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Reaction Titration: A Convenient Method for Titering Reactive Hydride Agents (Red-Al, $LiAlH_4$, DIBALH, L-Selectride, NaH, and KH) by No-D NMR Spectroscopy

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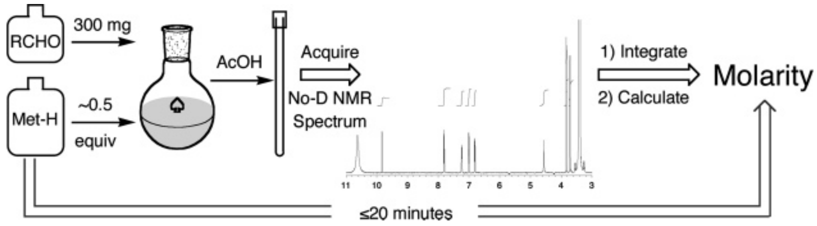
ABSTRACT



The concentration of reactive metal hydride (Met-H) reducing agents can be determined (in ≤20 min) using No-D NMR spectroscopy. The method involves (i) reacting Met-H with an excess of *p*-methoxybenzaldehyde, (ii) quenching with excess acetic acid, (iii) recording the No-D NMR spectrum of this homogeneous mixture, and (iv) deducing the concentration of Met-H from the % conversion (as measured by integration). By a conceptually related method, the titer of the basic alkali metal hydrides KH and NaH can also be determined.

The successful outcome of many selective reduction or acid−base reactions hinges upon knowing the reagent concentration accurately. Dynamic factors such as shelf life and previous handling history impacts the concentration of these reagents. Reliable and easily implemented methods for determining these titers are valuable.

We recently reported a No-D ^1H NMR-based method for measuring the concentration of organolithium and -magnesium reagents.[1] There, the intensity of a resonance diagnostic of the reagent/analyte itself was compared directly with resonance(s) from an added, inert, internal standard (usually, 1,5-cyclooctadiene, COD). Once learned, this direct observation method requires ca. 10 min of an experimentalist's time and is very reliable.

During the course of that study we observed that many metal hydride species (Met-H) did not present diagnostic resonances in the ^1H NMR spectra that could be exploited in the same way.[2] This required development of an alternative protocol;[3] we chose a "reaction titration". We imagined that an excess (ca. 2-fold) of a suitably reactive compound could be treated with a Met-H solution of known volume. In principle, many reactive titrants will work; we settled on the readily available, shelf-stable, and easily handled *p*-methoxybenzaldehyde (*p*-anisaldehyde, **1**).

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[1] Hoye, T. R.; Eklov, B. M.; Voloshin, M. *Org. Lett.* **2004**, *6*, 2567−2670.

[2] For example, for problems associated with observing the protons in $LiAlH_4$ by ^1H NMR spectroscopy in THF and diethyl ether, see: (a) Horne, D. *J. Am. Chem. Soc.* **1980**, *102*, 6011−6014. (b) Andrianarson, M. M.; Avent, A. G.; Ellerby, M. C.; Gorrell, I. B.; Hitchcock, P. B.; Smith, J. D.; Stanley, D. R. *J. Chem. Soc., Dalton Trans.* **1998**, 249−253.

[3] Other methods for assaying metal hydride species are known. In our experience, gas titration protocols (Aldrich Technical Bulletin AL-123 and Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; John Wiley and Sons: New York, 1973; pp 21−244), although reliable once mastered, have an unfavorable learning curve and consequently are not routinely used. Alternative, colorimetric methods applicable to $LiAlH_4$ (and Red-Al) have also been described: Brown, E.; Lézé, A.; Touet, J. *Tetrahedron Lett.* **1991**, *32*, 4309−4310. Love, B. E.; Jones, E. G. *J. Org. Chem.* **1999**, *64*, 3755−3756.

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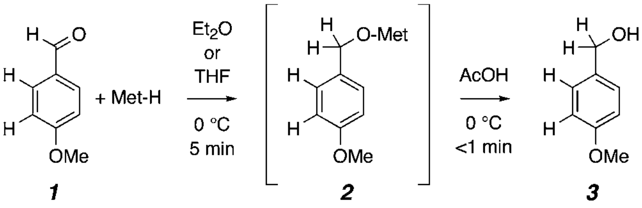
The method capitalizes on the ease with which ^{1}H NMR spectral data can be obtained for solutions that do not contain deuterium enrichment.[4] That is, all of the spectra shown and data described here were obtained as No-D ^{1}H NMR spectra. They were recorded in unlocked mode using routine equipment and with equal ease as for conventional, locked samples.

When a solution of **1** in an ethereal solvent was treated with various Met-H hydride reducing agents and then examined by NMR spectroscopy, broad resonances for the metal alkoxides **2** were often observed (Scheme 1). Spectral quality was improved when the various metal salts were protonated to produce in situ the neutral *p*-methoxybenzyl alcohol (**3**). Addition of glacial acetic acid to **2** rendered homogeneous, single-phase solutions,[5] thereby avoiding the possibility of undesirable partitioning of product alcohol **3** from unreacted aldehyde reactant **3** during an aqueous workup procedure. The No-D spectrum of each of these solutions[6] gave excellent quality data[7] from which it was easy to measure the ratio of **3** to **1** (i.e., %conversion). In turn, the concentration of Met-H solution could be trivially deduced.[9] The entire operation required ≤20 min to complete.

Scheme 1



All of the Met-H reducing agents we have studied by reaction titration are listed in Table 1. The raw No-D spectral data were of comparable quality for each Met-H. Each was analyzed in duplicate, and the reproducibility was very good.

Table 1. Concentration of Metal Hydride Solutions Determined (in Duplicate) by Reaction Titration with *p*-Anisaldehyde (**1**)

met-H species	concentration (M)
Red-Al (PhMe)[a]	3.19 (±0.09)
$LiAlH_4$ (Et_2O)[8]	0.81 (±0.01)
DIBAL-H (PhMe)[b]	1.39 (±0.02)
DIBAL-H (hexanes)[c]	0.54 (±0.02)
L-Selectride (THF)[d]	1.00 (±0.01)
L-Selectride (THF)[d,e]	1.04 (±0.01)

[a] From a new commercial bottle having nominal concentration of 65% w/w (3.2 M). [b] From a commercial bottle having nominal concentration of 25% w/w (1.5 M). [c] From a substantially aged commercial bottle containing a substantial amount of precipitate and having nominal concentration of 1.0 M. [d] From a new commercial bottle with nominal concentration of 1.0 M. [e] This measurement was made by the "direct observation" method (see Figure 2).

Data for one representative sample, sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, "65+ wt %" in toluene), are shown in Figure 1. Every signal in the spectrum can be assigned (including the ^{13}C satellite peaks at δ 3.53 and 3.47 ppm for the Et_2O solvent). Aromatic proton resonances for unreacted aldehyde **1** vs product alcohol **3** are readily discernible from one another and from those of toluene. The methoxy resonances for **1** and **3** are distinguishable if diethyl ether rather than THF is used as solvent. Even 2-methoxyethanol (**4**), the protonolysis byproduct from Red-Al, is readily observed [at δ 3.66 (t) and 3.29 (s) ppm], can be identified, and is present in the proper proportion.

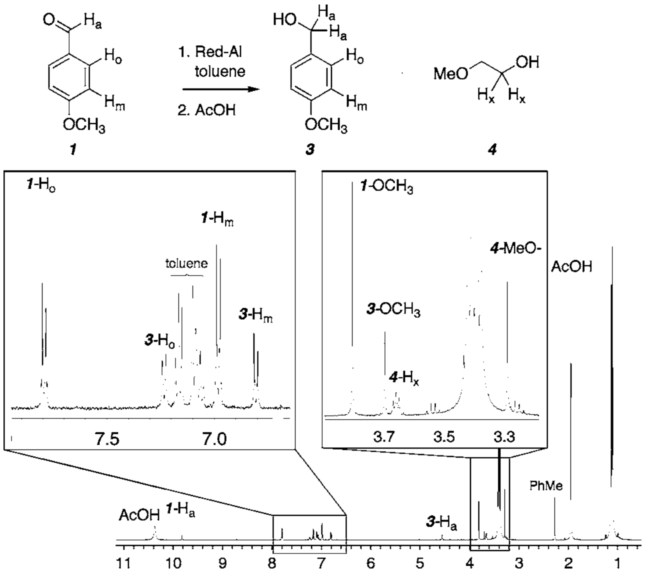


Figure 1. No-D ^{1}H NMR spectrum of the solution resulting from reaction titration of Red-Al in toluene/Et_2O against excess *p*-methoxybenzaldehyde (**1**). Integration provides a titer of 3.28 M.

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[4] Hoye, T. R.; Eklov, B. M.; Ryba, T. D.; Voloshin, M.; Yao, L. J. *Org. Lett.* **2004**, *6*, 953−956.

[5] **Typical Reaction Titration Procedure. (a) For Reducing Agents.** An accurately weighed sample of *p*-anisaldehyde (**1**, ca. 300 mg, ca. 2.5 mmol) in THF (3 mL) was cooled to 0 °C under a nitrogen atmosphere. A precisely measured volume of the reducing Met-H solution (ca. 1.25 mmol) was added dropwise over 30−60 s. The mixture was stirred for 5 min, and glacial acetic acid (typically ca. 2 mL, although in instances where resonances of the product **3** were broad in the initial No-D spectrum, addition of more AcOH was advantageous) was added rapidly (ca. 5 s) with vigorous stirring. [In the instance of DIBAL-H, the AcOH was added cautiously since protonolysis of Al-C bonds was exothermic and accompanied by some gas evolution. Once this subsided the remaining AcOH was added rapidly.] An aliquot of the resulting homogeneous solution (ca. 0.7 mL) was transferred to a 5 mm NMR tube. The tube was capped in the normal fashion, and the spectrum was recorded.[6] No additional precautions were necessary to protect the sample from exposure to air or moisture. **(b) For NaH and KH.** NaH (∼75 mg) was accurately weighed into an oven-dried, 25 mL round-bottom flask equipped with a magnetic stir bar and septum. Under a nitrogen atmosphere dry THF (∼10 mL) was added by syringe. This gray suspension was cooled to 0 °C, and neat ethyl diethylphosphonoacetate (**5**, 1.00 mL, 4.94 mmol) was added dropwise by syringe over 60 s. Gas evolution began after a short incubation period and continued for a few minutes until a pale yellow, homogeneous solution was generated. An aliquot of this solution (∼1 mL) was transferred to an NMR tube. The tube was capped in the normal fashion, and the spectrum was recorded.[6] The hydride content of KH was determined in a completely analogous manner.

A commercial solution of lithium tri-*sec*-butylborohydride (L-Selectride) in THF (“1.0 M”) was examined by reaction titration against **1** and measured to be 1.01 M. The No-D spectrum of the reagent solution itself showed that the hydrocarbon resonances associated with the reducing agent were quite evident. This meant that it was possible to use the direct observation titration method[1] in a comparative sense for this particular Met-H. The ^{1}H NMR spectrum of the commercial solution of L-Selectride in THF (“1.0 M”), doped with COD, is shown in Figure 2. Using the direct observation protocol, we determined the titer of this solution to have the corroborating value of 1.04 M.

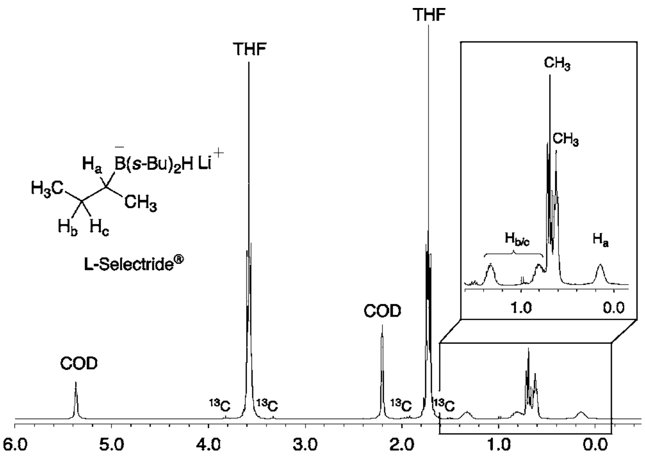

Figure 2. No-D ^{1}H NMR spectrum of a solution of L-Selectride containing COD. Integration provides a “direct observation” titer of 1.04 M.

The alkali metal hydrides sodium (NaH) and potassium hydride (KH) are very useful bases. They are also notorious for having uncertain hydride contents (activity), largely dependent upon history of handling and storage of a given sample. We have identified an acid/base reaction titration that permits the amount of active hydride to be measured. Ethyl diethylphosphonoacetate (**5**) in THF proved to be a convenient titrant. Its No-D ^{1}H NMR spectrum is shown in the top panel (a) of Figure 3. Upon reaction of a carefully measured amount of **5** with a carefully measured but substoichiometric amount of NaH at 0 °C, gas is evolved, the initial suspension becomes homogeneous, and a new resonance appears for H_y in **6** (2.5 ppm), upfield of the original resonance for the methylene protons, H_x (2.9 ppm), in **5**. Fortunately, proton exchange between the carbon acid

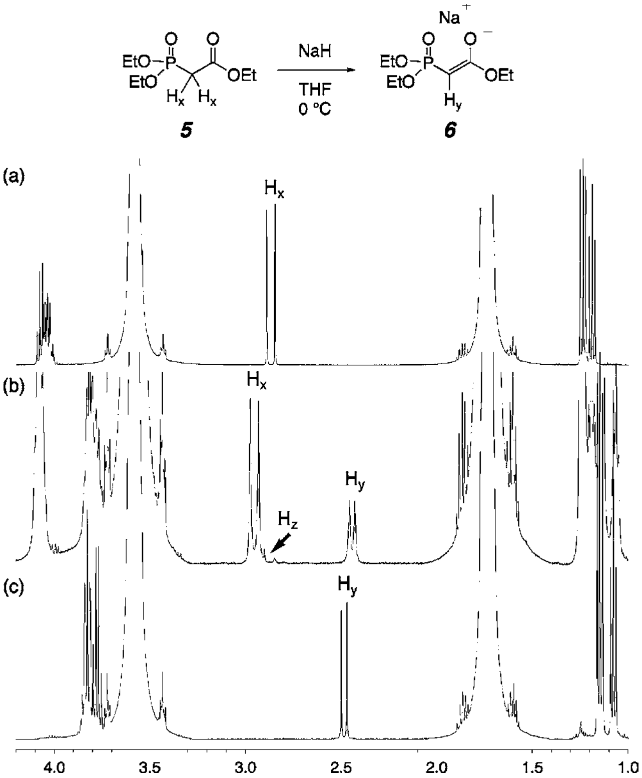

Figure 3. No-D ^{1}H NMR spectra (500 MHz) of phosphonoacetate **5** in THF before (panel a) and after reaction with ca. 0.5 equiv of “dry” (no mineral oil) NaH (panel b) and after exposure to excess NaH (an additional ~1.0 equiv) (panel c).

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(6) **Data Acquisition.** Spectra were recorded[4] at ambient temperature on Varian (INOVA or VXR) instruments at 300 or 500 MHz. Important parameters for collection of the No-D NMR spectra are the acquisition time, delay, transmitter power, pulse width, and number of transients. [For an example where some of these issues were addressed for a sample in a non-deuterated solvent medium (in the context of ^{1}H NMR analysis of a solvolysis rate study), see: Creary, X.; Jiang, Z. *J. Org. Chem.* **1994**, *59*, 5106−5108]. Guiding principles are to collect nearly all of the signal (by acquiring magnetization decay for several T_1s), to use a sufficiently low transmitter power to avoid baseline artifacts in the transformed spectrum, and to have the total time for the experiment be short. For solutions of relatively high concentration ($\leq$0.1 M), signal-to-noise is generally excellent even when a single transient is collected. Once parameters were identified that resulted in relative intensities of the aromatic resonances within **1** as 2.00:2.00 ± 0.04 and of the aromatic vs aldehyde resonance of 2.00:1.00 ± 0.02, the parameters and protocol were deemed acceptable. Values used for all spectra here (regardless of whether at 500 or 300 MHz) were at = 20 s, d1 = 20 s, tpwr = 46, and pw = 7.5 μs (resulting in a ca. 22.5° pulse). Most typically, data sets of four scans (nt = 4) were used.

(7) **Data Workup and Analysis.** Care was taken to achieve flat spectral and integral baselines by phasing the spectrum and adjusting the level/tilt of the integral or by performing a baseline correction. Integrals were cut above a flat baseline but inside the ^{13}C satellite peaks. For a recent discussion of more of the issues relevant to quantitative proton NMR measurements (qHNMR), see: Pauli, G. F.; Jaki, B. U.; Lankin, D. C. *J. Nat. Prod.* **2005**, *68*, 133−149.

(8) We prefer to generate solutions of ethereal $LiAlH_4$ on an as-needed basis. We typically use solid $LiAlH_4$ pellets as the source. Solutions in Et_2O are preferred to those in THF because the density of the latter solvent is closely matched to the gray, insoluble impurities that are typically present in all solid sources of $LiAlH_4$. Those particulates are reluctant, even upon centrifugation, to settle and leave a clear supernatant. A convenient method for approximating the quality of a $LiAlH_4$ pellet is to monitor the gain in mass upon exposure to the atmosphere. The $LiAlH_4$ slowly reacts with atmospheric moisture; the rate is faster in an atmosphere of high humidity (1−2 days). A gravimetric change associated with the reaction shown in eq 1 is roughly obeyed.

$$LiAlH_4 + 2H_2O = LiAlO_2 + 4H_2$$

(9) If the number of mmol of **1** and the volume of solution of Met-H of unknown titer are precisely known and the Met-H is fully consumed prior to quenching of the metal alkoxide (with AcOH), then the concentration of the Met-H solution ([Met-H]) follows from the following relationships: [Met-H] = (mmol **1**)(%conversion)/(volume of Met-H solution in mL) where %conversion = (integral of **3**)/[(integral of **1**) + (integral of **3**)].

5 and its conjugate base **6** is slow on the NMR time scale so that discreet, quantifiable resonances for each are present.[10] As an aside and as the spectrum in panel c indicates, upon treatment with an additional amount of NaH (total of >1 equiv), phosphonate **5** is fully and cleanly converted to a stable solution of anion **6**. Integration of the spectrum in panel b (i.e., of the system at partial conversion), now of the resonances at 2.9 ppm (i.e., those associated with the methylene group of **5**) vs those at 2.5 ppm (i.e., those associated with the vinylic methine proton of **6**), allowed determination of the hydride content of the sample of NaH. The numerical treatment was entirely parallel to that used for the reducing hydrides.[9] Potassium hydride (in mineral oil) was successfully analyzed in an analogous fashion.

We considered that this reaction titration method might be used to quantify the concentration of various metal carbanionic species (e.g., RLi and RMgX). This possibility was briefly examined with *p*-anisaldehyde, but complications from Cannizarro-like redox events were observed.[11] While it is likely that other carbonyl compounds could be identified that would avoid these difficulties, this was not pursued further.

Finally, while we have not done so, there is every reason to think that this reaction titration strategy could be used for many additional reactive hydride reagents, such as boranes, Super-Hydride, and hydridoborate reagents. The method described here provides a reliable and fast way to deduce the concentration of reactive metal hydride reducing agents. The range of examples of specific reagents that are reported attests to the generality of the method.

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[10] The presence of the small resonance, labeled H_z, slightly upfield of H_x in the panel b spectrum of Figure 3 was a concern. It meant that a third species was present, and we observed that the intensity of H_z varied with the source of NaH. We could also observe three resonances in the ^{31}P NMR spectrum. These were assigned to **5** (19.8 ppm, the value of **5** in $CDCl_3$ vs external 85% aq H_3PO_4), **6** (~39.9 ppm), and the minor unknown species (~28.5 ppm). The ^{31}P relative intensities paralleled those of H_x vs H_y vs H_z. The similarities of the H_x and H_z proton chemical shifts and their $^2J_{H,P}$ coupling constants (22.0 and 19.5 Hz, as opposed to 13.5 Hz for the H_y $^2J_{H,P}$ value) suggested that the unknown species was a methylene-containing entity rather than a deprotonated anionic species. That the unknown was closely related to **5** or **6** (rather than, e.g., the carboxylate from a saponification event) was demonstrated by the addition of a (slight) excess amount of NaH to the solution shown in panel b, which gave rise to the spectrum in panel c. That is, anion **6** was the sole product, an outcome again mirrored in the ^{31}P spectrum. The multiplicity of the proton coupled ^{31}P resonance for this unknown further indicated the presence of a CH_2 methylene ($^2J_{H,P} = 19.5$ Hz). Finally, we observed that purposely destroying ca. half of a sample of NaH with water to produce NaOH and then adding phosphonate **5** gave spectra (^1H and ^{31}P) in which resonances from the unknown were ca. equal in intensity to those of anion **6**. Even this sample could be refocused to give a clean spectrum of **6** when the solution was subsequently treated with excess NaH. All of these observations are consistent with the unknown being a 1:1 complex (perhaps aggregated) between NaOH and the neutral phosphonate **5**. Incidentally, this suggests that one can assess the relative amounts of both NaH and NaOH in THF by this method.

[11] The clearest evidence of this came from the addition of vinylmagnesium bromide to **1**, in which case 4-methoxybenzyl alcohol **ii** and vinyl ketone **iii** were observed in addition to **i**.