work is described below in some detail.

Reductive cyclization of **31** using $Li/NH_3/t$-BuOH gave[101] a mixture of **32** and **33**. The over-reduction of **32** to **33** was analogous to the reduction of linalool to 3,7-dimethyl-octa-2,7-diene observed by Birch.[17] To prevent formation of **33** it appeared necessary to ensure that the intermediate anion **34** does not protonate to **32** before the destruction of the excess alkali metal.

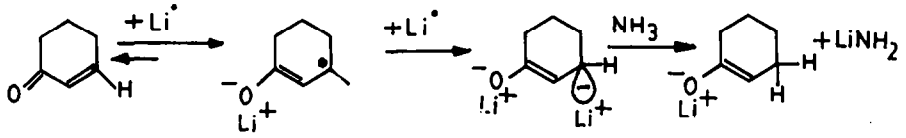


31 **32** **33** **34**

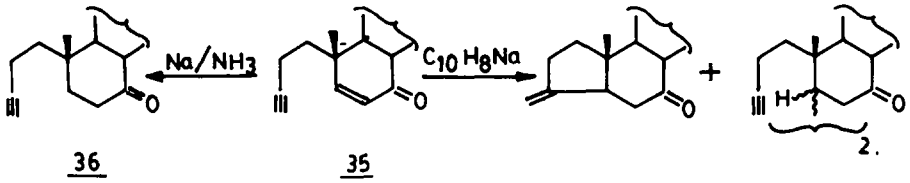
This was first achieved using aprotic conditions. Use of naphthalene sodium gave **32** accompanied by starting material.[102] No trace of **33** was seen. We concluded that the reductive cyclization with both reagents was giving the anion **34** which was being protonated *in situ* in $Na/NH_3/t$-BuOH but not by $C_{10}H_8Na$/THF. We realized that here was an opportunity to find out experimentally whether NH_3 itself could *either* proton transfer to *or* hydrogen bond the oxyanion **34** and thereby facilitate acceptance of an electron/Na leading via **32** or directly to over-reduction product **33**.

Leaving out *t*-BuOH did diminish the amount of **33** but did not eliminate it. This was actually due to extreme sensitivity of the compound to traces of moisture. When additional precautions were taken, such as adding the alkali metal without opening the reaction vessel and destroying the excess by sodium benzoate, formation of **33** could be prevented. Not only had we succeeded in developing a diagnostic system for testing whether ammonia was free of moisture and related proton donors but in addition we had shown that *neither* proton transfer *nor* hydrogen bonding aided reduction takes place in NH_3 as solvent although the alkoxide **34** is a stronger base than either the 1,4 radical anion or the *ketyl* radical anion. This clear-cut result allows us to rule out not only "e^-, H^+ (proton transfer), e^-" but also "e^-, H^+ (hydrogen bonding), e^-" mechanism for alkali metal/NH_3 reductions of α,β-unsaturated as well as saturated ketones wherein extraneous proton donors have been rigorously excluded.

The mechanism has to be "e^-, e^-, H^+, H^+" with either or both e^- being replaced by alkali metal atom. Thus one may represent cyclohexenone reduction as follows:



Some indirect evidence is available as to how fast these reactions are in that Na/NH_3 (anhydrous) converts the cholestane derivative **35** to **36** in 96% yield in less than five minutes.[19] Reaction of the same substrate **35** with $C_{10}H_8Na$/THF is also over in less than five minutes. The latter reagent does not give any **36** but only the products shown below.



36 **35**

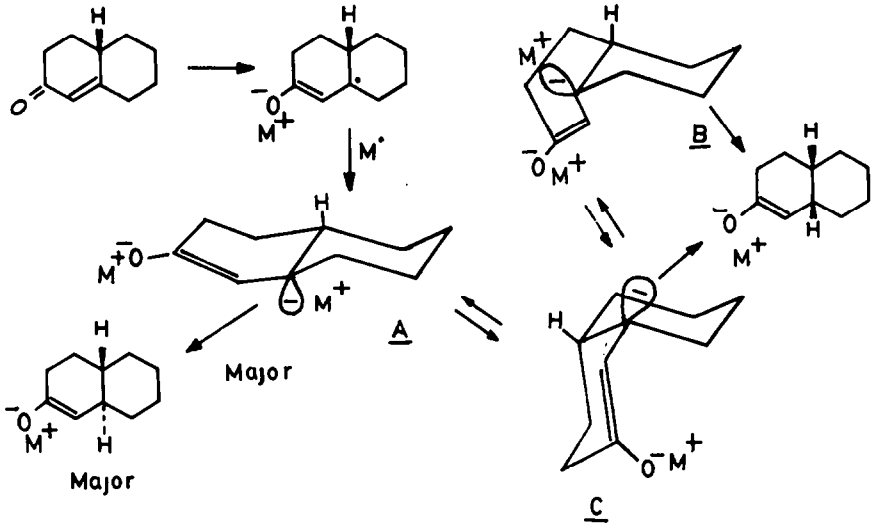
These results are best understood by taking into account the fact that $C_{10}H_8Na$ is a weaker reducing agent[102] in terms of Na atom transfer than Na/NH_3. Thus the failure of the former reagent to convert **35** to **36** can be ascribed to its inability to convert a counterion associated 1,4 radical anion to counterion associated 1,4 dianion.

The failure to obtain any dihydro dimers in Na/NH_3 reduction is in conformity with the expectation that the conversion to the counterion associated 1,4 dianion by addition of Na to the 1,4 radical anion must be quite fast with this reagent. Fast protonation of the carbanion by NH_3 at the β position can be expected in view of the strongly basic character of the 1,4 dianion.

Stereochemistry of protonation at the β position becomes an important issue when the parent cyclo-alkenone moiety has an alkyl substituent at the β position. Included are the cases wherein the α,β double bond is exocyclic to another ring as in some bicycloalkenones.

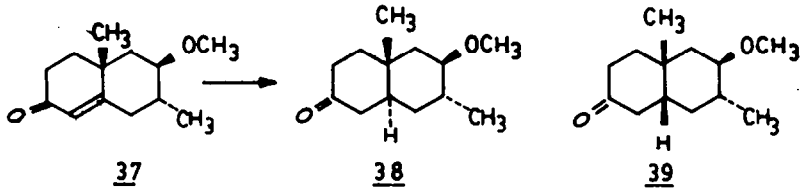
Barton[6] had proposed that the 1,4 dianion produced would rapidly equilibrate between two possible "configurations" of the carbanions and presumed that each would protonate with retention of configuration to give the corresponding stereoisomer. The major conformer[103] would hence give the major product. Assuming protonation with retention of "configuration" leads to the conclusion that the thermodynamically more stable product should be obtained. The early study[6] was mainly on natural products where the choice was between getting a *cis* 2-decalone and a *trans* 2-decalone derivative. Invariably the more stable *trans* compound was obtained.

An updated version of the Barton proposal is presented in Scheme 13 with respect to the parent 1(9)-octalin-2-ones.[104] Here the stereochemistry of the product is dependent upon three factors: (1) The carbanion at the β position in the 1,4 dianion is sp^3 hybridized. (2) Of the three possible carbanion conformations the one in which it is axial to both rings, namely A, is more stable than the other two. (3) Protonation with retention of configuration must take place at approximately the same rates so that the *trans*:*cis* ratio should be close to A:B+C.

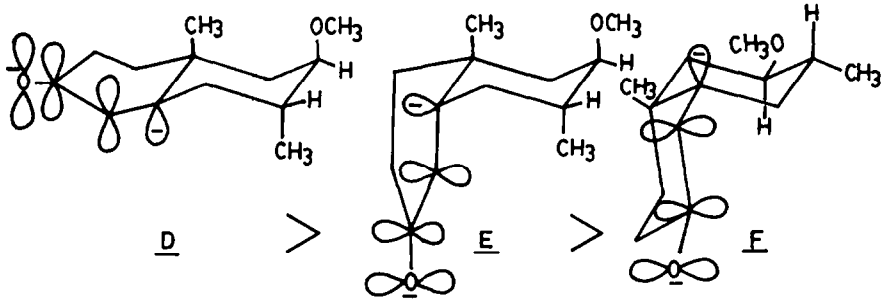


Scheme 13.

Starting from an observation by Stork,[5] several examples have come to light[1] where the thermodynamically more stable product is not the major one. Thus the above mechanism needed replacement. In place of it Stork introduced[5] "the axial protonation rule" according to which there is a preference for protonation *axially* (at the β position) to the 6-membered ring containing the enone system. Thus in the Li/NH_3 reduction of 1(9)-octalin-2-one (Scheme 13), the estimated[105] amount, using non-bonded interactions, of conformation A at equilibrium is 80%. This should have given a *trans*:*cis* ratio of 80:20. That actually found is 99:1. The result is definitely inconsistent with thermodynamic criteria wherein relative stabilities of different conformations of the 1,4 dianions are estimated using non-bonded interactions alone. A rather convincing example of this is the conversion of **37** to **38** by Li/NH_3. The dianion precursor of **38** has been estimated,[5] using non-bonded interactions, as being less stable than the dianion precursor of **39**. Yet no **39** is produced.



The results are consistent with the "axial protonation rule". In explaining the basic concept Stork[5] states "the energies of the stereoelectronically allowed transition states rather than those of the reduction products determine the stereochemistry of the latter." The stereoelectronically allowed transition states are the ones in which the C—H bond being formed at the β position is parallel to the p orbitals of the adjacent C—C double bond thereby permitting overlap. Whether the species being protonated is the 1,4 radical anion or the 1,4 dianion is a question that could not be answered at that time. But as explained above, we need no longer consider the 1,4 radical anion. Proton transfer from NH_3 to the strongly basic 1,4 dianion is expected to be very fast[94] and highly exothermic and hence a transition state resembling reactants can be safely assumed.[106] Thus in the transition state the carbon at the β position must still retain considerable carbanion character with only nominal C—H bond formation. Further, unless some strong steric interactions intervene, the energy differences between the transition states for protonation must be almost the same as the energy differences in the ground states of the corresponding 1,4 dianion precursors. The stereoelectronic factors that were assumed to play a part in determining relative transition state energies must now be considered as playing a role in determining the relative ground state energies of the corresponding 1,4 dianions. Thus the original explanation for the formation of **38** from **37** in spite of the greater stability of **39** over **38**, has to be restated in terms of the relative stabilities of the 1,4 dianion precursors **D**, **E** and **F**. As shown in Scheme 14 the precursor of **39**, **F**, is considered as the least stable of the three because the lone pair of electrons on the carbon at the ring junction is incapable of overlap with the enolate ion. Such an overlap is permitted in both **D** and **E**. Between the two, **D** is preferred on grounds of lesser non-bonded interactions. An alternative conformation in which the ring not containing the enolate system takes up the boat form[107] can also be expected to have stereoelectronic stabilization and could also have been a precursor of the *trans* compound **38**.



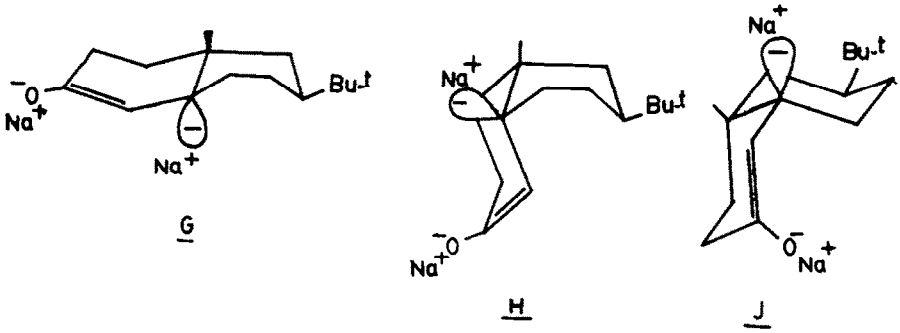
Scheme 14.

From the above discussion it should be clear that the "axial protonation rule" represents "thermodynamic" rather than "kinetic" control but with one difference. Normally thermodynamic control refers to products. In the present case we refer to the 1,4 dianions i.e. the order of stability of the 1,4 dianions will be reflected in the ratio of products. This will happen because (1) the dianions are presumed to be in equilibrium and (2) almost equal rates of protonation can be expected for reasons already given.

The above concepts and hence the "axial protonation rule" itself runs into a number of difficulties. A major one is the question of carbanion stabilization by overlap with the enolate ion in the 1,4 dianion. We can do no better than quote a comment made by Zimmerman[108] in this connection: "intuitively one would guess that there would be only weak interaction of the β carbon electron pair and accompanying negative charge with the already electron rich enolate system."

Another problem with the "axial protonation rule" is best appreciated in connection with 1(9)-octalin-2-one having a bulky 6β substituent in addition to a 10β methyl. In these cases the major product of Li/NH_3 reduction is the *cis* decalone. Thus 6β-*t*-butyl, 10β-methyl-1(9)-octalin-2-one is reduced by $Na/NH_3/CH_3OH$ to the saturated *cis* decalone derivative in 99% yield. Caine[96b] has discussed the reduction in terms of three possible conformations **G**, **H** and **J** (Scheme 15).

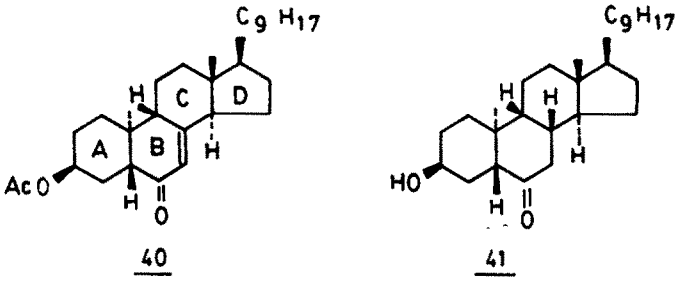
Protonation of the 1,4 dianion axially to the ring containing the enolate moiety, in conformation **H** can account for the *cis* product which predominates. Caine has, however, pointed out that **H** is not the only conformation to be stereoelectronically "stabilized".[96b] According to him if one rejects



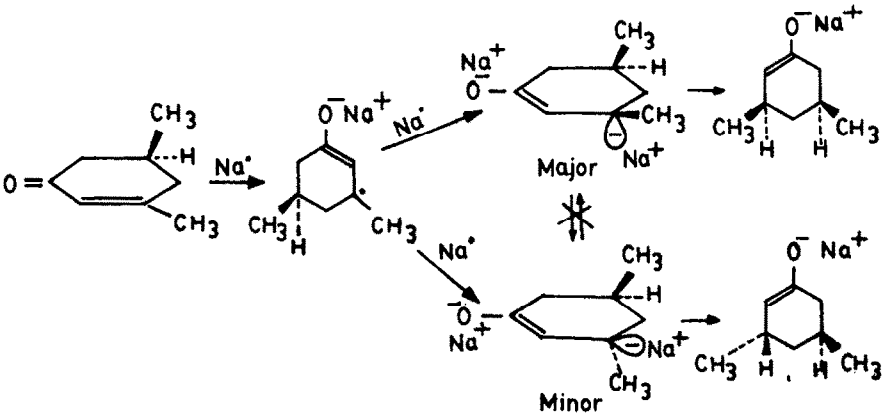
Scheme 15.

conformation **J** on stereoelectronic consideration, the major product should have been *trans*, derived from **G**, which in addition to having stereoelectronic "stabilization" appears to be favoured over **H** on steric grounds as well. Looking back one can see that Caine[96b] showed rare insight in indicating a clear preference for **J** as the precursor of the major product formed by protonation with retention of configuration. In **J** (Scheme 15) the carbanion is seen to be equatorial to the ring containing the enolate. At the same time it is seen to be *axial* to the "other ring" i.e. to the ring to which the α,β double bond of the original enone is *exo*.

It is of considerable interest that one of the exceptions cited by Barton[23] to the "axial protonation rule" viz. the reduction of **40** to **41** is readily explained in terms of protonation *axial* to *ring C* i.e. to the "other ring". Relative stabilities of 1,4 dianions, including stereoelectronic stabilization, has not proved to be a reliable guide to the stereochemistry of the reduction. Experts in the field seem to have concluded as much. Thus Caine states[96c] "it seems more likely that there is a *kinetic preference* for the formation of dianion from the radical anion intermediate, and that this species undergoes protonation more rapidly than equilibration". Almost the same words have been used by Deslongchamps.[100]



The kinetic preference for the formation of *cis* 3,5-dimethylcyclohexanone in 75% yield[109] in reduction of 3,5-dimethylcyclohex-2-en-1-one with $Li/NH_3/THF$ has then to be represented as shown in Scheme 16.

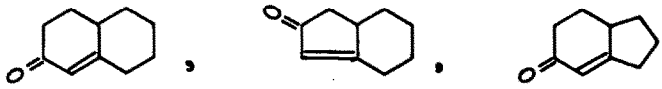


Scheme 16.

The scheme is reminiscent of Path A of Scheme 1 Section 1. Thus the onus for determining the stereochemistry of the reduction product shifts to the step involving alkali metal addition to the 1,4 radical anion.

One way of explaining the preferential formation of the 1,4 dianion precursor of the *cis* compound of Scheme 16 is to use a modified version of the "axial protonation rule" of Stork. Consider the addition of alkali metal to the 1,4 radical anion. The energies of the transition states leading to the two different 1,4 dianions could be different. If it is postulated that the transition state for axial approach of the alkali metal is of lower energy because of greater overlap with the enolate system then it is possible to explain those cases which were adequately accounted for by using the original "axial protonation rule". It is not clear whether such a postulate is valid for an electron transfer to an sp^2 carbon just because it is accompanied by M^+. It is doubtful whether this pathway can account fully for the observed stereochemistry except where strong steric factors are operative. In other cases some contribution cannot be ruled out.

Against this background, it was worth considering whether the concepts used for explaining the stereochemistry of reduction of saturated ketones with alkali metal/EtOH were also applicable for enone reductions. We have found this approach attractive as well as versatile in that it can explain many observations related to stereochemistry of alkali metal/NH_3 reductions of compounds having the following moieties:

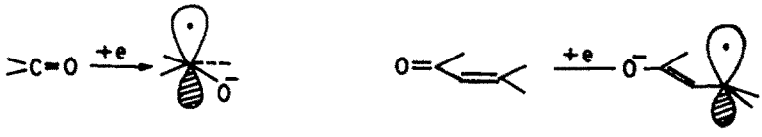


The rest of this section is devoted to expounding this concept. We are confident that the ideas will encourage appropriate experimentation as well as calculations which will result in further progress in explaining a relatively large amount of data.

The starting point of our concept is the structure of the 1,4 radical anion derived by adding an electron or alkali metal to an α,β-unsaturated ketone. The electron is added to the π^* orbital which then becomes the SOMO of the 1,4 radical anion. Theoretical calculations[110] as well as ESR evidence[111] indicates that the *coefficient* of the SOMO at the β position is larger than at the α position of the α,β-unsaturated ketone system. It is also larger than at the carbon to which the oxygen is attached. Hence for Frontier Molecular Orbital (FMO) controlled reactions the maximum reactivity is expected at the carbon at the ring junction in the enones specified above.[56] This makes it easier to accept that the transition state for 1,4 dianion formation involves addition of an electron or an alkali metal at this position. In the 1,4 radical anion this "β" carbon is normally pictured as being sp^2 hybridized with the "**p**" orbital at this position effectively overlapping with the enolate system. One can safely assume that the effectiveness of such overlap will hardly diminish if the β carbon becomes slightly pyramidalized.

We need to assume such pyramidalization leading to one of the two lobes of the **p** orbital becoming larger than the other or being *extended* using the term introduced by Fukui.[39]

Given below is a comparison between the effect of electron addition to a saturated ketone and an enone together with the effect of slight pyramidalization in both cases.

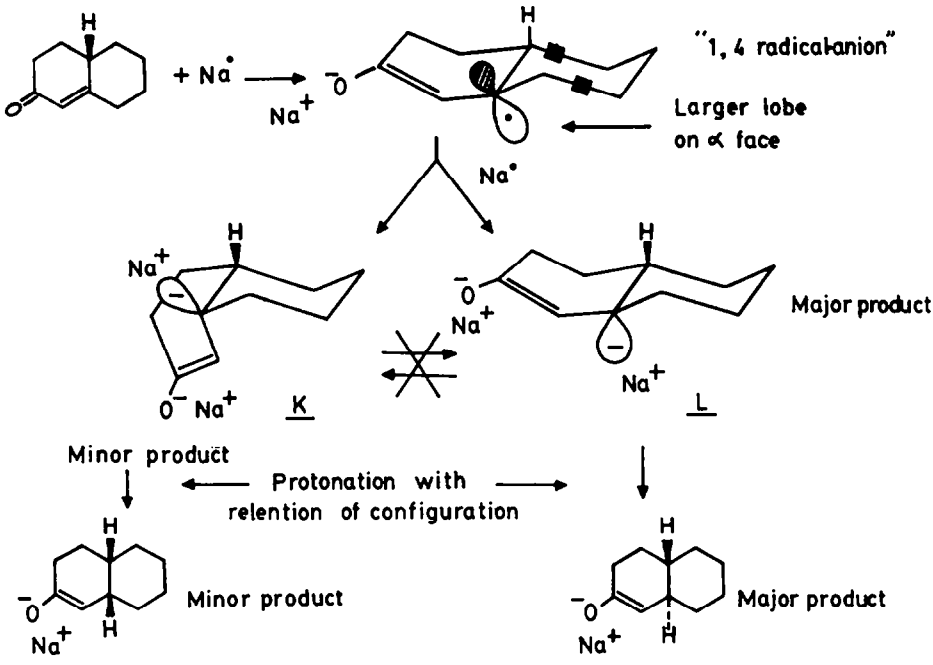


Whereas non-planarity in ketyl radical anions was initially unacceptable it was later accepted on account of theoretical calculations and re-interpretation of ESR evidence (see Section 1). It is not beyond the realm of possibility that the same thing will happen and evidence forthcoming[112] of slight pyramidalization at the β position of the 1,4 radical anion derived by addition of an electron/alkali metal to an α,β-unsaturated ketone system.

It is a basic tenet of our proposal that such partial pyramidalization exists and that the *direction* of pyramidalization is governed by the perturbation due to the σ framework.

The remaining postulates are the same as those discussed in detail in Section 1.

Given in Scheme 17 is the new interpretation of the reduction of "1(9)-octalin-2-one" incorporating all our previous postulates.



Scheme 17.

A few comments on Scheme 17 will clarify the concept further. The 1,4 radical anion produced by Na$^{\bullet}$ addition to the enone is slightly pyramidalized at the β position with orbital extension in the quasiaxial direction relative to both rings. Na$^{\bullet}$ addition occurs to a much greater extent from the α face to the **p** orbital at the β carbon mainly because the size of the lobe is larger on this face than on the β face. The assumption is that the rates of formation of the two carbanions is approximately proportional to the coefficient of the lobes on the two sides of the nodal plane of the "**p**" orbital on the β carbon. Thus there is a *kinetic factor* favouring the formation of **L** over **K** (Scheme 17). These two are not in equilibrium. The carbanions at the β position in **L** and **K** are probably fully pyramidalized. Protonation with retention of configuration completes the picture. Rates of protonation are anticipated to be nearly equal but this is immaterial if **L** and **K** are not in equilibrium. The major product has to be the enolate of the *trans* decalone.

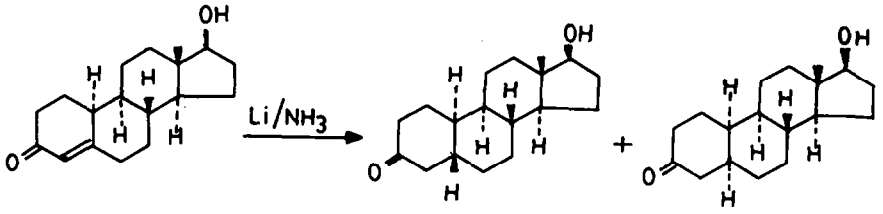
Thus the stereochemistry of the reaction becomes directly linked to the direction of orbital extension or in other words the direction of pyramidalization at the β position. This can be correctly anticipated if the perturbation at the β carbon by the whole σ framework can be estimated. In a limited number of cases the qualitative approach, used in Section 1, may suffice.

Thus in Scheme 17 the orbital extension in the 1,4 radical anion is seen to be the result of perturbation by the two C—C σ orbitals of the six-membered ring not containing the enolate system. This interaction leads to orbital extension in the axial direction relative to the ring referred to earlier as the "other ring." The influence of the ring is equivalent to that of the cyclohexane ring in the orbital extension of a cyclohexyl radical towards the axial direction discussed earlier. The six-membered ring should preferably be in the chair conformation as happens to be the case in the example in Scheme 17.

Whenever the ring to which the enone is *exo* has a preferred chair conformation, interpretation is very much simplified. But this does not mean that no interpretation is possible in other cases. One has to judge which C—C σ orbitals on the carbon adjacent to the β carbon is likely to make the dominant contribution to the Fukui effect by virtue of having a HOMO nearer in energy to the SOMO and being nearly perpendicular to the nodal plane of the **p** orbital at the β carbon. Where the direction of pyramidalization cannot be easily estimated it is hoped that ESR data may provide the answer.

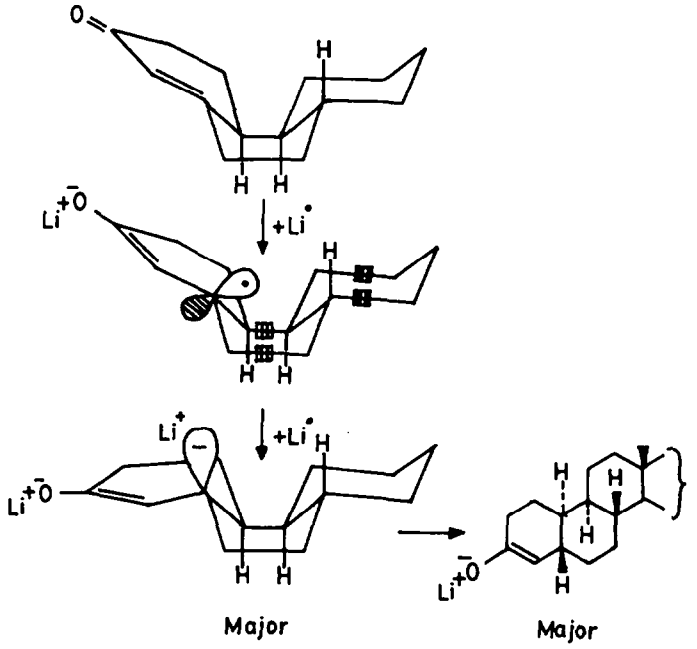
One of the test cases for the applicability of our concept was the stereochemistry of the following reaction.[113]

The major product has an A/B *trans* ring junction. This is a case where the product with A/B



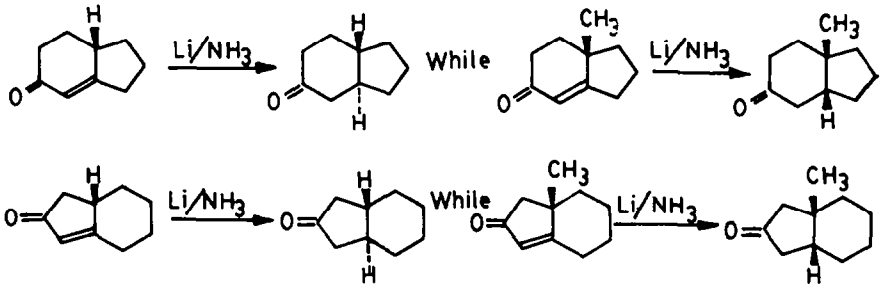
cis ring junction is more stable. This represents one of the cases where the enone reduction with Li/NH_3 gives the thermodynamically less stable product in respect of the stereochemistry at the β position.

In Scheme 18 is given a reasonable conformation for rings A, B and C of **42**. In the corresponding radical anion the **p** orbital is shown to be extended in the β direction as a result of contributions by the σ orbitals indicated.



Scheme 18.

In the case of hydrindenones having a double bond exocyclic to one of the rings we are able to offer a tentative explanation for the following interesting phenomenon.[114]



We simply proceed with the assumption that irrespective of whether the double bond is exocyclic to the six-membered ring or the five-membered ring the overall effect of the σ framework excluding the angular substituent is to cause orbital extension towards the "α" direction. The effect is expected to be weak because the C—C bonds concerned are nearer the nodal plane of the "**p**" orbital at the ring junction. The angular substituent, on the other hand, is much better situated for interaction as

it is almost parallel to the concerned orbital. When this substituent is hydrogen the corresponding C—H bond is unable to influence the orbital extension because of the large SOMO–HOMO energy difference. With an alkyl group at the angular position the situation changes. The C—C σ orbital dominates so that the orbital extension is now in the β direction resulting in the production of the *cis* hydrindanone.

5. MECHANISM AND STEREOCHEMISTRY OF REDUCTION OF SATURATED CYCLIC KETONES BY ALKALI METAL/NH_3

5.1. *The absence of added proton donors*

Only recently has it been realized, though not widely known, that a number of reactions claimed to have been done using alkali metal/NH_3 in the absence of added proton donors, have actually been carried out in their presence, albeit in small quantities. As pointed out earlier, quenching with ethanol may, at times, be equivalent to adding it as a proton donor.

The question of proton availability is the central issue with respect to both mechanism and stereochemistry of reduction of saturated cyclic enolizable as well as non-enolizable ketones. In this respect their behaviour contrasts with that of α,β-unsaturated ketones. The latter are much easier to work with since stereochemistry of reduction at the β position is not subject to wide variations dependent on presence or absence of EtOH or *t*-BuOH.

Variations in stereochemistry of reduction of (+)-camphor[115] in presence or absence of ammonium chloride are given in Table 3. The results provide justification for putting reactions of saturated ketones with alkali metal/NH_3 with and without added proton donors in different categories.

Table 3. Ratio of borneol : isoborneol formed in reductions of (+)-camphor with various alkali metals in NH_3 in absence or presence of proton donor[115]

Metal	Li		Na		K	
	A	B	A	B	A	B
Borneol : Isoborneol	80 : 20	94 : 6	60 : 40	90 : 10	42 : 58	90 : 10

A = absence of proton donor : B = presence of ammonium chloride.

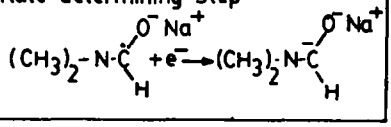
Those who are aware of these limitations supply as many details as possible about the experimental conditions actually used.[116] Observations are recorded as to whether the blue colour developed and whether it persisted till the time of quenching. Thus if the blue colour never developed the reaction may have taken place on the metal surface. If it has persisted till the time of quenching it is possible that some enolate anion is still present. Addition of a proton donor could result in regeneration of the ketone which gets further reduced *in its presence* before the colour disappears.

How does one then decide as to which experiments described in the literature can be considered as belonging to the category specified by the heading of this section?

For enolizable cyclohexanones the most reliable experiments are those where *either* the total consumption of the alkali metal in the reduction has been determined and found to be *1 gm. atom* per *1 gm. mol.* of ketone *or* where ratio of reduction product to recovered starting ketone is close to unity. Such observations have been made in the case of acetone[117] and cyclopropyl methyl ketone[118] but for cyclohexanones none had been made prior to our work.[19,10]

Hence it was of considerable interest to find the same 1 : 1 relationship in terms of the consumption of alkali metal, as well as ratio of product to starting material, in the Na/NH_3 reduction of dimethyl formamide (DMF). The kinetics of the reaction, studied by Dewald,[119] assume considerable significance in the absence of comparable studies with aldehydes and ketones. Dewald found that the reaction obeyed a fourth order rate law which is given below. Also quoted is the third and rate determining step. In the first step an ammoniated electron is regarded as adding reversibly to DMF to give the radical anion. In the next step the radical anion presumably reacts reversibly with Na^+ to give the counterion associated radical anion required for the rate-determining step. The dianion produced in this step is presumed to react with DMF in a fast post rate-determining step.

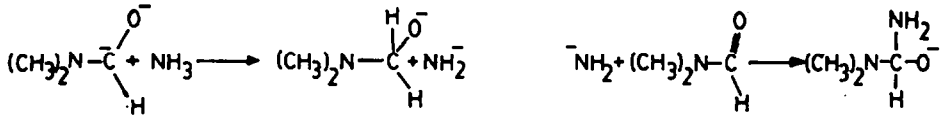
Kinetics of reaction of DMF with Na/NH_3

Rate law	Interpretation
$-\frac{d[e^-]}{dt} = k[Na][e^-]^2[DMF]$	Rate determining step 

The important features of Dewald's findings are:

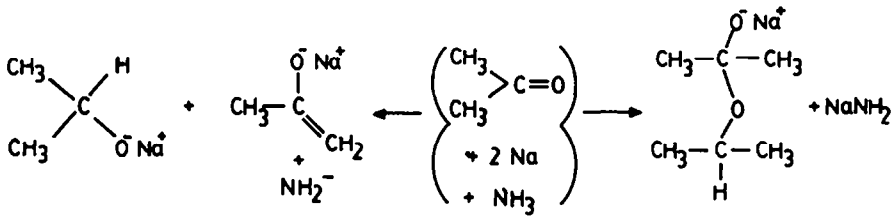
(1) A vicinal *dianion* associated with one counterion is being produced.
(2) Unreacted DMF is available for reaction in a post rate-determining step.
(3) Half the DMF taken gives a product or products which are resistant to further reduction but which give back starting material on work up.

Since DMF is non-enolizable its recovery may be due to the following fast reaction.[120]



The dianion mechanism has been assumed as being applicable to ketones by Dewald.[119] The possibility cannot be denied. An important feature that needs to be emphasized is the proposed formation of monocation associated dianion from DMF. If such a dianion can be produced by Na/NH_3 then the same reducing system should be capable of producing a dianion, associated with one or two counterions, from cyclic ketones. Literature references about production of dianions from ketones are not restricted to the work of Barton[6] and Rassat.[32] Bellamy[118] and Bunnett[121] have found no difficulty in accepting them. Hence it is beyond comprehension as to why a recent reviewer[2] chooses to regard the Barton mechanism as being of historical importance and beyond "resurrection." The only reason given to back the statement is that "House has refuted the mechanism on reasonable mechanistic grounds." House actually rejected the dianion mechanism for α,β-unsaturated ketones on the grounds that the reduction potential available with Na/NH_3 is insufficient to reduce 1,4 radical anions to the 1,4 dianion. If this contention is valid as far as production of 1,4 dianion is concerned then vicinal dianion formation from a saturated ketone can be ruled out. But, as pointed out in the previous section, House himself detected the fallacy in his arguments and postulated alkali metal transfer to explain the reduction of acetylenes.[98] Formation of 1,4 dianion associated with counterion/s by alkali metal transfer is, as discussed earlier, a step in the *only* acceptable mechanism for reduction of enolizable as well as non-enolizable α,β-unsaturated ketones. Thus the Barton mechanism proposing vicinal dianion formation from saturated ketones no longer stands automatically rejected.

Before discussing the relative merits of different mechanisms it is desirable that we examine the implication of another observation of Dewald. The stoichiometry determined for the reduction of acetone[117] suggests the formation of enolate anions and/or hemiketal anions as illustrated below.



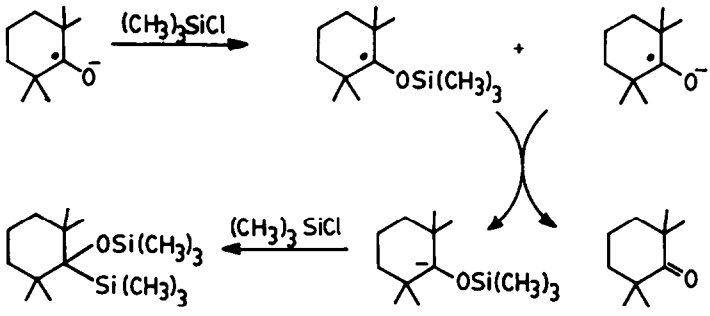
This explains why 50% of the starting ketone is recovered on work up. There is, however, a possibility that slow regeneration of the ketone from the enolate or hemiketal anion occurs in the reaction mixture itself and hence a 1 : 1 mixture of Reduction : Recovery is not necessarily found in spite of having taken adequate precautions to exclude proton donors. Our observation is that lithium

enolates of cyclohexanones survive and regenerate the ketone to the extent of 50% on work up provided the quenching of the blue solution is done with sodium benzoate after a short period.[10] Stability is less for potassium enolate of cyclohexanone and much less for all enolates of cyclopentanone.[95] Hence other criteria have to be used for determining whether the technique being followed serves to exclude moisture as well as other proton donors. Use of redistilled NH_3 **is a must** preferably over alkali metal or a derivative thereof. The need for use of a proper quenching agent has already been stressed. If in the reduction of a specific substrate *different* yet reproducible mixtures are obtained using Li/NH_3 and K/NH_3 the likelihood is that the precautions taken were adequate. In our laboratory we do a periodic check by subjecting the steroidal acetylenic ketone **31** to reductive cyclization using Na/NH_3. Formation of detectable amounts of 3-methyl-A-norcholest-3(5)-ene, **33**, indicates that adequate precautions are not being taken.

It has already been pointed out that the observation that allyloxy anion **34** does not abstract proton from NH_3 eliminates the possibility of proton abstraction by any alkoxide of comparable basicity from NH_3. Since the ketyl radical anion is less basic[84] than a secondary alkoxide the possibility of proton abstraction from NH_3 by the former can also be ruled out.

If a proton cannot be added, reduction of non-enolizable ketones has to proceed by electron or alkali metal addition to give a dianion associated with counterion/s. Reduction of fenchone, a non-enolizable ketone, must proceed by this mechanism. Coulombeau and Rassat[32] have found that fenchone gives mainly the *endo* alcohol and have proposed a dianion mechanism. It is of interest that Huffman[12] has shown that fenchone reduces 1.58 times faster than 4-methyl cyclohexanone.

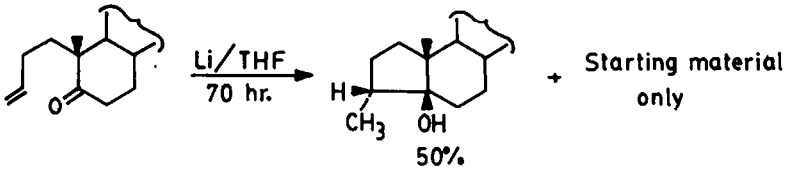
Radical anions have been generated in THF[122] from non-enolizable ketones. Addition of another electron or alkali metal to these may not be possible in THF in absence of NH_3. Even in the latter it could be a slow process but only marginally so otherwise no reduction would have taken place. Rautenstrauch[122] found 2,2,6,6-tetramethylcyclohexanone reacts with Li in THF at $-75°$ to give a paramagnetic species. This was assigned an ion quadruplet structure in view of such a structure being assigned by Hirota[123] to the paramagnetic species produced from hexamethyl acetone by reduction. On treatment with D_2O in excess the radical anion obtained from the non-enolizable cyclohexanone gave equal amounts of the 1-deuterio-2,2,6,6-tetramethylcyclohexanol and starting ketone. This could be due to O-deuteration of the radical anion followed by disproportionation but it need not. As proposed by Rautenstrauch an electron transfer to the O-deuterated radical anion or ketyl from another molecule of radical anion itself could account for the result. The deuteroxy carbanion produced in 50% yield can be expected to take up deuterium at carbon. In our opinion the course of reaction followed in the presence of trimethyl silyl chloride is correctly interpreted[122] as shown in Scheme 19, but the possibility that some of the disilyl compound is produced from a dianion cannot be excluded.



Scheme 19.

Rautenstrauch then went on to study[124] the reaction of various alkali metal combinations including Li/THF with the enolizable ketone 2,2-dimethylcyclohexanone-6-d_2. No ESR was observed but a slow reaction led to an equimolecular mixture of the trideuterated alcohol, 2,2-dimethylcyclohexanol-1-d-6-d_2, and the monodeuterated ketone 2,2-dimethylcyclohexanone-6-d. The reaction took about 6 h and was accompanied by pinacol formation. Of relevance to this example is our finding that cyclization of the steroids **43** to **44** using Li/THF for 70 h gave *neither* reduction to secondary alcohol *nor* pinacolization.

Reaction of **43** with $C_{10}H_8Na$/THF led to 95% recovery. An unidentified product in about 3% yield may be **44**.

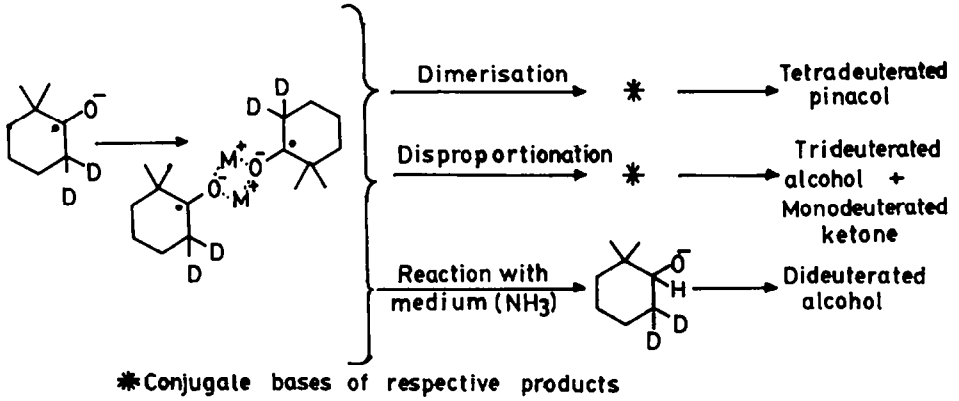


43 44

Attention has been drawn to the experiments in THF because of the assumption by both Rautenstrauch and Huffman that not only does the same mechanism apply for the reaction in Li/NH_3/THF but in addition and in spite of absence of any ESR evidence, the same ion quadruplet is the key obligatory intermediate in the reductions. Huffman[2] goes so far as to state that "the stereochemistry of the reduction product is governed by the detailed geometry of the ketyl dimer." The interesting point is that even for the persistent ketyl radical anion from hexamethylacetone *Hirota has abandoned the ketyl dimer or ion quadruplet concept*[125] in favour of several species in equilibrium—the prominent being association of a paramagnetic species with either one or two diamagnetic pairs.

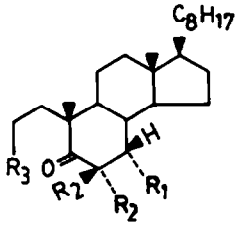
Hence it is desirable that for reactions in NH_3 one proceeds without any preconceived notions about the nature and properties of the species with which the initially produced radical anion may be in equilibrium. Nor are we concerned here with the correctness or otherwise of the mechanism proposed by Rautenstrauch[124] for the *slow* reaction that takes place in Li/THF. We have demonstrated that solutions of alkali metals in NH_3 reduce stereoidal 6-membered ketones to the extent of 50% in less than four minutes at $-33°C$ and that no further reduction is noted over the next ten minutes.[10] This is readily understood if an equimolecular mixture of the alcoholate and the enolate is produced within four minutes. The 1 : 1 relationship found in very careful work has already been commented on. The implication is that a bimolecular step is involved wherein the hydrogen α to an enolizable ketone ends up at the carbinol carbon of the secondary alcohol. To Rautenstrauch must go the credit for demonstrating this conclusively[124] by extending the studies on 2,2-dimethylcyclohexanone-6-d_2 in alkali metal/THF to "dissolving alkali metal" in NH_3 and to "solution of alkali metal" in NH_3. The former method called the "normal mode" refers to reactions taking place either on the metal surface or very near it. This is because the alkali metal is added last and does not dissolve in the bulk of NH_3. It reacts when it has just started dissolving as is seen by the blue tinge that the metal develops. The "inverse mode" uses a preformed blue solution of the alkali metal in NH_3. All the experiments of our group have been performed using a preformed solution at $-33°$. The only difference from Rautenstrauch's inverse mode is that his experiments were carried out at $-75°$. He obtained equal amounts of trideuterated alcohol and monodeuterated ketone. Significant amounts of 2,2-dimethylcyclohexanol-6-d_2 were produced particularly in the reaction using lithium.

According to Rautenstrauch[124] these reactions can be explained assuming "extremely rapid and efficient association, of ketyl radical anions, to give ion quadruplets and these then immediately decay." The "decay" modes are given in Scheme 20 which represents the original proposal.[124]



Scheme 20.

It is not clarified whether reaction with NH_3 consists of proton abstraction or of hydrogen atom abstraction from NH_3. This aspect cannot be overlooked. Proton abstraction is consistent with the findings[124] that reaction with medium takes place to a much greater extent with Li (50%) than with Na or K (10 to 20%). Greater co-ordination of Li^+ with NH_3 could account for the result. Though equal amounts of the trideuterated alcohol and monodeuterated ketone were obtained an examination of the data reveals that the ratio of total alcohol : total ketone was not 1 : 1. This would be inconsistent with proton abstraction from NH_3. The NH_2^- produced in this manner could be expected to abstract a proton from α to the ketone to give an enolate ion. The enolate of dimethylcyclohexanone can be expected to survive till work up. Thus total alcohol : total recovered ketone should be 1 : 1. We observed[126] this ratio in the reaction of 4,5-secocholestan-5-one-6-d_2, **45** (see Chart 5) in both Na/NH_3 and Li/NH_3 reductions, though the amount of 4,5-secocholestan-5β-ol-5α,6β,6α-d_3 relative to 4,5-secocholestan-5β-ol-6-d_2 decreased from 85 : 15 to 65 : 35.



31	$R_1 = R_2 = H$;	$R_3 = -C \equiv CH$
43	$R_1 = R_2 = H$;	$R_3 = -CH = CH_2$
45	$R_1 = H$;	$R_2 = D$;	$R_3 = -CH_2-CH_3$
46	$R_1 = CH_3$;	$R_2 = H$;	$R_3 = -C \equiv CH$
47	$R_1 = R_2 = H$;	$R_3 = -CH_2-C \equiv CH$
48	$R_1 = R_2 = H$;	$R_3 = -C \equiv C-CH_3$

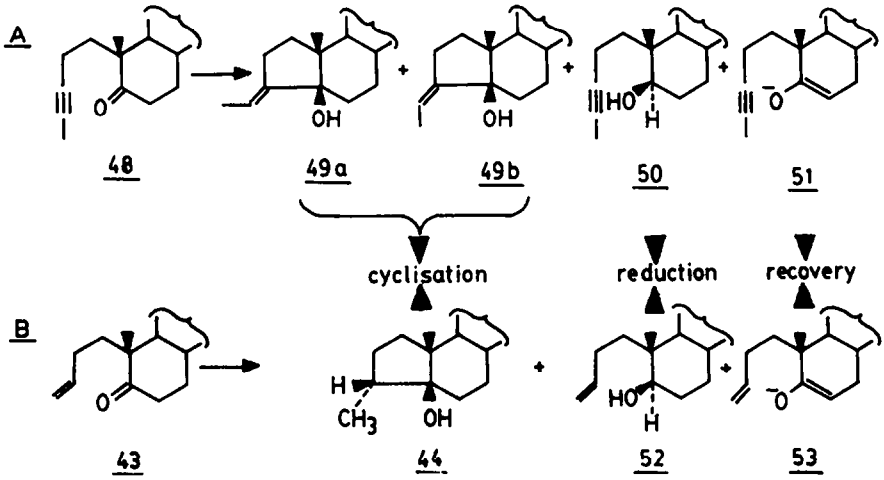
Chart 5.

Reference has been made[2] to our "revival" of the Barton mechanism. This was an off-shoot of our studies on the scope and mechanism of the Stork Reductive Cyclization.[127]

A brief account of the result is essential for understanding how this enabled us to eliminate *all* except the dianion mechanism for the reduction of cyclic ketones by alkali metal/NH_3.

Ring A secocholestanes given in Chart 5 were all subjected to reductive cyclization under aprotic conditions by using $C_{10}H_8Na$ in THF.

An extensive study of stereochemistry and mechanism was undertaken.[103] Stereoselective cyclization to **A/B** *cis* compounds was observed in all cases including **46** and **47**. It was concluded that the reaction was under FMO control. The reaction of **48** with $C_{10}H_8Na$/THF was particularly important. Both **E** and **Z** isomers of the 3-ethylidene-A-norcholestan-5β-ol were obtained. The effect of concentration and temperature on the **E** : **Z** ratio left no doubt that the slow step in cyclization of **48** was radical attack by the ketyl radical anion on the triple bond to give a vinyl radical. The vinyl radicals, unlike vinyl carbanions, are not configurationally stable and hence the mixture of **E**, **Z** isomers **49a** and **49b** (Scheme 21) is produced. No reduction to the secondary alcohol **50** is observed. The enolate **51** is produced because naphthalene sodium is also a strong base. On work up some starting material is hence recovered.

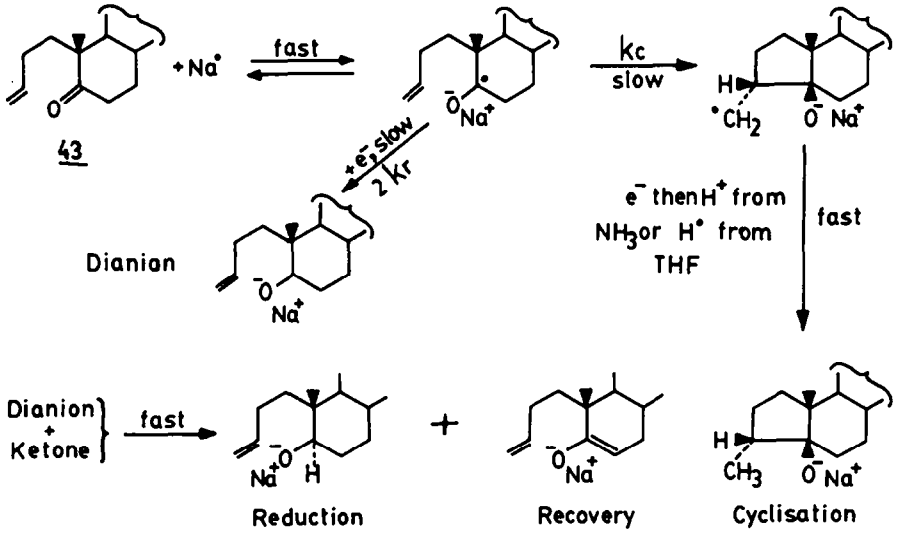


Scheme 21.

The data given in Scheme 21 refer to the result of Na/NH_3/THF reaction. Strict exclusion of proton donor/s was required. As discussed earlier the technique for this was developed in order to prevent overreduction product **33** from being formed in the reductive cyclization of **31** to **32** by Na/NH_3/THF (see Section 4). Another reaction discussed in that chapter which is very much relevant here is the reaction of the acetylenic enone, **35**, which demonstrates that, unlike Na/NH_3, naphthalene sodium is unable to reduce the 1,4 radical anion to 1,4 dianion. Hence it is to be expected that the latter reagent will not add a second electron/atom of alkali metal to the ketyl radical anion derived from a saturated ketone. Hence a reasonable explanation for the formation of secondary alcohols **50** and **52** (Scheme 21) from **48** and **43** respectively in Na/NH_3/THF reduction but not when $C_{10}H_8Na$/THF is used, is that dianion formation is necessary for reduction to the secondary alcohols. The above observations strongly imply that formation of secondary alcohols by disproportionation of ketyl radical anions or other associated species such as ion quadruplets occurs very slowly, *if at all.*

Against this background a systematic study of the alkali metal/NH_3 reaction relevant to the mechanism of reduction of cyclohexanones by the reagent was undertaken.[128]

In a semiquantitative study the amounts of cyclized, reduced and recovered material i.e. **49a**+**49b**, **50** and **48** from **48**; and **44**, **52** and **43** from **43** (Scheme 21) were determined. It was expected that the ratio of reduction : recovery i.e. **50** : **48** and **52** : **43** should be close to 1 : 1. This is seen to be so in the data given in tables in our paper[10] relating to the observations on the acetylenic ketone **48** and the ethylenic ketone **43** respectively. The ratio of reduction : recovery is seen to be very close to one in both cases except when the time given is a fraction of a minute. The ratio of reduction : cyclization *varies with the concentration of the alkali metal but is independent of ketone concentration.* Equating the ratio of amounts to the ratio of rates it follows from the data in the tables[10] that the ratio of rate of reduction to rate of cyclization is *directly proportional* to alkali metal/electron concentration. This is the relationship to be expected on the basis of Scheme 22,[128] where both products are formed from the radical anion. This common intermediate can be expected to be formed fast and reversibly from ketone + alkali metal/electron. The reduction to the dianion and the subsequent fast reaction of the latter with the ketone apparently follows the same pattern as that proposed by Dewald[119] for DMF except that there is uncertainty as to the number of counter-ions involved in the various steps. The simultaneous slow cyclization of the radical anion was the key to unravelling the mystery which has plagued so many for so long. The value of the constant in the last column represents $2k_r \div k_c$. A comparison of the two tables indicates that the rate of cyclization is less for **43** than for **48** if the reasonable assumption is made that k_r is the same for both.



Scheme 22.

The fact that the ratio of reduction to cyclization is independent of ketone concentration is quite clear from the two tables. Yet is has become necessary to lay special emphasis on this observation.

This finding *cannot* be explained by assuming cyclization from a monomeric radical anion and reduction via disproportionation from a dimeric ion quadrupole where the said monomer and dimer are in equilibrium. It is unfortunate that Huffman[2] makes a comment in a review article that our results can be accommodated within the framework of a Scheme which he formulates. How it can be done is left to the reader for the simple reason that it *cannot be done.*

In Chart 6 are given some of the proposed mechanisms for reduction of ketones with $Na/NH_3/THF$ as applied to substrates such as **43** and **48** and hence include a slow cyclization of a radical anion or equivalent. In each case the expected dependency of (rate of reduction)/(rate of cyclization) (which is simply called "ratio" in the chart) on concentration of ketone and/or electron (e^-, but replaceable by Na^*) has been worked out. Details of the post rate-determining steps are not spelt out unless necessary.

Chart 6.

Huffman

$$\text{ketone} + e^- \overset{K_1}{\rightleftharpoons} \text{radical anion} \xrightarrow{k_c} \text{cyclization}$$

$$2 \text{ radical anion} \overset{K_2}{\rightleftharpoons} \text{dimer (or ion quadrupole)}$$

$$\text{dimer} \xrightarrow{2k_r} \text{reduction} + \text{recovery}$$

$$\text{ratio} = \frac{2k_r}{k_c} \times K_1 \times K_2 \times [\text{ketone}] \times [e^-].$$

Rautenstrauch

$$\text{ketone} + e^- \overset{K_1}{\rightleftharpoons} \text{radical anion}$$

$$2 \text{ radical anion} \xrightarrow{\text{fast}} \text{ion quadrupole}$$

$$\text{ion quadrupole} \xrightarrow{2k_c} \text{cyclization} + \text{radical anion}$$

$$\text{ion quadrupole} \xrightarrow{2k_r} \text{reduction} + \text{recovery}$$

$$\text{ratio} = \frac{k_r}{k_c}.$$

Unlike the proposals in Chart 6, the dianion mechanism requires that the ratio equals $2k_r \times [e^-] \div k_c$. It is the only one consistent with the relationship discovered by our group. It can be assumed to apply for all $Na/NH_3/THF$ reactions of cycloalkanones. If Li^* is used in place of Na^* the ratio is still found to be dependent on alkali metal concentration and independent of ketone concentration.[78] The relationship established by our group only specifies that the same species is involved in the rate-determining step for cyclization and together with an electron in the rate determining step for reduction. Further it should have the properties of a radical anion but it does not have to be a monomeric radical anion.

In fact a couple of puzzling observations have made it essential to modify Scheme 22 substantially.

Compound **46** (Chart 5) cyclizes to an **A/B** *cis* compound in 84% yield in spite of having a 7α-methyl substituent. The rest is recovered starting material. Though the reagent is $Na/NH_3/THF$ no reduction product is obtained. The stereochemistry of cyclization was anticipated provided the reaction was under FMO control. Steric hindrance by the 7α-methyl group was not expected to come into play for a transition state resembling starting material. But for the same reason formation of dianion should also be facile and yet no secondary alcohol was produced. Steric hindrance to accepting a proton from a ketone molecule could not be the explanation as in such cases the smaller NH_3 molecule would have to provide a proton as discussed later.

The second puzzling feature was why electron transfer from dianion to ketones does not take place when the two molecules approach each other.

The answer was to forget Dewald kinetics and formulate a new scheme which could serve to remove the above irritants. In allowing for the possibility of electron/alkali metal transfer from dianion to ketone the dianion is no longer restricted to giving rise to reduction products such as

secondary alcohols. Scheme 22 has been modified to Scheme 23 the kinetics of which can be expected to be quite complex.

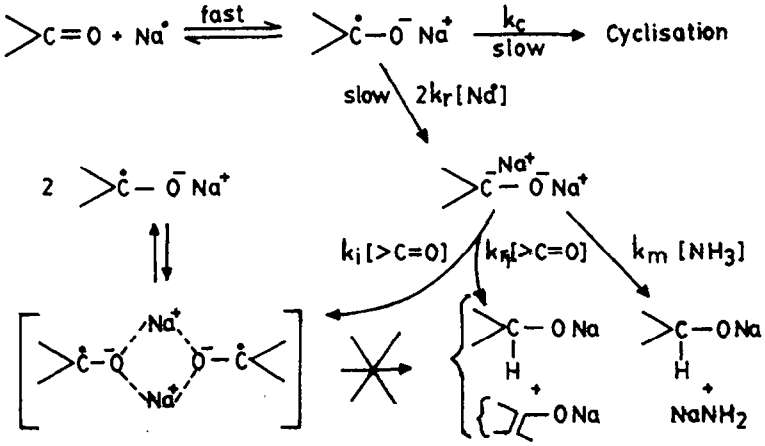
For simplicity it is assumed that only the mono radical anion cyclizes but nothing prevents the association of two or more molecules where the associated species are in rapid equilibrium with the monomer.

The dissociation of the ion quadrupole or "dimer" shown in Scheme 23 makes the radical anion available for a further "cycle." The relationship established by our group is expected to hold even if more than one cycle is completed in the given time.

The dianion reaction with the ketone is shown to follow three fast *irreversible* pathways simultaneously. Disproportion of the ion quadrupole to the secondary alkoxide and enolate either by hydrogen atom transfer or by electron followed by proton transfer is ruled out. In fact electron transfer in the direction shown in the present scheme (Scheme 23) is definitely far more likely on thermodynamic grounds.

If the formation of the ion quadrupole is much faster than proton abstraction by dianion from the ketone or from NH_3 then even if $2k_r$ and k_c are about equal in value only cyclization would be observed. Such must be the case as far as reaction of **46** is concerned.

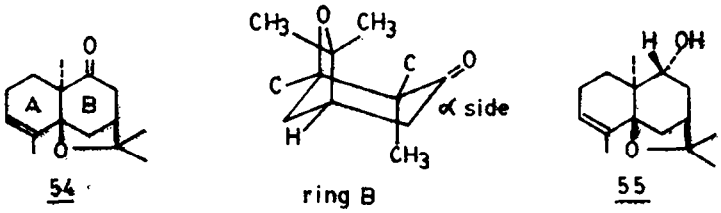
We next come to the question of conversion of the dianion to the conjugate base of the secondary alcohol. The process has to be a proton abstraction. The deuterium transfer experiments[124] indicate that with enolizable ketones the proton (or deuteron) α to the ketone is transferred to the carbon of the dianion. The preference for this over proton donation by NH_3 is possibly due to the preference for proton transfer between a "soft" base and a "soft" acid.[20]



Scheme 23.

Yet ones does expect protonation by NH_3 to be more competitive if Li^+ is available for coordination than when Na^+ or K^+ is present. Attention has already been drawn to studies using **45** (Chart 5) which are in line with this expectation.

The other situation in which NH_3 may provide the proton is where steric hindrance prevents the dianion from positioning itself for proton abstraction from α to a ketone. This must be the case in the reaction of 9-oxo-α-agarofuran **54** with Na/NH_3/ether free of proton donors[29] to give the corresponding 9α-ol, **55**. Ring B of **54** is expected to prefer the chair conformation shown below. The substituted bridge on the β side can be expected to prevent delivery of proton by **54** to the dianion. Evidence to this effect is presented in the next section. The formation of **55** must be due to protonation by NH_3.



54 55

With Scheme 23 for reference we can now turn to the stereochemistry of reductions by alkali metal/NH_3 of saturated cyclic ketones. It is clear from the scheme that the dianion has a crucial role to play. The nature of the counterion/s can hence be expected to play a part i.e. the stereochemical results can be expected to depend more on amount of Li^+ or K^+ present than whether lithium or potassium metal is used for the reduction.

The role of counterion was first demonstrated by Murphy and Sullivan.[115] The results obtained by them on the stereochemistry of reduction of (+)-camphor are given in Table 4. Similar obser-

Table 4. Ratio of alcohols obtained in alkali-metal NH_3 reduction of (+)-camphor in the presence of salts

Metal	Salt	Ratio (metal : salt)	Ratio (endo : exo)
Li	LiBr	1 : 5	80 : 20
K	LiBr	1 : 5	76 : 24
Li	KBr	1 : 5	53 : 47
K	LiBr	1 : 1	66 : 34
Li	KBr	1 : 1	67 : 33

vations were made in our laboratory with respect to the alkali metal/NH_3 reduction of 16-oxo-pregn-5-ene, **6**.[79] Results are given in Table 5. The reduction of 6-oxo-cholestane follows the same pattern[78] giving an excess of the axial cholestan-6 β-ol when K^+ is present as a counterion. Many such examples are expected to come to light with more work of this nature. But moisture and/or proton donors have to be strictly excluded. This is borne out by the data obtained[29] in alkali metal/NH_3 reduction of 9-oxo-α-agarofuran **54**, wherein the stereochemistry of reduction was markedly different in the presence of EtOH.

Table 5. Alkali-metal NH_3 reduction of pregn-5-en-16-one-6

Metal	Salt	Ratio (metal : salt)	Ratio (16α : 16β OH)
Li	—	—	57 : 43
Li	KBr	1 : 5	40 : 60
Na	—	—	43 : 57
Na	KBr	1 : 5	31 : 69
K	—	—	24 : 76

In all cases where Li/NH_3 and K/NH_3 give different stereochemical results it is observed that Na/NH_3 gives epimer ratios in between the two. In all the examples quoted above K/NH_3 gives as the major product the stereoisomer expected as a result of proton delivery at carbon from the least hindered side. Why this happens is not clear at the moment but is probably due to non-bonded interactions in the transition state. The transition state referred to above is that for the post rate-determining step in which a dianion associated with one or two K^+ ion/s abstracts a proton from α to a ketone group. Such a bimolecular reaction is required to explain an exciting observation made by Rautenstrauch[130] and confirmed in our laboratory.[131]

Rautenstrauch resolved a controversy about the stereochemistry of reduction of camphor by K/NH_3. The major product obtained in Europe was *exo*-borneol whereas that obtained at Clemson was *endo*-borneol.[132]

He established that optically active camphor gives mainly *exo*-borneol while racemic camphor yields *endo*-borneol as the major product. This unusual enantioselectivity can be explained both in terms of dianion ketone reaction or radical ion disproportionation according to Rautenstrauch[131] who, however, prefers an ion quadrupole disproportionation mechanism. In view of the above findings the former is to be preferred and the enantioselectivity explained as follows. The transition state for (−)-*exo*-borneol formation must be lower than that for (+)-*endo*-borneol formation when a dianion from (+)-camphor is abstracting a proton from (+)-camphor. With (±)-camphor the

lowest energy transition state must be for reaction of dianion from (+)-camphor with (−)-camphor, and dianion from (−)-camphor with (+)-camphor. This lowest energy transition state presumably having minimum non-bonded interactions, must favour *endo*-borneol formation. The overall result is thus preferential formation of (±)-*endo* borneol from (±)-camphor. Though not specifically indicated in Scheme 23 it should be understood that when two different approaches are possible for the dianion to approach the ketone molecule, then two different k_{r_i}'s and $k_{i'}$'s have to be considered. Their values finally determine the stereochemistry of the reduction.

In seeking an explanation for the differences in behaviour with K^+ as counterion/s and that with Li^+ as counterion/s one realizes that there are many aspects that we are ignorant about.

Is the dianion planar or pyramidal? Is it planar when associated with two counterions and pyramidal when only one counterion is present? The possibility of a planar dianion when two Li^+ cations are associated with it cannot be lightly dismissed. According to Streitweiser (Jr.) such dicarbanion ion triplets may have enhanced electronic stablization.[133] For an equivalent coupling of lone pairs of electrons on carbon and oxygen with two lithium cations placed on the line perpendicular to and bisecting the C—O bond a planar structure for the dianions appears desirable. Such an ion triplet may not be feasible if Li^+ is replaced with K^+ and may account for the difference in behaviour. On the other hand, if only pyramidalized anions are present is this system configurationally stable and, if so, does the reaction take place with retention or inversion of configuration?

Thus whereas the mechanism can be considered as being established a full understanding of the factors responsible for the different stereochemical results obtained with Li/NH_3 and K/NH_3 is still proving elusive.

5.2. *The presence of added proton donors*

Li/NH_3/THF (or DEE)/EtOH reductions of cyclic ketones have been extensively used in synthesis. They are undoubtedly quite valuable because they are convenient to carry out. No rigorous precautions are required and at the same time formation of pinacols and recovery of starting material is avoided. So an understanding of such reductions is highly desirable.

Use of other alcohols as well as ammonium salts and also replacement of Li by Na is, however, not uncommon. In ammonia as solvent all alcohols are acids and ammonium salts are strong acids. Hence the reaction conditions using these additives can be regarded as being considerably different from those dealt with in the previous section. They can be expected to influence the mechanism as well as the stereochemistry of the reduction. One instance of remarkable change in stereochemistry[115] has already been cited. (See Table 3, Section 5.1). An equally remarkable result has been obtained with 9-oxo-α-agarofuran **54**. The ratio of 9α-ol:9β-ol was found[29] to be 1.4, 0.3, and 0.2 with Li/NH_3, Na/NH_3 and K/NH_3 respectively. But in presence of excess EtOH all three reducing systems gave a ratio greater than 99. These two represent extreme cases. In others the change in ratio of epimers in going from say Li/NH_3/THF to Li/NH_3/THF/EtOH is nominal or even nil. A recent review[2] cites these examples and also evidence of change in ratio with the acidity of the proton donor.

Because of its strongly acidic nature Rautenstrauch recommends the use of ammonium chloride for obtaining the thermodynamically more stable epimer in high yields by the House mechanism.[116] Both he and Huffman[2] regard the House mechanism as applying i.e. ketone → ketyl radical anion → ketyl → hydroxy carbanion → secondary alkoxide. The proton for the ketyl radical anion to ketyl step is regarded as coming from the added acidic proton donor. Either this proton or another proton from the acid finds its way to the carbinol in the final step. In conformity with this (+) camphor-3-d_2 on reduction with alkali metal/NH_3/NH_4Cl, gives (+) *endo* borneol-3-d_2. In connection with the formation of *endo* borneol as the major product, Huffman[2] has pointed out that under the same reaction conditions norcamphor gives the *less stable endo* norborneol and hence stability considerations do not determine the stereochemistry.

Alkali metal/NH_3 reductions in presence of NH_4^+ or of large excess of EtOH bear more than a formal resemblance to Na/EtOH or Li/EtOH reductions discussed at length in Section 1. The same epimer is obtained as the major product in both cases irrespective of thermodynamical stability. We submit that the mechanism given in Scheme 9 is also applicable here and that the stereochemistry is under FMO control.

With smaller quantities of less acidic proton donors the stereochemical results are often different. This evidence supports the possibility that more than one mechanism is simultaneously operative. One of these can be presumed to be the same as the one suggested in the previous paragraph. The other is capable of giving a different stereochemical result which is akin to that obtained in the absence of the proton donor. In some cases at least the proton donor may no longer be present though it is assumed to be available. Thus MeOH or EtOH added in one mg mol quantity to three mg atoms of Na inNH_3 is likely to be converted to $NaOR+H_2$ quite fast. Then the dianion mechanism would apply and govern the stereochemistry.

In addition to stereochemistry as a probe for the mechanism another powerful tool exists viz. use of deuterated substrates. When the two are combined a lot of useful data is generated. The first to carry out such a study was Rautenstrauch.[116] To date only two other groups have used this tool—one at Clemson[29] and the other in Bombay.[79]

9-Oxo-α-agarofuran-8-d_2 (containing 25% d_1) on reduction with Na/NH_3/*t*-BuOH gives a significant amount of trideuterated 9β-ol while no trideuterated 9α-ol is obtained. Whatever deuterium that is present in the latter is only at the 8 position. Thus whereas the source of deuteron/proton in 9β-ol formation must be the ketone and/or *t*-BuOH, the source of proton for 9α-ol formation is exclusively *t*-BuOH. This is readily understood if one makes the assumption that the intermediate undergoing protonation prefers to pick up a proton from α to the ketone to taking one from *t*-BuOH. *When the former is prevented the latter prevails.* In case of formation of 9α-ol, steric hindrance is readily visualized as the factor which prevents delivery of deuterium from α position of the ketone molecule to the carbinol carbon. The suggested preference for taking up a proton from a less acidic species has to be linked up with proton transfer from a *soft* acid to a *soft* base. It cannot be a radical anion or dimer reacting at carbon as neither are basic enough to abstract a proton from α to a ketone. At very low alcohol concentration it could be a dianion. But it may also be the hydroxy carbanion behaving as a soft base.[134] Thus contrary to what has been believed by previous authors the House mechanism may be responsible for formation of at least some of the trideuterated products observed in alkali metal/NH_3/THF/ROH reduction of the dideuterated derivatives of the following: 2,2-dimethylcyclohexanone,[124] (+)-camphor[116] and 9-oxo-α-agarofuran.[29]

CONCLUSIONS

We conclude that:

1. (i) Mechanism of reduction of saturated ketones by alkali metal/lower alcohol is best represented by Scheme 9. (ii) Stereochemistry of such reductions is dictated by the structure of the slightly pyramidalized ketyl radical anion. The direction of pyramidalization or orbital extension is the result of FMO interactions except in a few cases where steric factors dominate over stereoelectronic factors.

2. (i) With alkali metals in the presence of higher or branched alcohols and at higher temperatures hydride transfers may intervene to varying extents. (ii) If hydride transfer is allowed to go to completion the major epimer that is obtained will be the thermodynamically more stable one.

3. (i) Alkali metal/NH_3 reductions of α,β-unsaturated ketones proceed via dianions as suggested by Barton. Mechanism summarized in Scheme 17 applies. (iii) As indicated in the above Scheme the stereochemistry of reduction at the β position of conjugated enones is regarded as being controlled by σ framework interaction with the SOMO of the corresponding 1,4 radical anion. This appears to fit the data better than earlier concepts.

4. (i) A critical assessment of all available data connected with alkali metal/NH_3 (free of proton donors), reduction of cyclic saturated ketones indicates that the mechanism is as shown in Scheme 23. No other mechanism is capable of explaining all the data. (ii) A rational explanation of the stereochemistry of reduction of above compounds is still proving elusive. The only headway made is in respect of reductions using K/NH_3/THF systems. The dianion derived from an optically active ketone picks up a proton from the less hindered side.

5. In alkali metal/NH_3 reductions in presence of proton donors such as alcohols the House mechanism is in control to a larger extent than appreciated so far. This requires the assumption that the hydroxy carbanion intermediate behaves as a soft base.

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