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No-D NMR (No-Deuterium Proton NMR) Spectroscopy: A Simple Yet Powerful Method for Analyzing Reaction and Reagent Solutions

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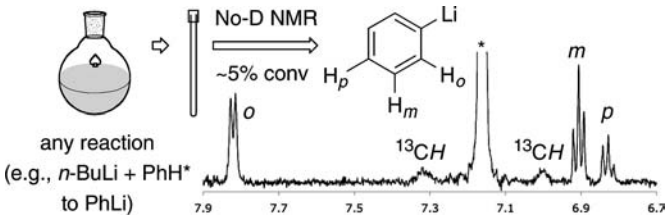
ABSTRACT



The title technique is a convenient and powerful method for directly monitoring or assaying any reaction mixture or reagent solution. Examples of some common processes (Fischer esterification, lithiation, butyllithium/THF compatibility, olefin metathesis, and a quantification assay), each interrogated in its native solvent, are presented. The spectral data are easy to acquire, and the information content makes a compelling case for routine use of No-D NMR spectroscopy.

Most introductory discussions of proton NMR spectroscopy include the fact that ^{1}H NMR spectra are typically recorded in solutions prepared with deuterated solvents. The rationale is, of course, that this enables observation of the protons of interest without the interference from solute protons. Although there are certain and obvious advantages to following this practice, the use of solvents lacking protons ($CDCl_3$, D_2O, CCl_4, etc.) is by no means a necessity. In fact, by using the strategy described here of collecting NMR spectra in nondeuterated solvents (No-D NMR), one can *routinely examine any* (and all) *reaction or reagent* solution(s).[1] Scale, economics, and premeditation of the studies are not issues.

We show representative examples of ^{1}H NMR spectra of reaction mixtures that contain no deuterium atoms (other than those of natural abundance). Consequently, these No-D NMR spectra were recorded in unlocked mode. These examples represent only a small sampling of the informative data that can be readily obtained for any type of reaction or reagent. We present them, in part, to show that the paradigm[2] of routinely recording proton NMR spectra in deuterium-enriched solvents is unwarranted.

The concentration of most neat organic solvents is ca. 10 M. The concentration of the reactants in most reaction solutions is in the range of 0.1−1 M (and of solutions of most commercial reagents ca. 0.5−2.5 M). Thus, the ratio of solvent to solute/analyte molecules is usually between 100:1 and 10:1 in most solutions of interest. It is a

(1) We do not mean to imply that this is a new concept. To be sure, samples of biological macromolecules are routinely recorded in a 9:1 ratio of H_2O/D_2O and nuclei other than protons (e.g., ^{31}P, ^{19}F, ^{15}N, ^{11}B, etc.) are also often examined in nondeuterated solvents.[2] Moreover, although more specialized applications in various areas (e.g., LC NMR, food science, mechanistic studies, MRI, oil and petroleum industries, and quality control) can be found, use by preparative organic chemists is not at all routine.

(2) Anecdotal comments such as the following underscore the engrained nature of the practice: "I have run countless ^{31}P (or ^{19}F) spectra directly of aliquots from reaction mixtures in nondeuterated solvents, but never once did I think to put the sample tube into a proton probe and collect a ^{1}H NMR data set!"

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straightforward matter for most NMR spectrometer hardware to handle dynamic ranges of proton intensities of greater than 4 orders of magnitude.[3]

It is our intent here to show how the data are collected and the variety of information types that can be obtained. Although the examples presented are all of known processes, each is representative of a class of reaction or reagent that chemists might want or need to interrogate.

The first example (Figure 1) is the simple Fischer esterification[4] of acetic acid (**1**) with ethanol (**2**).[5] A 1:4 molar

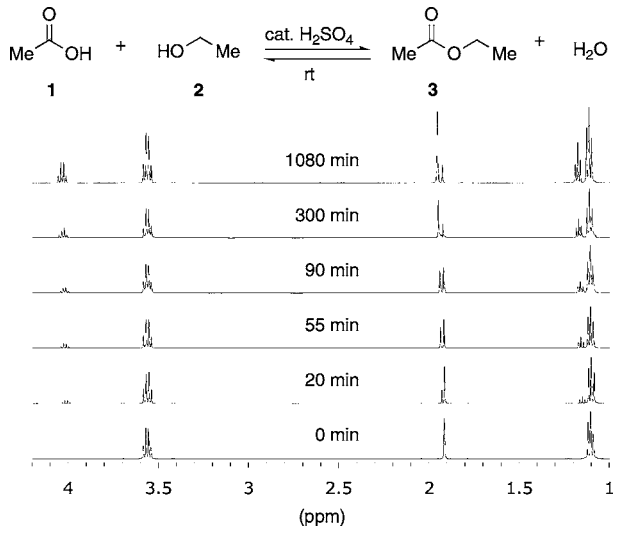

Figure 1. Fischer esterification of acetic acid in ethanol (1:4 molar ratio).

ratio of AcOH/EtOH was treated with 1 mol % of concentrated H_2SO_4. A 600-μL aliquot was removed to a sample tube and thereafter used to monitor reaction progress toward an equilibrium mixture by No-D ^{1}H NMR spectroscopy. The excellent resolution and quantitative features of the spectra are noteworthy. This is a good experiment for first-time users.

The second example (Figure 2) is the lithiation of benzene (**4**)[6a] by *n*-BuLi and TMEDA[6b] in hexanes at room temperature. Spectrum (a) shows the No-D NMR spectrum of *n*-BuLi in hexanes (2.0 M) containing 1.0 equiv of benzene. Notice that one can decipher the individual components in the hexanes [methylcyclopentane (**i**), *n*-hexane (**ii**), *iso*-hexane (**iii**), 2,3-dimethylbutane (**iv**), and cyclohexane (**v**)

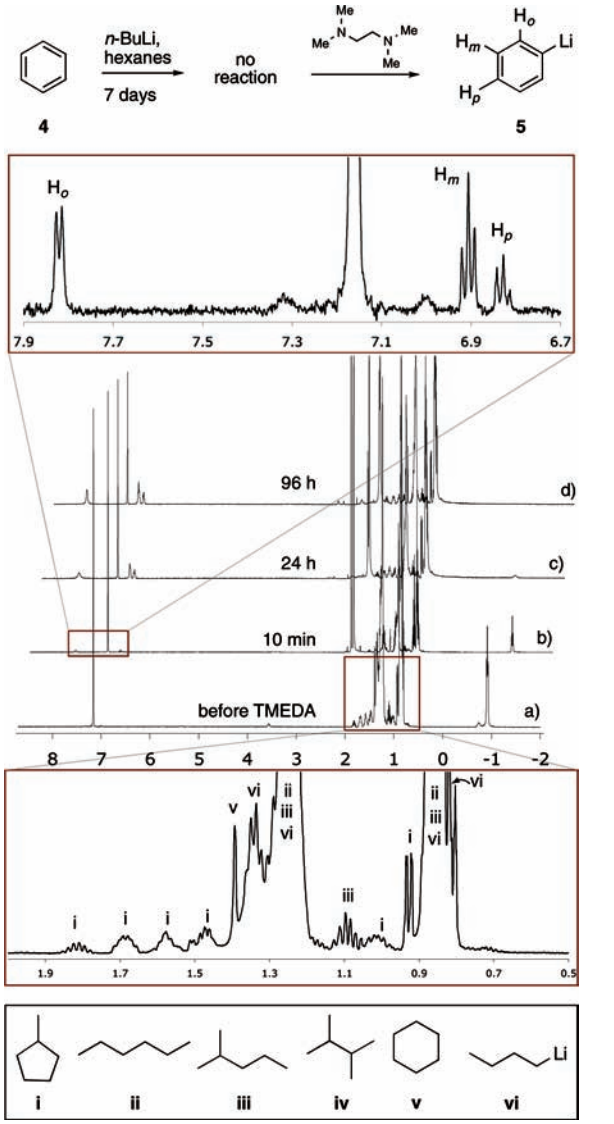

Figure 2. Metalation of benzene with *n*-BuLi in hexanes with TMEDA [spectra (a)−(d) are offset for clarity].

in the bottom expansion]. This sample had already stood for 1 week in the NMR tube sealed only with a standard plastic cap. No conversion to phenyllithium (**5**) was observed before addition of TMEDA. Spectrum (b) was recorded 10 min after the addition of 1.0 equiv of TMEDA; some phenyllithium[6c] (∼5%) is already apparent (top expansion). Spectra (c) and (d) (24 and 96 h) show ∼90% and essentially full consumption of *n*-BuLi. A full equivalent of TMEDA was required; use of a substoichiometric amount of the TMEDA promoter (data not shown) stopped at a much lower conversion to PhLi (product inhibition?).[6d]

All of the spectra shown here were straightforward to record. Our experience suggests that the art of learning to reliably shim a sample[7] has analogy with learning to ride a bicycle. Typically, users new to the technique find that after a dozen or so samples they are able to shim and collect quality data sets with no greater investment of effort or time than is required for an analogous deuterated sample.

(3) Solvent suppression routines were not used for any of the spectra shown here. However, particularly for more dilute samples, they can lead to better spectral quality. Another contributing factor to routinely achieving the quality of the spectra presented here is that most modern NMR spectrometers suffer very little from magnet drift and, therefore, give narrow lines when run in unlocked mode.

(4) Fischer, E.; Speier, A. *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 3252−3257.

(5) All spectra shown here were recorded on a Varian INOVA 500 instrument, but the technique is applicable to any spectrometer. Factors influencing instrument choice for No-D experiments are no different than those for conventional locked mode acquisition.

(6) (a) Langer, A. W., Jr. *Trans. N.Y. Acad. Sci.* **1965**, *27*, 741−747. (b) Eberhardt, G. G.; Butte, W. A. *J. Org. Chem.* **1964**, *29*, 2928−2932. (c) Ladd, J. A. *Spectrochim. Acta* **1966**, *22*, 1157−1163. (d) Rausch, M. D.; Ciappenelli, D. J. *J. Organomet. Chem.* **1967**, *10*, 127−136.

The well-known decomposition of tetrahydrofuran (**6**) by *n*-BuLi at room temperature is the third example (Figure 3).[8]

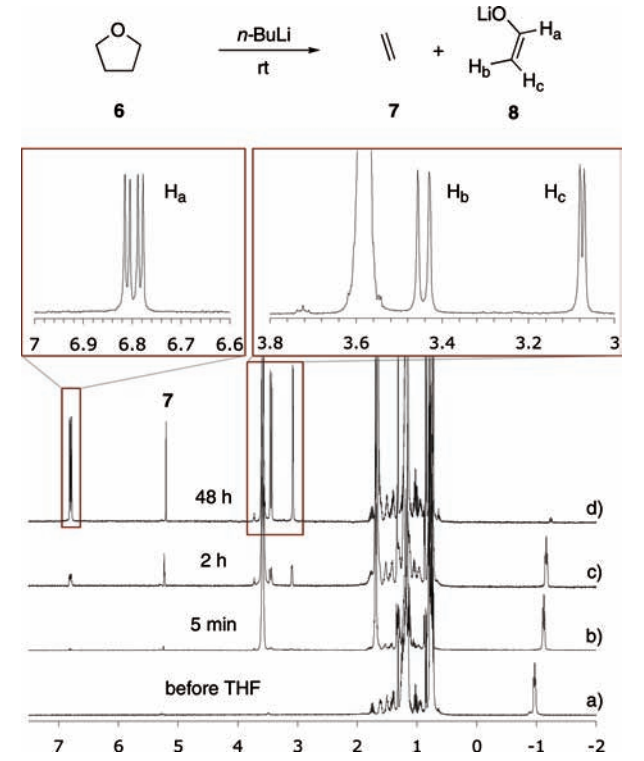

Figure 3. Generation (and stability) of ethylene and acetaldehyde enolate by THF decomposition with *n*-BuLi.

Spectrum (a) is of a sample of *n*-BuLi in hexanes that had stood in a capped NMR tube for 24 h. In addition to the diagnostic resonance at −0.95 ppm for the RCH_2Li protons, the broad resonances at 3.5 and −0.9 ppm are attributed to *n*-BuOLi or *n*-BuO_2Li and its mixed aggregate with *n*-BuLi,[9] respectively. Spectrum (b) reports that 5 min after addition of THF (**6**, 4.5 equiv), the onset of its decomposition into ethylene (**7**) and the lithio-acetaldehyde enolate (**8**) is observable. The RCH_2Li resonance is shifted upfield by 0.2 ppm upon addition of THF in response to dynamic THF/*n*-BuLi complexation.[10] Over time [spectra (c) and (d) at 2 and 48 h] resonances for each of the decomposition products grew. Even at partial conversion [~40% in (c)] the large adjacent THF resonance does not obscure the (*O*-*Z*)-vinyl proton (H_b) of **8**. After 48 h all *n*-BuLi was consumed. Even though it was not the intent of this ambient temperature experiment, we subsequently judged the half-life for decomposition to be ~2 h, quite consistent with the known value.[8d] This well-resolved spectrum of LiOCH=CH_2 (**8**) maintained its character for at least a week for a sample (again) protected only with a standard plastic cap.

To further demonstrate the sensitivity and generality of monitoring reaction progress in nondeuterated solvents, the fourth example includes spectra of a ring-closing metathesis reaction (Figure 4). A solution of allyl acrylate (**9**, 0.5 M in C**H**$_2$Cl$_2$) was exposed to 10 mol % Grubbs first generation ruthenium precatalyst (**G1**). At 1 min [spectrum (a)], conversion of a portion of **G1** (δ 20.0 ppm) into the Ru-loaded substrate (**13**) is evident (δ 18.9 ppm, t, J = 4.4 Hz).[11] Spectrum (b), taken at 4.5 min, shows that **G1** is nearly consumed. The extent of formation of styrene (**10**) [δ 6.7 (dd, J = 16.9 and 10.9 Hz) and 5.7 (d, J = 16.8 Hz) ppm] correlates with consumption of **G1**.

Formation of γ-butenolide (**11**) [δ 7.6 (dt, J = 5.8 and 1.5 Hz) and 6.1 (d, J = 5.8 Hz) ppm] and *E*- and *Z*-dimer (**12**)[12] is evident and continues as long as resonances due to any resting carbene are observable. At 64 min [spectrum (c)], the methylidene carbene **14** (δ 18.9 ppm, s) is the only identifiable ruthenium-containing species. After 3 h no carbene resonances remained observable (not shown). At 48 h no further conversion (compared to 3 h) had occurred, so an additional 10 mol % of **G1** was added. One minute later [spectrum (d)] it was obvious that reaction had been reinitiated. A similar profile of conversion and alkylidene

(7) (a) Gilman, H.; Gaj, B. J. *J. Org. Chem.* **1957**, *22*, 1165−1168. (b) Honeycutt, S. C. *J. Organomet. Chem.* **1971**, *29*, 1−5. (c) Jung, M. E.; Lyster, M. A. *Tetrahedron Lett.* **1977**, *43*, 3791−3794. (d) Stanetty, P.; Mihovilovic, M. D. *J. Org. Chem.* **1997**, *62*, 1514−1515 ($t_{1/2}$ = 1.78 h at 20 °C).

(8) There are several methods that can be used to shim the proton probe to a No-D sample and tube. These include (a) the initial use of a reference tube of the same volume of deuterated solvent, which is locked and shimmed as usual and then replaced with the No-D sample; (b) recalling/reentering a set of previously used shim settings known to be optimal for the solvent in use; (c) the use of a capillary insert containing a deuterated sample of the same solvent, which can be locked and shimmed; (d) gradient shimming; (e) shimming the No-D sample using the FID (see "shimming using the FID" below); and (f) shimming the No-D sample using the spectrum (see "shimming using the spectrum" below). Method (c) is a reliable way to start, and methods (c) and (d) are compatible with autosamplers. We use methods (e) or (f) for nearly all samples (including all spectra shown here). Although the following instructions refer to software (VNMR 6.1) on a Varian, Inc. instrument,[5] they are sufficiently generic to be helpful to users of other manufacturers' equipment. **Initial Setup.** Use a typical volume (e.g., ca. 600−700 μL) of a solution of solute in nondeuterated solvent with a concentration of, say, 0.1−1 M (ca. 100:1 to 10:1 solvent/solute). Set the spectrometer parameters as you would for a deuterated sample [e.g., nucleus, solvent (if "known" to the spectrometer, otherwise choose anything), initial shim parameters, spectral width, etc.]. Turn off the "Lock" but spin the sample. Acquire a single scan spectrum. Phase this initial "unshimmed" No-D ^{1}H NMR spectrum. Select, expand, and note a "reporter resonance" of known peak shape (a solvent peak is usually a good choice, but any peak of known multiplicity will suffice). Run the FID/Spectrum macro ⟨gf⟩ and enter the interactive acquisition display process ⟨acqi⟩ (to allow observation of the real-time FID or spectrum). **(e) Shimming using the FID.** After performing the initial setup, select the FID button and then increase the gain until the FID level is between 500 and 1000 (to allow easier observation of small changes in the FID level). Adjust the shims, allowing the FID level to stabilize before making each additional adjustment, until a maximum FID level (numerical) has been achieved. **(f) Shimming using the Spectrum.** Shim by monitoring the increase in reporter peak intensity (numerical and/or graphical) and peak symmetry. Don't be discouraged by initial poor-looking peak shape. **In general**, note that the response to a change in shim settings will occur more slowly here than it will when shimming on a deuterated sample in locked mode. The process of shim optimization is otherwise quite analogous for samples in nondeuterated vs deuterated solvents. Once the shims are optimized, exit "acqi" and take another one pulse spectrum. If the overall spectrum quality is acceptable, proceed with recording the spectrum. Shimming the second through the *n*th sample at the same sitting will usually be easier.

(9) (a) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805−1810. (b) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H.-R. *J. Am. Chem. Soc.* **1985**, *107*, 1810−1815.

(10) Keresztes, I.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 10228−10229 and references therein.

(11) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 8, 100−110.

(12) Sueltemeyer, J.; Doetz, K. H.; Hupfer, H.; Nieger, M. *J. Organomet. Chem.* **2000**, *606*, 26−36.

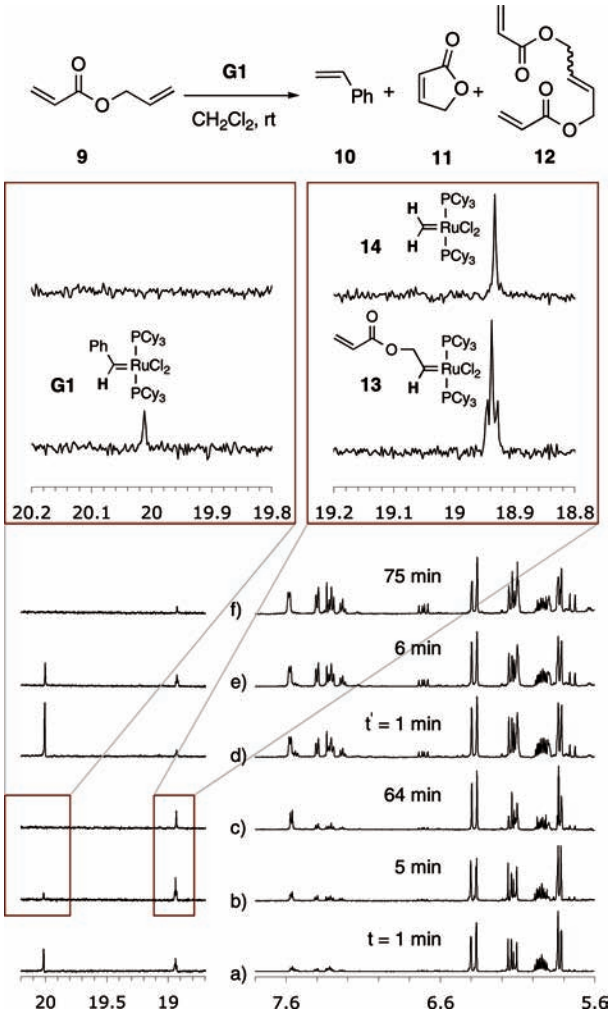

Figure 4. RCM of allyl acrylate to produce γ-butenolide. The region from δ 18.5−20.5 is increased vertically (5×) for easier visualization.

depletion [spectra (d)−(f)] emerged. A considerable amount of information and insight is obtained from this simple experiment.

Finally, a number of more specific applications are under study. Among these are various "titration" methods for quantifying the amount of a solute of interest (e.g., organolithium, Grignard, and metal hydride species). To whet palates here, we show (Figure 5) an assay of ethanol content in various aqueous solutions as determined by integration against an internal standard (*p*-NaOPhCO$_2$Na, **15**).[13] The inset table shows the reported and observed values for a set of such solutions. Integration of resonances in the No-D spectra of the standards of known concentration (entries 1−4) demonstrated the quantitative reliability of the measurements (R^2 = 1.000). Assay of commercially available solutions (entries 5−8) suggested systematic overreporting of ethanol titers.

sample	% EtOH reported	% EtOH observed
std-2	2.00	2.02
std-5	5.00	4.86
std-25	25.00	24.96
std-50	50.00	49.92
Miller Lite®	4.2	3.5
Goose Island®	5.2	4.7
Jack Daniels®	43.0	41.2
Tanqueray®	47.3	46.7

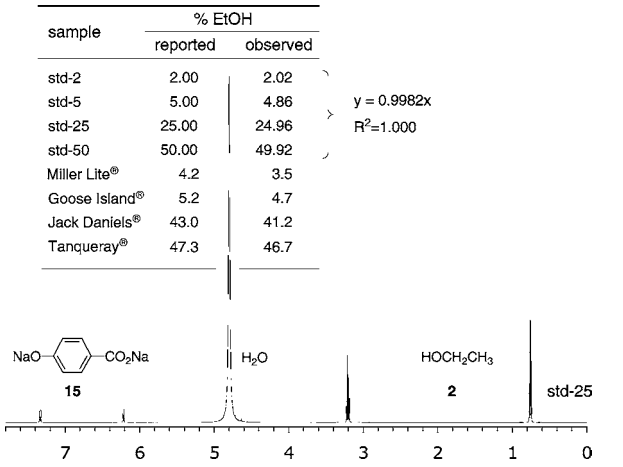

Figure 5. Quantitative assay of aqueous ethanol solutions.

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Supporting Information Available: Enlarged, uncompressed (high resolution) versions of the figures in both black-on-white (printable) and color (displayable) formats. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) A known quantity of *p*-hydroxybenzoic acid (typically 50−70 mg) was added to a solution (1.00 mL) of aqueous ethanol, and 40% aqueous NaOH (~100 μL) was added to deprotonate and solubilize the standard acid. No-D ^{1}H NMR data were collected (4−8 transients) with an acquisition time and a pulse delay of 20 s each to ensure complete relaxation and quantitative proton integration. Pulse widths (transmitter power) were reduced to remove baseline spectral artifacts and increase integration accuracy. Using these protocols the H_o vs H_m resonances integrated reliably to 1.00 ± 0.02.