Notes

Concerning the Stereoselectivity of Lithium Tri-*tert*-butoxyaluminum Hydride

E. C. Ashby,* John P. Sevenair, and Frank R. Dobbs

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

Received June 17, 1970

The preparation[1-4] and reactions[5-11] of lithium alkoxyaluminum hydrides have been extensively studied in recent years. Considerable useful synthetic information has been obtained, but the mechanisms of such reductions are not well understood. Empirical rules have been developed for such reactions, but exceptions to these rules exist.

The selectivity of a complex metal hydride as a reducing agent depends largely on its steric bulk; a larger hydride molecule is expected to give a higher yield of products resulting from attack at the least hindered side of an asymmetric molecule. As expected from this, lithium trimethoxyaluminum hydride is more selective than lithium aluminum hydride. However, this presumably less bulky methoxy compound is also more selective than the corresponding *tert*-butoxy hydride in a wide range of systems.[5,10] The results obtained by Brown and Deck,[10] and by Haubenstock and Eliel,[5] are summarized in Table I.

Table I

Reaction of Cyclic and Bicyclic Ketones

Ketone reduced	Reducing agent	% less stable alcohol in product	Note
3,3,5-Trimethylcyclohexanone	$LiAlH_4$	52	*a,c*
	$LiAlH(OMe)_3$	75	*a,c*
	$LiAlH(OEt)_3$	83	*a,c*
	$LiAlH(O\text{-}i\text{-}Pr)_3$	54	*a,c*
	$LiAlH(O\text{-}tert\text{-}Bu)_3$	73	*a,c*
Norcamphor	$LiAlH_4$	89	*b,d*
	$LiAlH(OMe)_3$	98	*b,d*
	$LiAlH(OEt)_3$	85	*b,d*
	$LiAlH(O\text{-}tert\text{-}Bu)_3$	93	*b,d*
Camphor	$LiAlH_4$	92	*b,e*
	$LiAlH(OMe)_3$	99	*b,e*
	$LiAlH(O\text{-}tert\text{-}Bu)_3$	93	*b,e*
Isopinocamphone	$LiAlH_4$	89	*b,e*
	$LiAlH(OMe)_3$	98	*b,e*
	$LiAlH(O\text{-}tert\text{-}Bu)_3$	84	*b,e*
2-Methylcyclopentanone	$LiAlH_4$	24	*b,f*
	$LiAlH(OMe)_3$	44	*b,f*
	$LiAlH(OEt)_3$	23	*b,f*
	$LiAlH(O\text{-}tert\text{-}Bu)_3$	28	*b,f*
2-Methylcyclohexanone	$LiAlH_4$	24	*b,f*
	$LiAlH(OMe)_3$	69	*b,f*
	$LiAlH(OEt)_3$	26	*b,f*
	$LiAlH(O\text{-}tert\text{-}Bu)_3$	30	*b,f*
2-*tert*-Butylcyclohexanone	$LiAlH_4$	58	*b,f*
	$LiAlH(OMe)_3$	64	*b,f*
	$LiAlH(O\text{-}tert\text{-}Bu)_3$	54	*b,f*

[a] Reference 5, ether solvent. [b] Reference 10, THF solvent. [c] Unstable alcohol is trans. [d] Unstable alcohol is exo. [e] Unstable alcohol is endo. [f] Unstable alcohol is cis.

The failure of lithium tri-*tert*-butoxyaluminum hydride (I) to follow the usual pattern has been attributed to a change in reaction mechanism. It has been suggested[6,10] that di-*tert*-butoxyaluminum hydride (II) is involved as the actual reducing species, as in the following eq 1 and 2.

$$\underset{\text{I}}{\mathrm{LiAlH(O\text{-}\mathit{tert}\text{-}Bu)_3}} \rightleftarrows \underset{\text{II}}{\mathrm{HAl(O\text{-}\mathit{tert}\text{-}Bu)_2}} + \mathrm{LiO\text{-}\mathit{tert}\text{-}Bu} \qquad (1)$$

$$\mathrm{HAl(O\text{-}\mathit{tert}\text{-}Bu)_2} + \text{ketone} \longrightarrow \text{products} \qquad (2)$$

The infrared spectra in solution and the reducing characteristics of independently prepared I and II were compared, and evidence was obtained which is incompatible with this hypothesis. The infrared spectra of the two hydrides, at a concentration of 0.3 *M* in THF solution, were obtained and compared. It was found that the aluminum–hydrogen stretching band of II appeared at 1860 cm^{-1}; the same band in I appeared at 1760 cm^{-1}, and no shoulder or weak band was visible at 1860 cm^{-1}. This experiment indicates that the equilibrium concentration of II in I is less than 1%.

This experiment does not rule out the possibility that II, while present in very low concentration, reacts with ketones so much faster than I that it is the primary reacting species. To test this hypothesis, it was decided to compare the stereoselectivity of I and II in the reduction of cyclic and bicyclic ketones. The ketones chosen for this purpose were 2-methylcyclohexanone, 3,3,5-trimethylcyclohexanone, norcamphor, and camphor.

Reductions were carried out at 0° in THF solution. The samples were hydrolyzed after 2 hr of reaction, and the yields of alcohols and recoveries of starting material were determined by vpc. These data are given in Table II. It can be seen that the stereoselectivity differs significantly in several cases. Since all the reductions were carried out under the same conditions, the recoveries of starting material and yields of total alcohol may be used as rough kinetic data; these show that the two hydrides reduce ketones at similar rates.

---

* To whom correspondence should be addressed.

(1) H. C. Brown and R. F. McFarlin, *J. Amer. Chem. Soc.*, **78**, 252 (1956).
(2) G. Hesse and R. Schrödel, *Justus Liebigs Ann. Chem.*, **607**, 24 (1957).
(3) O. Schmitz-DuMont and V. Habernickel, *Ber.*, **90**, 1054 (1957).
(4) H. C. Brown and C. J. Shoaf, *J. Amer. Chem. Soc.*, **86**, 1079 (1964).
(5) H. Haubenstock and E. L. Eliel, *ibid.*, **84**, 2363 (1962).
(6) D. C. Ayres and W. Sawdaye, *Chem. Commun.*, 527 (1966).
(7) J.-C. Richer, *J. Org. Chem.*, **30**, 324 (1965).
(8) H. C. Brown and C. P. Gang, *J. Amer. Chem. Soc.*, **86**, 1085 (1964).
(9) H. C. Brown and P. M. Weissman, *ibid.*, **87**, 5614 (1965).
(10) H. C. Brown and H. R. Deck, *ibid.*, **87**, 5620 (1965).
(11) H. C. Brown and N. M. Yoon, *ibid.*, **88**, 1464 (1966).

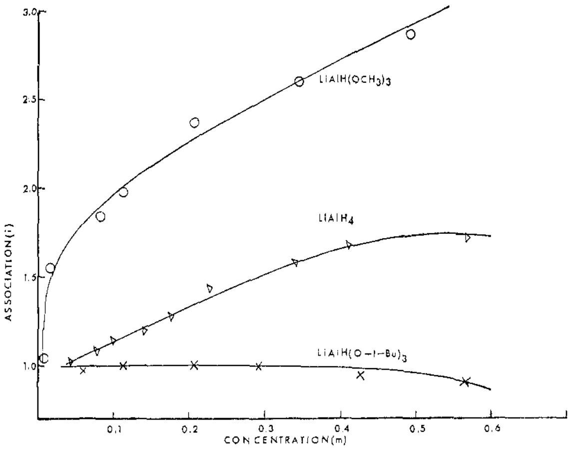


Figure 1.—Association of lithium trialkoxyaluminum hydrides in tetrahydrofuran.

Table II

Selective Reduction of Ketones Using $LiAlH(O\text{-}tert\text{-}Bu)_3$ and $AlH(O\text{-}tert\text{-}Bu)_2$

	Hydride	% total alcohol yield using I	II	% starting material recovered using I	II	% unstable isomer using I	II
2-Methylcyclohexanone	*a*	45	52	55	35	36	56
	b	98	71	0	0	38	54
3,3,5-Trimethylcyclohexanone	*a*	94	45	1	40	93	74
	b	88	93	0	0	95	80
Norcamphor	*a*	47	40	48	59	94	90
	b	94	89	0	4	95	93
Camphor	*a*	15	11	81	89	94	75
	b	33	41	58	60	94	80

[a] 1.5:1 molar excess of hydride used. [b] 4.5:1 molar excess of hydride used.

If the concentration of II is less than 1% of that of I, the rate of reduction by II must exceed that of I by at least a factor of 100 for II to be the major reducing species. It may therefore be concluded that the disproportionation reaction proposed[6,10] is not responsible for the lesser stereoselectivity of I.

An alternative explanation for the order of selectivity of the lithium trialkoxyaluminum hydrides is suggested by the association data obtained for these compounds in THF solution. These data are shown in Figure 1. It was found that lithium trimethoxyaluminum hydride displays an increasing degree of association with increasing concentration, while I is monomeric over the same concentration range. The parent compound, lithium aluminum hydride, displays intermediate characteristics. All other factors being equal, a *tert*-butoxy compound is expected to be bulkier than a methoxy compound, but dimerization and higher polymerization of the methoxy compound may produce a reducing agent bulkier than the monomeric $LiAl(O\text{-}tert\text{-}Bu)_3H$.

In order to test this conclusion further, the stereoselectivity of $LiAl(OMe)_3H$ and $LiAl(O\text{-}tert\text{-}Bu)_3H$ toward 2-methylcyclohexanone was evaluated as a function of concentration. Since $LiAl(O\text{-}tert\text{-}Bu)_3H$ appears to be monomeric over a wide concentration range (Figure 1), the ratio of alcohols produced on reduction of 2-methylcyclohexanone should not vary with concentration of the hydride reagent. On the other hand, if association of the reagent is important, a significant change in the ratio of alcohols should be observed as a function of concentration with $LiAl(OMe)_3H$, since the association of this hydride does change with concentration. The data in Table III show clearly that the formation of the less stable alcohol remains essentially constant over a 50-fold change in concentration when $LiAl(O\text{-}tert\text{-}Bu)_3H$ is used whereas the formation of the less stable alcohol changes significantly in the concentration range where the association of $LiAl(OMe)_3H$ changes the most (0.01–0.1 *M*).

Table III

Effect of Hydride Concentration on the Reduction of 2-Methylcyclohexanone

Molal concn	% less stable isomer $LiAl(O\text{-}tert\text{-}Bu)_3H$	$LiAl(OMe)_3H$
0.01	23	28
0.10	25	61
0.30	25	62
0.50	26	63

The results of these studies indicate clearly that the steric requirement of a hydride cannot be judged by its empirical formula, but rather molecular association studies are required in order to determine its molecular aggregation in solution at the concentration at which it is being employed as a reducing agent.

Experimental Section

Materials.—Tetrahydrofuran was purified by distillation from sodium aluminum hydride under a nitrogen atmosphere. Methanol was purified by distillation from magnesium turnings under a nitrogen atmosphere. *tert*-Butyl alcohol was purified by fractional crystallization. The liquid ketones, 2-methylcyclohexanone and 3,3,5-trimethylcyclohexanone, were purified by vacuum distillation; the solids, norcamphor and camphor, were purified by sublimation under vacuum.

Lithium aluminum hydride solutions in THF were prepared by stirring slurries for 2 days, followed by removal of solids by filtration. Sulfuric acid (100%) was prepared from water and fuming sulfuric acid. Aluminum hydride was prepared by the addition of 100% sulfuric acid to the lithium aluminum hydride solution, followed by removal of the precipitated lithium sulfate.[11] Lithium trimethoxyaluminum hydride and lithium tri-*tert*-butoxyaluminum hydride were prepared by the slow addition of the respective alcohols to the lithium aluminum hydride solution.[4] Di-*tert*-butoxyaluminum hydride was prepared by the slow addition of *tert*-butyl alcohol to the aluminum hydride solution.[12]

Aluminum was determined by complexation with EDTA and back titration with zinc acetate. Active hydride was determined with a Toepler pump by measuring evolved hydrogen after hydrolysis.

Reduction Procedure.—A 25-ml flask, containing a magnetic stirring bar and fitted with a septum stopper and two syringe needles as nitrogen inlet and outlet, was flamed out to remove residual oxygen and water. In the comparison of $LiAl(O\text{-}tert\text{-}Bu)_3H$ and $Al(O\text{-}tert\text{-}Bu)_2H$, 5 ml of a 0.213 *M* solution of the ketone in THF was added. The flask was cooled to 0°, and a sufficient amount of the hydride solution was then added by syringe to provide the desired excess. In the comparison of relative yield *vs.* molal concentration, a solution of the desired molality was added to the reaction flask and cooled to 0°. A small sample of 2-methylcyclohexanone was then added by syringe, with vigorous stirring. The volume of ketone was in all cases less than 3% of that of the hydride solution. After 2 hr, the reaction mixture was hydrolyzed using 5 ml of saturated aqueous ammonium chloride solution. The internal standard for vpc analysis was then added and analyses were carried out.

---

(12) K. Suchy, Dissertation, University of Munich, Munich, Germany, 1966, working under H. Noth.

A diglycerol column at 90° was used to separate the products of the 2-methylcyclohexanone reduction, and a Carbowax 20M column at 125° was used to separate the products in the cases of 3,3,5-trimethylcyclohexanone, norcamphor, and camphor.

Association.—The determination of the association of air- and moisture-sensitive compounds by ebullioscopic techniques is described elsewhere.[13,14] The association studies were carried out in tetrahydrofuran at a pressure of 740.0 mm.

Registry No.—I, 17476-04-9; II, 15649-65-7; LiAl(OMe)$_3$H, 12076-93-6; 2-methylcyclohexanone, 583-60-8.

Acknowledgment.—We wish to acknowledge the support of this work by the Petroleum Research Fund (Grant No. 3211-A3, 4) and the Quality Improvement Funds of the Georgia Institute of Technology.

---

(13) F. W. Walker and E. C. Ashby, *J. Chem. Educ.*, **45**, 654 (1968).

(14) F. W. Walker and E. C. Ashby, *J. Amer. Chem. Soc.*, **91**, 3845 (1968).

Structure and Synthesis of Kahweofuran, a Constituent of Coffee Aroma

G. BÜCHI* AND P. DEGEN

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

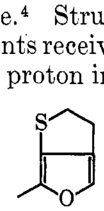
F. GAUTSCHI AND B. WILLHALM

Research Laboratories Firmenich et Cie., Geneva, Switzerland

Received August 7, 1970

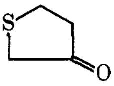
In the course of detailed analyses of coffee concentrates, a substance with the empirical formula C_7H_8OS, but of unknown constitution, was isolated.[1] In the present paper we outline work on the structure and synthesis of this aroma constituent which we have named kahweofuran (Arab. qahweh, coffee).

The infrared spectrum shows no absorptions which could be ascribed to hydroxyl, mercapto, or carbonyl functions, and it was concluded that both oxygen and sulfur atoms are part of heterocyclic rings. The much more revealing nuclear magnetic resonance spectrum exhibits a one-proton signal at δ 6.91 ascribable to a proton attached to either α or β position of a thiophene ring or to the α position of a furan ring.[2] No other aromatic protons are discernible and the unknown consequently is a trisubstituted furan or thiophene. One of these substituents is a methyl group and the chemical shift of the three-proton singlet (δ 2.17) agrees best with the presence of a 2-methylfuran or a 3-methylthiophene.[3] The remaining two substituents are part of a five-membered ring containing two carbon and one heteroatom. Resonances caused by protons attached to these two carbon atoms appear as a A_2B_2 pattern and comparison of the low-field signals centered at δ 3.57 with those present in the spectra of tetrahydrofuran and tetrahydrothiophene strongly suggest the presence of the latter part structure.[4] Structure **1** tentatively generated by these arguments receives further support from the fact that the furan proton in **1** couples to the high-field methylene protons with J = 1.5 Hz in full agreement with the situation encountered previously in 3-methylfuran where benzylic coupling to H_2 is 1.2 Hz, while coupling to H_4 is only 0.5 Hz.[5]

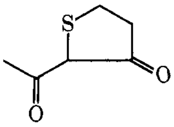


1

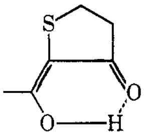
More definitive evidence in favor of structure **1** for kahweofuran was provided by synthesis. Condensation of 3-ketotetrahydrothiophene (**2**)[6] with ethyl acetate in the presence of sodium hydride gave a mixture of β diketones, containing 85% 2-acetyl-3-keto-tetrahydrothiophene (**3** and **4**) and 15% isomer **5**. The ultraviolet absorption maximum (286 mμ) of the minor isomer **5** is strikingly similar to that of 2-acetylcyclohexanone[7] in both neutral and basic solution, while that of the desired isomers **3** and **4** is shifted to 353 mμ and shows no bathochromic displacement on addition of base. Nuclear magnetic resonance spectra in carbon tetrachloride solutions revealed isomer **5** to be completely enolic, while the desired intermediate is a mixture containing 80% enol **4** (or its tautomer) and 20% diketone **3**.



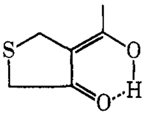
2



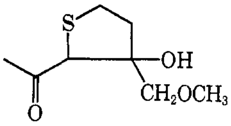
3



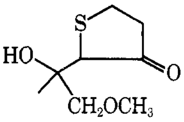
4



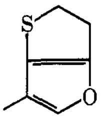
5



6



7



8

Before proceeding with a discussion of the synthesis, it should be pointed out that the preferential formation of the 2-acetyltetrahydrothiophenes **3** and **4** was anticipated because the intermediate carbanion leading to 2 substitution is stabilized by the 3d orbitals of the neighboring sulfur atoms[8,9] as well as by the carbonyl group. In analogy to the essentially quantitative alkali-catalyzed hydrolysis of 2-acetylcyclopentanone to δ-acetylvaleric acid,[10] we anticipated an organometallic reagent to preferentially add to the cyclic carbonyl function in **3**–**4**. In fact, the addition of methoxymethyl magnesium chloride[11] yielded a mixture of adducts containing two parts of the diastereomeric hydroxy ketones

---

* To whom correspondence should be addressed.

(1) M. Stoll, M. Winter, F. Gautschi, I. Flament, and B. Willhalm, *Helv. Chim. Acta*, **50**, 628 (1967). The isolation of kahweofuran is described on p 656.

(2) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, England, 1969, p 209.

(3) Reference 2, p 173.

(4) Reference 2, p 199.

(5) S. Rodmar, S. Forsen, B. Gestblom, S. Gronowitz, and R. A. Hoffman, *Acta Chem. Scand.*, **19**, 485 (1965).

(6) H. Wynberg, A. Logothetis, and D. Ver Ploeg, *J. Amer. Chem. Soc.*, **79**, 1972 (1957). The overall yield was improved substantially when the crude mixture of 2- and 4-carbomethoxy- and -carbethoxy-3-ketotetrahydrothiopenes was *not* purified by distillation.

(7) H. Smith, *J. Chem. Soc.*, 803 (1953).

(8) K. C. Bank and D. L. Coffen, *Chem. Commun.*, 8 (1969).

(9) A similar case was described by R. B. Woodward and R. H. Eastman, *J. Amer. Chem. Soc.*, **68**, 2229 (1946).

(10) S. Hünig and W. Lendle, *Chem. Ber.*, **93**, 913 (1960).

(11) F. Runge, E. Taeger, C. Fiedler, and E. Kahlert, *J. Prakt. Chem.*, **19**, 37 (1963); H. Normant and C. Crisan, *Bull. Soc. Chim. Fr.*, 459 (1959).