The Mechanism of Metal–Ammonia Reduction of Camphor

By **W. S. Murphy** * and **D. F. Sullivan,** Department of Chemistry, University College, Cork, Ireland

The reduction of camphor by active metals in liquid ammonia occurs by an electronation–protonation mechanism. Evidence is presented which indicates that protonation of a non-planar anion radical is involved in one if not the only route in the absence of a large excess of metal. A dianion seems to be involved when a large excess of metal is present. The effects of metal cations and a proton source are discussed. The camphor analogue of pinacol has been isolated and characterised.

HUFFMAN AND CHARLES [1] sought to provide a satisfactory explanation for the steric course of reduction of saturated cyclic ketones by active metals in liquid ammonia. Although they could not explain the variation between their results and those of earlier studies, they suggested a dual mechanism which involved protonation of a dianion in hindered ketones and of an anion radical in unhindered ketones. Taylor,[2] on the assumption that ketyls are planar, considered that

[1] J. W. Huffman and J. T. Charles, *J. Amer. Chem. Soc.,* 1968, **90,** 6486.

[2] D. A. H. Taylor, *Chem. Comm.,* 1969, 476.

M M

unequal rates of protonation of equilibrating dianions was the explanation. Fry and Reed,[3] in a related study, suggested the anion radical route. Coulombeau and Rassat,[4] in a detailed study, were undecided on this issue. However, House and his co-workers [5] could find no evidence for dianion formation during the reduction of $\alpha\beta$-alkenones.

All other reasonable mechanisms were considered and tested before we investigated the electron–proton-ation type mechanism. We found that lithium iso-borneolate and camphor did not interact in liquid ammonia. If a hydride ion mechanism [6] operated some borneol would be expected.* Our result was confirmed by the absence of a reaction between lithium isopropoxide and camphor in liquid ammonia. A hydrogen abstrac-tion mechanism is conceivable. Conditions were de-veloped to detect hydrazine by benzaldehyde azine [8]
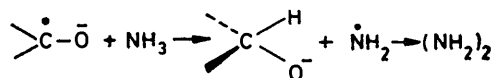
formation. However, no hydrazine was detected from the reaction of lithium with camphor. An alternative is the reduction of camphor when in the enol form. This route can be immediately dismissed since camphenilone (3,3-dimethylnorbornan-2-one) and fenchone (1,3,3-tri-methylnorbornan-2-one) undergo smooth reduction [9] under normal conditions in liquid ammonia. Finally a mechanism involving the intermediacy of a pinacol dianion was considered, analogous to the behaviour of tetraphenylethylene glycol.[10] The dianion of the cam-phor analogue of pinacol was stable in liquid ammonia.
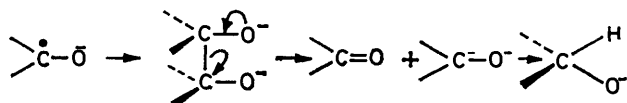
We concluded that an electronation–protonation mechan-ism [11] must be involved.

Our results (Table 1) confirm those of Ourisson [9] and Rassat [4,9] but are at variance with those of Huffman and Charles.[1] The effect of additional metal cations pro-vided interesting results [12] (Table 2). Comparison of the first entry with that in Table 1 indicates that a salt effect is not operative. The results are almost exactly those predicted from the statistical ratio of metal cations. Steps 1 and 2 (Scheme 1) follow from these results.

Although step 2 may be reversible under certain con-ditions we consider that steps 3 and 4 are irreversible, since the results depend on the ratio of M^+ to M'^+ but not on the tendency of the metal cations to form intimate

SCHEME 1

or solvent-separated ion pairs.[13] The dissolving metal M is ionised in a discrete step before reaction with the ketone takes place (steps 1 and 2). This nullifies Huffmann's [1] and Nelson's [14] suggestion that the re-ducing power of the metal is responsible for the variation of product with metal. The metal is ionised before it reacts. Also the relative percentages of ' pinacol ' formed (Table 1) are in the reverse order to that expected

TABLE 1

Reduction of (+)-camphor in the absence of an added proton donor [a]

Metal [b]	Yield of alcohols (%)	Isoborneol (%) [e]	Yield of pinacol (%)
Li [d]	25	20	70
Na	75	40	20
K	95	58	0
Cs	95	78	0
Ca	95	27	0
Sr	99	30	0
Ba	95	29	0

[a] Ammonium chloride added after 30 min. [b] Metal (2 g atom) added to the solution of ketone (1 mol) in ammonia. [e] Expressed as a ratio to borneol. [d] Bornane (ca. 5%) was formed.

on the basis of the reducing power of the metals. A formal carbon–metal bond was suggested by Barton [11b] and more recently by House.[5] We feel that these results (Table 2) probably disprove the existence of such an intermediate, since its formation would involve a preference by the ketone for the dissolving metal, as has been suggested.[4c] At least for the metals we have investigated, this is not the case. The results in Table 2 indicate that dianion formation, if it occurs at all under these conditions, is slow relative to the overall rate of formation of the complexed anion radical (Scheme 2). It is also obvious that the ' pinacol ' is formed after

* The equilibrium mixture of borneols at −33° contains borneol (80%) and isoborneol (20%).[7]

[3] A. J. Fry and R. G. Reed, J. Amer. Chem. Soc., 1969, 91, 6448.

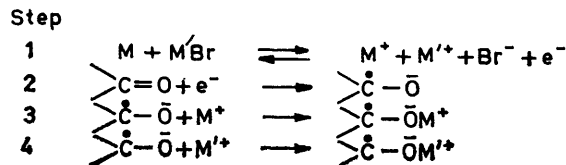[4] A. Coulombeau and A. Rassat, (a) Bull. Soc. chim. France, 1965, 3338; (b) Chem. Comm., 1968, 1587; (c) Bull. Soc. chim. France, 1970, 4399.

[5] H. O. House, R. W. Giese, K. Kronberger, J. P. Kaplan, and J. F. Simeone, J. Amer. Chem. Soc., 1970, 92, 2800.

[6] (a) H. O. House, H. C. Millar, C. G. Pitt, and P. P. Wickham, J. Amer. Chem. Soc., 1963, 28, 2407; (b) H. O. House, ' Modern Synthetic Reactions,' Benjamin, New York, 1965, p. 55.

[7] C. F. Wilcox, M. Sexton, and M. F. Wilcox, J. Org. Chem., 1963, 28, 1079.

[8] B. T. Gillis and M. P. LaMontagne, J. Org. Chem., 1967, 32, 3318.

[9] G. Ourisson and A. Rassat, Tetrahedron Letters, 1960, 16.

[10] C. B. Wooster, J. Amer. Chem. Soc., (a) 1928, 50, 1388; (b) 1937, 59, 377.

[11] (a) D. H. R. Barton and C. H. Robinson, J. Chem. Soc., 1954, 3045; (b) D. H. R. Barton and G. A. Morrison, Fortschr. Chem. org. Naturstoffe, 1961, 19, 223.

[12] Preliminary communication, W. S. Murphy and D. F. Sullivan, Tetrahedron Letters, 1971, 3707.

[13] T. E. Hogen-Esch and J. Smid, J. Amer. Chem. Soc., (a) 1966, 88, 315; (b) 1968, 90, 4654.

[14] A. L. Wilds and N. A. Nelson, J. Amer. Chem. Soc., 1953, 75, 5362; see however, C. Djerassi, ' Steroid Reactions,' Holden-Day, San Francisco, 1963, p. 287.

association of the anion radical with the metal cation (Scheme 2).

TABLE 2

Reduction of (+)-camphor in the presence of alkali metal salts [a]

Metal	Salt	Ratio (metal : salt)	Isoborneol (%) [b]	Yield of pinacol (%)	Yield of alcohols (%)
Ihey	LiBr	1 : 5	20 (20) [c]	75 (70) [c]	25 (30)
I	LiBr	1 : 5	24 (26)	60 (62)	40 (38)
I,,	KBr	1 : 5	47 (51)	30 (17)	70 (83)
K	LiBr	1 : 1	34 (39)	40 (40)	60(60)
Li	KBr	1 : 1	33 (39)	40 (40)	60 (60)
K	CsBr [d]	1 : 1·5 [c]	68 (70) [f]	0 (0)	95 (100)

[a] The metal is added to the solution of (+)-camphor and salt. [b] Ratio of isoborneol to borneol. [c] Figures in brackets are predicted by averaging the effects of the metal cations. [d] Ammonia was saturated with CsBr. [e] Ratio based on the known solubility of CsBr (H. H. Sisler, ' Chemistry in Non-aqueous Solvents,' Chapman and Hall, London, 1965, p. 32). [f] Bornane (ca. 5%).

The effect of the presence of ammonium chloride during the reduction was studied (Table 3). Reduction by this method is extremely fast and exothermic. The reaction is complete as soon as all the camphor has been added. The results for the three metals are almost identical (Table 3). The metal cations are therefore not affecting

TAB   }

Reduction of (+)-camphor in the presence of ammonium chloride [a]

Metal	Isoborneol (%) [b]	Yield of pinacol (%)	Yield of alcohols (%)
Li	6	0 [c]	95
Na	10	0	95
K	10	0	95

[a] Metal (2 g atom) added to ammonium chloride (3 mol) and camphor (1 mol). [b] Expressed as a ratio to borneol. [c] Confirmed by t.l.c.

the course of the reaction. We consider that these results confirm the suggestion of discrete steps 1 and 2 (Scheme 1). The anion radical is protonated before it associates with the metal cation. Thus the same intermediate is involved in each of the three reactions (Table 3). A dianion will not be involved. The anion radical can be protonated initially on the carbon or on the oxygen atom. It is considered [15] that any factor which reduces coulombic repulsion between anion radicals will facilitate pinacol formation. Thus if the anion radical was protonated initially on the oxygen atom the radical formed should be capable of dimerising. Since no pinacol is formed we consider that protonation occurs initially on the carbon atom, at least under these conditions. These results (Table 3) prove that the anion radicals are not trigonal under these conditions as has hitherto been assumed.[2] If the ketyl carbon atom were planar then the direction of protonation should follow Richer's rules,[16] i.e. the proton should attack from the least hindered side to give a predominance of isoborneol. The exo–endo ratio (Table 3) is probably a reflection of the relative rates of formation of the epimeric anion radicals, which are protonated faster than they epimerise
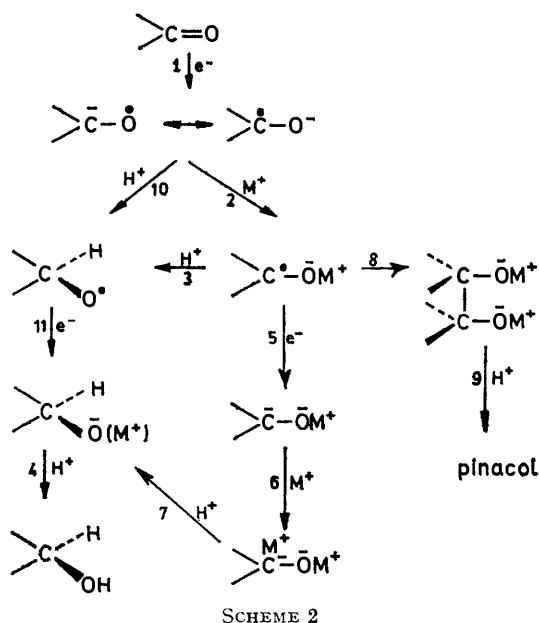
SCHEME 2

Coulombeau and Rassat,[4b] who studied the reduction without an added proton source, consider that the crucial step is not protonation but the passage of the carbonyl group from the trigonal to the pyramidal form (anion radical or dianion), and that the epimeric anion radicals (or dianions) do not equilibrate. If these suggestions are correct then the exo–endo ratio of borneols derived from the reduction in Table 3 should be the same as in Table 2. The results of these two Tables would differ if the anion radicals equilibrated before complexation with the metal cation in the absence of ammonium chloride. However this suggestion does not explain the effect of the variation in metal on the exo–endo ratio (Tables 1 and 2). If, as we think, Coulombeau and Rassat's [4b,c] basic deductions are correct, then it is necessary to suggest in the absence of a proton donor, an unequal rate of complexation by the metal cations with the free equilibrating epimeric anion radicals. This rate difference will depend on a balance between the rotation barrier effect [4b] and the complex effect.[4b] The complexed anion radicals must be protonated faster then they epimerise.

We studied the effect of a large excess of metal in the absence of a proton donor (Table 4). It is difficult to explain the differing results of Table 2 and Table 4 other than by invoking the formation of a dianion (sequence 2 ⟶ 5 ⟶ 6; Scheme 2). The yield of pinacol has decreased. We have noted that pinacol formation occurs only between complexed anion radicals. Since the rate of formation of these ion-paired species will be greater

[15] J. Fried and N. A. Abraham, Tetrahedron Letters, 1964, 1879.
[16] J. C. Richer, J. Org. Chem., 1965, 30, 324.

when a large excess of metal (or metal cation) is present, then the percentage of pinacol should increase unless a dianion is involved. Conversely we feel these results (Table 4) suggest that reduction by dissolving metals

TABLE 4

Reduction of (+)-camphor by a large excess of metal

Metal [a]	Isoborneol (%) [b]	Yield of pinacol (%)	Yield of alcohols (%)
Li	18	45	55
Na	33	0	95
K	51	0	95

[a] Camphor (1 mol) added to the solution of metal (20 g atom) in ammonia. [b] Expressed as a ratio to borneol. [c] Traces of bornane were indicated by g.l.c.

under normal conditions (Table 2) does not involve dianions exclusively, if at all.

The variation of the *exo–endo* ratio with the nature of the metal has been adequately discussed elsewhere. However, alkaline earth metals provide anomalous results in that the product is independent of the nature of the metal (Table 1). We suggest, since calcium is recovered as a hexammonate from liquid ammonia,[17] that the alkaline earth metal cations are strongly solvated by ammonia. This could result in a cationic species too large to complex with an anion radical, and the effects of the three metals would thus be equal. An essentially free anion radical would explain the absence of pinacol and afford an *exo–endo* ratio similar to that obtained with the large tetraethylammonium cation.[4b,c]

(−)-Camphor pinacol (2,2′-bibornanyl-2,2′-diol) was isolated as a solid of m.p. 114—115°. Though isolated as an oil from the reduction of camphor by Huffman,[1] who did not specify whether (+)- or (±)-camphor was used, and though it was not described by Coulombeau and Rassat,[4b,c] its reported m.p.[18] suggests diastereoisomerism.

We feel that these results, while contributing to a better understanding of the mechanism, extend the synthetic value of this mode of reduction. Closer attention to the variables outlined should resolve the anomalies in the metal–ammonia reduction of 12-ketosteroids.[19]

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 257 spectrophotometer. Optical rotations were measured for solutions in benzene with a Perkin-Elmer 141 polarimeter. The mass spectrum was obtained with a Hitachi–Perkin-Elmer RMS-4 instrument. T.l.c. was performed on 10 × 20 cm plates coated with Kieselgel HF$_{254}$ (Merck). Spots were located by treatment with iodine vapour. For preparative t.l.c. Kieselgel PF$_{254}$ (Merck) on 100 × 20 cm plates was used, and materials were located by u.v. illumination. R_F Values (benzene as eluant) were as follows: bornane 0·90, 2,2′-bibornanyl-2,2′-diol (camphor pinacol) 0·76, camphor 0·60, isoborneol 0·50, borneol 0·20. Standardised aluminium oxide (grade II; Woelm) and silica gel

(grade II) were used for column chromatography. G.l.c. was performed with a Pye Unicam 104 chromatograph equipped with a flame ionisation detector. A copper column (17 ft × ¼ in) packed with 10% Carbowax 20M on Chromosorb W 80—100 mesh completely resolved borneols at 165° with a nitrogen flow rate of 40 ml min⁻¹. The relative percentages of each compound were determined from peak areas. Absolute percentages were obtained by reference to the internal standard menthol, a known weight of which was added to the crude product before injection. Response of the different compounds relative to menthol was determined and corrections were applied where appropriate; relative retention times: menthol 1·00, bornane 0·15, camphor 0·78, isoborneol 1·15, borneol 1·30.

General Reduction Procedure.—The method used was essentially unchanged throughout the study. Details of two reductions only are therefore given below. However, close attention to experimental detail is necessary to obtain reproducible results.

Reduction of (+)-Camphor with Potassium.—(+)-Camphor (1·52 g, 0·01 mol) in dry ether (10 ml) was added dropwise from a pressure-equalising dropping funnel to ammonia (200 ml) which had been distilled directly into the flask and to which small pieces of potassium had been added until the blue colour persisted. The volume of ammonia was kept constant by the use of a cold-finger condenser containing solid carbon dioxide–acetone and was maintained under a positive pressure of dry nitrogen. The solution was magnetically stirred with a Teflon-coated stirring bar while potassium (0·85 g, 0·022 g atom) was added in small pieces. The solution turned blue and remained blue for the duration. After 30 min the reaction was terminated by the addition of excess of ammonium chloride. The ammonia was replaced by ether. Water (50 ml) was added. Separation of the layers was followed by extraction with ether (4 × 50 ml). The extract was dried and evaporated at room temperature to yield a white solid (1·48 g, 97%). G.l.c. analysis indicated that the product consisted only of borneol (42%) and isoborneol (58%). The absence of other components was confirmed by t.l.c.

Reduction of (+)-Camphor with Lithium in the Presence of Potassium Bromide.—Ammonia (200 ml) was distilled on to dry potassium bromide (2·38 g, 0·02 mol) in a three-necked flask (500 ml) fitted with a solid carbon dioxide–acetone condenser under positive nitrogen pressure. (+)-Camphor (1·52 g, 0·01 mol) in dry ether (10 ml) was added to this solution from a pressure-equalising dropping funnel. Lithium (0·15 g, 0·022 g atom) was added slowly in small pieces. A white precipitate formed. The resulting blue solution was stirred for 30 min and then neutralised with excess of ammonium chloride. The same work-up procedure as in the foregoing experiment yielded a white solid (1·45 g, 96%). G.l.c. analysis indicated the presence of borneol and isoborneol in the ratio of 67 : 33 (55% combined yield). T.l.c. showed the presence of a third component. (−)-*Camphor pinacol* (2,2′-bibornanyl-2,2′-diol) (0·60 g, 40%) was isolated by column chromatography as a white solid, m.p. 114—115° (lit.,[17] 156°) (Found: C, 78·4; H, 11·05%; M^+, 306. $C_{20}H_{34}O_2$ requires C, 78·35; H, 11·1%; M, 306), $[\alpha]_D^{20}$ −80·1° (c 5·0 in benzene), $\nu_{max.}$ 3640 cm⁻¹.

Reduction of (+)-camphor in the presence of ammonium chloride was undertaken in the same manner on the same

[17] B. A. Kazanskii and I. V. Gostunskaya, *Zhur. obshchei Khim.*, 1955, **25**, 1704 (*Chem. Abs.*, 1956, **50**, 5540b).

[18] R. Criegee, E. Buckner, and W. Walther, *Ber.*, 1940, **73**, 571.
[19] J. W. Huffman, D. M. Alabran, T. W. Bethea, and A. C. Ruggles, *J. Org. Chem.*, 1964, **29**, 2963.

scale. The relative quantities of reactants were: (+)-camphor (0·01 mol), alkali metal (0·022 g atom), ammonium chloride (0·03 mol).

Oxidation of (—)-*Camphor Pinacol* (2,2′-*Bibornanyl*-2,2′-*diol*).—Camphor pinacol (0·76 g, 0·0025 mol) was dissolved in distilled acetic acid (20 ml) with lead tetra-acetate (2·2 g, 0·0050 mol). The solution was heated at 50° for 30 min, then allowed to cool to ambient temperature with stirring (30 min). Water (100 ml) was added and the resulting red brown solution was extracted with ether (4 × 50 ml). The extract was dried (Na_2SO_4) and evaporated to dryness at room temperature. The white solid (0·75 g, 100%) was camphor, m.p. 174—176° (from ethanol), $\nu_{max.}$ 1750 cm^{-1}. G.l.c. analysis confirmed the formation of camphor (0·005 mol).

Attempted Reaction between Lithium Isoborneolate and (+)-*Camphor*.—Lithium (0·075 g, 0·011 g atom) was added in small pieces to dry distilled ammonia (200 ml) containing a catalytic quantity of iron(III) nitrate. When all the metal had reacted (disappearance of blue colour), isoborneol (1·54 g, 0·01 mol) in dry ether (10 ml) was added. After 15 min, camphor (1·52 g, 0·01 mol) was added in dry ether (10 ml). The solution was stirred for 30 min and was worked up as before. The solid product (3·00 g, 98%) consisted only (g.l.c.) of isoborneol and camphor (1 : 1).

The same result was obtained when propan-2-ol (0·60 g,

0·01 mol) was used in place of isoborneol under identical conditions.

Attempted Equilibration of (—)-*Camphor Pinacol*.—Lithium (0·15 g, 0·022 g atom) was added in small portions to dry distilled ammonia (200 ml) containing a catalytic quantity of iron(III) nitrate. After 30 min all the lithium had reacted. (—)-Camphor pinacol (1·13 g, 0·01 mol) in dry ether was added (10 ml). The solution was refluxed for 1 h. Excess of ammonium chloride was then added. The customary work-up yielded camphor pinacol (1·07 g, 94·6%), m.p. 114—115°. G.l.c. confirmed the absence of both borneols and camphor.

Search for Hydrazine.—Camphor (1·13 g, 0·01 mol) was reduced by lithium (0·15 g, 0·022 g atom) as already described. The aqueous layer remaining after work-up was neutralised with dilute hydrochloric acid. Benzaldehyde (2·12 g, 0·02 mol) in ethanol (10 ml) was then added. No benzaldehyde azine was formed.

A blank experiment was carried out as follows. Hydrazine hydrate (0·5 g, 0·01 mol) was added to (+)-camphor (1·13 g, 0·01 mol) in ammonia (200 ml). The aqueous layer after work-up was neutralised with dilute hydrochloric acid. Benzaldehyde (2·12 g, 0·02 mol) in ethanol (10 ml) was added. A green-yellow precipitate proved to be benzaldehyde azine (1·6 g, 75%), m.p. and mixed m.p.[8] 91—93°.