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No-D NMR Spectroscopy as a Convenient Method for Titering Organolithium (RLi), RMgX, and LDA Solutions

Thomas R. Hoye,* Brian M. Eklov, and Mikhail Voloshin

Department of Chemistry, 207 Pleasant Street, SE, University of Minnesota, Minneapolis, Minnesota 55455

hoye@chem.umn.edu

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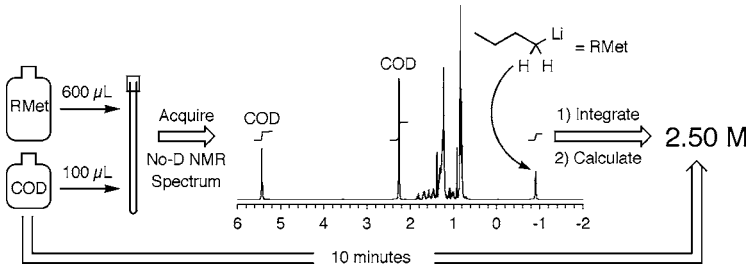
ABSTRACT



The concentration of organolithium, organomagnesium halide, and lithium diisopropylamide solutions can be reliably determined using No-D NMR spectroscopy by integration against the added internal standard 1,5-cyclooctadiene (COD) (or cyclooctene). In addition, common impurities and degradation products can be assessed.

No-D NMR (or no-deuterium Proton NMR) spectroscopy involves recording ^{1}H NMR spectra of samples dissolved in ordinary, non-deuterium-enriched, laboratory solvents.[1] In addition to being useful for in situ monitoring of reaction mixtures, we have found that No-D NMR spectroscopy also provides a convenient and reliable method for determining the concentration of many common reagents. This is especially helpful for air- and moisture-sensitive reagents, like reactive organometallic species.

n-Butyllithium is the potential energy source for a plethora of reactions in organic chemistry. Of course, several reliable methods for titration of commercial solutions of alkyllithium and Grignard reagents are known. However, few would argue that this type of quantification is performed as frequently as it should. As we show here, determining the concentration of these solutions by No-D NMR spectroscopy is accurate, easy, and fast. Both Reed and Urwin and Silveira, Jr., Bretherick, Jr., and Negishi developed direct NMR-based analyses of butyllithiums 25−35 years ago (using added mesitylene or benzene as an internal standard) that appear to have been largely overlooked.[2] As the results presented here emphasize, they should not have been. Also, Kamienski has provided an excellent summary of alkyllithium titration methods (including both "wet-" and NMR-based methods).[3]

In No-D spectroscopy, an aliquot of any solution is simply placed in a conventional NMR sample tube and the ^{1}H NMR data are recorded. Typically, the instrument is in the unlocked mode. Spectra are collected in the same time frame as that of a conventionally locked and shimmed sample. Perfectly adequate levels of signal-to-noise and resolution are routinely attained, in part due to the fact that modern spectrometer hardware exhibits little field drift during data acquisition.

(1) Hoye, T. R.; Eklov, B. M.; Ryba, T. D.; Voloshin, M.; Yao, L. J. *Org. Lett.* **2004**, *6*, 953−956.

(2) (a) Urwin, J. R.; Reed, P. J. *J. Organomet. Chem.* **1968**, *15*, 1−5. (b) Reed, P. J.; Urwin, J. R. *J. Organomet. Chem.* **1972**, *39*, 1−10. (c) Silveira, A., Jr.; Bretherick, H. D., Jr.; Negishi, E. *J. Chem. Educ.* **1979**, *56*, 560−560.

(3) Kamienski, C. W. *FMC Lithium Link*, Winter 1994, *Titration Methods for Commercial Organolithium Compounds*. http://www.fmclithium.com/tech/lithiumlinks.asp (accessed May 2004).

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Reagent solutions of interest typically have concentrations of 1−2 M. Since most neat organic solvents are ca. 10 M, the solvent:solute ratio is ca. 5−10:1. Not only is it easy to see the solute species of interest, but data can be collected under conditions (see below) that give quantitatively reliable values.

The strategy for quantifying NMR samples is simple. A precisely measured amount of a (wisely chosen) standard is combined with a known volume of the solution of interest. The No-D spectrum is recorded and the concentration determined from the integral ratios. We have settled upon the use of 1,5-cyclooctadiene (COD) as an internal integration standard for determination of all of the butyllithiums and the workhorse lithium amide, LDA (lithium diisopropylamide). COD is widely available, stable, dry, easily transferred, and unreactive to RLi/hydrocarbon solutions (at least in the absence of an activator like TMEDA[4]). It also gives two different proton resonances (vinylic and allylic) for assessing integration self-consistency.[5] When the data were collected and analyzed appropriately,[6] very reliable ratios (1.00:2.00 ± 0.04) of the two COD resonances were consistently observed.

The No-D NMR spectrum of *n*-BuLi in hexanes containing ca. 12 vol % COD is shown in Figure 1. All of the spectra shown here were recorded from samples prepared in essentially the same manner.[7] We determined this solution of

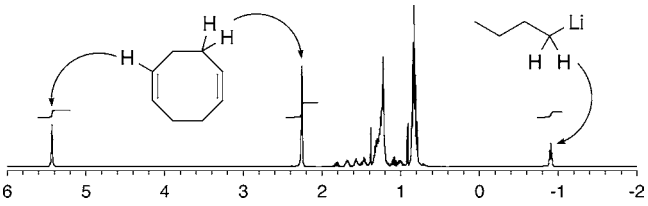

Figure 1. No-D NMR spectrum of *n*-BuLi (600 μL) in hexanes containing 1,5-cyclooctadiene (COD, 82.3 mg). Integration[6] provides a titer of 2.50 M.

n-BuLi to be 2.50 M. Comparison of the NMR-derived values with those from a more traditional titration method shows excellent agreement, as described below for all of the anionic species. As an aside and as noted before,[1] all of the hexanes solvent resonances can be assigned to the responsible C_6-hydrocarbons (*n*- and *i*-hexane, cyclohexane, methylcyclopentane, and 2,3-dimethylbutane).

The No-D NMR spectrum of *sec*-butyllithium in cyclohexane/hexane (92:8) containing ca. 12 vol % COD is shown in Figure 2. We determined this sample to be 1.32 M. Other

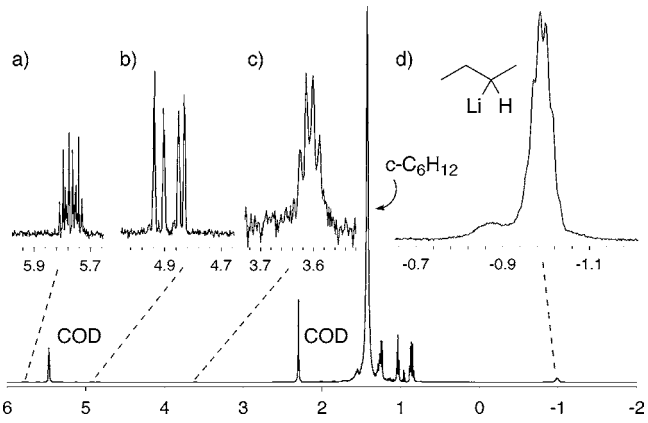

Figure 2. No-D NMR spectrum of *sec*-BuLi in cyclohexane/hexanes (92:8) containing COD. The insets are expansions of resonances from 1-butene (a and b), lithium *sec*-butoxide (c), and *sec*-BuLi (d).

noteworthy observables in the *s*-BuLi spectrum are (i) a single resonance [(br) sextet at δ −1.0 in inset d] for the C(2)-methine proton, consistent with an equilibrating mixture of the stereoisomeric dimeric, tetrameric, and hexameric aggregates known to exist for *s*-BuLi in hydrocarbon solution;[8] (ii) the presence of a low level of 1-butene [insets a and b (and 2-butenes, when COD is absent)] indicative of

(4) (a) Gausing, W.; Wilke, G. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 371−372. (b) Wetzel, T. G.; Dehnen, S.; Roesky, P. W. *Organometallics* **1999**, *18*, 3835−3842.

(5) (a) Gerritz, S. W.; Sefler, A. M. *J. Comb. Chem.* **2000**, *2*, 39−41. (b) The T_1 relaxations for COD (6.5 s for the allylic and 11.2 s for the vinylic resonances) are longer than those measured for the anions (e.g., the *n*-BuLi C(1)-methylene protons have a T_1 relaxation time of 0.85 s). Thus, if the COD integrals are in agreement (i.e., ca. 2.0:1.0), one can safely assume that the anion resonances have fully relaxed as well.

(6) **Data Acquisition.** Spectra were recorded 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 (≥0.1 M), signal-to-noise is generally excellent even when a single transient is collected. Once parameters that resulted in relative intensities of COD resonances within 1.00:2.00±0.04 were identified, the protocol was deemed to be sufficient. Values used for all spectra here were at = 20 s, d1 = 20 s, tpwr = 46 and pw = 7.5 μs (resulting in an ca. 22.5° pulse), and nt = 2−4. We observed no meaningful differences in the determinations for the same sample using nt = 1, 2, 4, or 16. **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 (and to avoid the small resonance due to vinylcyclohexene (≤0.4%)) contaminant typically present in COD. To assess the impact of subjectivity in interpretation of the integral values, independent analysis of the same COD spectral data set by three different researchers gave allylic to vinylic resonance ratios of 2.011, 2.008, and 1.992 to 1.000 (i.e., <1% maximum variation).

(7) **Sample Preparation.** The hydrocarbon reference (ca. 100 μL 1,5-cyclooctadiene or cyclooctene) was added to a tared 5 mm NMR tube, and the mass of the standard was recorded. [Although the tube typically was flushed with nitrogen prior to adding the standard, this is not essential. Consider that if the headspace (ca. 2 mL) of a 5 mm tube at 25 °C contains air at 100% relative humidity, there is ca. 20 μmol of oxygen and ca. 3 μmol of water, contaminant levels sufficient to consume only ca. 0.1% of the active species present in a 1 mL aliquot of 2.5 M butyllithium.] A precise volume of the anion solution (600 μL) was added; the tube was capped with a standard plastic NMR tube cap, and the tube was agitated to homogenize the solution. Shimming was performed as described in detail in ref 1. After data acquisition,[6] the integral value[6] for the methylene resonance for RCH_2Li at −0.9 ppm was compared to those of COD.

(8) Fraenkel, G.; Henrichs, M.; Hewitt, M.; Su, B. M. *J. Am. Chem. Soc.* **1984**, *106*, 255−256.

thermal ejection of LiH over time;[9] (iii) the presence of lithium *s*-butoxide (ca. 3.6 ppm in inset c); and (iv) spectroscopic evidence for *s*-BuLi aggregates containing *s*-BuOLi (br shoulder at ca. −0.9 ppm in inset d). When present, this resonance should be included in the *s*-BuLi integral.

The No-D spectrum of *tert*-butyllithium in pentane containing ca. 12 vol % COD is shown in Figure 3. Spectrum

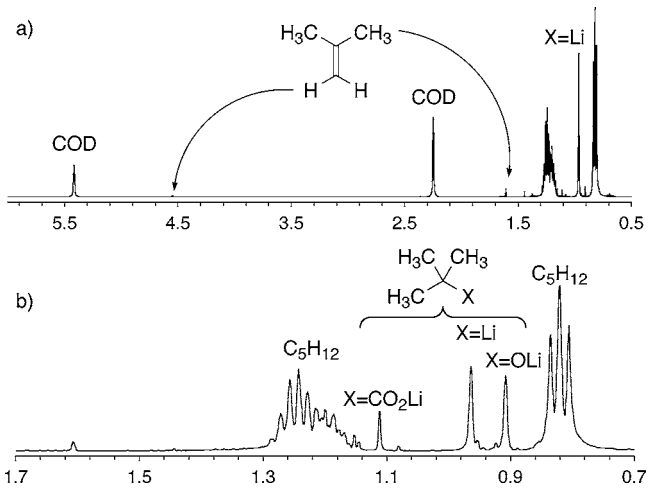

Figure 3. No-D NMR spectrum of *tert*-BuLi in pentane containing COD from (a) a high-quality and (b) a low-quality source.

a is of a sample taken from a reasonably fresh bottle of *t*-BuLi, which we determined to be 1.63 M. Even though the resonance from the *tert*-butyl group of *t*-BuLi is quite close in chemical shift to flanking solvent (pentane) resonances, one can still obtain reliable titers (cf. Table 1). Spectrum b is of a sample taken from an older bottle of the reagent that had been handled in a manner typical of a multiuser environment. A significant amount of the original *t*-BuLi content has been lost due to reaction with reactive species present in air (O_2, CO_2, and H_2O).

Methyllithium, although commercially available as a solution in diethyl ether, is difficult to store under conditions where its titer is maintained. Occasional users of a common stock solution learn this by experience. Ether is difficult to maintain in common storage vessels, and the inherent reactivity of MeLi with Et_2O ($t_{1/2}$ ca. 6 months at 25 °C)[10] requires that reagent solutions be stored in the cold. Various "on-demand" laboratory preparations of MeLi have been reported.[11] We have used one[12] that is easy to perform and results in a solution of MeLi in THF or ether that can be titered and used directly. This is especially convenient for those who may require small amounts of MeLi solutions on an intermittent (or "on-call") basis. The No-D spectrum of methyllithium in THF, produced in the above fashion containing ca. 12 vol % COD, was determined to be 0.72 M.

The No-D spectrum of a solution of lithium di-*iso*-propylamide·THF in hexanes containing ca. 12 vol % COD is shown in Figure 4. We determined this sample to be 1.22

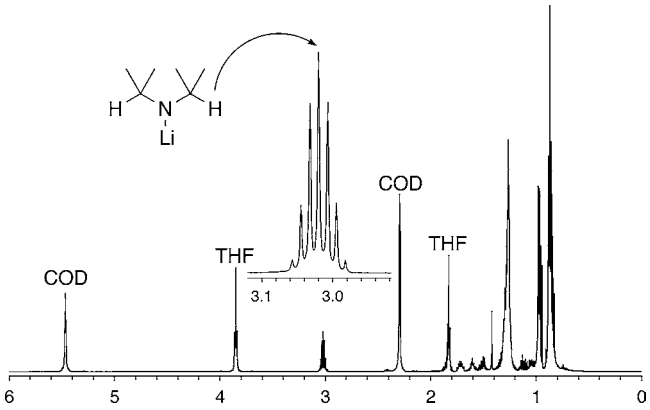

Figure 4. No-D NMR spectrum of LDA in hexanes containing COD and 1.0 equiv of THF. The inset is an expansion of the *i*-Pr methine resonance.

M. The LDA methine septet at δ 3.02 ppm is shown in the inset. Samples containing a slight excess of diisopropylamine (not shown) contain a resonance for the isopropyl methine at δ 2.85 ppm. On the other hand, samples containing a slight excess (even 1−2%) of *n*-BuLi show a resonance for RCH_2-Li protons at δ −1.04 ppm.

The No-D spectrum of a (commercial) solution of allylmagnesium chloride containing ca. 12 vol % of COD is shown in Figure 5. We determined this sample to be 1.20 M. The well-established[13] equivalence at ambient temperature

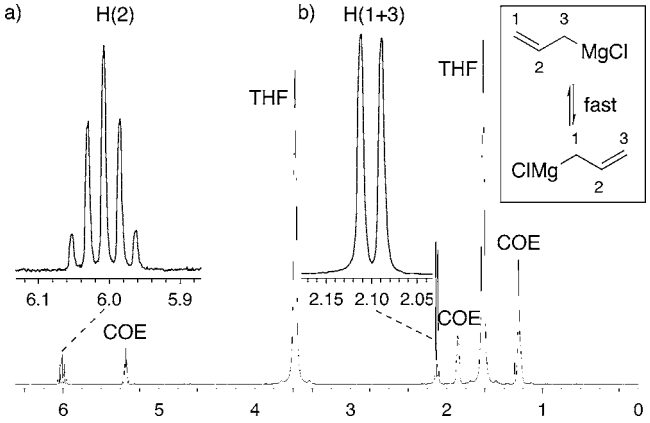

Figure 5. No-D NMR spectrum of allylmagnesium chloride in THF containing cyclooctene (COE). The insets are expansions of resonances from (a) the single internal and (b) the four equivalent terminal protons.

(9) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon Press: Oxford, UK, 1974; pp 198−199.
(10) Gilman, H. A.; Haubein, A. H.; Hartzfeld, H. *J. Org. Chem.* **1954**, *19*, 1034−1040.

of all four terminal protons of the allyl anion moiety is evident (δ 2.10, d, $J = 5$ Hz, 4H). The No-D spectrum of a (homemade) solution of vinylmagnesium bromide containing ca. 12 vol % COD is shown in Figure 6. We determined

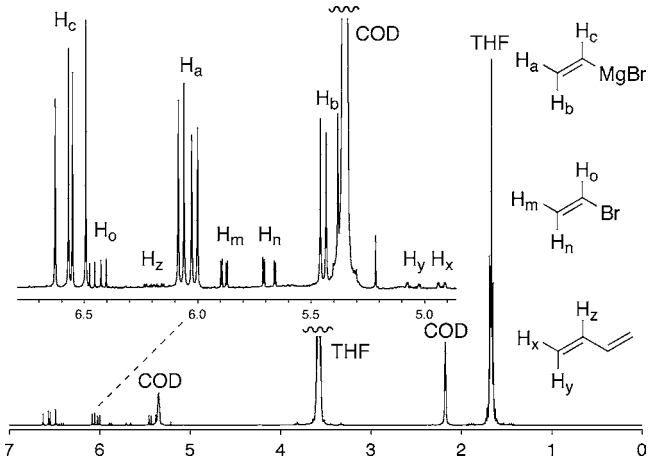

Figure 6. No-D NMR spectrum of vinylmagnesium bromide (H_a−H_c) in THF containing COD. The inset is an expansion of the vinylic resonances that shows residual CH_2═CHBr (H_m−H_o; ca. 10%) and 1,3-butadiene (H_x−H_z; ca. 2%).

this sample to be 1.25 M. Notice that residual vinyl bromide and byproduct 1,3-butadiene are observable. We have also examined EtMgCl, EtMgBr, and diethylzinc solutions, and each is well behaved. Thus, the method can be used for analysis of Grignard and organozinc reagents as well as organolithiums.

The concentrations determined by this No-D NMR method were compared to those from a more classical colorimetric titration.[14] Importantly, the results are in excellent agreement (Table 1); we leave the question of which is closer to fact to the opinion of the reader. What is undeniable is that the No-D NMR method is quicker (each pair of NMR determinations took ≤20 min to perform) and, therefore, more conveniently (and likely to be) performed.

Table 1. Comparison of Concentration Values Determined by No-D NMR Spectroscopy vs a Conventional Colorimetric "Wet" Titration[a,14]

species	NMR		colorimetric	
n-BuLi	2.50	2.50	2.45	2.50
s-BuLi	1.32	1.34	1.33	1.36
t-BuLi	1.63	1.68	1.71	1.71
LDA	1.22	1.23	1.18	1.20
MeLi	1.41	1.42	1.53	1.54
EtMgCl	0.86	0.87	0.88	0.89
allylMgCl	2.04	2.05	1.96	1.97
vinylMgBr	1.25	1.25	1.25	1.27
Et_2Zn	0.94	1.01	not performed	

[a] Average difference in the two sets of measurements is 0.21%, while the average unsigned difference is 2.9%.

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Supporting Information Available: Enlarged, uncompressed (high-resolution) versions of Figures 1−6 and No-D NMR spectra of solutions of MeLi/Et_2O, EtMgCl/Et_2O, and Et_2Zn/hexanes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Rathman, T. L. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley: Chichester, 1995; Vol. 5, pp 3530−3532.

(12) Reynolds, K. A.; O'Hagan, D.; Gani, D.; Robinson, J. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3195−3208. MeI (neat) was added to a solution of *n*-BuLi in hexanes at 0 °C. The MeLi produced precipitated as a white powder. The supernatant was removed following centrifugation. The MeLi was suspended in fresh hexanes and centrifugation/solvent removal repeated. The resulting white solid was dissolved in Et_2O (or THF) immediately prior to NMR analysis and use.

(13) Whitesides, G. M.; Nordlander, J. E.; Roberts, J. D. *Discuss. Faraday Soc.* **1962**, *34*, 185−190.

(14) Colorimetric titrations were carried out using 1,6-dihydro-6-butyl-2,2′-bipyridine (**1-*H***) as the indicator, as described for lithium amide bases (Ireland, R. E.; Meissner, R. S. *J. Org. Chem.* **1991**, *56*, 4566−4568). We are not aware that this procedure has been extended from R_2NLi to carbanionic (R-Met) species. Aliquots from an ethereal stock solution of *l*-menthol (ca. 1.3 g in a 10 mL volumetric flask) were used as the standard acid. 2,2′-Bipyridine (ca. 5 mg) was added to an oven-dried flask equipped with a magnetic stirbar, capped with a septum, and flushed with dry nitrogen. Regardless of what anion was to be subsequently titrated, a pretitration with *n*-BuLi was performed. This served both (i) to rid the system of spurious impurities that, in our experience, routinely tend to result in low titer values for the first in a series of multiple measurements in the same vessel and (ii) to produce in situ the same indicating species, namely, the *n*-BuLi-bipy adduct **1-*Met***. This protocol results in the generation of the same yellow (**1-*H***) to blood red (**1-*Met***) change at the endpoint for any of the species indicated in Table 1, regardless of metal counterion or solvent. Thus, an initial 500 μL aliquot of the menthol solution was added to the flask, and *n*-BuLi was added dropwise until the deep blood red color from **1-*Met*** persisted. A 1000 μL aliquot of the menthol solution was added to this deep red solution, the first drop of which gave rise to the bright yellow solution of **1-*H***. A solution of the organometallic of interest was added dropwise until the blood red color persisted. Typically, 3−4 serial measurements of the same anion were repeated in the same flask.