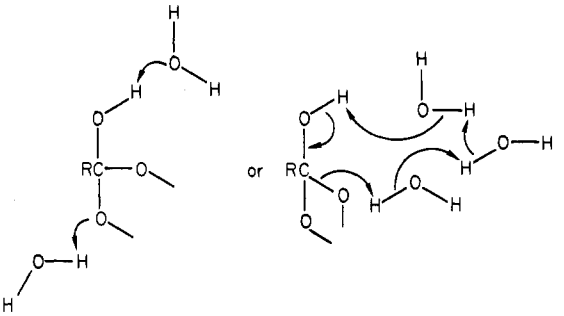
I). (ii) The Brønsted α value for decomposition of dimethyl hemiorthobenzoate is 0.46,[18] whereas trimethyl orthobenzoate hydrolysis is not buffer catalyzed[60] ($\alpha >$ 0.8). (iii) With ortho esters a significant increase in rate is observed on substituting H by Me, as expected since the methyl stabilizes the cation. Hemiorthoformates on the other hand show a very similar reactivity to hemiorthoacetates (Table I). It can be noted that rejection of this mechanism implies also a rejection of the mechanism normally written for acid-catalyzed ester alcoholysis (and hydrolysis). This involves a preequilibrium protonation of the ester, followed by addition of alcohol (or water), and this is the reverse of eq 9.

The eq 9 mechanism has also been rejected for aldehyde hydrates and hemiacetals[48b,51] and the mechanism of eq 10 favored. This reaction, however, seems also to be ruled out for the hemiorthoesters in that for certain catalysts rate constants for the slow step considerably larger than the diffusion limit are required.[18] We considered the possibility of a "1-encounter" mechanism,[61] in which the acid that donates the proton then acts as a base to deprotonate the hydroxy group before diffusional separation. This suggestion has the drawback that in the previous system for which this mechanism was proposed,[61] the addition of hydrogen peroxide to aldehydes, Brønsted α values were near unity. Capon[9] has proposed a fully concerted mechanism, with a proton being simultaneously donated to the departing alkoxy group by the acid catalyst and removed from the hemiorthoester hydroxyl by water solvent. This mechanism, however, appears entropically difficult, particularly in the reverse direction. We conclude that the acid mechanism is not yet established, and further work is needed.

The Water Reaction

The possibility that water is simply acting as another general acid or general base can be rejected on the grounds that even after correction to second-order units, the points for this catalyst lie well above the acid and base Brønsted lines.[18] Other experimental observations include (a) a near zero ρ value (for dimethyl hemiorthobenzoates[18] and for 2-hydroxy-2-aryl-1,3-dioxolanes),[13] (b) very little effect of substituting methyl by CH_2Cl and $CHCl_2$,[9] (c) k_{H_2O}/k_{D_2O} = 4.5 (for 2-hydroxy-2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane),[26] and (d) $\Delta S^{\ddagger}$ = −22 eu for the pH-independent ring opening of 2-hydroxy-2-phenyl-1,3-dioxolane.[26] The last two observations suggest a highly structured transition state with a considerable proton-transfer component, and the mechanism favored by both us[18] and Capon[9] involves a concerted process with water molecules simultaneously donating and removing protons, perhaps in a cyclic fashion through a solvent bridge.[62]



Concluding Remarks

Tetrahedral intermediates of the hemiorthoester type have now been shown to have a sufficient lifetime to be observed in aqueous solution, providing that they are generated from more reactive precursors. These observations not only establish that these are reasonable intermediates for O,O-acyl transfer reactions but they also permit direct kinetic and mechanistic study of the decomposition process. Further work should provide a detailed understanding of mechanistic behavior not only for the decomposition process but also for the microscopic reverse, an ester alcoholysis or hydrolysis.

The continued support of the Natural Sciences and Engineering Research Council of Canada is acknowledged. Grants from the Research Corp. and the J.. P.. Bickell Foundation are also acknowledged.

(60) Bull, H. G.; Koehler, K.; Pletcher, T. C.; Ortiz, J. J.; Cordes, E. H. *J. Am. Chem. Soc.* 1971, *93*, 3002–3011.
(61) Sanders, E. G.; Jencks, W. P. *J. Am. Chem. Soc.* 1968, *90*, 4377–4386.
(62) Eigen, M. *Discuss. Faraday Soc.* 1965, *39*, 7–15.

Metal–Ammonia Reductions of Cyclic Aliphatic Ketones

JOHN W. HUFFMAN

Department of Chemistry, Clemson University, Clemson, South Carolina 29631

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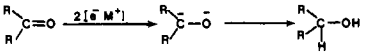
The reduction of aliphatic cyclic ketones by alkali metals in liquid ammonia was first employed about 30 years ago as an alternative to the sodium–alcohol procedure for the stereoselective conversion of 11-keto steroids to the 11α-(equatorial) alcohols.[1] Subsequently this reaction has found limited use as a method for the reduction of ketonic carbonyl groups in other steroids and in the synthesis of various natural products.

Scheme I



John W. Huffman was born July 21, 1932, in Evanston, IL, received his B.S. from Northwestern University and Ph.D. from Harvard University. He was Assistant Professor of Chemistry at Georgia Institute of Technology from 1957–1960 and joined the faculty at Clemson University in 1960. During 1965–1970 he held a National Institutes of Health Career Development Award. In addition to the work described in this Account, his research is concerned with the synthesis of natural products, particularly terpenoids, and various aspects of the conformational analysis of carbocyclic systems.

(1) Sondheimer, F.; Yashin, R.; Rosenkranz, G.; Djerassi, C. *J. Am. Chem. Soc.* 1952, *74*, 2696. Heuser, H. L.; Anliker, R.; Jeger, O. *Helv. Chim. Acta* 1952, *35*, 1537.

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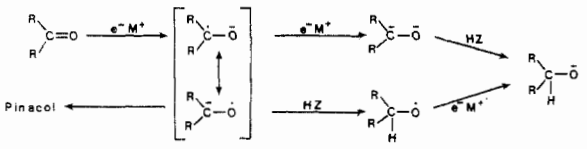
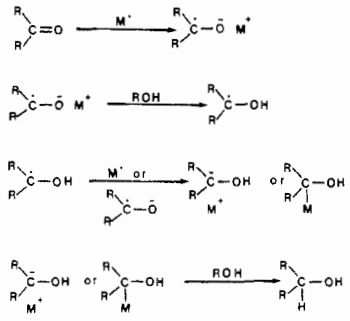
Scheme II



Scheme III



However, the stereochemical course of these reductions has proven to be rather unpredictable. That has generated interest in their detailed mechanism and the stereochemical consequences thereof.

Prior to the early 1950s, although many classes of compounds had been subjected to reaction with active metals in ammonia, very few reductions of ketones, with the exception of benzophenone, had been studied under these conditions.[2] In his early, classical papers on conformational analysis, Barton generalized that sodium–alcohol reduction of cyclohexanones would invariably afford mixtures of product alcohols rich in the thermodynamically more stable epimer.[3] A few years later this generalization was extended to the mechanistically similar metal–ammonia reductions and a mechanism (Scheme I) was suggested to explain these empirical observations.[4]

However, in 1960 it was reported that under certain conditions the reduction of camphor with potassium in ammonia affords as the major product isoborneol, the less stable epimeric alcohol.[5] Subsequently we found that reduction of various 12-keto steroids with lithium in ammonia gave as the major product the less stable 12α-(axial)-ol.[6] In an effort to develop a mechanistic explanation for these results we undertook a systematic investigation of the reduction of several substituted cyclohexanones, camphor and norcamphor.[7] Simultaneously, Rassat's group studied the reduction of several bicycloheptanones[8] and the reduction of camphor under a variety of conditions was carried out by Murphy and Sullivan.[9] These studies resulted in the suggestion of more or less similar mechanisms (Scheme II) for these reductions by all three groups, in spite of certain differences in experimental results.[7-9]

Table I
Reductions of Selected 12-Keto Steroids by Lithium–Ammonia

ketone	proton donor	12β-ol/ 12α-ol	ref
1	*n*-PrOH	0.3	6
1	none	9[a]	6
2	MeOH	0.4	15
2	*t*-BuOH	0.7	15
2	none	4	15
3	MeOH	0.4	15
4	MeOH	9	15
4	*t*-BuOH	>10[b]	
4	none	*c*	15

[a] Plus pinacol (40%). [b] 12α-ol was not detected. [c] Pinacol is the major product.

In 1972, House reinterpreted these data in the light of extensive work in his laboratory on the dissolving metal and electrochemical reductions of α,β-unsaturated ketones.[10] Although the House mechanism (Scheme III) appears to have been rather widely accepted, subsequent work by Rautenstrauch produced results inconsistent with this reaction path.[11,12] In particular, deuterated dimethylcyclohexanone affords products in which reduction occurs by deuterium transfer to the carbonyl group within a ketyl dimer.[11] More recently it has been suggested that this hydrogen-transfer path predominates in the metal–ammonia reduction of ketones under most conditions;[12] however, this conclusion is not entirely consistent with the available experimental data. In this Account, we review the history of this mechanistically controversial reaction and, on the basis of recent work from our laboratory, suggest a revised mechanism that appears to be consistent with all of the available experimental data.

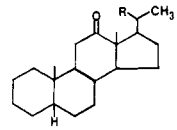
Traditionally, the metal–ammonia reduction of ketones has been performed by either of two principal methods. In one, the reaction is carried out by direct interaction of the substrate ketone, usually dissolved in an inert solvent such as Et_2O or tetrahydrofuran (THF), with an ammonia solution of the alkali metal under essentially aprotic conditions. Alternatively, and more commonly, some substance more acidic than ammonia (NH_4Cl or an alcohol) is present during the reduction. These are described respectively as reduction in the absence and in the presence of a proton donor.[13] Empirically, reductions in the absence of a proton donor may give different ratios of epimeric alcohols than those in the presence of a proton donor. The acidity of the proton donor may affect the product ratio. In the absence of a proton donor, the course of the reduction may vary as a function of the metal. It is generally assumed that the actual reducing agent in metal–ammonia reductions is a solvated electron and the notation e^-M^+ will be used to indicate this species.[14]

(2) Watt, G. W. *Chem. Rev.* **1950**, *46*, 317. Birch, A. J. *Q. Rev., Chem. Soc.* **1950**, *4*, 69.
(3) Barton, D. H. R. *Experientia* **1950**, *6*, 316; *J. Chem. Soc.* **1953**, 1027.
(4) Barton, D. H. R.; Robinson, C. H. *J. Chem. Soc.* **1954**, 3045.
(5) Ourisson, G.; Rassat, A. *Tetrahedron Lett.* **1960**, *21*, 16.
(6) Huffman, J. W.; Alabran, D. M.; Bethea, T. W. *J. Org. Chem.* **1962**, *27*, 3381. Huffman, J. W.; Alabran, D. M.; Bethea, T. W.; Ruggles, A. C. *Ibid.* **1964**, *29*, 2963.
(7) Huffman, J. W.; Charles, J. T. *J. Am. Chem. Soc.* **1968**, *90*, 6486.
(8) Columbeau, A.; Rassat, A. *Chem. Commun.* **1968**, 1857; *Bull. Soc. Chim. Fr.* **1970**, 4399, 4404.
(9) Murphy, W. S.; Sullivan, D. F. *J. Chem. Soc., Perkin Trans. 1* **1972**, 999.
(10) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; pp 152–158; Bowers, K. W.; Giese, R. W.; Grimshaw, J.; House, H. O.; Kolodny, N. H.; Kronberger, K.; Roe, D. K. *J. Am. Chem. Soc.* **1970**, *92*, 2783. House, H. O.; Giese, R. W.; Kronberger, K.; Kaplan, J. P.; Simeone, J. F. *Ibid.* **1970**, *92*, 2800.
(11) Rautenstrauch, V.; Geoffroy, M. *J. Am. Chem. Soc.* **1977**, *99*, 6280.
(12) Rautenstrauch, V.; Willhalm, B.; Thommen, W.; Burger, U. *Helv. Chim. Acta* **1981**, *64*, 2109.
(13) Various modes of addition, concentrations of metal, nature of the cosolvent, etc. have been examined but appear to have relatively little effect on the course of the reductions.

The House Mechanism and Before

In his original mechanism, Barton suggested (Scheme I) the direct reduction of the ketonic carbonyl group to a tetrahedral, vicinal dianion in which the oxygen atom adopted the more stable orientation. Protonation of the dianion at carbon would afford the more thermodynamically stable alcohol as the major product.[4]

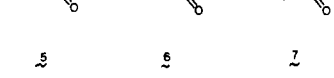
Ourisson and Rassat's reductions of camphor[5] and our work on the reduction of 12-keto steroids (1–4), selected examples of which are shown in Table I, clearly indicated that in contrast to Barton's generalization these reductions may in some instances afford the less stable of a pair of epimeric alcohols. In our early work,



1 R = n-C_3H_7 3 R = CH_3
2 R = C_2H_5 4 R = H

it was found that 12-cholanone (1) affords predominantly the thermodynamically less stable axial 12α-ol on reduction by lithium in ammonia in the presence of a proton donor, while a 12-keto sapogenin with a constrained steriodal side chain and a 12-ketopregnane similar to 4 both gave the equatorial and stable 12β-ol as the major product under similar conditions.[6] It was also found that reduction of ketone 1 in the absence of a proton donor affords primarily the 12β-ol plus significant amounts of pinacol.[6] Subsequent investigation showed that while the overall length of the steriod side chain was unimportant in governing the course of these reductions, the presence of a tertiary carbon at C-20 in ketones 2 and 3 leads to behavior similar to that of ketone 1.[15] This effect is attributed to a preferred conformation about the C-17–C-20 bond in ketones 1–3 in which the C-21 methyl group shields the face of the carbonyl group.[6,15] To explain these data, we originally suggested a mechanism in which a dianion (Scheme I) was kinetically protonated in the presence of a proton donor, whereas thermodynamic control prevailed in the absence of a donor.[6]

Our study of the reduction of a series of substituted cyclohexanones (2-, 3-, and 4-methyl, 4-*tert*-butyl, and 3,3,5-trimethyl) with lithium in ammonia in the presence and absence of proton donors indicated very high equatorial to axial ratios (99/1 with the exception of 3-methylcyclohexanone, 94/6).[7] In the same study, it was found that reduction of norcamphor (5) with lith-



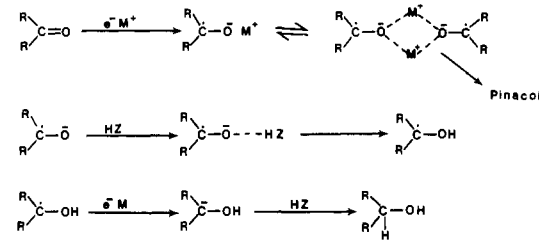
5 6 7

ium, in ammonia, in the presence or absence of proton donors (NH_4Cl, EtOH, *t*-BuOH), invariably gave the less stable endo alcohol as the major product (>68%).[7] Similar product ratios were obtained by Coulombeau and Rassat, who found that several methyl-substituted bicycloheptanones also afforded the endo alcohol as the major product on metal–ammonia reduction regardless of the relative stabilities of the product alcohols.[8]

Table II
Reduction of Camphor with Various Metals in the Absence of an Added Proton Donor

metal	borneol/isoborneol	ref
Li	5.2	7, 16
Li	3.4	8
Li	4.0	5, 9
Na	4.3	7, 16
Na	1.4	8
Na	1.5	5, 9
K	3.8	7, 16
K	0.7	8
K	0.7	9
K	0.4	5

Scheme IV



Camphor (6) proved exceptional in that, while reduction in the presence of proton donors gave high percentages (>85%) of the stable endo alcohol (borneol),[7-9,12] reductions in the absence of a proton donor were puzzling (Table II). We found that reduction of camphor with lithium, sodium, or potassium gave 16–21% of the exo alcohol,[7] while Rassat's group and Murphy and Sullivan found that progressively greater amounts of the exo alcohol were formed with sodium and potassium,[8,9] as reported previously.[5] Several years later a concerted effort was made in our laboratory to duplicate as carefully as possible the conditions of the other groups; however, we were unable to confirm their results.[16]

On the basis of these studies, and in spite of the differences in product ratios listed in Table II, rather similar revisions in the Barton mechanism were suggested by all three groups. This variation (Scheme II, in which HZ is a proton donor) superimposes a radical–anion mechanism upon that outlined in Scheme I.[7,9] We assumed that in the presence of relatively acidic proton donors (MeOH, NH_4Cl) kinetically controlled protonation of the radical anion would prevail, while in the absence of a proton donor, a dianion mechanism would be operative.[7] The other groups suggested that the dianion adopts a preferred geometry dictated by the formation of a metal–carbon bond of unspecified type.[8,9]

House reinterpreted these data and proposed a further revision (Scheme III) in the mechanism on the grounds that alkali metals in ammonia did not have reduction potentials sufficiently large to generate vicinal dianions from aliphatic ketones and that protonation of the ketyl should occur on oxygen rather than on carbon.[10] We subsequently suggested a slightly revised version of the House mechanism (Scheme IV), which at the time appeared to accommodate the available experimental data.[16] It was found that the relative rates

(14) A detailed discussion of the chemistry of active metals in ammonia is beyond the scope of this Account. For a brief review and leading references, see Caine, D. *Org. React.* **1976**, *23*, 1.
(15) Huffman, J. W.; Copley, D. J. *J. Org. Chem.* **1977**, *42*, 3811.
(16) Huffman, J. W.; McWhorter, W. W. *J. Org. Chem.* **1979**, *44*, 594.

Table III
Relative Rates of Lithium–Ammonia Reduction of Ketones

ketone	relative rate: presence of EtOH	relative rate: absence of EtOH
4-methylcyclohexanone	1.00	1.00
4,4-dimethylcyclohexanone	0.99	0.93
cyclohexanone	1.32	0.97
4-*tert*-butylcyclohexanone		1.07
fenchone (7)	2.03	1.58
3,3,5,5-tetramethylcyclohexanone	2.65	1.31
camphor (6)	2.88	1.36
norcamphor (5)	3.12	1.22

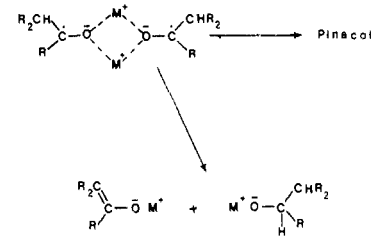
of reduction of several ketones with lithium–ammonia–EtOH followed I-strain order, but that in the absence of a proton donor the rates followed no defineable pattern (Table III).[16] Also reduction of 12-keto steroid **2** using *t*-BuOH, a relatively weak acid, as proton donor gave a product ratio intermediate between that in the absence of a proton donor and in the presence of MeOH (Table I).[15] Also consistent with the revised mechanism were the observations of Hirota that simple ketyls exist in equilibrium with dimeric (or higher) species and that ketyls form relatively stable solvated species with alcohols.[17]

Since the relative rate data (Table III) in the presence of a proton donor followed I-strain order, it was concluded that some step prior to the conversion of the trigonal carbonyl group to a nontrigonal species is the slow step in the reduction. Protonation of the carbanion under these conditions was considered to be extremely fast (i.e., faster than the geometrical reorientation of the anion). In the absence of an added proton donor, ammonia, a very weak acid, could serve as a proton donor, but at a rate slower than that of a stronger acid, permitting reorientation of the carbanion and the possible formation of different ratios of products than obtained in the presence of a stronger acid. The randomization of the relative rates under these conditions was ascribed to a decrease in the rate of protonation to the point where it was competitive with some earlier step.

After the House Mechanism

Although the House mechanism and variations such as that presented in Scheme IV seemed to be generally accepted, a series of elegant studies by Rautenstrauch have cast considerable doubt on its validity. First, it was found that the ketyl dimer generated from a nonenolizable ketone, 2,2,6,6-tetramethylcyclohexanone, is stable in THF at −75 °C and on quenching with water disproportionates to a molecule of ketone and a molecule of alcohol.[18] In a second study, reduction of 2,2-dimethylcyclohexanone-*6,6-d*$_2$ with lithium, sodium, or potassium in ammonia in the absence of a proton donor gave significant amounts of product alcohol in which deuterium has been transferred from the α-position of the ketone to the carbinol carbon of the product alcohol.[11] The net result is the production of a mixture of the reduced alcohol (as the alkoxide) and the enolate

Scheme V



of the starting ketone (Scheme V). This path accounts for approximately 50% of the product with lithium and 80–90% with sodium or potassium. In the presence of alcohols the amount of product arising by deuterium transfer was found to be considerably less (19–36%).[11]

In a recent very careful study of the reduction of camphor-*3,3-d*$_2$, Rautenstrauch found that in the absence of proton donors the bulk of the reduction products arise from deuterium transfer, while in the presence of ammonium chloride very little deuterium transfer occurs.[12] In agreement with virtually every other study of these reductions, he found that the formation of pinacols was maximum with lithium and negligible with potassium. On the basis of these data and the observation that alcohols are considerably less acidic than a protonated ketyl,[19] Rautenstrauch concluded that reduction by way of the House mechanism does not compete with hydrogen transfer, except in the presence of ammonium chloride.[12] While the overall course of the hydrogen transfer path is almost certainly that depicted in Scheme V, the exact nature of the hydrogen-transfer step remains unknown.

On the basis of both deuterium labeling and product distribution studies, Rautenstrauch suggests that reductions in the presence of ammonium chloride proceed via the House mechanism (Scheme III or IV), probably by way of a monomeric ketyl, and should invariably afford the more stable epimeric alcohol.[12] However, it should be noted that norcamphor (**5**) on reduction in the presence of ammonium chloride had previously been reported to afford the *less* stable endo alcohol as the major reduction product.[7]

As a corrollary to the studies discussed above, Rautenstrauch has resolved the long-standing controversy regarding the reduction of camphor in the absence of proton donor (Table II).[20] The differences in product ratios observed by our group[7,16] and the others[5,8,9,12] were caused by the fact that our work was carried out with (±)-camphor, while the other groups used (+)-camphor. In terms of the hydrogen-transfer mechanism (Scheme V), (±)-camphor affords a mixture of ketyl dimers, which consists of equal parts of the enantiomeric ketyl dimers derived from (+)- and (−)-camphor and a diastereomeric ketyl dimer that incorporates a molecule each of (+)- and (−)-camphor. The observed differences in product ratio are caused by differing paths and/or rates of disproportionation of these diastereomeric ketyl dimers.[20]

Although Rautenstrauch's work was most carefully executed and introduced new mechanistic concepts into the metal ammonia controversy, the conclusions that were reached are not entirely consistent with all of the experimental data from other laboratories. Besides the

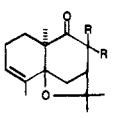
(17) Hirota, N. *J. Am. Chem. Soc.* **1967**, *89*, 32. Nakamura, K.; Wong, B. F.; Hirota, N. *Ibid.* **1973**, *95*, 6919. Chen, K. S.; Mao, S. W.; Nakamura, K.; Hirota, N. *Ibid.* **1972**, *94*, 4419. Hirota, N.; Weissman, S. I. *Ibid.* **1960**, *82*, 4424.
(18) Rautenstrauch, V.; Geoffroy, M. *J. Am. Chem. Soc.* **1976**, *98*, 5035.
(19) Laroff, G. P.; Fessenden, R. W. *J. Phys. Chem.* **1973**, *77*, 1283.
(20) Rautenstrauch, V. *Helv. Chim. Acta* **1982**, *65*, 402.

Table IV
Metal-Ammonia Reductions of 9-Keto-α-agarofuran (8)

metal	proton donor	9α-ol/9β-ol
Li	EtOH	99
Li	none	1.4
Na	EtOH	99
Na	EtOH (1 equiv)	0.5
Na	*t*-BuOH	1.2
Na	none	0.3
K	EtOH	99
K	none	0.2

observation that norcamphor affords principally *endo*-norborneol on reduction with metals in ammonia–ammonium chloride,[7] the mechanism outlined in Scheme V fails to explain the variations in product ratios found as a function of proton donor in the reduction of 12-keto steriods (Table I).[6,15]

At this point serendipity intervened in the form 9-keto-α-agarofuran (8), a compound prepared in our



8 R = H
9 R = D

laboratory as an intermediate in the synthesis of some highly oxygenated sesquiterpenes.[21] It has proven to be a most sensitive substrate for the study of the metal–ammonia reductions of saturated ketones (Table IV).[22]

Reduction of ketone 8 in the presence of excess ethanol gives almost exclusively the more stable equatorial 9α-ol; however, reduction in the absence of a proton donor gives progressively more of the less stable axial 9β-ol, as one progresses from lithium to potassium, a situation reminiscent of the reduction of (+)-camphor under similar conditions (Table II).[5,8,9,20] The use of 1 equiv of ethanol or less acidic proton donor, *tert*-butyl alcohol, affords intermediate product ratios.[22]

While these data are difficult to reconcile with either the House (Scheme III or IV) or Rautenstrauch mechanism (Scheme V), they can be interpreted in terms of a combination of both mechanisms. This tentative conclusion was supported by reduction of a dideuterio derivative of ketone 8 (**9**, 75% d_2, 25% d_1), which gave two significant results. First, the equatorial 9α-ol obtained from this reduction contained *no detectable deuterium at the carbinol position*, indicating that none of this material arose via a hydrogen-transfer path. The axial 9β-ol, however, contained 43% of material labeled at this position, indicating that a significant amount of this epimer must have been formed by hydrogen transfer (Scheme V).[23] The second significant result of the reduction of ketone **9** was a change in the product ratio of 9α to 9β-ol from 1.2 to 2.6. The decrease in the relative amount of 9β-ol is attributed to a primary deuterium isotope effect that is expected to be operative in the hydrogen-transfer path but that is absent from a House type mechanism.

On the basis of these data, it is apparent that reduction by hydrogen transfer and protonation of an intermediate are competitive reaction paths, the relative rates of which in a given system dictate the course of the reduction. Consideration of all of the data outlined above leads to the conclusion that, in the presence of a relatively acidic proton donor (NH_4Cl, EtOH), a protonation path is favored, while the absence of a proton donor favors hydrogen transfer. In the presence of a less acidic proton donor (*tert*-butyl alcohol), both paths contribute significantly to the formation of the products. The situation is further complicated by the possibility of pinacol formation, particularly when using lithium in the absence of a proton donor. A mechanism describing these competitive reactions is depicted in Scheme VI.

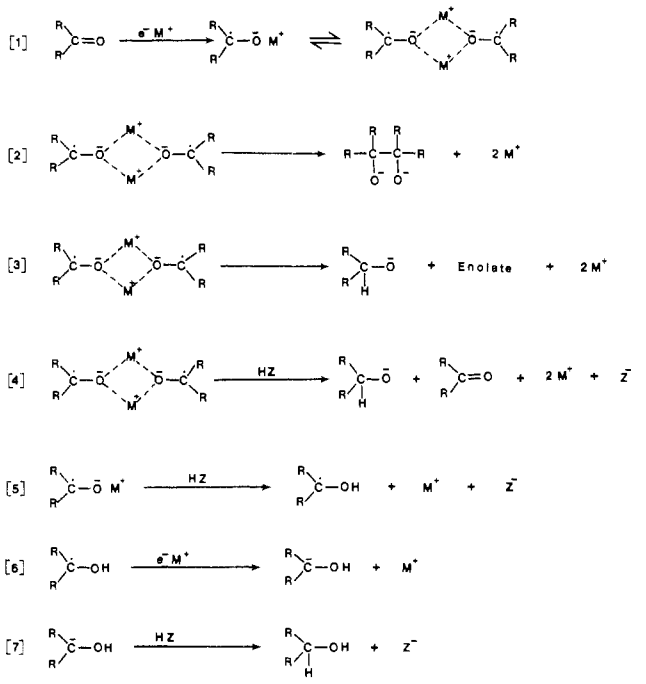
The first step is the well-documented transfer of an electron to the ketonic carbonyl generating a radical anion (ketyl) that exists in equilibrium with a dimeric (or higher) species (Scheme IV, [1]), which for aliphatic ketyls strongly favors dimeric or polymeric ion pairs.[17,18] These ketyl dimers are known to have open to them two competing reaction paths: collapse to a pinacol (Scheme IV [2]) and disproportionation to a molecule of alkoxide and a molecule of enolate (Scheme VI, [3], and Scheme V).[11,12] While [3] clearly explains the formation of alcohols by hydrogen transfer, the detailed mechanism of reduction involving an exogeneous proton donor cannot be stated unambiguously.

One possible mechanism (Scheme VI, [4]) is based on analogy with the observation that the stable ketyl dimer of 2,2,6,6-tetramethylcyclohexanone on quenching with water rapidly disproportionates to a molecule of alcohol and a molecule of ketone.[18] A second path (Scheme VI, [5] to [7])[25] is essentially that of the House mechanism and invokes protonation of the ketyl (monomer or dimer) to give a carbinol radical, presumably via an appropriately solvated ketyl intermediate.[17] At the present time there are insufficient experimental data clearly to differentiate between these reaction paths. However, given the magnitude of the half-lives of radical anions described by House[10] and the stability of ketyls solvated by alcohols,[17] it seems likely that reduction occurs via the ketyl dimer. Also, it is known that addition of a proton donor to a stable ketyl dimer triggers rapid disproportionation to a molecule of ketone and a molecule of alcohol.[18] Since there is no a priori reason for the ketyl dimer derived from an enolizable ketone to undergo reaction with a proton donor by a different path than a nonenolizable ketone, protonation via [4] appears to be more probable than [5] or [7].

The extent to which each path described in Scheme VI contributes to the overall reaction now becomes a function of (a) the acidity of an added proton donor, if present (b) the metal used for the reduction, and (c) the structure of the substrate ketone. In the absence of an added proton donor, the principal reaction paths for an enolizable ketone are dimerization ([2]) and hy-

(21) Huffman, J. W.; Hillenbrand, G. F. *Tetrahedron* **1981**, *37*, Suppl. 9, 269. Huffman, J. W.; Desai, R. C. *J. Org. Chem.* **1982**, *47*, 3254.
(22) Huffman, J. W.; Desai, R. C.; LaPrade, J. E. *J. Org. Chem.* **1983**, *48*, 1474.
(23) Given the facts that the substrate ketone contained 25% d_1 material, that the enolate of ketone **9** is protonated after its generation and then reenters the reduction sequence, and that an isotope effect of undertermined magnitude exists in the hydrogen transfer path, it is probable that the bulk of the 9β-ol arises via this route.
(24) Pradhan, S. K.; Kadam, S. R.; Kolhe, J. N. *J. Org. Chem.* **1981**, *46*, 2633; Pradhan, S. J.; Sohani, S. V. *Tetrahedron Lett.* **1981**, *22*, 4133.
(25) One of the reviewers has suggested an intramolecular proton shift as an alternative to [7], leading to the alkoxide of the product alcohol. This reaction path also accommodates the available experimental data.

Scheme VI



drogen transfer ([3]). A nonenolizable ketone has available only dimerization, or may remain as the ketyl dimer, although radical reactions with solvents can intervene.[18] In the presence of a proton donor, reduction via [4] and/or [5] to [7] will occur in competition with [2] and [3], the extent of which will be governed by the acidity of the proton donor.

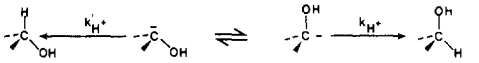
Very recently Pradhan et al. have resurrected the classical Barton dianion mechanism and attempted to justify this path on the basis of frontier molecular orbital theory.[24] However, not only can all of the results cited by these authors be accommodated within the framework of the mechanism outlined in Scheme VI but there is *absolutely no evidence for the formation of dianions from aliphatic ketones in the presence of metals in ammonia.* This mechanism was refuted on reasonable mechanistic grounds by House[10] and it is known that ketyls derived from aliphatic ketones are stable in the presence of excess metal.[17,18]

Stereochemical Consequences

Although the empirical generalization was made many years ago that dissolving metal reductions afford the more stable of a pair of epimeric alcohols,[3] the data summarized above clearly indicate that this conclusion is invalid.

For those reductions, usually in the absence of a proton donor, in which the hydrogen-transfer path prevails, the stereochemistry of the reduction products is governed by the detailed geometry of the ketyl dimer. At present, this leads to the conclusion that for a given ketone the stereochemical outcome of reduction under these conditions is essentially unpredictable. For reductions that proceed by way of protonation of an intermediate, the stereochemical outcome is determined by the direction of protonation. In terms of a carbanion intermediate (Scheme IV, [5] to [7]) the stereochemistry is determined by a combination of the relative rate of protonation of each epimer of the carbanion ($k_{H^+}/k_{H^{+\prime}}$) combined with the relative stability of these epimers (Scheme VII). Assuming that the carbanion undergoes

Scheme VII



inversion faster than capture of a proton,[26] those ketones in which there is a large energy difference between the derived pair of epimeric alcohols, such as 11-keto steroids and 9-keto-α-agarofuran (8), should afford primarily the more stable epimeric alcohol. For those ketones in which there is less energy difference between the epimeric alcohols, the product distribution should be based on the relative rates of protonation of the epimeric carbanions. Although this mechanism adequately explains the stereochemical course of the reductions discussed above, experimental verification of the detailed reaction path is still required.

From the standpoint of synthetic utility, metal–ammonia reduction of cycloalkanones is most applicable to the preparation of the more stable epimeric alcohol derived from a sterically hindered ketone such as the preparation of 11α-hydroxy steroids.[1] The reduction of other ketones usually affords product mixtures qualitatively similar to those obtained by borohydride reductions, an observation we have made previously.[6,7,15,16,22] For selected ketones, reduction in the absence of a proton donor may afford mixtures rich in epimeric alcohols that are difficult to obtain by other methods, for instance, 12β-hydroxy steroids containing a free side chain and a tertiary carbon at C-21.[6,15]

From an experimental standpoint, to promote reduction via a protonation path (Scheme VI, [4] and/or [5] to [7]), the reaction should be carried out with an excess of the most acidic proton donor practicable (NH_4Cl, MeOH). For reductions in the absence of a proton donor, the use of lithium promotes pinacol formation; however, product ratios may vary when sodium or potassium is used, and the stereochemical consequences of the reduction are essentially unpredictable at present.

Summary

After two decades of controversy and not a little confusion, a mechanism (Scheme VI) is suggested for the metal–ammonia reduction of cycloalkanones that appears to accommodate all of the experimental data presently available.

The principal difference between this and earlier mechanisms is the suggestion that the initially formed ketyl dimers have open to them three competitive reaction paths: dimerization to pinacols, hydrogen transfer affording an enolate and an alkoxide, and protonation to give ultimately a molecule of ketone and presumably a carbanion. The extent to which each path contributes is a function of a number of variables among which are the structure of the substrate ketone, the presence or absence of a proton donor, and the acidity of a proton donor that may be present.

The stereochemistry of the product alcohols derived by the hydrogen-transfer path is a function of the structure of the ketyl dimer, which may be profoundly influenced by the nature of the metal cation. For those alcohols obtained via protonation, the stereochemistry may be controlled by a combination of the relative

(26) Hoz, S.; Aurbach, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 2340. Stille, J. K.; Sannes, K. N. *Ibid.* **1972**, *94*, 8489. See, however, Cram, D. J.; Bradshaw, J. S. *Ibid.* **1963**, *85*, 1108 and many other papers in this series.

stabilities of the epimeric carbanions and their relative rates of protonation.

I would like to thank my various co-workers whose names appear in the footnotes. Much of this work was supported by the National Institutes of Health and more recently by the National Institute on Drug Abuse. I also wish to thank Professor André Rassat and Dr. Valentin Rautenstrauch for helpful and open conversations and/or correspondence concerning these reactions. Finally, this Account was prepared during a sabbatical at Colorado State University; I wish to thank Professor Albert I. Meyers for his hospitality and encouragement.

Titanium-Induced Dicarbonyl-Coupling Reactions

JOHN E. MCMURRY

Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, New York 14853

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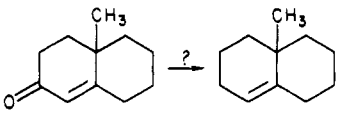
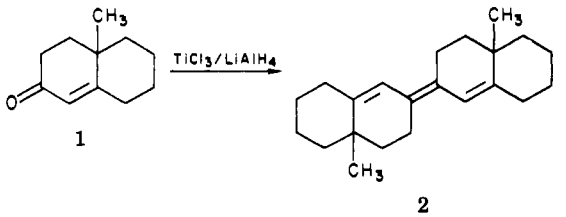
As often happens in scientific research, our discovery was made by accident. Some years ago we needed to carry out the high-yield transformation of an α,β-unsaturated ketone into the corresponding olefin without migration of the double bond. This kind of transformation often fails with classic methods of ketone deoxygenation such as the Wolff–Kishner reaction or dithioacetal desulfurization, and we therefore sought to devise a new method.



It occurred to us that the ideal method would be a one-pot reaction in which a good hydride donor such as $LiAlH_4$ might be used in conjunction with an appropriate transition-metal salt. If initial hydride reduction of the carbonyl group were to be followed by strong coordination of the alkoxide anion with the metal, a *second* hydride delivery might occur in an S_N2-type fashion, leading to the desired product. In light both of the great strength of the titanium–oxygen bond and of our previous experiences with titanium chemistry,[1] $TiCl_3$ was the obvious first choice to use in trying out our idea. We therefore prepared a slurry of anhydrous $TiCl_3$ in tetrahydrofuran (THF), added 0.5 mol equiv of $LiAlH_4$, added our enone, and set about determining what had happened.

Just as we had hoped, the product obtained by $TiCl_3/LiAlH_4$ treatment of enone 1 was indeed a hydrocarbon, but much to our surprise, a reductive dimerization had occurred, giving an 80% yield of triene 2. The transformation that had occurred—reductive dimerization of a ketone to yield an alkene—was an unknown reaction at the time although two other groups, led by Mukaiyama[2] in Japan and Tyrlik[3] in Poland, made similar discoveries almost simultaneously.



1 2

We immediately recognized that the actual results of our experiment were of potentially far greater significance than the "desired" results, and we therefore began to explore the scope of the new reaction. We soon learned that the reductive coupling reaction was not limited to α,β-unsaturated ketones but was general for all manner of ketones and aldehydes. We also soon learned that many reducing agents besides $LiAlH_4$ can be used with $TiCl_3$ in the reaction, and we settled on zinc–copper couple as the safest and most convenient.

As indicated by the brief list of selected results[4] given in Table I, the coupling reaction is successful for saturated and unsaturated ketones, saturated and unsaturated aldehydes, aryl ketones and aldehydes, and diaryl ketones. One of the more interesting examples in Table I is the reaction of pentanal (entry 4), which demonstrates that the titanium-induced dicarbonyl coupling normally leads to a cis/trans mixture of olefinic products. Although the more stable isomer predominates, a control experiment has demonstrated that the observed product mixtures are kinetically formed; the titanium reagent does not isomerize olefin geometry. A second interesting result in Table I is the coupling reaction of retinal to yield β-carotene, a substance used as a yellow food-coloring agent and source of vitamin A (entry 5). This high-yield titanium-based synthesis is now licensed for use in the commercial production of β-carotene.[5]

Mechanism of the Titanium-Induced Dicarbonyl-Coupling Reaction

What is the nature of the titanium reagent, and how does the dicarbonyl-coupling reaction occur? We suggested early on[4] that titanium is present in the form of highly surface-active Ti(0) particles, a suggestion that has recently received confirmation in careful studies carried out by Geise.[6] We were also able to show early on that the overall coupling reaction takes place in two

John McMurry received his B.A. degree in 1964 from Harvard College and his Ph.D. in 1967 from Columbia University where he worked with Gilbert Stork. After 13 years on the faculty of the University of California, Santa Cruz, he moved in 1980 to Cornell University where he is presently Professor of Chemistry. Since 1975 he has made life difficult for countless authors in his capacity as Associate Editor of *Accounts of Chemical Research*.

(1) J. E. McMurry, *Acc. Chem. Res.*, 7, 281 (1974).
(2) T. Mukaiyama, T. Sato, and J. Hanna, *Chem. Lett.*, 1041 (1973).
(3) S. Tyrlik and I. Wolochowicz, *Bull. Soc. Chim. Fr.*, 2147 (1973).
(4) J. E. McMurry, M. P. Fleming, K. L. Kees, and L. R. Krepski, *J. Org. Chem.*, 43, 3255 (1978).
(5) U.S. Patent 4 225 734.
(6) R. Dams, M. Malinowski, I. Westdorp, and H. Y. Geise, *J. Org. Chem.*, 47, 248 (1982).

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