THE MECHANISM AND STEREOCHEMISTRY OF REDUCTIONS OF OPEN-CHAIN KETONES BY SODIUM DIHYDRIDO-BIS(2-METHOXYETHOXY)ALUMINATE*

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The paper deals with the reduction of 3-phenyl-2-butanone by the hydride $NaAlH_2(OCH_2.CH_2OCH_3)_2$ and its derivatives $NaAlH(OR)(OCH_2CH_2OCH_3)_2$ in benzene, diethyl ether and tetrahydrofuran. As in the case of 3,3,5-trimethylcyclohexanone, the reduction has been found to proceed by the "zipped-down" mechanism. In the essential features the effective size (bulkiness) of a hydride manifests itself alike in the reduction of the two ketones.

The stereochemical course of the reduction of 3,3,5-trimethylcyclohexanone by sodium dihydrido-bis(2-methoxyethoxy)aluminate and the derived trialkoxy hydrides $NaAlH(OR)(OCH_2CH_2OCH_3)_2$ has been the subject of our previous papers[1,2]. We have inferred from the results that the reduction of cyclohexanone and substituted cyclohexanones by sodium dihydrido-bis(2-methoxyethoxy)aluminate proceeds by the "zipped-down" mechanism and that the effective bulkiness of a hydride is not just an additive quantity computable from its structure. The stereochemical course of the reaction is the resultant of a concerted effect of a number of factors, mainly association and solvation, which may play different roles in the reduction of different ketones[1]. To eliminate the factor of contingency given by the choice of model the objective of this work was to corroborate and extend the previous conclusions, drawn from the reduction of the substituted cyclohexanone by results of the reduction of ketones of a different type. We have chosen 1-phenyl-1-alkyl-2-propanones, because Chérest and Felkin reported[3] that the stereochemical course of reduction of these open-chain ketones was controlled by the same factors as the reduction of cyclohexanone-type ketones.

The effective size of an agent is interpreted by us on the basis of Chérest and coworkers' model[4].

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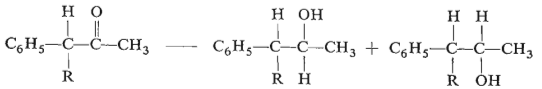
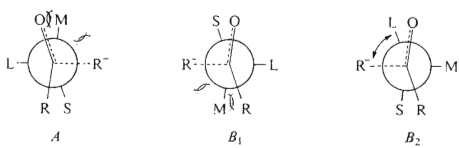
According to this interpretation the steric course of the reduction of open-chain ketones by complex hydrides is controlled primarily by Pitzer's tension in the transient, "reactant-like" states with staggered conformation, the postulate being that the do-



I *IIa* *IIb*

$R = CH_3$; C_2H_5; i-C_3H_7

minating conformations are *A*, B_1 and B_2 (Newman's projection) with the least steric interactions of R and R^-. The ratios of the transition state conformations, $A : B_1$ and/or $A : B_2$, then determine the stereoselectivity of the reaction.



A B_1 B_2

The effective size of hydrides has been investigated on the reduction of 3-phenyl-2-butanone in which $R = M = CH_3$, $S = H$, $L = C_6H_5$ and $R^- = NaAlH_2.(OCH_2CH_2OCH_3)_2$ or $NaAlH(OR)(OCH_2CH_2OCH_3)_2$. The interpretation of the size of R^- is based on the following assumption: *1.* In the chosen model, where L denotes an electronegative group, the conformation B_2 can be disregarded in view of the very strong interaction of L and R^- so that in the first place it is necessary to consider the conformations *A* and B_1, where the distance between L and R^- is maximum. *2.* An increase in the size of R^- manifests itself in these conformations by a stronger interaction between R^- and M; this effect is more significant in B_1 than in *A* since in the former case the $R^- - M$ interaction is combined with the strong $M - R$ interaction whereas in the latter with only a weak interaction between M and the carbonyl oxygen[4]. In this connexion it is also evident that the combination of interactions will have a stronger effect in models with a relatively small M in which the B_1 conformation may still play an important role.

The results of this work show that in the reduction of open-chain ketones the order of the studied hydrides according to their effective size is the same as in the reduction of 3,3,5-trimethylcyclohexanone: *1.* The reduction of 3-phenyl-2-butanone by sodium

dihydridodialkoxyaluminate, $NaAlH_2(OCH_2CH_2OCH_3)_2$, was less stereoselective than the reduction by sodium hydridotrialkoxyaluminates, $NaAlH(OR)(OCH_2CH_2.OCH_3)_2$, irrespective of the character of R in the alkoxyl, *i.e.* even if R = isopropyl (Table I). This result extends validity of the postulated "zipped-down" mechanism, derived previously from the reduction course of 3,3,5-trimethylcyclohexanone in benzene[1] and tetrahydrofuran[2], which now appears to apply even to open-chain ketones in these solvents and in diethyl ether. *2.* In accordance with our previous results obtained with the cyclohexanone-type ketone, the stereoselectivity was relatively high in the reduction by $NaAlH(OCH_3)(OCH_2CH_2OCH_3)_2$. Thus in all the three solvents the content of the *erythro* form *IIb* was greater than in the reduction by $NaAlH.(O\text{-}t\text{-}C_4H_9)(OCH_2CH_2OCH_3)_2$ (Table I). The differences are not substantial (3–6%) but are statistically significant according to Lord's test. This observation is rather striking, since comparison of the additive sizes of the small methyl and the bulky tert-butyl would suggest the very opposite. The probable explanation seems to be a greater tendency of $NaAlH(OCH_3)(OCH_2CH_2OCH_3)_2$ to associate than that of alkoxy hydrides with bulkier alkoxyls. This view is substantiated by the results published by Ashby and coworkers[5]; these authors succeeded in correlating a similar phenomenon, observed in the reduction by tetrahydrofuran solutions of $LiAlH.(OCH_3)_3$ and $LiAlH(O\text{-}t\text{-}C_4H_9)_3$, with association of these hydrides in tetrahydrofuran. *3.* The stereoselectivity of reduction by $NaAlH_2(OCH_2CH_2OCH_3)_2$ has been found to be statistically highest (significantly) in tetrahydrofuran (Table I); this

TABLE I

Contents (%) of the *erythro* Isomer *IIb* in the Reductions of 1-Phenyl-1-alkyl-2-propanones (*I*) by Hydrides $NaAlHX(OCH_2CH_2OCH_3)_2$ at 25°C in Different Solvents

R	X	Benzene	Ether	Tetrahydrofuran
CH_3	H	68	70	73
	OCH_3	83	85	82
	OC_2H_5	75	79	81
	O—i-C_3H_7	77	78	79
	O—t-C_4H_9	80	79	79
	$OCH_2CH_2OCH_3$	77	79	74
C_2H_5	H	74	76	78
	$OCH_2CH_2OCH_3$	82	84	80
i-C_3H_7	H	80	80	80
	$OCH_2CH_2OCH_3$	86	85	84

fact can be interpreted by the assumption that even in the reduction of the studied ketone the specific solvation affinity of this hydride to tetrahydrofuran plays an important role[2].

Also reduced were 3-phenyl-2-pentanone (*I*, R = C_2H_5) and 3-phenyl-4-methyl-2-pentanone (*I*, R = i-C_3H_7) by $NaAlH_2(OCH_2CH_2OCH_3)_2$ and $NaAlH(OCH_2.CH_2OCH_3)_3$ in benzene, diethyl ether and tetrahydrofuran (Table I). In all the three solvents the growth of R in *I* (M in models *A*, B_1 and B_2) manifests itself by an increase in stereoselectivity. This fact accords with Chérest's assumption[4] that an increase in M furthers the *A* conformation at the expense of the B_1 conformation. By comparing the stereoselectivities of reduction by $NaAlH_2(OCH_2CH_2OCH_3)_2$ and by $NaAlH(OCH_2CH_2OCH_3)_3$ it is apparent that even in the models with bulkier M the additive growth of R^- brings about the expected increase in stereoselectivity whereas a larger effective size of $NaAlH_2(OCH_2CH_2OCH_3)_2$ caused by the solvating action of the solvents is statistically significant even in *I* with R = C_2H_5 (like with R = CH_3), but not in the model with a bulky M (*I*, R = i-C_3H_7).

The results show that physico-chemical data on the association[6,7] and solvation[7,8] of a hydride are not yet a sufficient basis for predicting the stereochemical course of the reduction of a ketone. What is evidently essential is the stability or lability of the association and solvation aggregations, which may naturally be different in the use of model compounds with different steric demands.

EXPERIMENTAL

Chemicals

The ketones, obtained by acidolysis of the corresponding acylmalonic esters[9], were distilled over a column (3-phenyl-2-butanone, b.p. 85·5—87°C/9 Torr; 3-phenyl-2-pentanone, b.p. 65—66°C : : 0·3 Torr) and kept over a molecular sieve. A benzene solution of sodium dihydrido-bis(2-methoxyethoxy)aluminate was prepared by dilution of a 70% stock solution with benzene. The solutions of a hydride in diethyl ether and tetrahydrofuran were obtained by dissolving the residue after distilling off benzene from the 70% stock solution (5 h at 10°C/0·5 Torr) in the chosen solvent.

Reductions by $NaAlH_2(OCH_2CH_2OCH_3)_2$ were effected by adding 0·5 g of a ketone to 20 ml of an about 5% solution of the hydride in a chosen solvent and stirring the mixture for 1 h at 25°C under nitrogen. After hydrolysis (0·5 ml of water was added) the solution was separated from the hydrolytic products. The proportion of the *erythro* and *threo* alcohols in the solution was determined by gas chromatography in a chromatograph Chrom III on Chromosorb with 20% Carbowax 20 M at 160°C (3-phenyl-2-butanols) or 170°C (3-phenyl-2-pentanols and 3-phenyl-4-methyl-2-pentanols). The standards were the pure *erythro* and *threo* alcohols, separated from each other by preparative gas chromatography or by distillation of their esters with phthalic acid and 3-nitrophthalic acid[10].

Reductions by $NaAlH(OR)(OCH_2CH_2OCH_3)_2$ were performed analogously. The only difference was that prior to the reaction a calculated amount of the corresponding alcohol was added at 25°C under stirring to a solution of the hydride in a given solvent.

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