

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

The Mechanism of the Meerwein-Ponndorf-Verley Reaction. A Deuterium Tracer Study

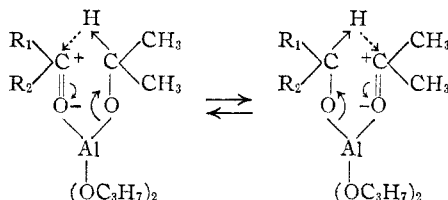
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The mode of hydrogen transfer during the Meerwein-Ponndorf reduction of cyclohexanone with aluminum isopropoxide in carbon tetrachloride solution has been investigated using deuterium. Cyclohexanone was reduced with aluminum isopropoxide containing deuterium mainly on the carbinol carbon atoms, and the deuterium transfer determined. The amount of deuterium transfer independent of the reduction reaction was also determined. It has been shown that the reduction proceeds with hydrogen transfer mainly from the carbinol carbon atom of the isopropoxide groups to the carbonyl carbon atom of the ketone. The results of this investigation are consistent with a mechanism, suggested by previous workers, which involves a "cyclic" structure as the intermediate reaction complex.

Earlier investigators suggested that the Meerwein-Ponndorf-Verley reaction involves a reaction complex which has a "cyclic" structure for the essential hydrogen transfer step.¹ More recent work on the stereochemical nature of the reaction² has given strong support to this suggestion.

A "cyclic" intermediate requires that the hydrogen transfer from the carbinol group to the carbonyl group be specific. The present work was undertaken to demonstrate this specificity of hydrogen transfer by using deuterium as a tracer atom. It was found that the transfer takes place in the absence of any alcohol, indicating that the transfer involves only the groups attached to the aluminum atoms. The results of the present study are in agreement with the cyclic mechanism proposed by earlier workers. This mechanism may be shown as



The data from this study leave no doubt as to what hydrogen is transferred. They do not, however, give an answer as to the mode of that transfer (*i.e.*, by the transfer of hydrogen from the carbinol carbon of the coordinated aluminum isopropoxide or by the attack of another molecule of the coordinated complex).

Experimental

Highly purified reagents were used in every case. The deuterium gas (99.5% purity) was obtained from the Stuart Oxygen Co. and the lithium aluminum deuteride (91% purity) from Metal Hydrides, Inc.

Deuterium Analysis.—One-milliliter samples were burned by passing the organic vapors entrained in dry nitrogen over an excess of cupric oxide heated to 600°. The copper was then reoxidized by heating in a stream of oxygen which had been dried by passage over Drierite. The water of combustion was frozen out of the effluent gas in a Dry Ice-alcohol trap and was purified by heating with 1 g. of silver oxide and then distilling into a second trap immersed in a freezing bath by evacuating the system to 20–30 mm. pressure. The sample was then sublimed into a third

trap at 1–3 mm. pressure and stored in a paraffin-lined screw-cap vial until its density was determined.

The falling-drop method of deuterium analysis was used essentially as described by Cohn.³ The pipet was a modification of that described by Rosebury and van Heyningen⁴ and was constructed of stainless steel with a plunger diameter of 0.180 in. giving a constant-size drop of between 7–8 cu. mm. with one complete revolution of the micrometer screw.

Two liters of deuterium gas was burned, and the density of the water sample determined using a 0.5-ml. weighing pipet, weighed to ± 0.01 mg. Using the data of Wirtz,⁵ the mole fraction of deuterium oxide was calculated and a series of samples in the range from 0–2% deuterium oxide was prepared by weight using water freshly distilled from alkaline permanganate as a diluent. A plot of the drop-times against the per cent. deuterium oxide was constructed and served as an empirical calibration curve.

Deuteration of Acetone.—Acetone in xylene solution was reduced with deuterium over platinum oxide.⁶ The mixture was fractionated through a Todd fractionating column⁷ and the fraction boiling at 81–83° was used for conversion to aluminum isopropoxide.

Reduction with Lithium Aluminum Deuteride.—In a 250-ml. round-bottom flask equipped with addition funnel, condenser protected with a calcium chloride tube, and a magnetic stirrer were placed 1.01 g. (0.0239 mole) of lithium aluminum deuteride and 50 ml. of anhydrous ether. After the mixture had refluxed for 0.5 hour, a solution of 6.25 ml. (0.085 mole) of anhydrous acetone in 25 ml. of anhydrous ether was added over a 45-minute period. After heating for an additional 30 minutes, the complex was hydrolyzed by adding 50 ml. of 3 *N* hydrochloric acid. The alcohol was isolated by continuous extraction with ether for 12 hours, 25 ml. of anhydrous isopropyl alcohol being added to the water layer after the first hour. The dried ether extract was diluted with 75 ml. more isopropyl alcohol and the product isolated by fractionation.

Conversion to Aluminum Isopropoxide.—One hundred milliliters (1.31 moles) of the alcohol was heated with 13.5 g. (0.500 mole) of aluminum foil, 5 g. of aluminum isopropoxide being added as a catalyst. After 12 hours the material was distilled in vacuum and 85.7 g. (83.3% of the theoretical amount) of aluminum isopropoxide was isolated.

Determination of Deuterium Distribution.—The alkoxide was hydrolyzed by adding dilute sulfuric acid and the alcohol isolated as the azeotrope by direct distillation. After drying, the pure alcohol boiled from 82.5–83.0°. One milliliter of this was burned to water and analyzed for deuterium content.

A sample of alcohol was oxidized by adding 2.0 g. of sodium dichromate dihydrate, 2.5 ml. of water and 1.6 ml. of concentrated sulfuric acid per milliliter of alcohol. The acetone was isolated by distillation and after drying and redistillation boiled from 56.0–56.5°. Combustion of one milliliter of this compound and analysis of the water pro-

(3) M. Cohn, "Preparation and Measurement of Isotopic Tracers," J. Edwards, Ann Arbor, Michigan, 1947, p. 51.

(4) F. Rosebury and W. van Heyningen, *Ind. Eng. Chem., Anal. Ed.*, **14**, 363 (1942).

(5) K. Wirtz, *Physik. Z.*, **43**, 465 (1942).

(6) L. Friedman and J. T. Turkevich, *This Journal*, **74**, 1666, 1669 (1952).

(7) F. Todd, *Ind. Eng. Chem., Anal. Ed.*, **17**, 175 (1945).

(1) R. B. Woodward, N. L. Wendler and F. J. Brutschy, *This Journal*, **67**, 1425 (1945); R. Baker and L. Linn, *ibid.*, **71**, 1425 (1949).

(2) L. M. Jackson, A. Macbeth and J. Mills, *J. Chem. Soc.*, 2641 (1949); W. E. Doering and R. W. Young, *This Journal*, **72**, 631 (1950).

duced allows the calculation of the amount of methyl group deuterium. The amount of deuterium on the carbinol carbon atom was obtained by subtracting this amount from the total deuterium content of the original alcohol.

Reduction of Cyclohexanone.—Cyclohexanone (0.15 mole) was reduced by heating with a solution of 0.21 mole of the tagged aluminum isopropoxide in 150 ml. of carbon tetrachloride for 9.5 hours, the acetone produced during the reaction being separated by fractionation through a 30-cm. packed column and being collected directly in a 50-ml. volumetric flask immersed in a freezing mixture. The solution was then cooled and the carbon tetrachloride drawn off under reduced pressure. Hydrolysis was effected under reflux by adding 3.33 *N* sulfuric acid and the solution was then ether extracted. Distillation of the dried ether extract through the Todd column yielded first a small amount of the carbon tetrachloride-isopropyl alcohol azeotrope, then pure isopropyl alcohol, b.p. 82–83°, and cyclohexanol, b.p. 33–35° at 39–41 mm. pressure.

The acetone-containing mixture in the volumetric flask was allowed to warm to room temperature and diluted to the mark with carbon tetrachloride. Two 5-ml. aliquot portions were analyzed for acetone by the method of Bryant and Smith⁸ modified by using a pH meter and titrating to the pH of a blank. This permits the calculation of the percent. of reduction. The remainder of the solution was fractionated through the Todd column, the fraction boiling from 56.0–56.5° being used for the deuterium determination.

The deuterium content of the acetone and of the isopropyl alcohol isolated was determined as previously described. The total amount of deuterium in the cyclohexanol was determined by combustion, and the amount of isotope present on positions other than the carbinol carbon atom was determined by analysis of the water of combustion from cyclohexanone produced by the acid dichromate oxidation of a portion of the cyclohexanol.

Determination of Exchange.—A solution of 0.21 mole of tagged aluminum isopropoxide in 150 ml. of carbon tetrachloride was heated under nitrogen with 0.15 mole of cyclohexanol. The isopropyl alcohol liberated by alcohol interchange was completely removed by slow distillation, requiring 2 hours and the mixture was refluxed for 7.5 hours more. The products were isolated and analyzed for deuterium distribution as described previously.

The alcohol-carbon tetrachloride azeotrope produced during the alcohol interchange was analyzed exactly as described previously for the analysis of isopropyl alcohol, except that 8 g. of silver wire was placed in the combustion train to remove the halogen.

Determination of the Effect of Alcohols as Solvents.—A solution of 0.57 mole of redistilled aluminum isopropoxide in 300 ml. of the solvent or solvent-pair being studied was heated with 0.4 mole of cyclohexanone. The acetone was removed by slow distillation through a 30-cm. packed column and the heating was continued until the distillate gave no test with dinitrophenylhydrazine solution.⁹ The solution was cooled and the solvent removed under reduced pressure. Hydrolysis was effected under reflux by adding 290 ml. of 3 *N* hydrochloric acid while cooling in an ice-bath and the product was extracted with five 100-ml. portions of ether. The cyclohexanol was isolated by fractionation of the dried ether solution at 1–3 mm. pressure using a Vigreux column, or at atmospheric pressure using the Todd column.

Discussion

The percentage reduction obtained in the solvent mixtures studied, which appear in Table I, indicate the excellence of isopropyl and *t*-butyl alcohols as compared with normal alcohols or carbon tetrachloride. This effect is not a mass effect as is seen by the last four determinations in which only 0.5 mole of alcohol was present as compared with 0.57 mole of aluminum isopropoxide and 0.4 mole of ketone. Since it was noted that the amount of non-volatile polymer was least when the percentage reduction was highest, it is proposed that the func-

tion of the isopropyl alcohol is to inhibit the side-reaction of aldolization. Such an effect has been noted in the Tschitschenko reaction,¹⁰ and may also explain the lower yields noted in the aluminum *t*-butoxide catalyzed aldol condensation of ketones when *t*-butyl alcohol is used as a solvent instead of dioxane or toluene.¹¹ The low yields observed when primary alcohols were present are probably due to the formation of the corresponding normal alkoxide which is a poorer reducing agent than the isopropoxide.

TABLE I
EFFECT OF SOLVENT

Solvent	Cyclohexanol, % of theory
Carbon tetrachloride	68 ^a
<i>n</i> -Propyl alcohol	63 ^a
Isopropyl alcohol	83 ^a
<i>t</i> -Butyl alcohol	82 ^a
Carbon tetrachloride	62 ^b
Isopropyl alcohol	74 ^b
<i>t</i> -Butyl alcohol	69 ^b
<i>n</i> -Butyl alcohol	55 ^b
Carbon tetrachloride + 0.5 mole isopropyl alcohol	73 ^b
Carbon tetrachloride + 0.5 mole <i>t</i> -butyl alcohol	70 ^b
Carbon tetrachloride + 0.5 mole <i>n</i> -butyl alcohol	63 ^b

^a Isolation by distillation using the Todd column. ^b Isolation by distillation using a 30-cm. Vigreux column.

The composition of the various batches of aluminum isopropoxide containing deuterium is given in Table II. The methyl group deuterium present in those samples prepared using lithium aluminum deuteride was apparently introduced during the reaction with aluminum metal, since preliminary experiments showed that from 2–6% of the deuterium initially present in the number 2 position of the alcohol would migrate to the methyl group during this reaction. The compounds prepared using deuterium gas contained more methyl group deuterium due to the exchange occurring during the hydrogenation itself.⁶

TABLE II
ALUMINUM ISOPROPOXIDE COMPOSITION

Mole %	D ₂ reduction			LiAlD ₄ reduction	
$\begin{array}{c} \text{CH}_3 \\ \\ \text{—O—C—D} \\ \\ \text{CH}_3 \\ \\ \text{CH}_2\text{D} \\ \\ \text{—O—CH} \\ \\ \text{CH}_3 \end{array}$	6.384	5.752	5.882	3.420	3.836
$\begin{array}{c} \text{CH}_3 \\ \\ \text{—O—CH} \\ \\ \text{CH}_3 \end{array}$	0.4320	0.8748	0.8316	0.1944	0.3132

The initial and final deuterium distribution observed when cyclohexanone was reduced with tagged aluminum isopropoxide is given in Table III. The amount of deuterium transferred by exchange independent of the reduction as determined by equilibrating tagged aluminum isopropoxide with cyclohexanol in the absence of oxidizing agents appears in Table IV. The composition of the mixed alkoxide is calculated from the initial deu-

(8) S. Siggia, "Quantitative Organic Analysis via Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 17.

(9) H. Lund, *Ber.*, **70**, 1520 (1937).

(10) W. Child and H. Adkins, *THIS JOURNAL*, **45**, 3013 (1923).

(11) W. Wayne and H. Adkins, *ibid.*, **62**, 3401 (1940).

TABLE III
 DEUTERIUM DISTRIBUTION—REDUCTION OF CYCLOHEXANONE^a

	Moles D as CH_3 $-\text{OCD} \times 10^4$ CH_3	Moles D as CH_2D $-\text{OCH} \times 10^4$ CH_3	Moles D as CH_2D $\text{O}=\text{C} \times 10^4$ CH_3	Moles D as D $-\text{O}-\text{C}_6\text{H}_{10} \times 10^4$	Moles D as D $\text{H}-\text{C}_6\text{H}_{10} \times 10^4$	Moles D Total $\times 10^4$	Cyclohexanol % of theory
Experiment 1							
Init.	362.4	55.1				417.5	
Final	318.6	24.5	3.5	59.4	4.5	410.5	68.0
	43.8	30.6				-7.0	
Experiment 2							
Init.	370.5	52.4				422.9	
Final	338.5	29.6	3.4	47.9	4.3	423.7	61.5
	32.0	22.8				0.8	
Experiment 3							
Init.	370.5	52.4				422.9	
Final	335.8	28.8	2.6	52.4	4.2	423.8	64.8
	34.7	23.6				0.9	
Experiment 4							
Init.	215.5	12.2				227.7	
Final	179.0	9.3	0.0	28.0	5.6	221.9	71.4
	36.5	2.9				-5.8	
Experiment 5							
Init.	241.6	19.7				261.3	
Final	208.6	11.5	0.5	27.7	4.8	253.1	66.4
	33.0	8.2				-8.2	

^a Each experiment contained 0.21 mole of aluminum isopropoxide, 0.15 mole of cyclohexanone and 150 ml. of carbon tetrachloride.

terium distribution in the alkoxide and that in the alcohol isolated from the distillate, and represents the theoretical composition of the alkoxide produced if no deuterium transfer occurred during alcohol interchange. From the data it is apparent that the hydrogen atoms equilibrate under conditions where the reduction reaction cannot occur. The deuterium content of the carbinol carbon atoms is essentially unchanged during this treatment.

In interpreting the data given in Table III, it must be remembered that initially 0.21 mole of aluminum isopropoxide or 6300×10^{-4} mole of isopropoxide groups are present. The first two entries show that in Experiment 1, there is 362.4×10^{-4} mole of alcohol tagged on the carbinol carbon, and 55.1×10^{-4} mole of alcohol tagged in the methyl group, the remaining 5882.5×10^{-4} mole being untagged.

At the end of the reaction, 68.0% or 102.0×10^{-4} mole of the cyclohexanone has been reduced. Thus the total amount of cyclohexanol produced is 102.0×10^{-4} mole of which 59.4×10^{-4} mole contains deuterium on the carbinol carbon and 4.5×10^{-4} mole contains deuterium elsewhere in the molecule. The quantity of acetone produced is also 102.0×10^{-4} mole of which 3.5×10^{-4} mole contains deuterium in the methyl group. The amount of isopropoxide remaining is $6300 \times 10^{-4} - 102 \times 10^{-4}$ or 6198×10^{-4} mole of which 318.6×10^{-4} mole is tagged on the carbinol carbon and 24.5×10^{-4} mole is tagged in the methyl group.

In the exchange experiment reported in Table

IV, there was present initially 6300×10^{-4} mole of isopropoxide groups. The distillate contained 1500×10^{-4} mole of isopropyl alcohol displaced by the cyclohexanol added, and the mixed alkoxide and final alkoxide both contained 4800×10^{-4} mole of isopropoxide groups and 1500×10^{-4} mole of cyclohexanol. The number of moles of the various deuterium-containing species are listed in the table.

 TABLE IV
 DEUTERIUM DISTRIBUTION DURING EXCHANGE

	Moles D as CH_3 $-\text{OCD} \times 10^4$ CH_3	Moles D as CH_2D $-\text{OCH} \times 10^4$ CH_3	Moles D as D $-\text{O}-\text{C}_6\text{H}_{10} \times 10^4$	Moles D as D $\text{H}-\text{C}_6\text{H}_{10} \times 10^4$
Initial ^a	241.6	19.7		
Distillate	59.6	3.1		
Mixed				
alkoxide	182.0	16.6		
Final	183.7	7.8	0.3	3.3

Moles D unaccounted for = 3.6×10^{-4}

^a This experiment used 0.21 mole of aluminum isopropoxide, 0.15 mole of cyclohexanol and 150 ml. of carbon tetrachloride.

If it is assumed that the amount of exchange is proportional to the initial methyl group deuterium content, the amount of deuterium transferred by exchange may be calculated for each species of molecule present in Experiments 1-5, in Table V, by multiplying the amount transferred in the exchange experiment by the ratio of the initial

methyl group deuterium content in the experiment in question to that present in the exchange experiment. Subtracting these corrections from the observed over-all deuterium change gives the deuterium change due to the reduction reaction itself. The data in Table V have been calculated in this manner.

Since the acetone produced during the reaction is effectively removed into the fractionating column as soon as it is formed and is therefore unavailable for complete exchange, the corrections applied are probably somewhat too high as is evidenced by the negative values in columns 2 and 5 of Table V.

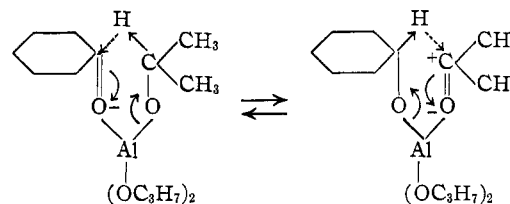
TABLE V
REDUCTION OF CYCLOHEXANONE—CORRECTED FOR EXCHANGE

Ex- peri- ment	Δ Moles D as CH_3 $\times 10^4$	Δ Moles D as CH_2D $\times 10^4$	Moles D as CH_2D $\times 10^4$	Moles D as CH_2D $\times 10^4$	Moles D as CH_2D $\times 10^4$
	$-\text{OCD}-\text{CH}_3$	$-\text{OCH}-\text{CH}_3$	$\text{O}=\text{C}-\text{CH}_3$	$\text{O}-\text{C}(\text{D})-\text{CH}_3$	$\text{O}-\text{C}(\text{D})-\text{CH}_3$
1	49.5	1.4	3.5	58.4	-6.5
2	37.4	-6.0	3.4	47.0	-6.2
3	40.1	-4.2	2.6	51.5	-6.2
4	37.8	-3.6	0.0	28.2	3.2
5	35.0	-2.2	0.5	27.9	0.9

Although the individual determinations of deuterium content have an absolute error of only ± 0.002 mole per cent. deuterium oxide, it is necessary to determine the change in deuterium content of the carbinol positions by difference, thus giving these quantities a relative probable error of 5–6%. Since the data in Table V are also computed by difference, the probable error here is increased to

about 10%. Unavoidable systematic errors are also present due to the difference in initial deuterium concentration between the exchange experiment and the reduction experiments and to the absence of enolizable ketone during the exchange experiment.¹² Taking these factors into account, the agreement between the amount of deuterium lost from the carbinol carbon atom of the isopropoxide and that appearing on the carbinol carbon atom of the cyclohexanol must be considered satisfactory. Any appreciable involvement of the methyl group hydrogen atoms in the reduction is unlikely in view of the fact that the amount of deuterium lost from the methyl group is essentially the same during the reduction as during the exchange reaction.

The above data indicate that hydrogen atoms are transferred during the Meerwein-Ponndorf reaction predominantly if not solely from the carbinol carbon atom of the alkoxide to the carbonyl carbon atom of the ketone. This is entirely consistent with the proposed mechanism involving the activated complex



(12) A more complete discussion of errors is given in the Ph. D. thesis of E. D. Williams, Jr., University of Pennsylvania, 1952.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, STANDARD OIL COMPANY (INDIANA)]

Disproportionation of Alkylbenzenes. I. Product Distribution and Rate Studies

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The disproportionation of alkylbenzenes has been studied with hydrogen fluoride–boron trifluoride catalysts to determine the effect of catalyst concentration on the distribution of reaction products and on the rate of disproportionation. Excess hydrogen fluoride and minor amounts of boron trifluoride partially convert ethylbenzene into benzene, some diethylbenzene and much triethylbenzene; equilibrium lies on the side of undisproportionated ethylbenzene. With excess boron trifluoride, ethylbenzene is 95% disproportionated to benzene and diethylbenzene; no triethylbenzene is formed, and the diethylbenzene is exclusively the meta isomer. Rate studies on *m*-xylene show that migration of alkyl groups is much slower than with ethylbenzene. The rate of disproportionation is a function of temperature and of boron trifluoride concentration and appears to fit a second-order curve. The amount of mesitylene in the trimethylbenzene fraction increases with increasing boron trifluoride concentration and approaches 100% under relatively mild conditions. The dependence of product distribution and of rates of alkylbenzene disproportionation upon boron trifluoride concentration is attributed to preferential complex formation with the starting material and to resulting variations in the amount of hydrocarbon present in the catalyst phase.

The disproportionation of alkylbenzenes to higher and lower homologs with Friedel–Crafts catalysts has been the subject of numerous investigations.¹ As in the field of aromatic alkylation and isomerization, there have been conflicting reports concerning the orientation and configuration of the alkyl group in the disproportionation products. The role of the catalyst and the reaction mechanism have also been subjects of much speculation.¹

Because recent studies involving HF–BF₃ catalyst systems helped to explain some of the

anomalies and apparent discrepancies in the field of methylbenzene isomerization,² similar techniques have been applied to the related reaction of disproportionation. The isomerization studies had shown that the acidity and amount of catalyst markedly affect the course of the reaction; a highly acidic catalyst selectively combines with the most basic alkylbenzene isomer and thereby allows isomerization to give an almost quantitative yield of that isomer. Because disproportionation re-

(1) D. V. Nightingale, *Chem. Revs.*, **25**, 329 (1939).

(2) D. A. McCauley and A. P. Lien, *THIS JOURNAL*, **74**, 6246 (1952).