Use of the latter technique[8] with cyclohexene and styrene yields, respectively, the dinitrogen trioxide adduct (10%) of cyclohexene and a product whose infrared spectrum is consistent with the dinitrogen trioxide adduct of styrene but which could not be purified because of its extremely low solubility.

It has been suggested that nitrosyl formate does not have an independent existence but the reaction proceeds by addition of a positive species, NO^+, to the double bond followed by termination by the most populous nucleophile present, formic acid. Addition of nitrosyl chloride to cyclohexene in a large molar excess of formic acid (approximately 15:1) yields only the nitrosyl chloride adduct, dimeric *trans*-2-chloronitrosocyclohexane, in good yield; no formic acid addition is observed. We conclude tentatively that nitrosyl formate must have a finite lifetime, albeit short, but until the compound is prepared and added to double bonds we cannot be positive (see later discussion, however, on nitrosyl benzoate).

Perchloric acid was chosen as the strong acid to catalyze the decomposition of isoamyl nitrite by acetic acid because the perchlorate ion is a poor nucleophile and should not react with intermediate nitrosonium ions or ion pairs derived from the olefins. When a solution of 2,3-dimethyl-2-butene in isoamyl nitrite is added to a cold acetic acid solution containing a catalytic quantity of 70% perchloric acid, an immediate blue color develops indicative of a monomeric nitroso compound (tertiary nitroso group), and work-up yields the expected product, 2,3-dimethyl-2-acetoxy-3-nitrosobutane (**12**), a royal blue liquid.

Alternatively, reaction of an olefin with a stable nitrosonium salt in which the anion is not a nucleophile, for example, nitrosonium tetrafluoroborate, should yield a nitrosonium intermediate ion pair capable of reaction with a nucleophile, such as acetic acid or acetate ion. Reaction of 2,3-dimethyl-2-butene with nitrosyl tetrafluoroborate and sodium acetate–acetic acid yields the expected 2,3-dimethyl-2-acetoxy-3-nitrosobutane (**12**), identical in every respect with the product from the olefin and isoamyl nitrite–acetic acid–perchloric acid.

Finally, to ascertain whether preformed nitrosyl acylates can add to double bonds, nitrosyl benzoate was prepared.[9] Its addition to 2,3-dimethyl-2-butene is a facile reaction at 0°, and a single product, 2,3-dimethyl-2-benzoyloxy-3-nitrosobutane (**13**), is obtained in essentially quantitative yield. It is a royal blue liquid that is readily hydrolyzed even on exposure to moist air. Its nmr spectrum shows two singlets at 1.0 and 2.12 ppm (6 H each) and a multiplet at 7.5 ppm (5 H). The ir, uv, and visible spectra are also consistent with the proposed structure. Ir shows nitroso absorption at 1550, ester at 1710 and 1130, and monosubstituted benzene at 710 cm^{-1}. The visible spectrum shows a weak band at 702 mμ (ε 19) and the uv absorption peaks expected for ester and benzene ring absorptions.

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The Metal–Ammonia Reduction of Ketones[1]

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Abstract: The reductions of a series of cyclohexanones, norbornanone, and camphor by alkali metals in liquid ammonia have been carried out. The reductions of the cyclohexanones afford a distribution of products corresponding to nearly exclusive formation of the equatorial alcohol based on the ground-state conformer population of the ketone. Norcamphor gives 68–91% of the thermodynamically less stable *endo*-norborneol, depending on the conditions of the reduction, while camphor affords nearly an equilibrium mixture of borneol and isoborneol. A reaction path consistent with these data is suggested.

Following Barton's classical papers which laid the foundations for that area of organic chemistry known as conformational analysis,[3] it has been widely accepted that dissolving metal reductions of saturated cyclic ketones give rise to either exclusively the thermodynamically stable alcohol or to mixtures in which this isomer predominates.[3,4] In spite of several cases where mixtures rich in the thermodynamically unstable alcohols are obtained from either metal–ammonia[5] or sodium–alcohol reduction[6] of a ketone, even contemporary workers state that these reductions invariably afford the stable epimer.[7]

A mechanism for these reactions, and also the reduction of α,β-unsaturated ketones, was suggested some years ago by Barton,[8] and later explanations for the

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(1) This work was supported in part by Career Development Award K3-GM-5433 from the National Institutes of Health.

(2) NASA Fellow, 1964–1967.

(3) (a) D. H. R. Barton, *Experientia*, **6**, 316 (1950); (b) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(4) (a) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956); (b) W. Klyne, *Progr. Stereochem.*, **1**, 57, 74 (1954); (c) W. G. Dauben and K. S. Pitzer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 47; (d) W. Huckel, M. Maier, E. Jordan, and W. Seegar, *Ann.*, **616**, 46 (1958).

(5) (a) G. Ourisson and A. Rassat, *Tetrahedron Lett.*, **21**, 16 (1960); (b) J. W. Huffman, D. M. Alabran, T. W. Bethea, and A. C. Ruggles, *J. Org. Chem.*, **29**, 2963 (1964).

(6) (a) H. O. House, H. C. Miller, C. G. Pitt, and P. P. Wickham, *ibid.*, **28**, 2407 (1963); (b) A. C. Cope, J. M. Grisar, and P. E. Peterson, *J. Amer. Chem. Soc.*, **82**, 4299 (1960).

(7) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, **23**, 3511 (1967).

(8) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

Table I

Ketone	Proton source	Stable alcohol,[a] %	Method of reduction[b]
4-*t*-Butylcyclohexanone	*n*-Propyl alcohol	99	A
4-*t*-Butylcyclohexanone	*t*-Butyl alcohol	98	A
4-Isopropylcyclohexanone	Ethyl alcohol	99	A
4-Methylcyclohexanone	Ethyl alcohol	99	A
3-Methylcyclohexanone	Ethyl alcohol	94	A
3-Methylcyclohexanone	NH_4Cl	94	A
3-Methylcyclohexanone	Ethyl alcohol	94	B
3-Methylcyclohexanone	NH_4Cl	95	B
2-Methylcyclohexanone	Ethyl alcohol	99	A
2-Methylcyclohexanone	NH_4Cl	99	A
2-Methylcyclohexanone	Ethyl alcohol	99	B
2-Methylcyclohexanone	NH_4Cl	99	B
3,3,5-Trimethylcyclohexanone	Ethyl alcohol	99	A
3,3,5-Trimethylcyclohexanone	Ethyl alcohol	99	B

[a] These figures represent the ratio of stable to unstable alcohol in the reaction mixture. [b] See text.

formation of unstable epimers in the reduction of saturated ketones were offered by House and Barton.[6a,9,10] Although the stereochemistry of the reduction of α,β-unsaturated ketones has now been clarified,[11] no satisfactory explanation for the steric course of the reduction of saturated cyclic ketones with active metals in ammonia has yet been suggested.

Although there are numerous uses of these reductions cited in the literature and they have found considerable utility in the steroid field, there have apparently been no detailed studies of these reactions described to date. We have undertaken such a study with the objective of defining more clearly the steric parameters affecting these reactions as well as attempting to clarify the effects of various metals and proton donors on the course of the reductions.

Results

It was originally felt that the ideal substrate ketone for the purpose of this study would be a simple, conformationally homogeneous cyclohexanone and a series of reductions of 4-*t*-butylcyclohexanone were carried out. These reductions were effected with lithium in ammonia, using one of two basic procedures. The first of these (method A, see Experimental Section) entailed the addition of the active metal (lithium, sodium, potassium, rubidium) to a stirred mixture of ketone, cosolvent (ether), and a proton donor (ammonium chloride or an alcohol) in distilled and dried liquid ammonia. The second procedure (method B) was carried out by stirring the ketone with the active metal for 30 min, then adding the proton source.

The reduction of 4-*t*-butylcyclohexanone by procedure A, using either *n*-propyl alcohol or *t*-butyl alcohol as a proton source gave 99% of the *trans*-alcohol. When other simple cyclohexanones were reduced by either procedure, there was formed a minimum of 94% of the stable alcohol. These results are summarized in Table I. To have reference samples available as gas chromatography standards, pure samples of the appropriate cyclohexanols were either obtained from commercial sources or prepared from the corresponding ketone. Lithium–ammonia reduction of the ketone gave the stable epimeric alcohol, and the less stable isomer was prepared from the tosylate of the former by treatment with aqueous dimethylformamide.[12]

In order to ensure that the process observed was essentially irreversible, 4-*t*-butylcyclohexanone was reduced in the presence of *cis*-4-*t*-butylcyclohexanol, and it was found that the *cis*-alcohol was recovered unchanged. Also, in order to exclude the possibility that one conformer of the ketone was being reduced much more rapidly than the other,[13] a mixture of 4-methylcyclohexanone and 4,4-dimethylcyclohexanone was reduced with less than an equivalent amount of lithium. Since the molar ratio of product alcohols was the same as that of the ketones subjected to reduction, it is clear that no unusual alkyl ketone effects are operative in these reductions.

Since there were no noticeable variations in product ratios with variation in proton donor or method of reduction in the substituted cyclohexanones, a different substrate ketone, norcamphor, was studied. The results of these reductions are summarized in Table II. It will be noted that in this case the amount of the thermodynamically stable *exo*-alcohol ranges from 9 to 32%.

Since the yields in the reductions are not high (11–58%), an effort was made to ensure that the data obtained had real significance. First, duplicate runs were carried out and the ratio of product alcohols was found to be reproducible to within ±1%. Also, since

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(9) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 55. Although this mechanism is suggested for metal–alcohol reduction, in both these and metal–ammonia reductions the reactive species is almost certainly a solvated electron and the mechanisms should be similar: D. C. Walker, *Quart. Rev.* (London), **21**, 79 (1967), and references therein.

(10) D. H. R. Barton and G. A. Morrison, "Fortschritte der Chemie Organische Naturstoffe," Vol. XIX, Springer Verlag, Vienna, 1961, pp 223–225. These authors suggest the intermediacy of organometallic compounds; however, there appear to be no data to support this hypothesis.

(11) (a) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965); (b) M. J. T. Robinson, *Tetrahedron*, **21**, 2375 (1965); (c) S. K. Malhotra, D. F. Moakley, and F. Johnson, *Tetrahedron Lett.*, 1089 (1967).

(12) R. T. Blickenstaff and F. C. Chang, *J. Amer. Chem. Soc.*, **80**, 2906 (1958). Although the yields of cyclohexanols prepared by this procedure are not high, this method is excellent for preparing pure samples of the desired compounds.

(13) In other words, if it is assumed that the principal conformers of 4-methylcyclohexanone are i and ii, then it seemed essential to know if

i ii

one conformer was reduced at a considerably different rate then the other.

Table II

Metal	Proton source	*exo*-Nor-borneol,[a] %	Yield (*exo* + *endo*), %	Method of reduction[b]
Li	NH_4Cl	11		A
Li	Ethyl alcohol	15	58	A
Li	*t*-Butyl alcohol	20		A
Li	NH_4Cl	29	22	B
Li	Ethyl alcohol	27	*c*	B
Li	*t*-Butyl alcohol	32	36	B
Na	NH_4Cl	11		A
Na	Ethyl alcohol	15	42	A
Na	*t*-Butyl alcohol	18	13	A
Na	NH_4Cl	29	11	B
Na	Ethyl alcohol	29		B
Na	*t*-Butyl alcohol	27	22	B
K	NH_4Cl	10		A
K	Ethyl alcohol	10	50	A
K	*t*-Butyl alcohol	14		A
K	NH_4Cl	19		B
K	Ethyl alcohol	20		B
K	*t*-Butyl alcohol	29	18	B
Rb	Ethyl alcohol	9		A
Rb	Ethyl alcohol	9		B

[a] These figures represent the ratio of *exo*- to *endo*-norborneol. [b] See text. [c] Affords 28% yield of the pinacol.

Table III

Metal	Proton source	Borneol,[a] %	Yield (borneol + isoborneol), %	Method of reduction[b]
Li	NH_4Cl	90	64	A
Li	Ethyl alcohol	89	42	A
Li	*t*-Butyl alcohol	87	32	A
Li	NH_4Cl	85		B
Li	Ethyl alcohol	84[d]	*c*	B
Li	*t*-Butyl alcohol	86		B
Na	NH_4Cl	89	62	A
Na	Ethyl alcohol	87		A
Na	*t*-Butyl alcohol	85		A
Na	NH_4Cl	82		B
Na	Ethyl alcohol	81[e]		B
Na	*t*-Butyl alcohol	80		B
K	NH_4Cl	88		A
K	Ethyl alcohol	87		A
K	*t*-Butyl alcohol	82		A
K	NH_4Cl	81		B
K	Ethyl alcohol	78[f]	41	B
K	*t*-Butyl alcohol	79		B

[a] These figures represent the ratio of borneol to isoborneol. [b] See text. [c] Affords 17% of the pinacol. [d] Ourisson and Rassat[5] report 81%. [e] Lit.[5] 60%. [f] Lit.[5] 30%.

Table IV[a]

Metal	Cosolvent	*exo*-Nor-borneol, %	Yield (*exo* + *endo*), %
Li	None	17	58
Li	Ether	13	55
Li	Tetrahydrofuran	21	69
Na	None	14	39
Na	Ether	14	42
Na	Tetrahydrofuran	15	34

[a] All reductions were performed by method A, ethyl alcohol is present as a proton donor in all cases.

both *exo*- and *endo*-norborneol are quite volatile, a blank run was carried out using a predetermined ratio of norborneols. The ratio of recovered alcohols was within ±2% of the original mixture although there had been some loss of material. Finally, since the method used to calculate yields permitted the estimation of all the volatile products, apparently material was either being lost during the isolation of products or in the formation of nonvolatile products (or both). In one rather large-scale run, an effort was made to isolate the nonvolatile product(s) and a compound having the properties of norcamphorpinacol was obtained in 28% yield.

Since Ourisson's original work demonstrating that metal–ammonia reduction of ketones did not necessarily produce the more stable alcohol[5a] indicated rather dramatic changes in product ratio in going from lithium to potassium in the reduction of camphor, the reduction of norcamphor under a variety of conditions was carried out (Table II). The rather large changes in product ratio with changes in reaction condition were not reflected in these reductions, and a similar series of reductions of camphor were carried out, the results of which are listed in Table III. In two of the three cases where an attempt was made to reproduce the results of the French workers, there was a considerable deviation from the earlier data.[14] As in the case of norcamphor, it was again possible to obtain camphorpinacol from these reductions.

A final variable to be examined was the effect of cosolvent on both the course and yield of these reductions. It has been reported that in the reduction of certain steroidal ketones, the use of ether as a cosolvent promotes the formation of pinacols, while tetrahydrofuran retards this bimolecular reduction.[15] A series of reductions of norcamphor were carried out by the procedure referred to as method A, above, using ethyl alcohol as a proton donor. These results are summarized in Table IV, and it will be noted that there were no dramatic changes in either product ratio or yield.

Discussion

Two reaction paths for the dissolving metal reduction of ketones have previously been presented in the literature. The first of these, that suggested by Barton,[8] proceeds by a stepwise two-electron reduction of a ketone to the corresponding dianion. This species is presumed to be tetrahedral and to exist in the thermodynamically preferred steric orientation. Protonation of this dianion should afford principally the alkoxide ion derived from the more stable alcohol.

A later reaction path proposed by House[6a,9] suggests a one-electron transfer to give a radical anion which is then protonated from the least hindered side, giving in most cases the thermodynamically unstable alkoxide. It was assumed that this alkoxide, in most cases, is isomerized *via* a hydride transfer path, to the stable alcohol. In the case of those alcohols which are oxidized with difficulty to the ketone, the isomerization would not be expected and the less stable alcohol would be obtained.

The mechanism suggested by Barton[8] fails to explain the formation of the less stable of a pair of epimeric alcohols as was observed in the reduction of certain

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(14) Neither we nor Professors Ourisson and Rassat can explain these discrepancies (G. Ourisson and R. Rassat, private communications). The differences may lie in either the purity of the ammonia or the metal, or may be of a more subtle nature.

(15) J. Fried and N. A. Abraham, *Tetrahedron Lett.*, 28, 1879 (1964).

12-keto steroids[5b] and certain ketones related to marrubiin.[16] The sequence suggested by House,[6a,9] while satisfactorily explaining the production of a preponderance of the less stable alcohol, predicts that an equilibrium mixture of alcohols will be the result of dissolving metal reductions of ketones in most cases. A comparison of the results obtained in the metal–ammonia reduction of simple cyclohexanones (Table I) with the equilibrium ratios of these alcohols (Table V) indicates that *in no case is the equilibrium concentration of the more stable alcohol obtained.* Instead almost exclusive (98%) formation of the equatorial alcohol after making the appropriate corrections for the ground-state conformational equilibrium of the substrate ketone[17] is observed.

Table V

Ketone	Stable alcohol at equilibrium,[a] %
4-*t*-Butylcyclohexanone	88
4-Methylcyclohexanone	84
4-Isopropylcyclohexanone	86
3-Methylcyclohexanone	87
2-Methylcyclohexanone	90
3,3,5-Trimethylcyclohexanone	99

[a] Calculated for −33° using the data of E. L. Eliel, S. H. Shroeter, T. J. Brett, F. J. Biros, and J. C. Richer, *J. Amer. Chem. Soc.*, **88**, 3327 (1966).

The reductions of norcamphor summarized in Table II are noteworthy in that the less stable *endo*-norborneol predominates *under all conditions.*[18] Although rather low yields and relatively small differences in product ratios between runs carried out using only slightly differing conditions are observed, several over-all trends are noticeable.[19] These are the use of metals of lowering reducing power (*e.g.*, potassium or rubidium)[20] gives more of the thermodynamically unfavored *endo*-alcohol. By decreasing the acidity of the proton donor, more of the *exo*-alcohol is formed, and carrying out the reaction in the absence of an external proton source leads principally to a decrease in the yield of monomeric reduction products, almost certainly due to the formation of pinacols. In those cases where the proton donor was added after the ketone and metal, the percentage of *exo*-norborneol is greater and there is relatively little variation in product ratio with variation in proton donor. It seems probable that in these cases ammonia, a very weak acid, is serving as a proton donor.[21]

The similar series of reductions, carried out on camphor (Table III), gave markedly different results in that borneol, the stable *endo*-alcohol, is the principal product.[22] The yields in this series are higher than those in the norcamphor series and again a pinacol is isolated under certain conditions. The changes in product ratio with variation in metal and proton donor are less than in the case of the norcamphor reductions; however, the addition of the proton donor to the solution of metal and ketone gives a product ratio very close to the calculated equilibrium mixture of alcohols.

To explain these results we wish to suggest the following reaction path. First, the ketone reacts with the metal (or an appropriate solvated electron) to give a radical anion. This radical anion has open to it several competitive reaction paths: first, dimerization to the pinacol; second, protonation to give an alkoxide radical, and finally, reduction to a vicinal dianion. Protonation of the radical anion would give rise to an alkoxy radical which would then be further reduced to an alkoxide ion. This path would result in protonation from the least hindered side of the carbonyl carbon atom and would give product ratios similar to those observed in the metal hydride reduction of ketones. In the case of cyclohexanones this will result in principally axial proton attack,[23] while in norcamphor the proton will be added largely from the *exo* side to give *endo*-norborneol.[24] Finally, reduction of the radical anion to the dianion will give a more or less tetrahedral species which should give rise to approximately an equilibrium mixture of products as suggested by Barton.[8] If it is assumed that the relative rates of protonation of a radical anion and its reduction to a dianion are of the same order of magnitude, with protonation normally being the faster process, but with the reverse being the case for ketones with a sterically hindered carbonyl group, then our results may be readily interpreted.

It has been shown[25] that camphor reacts much more slowly with sodium borohydride than does norcamphor. This same difference in reactivity should apply to the protonation of the radical anions derived from these ketones, and if the rate of protonation of the camphor radical anion is suppressed, then the principal path for reduction would be that through the dianion, leading to the observed near-equilibrium distribution of product alcohols (Table III). A similar argument may be applied to the dissolving metal reductions of 11-keto steroids which afford the 11α-ols.[26–32] In this instance

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(16) D. M. S. Wheeler, M. M. Wheeler, M. Fetizon, and W. H. Castione, *Tetrahedron*, **23**, 3909 (1967).

(17) The only ketone reduced which does not contain at least 98% of the conformer with the equatorial alkyl group at −33° is 3-methylcyclohexanone. For this compound ΔG_{CH_3} is assumed to be 1.27 kcal/mol, corresponding to a 3-alkyl ketone effect of 0.6 kcal/mol (E. L. Eliel, N. C. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, p 114).

(18) From the data of Eliel (ref *a*, Table V) the equilibrium mixture at −33° should contain 99% *exo*-norborneol.

(19) Deviations between duplicate runs carried out more than 1 year apart agreed within ±1%. A blank run indicated that the mechanical loss of product alcohols would not affect the results more than ±2%.

(20) A. P. Krapcho and A. A. Bothner-By [*J. Amer. Chem. Soc.*, **81**, 3658 (1959)] have found that lithium reduces benzene considerably faster than does potassium. See also J. F. Eastham, C. W. Keenan, and H. V. Secor, *J. Amer. Chem. Soc.*, **81**, 6253 (1959), and A. P. Krapcho and A. A. Bothner-By, *ibid.*, **82**, 751 (1960).

(21) It has been observed that ammonia can serve as a proton donor in the reduction of α,β-unsaturated ketones.[11a]

(22) The equilibrium concentration of borneol at −33° can be calculated to be 80% using the data of C. F. Wilcox, M. Sexton, and M. F. Wilcox, *J. Org. Chem.*, **28**, 1079 (1963).

(23) J. C. Richer, *ibid.*, **30**, 324 (1965). See also S. R. Landor and J. P. Regan, *J. Chem. Soc., C*, 1159 (1967).

(24) P. von R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 701 (1967), and references therein.

(25) H. C. Brown and J. Muzzio, *ibid.*, **88**, 2811 (1966).

(26) W. S. Allen, S. Bernstein, M. Heller, and R. Littell, *ibid.*, **77**, 478 (1955).

(27) F. Sondheimer, O. Mancers, G. Rosenkranz, and C. Djerassi, *ibid.*, **75**, 1282 (1953).

(28) K. Heusler, H. Heusser, and R. Anliker, *Helv. Chim. Acta*, **36**, 652 (1953).

(29) F. Sondheimer, R. Yashin, G. Rosenkranz, and C. Djerassi, *J. Amer. Chem. Soc.*, **74**, 2696 (1952).

(30) H. L. Herzog, M. A. Jevnik, and E. B. Hershberg, *ibid.*, **75**, 269 (1953).

(31) J. B. Bream, D. C. Eaton, and H. B. Henbest, *J. Chem. Soc.*, 1974 (1957).

(32) H. L. Heuser, R. Anliker, and O. Jeger, *Helv. Chim. Acta*, **35**, 1537 (1952).

sodium borohydride reduces the ketone extremely slowly to give the highly hindered axial 11β-ol. In terms of the above mechanism for metal–ammonia reductions, the rate of protonation of the radical anion would be greatly suppressed, either due to steric hindrance, or more probably to a dramatic increase in activation energy for protonation due to the incipient axial–axial interactions with C-18 and C-19 in the transition state. The suppression of the rate of this path would again be expected to lead to formation of the tetrahedral dianion with the formation of an equilibrium mixture of alcohols. In the case of an 11-substituted steroid this path would be expected to result in the almost exclusive formation of the equatorial 11α-ol, as is observed.

The variations in method of reduction, acidity of proton donor and reductive power of the metal in the norcamphor series (Table II) agree well with this reaction path. The addition of a proton source after the reaction has proceeded for time (method B) would suppress the rate of protonation of the radical anion, lead to a greater percentage of the more stable alcohol and decrease the over-all yield due to pinacol formation. The use of less powerful reducing agents (*e.g.*, potassium and rubidium)[20] would be expected to retard the rate of dianion formation and lead to an increase in the amount of the alcohol formed by approach of the proton from the least hindered side. The use of less acidic proton donors would suppress the rate of protonation and would lead to the formation of an increased amount of the more stable alcohol. The data in the camphor series (Table III) do not show a sufficient variation with changing reaction conditions to permit any reasonable conclusions to be drawn from them.[33]

This reaction sequence also appears to explain satisfactorily the apparently anomalous results obtained in the reduction of 12-keto steroids.[5b] Those compounds similar to 12-cholanone, having two alkyl substituents at C-20 and a "free" side chain, are reduced by both dissolving metals and sodium borohydride to the unstable 12α-ols while those with either one alkyl substituent at C-20 (pregnanes) or with the side chain held rigidly (hecogenin) are reduced by both methods to give largely the equatorial 12β-ol. The metal–ammonia reductions of 12-keto steroids then appear not to be anomalous, but are instead a case of protonation of the radical anion from the least hindered side.[34]

Conclusions

It has been demonstrated both in this work and in that reported earlier[5] that, contrary to the published generalizations,[3,4,8,10] the reductions of saturated, cyclic ketones by active metals in ammonia *do not necessarily afford the more stable alcohol.* Rather, in the case of simple unhindered ketones the product distribution will be governed by the direction of attack of a proton on a species (probably a radical anion) obtained by the reaction of the ketone with either the dissolved metal or a solvated electron. In the case of a hindered ketone, or one which reacts sluggishly at the carbonyl carbon atom, the product ratio will tend to approach that of an equilibrium mixture.

Although the reaction path presented here may not be correct in detail, it satisfactorily accounts for the products obtained, not only in the experiments reported in this paper, but also those reported elsewhere in the literature.

Experimental Section[35]

Reagents. All the ketones used in this study with the exception of 4,4-dimethylcyclohexanone were obtained from commercial sources. These materials, if not homogeneous to glpc, were purified by distillation or recrystallization.

4,4-Dimethylcyclohexanol was prepared by the following modification of the method of Eliel.[36]

Freshly distilled methyl vinyl ketone (70 g) was mixed with 72 g of freshly distilled isobutyraldehyde, 100 ml of water, and 50 ml of methanol. This solution was added slowly to a well-stirred solution of 3.7 g of potassium hydroxide in 20 ml of methanol and 5 ml of water, and the temperature was raised slowly to 80°. After cooling, 100 ml of water was added, the mixture was extracted with seven portions of ether, the organic layers were combined, washed with water, dried, and concentrated to a small volume. Distillation under vacuum gave 51.7 g of material, bp 31–45° (0.5 mm). This material was hydrogenated in 165 ml of glacial acetic acid over 0.85 g of platinum oxide at 50–55 psig for 21 hr. The reaction mixture was filtered through Celite, diluted with 500 ml of water, and extracted with ether. The organic layers were combined, washed with water, 5% aqueous sodium bicarbonate, again with water, and dried, and the solvent was evaporated to yield a mixture of 4,4-dimethylcyclohexanol, its acetate, and the corresponding ketone. This material was heated at reflux with 40 g of potassium hydroxide in 200 ml of water and 200 ml of methanol for 4 hr, diluted with 300 ml of water, and extracted with ether. The organic layers were combined, dried, filtered, and concentrated to give 46.0 g of brown oil. The infrared spectrum showed strong hydroxyl absorption at 2.9 μ, carbonyl absorption at 5.86 μ, and peaks at 7.21 and 7.32 μ, assigned to the geminal dimethyl groups. This indicated that the product was apparently a mixture of 4,4-dimethylcyclohexanone and 4,4-dimethylcyclohexanol. To a solution of 10 g of this mixture dissolved in 150 ml of absolute ethanol was added 20 g of sodium borohydride in small portions, with shaking. This mixture was heated at reflux 1 hr and cooled, and the excess borohydride destroyed by the careful addition of hydrochloric acid. The mixture was concentrated; 300 ml of water was added and the solid filtered off. The liquid phase was extracted with ether and the organic layers were combined, dried, and concentrated. Distillation gave 3.0 g of viscous, water-white liquid, bp 43° (0.9 mm). The nmr spectrum showed a one-proton singlet at δ 2.84 (OH), a one-proton multiplet (C*H*OH) at 3.50, an eight-proton envelope centered at about δ 1.4, and two three-proton singlets at δ 0.89 and 0.92 (CH_3). This alcohol (3.0 g), was mixed with 3.5 g of phthalic anhydride and 5 ml of dry pyridine and heated on a steam bath for 2 hr. The mixture was poured onto a mixture of ice and dilute hydrochloric acid, extracted with ether and the extracts were washed with water, dried over magnesium sulfate, filtered, and concentrated. The residue was recrystallized from hexane–ethyl acetate (10:1) and twice from hexane, affording 4.0 g (62%) of the acid phthalate, mp 93–95° (lit.[36] mp 92.5–94°). A mixture of 3.0 g of this ester and 200 ml of 20% aqueous sodium hydroxide was heated at reflux 1 hr and then steam distilled. The distillate was extracted with ether and the organic layers were combined, dried,

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[33] W. G. Remers, G. J. Gibbs, C. Pidacks, and M. J. Weirs [*J. Amer. Chem. Soc.*, 89, 5512 (1967)] have recently suggested a similar duality of mechanism in the reduction of indoles and quinolines.

[34] The steric parameters in the steroid nucleus responsible for the selective α attack at C-12 in some cases and β attack in others are not entirely clear and are the subject of work in progress.

[35] 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 research chromatograph, utilizing a 10-ft column, ⅛ in. in diameter, packed with 10% Carbowax 20M on Chromosorb W, helium as the carrier gas, and using either a thermal conductivity or flame ionization detector. The chromatograms were integrated by means of a compensating polar planimeter. Nuclear magnetic resonance spectra were recorded on a Varian Associates A-60 nuclear magnetic resonance spectrometer using deuteriochloroform as solvent and tetramethylsilane as internal standard. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

[36] E. L. Eliel and C. A. Lukach, *J. Amer. Chem. Soc.*, 79, 5986 (1957).

filtered, and concentrated, giving 1.3 g of 4,4-dimethylcyclohexanol, homogeneous to glpc. A 20-g portion of the mixture of alcohol and ketone obtained from the above hydrogenation was dissolved in 130 ml of benzene and cooled to 0°. A solution of 5.4 g of sodium dichromate dihydrate in 85 ml of water, 25 ml of sulfuric acid, and 16 ml of acetic acid was added slowly, with vigorous stirring, and mixture was stirred at 0° for 1 hr, warmed to room temperature and stirred for 21 hr. The organic layer was separated and washed with water, three portions of 5% aqueous sodium bicarbonate, again with water, dried, and concentrated. The solid residue was sublimed, then crystallized from pentane, affording 2.3 g of white needles, mp 41.5–42°. The 2,4-dinitrophenylhydrazone[37] was prepared, mp and mmp 148.5–150°.

***trans*-4-*t*-Butylcyclohexanol** was obtained from the commercial mixture of 4-*t*-butylcyclohexanols by the method of Winstein,[38] mp 80–83° (lit.[38] mp 81–82°). This alcohol was homogeneous to glpc.

***cis*-4-*t*-Butylcyclohexanol.** A solution of 10.5 g of *trans*-4-*t*-butylcyclohexyl tosylate in 250 ml of dimethylformamide and 5.5 ml of water was heated on the steam bath 65 hr. The resultant mixture was poured into 500 ml of water, extracted with five portions of ether, and washed twice with water and the organic layer separated and dried. The ether was evaporated to afford 5 g (80%) of *cis*-4-*t*-butylcyclohexyl formate, which was, without purification, dissolved in a mixture of 10 g of KOH, 10 ml of water, and 100 ml of methanol and heated at reflux for 3 hr. The mixture was poured into 250 ml of water and extracted with ether. The organic layers were combined and dried; the solvent was evaporated. The residue was sublimed at oil pump pressure to give 2.2 g of material melting below 60°. Recrystallization from hexane afforded 0.94 g of *cis*-4-*t*-butylcyclohexanol, mp 77–81° (lit.[38] mp 81–82°), homogeneous to glpc.

***trans*-2-Methylcyclohexanol.** A solution of 10.0 g of 2-methylcyclohexanone in 75 ml of dry ether and 126 ml of dry ethanol was added to 500 ml of liquid ammonia. Lithium (12 g) was added in small pieces over a 70-min period. The blue color disappeared after 30 more min. The ammonia was evaporated, 750 ml of a mixture of ice and water was added, and the mixture acidified with hydrochloric acid, then extracted with four portions of ether. The organic layer was separated and dried; most of the solvent was removed. The residue was distilled at atmospheric pressure and the fraction with bp 163–166° was collected to give 6.4 g (63%) of water-white liquid, $n^{20}\mathrm{D}$ 1.455. Glpc indicated that this material was essentially homogeneous (99% one component). The acid phthalate was prepared, mp 125–126° (lit.[39] mp 125.2–125.8°).

***cis*-2-Methylcyclohexanol.** Treatment of 5.4 g of *trans*-2-methylcyclohexyl tosylate with aqueous dimethylformamide as described above in the preparation of *cis*-4-*t*-butylcyclohexanol gave 0.85 g of pure (glpc) *cis*-2-methylcyclohexanol. The acid phthalate had mp 101–104° (lit.[39] mp 104–105°).

***cis*-3-Methylcyclohexanol.** The reduction of 5.0 g of 3-methylcyclohexanone with lithium–ammonia in the manner described above gave 3.0 g (59%) of a mixture of 94% *cis*- and 6% *trans*-3-methylcyclohexanol, bp 171–173°. Purification of this material through the acid phthalate, mp 92.5–94° (lit.[40] mp 92.5–93.5°), gave 1.6 g of pure (glpc) *cis*-3-methylcyclohexanol.

***trans*-3-Methylcyclohexanol** was prepared in the same manner as *cis*-4-*t*-butylcyclohexanol. From 2.16 g of *trans*-3-methylcyclohexyl tosylate there was obtained 0.43 g of the *trans*-alcohol (95% pure by glpc). The acid phthalate had mp 65–69° (lit.[40] mp 68–71°).

***cis*- and *trans*-4-methylcyclohexanol** were commercially available materials (Aldrich Chemical Co.) and were homogeneous by glpc. Technical grade **borneol** (Matheson Coleman and Bell) was found to contain *ca.* 15% isoborneol. Purification of this material *via* the acid phthalate, mp 161–163°, gave *dl*-borneol which contained less than 2% isoborneol by glpc. **Isoborneol**, supplied by Matheson Coleman and Bell, was homogeneous (glpc) and was used as such without additional purification.

Norborneol. The reduction of 5.0 g of norcamphor with sodium borohydride in the usual manner gave 3.8 g of a mixture of *exo*- and *endo*-norborneol. These alcohols were heated for 2 hr on the steam bath with 5.0 g of phthalic anhydride in 6 ml of pyridine. The reaction mixture was taken up in methylene chloride, washed with two portions of dilute hydrochloric acid, then with water. The organic phase was extracted with two 100-ml portions of 5% aqueous sodium carbonate and the extracts were combined, acidified, and extracted with three portions of methylene chloride. The organic layers were combined, dried, and concentrated. The residue was recrystallized once from hexane, five times from cyclohexane, then twice from hexane–ethyl acetate (1:1) to afford 0.60 g of white plates, mp 110–112.5° (lit.[41] mp 110° for *endo*-norbornyl acid phthalate). This ester was heated at reflux 1 hr with 150 ml of 10% aqueous sodium hydroxide, then steam distilled. The distillate was extracted with three portions of ether and the organic layers were separated, combined, dried, and filtered. Removal of the solvent afforded 0.17 g of *endo*-norbornenol, 95% pure by glpc.

***exo*-Norborneol.** The commercial material supplied by the Aldrich Chemical Co. was homogeneous to glpc and was used without repurification.

Reductions. Method A. A solution of 0.200 g of ketone in 5 ml of dry ether was added to 50 ml of dry, distilled liquid ammonia. A proton source, 0.1 mol, was added, then 0.07 mol of metal was added in small pieces over 30 min. After the blue color disappeared, the ammonia was allowed to evaporate, 150 ml of water added, and the mixture acidified and extracted with three portions of ether. The extracts were combined, dried over magnesium sulfate, and filtered. The solvent was removed and the product analyzed by glpc.[42]

Method B. The metal, 0.07 mol, was dissolved in 50 ml of liquid ammonia. A solution of 0.200 g of ketone in 5 ml of dry ether was added and the mixture stirred for 30 min. At this point a proton source was added, and the mixture stirred until the blue color faded. The ammonia was evaporated and 150 ml of water was added to the residue. The mixture was acidified and extracted with three portions of ether. The organic layers were separated, combined, dried over magnesium sulfate, and filtered. The solvent was removed and the product analyzed by glpc.[42]

Competition Reduction of 4-Methylcyclohexanone and 4,4-Dimethylcyclohexanone. Method A. A solution of 0.1306 g of 4,4-dimethylcyclohexanone and 0.1170 g of 4-methylcyclohexanone in 7 ml of dry ether was added to 50 ml of dry liquid ammonia. Absolute ethanol, 1 ml, was added as proton source, followed by 0.014 g of lithium, one-half the equivalent amount. After 1 min the blue color faded and the ammonia was allowed to evaporate. Water was added and the solution acidified and extracted with ether. The extracts were combined, dried over magnesium sulfate, and filtered. The solvent was removed and the product analyzed by glpc. The mole percentages reduced were 4-methylcyclohexanone, 43.4; 4,4-dimethylcyclohexanone, 43.0.

Method B. A solution of 0.1288 g of 4,4-dimethylcyclohexanone and 0.1201 g of 4-methylcyclohexanone in 7 ml of dry ether was added to 50 ml of dry liquid ammonia in 0.014 g of lithium was added and the mixture stirred for 10 min, when the blue color disappeared. The ammonia was allowed to evaporate and water was added. The mixture was acidified and extracted with ether. The organic layers were separated, combined, dried over magnesium sulfate, and filtered. The solvent was removed and the product analyzed by glpc. The mole percentages reduced were 4-methylcyclohexanone, 50.8; 4,4-dimethylcyclohexanone, 47.3.

Attempted Equilibration of *cis*-4-*t*-Butylcyclohexanol by Lithium in Liquid Ammonia. A solution of 0.106 g of *cis*-4-*t*-butylcyclohexanol and 0.109 g of 4-*t*-butylcyclohexanone in 5 ml of dry ether was added to 45 ml of liquid ammonia. Absolute ethanol, 5 ml, was added as a proton source, then 0.5 g of lithium was added, in small pieces, over 10 min. The mixture was stirred for 4 hr, then 10 ml of absolute ethanol was added to destroy the excess lithium. When the blue color faded, the ammonia was allowed to evaporate and 200 ml of water was added. The mixture was acidified and extracted with ether. The organic layers were combined, dried

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[37] C. W. T. Hussey and A. R. Pinder, *J. Chem. Soc.*, 3525 (1961). We would like to thank Professor Pinder for a sample of this derivative.

[38] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955).

[39] W. Hückel and A. Hubele, *Ann.*, **613**, 27 (1958).

[40] W. Hückel and J. Kurz, *Chem. Ber.*, **91**, 1290 (1958).

[41] S. Beckman and R. Mezger, *Chem. Ber.*, **89**, 2738 (1956).

[42] In order to determine the accuracy of the method used for integrating the curves obtained by glpc, known mixtures of product alcohols were analyzed and the results were accurate to ±1%. The products were identified by comparison with known alcohols. In several cases (see Table II) yields were determined by adding a weighed amount of a known compound. Since in some runs the yields were quite low, a blank reduction was carried out in which a mixture of known amounts of *exo*- and *endo*-norborneol were subjected to the conditions of the reduction. No metal was used, however, and the alcohols were reisolated and their relative amounts determined. The percentages agreed to within ±2% of the original mixture, indicating that the loss of products during isolation did not markedly affect the product ratios.

over magnesium sulfate, and filtered. The solvent was removed and the product analyzed by glpc.[42] The product ratio obtained by integration of the peaks was 48% *cis*- and 52% *trans*-4-*t*-butylcyclohexanol.

Camphorpinacol. Reduction of 5.0 g of camphor by 12.5 g of lithium was carried out in the manner described as method B. The crude reaction product was heated at 40° (0.1 mm) for 24 hr to remove the monomeric material. The residue, 2.5 g, was chromatographed on 100 g of neutral alumina and elution with benzene afforded 0.87 g (17%) of yellow semisolid material. The nmr spectrum showed no proton adjacent to hydroxyl in the region δ 3.2–4.2 and the infrared spectrum was consistent with the structure of camphorpinacol. Although this material was homogeneous to tlc, it could not be crystallized and is probably a mixture of diastereomers. Oxidation of 0.060 g of this material with 0.50 g of lead tetraacetate gave 0.050 g of yellow oil which contained 8% camphor (glpc) and showed carbonyl absorption at 5.75 μ.[43]

Norcamphorpinacol. The reduction of 5.0 g of norcamphor by method B described above for the preparation of camphorpinacol gave 4.0 g of yellow oil. This material was taken up in benzene and chromatographed on 240 g of Bio-Rad neutral alumina. Elution with methylene chloride–2% methanol gave 2.7 g of a mixture of norborneols and pinacol. Rechromatography of this mixture on 100 g of neutral alumina and elution with methylene chloride–0.5% isopropyl alcohol gave 1.4 g (28%) of crystalline material, the infrared and nmr spectra of which were consistent with the structure of norcamphorpinacol. Four recrystallizations from hexane gave the analytical sample, mp 144° (sublimes).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.72; H, 9.98. Found: C, 75.44; H, 9.78.

Cleavage of Norcamphorpinacol. Impure norcamphorpinacol, 0.11 g, containing about 50% of the norborneols, was mixed with 1.0 g of lead tetraacetate and 15 ml of glacial acetic acid and stirred 3 hr at room temperature. Saturated sodium chloride solution was added and the mixture extracted with ether. The extracts were washed with 5% aqueous sodium carbonate, then with water, and dried; the solvent was removed through a Vigreux column, giving 0.40 g of a yellow semicrystalline material, 20% norcamphor by glpc. The infrared spectrum showed carbonyl absorption at 5.78 μ. The 2,4-dinitrophenylhydrazone was prepared, mp 126–129° (lit.[44] mp 131.5–132°), mmp 125–127° with an authentic sample.

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(43) R. Criegee, E. Buckner, and W. Walther [*Chem. Ber.*, **73**, 571 (1940)] have pointed out that camphorpinacol is extremely resistant to cleavage by lead tetraacetate.

(44) R. L. Bixler and C. Niemann, *J. Org. Chem.*, **23**, 742 (1958).

The Possibility of a Cyclic Mechanism for Acid-Catalyzed Ester Hydrolysis

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Abstract: The rates of hydrolysis of protonated ethyl benzoate and ethyl acetate in 12–79% sulfuric acid and the carbonyl oxygen-18 exchange of ethyl acetate have been found to be linearly dependent on the square of the activity of water. The observed kinetic dependence for hydrolysis and exchange was rationalized by hydrogen-bonded cyclic transition states consisting of protonated ester and two water molecules. The rates of hydrolysis of protonated ester were calculated from the observed concentration of protonated ester and ordinary rates of hydrolysis.

Acid-catalyzed ester hydrolysis is known to be first order in acid and ester.[1] The order in water was not known before our preliminary communication[2] because of the paucity of good water activity data[3] and the perturbing influence[4] of prior protonation equilibrium. We now wish to report complete results for the hydrolysis of two simple esters in sulfuric acid solutions. The concentration of protonated ester was determined in solutions with measurable rates of hydrolysis thereby allowing us to calculate the rate of hydrolysis of protonated ester. This rate was linearly dependent on the square of the activity of water.[5]

Hydrolysis and Carbonyl Oxygen-18 Exchange Data

Table I. Hydrolysis of Ethyl Acetate at 25.0°

% H_2SO_4	$-H_0$	k_{obsd}, sec^{-1}	$[BH^+]/[B]$	k_{BH^+}[b] × 10^2 sec^{-1}	a_{H_2O}
12.2[a]	0.46	1.88×10^{-4}	6.76×10^{-5}	278	0.942
16.4[a]	0.76	3.09×10^{-4}	1.05×10^{-4}	294	0.914
23.9[a]	1.29	5.61×10^{-4}	2.32×10^{-4}	242	0.836
25.5[a]	1.41	6.55×10^{-4}	2.76×10^{-4}	237	0.816
29.4[a]	1.68	7.97×10^{-4}	4.14×10^{-4}	193	0.761
33.43[a]	1.96	1.04×10^{-3}	6.24×10^{-4}	167	0.694
36.67[a]	2.18	1.28×10^{-3}	8.71×10^{-4}	147	0.633
43.56[a]	2.72	1.66×10^{-3}	1.96×10^{-3}	84.8	0.490
47.00	3.06	1.785×10^{-3}	3.18×10^{-3}	56.3	0.415
48.00[a]	3.17	1.92×10^{-3}	3.76×10^{-3}	51.2	0.393
51.55	3.55	1.86×10^{-3}	6.61×10^{-3}	28.3	0.317
55.60	3.98	1.97×10^{-3}	1.24×10^{-2}	16.1	0.238
56.25	4.05	1.84×10^{-3}	1.39×10^{-2}	13.4	0.225
59.18	4.37	1.84×10^{-3}	2.21×10^{-2}	8.49	0.176
59.88	4.45	1.83×10^{-3}	2.51×10^{-2}	7.48	0.164
66.32	5.25	1.21×10^{-3}	8.26×10^{-2}	1.58	0.078
68.97	5.64	9.03×10^{-4}	1.47×10^{-1}	0.704	0.054
69.88	5.79	9.03×10^{-4}	1.83×10^{-1}	0.584	0.047
73.55	6.33	4.44×10^{-4}	4.16×10^{-1}	0.151	0.0241
78.80	7.16	9.18×10^{-5}	1.41×10^{0}	0.0157	0.00769

[a] R. P. Bell, A. L. Dowding, and J. A. Noble, *J. Chem. Soc.*, 3106 (1955). [b] Hydrolysis.

The rate of hydrolysis of ethyl acetate in sulfuric acid solutions has been followed by titration, dilatometry, and changes in absorption at 200 mμ. These data are summarized in Table I and shows a rate

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(1) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

(2) C. A. Lane, *J. Am. Chem. Soc.*, **86**, 2521 (1964).

(3) J. Koskillalio, *Suomen Kemistilehti, B.*, **35**, 62 (1962).

(4) E. M. Arnett and G. W. Mach, *J. Am. Chem. Soc.*, **88**, 1177 (1966).

(5) The water activity is precisely known from the results of W. F. Giauque, E. W. Hornung, J. E. Kunzler, and T. R. Rubin, *ibid.*, **82**, 62 (1960).