Metal–Ammonia Reduction of Some Bicyclo[2,2,1]heptan-2-ones

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THE metal–ammonia reduction of ketones may give one of the two possible epimers[1–4] depending on the reaction conditions, and specially on the presence or absence of an added proton donor and on the nature of the reducing metal. Mechanisms previously proposed[3–6] do not satisfactorily explain the results.

We report reductions of ketones of the camphor series, when the proton donor (ethanol) is added half an hour after addition of the ketone to the reducing agent (Table 1).

TABLE 1

Metal / Ketone	Li	Na	K	Rb	Cs	Ca	Sr	Ba	Ba–$Et_4N^+Cl^-$[d]
Camphor									
$R=R^1=R^2=Me$[a]	23(21)	42(42)	60(70)	(77)	(82)	(28)		32(35)	39[e]
$R^3=R^4=H$[b]	55	20	0	0	0	0		0	0
Fenchone									
$R=R^3=R^4=Me$[a]	2	1·5	1			3		5	6
$R^1=R^2=H$[b]	0	0	0			0		0	0
Norcamphor[a]	30	30	20	17	17	25	30	30	9
$R=R^1=R^2=R^3=R^4=H$[b]	53	60	57	54	48	10	34	38	traces
1-Methylnorcamphor									
$R=Me$[a]	17	15	7	4	6	13	17	16	1 to 2
$R^1=R^2=R^3=R^4=H$[b]	35	55	15	traces	traces	traces	traces	traces	traces
α-Fenchocamphorone									
$R=R^3=R^4=H$[a]	23	17	21	30	33	35		29	25[e]
$R^1=R^2=Me$[b]	62	45		0	0	0		0	0

[a] The number in the first line gives the percentage of "*exo*"-alcohol, in the mixture "*exo*"-alcohol–"*endo*"-alcohol. For camphor, the number in brackets indicates the composition found by one of us (A.R.)[1], using g.l.c. Our analyses were made by the n.m.r. integral curve method.[3]

[d] The number in the second line gives the percentage of pinacols in the whole reduction mixture, as found by chromatography on alumina, either of the crude mixture, or after selective acetylation of the secondary alcohols (for norcamphor).

[c] To 250 cm^3 of anhydrous liquid ammonia 0·025 g. equiv. of metal and then 5 mmoles of ketone dissolved in 20 c.c. of anhydrous ethyl ether are added. After half an hour, the colour is destroyed by 3 c.c. of absolute ethanol and the product is extracted with ether. The yield of crude product is always close to 100% and no ketone is found (except e).

[d] One dissolves anhydrous tetraethyl ammonium chloride, then barium, and the ketonic solution after three minutes in liquid ammonia.

[e] Ketone absorption in the i.r. of *endo*-product.

In order to eliminate the influence of the metallic cation, we used barium reduction in the presence of tetraethylammonium chloride. Since barium chloride is insoluble in liquid ammonia, we believe that the main cation in solution is Et_4N^+. It is weakly solvated, owing to its size[7] but, more important, it cannot form a covalent bond, and therefore is only weakly associated with the organic radical-anion or dianion. These species are therefore exclusively complexed by ammonia. This hypothesis is supported by the absence of pinacol formation in this type of reduction, even with unhindered norcamphor. (We have verified moreover that $Cl^-Et_4N^+$ did not act through a salt-effect nor as a proton source.) The results of this type of reduction are given in Table 1, last column.

In order to estimate the influence of the relative thermodynamic stability of the two alcohol reduction epimers, we have equilibrated norborneols, 1-methylnorborneols, and fenchols, by the method recently described.[3] These results are summarized in Table 2.

These results give evidence that the stereochemistry of the reduction is not determined by the relative thermodynamic stabilities of the products, that none of the mechanisms formerly proposed[3,4,6] are adequate, and that this reaction is kinetically controlled. The ketone reacts with an electron to give a radical-ion: in liquid ammonia, and in the absence of an added proton source, this

TABLE 2

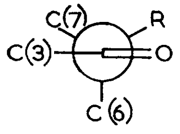
Alcohols	Fenchols[a]	Norborneols[a]	1-Methylnorborneols[a]	Borneols	α-Fenchocamphorols
Equilibrium *exo* : *endo* ratio	28±13/72±13[d]	75/25	60/40	30/70[b]	[c]
Stable alcohol	*endo*	*exo*	*exo*	*endo*	*endo*

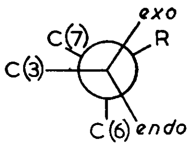
Notes: [a] At 170°; [b] ref. 8; [c] the equilibration for this pair has not yet been done; cryoscopic studies (ref. 9) suggest that the "*exo*" side is the most hindered, but these results must be used with care, as shown by the discrepancies, in the case of 1-methylnorborneols, between cryoscopic and equilibration data; [d] equilibration being very slow, equilibrium was not reached without destruction of the alcohols, but the *exo* : *endo* ratio is < 41 : 59 and > 15 : 85 (ref. 3).

radical-ion may be transformed into a dianion. The governing step is either the addition of the first or the second electron to the ketone, or the addition of a proton to the carbon of the carbanion (radical anion or dianion). We think that this last hypothesis must be rejected. In the reduction by barium–tetraethylammonium chloride, the predominant product is always the "*endo*"-alcohol. If the crucial step were protonation, we should obtain the *endo*-epimer when the *exo*-side is less hindered and the *exo*-epimer in the other case. Hence the crucial step is the passage from the planar form of the carbon atom C(2) (carbonyl) to a pyramidal form (radical-anion or dianion), and the steps between the ketone and the alcohols are irreversible. Therefore, we believe that during the reaction time, the two epimeric dianions (or radical-anions) are not in equilibrium, and that the last protonation step occurs with retention of configuration at C(2).

We suggest a reaction mechanism along these lines based upon two different effects: the first is a rotation-barrier effect, exclusively created by the bridgehead substituent, since the 3- substituents are identical, and symmetrically placed with respect to the C–O bond. When the carbonyl adds an electron, it is expected to become pyramidal.[10]

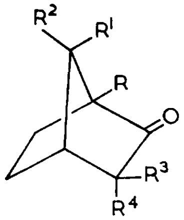
Displacement of the oxygen atom towards the *endo*-side decreases the energy of torsional interaction, while displacement towards the *exo*-side increases this interaction.[11,12]





We think that the interaction between the oxygen atom in the *endo*-position and the *endo*-substituents on the carbon atoms C(5) and C(6), or between the oxygen atom in the *exo*-position and the substituent in the 7-*syn*-position, appear only when C(2) has become pyramidal. Since this process is irreversible, these interactions do not control the stereochemistry of the reaction in this way.

However, they are at the origin of the second effect: they directly control the ease of carbanion–metal ion bond formation (or carbanion–ammonia in the Ba–NEt_4Cl reduction), *i.e.* the formation of a carbon–metal bond: the carbon atom is more easily attacked from the less hindered *exo*-side, except if there is a 7-*syn*-substituent. When steric hindrance increases, the ease of complex formation decreases.



If this steric hindrance is of the same order of magnitude from the "*exo*-" and "*endo*-" sides, the complexes are formed almost equally and the rotation barrier effect prevails: we believe that this is the case for norcamphor, where the variations of stereochemistry in terms of the metal used are weak and can be explained by the small difference of steric hindrance between the two sides: the larger the cation, the easier the complex formation from the "*exo*"-side, and the greater the ratio of *endo*-alcohol. The rotation barrier is raised by the bridgehead methyl group in 1-methylnorcamphor, and more "*endo*"-alcohol is produced than in the case of norcamphor.

But if a methyl group is added in the 7-*syn* position of norcamphor (as in α-fenchocamphorone) then the *exo*-side becomes more hindered than the *endo*-side. Complex formation favours the *exo*-alcohol, and the rotation-barrier effect favours the *endo*-alcohol. The complex effect thus reduces the rotation barrier effect, and the variations of stereochemistry in function of the metal are well explained by the mechanism formerly proposed for camphor.[3] This competition is enhanced with reduced camphor instead of α-fenchocamphorone; the rotation barrier is increased by the bridge-head methyl group, but now the *exo*-side becomes inaccessible to large cations: lithium alone can still complex both sides, and the rotation barrier effect prevails. But larger cations and ammonia preferably attack the *endo*-side, and this reduces or even cancels (in the case of K, Rb, and Cs) the rotation barrier effect.

Fenchone, which is very hindered from both sides, is poorly complexed, and the main factor is the rotation barrier: the *endo*-epimer prevails in all cases.

Reductions are carried out in the presence of a proton source, the ratio of pinacols is lowered and the *endo*:*exo* ratio is enhanced.

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