Conformational Analysis. XXI.[1a] Reduction with Metal Hydrides. XX.[1b] The Stereochemistry of Reduction of Ortho Esters with Lithium Aluminum Hydride and Mixed Hydrides

Ernest L. Eliel and Franz W. Nader

Contribution from the Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556. *Received August 13, 1969*

Abstract: Reduction of *cis-* and *trans*-2-methoxy-4,4,6-trimethyl-1,3-dioxane (III) with lithium aluminum deuteride or aluminum deuteride and of *cis-* and *trans*-2-methoxy-*r*-4,*cis*-6-dimethyl-1,3-dioxane (II) with aluminum deuteride proceeds with predominant retention of configuration. In contrast, reduction of either diastereoisomer of II and III with dichloroalane-*d* follows a course of stereoconvergence, giving in all cases predominantly the product with axial deuterium. The reduction of the 2-methoxy-4-methyl-1,3-dioxanes, *r*-2-methoxy-2,*trans*-4-dimethyl-1,3-dioxane, *r*-2-methoxy-2,*trans*-4,*trans*-6-trimethyl-1,3-dioxane, and *r*-2-methoxy-2,4,4,*trans*-6-tetramethyl-1,3-dioxane with several of the corresponding hydrides has also been studied. The mechanistic implications of the findings are discussed.

The difference in reductive capacity between lithium aluminum hydride (LAH) and the "mixed hydrides" derived therefrom by the addition of Lewis acids has been a matter of extensive study[2-12] and several reviews are available.[13-15] The nature of the reagent, depending on the proportions of lithium aluminum hydride and aluminum chloride,[16-18] may be alane (aluminum hydride, AlH_3), chloroalane (AlH_2Cl), or dichloroalane ($AlHCl_2$). The difference in reactivity of the three species seems to be caused by the decreased hydride donor (nucleophilic) and increased Lewis acid character induced by increasing halogen substitution; also compared to LAH, alane is a weaker nucleophile and stronger Lewis acid. Several salient demonstrations of the resulting difference in reactivity are available.[6,8,12]

The reduction of acetals and ketals with the above reagents has been extensively studied.[7,8,19,20] Acetals and ketals are stable toward LAH but are reductively cleaved by the various mixed hydrides. Ortho esters, in contrast, are reduced with LAH itself to give acetals or ketals.[21,22]

Recently we have succeeded[1a,23] in synthesizing several ortho esters of defined stereochemistry, *viz.* the 2-alkoxy-1,3-dioxanes I–III and VIII–X. It was found that compounds with axial alkoxy substituent react very smoothly with Grignard reagents to give 2-axially substituted alkyldioxanes; in contrast, starting materials with equatorial alkoxyl groups were inert toward Grignard reagents under mild conditions. We felt it would be of interest to study, in similar fashion, the stereochemistry of reduction of the 2-alkoxy-1,3-dioxanes with the various types of hydrides or (in case where one of the substituents at C-2 was hydrogen) deuterides.

Preliminary experiments with unlabeled hydrides indicated that, fortunately for the proposed study, cleavage of the exocyclic alkoxy group predominated over cleavage of the ring, as had been the case with Grignard reagents.[1a] Moreover, it was found that further reduction of the 1,3-dioxane (acetal!) products by the mixed hydrides was relatively slow compared to reduction of the ortho ester; this finding was expected in view of the rather sluggish reduction of some 1,3-dioxanes with alane[19] and chloroalane[18] reported in the literature. With LAH itself, there is, of course, no problem of overreduction.

The results of the reduction of the orthoformates 2-methoxy-4-methyl-1,3-dioxane (I), *cis-* and *trans*-2-methoxy-*r*-4,*cis*-6-dimethyl-1,3-dioxane (II),[24] *cis-* and *trans*-2-methoxy-4,4,6-trimethyl-1,3-dioxane (III), and the orthoacetates *r*-2-methoxy-2,*trans*-4-dimethyl-1,3-dioxane (VIII), *r*-2-methoxy-2,*trans*-4,*trans*-6-trimethyl-1,3-dioxane (IX), and *r*-2-methoxy-2,4,4,*trans*-6-tetramethyl-1,3-dioxane (X) with various hydride and deuteride species are summarized in Table I.

Reduction of compounds I, II, and III with LAH proceeded somewhat sluggishly and required a large excess of the reagent; reduction of *cis-* and *trans*-III

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(1) (a) Paper XX: E. L. Eliel and F. W. Nader, *J. Amer. Chem. Soc.*, **92**, 584 (1970); (b) paper XIX: E. L. Eliel and Y. Senda, *Tetrahedron*, in press.

(2) R. F. Nystrom, *J. Amer. Chem. Soc.*, **77**, 2544 (1954).

(3) B. R. Brown and A. M. S. White, *J. Chem. Soc.*, 3755 (1957).

(4) E. L. Eliel and D. W. Delmonte, *J. Amer. Chem. Soc.*, 80, 1744 (1958).

(5) E. L. Eliel and M. N. Rerick, *ibid.*, **82**, 1367 (1960).

(6) M. N. Rerick and E. L. Eliel, *ibid.*, **84**, 2356 (1962).

(7) E. L. Eliel, V. G. Badding, and M. N. Rerick, *ibid.*, **84**, 2371 (1962).

(8) E. L. Eliel, L. A. Pilato, and V. G. Badding, *ibid.*, **84**, 2377 (1962).

(9) P. T. Lansbury, D. J. Scharf, and V. A. Pattison, *J. Org. Chem.*, **32**, 1748 (1967).

(10) N. M. Yoon and H. C. Brown, *J. Amer. Chem. Soc*, **90**, 2927 (1968).

(11) H. C. Brown and N. M. Yoon, *ibid.*, **88**, 1464 (1966).

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(13) E. L. Eliel, *Rec. Chem. Progr.*, **22**, 129 (1961).

(14) A. Hajós, "Complexe Hydride," VEB Deutscher Verlag der Wissenschaften, Berlin, 1966, pp 290–308.

(15) M. N. Rerick in "Reduction," R. L. Augustine, Ed., Marcel Dekker, Inc., New York, N. Y., 1968, Chapter 1.

(16) E. Wiberg and M. Schmidt, *Z. Naturforsch.*, **6b**, 460 (1951).

(17) E. C. Ashby and J. Prather, *J. Amer. Chem. Soc.*, **88**, 729 (1966).

(18) H. Nöth and E. Wiberg, *Fortsch. Chem. Forsch.*, **8**, 321 (1967).

(19) U. E. Diner and R. K. Brown, *Can. J. Chem.*, **45**, 1297 (1967).

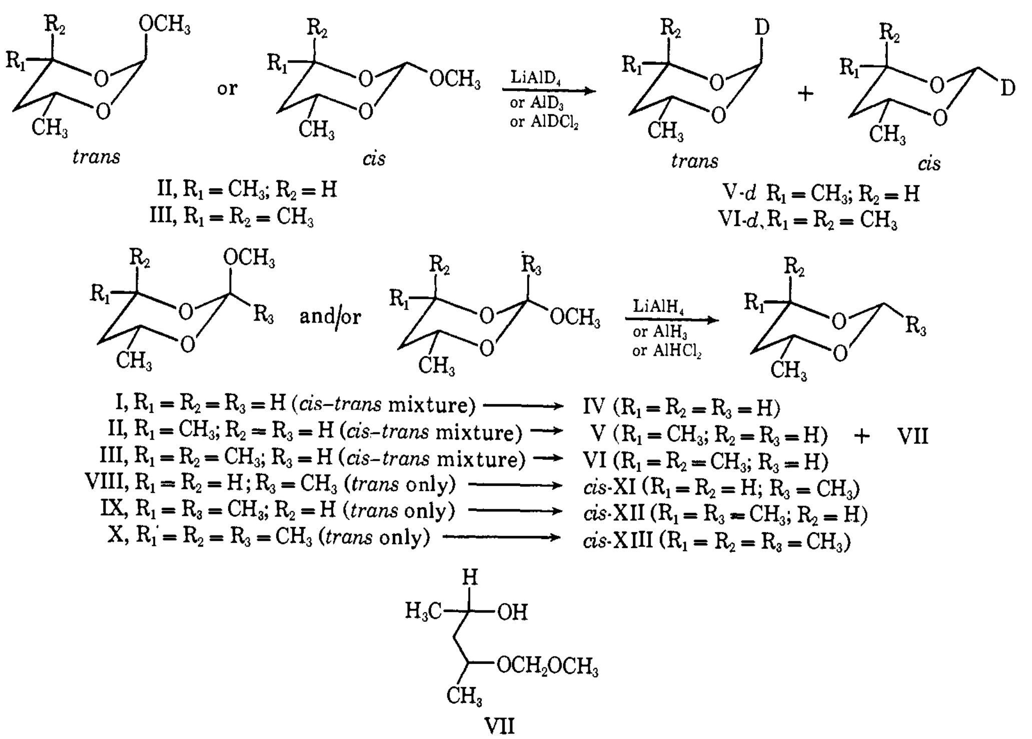
(20) U. E. Diner, H. A. Davis, and R. K. Brown, *ibid.*, **45**, 207 (1967).

(21) C. J. Claus and J. L. Morgenthau, *J. Amer. Chem. Soc.*, **73**, 5005 (1951).

(22) A. Roedig and E. Degener, *Chem. Ber.*, **86**, 1469 (1953).

(23) E. L. Eliel and F. Nader, *J. Amer. Chem. Soc.*, **91**, 536 (1969).

(24) Regarding the Beilstein nomenclature for *cis–trans* isomers here used, see ref 1a.



with $LiAlD_4$ (LAD) was considerably slower still.[25] In contrast, reductions with AlD_3, AlD_2Cl, and $AlDCl_2$ proceeded smoothly and in high yield. Side products, *e.g.*, those resulting from various types of ring cleavage, were found to constitute less than 15% of the product. In the reduction of II, the ring cleavage product VII was isolated in about 10% yield and characterized by elemental analysis and nmr spectrum. The mixed deuterides were prepared from $LiAlD_4$ and $AlCl_3$; in the synthesis of AlD_3 a slight excess of LAD was used to avoid the adventitious formation of chloroalanes.[26]

Table I. Results of the Reduction of Various 2-Methoxy-1,3-dioxanes

Compound	Diast[a] purity, %	Reducing reagent	Reaction time, hr	Product	Diast[b] purity, %	Yield, %
cis-trans I	*c*	$LiAlH_4$	5[d]	IV		57
cis-trans II	*c*	$LiAlH_4$	5[d]	V (+VII)[e]		50
trans-II	98	AlD_3	0.5[f]	*trans*-V-*d*	94	80
	98	$AlDCl_2$	0.5[f]	*trans*-V-*d*	89	34
cis-II	97	AlD_3	0.5[f]	*cis*-V-*d*	61	50
	97	$AlDCl_2$	0.5[f]	*trans*-V-*d*	92	77
cis-trans III	*c*	$LiAlH_4$	5[d]	VI		65
trans-III	99	$LiAlD_4$	5[d]	*trans*-VI-*d*	60	*g*
	97	AlD_3	0.5[f]	*trans*-VI-*d*	73	67
	97	$AlDCl_2$	0.5[f]	*trans*-VI-*d*	71	76
cis-III	97	$LiAlD_4$	0.5[f]	*cis*-VI-*d*	57	*g*
	96	AlD_3	0.5[f]	*cis*-VI-*d*	72	51
	96	AlD_3-HOMe	0.5[f]	*cis*-VI-*d*	73	83
	96	AlD_2Cl	0.5[f]	*trans*-VI-*d*	72	72
	96	$AlDCl_2$	0.5[f]	*trans*-VI-*d*	76	69
VIII	*h*	$LiAlH_4$	5[d]	*cis*-XI	99[i]	51
IX	*h*	AlH_3	0.5[f]	*cis*-XII	99[i]	85
		$AlHCl_2$	0.5[f]	*cis*-XII	99[i]	65
X	*h*	$LiAlH_4$	5[d]	*cis*-XIII	99[i]	67

[a] Remainder epimeric compound; composition determined by glpc. [b] Remainder epimeric compound; composition determined by nmr. [c] Composition not determined. [d] In refluxing benzene–ether 2:1. [e] *Ca.* 5–10% of ring cleavage product isolated and identified. [f] In ether at room temperature. [g] Not determined as more than half of the starting material was recovered, leading to contamination of the reaction product. [h] The sole isomer available is that having axial methoxyl (OMe *trans* to Me-4). [i] Determined by glpc.

The configuration of the starting ortho esters I, II, and III is firmly established by previous work,[1a] based on chemical shifts of H-2, dipole measurements, and Overhauser effect studies. Assignment of configuration of the monodeuterated products V-*d* and VI-*d* at C-2 was at first tentatively based on nmr study. It is

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(25) There appears to be a large isotope effect in the LAD reaction suggesting substantial transfer of hydride to the substrate in the transition state. However, the possibility that there was some chemical difference between the commercial LAD and LAH reagents accounting for the more sluggish reaction with the former cannot be excluded. Because of the need for a considerable excess of expensive LAD, we forwent studying the reaction of *cis*- and *trans*-II with this reagent.

(26) The presence of unreacted LAD was not considered important because of the slowness of its reaction. For an alternative synthesis of alane, see ref 11.

Table II. Nmr Shift Data[a] and Ir Bands of 1,3-Dioxanes Prepared by Reduction of 2-Methoxy-1,3-dioxanes

Compd	Purity,[b] %	$\nu_{H\text{-}2}$(ax.),[c] cps	$\nu_{H\text{-}2}$(equat),[c] cps	C–D stretching vibr,[c,d] cm^{-1} ν_D(equat)	ν_D(ax.)
IV		276.4	289.2		
V		276.8	290.2		
trans-V-*d*	94	(275)	*291*	(2250)[e]	*2125, 2090*
cis-V-*d*	61	*275.5*	(292)	*2255*[e]	(2125), (2090)
trans-VI-*d*	76	(287.5)	*279*	(2230), (2210)	*2130*[e]
cis-V-*d*	73	*287*	(279)	*2235, 2220*	(2125)[e]
VI		289	279		

[a] At 60 Mcps, CCl$_4$ solutions, TMS as standard. [b] Purity. Remainder epimer. [c] Number in parentheses refers to resonance signal or stretching frequency of the minor epimer, the italicized number refers to the major resonance or band. [d] ± 5 cm^{-1}. [e] Also shoulders.

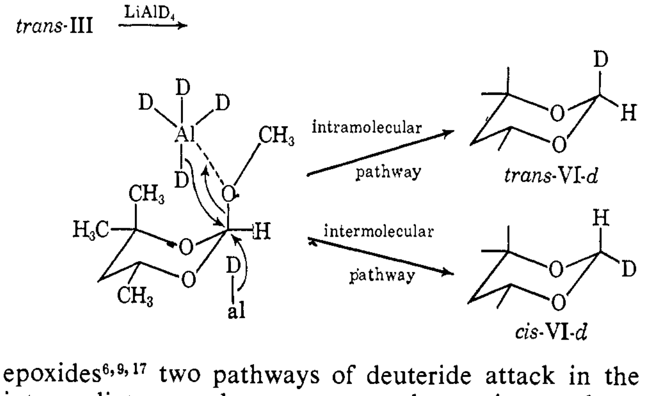
known that in 1,3-dioxanes, axial protons at C-2 resonate at higher field than equatorial ones,[27] similar to what is found in cyclohexanes. Table II summarizes the nmr chemical shifts of the C-2 protons in various deuterated and nondeuterated 1,3-dioxanes, IV–VI, obtained in the present reduction studies. Compounds IV and V showed an AB quartet corresponding to chemical shifts of 289–290 and 276–277 cps of which the latter was assigned to the axial and the former to the equatorial proton. On the basis of this assignment, the principal product of the reduction of *trans*-II with AlD$_3$ has an equatorial proton (*trans*-V-*d*) and the principal product of reduction of *cis*-II has an axial proton at C-2 (*cis*-V-*d*), *i.e.*, the AlD$_3$ reduction proceeds with predominant retention of configuration. Compound VI-*d* also shows an AB quartet for the protons at C-2 corresponding to chemical shifts of 279 and 289 cps. If these are assigned similarly as in V-*d*, the reduction product of *trans*-III (axial methoxyl), which is principally VI-*d* with an H-2 shift of 279 cps, would have to be assigned the configuration with axial H (equatorial D) and that of *cis*-III (equatorial methoxyl), VI-*d* with an H-2 shift of 287 cps, would have to be assigned the configuration with equatorial H (axial D), *i.e.*, the steric course of reduction of III would be the opposite of that of II. We feel that this interpretation is unreasonable, and that in VI the low-field proton is, in fact, the axial one and the high-field proton the equatorial.[28a] Such an assignment would take into account the downfield shift induced in the axial proton at C-2 by the *syn*-axial methyl group at C-4. A reversal of this type is not uncommon;[28b] thus, whereas the equatorial and axial C-2 protons in *trans*- and *cis*-II resonate at 311 and 302 cps, respectively,[1a] the corresponding protons in *trans*- and *cis*-III (where there is a *syn*-axial methyl group) resonate at 313 and 315 cps. With the reversed assignment, the reduction of both *cis*- and *trans*-III with either LAD or AlD$_3$ is seen to proceed with predominant retention of configuration.

The revised assignment is supported by infrared spectral data for the C–D stretching frequencies of *cis*- and *trans*-V-*d* and VI-*d* as shown in Table II. It is well established[29] that the C–D stretching mode for axial deuterium is found at lower frequency than that for equatorial deuterium. In fact (Table II), *trans*-V-*d* of 94% epimeric purity shows strong bands at 2125 and 2090 cm^{-1} (axial D) whereas *cis*-V-*d* of 61% epimeric purity shows a strong band at 2230 cm^{-1} (equatorial D) besides the weaker satellites at 2120 and 2090 cm^{-1} resulting from the *trans* impurity. The fact that the major C–D stretching frequency for the isomer of VI-*d* assigned the *trans* structure (axial D, 76% epimeric purity) is lower, at 2130 cm^{-1} than the major frequencies for the *cis* epimer (equatorial D, 73% epimeric purity) at 2220 and 2235 cm^{-1} may thus be taken as strong confirmation of the assignment made in Table II.

Reduction of III with LAD proceeds with very modest stereoselectivity whereas the stereoselectivity in the reduction of VIII to *cis*-XI and X to *cis*-XIII is high, no *trans*-XI or *trans*-XIII being detectable in the latter two cases. Since neither the starting material nor the product is likely to be epimerized by LAD or LAH (nonacidic!), the difference between the orthoformate and orthoacetate reduction must be real and is not an artifact of the much higher stability of *cis*-XI and *cis*-XIII compared to their *trans* epimers.[1a]

A possible explanation for the predominant retention of configuration (but with low stereospecificity) in the LAD reaction is embodied in the pentacoordinate aluminum derivative shown in Scheme I. In analogy with what has been proposed for alane reduction of epoxides[6,9,17] two pathways of deuteride attack in the intermediate complex are suggested: an intramolecular one proceeding with retention of configuration and one involving external deuteride which proceeds with inversion. For the orthoformates *cis*- and *trans*-III the intramolecular path is slightly preferred; that the preference is much greater for the orthoacetates VIII

Scheme I



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(27) J. Delmau and J. Duplan, *Tetrahedron Lett.*, 559 (1966); E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, 90, 3444 (1968).

(28) (a) Unless this reversal is accepted, one would have to admit that the reduction of *either cis*- or *trans*-III with AlDCl$_2$ gives product VI-*d* with *equatorial* deuterium which is contrary not only to the result with *cis*- and *trans*-II but also contrary to what is found in reaction with Grignard reagents (ref 1a) where *both trans*-III *and trans*-II give *axial* substitution products. (b) For example, the axial carbinol proton in an equatorial cyclohexanol is shifted *down*field by a *syn*-axial methyl group: E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Lett.*, 741 (1962).

(29) E. J. Corey, R. A. Sneen, M. G. Danaher, R. L. Young, and R. L. Rutledge, *Chem. Ind.* (London), 1294 (1954); M. Larnaudie, *J. Phys. Radium*, 15, 650 (1954); for a summary, see E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York, N. Y., 1965, p 144.

and X may be due to steric hindrance to rearward attack by the C-2 methyl group or to product development control, since by far the more stable product is formed.[30]

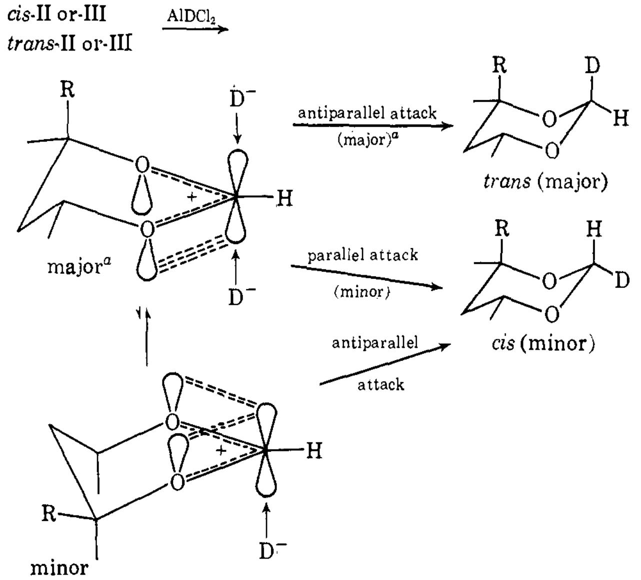
The stereochemistry of reduction with AlD_3 and AlH_3 is qualitatively similar to that with LAD and LAH (Table I). The reaction is exothermic and proceeds rapidly and smoothly in contrast to that with LAH. The stereospecificity in the case of III is higher, reflecting, perhaps, a more accessible intramolecular pathway for the tetracoordinate aluminum hydride complex analogous to that shown in Scheme I (one less D on Al) and, above, all, lessened competition with external attack by the less nucleophilic AlD_3 (compared to LAD). It is of interest that reduction of *trans*-II with AlD_3 is more stereospecific than the corresponding reaction of *trans*-III whereas *cis*-II is reduced less stereospecifically than *cis*-III. This difference most probably reflects steric approach control[1b] in the reduction of III: axial approach of deuteride is inhibited by the *syn*-axial methyl group at C-4 so that the formation of *trans*-VI-*d* (axial deuterium) from either *cis*-III or *trans*-III is depressed relative to the formation of *trans*-V-*d* from *cis*- or *trans*-II. The result is to lower the apparent stereospecificity, in the case of III for the axial (*trans*) isomer but to enhance it for the equatorial (*cis*) isomer. Reduction of the orthoacetate XI by AlH_3 is again completely stereospecific, involving axial attack of hydride.[32]

Reduction of *cis*-III with AlD_3–methanol (1:1) was studied to simulate the reducing species which is probably formed after reduction with AlD_3 has proceeded part way. That the stereochemical result of this reduction was the same as that using AlD_3 alone suggests that the stereoselectivity remains constant in the course of the (three-stage) reduction with alane-d_3.

Dichloroalane and its deuterated analog react vigorously with 2-methoxy-1,3-dioxanes. In contrast to the reaction with Grignard reagents,[1a] substrates with equatorial as well as those with axial methoxyl react readily. The possibility that epimerization occurs prior to reduction with the acidic $AlHCl_2$ or $AlDCl_2$ cannot be excluded but appears unlikely since the reduction is very fast.[33] The stereochemistry in this case is one of substantial stereoconvergence: both *cis*-II and *trans*-II give products very rich in *trans*-V-*d* (and essentially of the same composition); the same is true of *cis*- and *trans*-III, although in this case, presumably because of the steric approach difficulty mentioned earlier, the predominance of *trans*-VI-*d* over its *cis* epimer in the products is not quite so high. The orthoacetate IX is similarly reduced by axial attack to give the *cis* isomer *cis*-XII.

The result can be rationalized in similar fashion as the related one earlier observed for the Grignard reaction, namely by postulating axial attack of the nucleophilic reagent on the dioxocarbonium ion formed from the starting ortho ester by departure of methoxyl which is no doubt assisted electrophilically (Scheme II). Here, as in the case of the Grignard reagent, "antiparallel attack"[1a] on the intermediate ion to give *trans* product in the chair form is favored over "parallel attack" to give the *cis* product in the boat form. The main difference between the Grignard and dichloroalane reactions is that the former is also quite stereoselective as to the substrate: only the *trans* (axial) ortho ester reacts and this has been explained by the need of the reaction to be assisted by orbital overlap from the ring oxygens.[1a] Apparently such overlap is not needed in the $AlDCl_2$ reaction, for it cannot readily be provided when the starting material has the leaving group equatorial, yet the reaction proceeds with both *cis*-II and *cis*-III. The absence of need for electronic assistance presumably reflects an inherently lower activation energy, presumably due to the greater acidity of $AlHCl_2$ as compared to RMgX.

Scheme II



[a] The preference of this mode of attack over the other two is less when R = CH_3 than when R = H, both because of steric interference with "antiparallel attack" and because of larger population of the minor conformation.

The steric course of reduction of *cis*-III with AlD_2Cl is very similar to that with $AlDCl_2$ (Table I) in that the product is mainly *trans*-VI-*d* (axial D). Thus AlD_2Cl also appears to react *via* the dioxocarbonium ion, in contrast to AlD_3 and LAD. The similarity in chemical behavior of AlH_2Cl and $AlHCl_2$ has been noted before[34] as has the dissimilarity of $AlHCl_2$ and AlH_3.[6]

Bhattacharjee and Gorin have recently reported[35]

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(30) In the previous paper (ref 1b) we have argued strongly against the existence of product development control in LAH reductions of cyclohexanones. The present case is different in that one is dealing with a much slower reaction; thus by application of the Hammond postulate,[31] a productlike transition state is more likely.

(31) G. S. Hammond, *J. Amer. Chem. Soc.*, 77, 334 (1955).

(32) In reduction with the acidic reagents AlH_3 or $AlHCl_2$ epimerization of the product is not conclusively ruled out: *cis*-XII is greatly more stable than its *trans* epimer.[1a] The parallel with the reduction of VIII and X with the nonacidic LAH, however, makes any interpretation in terms of product epimerization implausible.

(33) The postulate of epimerization prior to reduction has another inherent implausibility: both reactions proceed *via* a dioxocarbonium ion (see below); in the case of the inability of equatorial methoxyl compounds to react with Grignard reagents, it is precisely the difficulty of forming this ion from the equatorial epimer which is at issue. In other words, if epimerization of the equatorial epimer can proceed, there is then no reason why reduction could not proceed either, and probably faster. We attempted to check for epimerization of starting material by allowing *cis*-II to react with an insufficient amount of $AlHCl_2$; unfortunately, no starting material survived: in the absence of hydride, the starting material appears to suffer rapid ring cleavage in the reaction medium.

(34) Reference 18 and earlier work there cited.

(35) S. S. Bhattacharjee and P. A. J. Gorin, *Can. J. Chem.*, 47, 1195 (1969); see also, *Carbohyd. Res.*, **12**, 57 (1970).

Table III. Physical Properties of the Various Compounds Prepared by Hydrogenolysis of 2-Methoxy-1,3-dioxanes

1,3-Dioxanes[a]	Formula	Prepared from	Reducing species	Yield, %	Bp (mm), °C	Analysis, % Calcd C	Calcd H	Found C	Found H
4-Me	IV	*cis–trans*-I	$LiAlH_4$	57	113 (744)[b]		*c*		
cis-4,6-Di-Me	V (+VII)[d]	*cis–trans*-II	$LiAlH_4$	50	28 (15)	62.07	10.34	62.27	10.37
r-2-*d*-*trans*,4-*trans*-6-Di-Me	*trans*-V-*d*	*trans*-II	AlD_3	80	126–127 (744)				
			$AlDCl_2$	34			*e*		
		cis-II	$AlDCl_2$	77	56–57 (43)				
r-2-*d*-*cis*-4,*cis*-6-Di-Me	*cis*-V-*d*	*cis*-II	AlD_3	50	56–57 (43)		*e*		
4,4,6-Tri-Me	VI	*cis–trans*-III	$LiAlH_4$	65	35–36 (15)[f]	64.61	10.77	65.04	10.89
			AlH_3–HOMe	84	139 (744)				
trans-2-*d*-4,4,6-Tri-Me	*trans*-VI-*d*	*trans*-III	$LiAlD_4$	*g*	142–143 (744)				
			AlD_3	67					
			$AlDCl_2$	76	66–67 (35)		*e*		
		cis-III	AlD_2Cl	72					
			$AlDCl_2$	69					
cis-2-*d*-4,4,6-Tri-Me	*cis*-VI-*d*	*cis*-III	$LiAlD_4$	*g*	141–142 (744)				
			AlD_3	51			*e*		
			AlD_3–HOMe	83	39–40 (18)				
cis-2,4-Di-Me	*cis*-XI	VIII	$LiAlH_4$	51	128–129 (744)				
							h		
r-2-*cis*-4,*cis*-6-Tri-Me	*cis*-XII	IX	AlH_3	85					
					55–56 (40)		*h*		
			$AlHCl_2$	65					
cis-2,4,4,6-Tetra-Me	*cis*-XIII	X	$LiAlH_4$	67	131–133 (745)		*h*		

[a] Major product listed. For exact composition, see Table I. [b] R. Leutner [*Monatsh. Chem.*, **66**, 222 (1935)] reports 113–114°. [c] Nmr and ir spectra compatible with assigned structure. [d] Also isolated compound VII, 5,7-dioxa-4-methyloctan-2-ol, bp 92° (15 mm), in 5–10% yield (*Anal.* Calcd for $C_7H_{16}O_3$: C, 56.76; H, 10.81. Found, C, 56.64; H, 10.75); nmr data (20% solution in CCl_4) AB quartet for OCH_2O, 275.8 cps; multiplet of CH(O–) (two protons), 233 cps, OCH_3 (singlet), 200.5 cps, OH (broad singlet), 172 cps, CH_2 (multiplet), *ca.* 95 cps; two CH_3 doublets, 70 and 66.5 cps. In an attempt to prepare the phenylurethan derivative, cleavage of the acetal function occurred and the bisphenylurethan of *meso*-2,4-pentanediol, mp 142–143° (from heptane–benzene), mixture melting point with a sample prepared from the diol, 143–144° was obtained (*Anal.* Calcd for $C_{19}H_{22}N_2O_4$: C, 66.67; H, 6.43; N, 8.19. Found: C, 66.98; H, 6.43; N, 8.22). [e] Identified by nmr comparison with the undeuterated compound. [f] R. F. Fischer and C. W. Smith, [*J. Org. Chem.*, **28**, 594 (1963)] report 56° (31 mm). [g] More than half the starting material was recovered and contaminated the product; yield not determined. [h] Reported in ref 1a.

that hydrogenolysis of 1,2-isopropylidene-3,5,6-orthoformyl-α-D-glucofuranose (XIV) with AlD_2Cl to 1,2-isopropylidene-3,5-methylene-*d*-α-D-glucofuranose involves retention of configuration. Unfortunately we cannot tell whether the stereochemical outcome of this reaction is in agreement with the observation made here (antiparallel attack on the intermediate dioxocarbonium ion), since the bridged orthoformyl derivative XIV may be conformationally mobile as between a chair and a boat form and the dioxocarbonium ion derived from it is probably conformationally mobile between two chair forms.[36]

In summary, we have shown that the stereochemistry of reduction of 2-alkoxy-1,3-dioxanes with LAD and alane-*d* involves predominant retention of configuration whereas a stereoconvergent formation of the product of antiparallel or axial attack is found when the reducing agent is AlD_2Cl or $AlDCl_2$. The latter reaction course resembles that previously found with Grignard reagents,[1a] except that only axially substituted 2-alkoxydioxanes react readily with the latter whereas both axially and equatorially substituted substrates react with the chloroalanes. For the reduction of ortho esters to acetals, alane is preferred over LAH because of its much faster reaction, the yields for the two reagents being comparable.

Experimental Section

The 2-methoxy-1,3-dioxanes I–III and VIII–X were prepared as described previously.[1a] The outcome of all reductions is summarized in Table III.

Reductions with LAH or LAD. The procedure of Claus, *et al.*,[21] was followed, using 1 mol of LAH or LAD per mol of methoxydioxane in solvent benzene–ether (2:1). After 5 hr refluxing the solution was cooled and excess LAH destroyed by addition of an amount of water equal in weight to that of LAH employed, followed by the same amount of 15% aqueous NaOH and finally three times that amount of water. After 30 min of stirring, a clear solution containing a granular precipitate was obtained. The solution was filtered with gentle suction, and the residue washed three times with warm ether. The combined filtrates were concentrated and the residue was distilled.

Reductions with AlH_3 or AlD_3. In a dry three-necked flask, equipped with magnetic stirrer, calcium chloride protected reflux condenser, and pressure-equalized dropping funnel, was placed 7.5 mmol (285 mg) of LAH in 30 ml of dry ether. There was added, portionwise, 2.5 mmol (334 mg) of anhydrous aluminum chloride with stirring and cooling. In one experiment (Table I) 10 mmol of methanol in 20 ml of dry ether was added at this point. Within 15 min, 15 mmol of the appropriate 2-methoxydioxane in 20 ml of dry ether was added to the alane solution, producing a vigorous reaction. After addition was completed, the mixture was stirred for 15 min, then 160 mg of water was added dropwise, followed by 160 mg of 15% aqueous NaOH and 160 mg of water. The white precipitate was filtered with slight suction and washed four times with 30-ml portions of warm ether. The extract was dried over potassium carbonate, concentrated, and distilled.

Reductions with $AlHCl_2$ or AlH_2Cl. The equipment was the same as for AlH_3. To a cooled solution of 10 mmol of LAH in 50 ml of dry ether was added 30 mmol of aluminum chloride portionwise. The appropriate methoxydioxane (20 mmol dissolved in 30 ml of ether) was added dropwise over 15 min, resulting in a vigorous reaction. Stirring was continued for 15 min at room temperature and then 3.5 ml of 15% aqueous NaOH was added dropwise. The precipitate was filtered with slight suction and washed with four 40-ml portions of warm ether. The subsequent work-up was as above.

Nmr and Ir Analysis. Nmr analysis of the deuterated 1,3-dioxane samples was carried out on a Varian Associates A-60A instrument. The compounds were investigated in 20–25% solutions in CCl_4, containing 2% tetramethylsilane as internal standard.

Analysis of the area ratio of the singlets assigned to the H-2

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[36] There is also a question as to the validity of the axial or equatorial assignment of the deuterium in ref 35.

protons (which is proportional to the ratio of epimers) was effected by expansion of this area with a sweep width of 100 (two to five scans). Each expansion was integrated five times with the integrator of the instrument, so that 10–25 area values were obtained for each isomer to calculate the epimer ratio. The precision of the values obtained by this operation was estimated to be ±2%.

The ir spectra were recorded with a Perkin-Elmer Model 457 instrument.

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Conformational Analysis. XXII. Conformational Equilibria in 2-Substituted 1,3-Dioxanes[1]

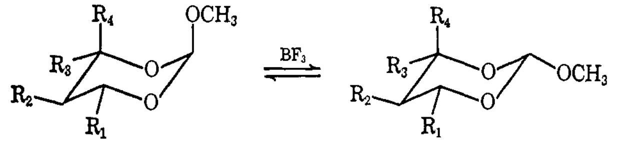
Franz W. Nader and Ernest L. Eliel

Contribution from the Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556. *Received September 20, 1969*

Abstract: Axial–equatorial equilibria in 13 2-substituted 1,3-dioxanes have been studied. The $-\Delta G°$ values (conformational energies) of the groups investigated (in kcal/mol) are: OMe, −0.36 to −0.62; Me, 3.98; Et, 4.04; *i*-Pr, 4.17; Ph, 3.12; *p*-FC_6H_4, 3.13; *p*-BrC_6H_4, 3.18; *p*-$CF_3C_6H_4$, 3.16; OMe/Me (*syn*-axial), 0.05; Me/Me *syn*-axial, ≥ 5.5 kcal/mol. The nmr spectra of all the compounds have been recorded and, in two cases, studied as a function of temperature. The implications of the results are discussed.

In connection with another problem[2] we had occasion to prepare a number of 2-alkoxy- and 2-alkyl-substituted 1,3-dioxanes. We have now investigated the *cis–trans* equilibria (axial–equatorial equilibria of the 2-substituent) in these compounds with the results shown in Tables I and II. The findings appear to be of sufficient interest to deserve documentation and discussion.

Table I. Equilibrium Data for 2-Methoxy-1,3-dioxanes



Compd	R_1	R_2	R_3	R_4	Equilibrium constant[a]	$\Delta G_{25}°$
II[b]	CH_3	H	H	H	0.546 ± 0.009	+0.36 ± 0.010
III	CH_3	H	CH_3	H	0.500 ± 0.014 (0.52[c])	+0.41 ± 0.016
IV	CH_3	H	CH_3	CH_3	1.084 ± 0.036 (1.06[c])	−0.05 ± 0.003
V	H	*t*-Bu	H	H	0.429 ± 0.012 (0.43[c])	+0.50 ± 0.014 (0.60[d])
I	H	H	H	H	0.35 ± 0.1[e]	+0.62 ± 0.15

[a] Solvent diethyl ether at 25°, determined by vpc, values corrected by response ratio. [b] References 3b, 4. [c] Obtained by nmr in CCl_4 solution (20%). [d] Value corrected for conformational heterogeneity. [e] Calculated from dipole moment measurements of the compound in benzene at 25°, μ = 2.24 D, μ_a = 1.953 D, μ_e = 2.910 D. The latter two values are the averages of the dipole moments of *trans*-II, -III and -IV and *cis*-II, -III, and -IV, respectively (ref 2). The error limits in this case are estimates; in all the other entries they are standard deviations.

The configurational assignments of the 2-methoxy-1,3-dioxanes, based on nmr spectra data, dipole moments, and nuclear Overhauser effects, have been discussed earlier.[2] Equilibrations were carried out by means of boron trifluoride etherate in ether;[3] equilibrium constants were determined by gas chromatography of the *cis–trans* mixtures at equilibrium and were checked by integration of distinctive nmr peaks of the components. The results are shown in Table I. Because of the "anomeric effect"[4,5] the axial isomers are generally the more stable.

The $-\Delta G°$ value for the 2-methoxy-*r*-4,*cis*-6-dimethyl-1,3-dioxanes (III),[6] −0.41 kcal/mol, is in agreement with that of −0.36 kcal/mol previously determined[3b,4] in 2-methoxy-4-methyl-1,3-dioxane (II), both diastereoisomers of which are evidently very nearly conformationally homogeneous. The value of −0.50 kcal/mol for 2-methoxy-5-*t*-butyl-1,3-dioxane (V), on the other hand, differs appreciably; moreover, as shown in Scheme I, this compound cannot be considered conformationally homogeneous and a correction must be applied to the value by taking into account that the $-\Delta G°$ value for a *t*-butyl substituent in the 5 position is only 1.4 kcal/mol[3] and thus $\Delta G°$ for the $T_1 \rightleftharpoons T_2$ equilibrium is only about 1.0 kcal/mol so that approximately 16% of the *trans* compound is in the diaxial conformation T_2.[7] The conformational energy of the

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(2) E. L. Eliel and F. W. Nader, *ibid.*, **92**, 584 (1970).

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