

ON THE BEHAVIOUR AND REACTIVITY
OF SOLUTIONS OF COMPLEX HYDRIDES. IV.*

THE EFFECT OF SOLVENT ON THE STEREOCHEMISTRY
OF REDUCTION OF 3,3,5-TRIMETHYLCYCLOHEXANONE
WITH SODIUM DIHYDRIDO-BIS-(2-METHOXYETHOXY)ALUMINATE

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Received June 14th, 1971

The high stereospecificity of the reductions of 3,3,5-trimethylcyclohexanone with sodium dihydrido-bis(2-methoxyethoxy)aluminum in tetrahydrofuran (especially at low concentrations of the agent), as against the reductions in diethyl ether and aromatic hydrocarbons, is interpreted in terms of a specific solvation effect of tetrahydrofuran on this hydride. The reduction of the ketone in tetrahydrofuran is assumed to proceed by a "zipped-down mechanism".

On the basis of our study¹, comparing the stereochemical courses of the reductions of 3,3,5-trimethylcyclohexanone with benzene solutions of sodium dihydrido-bis(2-methoxyethoxy)aluminum^{2,3}, $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$, and the derived trialkoxyhydrides, $\text{NaAlH}(\text{OR})(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$, a "zipped-down mechanism" for the reduction of ketones in this solvent has been proposed. The present paper describes an analogous study of the reductions in tetrahydrofuran. It appears that the reductions proceed by the same mechanism, judging by the higher content of *trans*-3,3,5-trimethylcyclohexanol after reductions with $\text{NaAlH}(\text{OR})(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ than after those effected with $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$, including the hydrides where R is a secondary alkyl (Table I). The postulates advanced by Haubenstock and Eliel⁴, discussed and employed in our preceding paper¹, allow of assuming the existence, even in tetrahydrofuran, of the stable $\text{NaAlH}(\text{OR})(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$, where R is the corresponding secondary alkyl, as intermediates of the reduction of ketones with $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$. Compared to the reductions in benzene, however, the contents of *trans*-3,3,5-trimethylcyclohexanol were always higher. This fact suggests a greater bulkiness of the reducing particle in tetrahydrofuran, favouring its attack on the equatorial, less hindered side of the molecule, giving rise to a product with an axial hydroxyl.

* Part III: This Journal 37, 2175 (1972).

This increase in the effective volume of the agent in tetrahydrofuran is obviously due to solvation. The strong solvation power of tetrahydrofuran manifested itself also in the reduction of 3,3,5-trimethylcyclohexanone with $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ in different solvents. In benzene¹, toluene and diethyl ether the proportion of the *trans*- and the *cis*-3,3,5-trimethylcyclohexanols was the same ($57 \pm 2\%$ of the *trans* isomer), whereas in tetrahydrofuran the ratio was different by about 10% in favour of the *trans* isomer ($68 \pm 2\%$). This fact shows that the solvation power of tetrahydrofuran compared to that of diethyl ether is greater not only for LiAlH_4 (ref.⁴), but also for the new hydride $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$.

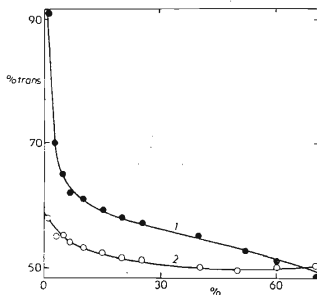


FIG. 1
Stereochemical Course of the Reduction of 3,3,5-Trimethylcyclohexanone with Differently Concentrated Solutions of $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ in 1 Tetrahydrofuran and 2 Benzene at 25°C

The axis of ordinates gives % of *trans*-3,3,5-trimethylcyclohexanol.

The solvation effect on the stereospecificity of the reduction has further been investigated by following the changes in stereospecificity of the reduction of 3,3,5-trimethylcyclohexanone with benzene and tetrahydrofuran solutions of $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ of various concentrations (1 to 70% [w/w] of the hydride). In the former case the proportion of the formed isomeric alcohols changed negligibly in this wide concentration range (by about 7% in favour of the *trans* isomer), whereas in the latter the change in stereospecificity with the concentration of the agent was considerable (by approx. 40% in favour of the *trans* isomer) (Fig. 1). This change was most marked in dilute tetrahydrofuran solution of the agent, where the *trans* isomer predominated, which indicates that the reducing particles get bulkier with diluting the solution. The course of the changes in stereospecificity with concentration of the agent suggests that the solvation effect (which is most operative in dilute solutions) outweighs the association effect (which would increase the stereospecificity in concentrated solutions, where the association degree of the hydride is higher⁵). The results show that the maximum changes in stereospecificity of the reduction of ketones with $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ can be expected to occur in tetrahydrofuran.

EXPERIMENTAL

Chemicals

The solutions of $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ in toluene, diethyl ether and tetrahydrofuran were prepared from a 70% benzene solution of the hydride by distilling off the solvent at 80–90°C *in vacuo* (1–2 Torr) and dissolving the residue in the chosen solvent. The ratio of the *trans*- to the *cis*-3,3,5-trimethylcyclohexanols was determined by gas chromatography¹.

Reductions with $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$

In the case of 5% solutions in toluene, diethyl ether and tetrahydrofuran the procedure was analogous to that described previously for the solutions in benzene¹ except that the ketone was added as a pure substance (not in the form of a solution). Solutions in benzene and tetrahydrofuran, of different concentrations, were prepared by the addition of the corresponding amount of the solvent to the starting 70% solution and the reduction was carried out as with the 5% solutions. The results are illustrated in Fig. 1.

TABLE I

Yield of *trans*-3,3,5-Trimethylcyclohexanol from the Reduction of 3,3,5-Trimethylcyclohexanone with 5% Solution of the Hydrides $\text{NaAlH}(\text{X})(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ in Tetrahydrofuran at 25°C

$\text{NaAlH}(\text{X})(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ was obtained by the reaction of $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ with 1 mol of the alcohol (ketone).

X	H	OCH_3	OC_2H_5	$\text{O}-i\text{-C}_3\text{H}_7$	OC_4H_9
<i>trans</i> isomer, %	68	76	77	76 (77)	77
X	$\text{O}-s\text{-C}_4\text{H}_9$	$\text{O}-t\text{-C}_4\text{H}_9$	$\text{O}-\text{C}_6\text{H}_{11}$ (cyclo)	$\text{OCH}_2\text{CH}_2\text{OCH}_3$	
<i>trans</i> isomer, %	76 (74)	81	79 (79)	77	

Reductions with $\text{NaAlH}(\text{OR})(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$

These were carried out with 5% solutions in tetrahydrofuran, adhering to the procedure employed previously with the benzene solutions¹. The results are given in Table I.

Acknowledgement is due to Mrs A. Nováková for technical assistance and to Dr J. Stuchlík for the chromatographic analyses.

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Translated by J. Salák.