PERKIN 2

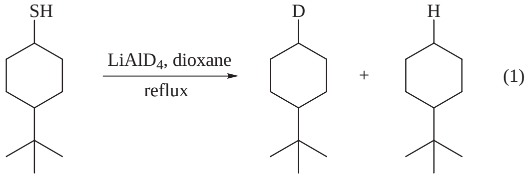
Reduction of thiols with $LiAlD_4$: a mechanistic study

Michael B. Smith *,†,[a] **and Joseph Wolinsky** [b]

[a] *Room 151, 215 Glenbrook Rd., Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269, USA*
[b] *Department of Chemistry, 1393 Brown Building, Purdue University, West Lafayette, Indiana 47907, USA*

Reduction of thiols with $LiAlD_4$, in refluxing dioxane, leads to alkane products that contain only about 60% deuterium. Current work strongly suggests that dioxane is the source of hydrogen incorporation in the product, probably *via* transfer from an intermediate thioalkoxy–aluminate species.

Lithium aluminium hydride is one of the more powerful reducing agents, and it is known to reduce molecules containing a heteroatom-functional group.[1] The reduction of ketones or aldehydes, acid derivatives, nitriles, epoxides, halides, sulfonate esters, and so forth, are well known reactions.[1] Molecules bearing an acidic hydrogen, such as alcohols, react with $LiAlH_4$ *via* deprotonation and formation of an alkoxyaluminate, so '*n*' equivalents of ROH react with $LiAlH_4$ to give $LiAlH_{4-n}(OR)_n$.[2] Many of these alkoxyaluminates are selective reducing agents in their own right.[3] Thiols similarly react to form thioalkyl derivatives, $LiAlH_{4-n}(SR)_n$.[2] When the reaction of thiols and $LiAlH_4$ is 'pushed' to higher temperatures in ether solvents, hydrogenolysis of the C–S bond to give the corresponding alkane derivative (C–SH→C–H). In connection with an investigation of the $LiAlH_4$ reduction of sultones,[4] Wolinsky examined the reduction of thiols [reaction (1)], with the goal of investigating the stereochemistry of this reduction by examining the deuterated hydrocarbon. Surprisingly, reduction led to a mixture of 42% of 4-*tert*-butyl[1-^{2}H]cyclohexane (**2**) along with a 58% yield of 4-*tert*-butylcyclohexane, **3**.[4] There was no conclusive explanation for this result, but an exchange with the solvent was postulated. This would form an intermediate species that reduced the C–S bond with an isotopic preference for transfer of hydrogen.



(1)

1 **2** **3**

We re-examined this reaction with the goal of determining how hydrogen was incorporated into the alkene product when $LiAlD_4$ was used as a reducing agent. In this current work, we prepared **1** using Eliel's method[5] and found that reduction with three molar equivalents of $LiAlD_4$ in refluxing dioxane gave 38.4% of **2** and 60.6% of **3**. An isotopic analysis of the product mixture by mass spectrometry showed that the dioxane solvent contained about 1.9% D. This experiment was repeated, but 4-*tert*-butylcyclohexanone was added to the reduction mixture prior to quenching in order to verify the amount of D remaining in the Al–D reagent. This experiment showed that 38.5% of **2** and 61.5% of **3** were formed, along with 89.2% of 4-*tert*-butyl[1-^{2}H]cyclohexanol and 10.8% of 4-*tert*-butylcyclohexanol.

In subsequent experiments, the readily available dodecanethiol was used, and reduction with five molar equivalents of $LiAlD_4$ in refluxing dioxane gave a mixture, 67% of dodecane and 33% of [^{2}H]dodecane. Mass spectral analysis of the reaction solvent indicated the presence of about 0.2% [$^2H_8$]dioxane. It was apparent that reduction of dodecanethiol gave results comparable to reduction of **1**. In several experiments, dodecanethiol was reduced with $LiAlH_4$ and then quenched with D_2O rather than H_2O, but dodecane was the only observed product with no trace of [^{2}H]dodecane by mass spectrometric analysis. The D or H is not incorporated at the workup stage.

We next varied the molar equivalents of $LiAlD_4$ relative to the amount of thiol. Refluxing a 1 : 1 mixture of dodecanethiol and $LiAlD_4$ for five hours in dioxane was followed by addition of 4-*tert*-butylcyclohexanone. No alkane product was observed, but 93.4% of 4-*tert*-butyl[1-^{2}H]cyclohexanol and 6.6% of 4-*tert*-butylcyclohexanol was obtained. If a Al–D↔Al–H exchange process is operative, it occurs rapidly relative to hydrogenolysis of the C–S unit. It is noted that when 4-*tert*-butylcyclohexanone was treated with $LiAlD_4$ in diethyl ether, at ambient temperature, only 4-*tert*-butyl[1-^{2}H]cyclohexanol was obtained, in greater than 90% yield, and no products were observed that did not contain deuterium. This confirmed that the $LiAlD_4$ was not contaminated with $LiAlH_4$. When a 1 : 2 mixture of dodecanethiol : $LiAlD_4$ was refluxed in dioxane for 75 hours and then treated with 4-*tert*-butylcyclohexanone, an 87% yield of dodecane, 13% of [^{2}H]dodecane, 99% of 4-*tert*-butyl[1-^{2}H]cyclohexanone, and 1% of 4-*tert*-butylcyclohexanol was obtained. Although an excess of $LiAlD_4$ gave a higher yield of deuterated alcohol from the ketone, there was no increased yield of deuterated products from the thiol. Again, it appeared that hydrogenolysis of the C–S bond required long reaction times.

Thermal decomposition of $LiAlH_4$ and $LiAlD_4$ is known to produce species that might be the source of hydrogen, and we examined their thermal stability under our reaction conditions. The decomposition temperature of $LiAlH_4$ was reported to be greater than 150 °C[6] and the products of this decomposition were LiH, AlH_3, Al and H_2. These products were formed separately at different transition temperatures. Interestingly, it was reported that $LiAlH_4$ decomposed *in vacuo* at a temperature as low as 105 °C to form AlH_3.[7] At higher temperatures, it was also shown that an Al–OH species was produced, along with Al–H.[6b] It is also important to note that AlH_4^- and AlD_4^- behave similarly in diethyl ether solutions.[8] In early studies, Garner and Haycock observed some thermal decomposition at temperatures between 98–104 °C.[6a] More interesting is the report that $LiAlH_4$ in diethyl ether–toluene solution can decompose at very low temperatures (50–140 °C) by a first-order autocatalytic type reaction.[9] When $LiAlH_4$ was complexed to TMEDA or THF, the decomposition temperatures were lowered significantly [as low as 35–90 °C for the $(AlH_4)_4$·

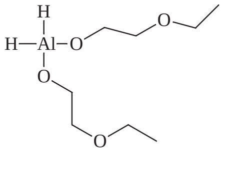
---

† E-Mail: smith@nucleus.chem.uconn.edu

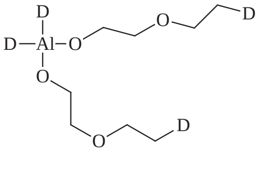
THF complex].[6c] Since the reduction of thiols with $LiAlD_4$ is done in refluxing dioxane (bp, 101–102 °C) for an extended period of time, the possibility of some thermal decomposition must be considered. If an Al–OD species is formed from reaction with $LiAlD_4$, it might exchange deuterium for a hydrogen in a reaction with the ether solvent. In general, however, the solvation of $LiAlH_4$ or $LiAlD_4$ is greatly diminished in dioxane and solvents other than diethyl ether or THF.[8,10] At the reflux temperature of dioxane there should be some solvation, and thermal degradation could produce AlD_3 and D_2 as well as LiD, which might be involved in a hydrogen–deuterium exchange. We first used non-ether solvents such as heptane and benzene, where hydride (or deuteride) exchange with solvent could not occur. It is noted that the solubility of $LiAlH_4$ in these solvents is much lower than in dioxane, and we observed that reduction of dodecanethiol in both cases gave about 5% dodecane and 5% dodec-1-ene, with considerable amounts of unreacted thiol. The formation of alkane and alkene products suggested disproportionation of an intermediate in this reaction. When $LiAlH_4$ was refluxed in either toluene or dioxane and then quenched with methanol, four equivalents of H_2 were generated in the toluene experiment upon workup with methanol but only two equivalents of H_2 were obtained from the dioxane experiment. Significantly, no hydrogen gas was produced upon heating prior to the methanol quench. This is not consistent with thermal degradation of $LiAlH_4$ or $LiAlD_4$ at the reaction temperature. Additional work with the $LiAlH_4$–dioxane system showed that about two equivalents of hydride from $LiAlH_4$ were consumed slowly at ambient temperatures without generation of H_2, but quenching with methanol liberated two equivalents of hydride. This points to formation of a dialkoxyaluminate intermediate. Similar results were obtained when the dioxane solution was refluxed. It was noted that when the thiol was added to this solution and the reaction was allowed to proceed for three days, no H_2 was liberated upon workup. This is consistent with an intermediate alkoxyaluminate reacting with thiol to form a $(RO)_nAl(SR')_{4-n}$ species. The lower rate of reduction is undoubtedly due to diminished solubility of $LiAlH_4$ in these solvents but the alkene and alkane products probably arise from decomposition of a thiol–aluminate complex or intermediate.

Does $LiAlH_4$ react with dioxane? It is known from work with 1,3-dioxolanes and 1,3-dioxanes that $LiAlH_4$ can react with these molecules at temperatures >80 °C to form alkoxyaluminates, although $LiAlH_4$ does not react with these molecules at lower temperatures.[11] It is also well known that aluminium hydride (AlH_3, usually generated from a mixture of $LiAlH_4$ and AlC_3) reacts with dioxolanes and dioxanes *via* reductive cleavage, so our observation that $LiAlH_4$ reacts with dioxane at reflux is not surprising. Since two equivalents of hydride are consumed, we assume that a dialkoxyaluminate such as **4** is formed. Attempts to detect the presence of such an intermediate by analyzing the products for the presence of 2-ethoxyethanol failed. None-the-less, we believe that the active reducing species in $LiAlH_4$–dioxane is either **4** or a closely related species, making **5** the active species from $LiAlD_4$. We assume that the methyl group in **5** contains a deuterium, consumed during the reaction of dioxane with $LiAlD_4$. Presumably, an Al–H↔Al–D exchange from a species such as **5** could lead to our observations.

Heating in dioxane is essential for reduction of the thiol. We reacted dodecanethiol with $LiAlH_4$ in refluxing heptane, and in refluxing diethyl ether and found less than 5% reduction to the alkane in both cases, along with recovered thiol. We also reacted $LiAlH_4$ with one equivalent of dodecanethiol and then added methanol to form a $Al(SR)(OMe)_3$ species. This was refluxed in dioxane and no reduction occurred, but dodecane disulfide was produced *via* air oxidation of the thiol. In one experiment, dodecanethiol and $LiAlH_4$ were mixed together in diethyl ether and then treated with an excess of 2-ethoxyethanol and this mixture was refluxed in dioxane. Once again, less than 5% of dodecane was observed and dodecanethiol was recovered unchanged. Clearly, no reaction occurred between $Al(OR)_4$ or $Al(SR)_n(OR)_{4-n}$ and dioxane.

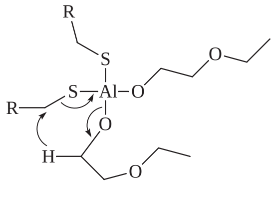


4



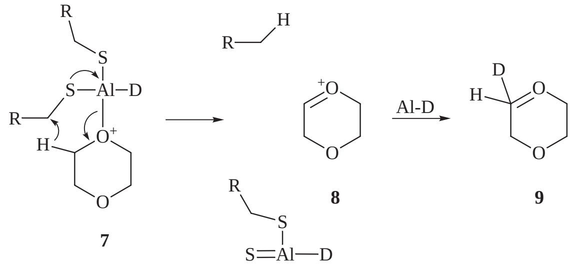
5

Where does the hydrogen come from in the reduction of thiols with $LiAlD_4$? Presumably, D_2 and/or H–D will escape from the medium at the reflux temperature of dioxane. Some exchange could occur but it is more likely that an Al–D species or a decomposition product containing an Al–D unit is exchanging with the α-H of the dioxane. This must occur prior to hydrogenolysis of the C–S bond, since our experiments involving added ketone showed hydrogen incorporation during reduction with $LiAlD_4$. Transfer of hydrogen from the α-carbon of the alkoxy unit in **6** to the α-carbon of the thiol unit is one possibility.



6

If the dioxane were complexed to the aluminium of the active intermediate to give **7**, hydrogen transfer could occur *via* a Meerwein–Ponndorf type reduction as shown. This mechanism would generate oxonium ion **8**, which could react with an Al–D species to give **9** (Scheme 1). This explanation would not require a formal H–D exchange and may fit the data as well or better than exchange *via* **4** or **5**.



Scheme 1

Our mechanistic rationales for this reaction therefore demand initial heating to induce formation of a thioalkyl–aluminate that either reacts with dioxane to give a species where hydrogen is transferred intramolecularly, or complexes with dioxane to give hydrogen transfer *via* a Meerwein–Ponndorf mechanism. Either process will lead to an alkane product without deuterium.

Experimental

All proton NMR spectra were recorded on a Perkin-Elmer R-32 NMR at 90 MHz using tetramethylsilane as an internal standard. All chemical shifts are reported in ppm downfield from tetramethylsilane. All chemicals were purchased from Aldrich Chemical Co. All solvents were distilled from CaH_2 or $LiAlH_4$, under a nitrogen blanket, into flame dried glassware prior to use. We prepared *cis*-4-*tert*-butylcyclohexanethiol from

4-*tert*-butylcyclohexanol using the procedure described by Eliel.[5,12]

4-*tert*-Butyl[1-^{2}H]cyclohexane

A dioxane solution (10 ml) of 4-*tert*-butylcyclohexanethiol (0.663 g, 3.846 mmol) and 0.482 g (11.48 mmol) LiAlD$_4$ was refluxed for 140 h, quenched with water, dried (MgSO$_4$) and solvents were removed *in vacuo* to give a clear oil. Purification *via* a 5′ SE-30 column at 117 °C gave 4-*tert*-butyl[1-^{2}H]cyclohexane:[13] ν_{max}(neat)/cm^{-1} 2257, 2146, 1961, 1942, 1862, 2941, 2179, 1482, 1451, 1393, 1368, 1235, 1191, 1125, 1116, 1035, 1000, 892 and 845. Mass spectral analysis indicated 39.4% D incorporation and 60.6% H incorporation in the alkane.

In a second experiment, a solution of 0.707 g (4.105 mmol) 4-*tert*-butylcyclohexanethiol and (12.726 mmol) LiAlD$_4$ in 25 ml of dioxane and 0.467 g (2.356 mmol) tetradecane (added as an internal standard) was refluxed for 140 h. Workup with D$_2$O, drying (MgSO$_4$) and removal of solvents gave an oil. Collection of products *via* glc from a 5′ SE-30 column at 117 °C gave *tert*-butylcyclohexane (38.5% D and 61.5% H by mass spectral analysis).

A solution of 9.733 g (3.619 mmol) of dodecanethiol and 0.136 g (3.246 mmol) LiAlD$_4$ in 50 ml of dioxane was refluxed for 4.5 hours and then treated with 0.457 g (2.965 mmol) of 4-*tert*-butylcyclohexanone. Workup and collection of the 4-*tert*-butylcyclohaxanol was followed by mass spectral analysis, which showed 93.4% D and 6.61 of H.

A solution of 0.7232 g (3.555 mmol) of dodecanethiol and 0.742 g (17.664 mmol) of LiAlD$_4$ in 50 ml of dioxane was refluxed 99 h and quenched with D$_2$O. Workup and collection of products *via* GLC from a 5′ SE-30 column at 170 °C. Mass spectral analysis indicated 66.7% dodecane(H) and 33.3% [^{2}H]-dodecane[14] and 0.2% [^{2}H$_8$]-dioxane.

A solution of 1.134 g (5.602 mmol) of dodecanethiol and 0.119 g (2.827 mol) of LiAlH$_4$ were refluxed 75 h in 50 ml of dioxane, treated with 0.321 g (2.08 mmol) of 4-*tert*-butylcyclohexanone, refluxed 0.5 h and quenched with water. Workup and collection of products *via* GLC from a 5′ SE-30 column at 185 °C and mass spectral analysis indicated: 0.9% [^{2}H]alcohol, 1.0% alcohol, 87.3% dodecane, 12.7% [^{2}H]dodecane, 0.1% [^{2}H]dioxane, 99.5% thiol and 0.5% [^{2}H]thiol.

A reaction vessel containing 0.052 g (1.378 mmol) LiAlH$_4$ in 150 ml dioxane was fitted with a gas trap and treated with 2.050 g (10.131 mmol) of dodecanethiol at ambient temperatures. During the first 30 min, a total of 165 ml of gas (4 equiv. = 135 ml) was collected. The slurry was refluxed for 18 h and then quenched with water (there was no exothermic reaction). The usual analysis by GLC on 5′ 20% FFAP at 145 °C indicated the presence of less than 1% dodecane.

A slurry of 0.099 g (2.609 mmol) of LiAlH$_4$ was stirred in 150 ml of dioxane, a gas trap was attached, and a dioxane solution of 2.1196 g (10.475 mmol) of dodecanethiol was added. Over a period of 3 h, 190 ml of gas was collected at ambient temperatures (4 equiv. = 257 ml) indicating that a total of 3 equiv. of hydride had been consumed.

Dodecanethiol was stirred with LiAlH$_4$ for 160 hours while the reaction was exposed to the air. Workup gave a white solid which gave white needles from ethanol: mp 33.0–34.9 °C (lit. mp, 34 °C)[15] for dodecyl disulfide; δ_H(CDCl$_3$) 0.90 (br t, 6H), 1.2 (br s, 36H), 2.70 (br t, 4H), 2.70 (br t, 4H) and 3.71 ppm (q, J = 7 Hz, 4H); *m*/*z* (Rel. Intensity): 401 (48), 141 (18), 239 (10), 200 (10), 86 (22), 82 (12), 84 (30), 70 (48), 68 (28), 57 (90), 55 (56), 43 (100) and 41 (58).

References

1 (*a*) M. B. Smith, *Organic Synthesis*, McGraw-Hill, 1994, pp. 345–361; (*b*) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Wiley-Interscience, New York, 1956; (*c*) N. G. Gaylord, *J. Chem. Ed.*, 1957, **34**, 367.

2 (*a*) H. Haubenstock and E. L. Eliel, *J. Am. Chem. Soc.*, 1962, **84**, 2363; (*b*) H. C. Brown and C. J. Shoaf, *J. Am. Chem. Soc.*, 1964, **86**, 1079; (*c*) H. Haubenstock and T. Mester Jr., *J. Org. Chem.*, 1983, **48**, 945.

3 (*a*) J. Malek and M. Cerny, *Synthesis*, 1972, 217; (*b*) H. C. Brown and N. M. Yoon, *J. Am. Chem. Soc.*, 1966, **88**, 1464.

4 Taken from the Ph.D. Thesis of Ronald L. Marhenke, Purdue University, 1970; Diss, Abstr. Int., B, 1971, **31**, 5883.

5 E. L. Eliel and B. P. Thill, *Chem. Ind.* (*London*), 1963, 88.

6 (*a*) W. E. Garner and E. W. Haycock, *Proc. R. Soc. London*, *Ser. A*, 1952, **211**, 335; (*b*) J. Block and A. P. Gray, *Inorg. Chem.*, 1965, **4**, 304; (*c*) J. A. Dilts and E. C. Ashby, *Inorg. Chem.*, 1972, **11**, 1230; (*d*) J. Mayet and J. Tranchant, *Bull. Soc. Chim. Fr.*, 1973, 510.

7 Yu. N. Shevchenko, N. N. Mal'tseva, V. A. Nazarenko, A. I. Golovanova and N. T. Kuznetsov, *Dokl. Akad. Nauk SSSR*, 1987, **296**, 362 (Engl., p. 411).

8 S. Heřmánek, O. Kríž, J. Plešek and T. Hanslík, *Chem. Ind.* (*London*), 1975, 42.

9 L. P. Ivanov, A. T. Kurekova, E. M. Abdulina and A. I. Gorbunov, *Zh. Fiz. Khim.*, 1988, **62**, 203 [*Chem. Abstr.*, 1988, **108**: 119 879g].

10 E. C. Ashby, F. R. Bobbsand and H. P. Hopkins Jr., *J. Am. Chem. Soc.*, 1975, **97**, 3158.

11 (*a*) H. A. Davis and R. K. Brown, *Can. J. Chem.*, 1971, **49**, 2563; (*b*) U. E. Diner and R. K. Brown, *Can. J. Chem.*, 1967, **45**, 1297; (*c*) D. E. Leggetter and R. K. Brown, *Can. J. Chem.*, 1963, **41**, 2671; (*d*) B. E. Leggetter, U. E. Diner and R. K. Brown, *Can. J. Chem.*, 1964, **42**, 2112; (*e*) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, 1964, **42**, 990.

12 E. L. Eliel and D. Kandasamy, *J. Org. Chem.*, 1976, **41**, 3899.

13 (*a*) D. Doddrell, W. Kitching, W. Adock and P. A. Wiseman, *J. Org. Chem.*, 1976, **41**, 3036; (*b*) P. A. Wiseman, *J. Org. Chem.*, 1975, **40**, 112.

14 (*a*) K. Nishiyama, M. Oba, M. Oshimi, T. Sugawara and R. Ueno, *Tetrahedron Lett.*, 1993, **34**, 3745; (*b*) Y. Aoyama, K. Midorikawa, H. Toi and H. Ogoshi, *Chem. Lett.*, 1987, 1651.

15 (*a*) S. Becker, Y. Fort, R. Vanderesse and P. Paubère, *J. Org. Chem.*, 1989, **54**, 4848; (*b*) E. Hoggarth and W. A. Sexton, *J. Chem. Soc.*, 1947, 815; (*c*) J. B. Baumann, *J. Org. Chem.*, 1971, **36**, 396; (*d*) T. J. Wallace, *J. Am. Chem. Soc.*, 1964, **86**, 2018.

Paper 8/00473K
Received 16*th January* 1998
Accepted 26*th March* 1998