

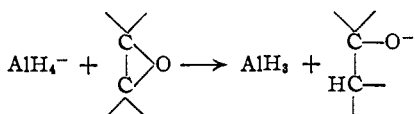
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Mechanism of Lithium Aluminum Hydride Reactions

BY LLOYD W. TREVOY¹ AND WELDON G. BROWN

With few exceptions the known reactions of lithium aluminum hydride with organic compounds consist essentially of the displacement of a strongly electronegative element (oxygen, nitrogen or halogen) on carbon by hydrogen. Non-polar groups, *e.g.*, isolated double bonds, are not affected. It is therefore reasonable to suppose that the reactions proceed by polar mechanisms. Moreover, the hydride reactions thus far reported have certain features in common with the more familiar nucleophilic displacement reactions on carbon and a common basis in mechanism is indicated.

The simplest assumption would be that hydride ion, furnished by dissociation of the complex hydride, functions as a nucleophilic reagent. But apart from the lack of evidence for such dissociation, a mechanism based upon the assumption of free hydride ions would not easily account for the characteristic differences in the reducing properties of different complex hydrides, *e.g.*, aluminohydrides *vs.* borohydrides. It appears more likely that the reactant is actually a series of complex aluminohydride ions, AlX_nH_{4-n} , where n progresses from zero to four during the course of a reaction, which act as carriers for hydride ion. The first phase of the reaction with an epoxide, for example, might then be formulated as



If the reactions proceed *via* the usual bimolecular displacement mechanism, as the above formulation is intended to suggest, there are two experimental tests which may be conveniently applied. One is the test as to whether inversion of configuration occurs on the carbon atom attacked. The other is the correlation with respect to relative reactivities and with respect to the point of attack, if two alternate paths are possible, with other reactions known to proceed by such a mechanism. An approach based on reaction kinetics does not appear to be feasible.

Suitable test cases for the experimental demonstration of inversion are provided by 1,2-dimethyl-1,2-epoxycyclopentane and 1,2-dimethyl-1,2-epoxycyclohexane which we find to be reduced by lithium aluminum hydride to the corresponding dimethylcyclohexanols. These tertiary alcohols are each known in two stereoisomeric forms, and the assignment of configuration on the

basis of infrared absorption spectra,² relative rates of dehydration³ and of hydrogenation,³ appears to be reasonably certain. The epoxides are presumed to have the *cis* configuration and inversion will have been demonstrated if the incoming hydrogen atoms take up positions *trans* to the hydroxyl groups in the reduction products.

The isomeric alcohols are characterized by differences in physical constants which, with the exception of the significantly lower boiling points of the *trans* isomers, are relatively minor. Identification of the reduction products on the basis of these differences (*cf.* Table I) is necessarily tenuous in view of the fact that neither the reduction products nor reference samples of the individual isomers could be obtained in pure form because of decomposition during distillation. The weight of evidence is in favor of the *trans* configuration for the reduction product in each instance; the observed boiling points and densities support such an assignment while the refractive indices and melting points are indecisive.

The tentative identification of the reduction product from 1,2-dimethyl-1,2-epoxycyclopentane as *trans*-1,2-dimethylcyclopentanol is substantiated by the observation that its melting point is strongly depressed by admixture of the *cis* reference sample but not by the *trans* reference sample. Similar confirmatory evidence for the dimethylcyclohexanols, which presented the greatest difficulty in purification, is lacking.

TABLE I

PHYSICAL CONSTANTS OF ISOMERIC DIMETHYLCYCLANOLS

	<i>cis</i> Form		<i>trans</i> Form		Obs. red. product
	Lit.	This work	Lit.	This work	
1,2-Dimethylcyclopentanol					
B. p.	69.6°/25° ^a	62°/17	58.4°/25° ^a	51°/17	53°/17
M. p.	28.9°	24-26	27.3°	24-25	23-24° ^e
n_D^{20}	1.4523 ^b	1.4516	1.4463 ^b	1.4506	1.4493
d_4^{20}	0.9088°		0.9005°	0.9094	0.9094
1,2-Dimethylcyclohexanol					
B. p.	82.8°/25° ^c		74.0°/25°	62.8°/17 35°/2.5	35°/2.5
M. p.	23.2°		13.2°	-3.5 to -1	-8 to -7 ^f
n_D^{20}	1.4648 ^d		1.4613 ^d	1.4587	1.4594
d_4^{20}	0.9250°		0.9187°	0.9189	0.9174

^a Chiurdoglu, *ref. 3*: the literature density values given here are for d_4^{20} . ^b Van Rysselberge, *Bull. soc. chim. Belg.*, 35, 316(1926). The refractive indices given by this author are for n_D^{20} ; all other values appearing in this table are n_D^{20} . ^c Chiurdoglu, *ibid.*, 47, 245 (1938). ^d Chiurdoglu, *ibid.*, 50, 20(1941). ^e Mixed m. p. with *cis*-1,2-dimethylcyclopentanol, -8 to -6°; mixed m. p. with *trans* form, 22-24°. ^f Mixed m. p. with *trans*-1,2-dimethylcyclohexanol, -6 to -5°.

(1) Standard Oil Company (Indiana) Research Fellow, 1947. Present address: University of Saskatchewan, Saskatoon, Saskatchewan.

(2) Chiurdoglu, Barchewitz and Freymann, *Bull. soc. chim. Belg.*, 47, 453 (1938).

(3) Chiurdoglu, *ibid.*, 44, 531 (1935).

With respect to directive effects in the bimolecular displacement reactions of unsymmetrical epoxides, the reactions of epoxides with sodium ethyl malonate are unquestionably of this type⁴ and will serve as a basis of comparison. Styrene oxide is attacked both by lithium aluminum hydride⁵ and by sodium ethyl malonate⁶ preferentially at the terminal carbon atom. That this is also true for 3,4-epoxy-1-butene and for epichlorohydrin is shown by the predominant formation of secondary alcohols in the hydride reductions (*cf.* Table II) in conjunction with the identification of the malonic ester condensation products in

TABLE II

REDUCTION OF EPOXIDES BY LITHIUM ALUMINUM HYDRIDE ^a		
	Product	Yield, %
Styrene oxide	α -Phenylethanol	75
3,4-Epoxy-1-butene	1-Butene-3-ol	58
	1-Butene-4-ol	13
Benzalacetophenone-oxide	1,3-Diphenylpropane-1,2-diol	79
	Propanol-2	88
Cyclohexeneoxide	Cyclohexanol	91

^a Reductions carried out in diethyl ether at its boiling point, except epichlorohydrin which was reduced in diethylcarbitol solution at 25°. Reaction times varied from twenty to forty-five minutes.

the former case by Russell and VanderWerf,⁶ and in the latter case by Traube and Lehmann.⁷

The isolation of some primary alcohol, representing attack by hydride at the secondary carbon atom of 3,4-epoxy-1-butene, does not invalidate the comparison since the observed yield in the malonic ester reaction (64%) does not preclude a minor reaction by the alternate path. In fact our findings are entirely consistent with the results of Bartlett and Ross⁸ for the alkaline methanolysis of 3,4-epoxy-1-butene and these authors present evidence to show that the reactions at the primary and secondary positions are both of the bimolecular displacement type. The explanation for concurrent attack at the secondary position (allyl-type activation) would apply with equal force to styrene oxide for which only one reduction product has been reported. In a re-examination of this point we obtained a small fraction of material boiling higher than α -phenylethanol, in the correct range for β -phenylethanol, but too small for further fractionation or identification. A substituent on the β -carbon atom of styrene oxide evidently shifts the main attack to the α -position, as is shown by the formation of 1,3-diphenylpropane-1,2-diol in high yield from benzalacetophenone oxide. In this reaction the reduction of the carbonyl group doubtless precedes opening of the epoxide ring.

(4) Grigsby, Hind, Chanley and Westheimer, *THIS JOURNAL*, **64**, 2606 (1942).

(5) Nystrom and Brown, *ibid.*, **70**, 3738 (1948).

(6) Russell and VanderWerf, *ibid.*, **69**, 11 (1947).

(7) Traube and Lehmann, *Ber.*, **34**, 1977 (1901).

(8) Bartlett and Ross, *THIS JOURNAL*, **70**, 926 (1948).

The replacement of chlorine by hydrogen, which accompanies (at a slower rate) the reduction of the epoxide ring of epichlorohydrin, is a normal type of reaction for lithium aluminum hydride. The examples previously reported,⁵ together with the further results given in Table III, show clearly that the trends in the reactivity of mono-halides exhibit the familiar pattern of nucleophilic displacements. A detailed discussion in substantiation of this conclusion does not appear to be necessary. However, the apparently anomalous behavior of diarylmethyl halides and of dihalides requires comment.

The abnormality shown by both diphenylbromomethane and 9-bromofluorene is the formation of substantial proportions of the corresponding tetraarylethanes. An explanation is to be found in the observation that fluorene reacts with lithium aluminum hydride to form an organometallic compound, demonstrated through the isolation of fluorene-9-carboxylic acid after carbonation. Presumably diphenylmethane is also sufficiently acidic to react similarly although this was not investigated. It is clear that the metallic derivatives, reacting with more of the halide, could give rise to the observed coupling products.

With 1,2-dihalides the normal displacement reaction is wholly or partly suppressed in favor of olefin formation. The latter is the principal reaction for 1,2-diiodides and for those 1,2-dibromides which can give rise to a conjugated olefin (*e.g.*, butadiene, styrene, stilbene) by the elimination of bromine. It is of interest to note that 1,4-dibromo-2-butene, which could furnish butadiene by bromine elimination, reacts instead by a normal displacement which is greatly facilitated by the allyl-type activation. Olefin formation from 1,2-dihalides can be regarded as nucleophilic displacements on halogen, as Winstein, Pressman and Young⁹ have shown for the halogen elimination brought about by iodide ion.

The inversion of configuration, which should accompany the normal displacement of halogen by hydrogen, could be observed experimentally only in the case of a tertiary halide. However, the tendency to undergo normal displacement is lowest for this type, and under forcing conditions, they react chiefly by dehydrohalogenation. In principle at least, the demonstration of inversion could be carried through for the case of a secondary halide reacting with lithium aluminum deuteride.

In pursuance of the stereochemical aspects of hydride reductions, some observations on the isomeric composition of the products from the reduction of 1,2-diketones (*cf.* Table IV) may be noted. Directive effects appear, and are enhanced somewhat by working at a low temperature, but in general the products appear to be mixtures of the various possible stereoisomers. Possibly the most interesting feature of these

(9) Winstein, Pressman and Young, *ibid.*, **61**, 1645 (1939).

results is the close relationship, in composition of the products, with catalytic hydrogenation and the sharp contrast in certain instances (*e.g.*, camphorquinone, camphor) with the products of reduction by active metals. This points toward a common steric element in the attack by a complex hydride ion on the one hand and the attack by a catalyst-hydrogen complex on the other.

In comparison with lithium aluminum hydride, the borohydrides of lithium and sodium differ principally in their lesser aggressiveness. At ordinary temperatures, the action of the borohydrides is confined to the more readily reducible types of groups.¹⁰ It is highly probable that the mechanism of their action is essentially similar, and that their lower reactivity is a consequence of the greater stability of the borohydride ion and of the reluctance with which it transmits a hydride fragment to an electron-deficient center.

Experimental

Reduction of 1,2-Dimethyl-1,2-epoxycyclopentane.—The epoxide was prepared by the procedure outlined by Bartlett and Bavley¹¹ except that the intermediate, 1,2-dimethylcyclopentanol-1, was subjected to fractional distillation through a Podbielniak Heligrad column in order to secure reference sample of the *cis* and *trans* isomers. Middle fractions from this distillation were then used in the further steps of the synthesis. Our product had a boiling point, 123.5–124° (741 mm.); the boiling point reported by the above-mentioned authors, 120–122.5° (20 mm.), is evidently misprinted in the original article.

The reduction of 20 g. (0.178 mole) of the epoxide by 0.118 mole of lithium aluminum hydride in diethyl ether solution took place relatively slowly. Spontaneous refluxing continued for two hours and thereafter the mixture was heated under reflux for an additional hour. The excess hydride was destroyed by the addition of water, alkali was added, and the product was worked up in the usual way. On distillation at 17 mm. pressure using a small wire-spiral column, the material was separated into unchanged epoxide, intermediate fractions, a main fraction of 8.2 g., b.p. 53–54° (17 mm.), and an insignificant residue of higher boiling material. On redistillation of the main fraction a forerun of lower boiling material was separated; the remainder of the distillate was characterized by the data given in Table I and is thus identified as *trans*-1,2-dimethylcyclopentanol-1.

Reduction of 1,2-Dimethyl-1,2-epoxycyclohexane.—The compound (b. p. 151.5–153.5° (747 mm.), n_D^{20} 1.4501) was prepared in 40% yield by the perbenzoic acid oxidation of 1,2-dimethylcyclohexene-1 following the procedure of Nametkin and Delektorsky.¹² Reduction occurred readily on the dropwise addition of 11 g. of the compound, diluted with ether, to 100 ml. of a solution containing 0.118 mole of lithium aluminum hydride, after which the mixture was allowed to stand for twenty minutes. Difficulty was experienced in purifying the product because of the tendency to dehydrate during prolonged distillations. The material from the first distillation using a short wire-spiral column, 8.2 g., b. p. 40–41° (2.5 mm.), was redistilled from a Claisen flask and the resulting product was characterized by the physical constants shown in Table I. The melting points were not sharp and the product was probably contaminated with olefin. A specimen of *trans*-1,2-dimethylcyclohexanol-1, separated from a synthetic mixture of the *cis* and *trans* forms by means of the Podbielniak column, behaved similarly, and on the basis of the close agreement in physi-

cal constants the reduction product is believed to be the *trans* isomer.

Reduction of Other Epoxides.—Styrene oxide was furnished through the courtesy of the Dow Chemical Company; 3,4-epoxy-1-butene through the courtesy of the Columbia Chemicals Division, Pittsburgh Plate Glass Company. The reduction of these, and the other epoxides shown in Table II, has been carried out by procedures similar to those outlined above. All of these reductions were rapid at the temperature of boiling ether. A reduction of 3,4-epoxy-1-butene, carried out at –40°, also occurred rapidly and the product had substantially the same composition as that obtained at the higher temperature. All of the products shown in Table II are known compounds and the identity was confirmed wherever possible by the preparation of known derivatives. Confirmation of the identity of 1,3-diphenylpropane-1,2-diol¹³ was provided by periodic acid oxidation which formed benzaldehyde and phenylacetaldehyde, identified as their dinitrophenylhydrazones.

Reduction of Halides.—Experiments relating to the reduction of halogen compounds are summarized in Table III. As noted, various higher-boiling solvents were employed to effect reduction of the more resistant types at elevated temperatures. These experiments were carried out with quantities of halide in the range 0.1 to 0.4 mole and with quantities of lithium aluminum hydride 30 to 100% in excess of theoretical. Hydrocarbon products were identified on the basis of physical constants except *trans*-butene-2, which was converted to the dibromide, *meso*-2,3-dibromobutane, b. p. 62–65° (32 mm.), n_D^{20} 1.5110; lit.¹⁴ b. p. 66.2–66.6° (30 mm.), n_D^{20} 1.5116. Hydrocinnamyl alcohol was identified as the *p*-nitrobenzoate, m. p. 46°; lit.¹⁵ m. p. 47–48°. The reduction product from *p*-bromophenacyl bromide, α -(*p*-bromophenyl)-ethanol, was converted to the *N*-phenylcarbamate, m. p. 103°; lit.¹⁶ m. p. 103–104°.

The reduction of 1,2,3,4-tetrabromobutane at 35° furnished an unsaturated liquid product of acid odor, containing bromine, and boiling over the range 90–118° (748 mm.). At 65°, in tetrahydrofuran, the reaction of the tetrabromide with lithium aluminum hydride produced butadiene. Again in the case of 2,3-diiodopropanol-1 a pure product was not isolated; the limited scale of the experiment (0.05 mole) did not permit a clean separation of allyl alcohol, indicated by bromine titration to be the chief product, from other substances of comparable volatility which were present.

In the reduction of 9-bromofluorene, an orange color appeared on the first addition of the halide, disappeared as the reaction progressed, and reappeared some thirty minutes after completing the addition. Dibiphenyleneethane, m. p. 247–247.5° after recrystallization from benzene-ethanol (lit.¹⁷ m. p. 247°), separated from a concentrated ether extract of the product. The residue from the mother liquor, taken up in petroleum ether and subjected to chromatographic adsorption, was separated into fluorene, a further small quantity of dibiphenyleneethane, and a small amount of an orange-colored substance which was not identified.

To confirm the intermediate formation of a metallic derivative of fluorene, suggested by the above-mentioned color phenomena, a mixture of fluorene (0.15 mole) and lithium aluminum hydride (0.0375 mole) in tetrahydrofuran (nitrogen atmosphere) was heated at 65° for forty-two hours at which time the evolution of gas had slackened and a deep red color had developed. Carbon dioxide was then introduced and the color gradually changed to orange. The greater part of the fluorene was recovered but fluorene-9-carboxylic acid, m. p. 225–226° (lit.¹⁸ m. p. 226 or 232°), was isolated in the amount of 4.6 g. (0.022 mole).

(13) Levy and Dvoletzka-Gombinska, *Bull. soc. chim.*, [4] **49**, 1772 (1931).

(14) Kharasch, Lambert and Urry, *J. Org. Chem.*, **10**, 303 (1945).

(15) Kirner, *This Journal*, **48**, 1111 (1926).

(16) Quelet, *Bull. soc. chim.*, [4] **45**, 88 (1929).

(17) Pinck and Hilbert, *This Journal*, **68**, 379 (1946).

(18) Jeanes and Adams, *ibid.*, **59**, 2620 (1937).

(10) Chaikin and Brown, *This Journal*, **70**, 122 (1948); Chaikin, Ph.D. Dissertation, The University of Chicago, 1948.

(11) Bartlett and Bavley, *This Journal*, **60**, 2416 (1938).

(12) Nametkin and Delektorsky, *Ber.*, **57**, 585 (1924).

TABLE III

REDUCTION OF HALIDES BY LITHIUM ALUMINUM HYDRIDE			
	Time, hr.	Product	Yield, %
In Diethyl Ether, at 35°			
Benzyl iodide	0.3	Toluene	86
<i>p</i> -Bromophenacyl bromide	1	α -(<i>p</i> -Bromophenyl)-ethanol	85
Triphenylchloromethane	0.3	Triphenylmethane	98
In Tetrahydrofuran, at 35°			
Benzyl bromide	2	Toluene	78
9-Bromofluorene	0.5	Fluorene	30
		Dibiphenyleneethane	34
In Tetrahydrofuran, at 65°			
Benzyl chloride	0.5	Toluene	72
1-Bromodecane	10	<i>n</i> -Decane	72
2-Bromoöctane ^a	10	<i>n</i> -Octane	30
ω -Bromostyrene	19	Styrene	49
<i>p</i> -Fluorotoluene	24	No reaction	
1-Chloro-2-iodobenzene ^b	0.5	Chlorobenzene	40
Ethyl α,β -dichloroethyl ether	0.5	Ethyl β -chloroethyl ether	53
Pentaerythrityl bromide		No reaction	
Ethyl 2,3-dibromo-3-phenyl propionate	1	Hydrocinnamyl alcohol	59
Diethyl bromomalonate	22	Trimethyleneglycol	5
Diphenylbromomethane	0.5	Diphenylmethane	38
Styrene dibromide	0.5	Tetraphenylethane	25
Styrene dibromide	0.5	Styrene	71
<i>meso</i> -1,2-Diphenyl-1,2-dibromoethane	4.5	<i>trans</i> -Stilbene	98
1,2-Dibromoöctane ^c	2	Octene-1	17
		2-Bromoöctane	26
In Diethylcarbitol, at 65°			
<i>trans</i> -1,4-Dibromo-2-butene	0.3	<i>trans</i> -2-Butene	72
In Dibutylcarbitol, at 65°			
2-Bromo-2-methyloctane	7	2-Methyloctenes	76
In Dibutyl Ether, at 80°			
<i>t</i> -Butyl iodide	3	Isobutane	
		Isobutene	

^a 29% recovered. ^b 38% recovered. ^c 22% recovered.

Reduction of 1,2-Diketones.—In the expectation that the stereochemical specificity of the hydride attack would be enhanced at a lower temperature, the reductions were carried out at -80° (Dry Ice-bath) as well as at 35° . The solvent employed throughout was diethyl ether. At -80° the reactions were noticeably slower, requiring one to two hours for completion as compared with twenty to

thirty minutes at 35° . The over-all yields were slightly improved at the lower temperature (*cf.* Table IV) but the most marked improvement was in the optical purity of optically active products. In no case, however, could the reduction be directed to the formation of a single stereoisomer. The product from *d*-camphor at -80° , representing the nearest approach, consisted chiefly of *d*(-)-isoborneol, m. p. 213° , 3,5-dinitrobenzoate m. p. 139° , $[\alpha]^{25D} -30.6^\circ$ (lit.¹⁹ m. p. 214° , 3,5-dinitrobenzoate m. p. 139° , $[\alpha]^{20D}$ in methanol -32.30°) and, as indicated by the low rotation, doubtless contained *d*(+)-borneol. The product from the reduction of *d*-2,3-camphorquinone, when purified simply by recrystallization, furnished physical constants in reasonably good agreement with literature²⁰ values for *cis*-2,3-camphaneglycol. But when purified by conversion to the isopropylidene derivative and regeneration, our product, m. p. 257° , $[\alpha]^{29D}$ in ethanol, -19.02° (lit.²⁰ m. p. $254-256^\circ$, $[\alpha]^{20D}$ in ethanol, -13.4°), had increased in specific rotatory power. Our product was therefore not optically homogeneous.

Cyclohexane-1,2-dione reacted with lithium aluminum hydride with the evolution of one mole of hydrogen gas and formed, as the only identifiable product, cyclohexanol-2-one, m. p. $139-142^\circ$ (lit.²¹ m. p. 138°), characterized as the phenylosazone, m. p. $152-153^\circ$ (lit.²² m. p. 153°).

TABLE IV

REDUCTION OF KETONES			
	Product	Yield at	
		35°	-80°
Benzil	Hydrobenzoin (<i>meso</i>)	81	90
	Isohydrobenzoin	5	..
<i>d</i> -Camphor	<i>d</i> (-)-Isoborneol	97 ^a	97 ^b
<i>d</i> -2,3-Camphorquinone	<i>d</i> -2,3-Camphaneglycol	97 ^c	98 ^d
Acenaphthenequinone	<i>cis</i> -Acenaphthyleneglycol	15	13
	<i>trans</i> -Acenaphthyleneglycol	45	50
Cyclohexane-1,2-dione	Cyclohexanol-2-one	41	
		^a $[\alpha]^{24D}$ (in methanol, <i>c</i> 10) -24.87° .	^b $[\alpha]^{24D}$ -30.6° .
		^c $[\alpha]^{28D}$ (in ethanol, <i>c</i> 7) -14.6° .	^d $[\alpha]^{24D}$ -17.3° .

Summary

A mechanism for reductions by lithium aluminum hydride, which involves a nucleophilic attack on carbon by complex hydride ions, is supported by (a) the occurrence of inversion in the reactions with bicyclic epoxides, (b) a comparison with sodium ethyl malonate with respect to the site of reaction in unsymmetrical epoxides, and (c) the behavior of organic halides toward the reagent. The reduction of 1,2-diketones by the hydride is shown to form products resembling, in isomeric composition, those formed in catalytic hydrogenation.

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(19) Lipp, *Ber.*, **74**, 8 (1941).(20) Rupe and Thommen, *Helv. Chim. Acta*, **30**, 942 (1947).(21) Halasz, *Ann. chim.*, **14**, 362 (1940).(22) Bergmann and Gerth, *Ann.*, **448**, 61 (1926).