Dissolving Metal Reduction of Cyclic Ketones

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The reduction of camphor by various alkali metals in liquid ammonia has been repeated and the ratio of epimeric alcohols found to be insensitive to the nature of the metal. The relative rates of reduction of 4-methylcyclohexanone, cyclohexanone, 4-*tert*-butylcyclohexanone, 4,4-dimethylcyclohexanone, 3,3,5,5-tetramethylcyclohexanone, fenchone, norcamphor, and camphor with lithium in ammonia in the presence and absence of ethanol have been determined. In the presence of ethanol the 4-substituted cyclohexanones and cyclohexanones are reduced significantly more slowly than the bicyclic ketones. In the absence of ethanol the relative rates are nearly equal. Based on these data and a number of other experiments, a modified mechanism for these reductions is proposed.

The stereoselective reduction of cyclic ketones by dissolving metals in general, and alkali metals in liquid ammonia in particular, is generally considered to be an effective method for preparing the more stable of a pair of epimeric alcohols, assuming an unhindered ketone as substrate.[1] Although it has been pointed out that reduction of strained or sterically hindered ketones may give rise to mixtures containing the less stable alcohol,[1] the stereochemical parameters affecting these reductions are not clear, nor has a completely satisfactory mechanism been suggested for them.

Some 25 years ago it was postulated that these reductions would invariably give a preponderance of the more stable alcohol,[2] and a mechanism was proposed based on these data.[3] Subsequently, it was observed that certain bicyclo[2.2.1]heptan-2-ones afforded the less stable epimeric alcohol upon reduction with alkali metals in liquid ammonia,[4] that various 12-keto steroids would afford the 12α-(axial)-ol on reduction with either lithium in ammonia or sodium in *n*-propyl alcohol,[5] and that certain azabicyclic ketones afforded the less stable epimer with sodium in alcohol.[6] Some authors have found considerable differences in product composition as a function of metal in the reductions,[4a,c,7] while others have not.[4b]

A variety of mechanisms have been proposed in an effort to explain the course of these reductions, beginning with a two-electron reduction of the carbonyl group to a vicinal dianion, thus rationalizing the formation of the stable epimeric alcohol as the major product of these reductions.[3] A number of attempts to explain the formation of the less stable epimeric alcohols from these reductions have been made. These include the formation of intermediate organometallics,[8] initial formation of the unstable epimer followed by equilibrium,[6] kinetically controlled protonation of a vicinal dianion,[5a,9] and a variety of mechanisms which involve the intermediacy of radical anions and dianions, depending upon reaction conditions.[4b,c,7] At this point, the most plausible mechanism for the reduction of ketones by alkali metals in ammonia is probably that outlined in House[1] and restated with slight modification in our recent study of the reduction of 12-keto steroids.[5b] In this mechanism the ketone is reduced initially to a radical anion, which in the presence of an added proton donor (usually an alcohol or ammonium chloride) is rapidly protonated, reduced to an anion, and then protonated again, giving rise to a rapid, kinetically controlled reaction. In the absence of a proton donor it has been suggested that the initially formed radical anion will have a longer lifetime, presumably complexed by the metal and/or solvated by ammonia.[5b]

Although this final reaction scheme seems to adequately explain the course of the metal–ammonia reduction of ketones, several questions remain unanswered. (1) The reduction of camphor with potassium in the absence of a proton source has been reported to yield either 40% borneol[4a,c,7] or 78% borneol[4b] under apparently similar conditions. This reaction is of importance in that it and the related reductions of camphor by rubidium[4a,c] and cesium[4a,c,7] are the only reported cases in which a variation in metal causes a significant change in product ratio. (2) Although these reductions are assumed to proceed by a relatively slow, initial one-electron reduction to a radical anion, followed by a rapid protonation–reduction–protonation sequence,[1] there is little if any experimental evidence for this scheme. (3) Although it has been suggested that in the absence of an added proton source ammonia can fulfill this role,[4b] no firm evidence for this has been presented. (4) Murphy and Sullivan have reported that product ratios in the reduction of camphor with lithium vary with the addition of salts of other alkali metals.[7] These data and the mechanistic interpretation thereof imply that the reduction potential in liquid ammonia of all the alkali metals is the same, which is almost certainly not correct.[10] (5) With the exception of the observation that 4-methylcyclohexanone and 4,4-dimethylcyclohexanone reduce at the same rate in the presence or absence of an added proton donor,[4b] no information concerning the relative rates of reduction of ketones by metals in ammonia is available.

In an effort to clarify the discrepencies noted above, and to gain additional insight into the course of these reductions, we have undertaken a reexamination of the potassium–ammonia reduction of camphor, a repetition of the reduction of camphor in the presence of added salts, a study of the relative rates of reduction of representative cyclohexanones and bicycloheptanones, and related studies designed to clarify the mechanism of these useful, if not fully understood, reactions.

Results

The only major experimental discrepency in the reported product ratios of the metal–ammonia reduction of various ketones is found in the reduction of camphor by potassium in ammonia in the absence of an added proton donor. Originally, Ourisson and Rassat reported a 7:3 ratio of isoborneol/borneol,[4a] we subsequently reported a 1:4 ratio,[4b] and finally both Coulombeau and Rassat[4c] and Murphy and Sullivan[7] reported a 6:4 ratio of exo/endo alcohol. Examination of the experimental details of the latter three reductions indicated that there were significant differences in the procedures.[11] Our original work used a greater than 20-fold excess of metal,[4b] while that of Coulombeau and Rassat used an approximately twofold excess.[4c,12] Murphy and Sullivan used an even smaller excess of metal and conducted their reductions in an inert atmosphere.[7]

At least two runs were made attempting to duplicate as exactly as possible the published conditions; the results of these experiments are summarized in Table I, entries 4, 5, and 8. In all cases the product ratios were, within experimental error, the same as those reported in our earlier work,[4b] with borneol the major product in all cases. In an additional effort

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Table I. Reduction of Camphor with Various Metals in the Absence of an Added Proton Source

entry	metal	borneol, % (this work)[a]	borneol, % (reported)[a]	yield (borneol + isoborneol), %[b]
1	Li	85	84,[c] 77[d]	45[d]
2	Li	80	80[e]	45[e]
3	Na	81	81,[c] 58,[d] 60[e]	75, 80,[d,f] 75[e,f]
4	K	79	78[c]	41[c]
5	K	82	40[d]	[g]
6	K	84[h]		
7	K[i]	82	40[d]	84[m]
8	K	84	42[e]	95[g]
9	Li[j]	83[k]	53[e]	42,[k] 70[e]
10	K[i,l]	80	32[e]	82, 95[e]

[a] A variety of methods for the reductions with potassium were used in an effort to reproduce the product ratios reported in ref 4c and 7. Each entry for potassium represents a minimum of two runs under the conditions reported previously. [b] Blank runs gave greater than 90% recovery of the volatile compounds. The balance of the reaction mixture is assumed to be pinacol. If no reference is given, this work. [c] Reference 4b. [d] Reference 4c. [e] Reference 7. [f] Pinacol (20%) was reported; balance of the product is assumed to be borneols. [g] No pinacol is formed (ref 4c and 7). [h] −78 °C; the procedure is that described in ref 4c; however, 16% of unreduced ketone was obtained. [i] 99.95% (Alfa Inorganics). [j] Potassium bromide was added to the ammonia prior to the metal. [k] 20 ± 4% unreduced ketone was obtained, this work. [l] Cesium bromide was added prior to the metal. [m] No pinacol is formed;[4c,7] yield data this work.

Table II. Rates of Lithium–Ammonia Reduction of Ketones in the Presence of Ethanol

ketone	registry no.	relative rate[a]
4-methylcyclohexanone	589-92-4	1.00
4,4-dimethylcyclohexanone	4255-62-3	0.99[b]
cyclohexanone	108-94-1	1.32
fenchone	1195-79-5	2.03
3,3,5,5-tetramethylcyclohexanone	14376-79-5	2.65
camphor	76-22-2	2.88
norcamphor	497-38-1	3.12

[a] ±0.2. The rates are normalized relative to 4-methylcyclohexanone and are the average of 2–5 runs. [b] Reference 4b.

Table III. Rate of Lithium–Ammonia Reduction of Ketones in the Absence of an Added Proton Donor

ketone	relative rate[a]
4-methylcyclohexanone	1.00
4,4-dimethylcyclohexanone	0.93[b]
cyclohexanone	0.97
4-*tert*-butylcyclohexanone[c]	1.07
norcamphor	1.22
3,3,5,5-tetramethylcyclohexanone	1.31
camphor	1.36
fenchone	1.58

[a] ±0.2. The rates are normalized relative to 4-methylcyclohexanone and are the average of 2–5 runs. [b] Reference 4b. [c] Registry no., 98-53-3.

to resolve this problem, the reduction was repeated at −78 °C (Table I, entry 6) and at the usual temperature (−33 °C) using extremely pure potassium (entry 7), both reductions under Coulombeau's conditions.[12] The reduction of camphor with lithium was also repeated, and the results agreed well with those reported (Table I, entries 1 and 2),[4b,c,7] while the reduction of camphor with sodium (entry 3) gave results agreeing with our earlier results,[4b] but not with the somewhat different data of the Irish[7] or French[4c] workers.

It is difficult to explain the wide discrepencies in product ratios reported from this laboratory and those of the other two groups. No significant changes in product ratio as a function of metal have been reported for any compound other than camphor, even the closely related ketones norcamphor (bicyclo[2.2.1]heptan-2-one), 1-methylnorcamphor (1-methylbicyclo[2.2.1]heptan-2-one), and α-fenchocamphone (7,7-dimethylbicyclo[2.2.1]heptanone).[12] Although an attempt has been made to rationalize the observation that there are profound changes in product ratios in the reduction of camphor as a function of the metal which are not observed in related compounds,[4c,12] these arguments which are based on those used to rationalize the course of metal hydride reductions do not appear to be entirely satisfactory. Although it is found that of these ketones only camphor shows a significant variation in product ratio as a function of the metal, comparison of the relative values for the partial rate constants for exo vs. endo attack in metal hydride reductions[13] would predict that 7,7-dimethylnorcamphor should be similar to camphor, yet the reported data indicate that it is reduced by potassium in ammonia in the same manner as norcamphor.[4c]

We are forced to reach the conclusion after concerted efforts to reproduce the experimental results obtained by Coulombeau and Rassat[4c,12] and Murphy and Sullivan[7] that either their experimentally determined data are in error or some subtle point in both of their published experimental procedures has been overlooked.[14]

An attempt was also made to duplicate the salt effects noted by Murphy and Sullivan[7] (Table I, entries 9 and 10); again, however, no significant changes in product ratios were noted when these reductions were compared with those using lithium in the absence of added salts (entry 1). In the presence of anhydrous potassium bromide approximately 20% of unreduced camphor was recovered, and the addition of cesium bromide had no effect. In view of our failure to reproduce the data reported by these workers for these two sets of conditions, no attempts were made to repeat the other salt effect experiments reported.[7]

In an effort to gain some knowledge of the relative rates of the various steps in these reductions, and also to learn something concerning the relative reactivities of various ketones toward metals in ammonia, a series of competitive reductions using lithium both in the presence of an added proton donor (ethanol, Table II) and the absence of any proton donor other than ammonia (Table III) were carried out. Due to difficulties in the analysis (overlapping of GLC peaks) of some of the multicomponent mixtures, it was necessary to carry out the reduction of various pairs of ketones and normalize the results relative to a common standard, 4-methylcyclohexanone. Sufficient experiments were carried out using different pairs of substrate ketones to insure that the relative rates were in fact additive. Those pairs of ketones for which detailed yield data were obtained are summarized in Table IV.[15] The relative rate data were obtained by reducing a mixture of nearly equimolar amounts of each ketone with 0.5 equiv of lithium, and the rates are based on the relative amount of each ketone consumed. Examination of the data in Table II indicates that the three unhindered cyclohexanones studied were reduced at essentially the same rate, while the bicyclic ketones and 3,3,5,5-tetramethylcyclohexanone were reduced two to three times faster. In the absence of an added proton donor the rates for all of the ketones were quite similar, although again the bicyclic compounds and tetramethylcyclohexanone were reduced somewhat faster.

We were somewhat concerned that the observed relative

Table IV. Yields of Products from Competitive Lithium–Ammonia Reductions of Ketones

entry[a]	ketones	%	alcohols, %[b]	registry no.	pinacols, %[c]	registry no.
1[d]	camphor	18	18		64	5649-82-1
	norcamphor	28	18		54	21656-44-0
2[e]	camphor	25	16		59	
	norcamphor	30	15		55	
3[f]	camphor	15	20		65	
	norcamphor	26	20		54	
4[d]	norcamphor	11	27		62	
	4-*tert*-butylcyclohexanone	21	34	98-52-2	45	19437-02-6
5[d]	norcamphor	13	26		61	
	4-methylcyclohexanone	25	35	589-91-3	40	68525-20-2
6[d]	norcamphor	41	12		47	
	fenchone	29	39	1632-73-1	32	68525-21-3
7[d]	3,3,5,5-tetramethylcyclohexanone	29	41	2650-40-0	30	68525-22-4
	4-methylcyclohexanone	44	28		36	
8[d,g]	4-*tert*-butylcyclohexanone	26	40		34	
	4-methylcyclohexanone	18	49		33	
9[h]	camphor	38	35		27	
	norcamphor	32	42		26	
10[h]	camphor	59	16		25	
	fenchone	34	61		5	
11[h]	norcamphor	12	56		32	
	4-methylcyclohexanone	72	11		17	
12[g,h]	fenchone	14	78		8	
	4-methylcyclohexanone	57	14		29	
13[g,h]	3,3,5,5-tetramethylcyclohexanone	23	64		13	
14	4-methylcyclohexanone	71	11		18	

[a] Unless noted, each entry is the average of 2–4 individual experiments. Yield data are ±5%. [b] In all cases, the product ratios agreed with those reported either in this work or in references 4b, 4c, or 7. [c] By difference. [d] Ketones were stirred for 20 s before addition of lithium; ethanol was added after 30 min. [e] Ketones were stirred for 5 min before addition of lithium; ethanol was added after 30 min. [f] Ketones were stirred for 15 min before addition of lithium; ethanol was added after 30 min. [g] Data from one experiment. [h] Ketones dissolved in ethanol–ether were added to a solution of lithium in ammonia.

rate data were at least in part the consequence of preferential addition of ammonia to the carbonyl group of the more reactive of a pair of ketones. In order to explore this possibility, various runs were made in which mixtures of camphor and norcamphor were stirred for varying lengths of time before the addition of the metal (Table IV, entries 1–3). In all cases the results were identical within experimental error, thus at least minimizing the possibility that the observed rate data were an artifact.[16]

Since it also seemed to be of interest to gain some at least qualitative information concerning the absolute rates of these reactions, the reduction (See Experimental Section) of norcamphor with sodium was carried out in the absence of a proton source with excess ethanol added immediately after the ketone. No ketone was recovered, and the product distribution was indistinguishable from those reactions which had been carried out for longer periods of time. These data indicate that the reactions are extremely fast and that the usual prolonged reaction times used in synthetic work are generally unnecessary.

The relative rates of reduction of camphor and norcamphor as a function of metal were also examined (Table V), and it was found that within experimental error there were no differences in the relative rates. As expected, however,[4c,7] considerably less pinacol was obtained with potassium than with sodium or lithium in the absence of a proton donor.

In order to insure that in the absence of an added proton donor ammonia was in fact filling this role, and that the product of these reactions was the alcohol (or alkoxide) rather than a species which could participate in the reduction of a second molecule of ketone, two types of experiments were performed.[17] In the first experiment cyclohexanone was reduced with insufficient (0.5 equiv) lithium in the absence of a proton source, and then norcamphor was added. Since no reduction of the norcamphor was observed, it is apparent that the metal had been completely consumed and the cyclohexanone reduced to a species, presumably the alkoxide, which was incapable of reducing norcamphor. The possibility that under these conditions ammonia could serve as a proton donor was confirmed when it was found (Table VI) that reduction of fenchone (1,3,3-trimethylbicyclo[2.2.1]heptan-2-one), a nonenolizable ketone, using insufficient lithium with neither a proton donor present nor added until after evaporation of the ammonia gave a good yield (86%, based on ketone consumed) of alcohol. 4-*tert*-Butyl- and 3,3,5,5-tetramethylcyclohexanone were reduced under similar conditions (Table VI); however, it was qualitatively observed that in the reduction of 4-*tert*-butylcyclohexanone the blue color of the dissolved metal took considerably longer to fade than it did in the case of fenchone, tetramethylcyclohexanone, or the other bicyclic compounds. The yield data were consistent with those for other compounds, and it was subsequently found that in the reduction of this compound or 4-methylcyclohexanone with approximately 1 equiv of lithium in the absence of an added proton donor that the blue color remained after 30 min. Isolation of the products showed that approximately 25% of unreduced ketone was obtained under these conditions (Table VI). A consideration of the stoichiometry of these reductions indicates that for every equivalent of alcohol produced in the absence of an added proton donor, 2 equiv of metal amide are formed. A 1-equiv amount of amide will certainly react with product alcohol to produce the alkoxide, and the second can then react with unreduced ketone to form the enolate, which is not reduced under the conditions of these reactions.[18]

Discussion

A consideration of the results summarized in Tables I–VI and the other data discussed above leads to several conclusions. First, there appears, at least in our hands, to be no sig-

Table V. Rates of Reduction of Camphor and Norcamphor as a Function of Metal. No Added Proton Source

metal	% pinacol[b] camphor	% pinacol[b] norcamphor	relative rate[a]
Li	63	54	1.12
Na	33	50	1.19
K	6	20	1.04

[a] Norcamphor = 1.00. [b] By difference based on repeated runs which gave a minimum of 90% recovery of all volatile components of the reaction mixture. The data for Li are the average of 11 runs and for Na and K of two runs. The yield data are ±5%; the relative rates are ±0.1.

Table VI. Reduction of Various Ketones with Lithium in the Absence of an Added Proton Source

ketone	equiv of Li	products (% yield) alcohol	ketone	pinacol[a]
4-methylcyclohexanone	0.97	54[b]	26	20
4-*tert*-butylcyclohexanone	0.53	35[b]	36	29
4-*tert*-butylcyclohexanone	0.94	57[b]	25	18
3,3,5,5-tetramethylcyclohexanone	0.50	31	39	30
fenchone	0.52	45[c]	52	3

[a] By difference. These figures represent a maximum yield. [b] Trans isomer only. A trace of *cis*-ol was formed. See ref 4b. [c] Endo isomer only. See ref 4c.

nificant differences in the stereochemistry of the product alcohols derived from various ketones by alkali metals in ammonia as a function of metal (Table I). In at least one case there is also no difference in the relative rates of reduction of a pair of ketones as a function of metal (Table V). There are, however, significant differences in the amount of pinacol formed as a function of both the metal (Table V)[4c,7] and the structure of the ketone (Tables IV and VI).[4c,7] The rate data in Table II in which various ketones were reduced in the presence of ethanol indicates that simple, noncrowded cyclohexanones are reduced somewhat more slowly than either the sterically distorted 3,3,5,5-tetramethylcyclohexanone[19] or the bicycloheptanones. These data are not inconsistent with the suggestion that an initial relatively slow one-electron reduction is followed by rapid protonation–reduction–protonation, leading to the product alcohol.[1,4c] As predicted by the above suggestion, the rates follow traditional "I-strain order" rather than the relative rates of reduction by sodium borohydride.[13] Although no pinacol was detected in the reduction of camphor with lithium in the presence of ammonium chloride (a very strong acid under these conditions),[7,12] in the presence of ethanol norcamphor affords 18% pinacol,[12] and the data in Table IV, entries 9–14, also provide evidence for the formation of pinacols in the presence of ethanol. These data indicate that the initially formed radical anion must have a finite lifetime in the presence of ethanol and that the rate of protonation of the radical anion is a function of the acidity of the proton donor. This has been noted earlier in the reduction of a 12-keto steroid.[5b]

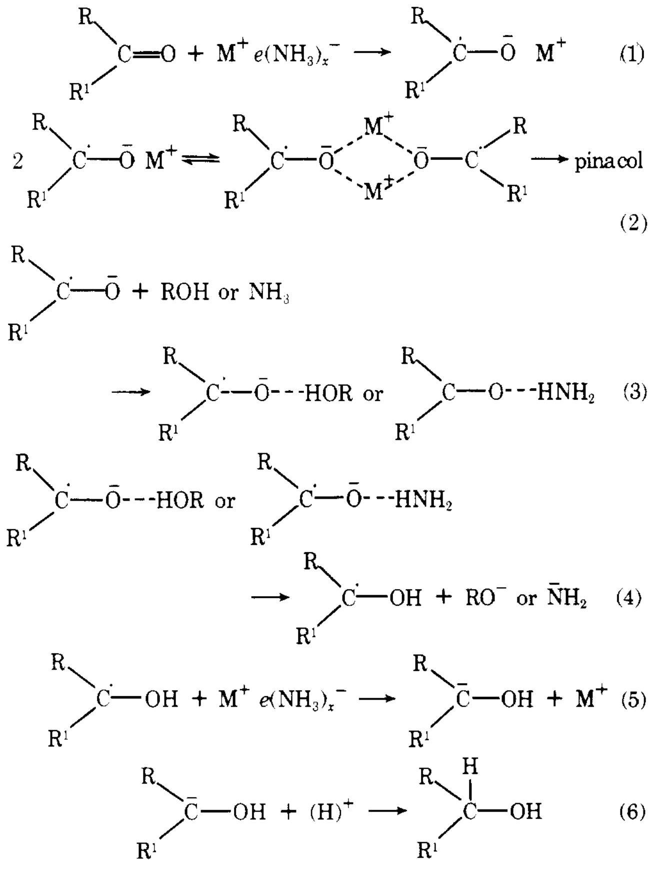
In the absence of an added proton donor, there is relatively little difference in the relative rates of reduction of the eight ketones studied. In view of the partial enolization of simple cyclohexanones under these conditions, the observed relative rates for these compounds are perhaps artificially supressed. A possible explanation for the data in Table III compared with those in Table IV is that the relative rates for formation of the radical anion and its protonation are comparable in the absence of an acid stronger than ammonia or an enolizable ketone. If the rate of the formation of the radical anion is slower for unhindered cyclohexanones than the bicyclic ketones, with the rate of protonation somewhat faster, the results presented in Table III can be explained.[20]

The reduction of the protonated radical anion must be fast relative to either of the first two steps, for even in the presence of less than an equivalent amount of metal and the absence of an added proton donor (Table VI) the product ratios are similar to those with excess metal.[4b,c] If this step were slow relative to the first step of the reduction, then reduction with less than 1 equiv of metal should lead to a buildup of radical anion and the formation of large quantities of pinacol, which is not observed.

In addition to the above data, any mechanism for the metal-ammonia reduction of ketones must be consistent with the published data for other systems. Among these data are the following. (1) Reductions of simple cyclohexanones give far more of the equatorial alcohol than is present at equilibrium.[4b] (2) Reductions of very hindered ketones (e.g., 11-keto steroids) invariably lead to the stable alcohol.[21] (3) The reduction of 12-keto steroids in which C-21 can shield the 12 position gives predominently the 12-α-ol when reduced with lithium in the presence of a proton donor, but the 12-β-ol in the absence of a proton donor.[5] (4) Variations in yields of pinacol as a function of metal, structure of the substrate ketone, and acidity of the medium are observed. (5) In the cases studied to date, bicycloheptanones invariably give the endo alcohol as the major product. A mechanism consistent with these data is presented in Scheme I. This sequence is similar to that suggested by House,[1] as modified in recent work from this laboratory.[5b]

The first step in the sequence is almost certainly reduction to the radical anion (ketyl, step 1). Direct experimental evidence for the reduction of aliphatic ketones to ketyls has been presented,[22] and the equilibrium between simple ketyls, presumably paired with the metal ion, and a dimeric species (step 2) has been studied.[23] It has been shown that ketyls

Scheme I



derived from aromatic ketones form relatively stable alcoholates,[24] and a similar solvated ketyl would presumably be the precursor responsible for the protonation leading to the product alcohols (steps 3 and 4). The dimeric species shown in step 2 has been suggested as the precursor to the pinacols,[23] and the extent of pinacol formation would then be a function of the position of equilibrium 2 and/or the geometry of the derived dimer. This geometry and the equilibrium would in turn be a function of the structure of the ketone and the nature of the metal.[22]

Protonation of the solvated radical anion, on oxygen, by either an added proton donor or ammonia would then lead to a stabilized radical (step 4).[25] This carbon radical would be reduced to the strongly basic carbanion (step 5), which would then be rapidly protonated, giving the product alcohol (step 6). Steps 3–5 must be somewhat faster than the preceding steps to explain the reductions described in Table VI (see above), and step 6 should be very rapid inasmuch as the postulated carbanion should be a much stronger base than any other species present in the system.

The reduction of the radical anion to a vicinal dianion as an explanation for the course of these reactions has been invoked by several workers;[3,4,5a,7] however, no evidence is found for dianion formation in the reduction of unsaturated ketones,[26] and it has also been pointed out that the reduction potentials of alkali metals are probably insufficient to effect the reduction of an aliphatic ketone to a vicinal dianion.[1]

According to the mechanism outlined in Scheme I, the steric course of these reactions would be controlled essentially by the establishment of equilibrium 2 and a combination of factors associated with steps 2, 3, and 4. The rate of steps 3 and 4 will be faster in the presence of a "strong" acid (ammonium chloride, ethanol) than a weak acid (ammonia). If these steps are fast relative to the establishment of equilibrium 2 or to the geometrical reorientation of the radical anion, then the steric course of the reduction will be governed by factors similar to those influencing the course of metal hydride reductions.[27] If, on the other hand, these steps are slow relative to either the establishment of equilibrium 2 or the reorientation of the radical anion, then the stereochemistry of the products will be governed by either the geometry of the dimeric radical anion or that of the solvated radical anion. This would be the case in the reduction of very hindered ketones such as the 11-keto steroids and adequately explains the results with 12-keto steroids.

The bicycloheptanones are a rather special case, in which the radical anions probably have a relatively long half-life.[28] In this case the preferential formation of the endo alcohol is probably a function of the preferred geometry of the dimeric radical anion and/or the solvated radical anion.[29] It is probably not, as had been suggested,[1,8,9] a function of complexation or reorientation of the carbanion formed in step 6. If this were the case, it would be expected that fenchone, a highly hindered ketone, should give markedly different results on reduction than does camphor or norcamphor. Actually both compounds give endo alcohol as a major product with lithium in ammonia, regardless of the conditions used.[4b,c,12] If the carbanion were the intermediate governing the steric course of the reduction, one would expect at least trends toward formation of the more stable alcohol in these systems, which are not observed.

Experimental Section[30]

Reagents. All the ketones used in this study were commercially available compounds which were purified by distillation, recrystallization, or sublimination, as appropriate, until homogenous to GLC. The alcohols used as standards were either commercial samples or were prepared by J. T. Charles.[31] Lithium wire and 99.95% potassium were obtained from the Alfa Division of the Ventron Corp., and sodium and potassium metals were obtained from Matheson Coleman and Bell. The ammonia was freshly distilled through sodium hydroxide pellets.

Reductions of Camphor with Potassium. A. Method of Huffman and Charles.[4b] To a solution of 2.74 g (70.01 mmol) of potassium in 50 mL of liquid ammonia was added 0.217 g (1.42 mmol) of camphor in 5 mL of dry ether. The reaction mixture was stirred at reflux for 30 min, ethanol was added to discharge the blue color, and the products were isolated as described.[30] Analysis of the reaction product showed 79% borneol and 21% isoborneol. Reported:[4b] 78% borneol, 22% isoborneol.

B. Method of Coulombeau and Rassat.[4c] To a solution of 0.202 g (5.17 mmol) of potassium in 50 mL of liquid ammonia was added 0.17 g (1.13 mmol) of camphor in 5 mL of dry ether. The reaction mixture was stirred at reflux for 20 min, and 3 mL of ethanol was added. The ammonia was evaporated by passing a stream of dry nitrogen through the reaction flask, and the products were isolated in the usual manner.[30] Analysis showed 82% borneol and 18% isoborneol. Reported by this method:[4c] 40% borneol, 60% isoborneol.

C. Method of Murphy and Sullivan.[7] To a solution of sufficient potassium in 50 mL of liquid ammonia to maintain a permanent blue color and maintained in a helium atmosphere was added 0.380 g (2.50 mmol) of camphor in 2 mL of dry ether. To this solution was added 0.246 g (6.29 mmol) of potassium, and the reaction mixture was stirred at reflux for 30 min. Ammonium chloride was added to quench the reaction, and the products were isolated in the usual manner.[30] Analysis showed 84% borneol and 16% isoborneol. Reported:[7] 42% borneol, 58% isoborneol. Repetition of various reductions using this procedure with lithium in the presence of potassium bromide or cesium bromide gave the results reported in Table I.

Reduction of Norcamphor with Sodium. To a solution of 0.173 g (7.52 mmol) of sodium in 50 mL of ammonia which had been stirred at reflux for 5 min was added 0.220 g (2.00 mmol) of norcamphor in 10 mL of dry ether. The reaction was immediately quenched with ethanol, and the products were isolated in the usual manner. Analysis of the reaction product showed no residual ketone, 72% *endo*-norborneol, and 28% *exo*-norborneol. The same results were obtained if the reaction was stirred for 20 or 40 min before the addition of ethanol.

Attempted Crossover Reduction of Cyclohexanone–Norcamphor. To a solution of 0.0205 g (2.95 mmol) of lithium in 50 mL of liquid ammonia was added a solution of 0.297 g (3.02 mmol) of cyclohexanone in 5 mL of ether. After 5 min, a solution of 0.330 g (3.00 mmol) of norcamphor in 5 mL of ether was added and the reaction was stirred at reflux for 30 min. The reaction was quenched by the addition of ethanol, and the products were isolated in the usual manner. Analysis of the reaction product showed no reduction of norcamphor, with 22% recovery of cyclohexanone and a 55% yield of cyclohexanol.

Competitive Reductions. A. Absence of an Added Proton Source. A solution of 2.00 ± 0.04 mmol of each ketone in 10 mL of dry ether was added to 50 mL of liquid ammonia, and the mixture was stirred for 20 s (or longer, see Tables III and V). To this solution was added, with stirring, 4.00 ± 0.04 mmol (0.5 equiv) of metal in one portion. The reaction mixtures turned blue immediately and remained blue for ca. 2 min. After 30 min, 3 mL of ethanol was added and the products were isolated and analyzed in the usual manner.

B. Presence of an Added Proton Source. These reductions were carried out in essentially the same manner as those in the absence of a proton donor; however, the ketones were added in a solution of 10 mL of dry ether and 10 mL of absolute ethanol. Following the addition of the metal, the reaction mixture was allowed to stir at reflux for 5 min after the disappearance of the transient blue color and the products were isolated and analyzed in the usual manner.

Reductions of Single Ketones with Lithium. A solution of 2.00 ± 0.04 mmol of ketone dissolved in 10 mL of ether was added to 50 mL of liquid ammonia, and the mixture was stirred for 20 s. Either 2.00 or 4.00 ± 0.04 mmol (0.5 or 1.0 equiv) of lithium was added, and the reaction was stirred at reflux for 30 min. In those cases (see Results) in which the solution remained blue, sufficient ethanol was added to discharge the color and the products were isolated and analyzed in the usual manner.

Registry No.—Li, 7439-93-2; Na, 7440-23-5; K, 7440-09-7; borneol, 507-70-0; isoborneol, 124-76-5; *endo*-norborneol, 497-36-9; *exo*-norborneol, 497-37-0; cyclohexanol, 108-93-0; ethanol, 64-17-5.

References and Notes

(1) H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, Menlo Park, Calif., 1972, pp 152–158, summarizes the work in this area prior to about 1970.

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(8) D. H. R. Barton and G. A. Morrison, *Fortschr. Chem. Org. Naturst.*, **19**, 223–225 (1961).

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(10) (a) A. P. Krapcho and A. A. Bothner-By, *J. Am. Chem. Soc.*, **81**, 3655 (1959); **82**, 751 (1960). (b) J. F. Eastman, C. W. Keenan, and H. V. Secor, *ibid.*, **81**, 6253 (1959). (c) C. Moreau in "Metal–Ammonia Solutions", G. Lepoutre and M. J. Sienko, Eds., W. A. Benjamin, New York, 1964, p 88, gives a reduction potential of −2.34 V for lithium, −1.89 V for sodium, −2.04 V for potassium, −2.06 V for rubidium, and −2.08 V for cesium. See also ref 1.

(11) The original work reported in ref 4a was never published in its entirety, and consequently no attempt was made to reproduce the exact experimental conditions.

(12) A. Coulombeau, Doctoral Thesis, University of Grenoble, 1968. We would like to thank Dr. A. Rassat for a copy of this thesis and for a helpful conversation concerning the methods reported in ref 4c.

(13) H. C. Brown and J. Muzio, *J. Am. Chem. Soc.*, **88**, 2811 (1966).

(14) Some years ago, one of us (J.W.H.) and Professor Rassat concluded after a prolonged discussion that these differences in experimental results were probably due to either differences in experimental procedures or purity and/or source of reagents. While the former explanation can be almost certainly excluded on the basis of the present work, the latter remains a viable alternative explanation. A second alternative, though not a necessarily satisfactory explanation, was suggested by the late Professor G. M. Kosalopoff of Auburn University (private communication to J.W.H.). This invokes so called "proximity effects", in which a given reaction follows one course in the Eastern Hemisphere and another in the Western Hemisphere.

(15) Several other combinations of the same ketones were also reduced, but detailed yield data were not obtained due to analytical difficulties. These data are included in the values given in Tables II and III.

(16) This possibility can, of course, not be rigorously precluded. If the ketone–carbinolamine equivalent were established within 20 s at -33 °C, then the data recorded in Tables II and III would represent a complex situation reflecting the equilibrium constant for carbinolamine formation and the relative rates of reduction. An experimental approach to the resolution of this dilemma does not appear to be immediately obvious.

(17) The alkoxide–ketone equilibrium question was resolved earlier,[4b] but the problem of stabilized radical anion–ketone equilibrium was not.

(18) For easily enolizable ketones (e.g., cyclohexanones) the possibility that the ketone may also serve as a proton donor cannot be excluded. Although ketones in general are stronger acids than ammonia, ammonia is present in far greater concentration, and the carbanion intermediate in these reductions is an extremely strong base. This anion can be protonated by ammonia, as in the reduction of fenchone, and it has been observed that in the reduction of unsaturated ketones ammonia can serve as a proton donor: G. Stork, P. Rosen, N. Goldman, and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965).

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(20) The relatively low yields of pinacols obtained with 4-methyl- and 4-*tert*-butylcyclohexanone (Table VI) relative to camphor and norcamphor (ref 4c and 7) are also consistent with this explanation.

(21) (a) F. Sondheimer, O. Mancera, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **75**, 1282 (1953); (b) S. Bernstein, R. Littell, and J. H. Williams, *ibid.*, **75**, 1481 (1953).

(22) N. Hirota and S. O. Weismann, *J. Am. Chem. Soc.*, **86**, 2538 (1964), and earlier papers in this series.

(23) N. Hirota, *J. Am. Chem. Soc.*, **89**, 32 (1967).

(24) (a) K. Nakamura, B. F. Wong, and N. Hirota, *J. Am. Chem. Soc.*, **95**, 6919 (1973); (b) K. S. Chen, S. W. Mao, K. Nakamura, and N. Hirota, *ibid.*, **94**, 4419 (1972).

(25) Various workers[4,7] have suggested protonation on carbon. This suggestion was criticized by House[1] on the basis of a charge localization argument. However, a better argument is based on the relative stabilities of the carbon and oxygen radicals derived from protonation on oxygen or carbon, respectively. Based on bond dissocation energies, the carbon radical is approximately 10 kcal/mol more stable than the oxygen radical [J. A. Kerr, *Chem. Rev.*, **66**, 465 (1966)], and assuming the conventional argument relating the nature of the transition state and activation energy, should be formed more rapidly. J. F. Garst and C. D. Smith, *J. Am. Chem. Soc.*, **98**, 1520 (1976), have found that benzophenone ketyl reacts with alkyl iodides exclusively at oxygen.

(26) K. Bowers, R. W. Giese, J. Grimslow, H. O. House, N. H. Kronberger, and D. K. Roe, *J. Am. Chem. Soc.*, **92**, 2783 (1970).

(27) This hypothesis is discussed in ref 5b and references therein.

(28) The relative rates of borohydride reduction[13] show that cyclohexanone is reduced nearly 100 times faster than norcamphor and nearly 10^5 times faster than camphor.

(29) Since relatively little is known concerning the exact geometry of these species,[22-24] it is difficult to speculate on the exact nature of effects responsible for the preferential formation of the endo alcohols. However, one can postulate an endo-like geometry for the radical anion which minimizes both the interactions with adjacent hydrogens, bridge substituents, and the endo hydrogen at C-6. A variation of this argument is presented in ref 4c.

(30) Melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Vapor phase chromatographic analyses were performed on an F&M Model 810 chromatograph using a 10 ft × $\frac{1}{8}$ in. column packed with 10% Carbowax 20M on Chromosorb W, helium as the carrier gas, with a flame ionization detector. The chromatograms were integrated by the width at half-height method and/or the relative weight of the peak. The two methods gave results which agreed within ±1% and which agreed with mixtures of known compositions within ±1%. All reactions were carried out in apparatus which had been flame-dried in a stream of dry nitrogen, and the reaction mixtures were protected from atmospheric moisture by means of a potassium hydroxide drying tube. Following the completion of each reduction, the ammonia was allowed to evaporate and the products were isolated by means of extraction with ether. The ethereal extracts were dried over magnesium sulfate, and the ether was removed by slow distillation through a Vigreux column. Blank runs using mixtures of ketones and alcohols of known concentrations indicated that for all of the compounds discussed, with the exception of cyclohexanone, the product ratios are accurate to ±1%. For cyclohexanone, the accuracy is ±4%. In those experiments in which yield data were obtained, a known amount of menthol was added as an internal standard. Blank runs indicate that the total recovery of all volatile products is in excess of 90%.

(31) J. T. Charles, Ph.D. Dissertation, Clemson University, 1968. See ref 4b.