Mechanism of the Lithium Aluminum Hydride Reduction of a Nonenolizable β Diketone[1]

Summary: The possible stereospecific lithium aluminum hydride ($LiAlH_4$) and lithium tri(*tert*-butoxy)aluminum hydride [$LiAl(O\text{-}t\text{-}Bu)_3H$] reductions of 2,2-dimethylindandione have been examined and the experimental conditions governing the range of the isomer distribution are described.

Sir: We have reinvestigated a previous report by Alder and Fremery[2] concerning the $LiAlH_4$ reduction of a nonenolizable β diketone, 2,2-dimethylindandione. The authors reported the product as a single compound; however, stereochemistry was not mentioned. Under Alder's reaction conditions of excess $LiAlH_4$ in refluxing diethyl ether, we obtained an approximately 1:1 mixture of *cis*- and *trans*-2,2-dimethylindandiol.

Akhtar and Marsh[3] have reported the $LiAlH_4$ (excess)/diethyl ether reduction of cholestan-5α-ol-3-one. To explain the preponderance of the cis product, cholestane-3α,5α-diol, the authors favored the formation of a complexed intermediate at the 5-hydroxyl position, thus forcing subsequent attack from the less hindered β side.

The minor product, cholestane-3β,5α-diol, may arise by at least two different pathways. One involves an intramolecular hydride transfer and another, an attack of a second $LiAlH_4$ molecule from the α side.

We attempted to determine if the second reduction step for such nonenolizable β diketones to the *trans*-diol is uniquely governed by steric approach control[4] or if an intramolecular hydride transfer occurs. Insights into the reaction mechanism were obtained by varying the equivalent ratio of the reactants and by using different reaction temperatures.

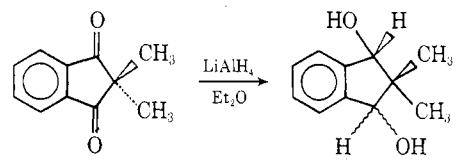
It became necessary to determine if kinetic control was operational under all the widely diverse conditions of reactant ratios and temperatures employed in this study. Each individual isomeric composition was determined at at least three different reaction times. They always agreed to within 2%. Therefore it is experimentally verified that no equilibration of products was taking place under any set of experimental conditions used.

The isomeric composition was determined by two procedures. Addition of the lanthanide shift reagent, $Eu(fod)_3$,[5] caused the methyl resonances of the two isomeric compounds to be sufficiently separated so that the an integration could be performed. The diols were also converted into their silyl ethers by treatment with a mixture of hexamethyldisilazane and trimethylchlorosilane.[6] The silylated ethers were separated by gas chromatography to evaluate the isomeric composition. Experimental agreement between the two methods was 3%.

By varying either the equivalent ratio of ketone to hydride or the temperature of the medium, the isomeric composition of the products was considerably altered. The results of these experimental variations are tabulated in Table I. The following trends are evident. As the equivalent amount of hydride is decreased, the relative amount of *trans*-diol increases. As the temperature of the reaction is decreased, the amount of *trans*-diol increases.

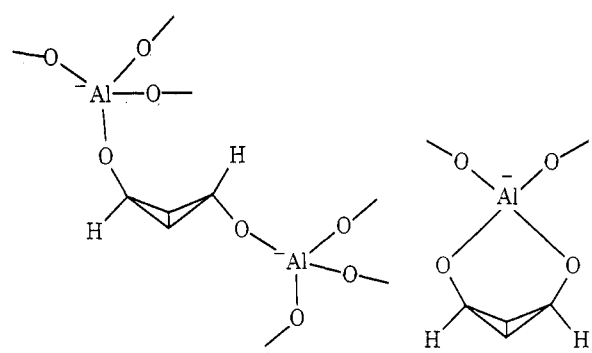
If the "Non-Crossing Rule"[7] were obeyed and if the product stabilities were known, then varying the temperature would lend insights into the relative importance of product development control vs. steric approach control. From the data it appears that no such insights may easily be gained because the relative amount of the isomers varied from one side of 50% to the other. It is reasonable to designate the *trans*-aluminate as the less stable product and to assign the *cis*-aluminate as the more stable product if their structures are as shown.

Table I



Ratio[a] of ketone:$LiAlH_4$	% relative isomers: At 34° Cis	At 34° Trans	At −78° Cis	At −78° Trans
0.5	53.6[b,c]	46.3	56.1[c,d]	43.7
1.0	35.5[b,e]	64.3	12.7[d,f]	87.1
2.0	28.8[b,g]	71.0	7.0[d,h]	92.8

[a] Equivalent reduction ratio (ERR). [b] Upon completion of hydride addition, immediate hydrolysis. [c] 100% conversion, based on NMR. [d] 3-hr reaction time, followed by hydrolysis. [e] 75% conversion, based on NMR. [f] 78% conversion, based on NMR. [g] 75% conversion, based on NMR. [h] 94% conversion, based on NMR.

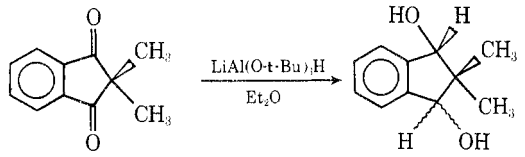


trans cis

If the above designations are valid, then the following conclusions may be drawn. As the amount of hydride, or the temperature is decreased, one finds a tendancy toward more of the trans product. Thus, excess $LiAlH_4$ favors product development control while minimal $LiAlH_4$ favors steric approach control. Likewise high temperature favors product development control while low temperature favors steric approach control.

In accounting for the trans product, the possibility of an intramolecular hydride reduction must be considered. Indeed, with less available hydride in solution, the tendency for intermolecular attack is lessened. If an intramolecular hydride transfer is operational, it should become more favored as the equivalent amount of $LiAlH_4$ is decreased, thus resulting in more trans product. This is the observed trend. However, it must be mentioned that it is currently accepted that, owing to a disproportionation mechanism,[8]

Table II



Ratio[a] of ketone:LiAl-(O-*t*-Bu)$_3$H	% relative isomers: At 34° Cis	At 34° Trans	At −78° Cis	At −78° Trans
0.03	98.2	1.7[b,c]		
0.5	62.3	37.5[b,c]		97[d,g]
1.0		97[b,e]		97[d,g]
2.0		97[b,f]		97[d,g]

[a] Equivalent reduction ratio (ERR). [b] 24-hr reaction time, followed by hydrolysis. [c] 95% conversion, based on NMR. [d] 6-hr reaction time, followed by hydrolysis. [e] 77% conversion, based on NMR. [f] 66% conversion, based on NMR. [g] 25% conversion based on NMR.

reductions with $LiAlH_4$ generally proceed uniquely from AlH_4^{-1} and not the mixed alkoxy hydrides, e.g., $AlH_2(OR)_2^{-1}$.

To exclude an intramolecular hydride transfer pathway, all but one of the hydrides on the reducing agent must be replaced. Reduction with LiAl(O-*t*-Bu)$_3$H fulfills this requirement. Examination of Table II reveals that as the equivalent amount of LiAl(O-*t*-Bu)$_3$H is decreased the *trans*-diol increases. Presumably the *trans*-diol results from the approach of a second LiAl(O-*t*-Bu)$_3$H from the same side as the bulky alkoxyaluminum function. Since the data from the $LiAlH_4$ reductions parallels that of the LiAl(O-*t*-Bu)$_3$H, we see no need, at least at present, to invoke an intramolecular hydride transfer to explain the *trans*-diol in the $LiAlH_4$ case.

In both the $LiAlH_4$ and LiAl(O-*t*-Br)$_3$H cases, it is possible that the carbonyl function first reduced may act as a neighboring group.[9] This group may then preferentially solvate the next reducing anion species, thus steering it in so that the trans product is formed. This explanation is consistent with the results obtained with minimal hydride and at low temperatures.

We are currently investigating 3-hydroxy-2,2-dimethylindanone under the same reaction conditions. Its aluminate is a possible intermediate in the reduction of 2,2-dimethylindandione. Experimental details and the completed work on this study will be reported at a later date.

References and Notes

(1) Presented at the 169th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1975.
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(3) M. Akhtar and S. Marsh, *J. Chem. Soc. C*, 937 (1966).
(4) E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970).
(5) Eu(fod)$_3$, tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate)-europium(III), Ventron's Eu-Resolve-II.
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(7) G. Klopman, "Chemical Reactivity and Reaction Paths", Wiley-Interscience, New York, N.Y., 1974, p 9.
(8) H. Haubenstock and E. L. Eliel, *J. Am. Chem. Soc.*, **84**, 2363 (1962).
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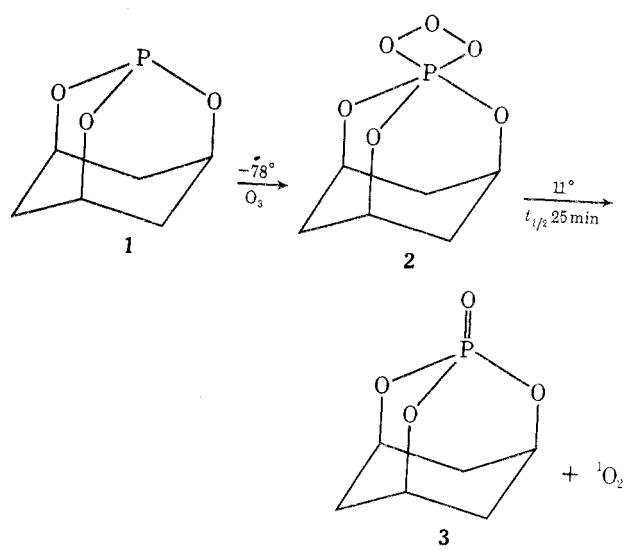
1-Phospha-2,8,9-trioxaadamantane Ozonide. A Convenient Source of Singlet Molecular Oxygen[1]

Summary: Thermal decomposition of 1-phospha-2,8,9-trioxaadamantane ozonide produces singlet molecular oxygen in quantitative yield (k_1 = 1.01 × 10^{-3} sec^{-1} at 18° in CH_2Cl_2).

Sir: The reactions of singlet molecular oxygen ($^1O_2$) with various organic substrates have been extensively investigated in recent years.[2] The possible role of $^1O_2$ in biological oxidation processes has also been of interest.[3] Singlet oxygen can be generated by photosensitization and by chemical methods such as the spontaneous decomposition of phosphite ozonides. Murray[4] and coworkers have shown that triphenyl phosphite ozonide decomposes at −30° to yield $^1O_2$ which may be trapped by an acceptor in solution. However, separation of the oxidation products from the triphenyl phosphate is often difficult. In addition, triphenyl phosphite ozonide is not sufficiently stable to permit storing this reagent conveniently.

It has been suggested that polycyclic phosphite ozonides should exhibit unusual stability as a result of restricted pseudorotation.[5,6] We wish to report that the adduct **2** obtained from the addition of ozone to 1-phospha-2,8,9-trioxaadamantane (**1**)[7] is a relatively stable ozonide which decomposes quantitatively to $^1O_2$ and phosphate **3**.



Singlet oxygen exhibits three modes of reaction with alkenes: 1,4 cycloaddition with conjugated dienes to yield cyclic peroxides, the "ene" reaction to form allylic hydroperoxides, and 1,2 cycloaddition to give 1,2-dioxetanes which subsequently cleave to carbonyl-containing products. Examples of these reactions using the ozonide **2** as the source of $^1O_2$ are summarized in Table I. A trapping experiment using a 5:1 excess of acceptor **8** gave a 95% yield of the product **9** based on ozonide **2**. One criterion for the intermediacy of singlet oxygen in a reaction is the product distribution obtained from 1,2-dimethylcyclohexene (**10**).[8] Decomposition of **2** in the presence of **10** in CH_2Cl_2 yields a ratio of the two hydroperoxides **11** and **12** which is consistent with the formation of free $^1O_2$ in the reaction.

In a typical experiment, a 0.12 *M* solution of the ozonide **2** in CH_2Cl_2 was prepared by the slow addition of a solution of 0.24 g (1.5 mmol) of **1** in 3 ml of CH_2Cl_2 to 10 ml of CH_2Cl_2 at −78° continuously saturated with ozone. After the addition is complete, dry nitrogen is bubbled through the solution to remove the excess ozone. A solution of the singlet oxygen acceptor in 1 ml of CH_2Cl_2 is added to an al-