Tetrahedron Letters,Vol.25,No.48,pp 5551-5554,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

STEREOCHEMICAL EVIDENCE FOR SINGLE ELECTRON TRANSFER MECHANISM IN THE REDUCTION OF CYCLIC KETONES WITH ALKOXYALUMINIUM DICHLORIDES

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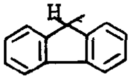
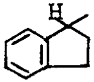
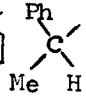
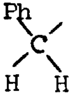
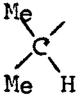
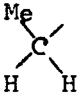
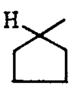
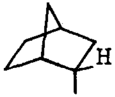
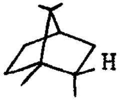
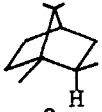
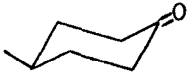
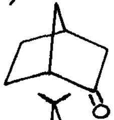
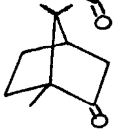
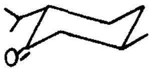
Summary: The stereochemical results of the reduction of cyclic ketones with alkoxyaluminium dichlorides do not conform to the conventional polar cyclic mechanism and may be explained by a single electron transfer mechanism.

Alkoxyaluminium dichlorides, $ROAlCl_2$ with hydrogen at α-carbon are good reducing agents for ketones,[1] the reduction going supposedly through a reversible H-transfer similar to Meerwein-Ponndorf-Verley (M-P-V) reaction. The one derived from bornan-2-exo-ol (XII) has proved particularly useful for its superior reactivity, high stereoselectivity (it affords the less stable epimeric alcohols in high excess),[1] and irreversibility of the reaction. Its optically active form has been successfully used for enantioselective reduction of a variety of prochiral ketones.[2] The results are interpreted on the basis of a cyclic mechanism (shown in A) or variations thereof.[3] In view of growing interest in the chemistry of complex hydrides, we have resumed the investigation with a host of these reagents (I)-(XII) and studied the stereochemistry of the reduction of a few typical cyclic ketones. 4-t-Butylcyclohexanone, an anancomeric system, represents unhindered cyclic ketones along with 2-, 3-, and 4-methylcyclohexanones; 3,3,5-trimethylcyclohexanone and norcamphor are moderately hindered while camphor and menthone are highly so. The results are summarised in Table 1 and discussed below.

The reagents prepared *in situ* by the action of anhydrous $AlCl_3$ on lithium tetra-alkoxyaluminium in ether in the presence of the ketone to be reduced are very reactive, specially the one derived from fluorenol (I), the reduction being effected in 5-10 min. at 0°C. The reactivity, however, diminishes with time and the reduction remains incomplete. The products are kinetically controlled and the possibility of equilibration of the alkoxyaluminium complexes is eliminated by suitable control experiments.

The stereochemical results (Table 1) with the reagents (I)-(XI) fall under three main categories. i) The unhindered cyclohexanones (entries 1-4) are reduced to the more stable equatorial alcohols preponderantly, in many cases more so than with $LiAlH_4$. Reagent (I) and (II) which are the bulkiest of all afford the highest ratio of such alcohols showing that 'steric approach control' (SAC) appears to be ineffective. ii) 3,3,5-Trimethylcyclohexanone and norcamphor (entries 5 and 6) give variable results with wider

Table 1. Stereochemistry of reduction of cyclic ketones with alkoxyaluminium dichlorides and related reagents

Entry No.	Ketones	Relative percentage[a] of the thermodynamically more stable alcohols by reduction with:													
		$ROAlCl_2$[b] for R =												$LiAlH_4$	Li-NH_3
															
		I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII[c]		
1		96-98 (95)[d]	90-95 (85)	80-85 (20)	85-88 (60)	87-89 (75)	75-90 (85)	70-72 (10)	70-75 (75)	-	95-97 (95)	55-60 (98)	8-10	89	98-99
2		84-88 (85)	75-80 (80)	-	-	-	-	-	-	-	-	-	10-11	81	99
3		89-92 (90)	78-80 (90)	-	-	-	-	-	-	-	-	-	8-9	88	94-95
4		80-88 (80)	-	-	-	-	-	-	-	-	-	-	2-3	70	99
5		75-95 (70)	83-85 (65)	-	-	63-65 (15)	22-32 (15)	- (0)	24-26 (40)	-	80-85 (70)	15-20 (20)	2	45	99
6		35-70 (45)	20-25 (50)	-	-	60-65 (20)	24-26 (20)	-	8-10 (20)	15-17 (70)	-	65-70 (8)	3-5	9	9-32
7		75-78 (10)[e]	-	-	-	-	-	-	-	-	-	-	-	10	79-90
8		62-65 (20)[e]	-	-	-	-	-	-	-	-	-	-	5	79	-

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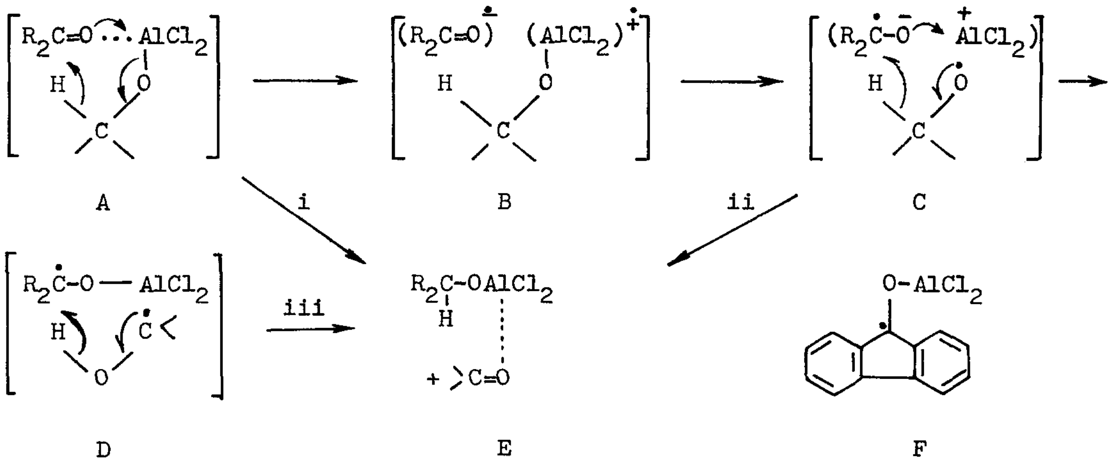
[a] Percentages were determined from at least three experiments by GC conducted on 10% Carbowax and 15% FFAP columns (2m) using FID. [b] Treatment with 1.5 mol reagents for 15-20 min. at ambient temperature. [c] Taken from ref. 1. [d] Yields are in parenthesis. [e] Treatment with 2 mol reagents for 4 hr.

product-spreads, the four nonaromatic reagents (VI)-(IX) exhibit SAC to a much greater extent than the aromatic ones (I), (II), and (V) while the results with reagents (X) and (XI) are anomalous. iii) Camphor and menthone (entries 7 and 8) are reduced only with the reagent (I) giving menthol and borneol (stabler epimers) in high excess. Reagent (XII), the first to be investigated,[1] however, behaves quite differently furnishing the less stable alcohols almost to the exclusion of the other epimers.

The results in general and with reagents (I) and (II) in particular bear a close resemblance to those of dissolving metal reductions[4] (Table 1, last column) in which H is transferred from a H-donor (ROH or NH_4Cl) to an alkoxy anion radical.[5] This observation along with the recent findings of Ashby _et al_ that aromatic ketones are reduced with metal hydrides[6] and alkoxides[7] through a radical intermediate formed by single electron transfer (SET) prompt us to suggest the following mechanism for these reductions.



The mechanism is similar to that proposed by Screttas and Cazianis[8] for M-P-V type reductions except in some minor details. The ketone first forms a complex (A) with the reagent which subsequently leads to a radical anion-cation pair (B) by SET and then to the radical (C). This in turn undergoes a rapid rearrangement[8] from O-radical to a more stable C-radical (D) and H is transferred (route iii) to $R_2\dot{C}$-OAlCl$_2$ from $\dot{C}$-OH (H-donor equivalent in Li-NH_3 reduction) to give the products (E). All these changes are reversible and take place inside the solvent cage. The protonated ketyl in D being more acidic than the corresponding alcohol[8] also reacts with the reagent (e.g., I) to form dichloroaluminium ketyl (F) which, according to Screttas and Cazianis, reduces $R_2CH\dot{O}$ (from starting ketone) by another SET (route iv). The stereochemistry of H-transfer in route (iii) follows from the preferred conformation of $R_2\dot{C}$-OAlCl$_2$ which explains the formation of more stable alcohols.[5] Two other pathways (i) and (ii), both reversible and much more sensitive to SAC are also available, their contributions depending on the steric situation and stability of the intermediate species. For cyclic ketones, attack from either side of C=O is sterically hindered, relatively speaking, and the reaction proceeds mainly <u>via</u> route (iii), particularly when $\dot{C}$-OH in species (D) is stabilised by resonance which explains most of the results. The cases with intermediate and variable stereochemistry may be rationalised on the basis of two or more competing mechanisms. Since the results arise out of a balance between several factors, a large product-spread is observed. The atypical behaviour of XII may be attributed to its high propensity for collapsing into camphor molecule (relief of steric strain) which helps it to react at an early stage (route i or ii).

No EPR signal, however, can be detected when fluorenone or benzophenone is added to $ROAlCl_2$ (e.g., VI and IX) in tetrahydrofuran (THF) indicating that no ketyl is present. On the other hand, when $AlCl_2$ is replaced by Li, K, or MgCl in the reagents, strongly paramagnetic solutions result.[7,8] This indicates that either the SET mechanism does not operate here (an unlikely proposition in view of the stereochemical results) or the radicals (as F) are destroyed on formation. We suggest that the ketyl (F) actually behaves as a mixture of fluorenone and $\dot{A}lCl_2$ and the latter readily couples with $R_2\dot{C}$-$OAlCl_2$ either directly or through SET (route iv).[8] As corroborative evidences, we have isolated norcamphorpinacol[4] in one of the equilibration experiment with norbornanol-complexes in THF. 4-<u>t</u>-Butylcyclohexanone when reduced with the reagent (I) and its α-D form shows the same stereochemistry (and reactivity), which is unusual if H is transferred from C rather than from O since such transfer is known to be more stereoselective[9] (also less reactive) for D than for H due to a possible 'tunnelling effect' of H which enables it to leave C from a longer distance so that transition states are less crowded. Finally, when the reductions are carried out in THF, the ratios of the stabler alcohols increase in all cases, more so with the reagent (XII) which gives 40% equatorial alcohols from 4-<u>t</u>-butylcyclohexanone and 3-cholestanone instead of 10% in ether. Evidently, there is now greater participation of the radical mechanism.

Authors are thankful to Dr. A.K.Pal of IACS, Calcutta-32 for EPR spectra.

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(Received in UK 30 August 1984)