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THE TRANSITION STATE IN THE REDUCTION OF KETONES BY COMPLEX METAL HYDRIDES. REASSESSMENT AND LIMITED REINCARNATION OF THE CONCEPT OF PRODUCT DEVELOPMENT CONTROL.

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Abstract: Using the conclusion of the previous communication, and other data, it is concluded that $NaBH_4$ reductions involve and product-like transition state and $LiAlH_4$ reductions involve a reactant-like transition state.

The position of the transition state on the reaction coordinate for lithium tri-t-butoxyaluminohydride (LTBA) reduction of ketones, reported in the previous communication (1) has implications beyond reductions by this reagent alone. The relative ordering of earliness or lateness of transition state in hydride reductions of ketones as a function of reductant has, to some extent, previously been possible by comparison of Hammett rho values in the reduction of aromatic ketones. (See Table 1).

Table 1 Reaction parameters of ketone reductions by different reducing agents.

Reductant	ρ	KIE	$\Delta S^{\ddagger}$ (cal. deg^{-1} $mole^{-1}$)	Position of Transition state (0.0 - 1.0)
$NaBH_4$	3.06(11)	0.6-0.7(7,8)	-42(17)	Presumably (0.6-0.7) product-like
$LiAl(OBu^t)_3H$	2.13(4)	0.95(1)	-36(16)	0.4-0.5 or 0.5-0.6
Metal alkoxide	1.45-1.75(3)	-	-	∿0.5
$LiAlH_4$	1.95(10)	1.3-1.4(9,10)	-26(9)	Probably (0.25-0.4) reactant-like

The problem with this analysis has been the difficulty of translating the relative order to an absolute extent of hydride transfer. Lamaty and coworkers, (2) provided the first translation by the use of comparative rho values for different nucleophilic additions, one of which had a known Bronsted exponent, and concluded that $NaBH_4$ reduction of ketones proceeded by a product-like transition state. More recently, Burnett and Kirk (3) compared the rho values with that for an essentially symmetrical alkoxide reduction (Meerwein-Ponndorf) and reached the same conclusion. Finally now, since the rho value for LTBA reduction has been measured, the kinetic isotope effect analysis reported in the previous communication (1) provides the closest and most direct probe to interpreting the rho values. Once again, since the rho value for $NaBH_4$ reductions (3.06) substantially exceeds that for the LTBA reduction (2.13), (4) which has a transition state occurring mid-way on the reaction coordinate, (1) the conclusion must be that $NaBH_4$ reductions have a transition state significantly later than the mid-point (i.e. significantly product-like).

The kinetic isotope effects and entropies of activation are also of interest in this respect. (See Table 1). Ignoring the perturbations of the secondary isotope effects (5), and of the substitution of B for Al, the product-like transition state for $NaBH_4$ reductions should manifest itself (see Figure of previous communication) in an inverse isotope effect. This is indeed the case. (6,7,8) The earlier transition state expected for $LiAlH_4$ should likewise give a normal (>1.0) isotope effect - a result again confirmed by experiment (9,10). The idea of this spectrum of transition states ($LiAlH_4$ reactant-like, LTBA mid-way, $NaBH_4$ product-like) is also supported by the spectrum of entropies of activation, greatest loss of translational freedom being experienced by the most product-like transition state. On the other hand, however, the difference in rho values for the LTBA reductions (2.13) and $LiAlH_4$ reductions (1.95) is very small. (12)

From a stereochemical viewpoint, the marked transition state (13) difference between $LiAlH_4$ and $NaBH_4$ reductions is highly noteworthy. Almost certainly the hope for the same explanation of stereoselectivity for these two reagents should be abandoned.

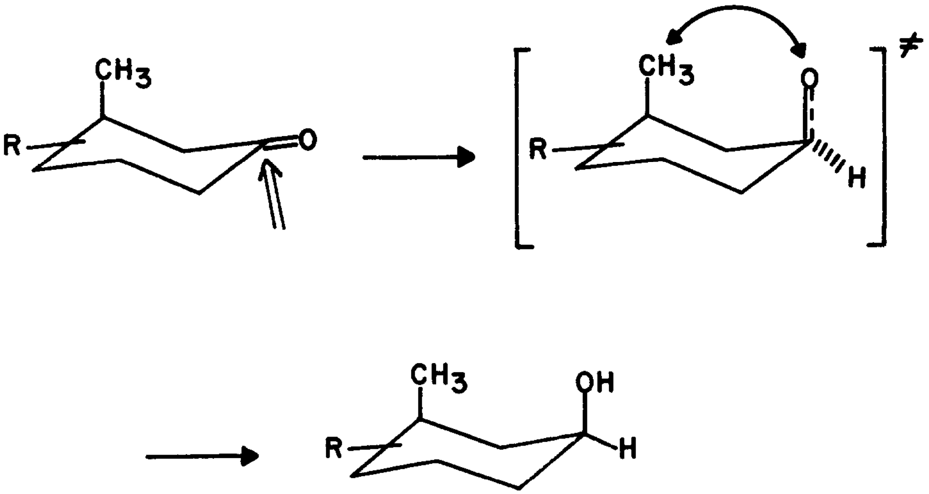

Figure 1. Product Development Control interaction in equatorial attack on cyclohexanones.

If $NaBH_4$ reductions involve a product-like transition state, product development control (14) should be observable. One of the consequences of product development control must be that substituents on the face of the carbonyl opposite to the face of hydride attack will decrease the rate of reduction. Ashby and Noding (15) have recently examined this question in the reduction of norbornanone derivatives by $LiAlH_4$ and found no contribution due to product development control. This is consistent with an early transition state in which these interactions are not significant for $LiAlH_4$ reductions. For reductions by LTBA and $NaBH_4$ the same question can be examined by the examination of equatorial attack on 3-substituted cyclohexanones (see Fig.1). The differential between equatorial attack on 3,3,5-trimethylcyclohexanone and 3,3,5,5-tetramethylcyclohexanone would appear to be a consequence of pure product development control. These rate constants are 0.16 and 0.089 mol^{-1} sec^{-1} respectively for LTBA reductions (16) and 1.1×10^{-3} and 1.9×10^{-4} mol^{-1} sec^{-1} for $NaBH_4$ reductions (17). These rate ratios of 1.8 ($LiAl(OBu^t)_3H$) and 5.8 ($NaBH_4$) are consistent with the notion of a mid-point transition state in LTBA reduction representing the onset of product development control, and a substantially later transition state for $NaBH_4$ reductions with a greater extent of product development control. These data do not conflict with those of Ashby and Noding (15) in view of the earlier transition state for $LiAlH_4$ reductions.

References

1. D.C. Wigfield and F.W. Gowland, previous communication.
2. P. Geneste, G. Lamarty, and J-P. Roque, Tetrahedron Letters 5007 (1970).
3. R.D. Burnett and D.N. Kirk, J.C.S. Perkin Transactions II, 1523 (1976).
4. D.C. Ayres, R. Sawdaye, and D.N. Kirk, J. Chem. Soc., B., 1133 (1970).
5. The kinetically significant step in $NaBH_4$ reductions is transfer of the first hydride. This is also true in $LiAlH_4$ reductions if $LiAlH_4$ is in excess.
6. R.E. Davis, R.E. Kenson, C.L. Kibby, and H.H. Lloyd, J.C.S. Chem. Commun., 593 (1965).
7. D.C. Wigfield and D.J. Phelps, Chem. Commun. 1152 (1970).
8. D.C. Wigfield and D.J. Phelps, Can. J. Chem., 50, 388 (1972).
9. E.C. Ashby and J.R. Boone, J. Amer. Chem. Soc., 98, 5523 (1976).
10. K.E. Wiegers and S.G. Smith, J. Amer. Chem. Soc., 99, 1480 (1977).
11. K. Bowden and M. Hardy, Tetrahedron, 22, 1169 (1966).
12. Raw rho values are clearly an oversimplification. Some refer to acetophenones, (11) other to benzophenones (4,9). Correlation coefficients reported for the Hammett plots range from 0.97 to 0.99, with the exception of a large deviation for the p-OMe substituent in the $NaBH_4$ reduction (11). A significant question appears to be the use of p, P' disubstituted benzophenones to the LTBA reductions, (4) in which double the value of sigma was used. If this is not fully justified, it would have the effect of making the apparent value of rho for LTBA reductions smaller than it should be.
13. "The" transition state for $NaBH_4$ and $LiAlH_4$ is perhaps an oversimplifying term in view of the four available hydrides in each reagent. For $LiAlH_4$ this is not a serious matter since in the presence of excess reductant, all reduction is done by the first hydride (9). For this and all other, mechanistic information refers only to this step. The difficulty lies

in extropolating mechanistic information to the question of stereoselectivity, since all four hydrides determine the latter.

14. W.G. Dauben, G.J. Fonken, and D.S. Noyce, J. Amer. Chem. Soc., 78, 2579 (1956).
15. E.C. Ashby and S.A. Noding, J. Org. Chem. 42, 264 (1977).
16. F.W. Gowland, Ph.D. Thesis, Carleton University 1977.
17. D.C. Wigfield and D.J. Phelps, J. Org. Chem., 41, 2396 (1976).

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