Observations on the stereochemistry of reduction of 2,6-dimethylcyclohexanones

Thomas E. Goodwin, Jennifer M. Meacham, and Mark E. Smith

Abstract: The reduction of *cis*-2,6-dimethylcyclohexanone with $NaBH_4$ in methanol is shown to produce predominantly the axial alcohol, an unexpected result based upon prior reports and current paradigms for similar cyclohexanone reductions. This finding prompted a careful and systematic investigation of the $NaBH_4$ and $LiAlH_4$ reductions of *cis*- and *trans*-2,6-dimethylcyclohexanones in various solvents, with additional results contrary to literature reports. Possible explanations for these discrepancies are given, an unusual solvent effect is noted, the rate of epimerization versus reduction is examined, molecular modeling results are reported, and an important caveat is offered for future stereochemical studies of this nature.

Key words: cyclic ketone reduction, stereochemistry, molecular modeling.

Résumé : On démontre que la réduction de la *cis*-2,6-diméthylcyclohexanone par le $NaBH_4$ dans le méthanol conduit d'une façon prépondérante à l'alcool axial; ce résultat est inattendu sur l'on se base sur les rapports antérieurs et sur les paradigmes actuels proposés pour les réductions de cyclohexanones semblables. Cette observation nous a amenés à réexaminer d'une façon soignée et systématique les réductions des *cis*- et *trans*-2,6-diméthylcyclohexanones par le $NaBH_4$ et le $LiAlH_4$ dans divers solvants; on a obtenu d'autres résultats sont contraires à ceux rapportés antérieurement. On présente diverses propositions pour expliquer ces différences; on note un effet de solvant inhabituel, on a examiné la vitesse d'épimérisation par rapport à la vitesse de réduction, on rapporte des résultats de modélisation moléculaire et on présente une mise en garde pour les futures études stéréochimiques de cette nature.

Mots clés : réduction de cétone cyclique, stéréochimie, modélisation moléculaire.

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Introduction

The stereochemical course of the reduction of cyclic ketones, especially cyclohexanones, has been a topic of intense theoretical and practical interest for decades (for a convenient tabular listing of examples, see ref. 1). In general, sterically undemanding reducing agents such as $LiAlH_4$ and $NaBH_4$ are known to approach simple cyclic ketones preferentially along what is apparently the more hindered axial trajectory, thus leading to the equatorial alcohol as the major reaction product. This tendency can be reversed by using reagents or substrates that are more sterically demanding. Reduction of *cis*-2,6-dimethylcyclohexanone (**1**) can yield two diastereomeric alcohols (**2** and **3**). The *trans* isomer (**4**) provides diastereomers **5** and **6**, which are easily interconverted by a ring flip, thus yielding for all practical purposes only the more stable conformer **5**. In a seminal paper, Wigfield and Phelps (2) reported that reduction of the *cis* isomer **1** with $NaBH_4$ in 2-propanol gave a **2**:**3** alcohol ratio of 62:38. Assignment of equatorial alcohol **2** as the major product was based on relative GC retention times and analysis of 60 MHz NMR spectra. Garner (3) found that reduction of **1** with $NaBH_4$ in methanol yielded two alcohols in a ratio of 68:32; by analogy to the earlier work, the major isomer was assumed to be equatorial alcohol **2** (see Scheme 1).

When we repeated the reduction of *cis*-2,6-dimethylcyclohexanone with $NaBH_4$ in methanol, the axial alcohol **3** was clearly the major product, an unexpected result based upon prior reports and current paradigms for similar cyclohexanone reductions (see Discussion). We have carefully and systematically reexamined the $NaBH_4$ and $LiAlH_4$ reductions of *cis*- and *trans*-2,6-dimethylcyclohexanones and report herein additional results that are not entirely in accord with prior reports. Possible explanations for the discordances are given, an unusual solvent effect is noted, the rate of epimerization versus reduction is examined, molecular modeling results are reported, and an important caveat is offered for other stereochemical studies of this nature.

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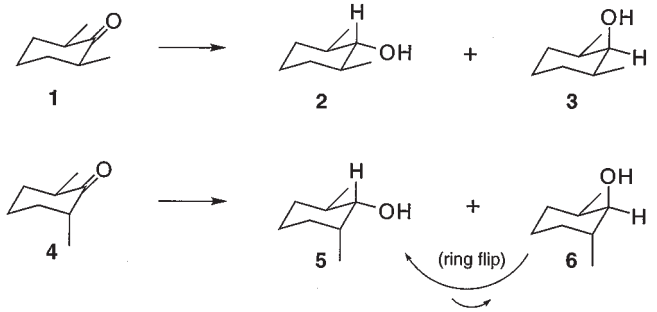
T.E. Goodwin,[1] J.M. Meacham, and M.E. Smith.
Department of Chemistry, Hendrix College, Conway, AR 72032, U.S.A.

[1]Author to whom correspondence may be addressed. Telephone: (501) 450-1252. Fax: (501) 450-3829. E-mail: Goodwin@Hendrix.edu

Results

The reduction of a mixture of *cis*- and *trans*-2,6-dimethylcyclohexanones was performed using $LiAlH_4$ in both diethyl ether and THF, as well as with $NaBH_4$ in both methanol and 2-propanol.[2] As much as possible, reaction conditions were standardized (see Experimental). The product mixtures were directly analyzed by GC–MS before any solvent evaporation, since we experienced product loss with

Scheme 1. Reduction products from 2,6-dimethylcyclohexanones.



use of a rotary evaporator. Product mixtures were also analyzed by ^{1}H NMR spectroscopy. Before preparation of NMR samples, the dried product solutions were placed in a hood to allow selective solvent evaporation at the ambient temperature.

Table 1 shows the ratio of products from reduction of *cis*-2,6-dimethylcyclohexanone as determined by both GC–MS and NMR.[3] Very little stereoselectivity is evident for reduction of the *cis* ketone with the notable exception of the $NaBH_4$ reduction in methanol for which our ratios are similar to those reported by Garner (3). In contrast, however, to the earlier assumption for this reductant–solvent combination, it is clear that the axial alcohol **3** predominates over the equatorial alcohol **2** in the product mixture as shown by 300 MHz ^{1}H NMR spectral analysis and integration. Specifically, the HCOH methine hydrogen for isomer **2** appears as a triplet (J = 9.6 Hz) at δ 2.70, while that for isomer **3** appears as a broad singlet at δ 3.53, thus they are easily distinguished. The analogous hydrogen for alcohol **5** appears as a doublet of doublets (J = 7.7, 4.1 Hz) at δ 3.32).[4]

There is less consonance between our ratios for reduction of the *cis* isomer with $NaBH_4$ in 2-propanol and the 62:38 ratio reported previously (2). This reaction was run again in our laboratories under the more dilute conditions and longer reaction time used in the former work (5), to provide a **2**:**3** ratio of 49:51 as determined by GC–MS.[5] In view of the product loss in this reaction when using a rotary evaporator, it is possible that differential evaporation of isomers **2** and **3** gave rise to the apparent predominance of **2** reported by earlier workers. Support for this conclusion is evidenced in entry D of Table 1, which reports essentially no selectivity by GC–MS, but a slight excess of alcohol **2** by NMR integration after solvent evaporation, a result more in line with the prior report (2).

Table 1. Relative percent of reduction products from 2,6-dimethylcyclohexanones.

		Compound no.	
Reagent–solvent	Method	**2**:**3**	(**2** + **3**):**5**
A. LAH–THF	GC–MS	49:51	80:20
	NMR	49:51	79:21
B. LAH–Et_2O	GC–MS	53:47	80:20
	NMR	54:46	79:21
C. $NaBH_4$–MeOH	GC–MS	29:71	80:20
	NMR	33:67	79:21
D. $NaBH_4$–*i*-PrOH	GC–MS	50:50	75:25
	NMR	54:46	71:29

Our $LiAlH_4$ data disagree with a tabulated **2**:**3** ratio of 62:38 in the literature (6), although the origin of that ratio is not clear and may be a mistaken citation of the Wigfield and Phelps data (2) using $NaBH_4$ in 2-propanol.[6] Our results are, however, in line with those of Boone and Ashby (7), who observed that $LiAlH_4$ reduction of the closely related *cis*,*cis*-4-*tert*-butyl-2,6-dimethylcyclohexanone in THF gave 53% of the equatorial alcohol (axial hydride addition).

The table also lists the ratio of products (**2** + **3**) derived from reduction of *cis*-2,6-dimethylcyclohexanone to that (product **5**) from the *trans* isomer. This ratio is of interest when compared to the ratio of reactant ketones (see footnote 2). The GC–MS and ^{1}H NMR spectral analyses reveal a constant ratio for entries A, B, and C, suggesting little if any epimerization of the reactant ketones before reduction. The exception is entry D ($NaBH_4$ in 2-propanol), where the proportion of alcohol **5** in the product mixture is higher than that of ketone **4** in the reactant mix. This phenomenon has been noted previously (2*a*). This discrepancy was found to be even more pronounced in a more dilute solution of 2-propanol (see footnote 5) where a (**2** + **3**):**5** ratio of 84:16 was determined by GC–MS, although the **2**:**3** ratio was essentially unchanged relative to entry D in Table 1. The $NaBH_4$ reduction of 2,6-dimethylcyclohexanones in 2-propanol is apparently significantly slower than for the other three reductant–solvent combinations, a difference which becomes even more pronounced upon dilution. This rate decrease then allows epimerization to take place prior to reduction, giving rise to variable results.

Discussion

Boone and Ashby (7) have presented clear evidence that equatorial α-methyl substituents on a cyclohexanone ring

[2] The mixture of *cis*- and *trans*-2,6-dimethylcyclohexanones was obtained from Aldrich and was labeled as 98% pure. By GC–MS, a *cis*:*trans* ratio of 80:20 was found, remarkably close to the 81:19 ratio reported by Garner (3) in 1993. A ratio of 79:21 by integration of the ^{1}H NMR spectrum of a $CDCl_3$ solution was also observed. As the results in Table 1 and discussion in the text reveal, minor ratio discrepancies of this sort are common, and thus are at least partly related to idiosyncrasies of the two measurement techniques.

[3] The values in Table 1 represent an average of duplicate, simultaneous reactions. The NMR ratios for the two LAH–THF reactions were 51:49 and 48:52. Otherwise, agreement was excellent between duplicate runs, with differences in relative product percentages between each pair of reactions averaging 0.4 for GC–MS analysis and 0.7 for NMR analysis.

[4] A similar chemical-shift trend and coupling pattern was reported for the analogous acetates (4*a*). Coupling constants for the HCOH methine hydrogen were calculated on MMX-minimized structures using PCMODEL (Serena Software) and are in good agreement with experimental values: **2** (t, J = 10.1 Hz), **3** (t, J = 1.8 Hz), and **5** (dd, J = 10.1, 4.6 Hz). The ^{1}H NMR calculation using PCMODEL is based on a modified Karplus algorithm (4*b*). The ^{13}C NMR spectral assignments for alcohols **2**, **3**, and **5** have been reported (4*c*).

[5] The ketone mix (89 μL) and $NaBH_4$ (29 mg) were reacted in 3.2 mL of 2-propanol for 23 h.

[6] K. Houk. Personal communication.

retard axial approach of $LiAlH_4$. A simple, yet compelling steric rationalization for this trend is that with each additional equatorial α-alkyl group, a new 1,3-diaxial-type interaction exists between the incoming axial nucleophile and a C—H bond on a rotamer of the alkyl group, thus disfavoring this approach trajectory (e.g., for *cis*-2,6-dimethylcyclohexanone, four such interactions would exist: one from each axial hydrogen on carbons 3 and 5, and one from each α-methyl). When the "nonbonded" electron isodensity surface (the molecule's "electron cloud") from 3-21G(*) ab initio calculations is examined, an increasing steric bias against axial approach of a nucleophile is observed as α-substitution increases.[7]

An explanation for the usual avoidance of equatorial approach of a small nucleophile to the carbonyl carbon of an unhindered cyclic ketone invokes torsional strain with neighboring axial α-hydrogens (8). Anh (9*a*) has proposed that axial approach of the nucleophile is most favorable when the axial α-hydrogens are closer to being perpendicular to the plane of the carbonyl group (the "flattening rule"), thus maximizing the n-σ^* interaction between the unshared electron pair of the nucleophile and the antibonding orbital of each axial α-C—H bond (the "antiperiplanar effect").[8]

To examine flattening in the present case, the dihedral angle has been determined between an axial α-hydrogen and the carbonyl for cyclohexanone, 2-methylcyclohexanone, and *cis*-2,6-dimethylcyclohexanone on structures generated by geometry optimization using AM 1 semi-empirical calculations, followed by single-point 3-21G(*) ab initio calculations. The angles are 105.1°, 111.0°, and 113.1°, respectively, thus leading to a correct prediction of an increased equatorial approach of the nucleophile with α-substitution based on Anh's flattening rule.

Nucleophilic additions to carbonyl groups are often considered to result from an interaction between the HOMO of the nucleophile and the LUMO of the carbonyl group. It is of interest to note that the absolute value of the LUMO[7] for cyclohexanone, 2-methylcyclohexanone, and *cis*-2,6-dimethylcyclohexanone is greater on the face of the ring corresponding to axial approach of the nucleophile, thus suggesting preferred nucleophilic approach from that direction. As α-substitution increases, however, steric factors may become more decisive than these orbital interactions. Notably, when the 2,6-dimethylcyclohexanone mixture was reduced with the bulky reducing agent $Li(s\text{-}Bu)_3BH$ in THF, none of product **2** could be detected, thus demonstrating that axial bond formation on ketone **1** is sterically disfavored.[9]

Conclusions

For reduction of *cis*-2,6-dimethylcyclohexanone with $LiAlH_4$ in diethyl ether or THF, or with $NaBH_4$ in 2-propanol, there is apparently a very close balance between factors that hinder and (or) encourage axial and equatorial hydride addition thus leading to little stereoselectivity. With $NaBH_4$ in methanol, however, formation of the axial alcohol **3** predominates. In an earlier mechanistic study on ketone reductions with $NaBH_4$ in a protic solvent, Wigfield and Gowland (12) found a kinetic order of 1.5 with respect to 2-propanol. Therefore, solvent clearly can play a role in the $NaBH_4$ reduction mechanism. Perhaps interaction of *cis*-2,6-dimethylcyclohexanone with methanol results in a subtle conformational shift, which increases the dihedral angle between the axial α-hydrogens and the carbonyl, thus leading to increased equatorial approach of the reducing agent. Whatever the reason, the solvent-dependent stereoselectivity reported herein provides further evidence of the important role that the solvent plays in $NaBH_4$ reductions. Finally, a caveat is proffered: our experience suggests that similar studies of reduction stereochemistry should analyze isomer ratios before solvent evaporation is attempted, to avoid possible alteration of product ratios through differential rates of evaporation.

Experimental

All reductions were run in duplicate for 1 h on 89 μL (82.3 mg; 0.652 mmol) of a commercial mixture (Aldrich) of *cis*- and *trans*-2,6-dimethylcyclohexanones (see footnote 2) and an excess of the reducing agent (0.738 mmol of $LiAlH_4$ or 0.714 mmol of $NaBH_4$) with stirring in 1 mL of solvent. In all cases, the ketones were added with caution to a stirring mixture of the reducing agent in the chosen solvent at the ambient temperature (approx. 20°C). The $NaBH_4$ reductions were cautiously quenched with 3 M HCl (1 mL), diluted with saturated NaCl solution (1 mL), and extracted with diethyl ether (3 × 1 mL). The $LiAlH_4$ reactions were cautiously quenched with H_2O (two drops), aqueous NaOH solution (15%; six drops), and again with H_2O (two drops), then filtered over Celite, which was rinsed with diethyl ether (4 mL). Ether solutions were dried over anhydrous Na_2SO_4.

The GC–MS analysis was carried out using a Hewlett Packard 5890 Series II chromatograph with an HP 5971A mass selective detector. The capillary column was an HP-5 (cross-linked 5% phenyl methyl silicone) with a length of 30 m, an inner diameter of 0.25 mm, and a film thickness of 0.25 μm. Baseline separation was achieved for all three alcohol products with an initial temperature of 60°C (hold 0.5 min), followed by a 4°C/min ramp to 90°C (hold 0.5 min), then a 10°C/min ramp to 100°C. The starting ketones were not detected in any of the product mixtures. The

[7] All ab initio calculations were carried out using MacSpartan Plus from Wavefunction, Inc.

[8] Another popular and useful hypothesis proposed by Cieplak (10*a*) assumes an electron-poor transition state for nucleophilic addition to a carbonyl, thence leading to reaction preferentially antiperiplanar to the best electron-donating vicinal bond. (For a review of arguments for and against the Cieplak model, see ref. 10*b*; for a cogent commentary and new data, see ref. 10*c*.).

[9] Throughout Discussion, an assumption has been made that the reduction of the cyclic ketones proceeds via the more stable chair conformers, yet it is possible that the less populous chair conformer is reduced more rapidly (cf. ref. 11). Examination of the nonbonded electron isodensity surface from 3-21G(*) calculations for the less stable chairs of 2-methylcyclohexanone, and *cis*-2,6-dimethylcyclohexanone reveals a clear steric preference for formation of the equatorial alcohol (axial approach of the nucleophile), which upon chair flip to the more stable conformer provides the axial alcohol. This is the same major product that would be expected from reduction of the more stable ketone conformer if the reaction outcome is controlled primarily by steric factors.

^{1}H NMR spectra were obtained on a Varian Gemini 300 MHz spectrometer.

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