SOLVATION EFFECTS ON STEREOCHEMISTRY OF REDUCTION OF 3,3,5-TRIMETHYLCYCLOHEXANONE WITH LITHIUM ALUMINUM TRI-t-BUTOXYHYDRIDE

H. HAUBENSTOCK* and S.-J. HONG

The City University of New York, The College of Staten Island, Staten Island, NY 10301, U.S.A.

(Received in USA 30 January 1978; Received in UK for publication 28 March 1978)

Abstract—Specific solvation effects on stereoselectivity in the reduction of a cyclohexanone by lithium aluminum tri-*t*-butoxyhydride have been studied by adding measured quantities of diethyl ether, tetrahydrofuran (THF) and methyl-substituted tetrahydrofurans to benzene solvent, and various amounts of THF to diethyl ether solvent. A steric hindrance effect in the case of bulky addends was observed, and a significant increase in stereoselectivity for less bulky addends was found. The results have been explained in terms of complexing, or steric hindrance to complexing, of the lithium cation.

Among the factors which affect the stereochemical outcome of reduction of a substituted cyclohexanone with a complex metal hydride is the choice of solvent. With alkoxy derivatives of LAH¹ the choice is usually limited to ether type solvents. However, it has been shown that even within this limited choice, there can be marked differences in selectivity in the reduction of moderately hindered ketones. For example, in the reduction of 3,3,5-trimethylcyclohexanone, 1 with LAH and its alkoxy derivatives, much higher proportions of the *trans* (axial) alcohol, 2 were formed in THF than in diethyl ether² (eqn 1).

The nature of the solvent can affect the stereochemistry of the reaction in a number of ways. The complex metal hydride reagent can have different degrees of association in different solvents. Association of reagent molecules has been demonstrated to affect stereochem-



istry.³ The nature of ionic species, types of ion pairs or free ions, may be determined by the nature of the solvent, as well as by concentration.⁴ Available evidence indicates that Li⁺ is specifically solvated by a maximum of four molecules of THF.⁴ It has also been demonstrated that CO groups may form four-to-one solvates with Li⁺ by the study of various solvent mixtures containing lithium salts.⁵ Furthermore, it has been shown that in reductions with LAH the presence of the cation as an electrophilic catalyst is absolutely essential to reduction.⁶ The specific solvation of the cation would be expected to exert some control over stereoselectivity in the reduction process.

This study involves the reduction of the model ketone 1 with lithium aluminum tri-t-butoxyhydride (LATH) in benzene and diethyl ether solvents. In each solvent a specific molar quantity of a potential solvating agent for Li⁺ has been added, and the stereochemistry of the reduction determined. The intent was to probe steric effects on selectivity with THF, methyl substituted THF derivatives and diethyl ether added to benzene, and with THF in various proportions added to diethyl ether. The LATH reagent was chosen because its single hydride reducing equivalent avoids the complication of having various intermediate reducing species involved. The ketone is ideal as a substrate in that it is highly sensitive to solvent effects,² and is effectively conformationally anchored. This minimizes any complication which might otherwise arise from a possible solvent effect on conformer distribution.

RESULTS AND DISCUSSION

The results in benzene solvent are summarized in Table 1. The experiments were carried out by stirring the addend with the reagent LATH for 15-30 min, then adding benzene, stirring further, and finally adding the ketone 1. Reaction times refer to the interval following ketone addition until hydrolysis (Experimental). With THF and 3-methyltetrahydrofuran, 4 addends in a four-toone addend/LATH mole ratio (entries 4 and 5), a markedly higher stereoselectivity was observed in comparison with reduction in benzene alone (entry 1). On the other hand diethyl ether was ineffective in altering the stereoselectivity (entry 2). Surprisingly, the more highly substituted addends 2,5-dimethyltetrahydrofuran, 5 (entry 6) and 2,2,5,5-tetramethyltetrahydrofuran, 6 (entry 7) were also completely ineffective in increasing stereoselectivity. A mole ratio of two-to-one THF/LATH was also ineffective in increasing the selectivity (entry 3).

In diethyl ether a mole ratio of two-to-one THF/LATH (Table 2, entry 2) was again insufficient to increase the stereoselectivity in comparison with reduction in diethyl ether alone (Table 2, entry 1). As was observed in benzene, a mole ratio of four-to-one THF/LATH did markedly increase stereoselectivity. The degree of selectivity is still somewhat lower than reduction in THF alone as solvent, which gives 88% trans (axial) alcohol,² however this latter result was obtained using an eight-toone THF/LATH mole ratio in ether (Table 2, entry 4).

The LATH reagent is approximately monomeric in THF in the concentration range used in this study.^{3,7}

Entry	Addend	Addend/LATH(mole ratio)	<pre>% trans(axial)alcohol, 2^b</pre>
1	-	_	60 [°] , 63 ^d
2	(c ₂ H ₅) ₂ 0	4	63
3	\bigtriangledown	2	62
4	\bigtriangledown	4	74, 76 ^d
5	\bigtriangledown	4	73 ^e
6 ^{f,g}	<u>▲</u>	4	63
7 ⁸	<u>ء</u> ۲ ۴	4	55

a reduction of 0.01 mole of <u>1</u>. LATH, 0.01 mole, approx. 0.4-0.5 M, reaction time 2-4 hrs. at room temperature. ^balcohols are normalized to 100%; 7-18% <u>1</u> in product, analysis by GLC. ^c21% <u>1</u> obtained. ^dresult of separate experiment. ^ereaction time 1.5 hr., 20% <u>1</u> obtained. ^fapprox. equal mixture of <u>cis</u> and <u>trans</u> addend isomers. Sreaction time 22 hrs.

	Table 2.	Reduction	of	1	in	diethyl	ether	with	LATH
--	----------	-----------	----	---	----	---------	-------	------	------

Entry	Addend	Addend/LATH(mole ratio)	Method of Addn. ^b	% trans(axial)alcohol ^C
1	-	-	-	73 ^d
2	THF	2	A, B ^e	71, 74 ^e
3	THF	4	A, B ^e	81, 81 ^e
_ 4	THF	8	A	87

^areduction of 0.01 mole of ketone. LATH, 0.01 mole, approx. 0.5 M, reaction time 2 hrs. ^bA: addend stirred with LATH followed by addition of diethyl ether, B: addend added to stirred LATH - diethyl ether mixture. ^calcohols are normalized to 1007; 10-15% of <u>1</u> obtained (18% in entry 3, method A). ^dref. 2. ^eresult of a separate experiment.

Specific solvation effects may be related to stereoselectivity by considering that molecules of e.g. THF coordinate with Li⁺. Presumably a maximum of four such ligand THF molecules may be involved.^{4.7} The cation is intimately involved as an electrophilic catalyst in the reduction process^{6.8} and it may be expected that with a ketone such as 1, the nature of the ligands attached to Li⁺ will affect the stereochemical outcome. Reduction, according to Ashby,⁴ would reasonably involve the displacement of THF from the coordination sphere of Li⁺ by a CO group.

We have observed that in the reduction of 1 with LATH in benzene (Table 1, entry 1), the reagent gradu-

ally goes into solution only after the ketone has been added. Similarly, LATH does not dissolve when stirred with the hindered addends 5 and 6. Solution only occurs in these cases by interaction with the CO group of the ketone, either prior to or concurrent with hydride transfer. On the other hand, LATH does go into solution almost entirely on stirring with THF (Table 1, entry 4) or with 4 (Table 1, entry 5). Subsequent addition of benzene does not precipitate the reagent. The Li⁺ is efficiently solvated by THF and 4 while it apparently is not by the more highly substituted THF derivatives 5 and 6. This is indicated by the lack of solubility of the hydride reagent and the essentially identical stereochemistry of reduction as with benzene itself. Diethyl ether falls into the same category as the hindered THF derivatives **5** and **6**. The explanation of these results is probably a steric one. Steric interactions between a bulky solvated Li^+ would prevent close approach of the anion AlH(O-t-C_4H_9)_3⁻ in an ion pair, and this precludes solvation of Li^+ and solution of the hydride.

In those experiments involving a THF/LATH molar ratio of four (Table 1, entry 4; Table 2, entry 3) the stereoselectivity was less than that observed in a large excess of THF as solvent,² or with a THF/LATH molar ratio of eight (Table 2, entry 4). In the former cases, either the Li⁺ has not achieved maximum complexation by THF, or THF plays a greater role in determining selectivity, possibly by also coordinating with aluminum during hydride transfer.

EXPERIMENTAL

Benzene (thiophene-free) was dried over 4A molecular sieve. THF and diethyl ether were distilled from LAH. These solvents gave no measurable hydrogen evolution on contact with LATH, as evidenced by using a wet test meter. LATH was obtained from the Ventron Corp. This reagent was judged to contain about 92% active hydride from the results of an experiment in which 0.020 mole of cyclohexanone was carefully reduced by the reagent (0.011 mole based on the formula weight). Reduction of 1 with this reagent in THF gave stereochemical results which corresponded closely with the reported value.² Compound 1 was prepared by oxidation of commercial 3,3,5-trimethylcyclohexanol.⁹

Compound 4 was obtained from Aldrich Chemical Co., and was distilled, b.p. 87-89°. Compound 5 was obtained from Pfaltz and Bauer Chemical Co. and was distilled, b.p. 91.5-93°. It was analyzed by GLC, IR and NMR spectroscopy and consisted of an approximately equal mixture of *cis* and *trans* isomers.

Compound 6 was prepared by the Wolff-Kishner reduction of tetrahydro-2,2,5,5-tetramethyl-3-furanone¹⁰ and had b.p. 113-116^o (Lit.¹⁰ 117^o); NMR (CCl₄): δ 1.19 (12H, singlet), δ 1.84 (4H, singlet); IR: strong bands at 1145 cm⁻¹ and 990 cm⁻¹. Tetrahydro-2,2,5,5-tetramethyl-3-furanone was prepared by cyclization of 2,5-dimethyl-3-hexyne-2,5-diol.¹¹ IR: 1754 cm⁻¹ (C=O), strong bands at 1156 cm⁻¹ and 990 cm⁻¹. NMR (CCl₄): δ 1.32 (6H, singlet), δ 2.38 (2H, singlet).

GLC analyses were carried out on a Hewlett-Packard Model 5750 instrument using a $12 \text{ ft} \times 0.125 \text{ in}$. 5% Carbowax 20 M column at 123° C. IR spectra were recorded with a Beckman IR-8 spectrophotometer and NMR spectra with a JEOL MH-100 instrument.

A representative example of the reduction procedure is given. Reduction of 1 with LATH in benzene in the presence of 5. Into a 100 ml 3-necked round bottom flask equipped with a magnetic stirrer, thermometer, addition funnel and condenser were placed 2.80 g (0.011 mole) of LATH. The flask had previously been flamed under N2 and filled with dry N2. 2,5-Dimethyltetrahydrofuran (4.0 g, 0.04 mole) was added and the mixture stirred for 23 min. Benzene (20 ml) was added dropwise with the apparatus attached to a wet test meter. No hydrogen evolution occurred, and the mixture was stirred under N2 for 34 min. The hydride reagent appeared undissolved, and the temp. of the mixture was 23°. Addition of 1 in 5 ml benzene resulted in a gradual temp. rise to 30°. The mixture was stirred under N2 for 22 hr, after which the LATH was almost entirely dissolved, the mixture being tranlucent, almost clear. Following hydrolysis with 10% H₂SO₄, extraction with ether, the combined organic laver was washed with satd NaHCO3 aq and NaCl aq and dried over MgSO₄. The product was concentrated by distillation through a 17 in. helix-packed column (oil bath) and analyzed by GLC (Table 1, entry 6).

Acknowledgement—The following support (to H. Haubenstock) is gratefully acknowledged: Faculty Research Award Program, The City University of New York, Grant numbers 11419 and 10198.

REFERENCES

- ¹J. Malek and M. Cerny, Synthesis 217 (1972).
- ²H. Haubenstock and E. L. Eliel, J. Am. Chem. Soc. 84, 2363 (1962).
- ³E. C. Ashby, J. P. Sevenair and F. R. Dobbs, J. Org. Chem. 36, 197 (1971).
- ⁴E. C. Ashby, F. R. Dobbs and H. P. Hopkins, Jr., J. Am. Chem. Soc. 95, 2823 (1973).
- ⁵M. K. Wong, W. J. McKinney and A. Popov, J. Phys. Chem. 75, 56 (1971); C. Lassigne and P. Baine, *Ibid.* 75, 3188 (1971); J.
- Wuepper and A. Popov, J. Am. Chem. Soc. 91, 4352 (1969).
- ⁶⁴ J.-L. Pierre and H. Handel, Tetrahedron Letters 2317 (1974);
- ^bH. H.andel and J.-L. Pierre, *Ibid.* 741 (1976); ^cH. Handel and J.-L. Pierre, *Ibid.* 2029 (1976).
- ⁷E. C. Ashby, F. R. Dobbs and H. P. Hopkins, Jr., J. Am. Chem. Soc. **97**, 3158 (1975).
- ⁸H. O. House, *Modern Synthetic Reactions*, 2nd Edn, p. 49. Benjamin, Menlo Park, California (1972).
- ⁹E. L. Eliel and H. Haubenstock, J. Org. Chem. 26, 3504 (1961).
- ¹⁰I. Szabó, K. Kovács and M. Bartók, Acta Chim. Acad. Scient. Hung. 51, 411 (1967).
- ¹¹F. Leonard, A. Wajngurt and H. Horn, J. Org. Chem. 21, 1402 (1956).