Tetrahedron Letters, Vol.22, No.41, pp 4133 - 4136, 1981
Printed in Great Britain

0040-4039/81/414133-04\$02.00/0

STEREOCHEMISTRY AND MECHANISM OF ALKALI METAL REDUCTIONS OF CYCLOALKANONES

Suresh K. Pradhan and Suhas V. Sohani
University Department of Chemical Technology,Matunga Rd.,Bombay 400019,India

Abstract: Work on steroidal 16-ones has indicated that whereas the stereochemistry of reduction of cycloalkanones by alkali metals in ethanol is linked with the FMO picture of the corresponding ketyl ion pair, the reduction of enolizable ketones by K in anhydrous ammonia is controlled by steric factors connected with proton abstraction by a dianion from alpha to a ketone.

No satisfactory explanation has been forthcoming which accounts for all the variations in the stereochemistry of reductions of cyclic ketones with alkali metals in alcohol and ammonia. The matter has been further complicated by contradictory claims[1,2,3] concerning the dependency of the borneol:isoborneol ratio on the metal or the cation in the metal/NH_3 reduction of camphor.

Our recent work[4,5] has yielded powerful tools with which to attack this problem but it was first desirable to resolve the above controversy. We have now done so, albeit indirectly, by a study of the reduction of pregn-5-en-16-one,(I), under a variety of conditions. This compound, like camphor, gives predominantly the less stable alcohol on reduction with $LiAlH_4$. The more stable epimer is the major product in the reduction of both with Na or Li in EtOH. In both there is a decrease in the percentage of this epimer on going from Na to Li. Hence the observation of a similar decrease in the sequence Li:Na:Li/KBr:K in metal/NH_3 reductions of I (see Table I) lends support to the similar claims for camphor[2,3].

TABLE I

Comparison of Stereochemistry of Alkali Metal Reductions of I with Camphor

reagent stable epimer[a]	Na/EtOH	Li/EtOH	Li/NH_3[b]	Na/NH_3[b]	K/NH_3[b]	Li/KBr/NH_3[b,c]
borneol	75[d]	67[d]	80[e,f]	60[e],81[f]	42[e],84[f]	53[e],83[f]
16α-ol[g]	85	63	55	42	22	30

a.as percentage of total alcohols. b.For I solvent was ammonia:THF (4:1). c.Li:KBr 1:5 mols. d.Ref.7. e.Ref.3. f.Ref.1. g.isolated by chromatography.

On the basis of the postulates given below it is not only possible to give a satisfactory explanation for all these findings but also for the observation that under the same conditions norcamphor gives mainly the <u>less</u> stable <u>endo</u> norborneol whereas camphor gives the <u>more</u> stable <u>endo</u> borneol.

1). The radical anion derived from a ketone by electron/alkali metal addition is a single species and not an equilibrium mixture of two.

2). This radical ion could be almost planar or partially pyramidalized depending on its structural environment. Thus in the chair conformation of cyclohexyl ketyl ion pair, in analogy with the Frontier Molecular Orbital (FMO), considerations relating to cyclohexyl radicals^8, the SOMO on carbon can be regarded as being extended in the axial direction as a result of perturbation by the 2-3 and 5-6 bond orbitals. As seen in Fig.A, this is accompanied by the oxygen taking up a quasi-equatorial position. In the ketyl ion pairs derived by reduction of both camphor and norcamphor the SOMO is extended in the exo direction. See Fig.B.

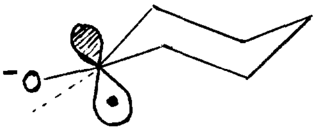


FIG. A

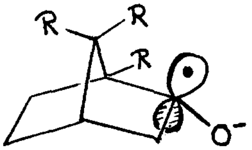


FIG. B

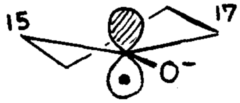
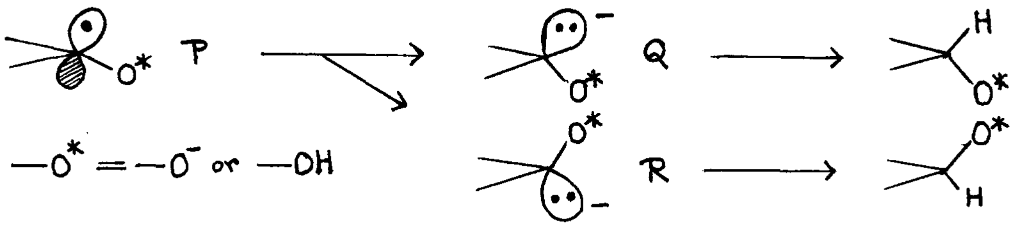


FIG. C

3). Whenever the orbital extension is predominantly in one direction, a secondary alcohol is produced by attachment of hydrogen from the same direction provided the reaction is carried out in the presence of large excess of proton donors of sufficient acidity. Reductions using alkali metals in EtOH or in liquid NH_3 containing NH_4Cl or MeOH or EtOH, fall within this category. Under these conditions an axial hydrogen gets attached in cyclohexyl derivatives while the attachment is exo in bornyl and norbornyl derivatives. The product need not be the thermodynamically stable epimer.

This postulate does not specify the path followed but it must clearly be the one shown in Scheme I taken in conjunction with the following additional 'sub-postulates' :- i). Unequal amounts of the two carbanions are formed from partially pyramidalized radical/radical anion by electron/metal addition.

SCHEME I



ii). The relative rates of formation of Q and R from P and hence the relative amounts of Q and R formed initially is roughly proportional to the relative sizes or coefficients of the lobes of the 'p' orbital on the carbon in P i.e. on the degree of pyramidalization. iii). With EtOH or NH_3 as solvent and in the presence of excess proton donors such as EtOH, MeOH or NH_4Cl, protonation of Q and R with retention of configuration is faster than interconversion between the two. Product formation is thus kinetically controlled.

4). In the absence of added proton donors, reductions with alkali metals in liquid NH_3 proceed via dianions having a longer life-time[5]. The stereochemical outcome is then governed by many factors but is predictable in some situations.

In order to test the validity of '2' and '3' attention was turned to 16-keto steroids. CD measurements of these[9] have indicated a conformation such that in the absence of substituents at 15 and 17 perturbation of the 'p' orbital at C-16 by the 14-15 and 13-17 bonds should not lead to pyramidalization Hence the ketyl ion pair formed by the addition of an electron plus counterion to androst-5-en-16-one,(II),should be practically planar as shown in Fig.C. Qualitative FMO considerations further predict that a single alkyl 17β substituent, as in I, should lead to pyramidalization with the 'p' orbital at 16 being extended in the β direction[10] whereas planarity should, on the whole, be restored by introducing an additional 17α alkyl substituent. To test this,17α-methyl-pregn-5-en-16-one,(III), was prepared and the three compounds II, I and III were subjected to Na/EtOH reductions. The only products were the epimeric 16-ols. Table II gives the details. The results of equilibrations[6] are also included for comparison. Na/EtOH reductions follow the predicted pattern.

TABLE II

16α : 16β -ols from alkylated androst-5-en-16-ones.

	I	II	III
Substitution	nil	17βEt	17αMe,17βEt
Na/EtOH[a]	53 : 47	85 : 15	52 : 48
Equilibration	71 : 29	82 : 18	61 : 39
$K/NH_3/THF$[b]	11 : 89	22 : 78	10 : 90

a. To compound in refluxing EtOH, Na is slowly added.

b. To solution of 118mg. of K in 20ml ammonia,150 mg. compound in 5 ml THF added rapidly.Stirred for 15 min. Then Na benzoate added.

Before leaving the subject of reduction in EtOH it is worth noting that Na/EtOH and Li/EtOH do not give identical results.Earlier work[7] and the result in Table I are highly significant. These cannot be explained if P of Scheme I were to be O-protonated prior to conversion to carbanion. Hence we tentatively propose that the major portion of the reaction proceeds by electron/alkali metal addition to the ketyl ion pair to give a mixture of dianions which are trapped, with retention of configuration, by the proton prior to equilibration The relative amounts of the epimeric dianions produced are governed by subpostulate 'ii'. The observed differences are then related to differences in degree of 'pyramidalization' of the ketyl ion pair associated with Na^+ on the one hand and Li^+ on the other. Greater ionic character in the former is consistent with the required greater pyramidalization in the ketyl ion pair having Na^+ as the counterion.

Only two sets of results[12] do not fall in line. Such apparent anomalies will be discussed in a full paper dealing with the above concepts in detail.

Different factors come into play in the reduction of enolizable ketones by alkali metals in ammonia free of added proton donors. The absence of the latter allows the dianions[5] to live longer. They may interconvert or not. Protonation may occur with retention or inversion of configuration or both. They, however, have access to only two proton sources viz. ammonia and the hydrogen α to the ketone[5]. We propose that with K^+, Rb^+ and Cs^+ as counterions[13] the dianions behave as 'soft'[14] bases and capture a proton at carbon from the latter source[5]. The requisite transition state ensures that steric approach dominates. Tables I and II bear testimony. Protonation by ammonia must become increasingly more important in going towards Li^+. To account for the facts it is assumed that 'exo' and 16β protonation occurs of the dianions from camphor and 16 ketones respectively, by ammonia.

REFERENCES AND NOTES

1. J.W.Huffman and W.W.McWhorter, J.Org.Chem., 1979, 44, 594.
2. A.Coulombeau and A.Rassat, Chem.Commun., 1968, 1587.
3. W.S.Murphy and D.F.Sullivan, J.Chem.Soc.Perkin Trans.I., 1972, 999.
4. S,K.Pradhan, S.R.Kadam, J.N.Kolhe, T.V.Radhakrishnan, S.V.Sohani and V.B. Thaker, J.Org.Chem., 1981, 46, 2622. Technique for metal/ammonia reductions described in detail.
5. S.K.Pradhan, S.R.Kadam and J.N.Kolhe, J.Org.Chem., 1981, 46, 2633.
6. As per C.F.Wilcox, M.Sexton and M.F.Wilcox, J.Org.Chem., 1963, 28, 1079.
7. D.N.Kirk and A.Mudd, J.Chem.Soc. (C)., 1969, 968.
8. K.Fukui, Theory of Orientation and Stereoselection, Springer Verlag, Berlin,1975, pp. 79-80.
9. D.N.Kirk and W.Klyne, J.Chem.Soc.Perkin Trans.I., 1976, 762.
10. According to Ref.9 the near twist conformation changes towards an envelope conformation on 17β substitution. But FMO picture is unaffected.
11. T.Kawamura, T.Koyama and T.Yonezawa, J.Amer.Chem.Soc., 1973, 95, 3220.
12. (a). J.W.Huffman and D.J.Copley, J.Org.Chem., 1977, 42, 3811.
    (b). P.A.Grieco, S.Burke, W.Metz and M.Nishizawa, ibid., 1979, 44, 152.
13. The importance of counterion rather than that of the metal was noted in Ref.3, contradicted in Ref.1, but now indirectly confirmed. (See Table I for effect of addition of KBr)
14. See Ref.5. Lithium cation is the 'hardest' amongst the alkali metal cations. I.Fleming, Frontier Orbitals and Organic Chemical Reactions, John Wiley, London, 1976, p.38. Hence tendency of the anion to abstract a proton from the relatively 'hard' ammonia is the greatest.

(Received in UK 10 July 1981)