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**STUDY ON THE BEHAVIOUR AND THE REACTIVITY
OF SOLUTIONS OF COMPLEX HYDRIDES. I.
CONTRIBUTION TO THE MECHANISM OF THE REDUCTION
OF KETONES WITH A BENZENE SOLUTION
OF SODIUM DI(2-METHOXYETHOXY)ALUMINUM HYDRIDE***

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In connection with our studies of alkoxyaluminum hydrides of alkali metals stable sodium di(2-methoxyethoxy)aluminum hydride, $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$, has been prepared^{1,2}. Its reducing capacity has been studied in a number of papers³⁻¹¹ from which it followed that in the majority of cases it is comparable with the reducing capacity of lithium aluminum hydride. In this respect it is not without interest to compare the mechanisms of the reductions with both agents. In addition to this the solubility of the new reagent in benzene (in which it is present in monomeric form¹² at the boiling point of the solvent enables us for the first time to follow the reductions with complex hydrides in solvents without donor atoms. For our study we investigated the course of the reduction of ketones which can give two epimeric alcohols.

Our procedure was similar to that of Haubenstock and Eliel¹³ who studied the reduction of 3,3,5-trimethylcyclohexanone using a series of ethereal and tetrahydrofuran solutions of lithium aluminum hydride and of alkoxyhydrides derived from it, $\text{LiAlH}_{4-n}(\text{OR})_n$, where R are primary, secondary, and tertiary alkyls. From the comparison of the ratios of epimeric alcohols obtained by reduction with the mentioned three types of alkoxyhydrides and the ratios of epimers found after the reduction with LiAlH_4 alone, the authors derived a "disproportionation" mechanism of the reduction of ketones, based on the assumption of the instability of alkoxyhydrides $\text{LiAl} \cdot \text{H}_{4-n}(\text{OR})_n$ with secondary R, which were considered earlier as possible intermediary steps of the reduction of ketones¹⁴.

In our work we also employed 3,3,5-trimethylcyclohexanone as a representative of ketones of cyclohexanone series with an only slightly sterically hindered keto group (caused by the axial methyl group in the position 3), in which the stereochemical course of the reduction may be

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directed both by "steric approach control" and by "product development control" effects¹⁵. For the sake of comparison we carried out the same series of reductions of (+)-camphor, representing rigid, strongly sterically hindered ketones with which the "product development" effect cannot exert its influence during the reduction.

The reductions were carried out with 6% benzene solutions of $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ or of the corresponding alkoxyhydride $\text{NaAlH}(\text{OR})(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$, where R is a primary, secondary, or tertiary alkyl group. Trialkoxyhydrides were prepared in situ by reacting $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ with one mol of the corresponding alcohol, and in the case of alkoxyhydrides derived from secondary alcohols alternatively by reduction of one mol of the corresponding ketone. For reductions the chosen temperature was 25°C which enabled comparison with the physico-chemical measurements¹⁶. The analysis of the ratio of the epimeric alcohols formed was carried out in both instances by means of gas chromatography. Its utilisation, in addition to other advantages, enables the elimination of the disturbing effect of the residues of the original ketone in the reaction mixture, which negatively influence the determination of the ratio of alcohols.

EXPERIMENTAL

Substances Used

A solution of $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ of the required concentration was prepared by dilution of a 70% benzene solution of this hydride with benzene; the benzene used was predried with sodium and distilled over $\text{NaAlH}_2(\text{OCH}_2\text{OCH}_3)_2$. Benzene which was not distilled over this hydride causes a spontaneous decomposition of the hydride on dilution. 3,3,5-Trimethylcyclohexanone (b.p. 97–98°C/43 Torr) was prepared by a known procedure^{17,18} and it was kept over a molecular sieve. (+)-Camphor (Carlo Erba) had m.p. 177–178°C. The ratio of epimeric alcohols in the reaction mixture was analysed gas chromatographically on a Chrom III apparatus at 130°C, using polyethylene glycol 1500 as stationary phase fixed on Chromosorb W 80/100 mesh. The ratio of epimeric alcohols was estimated by measuring the band width at half of its height. This method given the same values as the methods based either on the weighing of the bands or on their integration by means of an apparatus.

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

A) "Normal" procedure (method a): A 9% hydride solution (10 ml; 8.9 g; 3.96 mmol) was introduced into a vessel through a rubber closure by means of a syringe and the solution was brought to 25°C. (+)-Camphor (1.2057 g; 7.92 mmol) or 3,3,5-trimethylcyclohexanone (1.1105 g) in 5 ml of benzene were then added over 10 minutes. The resulting hydride concentration was 6%. After one hour stirring at 25°C the mixture was decomposed by 30 minutes stirring with 1 ml of water. The supernatant was decanted off from the separated products of hydrolysis, dried over sodium sulfate, and analysed by gas chromatography.

B) Using excess hydride (method b): The reduction was carried out as described above, except for the fact that 11.88 mmol (26.7 g) of 9% hydride solution were taken into the reaction and that the ketones were added in 15 ml of benzene.

C) "Inverse" procedure (method c): To 7.92 mmol of 3,3,5-trimethylcyclohexanone or (+)-camphor in 5 ml of benzene were dropwise added over 15 minutes 8.9 g of a 9% hydride solution. The reaction mixture was worked up and analysed as under A.

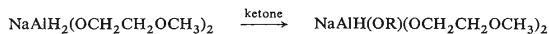
Reduction with $\text{NaAlH}(\text{OR})(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$

A) *Hydride prepared from alcohol (method d)*: The procedure was similar to that of method *a*; before the addition of 3.96 mmol of 3,3,5-trimethylcyclohexanone or (+)-camphor to the hydride solution, 3.96 mmol of the corresponding alcohol were added to it. The liberated hydrogen was measured and the mixture was stirred at the given temperature for half an hour. The working up of the reaction mixture was similar to method *a*.

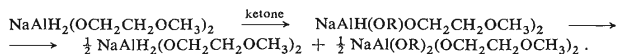
B) *Hydride prepared from ketone (method e)*: Before the addition of 3.96 mmol of 3,3,5-trimethylcyclohexane or (+)-camphor 3.96 mmol of the corresponding ketone were added to the hydride solution and the mixture was stirred at 25°C for one hour. The working up of the reaction mixture was carried out as in method *a*.

RESULTS AND DISCUSSION

From the first column in Table I it is evident that in the reduction of 3,3,5-trimethylcyclohexanone the proportion of the less stable isomer with an axial hydroxyl. (*trans*-3,3,5-trimethylcyclohexanol), is in all instances higher when the reduction is carried out with $\text{NaAlH}(\text{OR})(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ than when performed with the original hydride, $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$. This is also true in such cases when OR is an alkoxy derived from secondary alcohols. This fact differs radically from the results of the comparative study of the reduction carried out by Haubenstein and Eliel¹³ who on reduction of the mentioned ketone with LiAlH_4 or $\text{LiAlH}(\text{OR})_3$ found an increased proportion of *trans*-3,3,5-trimethylcyclohexanol only in cases when OR was derived from primary and tertiary alcohols, while the reductions with alkoxyhydrides with secondary alkoxy groups gave a similar ratio of isomers as in the reduction with LiAlH_4 (see Table I). This fact was utilised by the mentioned authors¹³ as the main and decisive argument for the formulation of their "disproportionation" hypothesis according to which alkoxyhydrides $\text{LiAlH}_{4-n}(\text{OR})_n$ containing secondary alkoxy groups (*i.e.* the possible products of ketone reduction) are generally unstable* and disproportionate immediately to LiAlH_4 and $\text{LiAl}(\text{OR})_4$. Thus, in this case the reducing agent is the original reagent over the whole reaction time.** The application of Haubenstein-Eliel's argument to our case may be used for the demonstration that alkoxyhydrides of the $\text{NaAlH}(\text{OR})(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ type are stable in contrast to the $\text{LiAlH}(\text{OR})_3$ type (OR is in both cases a secondary alkoxy), and that they occur as intermediates during the reduction of ketones with $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$. For the reduction of ketones by this reagent the "zipped down" mechanism may be proposed as the most probable.



$\xrightarrow{\text{ketone}} \text{NaAl}(\text{OR})_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$
but not the "disproportionation" mechanism



* The attempts of Brown and Shoaf¹⁹ at the preparation of various types of $\text{LiAlH}_{4-n}(\text{OR})_n$ also agree with the proposed hypothesis.

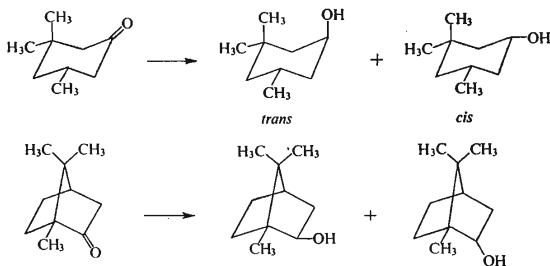
** The "disproportionation" mechanism can also explain¹³ the stereospecific insensitivity of the reduction of ketones with LiAlH_4 at different component ratio (for a remark concerning this problem see below, in the text).

TABLE I

Reduction of 3,3,5-Trimethylcyclohexanone and (+)-Camphor with $\text{NaAlHX}(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ Hydrides in Benzene at 25°C

The letters after the values indicate the methods used for reduction (see Experimental). For comparison the values of the reductions with LiAlH_4 or $\text{LiAlH}(\text{OR})_3$, where OR corresponds to corresponding X^{13} , are given in brackets

X	<i>trans</i> -3,3,5-Trimethylcyclohexanol, %			Isoborneol, %		
H	57a; (52)	59b; (55)	55c (55)	89a;	89b;	88c
OCH_3	77d (75)			90d		
OC_2H_5	71d (83)			90d		
O-i-C ₃ H ₇	70d; (54)	68e		89d;	90e	
OC_4H_9	69d			89d		
O-s-C ₄ H ₉	70d;	64e		91d;	89e	
O-t-C ₄ H ₉	72d (73)			90d		
O-C ₆ H ₁₁ (cyclo)	73d;	74e (58)		89d;	90e	
$\text{OCH}_2\text{CH}_2\text{OCH}_3$	67d			89d		



Reduction with $\text{NaAlH}(\text{OR})(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ give the proportion of the *trans* isomer in the range of 64 to 77%; at the same time it is evident that no simple correlation exists between the bulkiness of the OR group and the ratio of the isomers formed.

$\text{NaAlH}(\text{OR})(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ in which R is a secondary alkyl, were prepared in two ways, *i.e.* on reaction of one mol of the corresponding alcohol (method *d*), or on reduction of one mol of the corresponding ketone (method *e*) with sodium di(2-methoxyethoxy) aluminum hydride. The ratio of the 3,5,5-trimethylcyclohexanols formed is within the experimental errors in cases when R is isopropyl and cyclohexyl, while when R is a secondary butyl group, the proportion of the *trans* alcohol found was 6% lower with method *a* than when method *d* was applied.

For $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ the values of the representation of *trans*-3,3,5-trimethylcyclohexanol are given in the first line of Table I: at "normal" procedure of the reduction, using an equimolar amount of hydride (method *a*), using its excess (method *b*), and carrying the reaction out by the "inverse" procedure (method *c*). While with method *b* reduction takes place in the presence of excess $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$, in the last case the corresponding intermediate $\text{NaAlH}(\text{OR})(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ should be involved primarily during the reduction: the latter is much bulkier than the original reagent, and this fact should be reflected in the increase of the proportion of the *trans* alcohol. However, the proportion of the *trans* isomer is within the limits of error of the analytical method used. From this it follows that the considerations concerning the mechanism, which are based on the stereochemical course of the reduction at different ratios of the reacting components, are not substantiated, because the stereospecific insensibility may be found in both mechanisms under consideration. In the case of the "disproportionation" mechanism (reduction of ketones with LiAlH_4) alkoxyhydrides cannot manifest because of their instability¹³, while in the "zipped down" mechanism the alkoxyhydrides present in the reaction mixture cannot exert their influence if their reactivity is higher by an order of magnitude. Evidently, the latter case occurs during the reduction mentioned above.

From the second column in Table I it is evident that on reduction of (+)-camphor the difference between the ratio of the isomers formed on reduction with $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ and $\text{NaAlH}(\text{OR})(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ cannot be observed either. From the comparison of the analogous series of reductions of 3,3,5-trimethylcyclohexanone and (+)-camphor it follows that for the study of the mechanism of the reductions of ketones from the comparison of the ratios of the isomers formed, the type of flexible ketones displaying small sterical hindrance is suitable, while rigid, strongly hindered ketones are not.

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ELEKTROREDUKTION DER ENOLAT-ANIONEN DES 2-ACETYL- UND 2-BENZOYL-1,3-INDANDIONS

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In einer vorangehenden Arbeit¹ haben wir das polarographische Verhalten von 2-Acetyl-1,3-indandion und 2-Benzoyl-1,3-indandion untersucht. In der vorliegenden Arbeit, die an jene anknüpft, befaßten wir uns mit der präparativen Elektroreduktion der Enolat-Anionen dieser Verbindungen, mit der Isolierung der Reduktionsprodukte und ihrem Strukturnachweis.

EXPERIMENTELLER TEIL

Die präparative Elektroreduktion an einer großflächigen Quecksilberkathode bewerkstelligten wir mittels des in früheren Arbeiten^{2,3} beschriebenen Verfahrens und Geräts unter Anwendung von Lösungen der untersuchten Stoffe der Konzentration $1,2 \cdot 10^{-3} - 1 \cdot 10^{-3}$ mol/l bzw. bei Schaltung mit dem Potentiostat Ple des Forschungsinstituts SVÚOM der Konzentration $2 \cdot 10^{-4}$ bis $1 \cdot 10^{-4}$ mol in ca $10^{-2} - 10^{-3}$ mol/l NaOH unter Verwendung von Kaliumchlorid zur Einstellung der Ionenstärke auf den Wert $\mu = 0,1$. Nach Beendigung der präparativen Reduktion wurde das bei der Elektroreduktion zur Erhöhung der Löslichkeit angewandte Aceton im Vakuum abdestilliert und die Reduktionsprodukte durch Extraktion mit Äther bzw. Chloroform isoliert. Nach Entfernung des Extraktionsmittels wurden die Reduktionsprodukte an einer Säule aus neutralem Aluminiumoxid (Brockmannaktivität II) gereinigt. Als Elutionsmittel wurden Benzol-Chloroform-Mischungen verwendet.

Die IR-Spektren der Reduktionsprodukte wurden mit einem Zeiss-Spektrophotometer, Modell UR-20, in Chloroformlösungen der Konzentration ca. $6 \cdot 10^{-2}$ mol/l in Küvetten der Schichtdicke 0,08 mm im Spektralbereich $800 - 3800 \text{ cm}^{-1}$ aufgenommen. Zum Nachweis der intramolekularen Wasserstoffbindungen wurden die Spektren der Stoffe in Tetrachlormethan-Lösungen der Konzentration $2 \cdot 10^{-1} - 2 \cdot 10^{-4}$ mol/l in Küvetten der Schichtdicke 0,01–10 cm gemessen.

Die polarographischen Messungen wurden mit dem Polarographen LP-60 unter Anwendung des Schreibers EZ-2 vorgenommen.