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Diffusion Coefficient-Formula Weight (D-FW) Analysis of ^{2}H Diffusion-Ordered NMR Spectroscopy (DOSY)

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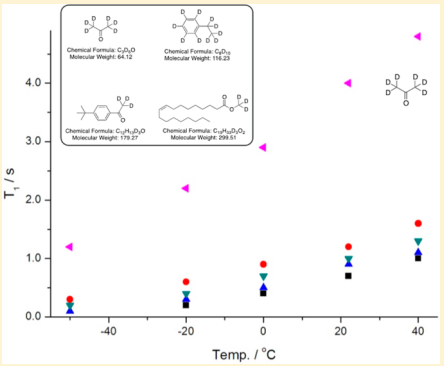
Supporting Information

ABSTRACT: We report extension of the D-FW analysis using referenced ^{2}H DOSY. This technique was developed in response to limitations due to peak overlay in ^{1}H DOSY spectra. We find a corresponding linear relationship (R^2 > 0.99) between log D and log FW as the basis of the D-FW analysis. The solution-state structure of THF solvated lithium diisopropyl amide (LDA) in hydrocarbon solvent was chosen to demonstrate the reliability of the methodology. We observe an equilibrium between monosolvated and disolvated dimeric LDA complexes at room temperature. Additionally we demonstrate the application of the ^{2}H D-FW analysis using a compound with an exchangeable proton that is readily labeled with ^{2}H. Hence, the ^{2}H DOSY D-FW analysis is shown to provide results consistent with the ^{1}H DOSY method, thereby greatly extending the applicability of the D-FW analysis.



INTRODUCTION

Pulsed gradient spin−echo (PGSE) diffusion NMR spectroscopy was conceived to measure diffusion coefficients and to deduce the hydrodynamic radii of molecules in solution by Stejskal and Tanner in the mid-1960s.[1] In 1992, the PGSE sequence was modified by C. S. Johnson to display the results in a two-dimensional format in which one dimension represents the regular chemical shift and the second dimension separates species by diffusion characteristics.[2] This experiment is now referred to as diffusion-ordered NMR spectroscopy (DOSY).[3] Our group and others have applied ^{1}H, ^{13}C, ^{19}F, and ^{31}P DOSY techniques to correlate relative diffusion with molecular weight using the technique referred to as diffusion coefficient-formula weight (D-FW) analysis.[4] Utility of the D-FW analysis was demonstrated by the measurement of formula weights of several reactive organolithium complexes in solution in our laboratory.[5] Reliable predicted formula weights of target complexes are calculated by a calibration curve in the D-FW analysis derived from the addition of appropriate molecular weight references to an analyte sample.[6] This referenced DOSY technique is especially beneficial for the study of various intermediates in solution and those systems not applicable to traditional mass spectrometric techniques, including air sensitive and reactive small molecules, such as organometallic compounds. Accordingly our practical experience with this referenced DOSY method led to the development of the use of isotopically labeled samples or analysis of nuclei other than ^{1}H when the analytes were inconvenient to analyze using ^{1}H DOSY. However, additional practical limitations arise. For example, a natural abundance ^{13}C DOSY experiment is prohibitively time-consuming for dilute samples, due to the low natural abundance of ^{13}C. ^{31}P DOSY is only applicable for analysis of phosphorus-containing compounds. Thus, it remains that among all the common NMR active nuclei, ^{1}H DOSY presents the best accuracy, shortest time/cost ratio, and widest application for the D-FW analysis. However, ^{1}H DOSY suffers from the serious limitation of overlapping resonances in the chemical shift dimension which lead to deceptive values in the diffusion dimension. In order to overcome this latter disadvantage, ^{2}H labeled D-FW analysis utilizing ^{2}H labeled internal reference standards are now introduced. Our group has previously developed an isotopically enriched ^{13}C DOSY technique and successfully applied this to the solution-state characterization of methyl lithium.[7] Considering the cost and effort associated with introduction of ^{13}C into most organic compounds, we now suggest that the least expensive and easiest isotopically labeling method that is amenable to D-FW analysis is deuterium labeling. Hence, we now report this referenced ^{2}H DOSY method as a necessary and important extension of the DOSY/D-FW toolbox. Examples of solution state ^{2}H NMR abound.[8] Only a few of these combine ^{2}H NMR and diffusion measurement.[9] Here we report the first use of the referenced ^{2}H DOSY method and a few applications.

RESULTS AND DISCUSSION

Experimental Temperature. Unlike the nuclei (^{1}H, ^{13}C, ^{19}F, ^{31}P) previously utilized for D-FW analysis, the nuclear spin quantum number (I) of deuterium is 1, which implies a quadrupole moment (Q) due to the nonspherically electron charge distribution around its nucleus. The dominant relaxation mechanism for a nucleus with the quadrupole moment is quadrupolar relaxation (R_{QR}), described by eq 1. In this

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equation T_1 is the longitudinal (or spin−lattice) relaxation time, μ is asymmetry of the electric field, q_z is the electric field gradient, and τ_c is the molecular correlation time (molecular or segmental rotation). This equation indicates that the molecular shape, chemical environment around the deuterium nucleus, and molecular tumbling rate all influence the relaxation time T_1. However, τ_c is more predicable and can be significantly influenced by experimental conditions. Thus, analysis at lower temperature leads to a longer τ_c, shorter relaxation time, and broader peaks. As shown in Figure 1, two commercially

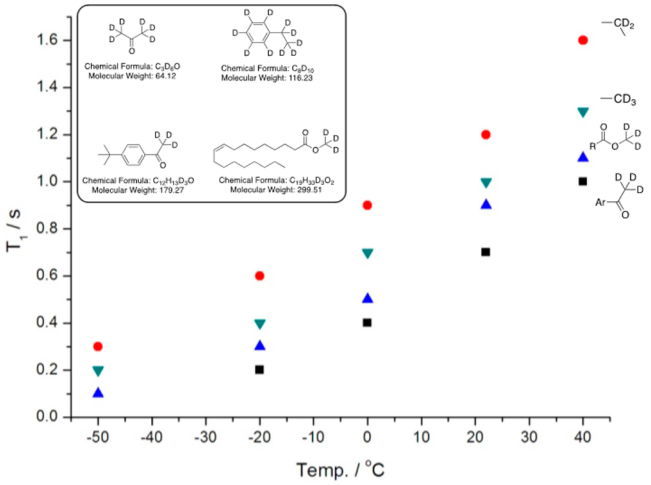

Figure 1. Dependence of T_1 on temperature.

available, perdeuterated compounds and two synthetically partially deuterated complexes, whose formula weight distribution is similar to the distribution of our successful ^{1}H DOSY/D-FW references, are used as models to monitor the dependence of relaxation time on temperature. A practical limitation of the D-FW analysis is that the diffusion experiment delay time (d20) must be shorter than T_1 for all peaks of interest. Based upon experimental conditions readily available with our current instrumentation (see Experimental Section) we recommend that the T_1 time should be longer than 50 ms for any ^{2}H signal utilized for D-FW analysis to allow set up of the appropriate diffusion time within the DOSY experiment. Therefore, the practical experimental temperature for ^{2}H DOSY should not be lower than −20 °C, in our laboratory at present. Moreover, considering that a larger molecular weight also reduces τ_c, a more practical experimental temperature for us at present is ambient temperature or higher.

$$R(^2\mathrm{H})_{\mathrm{QR}} = \frac{1}{T_{1(\mathrm{QR})}} = \frac{3}{2}\pi^2\left(1 + \frac{\mu^2}{3}\right)\left(\frac{Qq_z e^2}{h}\right)\tau_c \quad (1)$$

Internal References. Numerous commercially perdeuterated compounds are available that would serve as quite convenient internal references for ^{2}H DOSY/D-FW experiments. However, essentially all ^{2}H-labeled target complexes slated for analysis will be at most partially deuterated, due to the synthetic convenience of their preparation. Furthermore, analysis of completely perdeuterated compounds completely negates the advantage of utilizing ^{2}H isotopic labeling. However, it was not obvious at the outset whether the use of perdeuterated internal references to measure partially deuterated compounds was feasible. According to the modified Stokes−Einstein eq 2,[10] the diffusion coefficient (D) is influenced by the temperature (T), viscosity (η), particle shape (f_s), and radius (r). Therefore, correlation of diffusion coefficient to predict molecular weight requires that all the complexes in the solution have similar densities and hydrodynamic radii.[11] Since the size of deuterium is identical to that of a proton but with a 100% increase in mass, introducing more deuterium nuclei into a compound will increase the density, According to our previous observations, this may lead to a larger error in the prediction of molecular weight by D-FW analysis. On the other hand, proton nuclei comprise only a small percentage of the MW for most of organic compounds. Hence, the density change caused by introducing deuterium may not be significant enough to influence the D-FW analysis given that the relative accuracy we associate with MW determination is ±5%. Hence, in order to test whether perdeuterated compounds could be employed as internal references for ^{2}H DOSY/D-FW, four commercially available perdeuterated compounds were mixed with synthetic methyl oleate-d_3 deuterated ester and analyzed by ^{2}H DOSY/D-FW.

$$D = \frac{kT}{f_s(\mathrm{a,\ b})\pi\eta r} \quad (2)$$

As shown in Table 1 and Figures 2 and 3, commercially available perdeuterated actone, ethylbenzene, and acenaphthene present a good linear relationship with partially deuterated ester in our first attempt at using the ^{2}H nucleus for D-FW analysis. This result indicates that both perdeuterated and partially deuterated compounds can be applied together in ^{2}H DOSY experiments. This was also confirmed in the examples discussed later (*vide supra*). The only exception we observed is the use of commercially available perdeuterated

Table 1. D-FW Analysis of ^{2}H DOSY Data for the Test of Internal References

entry	compound	FW (g/mol)	D (m^2/s)	predicted FW (g/mol)	% error
1	acetone-d_6	64.1	2.82×10^{-9}	67.3	5
2	ethylbenzene-d_{10}	116	2.08×10^{-9}	111	−4
3	acenaphthene-d_{10}	164	1.70×10^{-9}	155	−5
4	chrysene-d_{12}	240	1.68×10^{-9}	158	−34
5	ester-d_3	300	1.10×10^{-9}	316	5

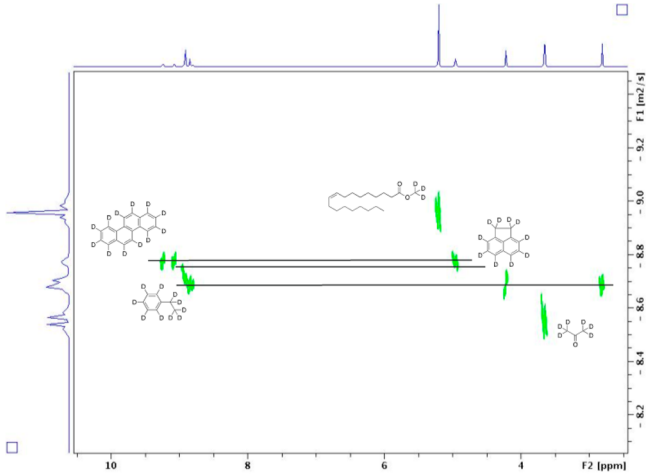

Figure 2. ^{2}H DOSY NMR in THF for the test of internal references.

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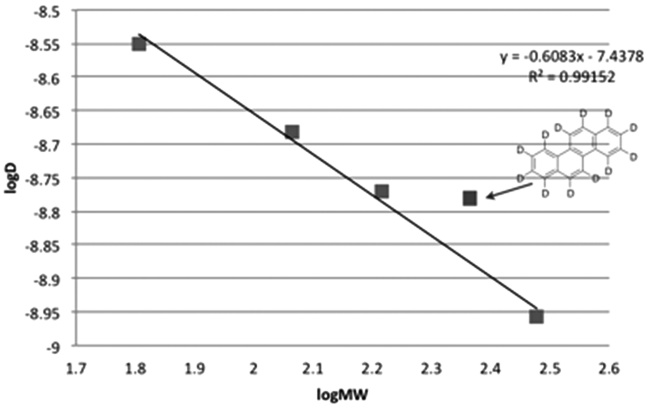


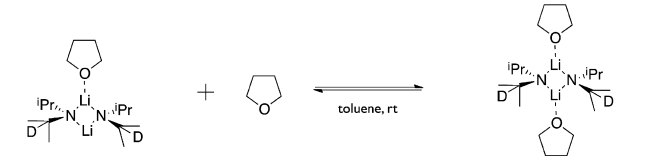
Figure 3. D-FW analysis of ^{2}H DOSY data for the test of internal references.

chrysene as a molecular weight standard. We suggest that the diffusion-behavior of chrysene is due to a dramatically different f_s value due to its distinctly flat molecular shape as well as the greater density of chrysene itself relative to the densities of other molecular weight standards and the analytes.

Application of an Organometallic Complex. LDA is known to exist as a disolvated dimer with THF in both solution sate and solid state. This has been determined by NMR analysis of [^{6}Li, ^{15}N]-LDA[12] as well as X-ray crystal structure[13] and NMR analysis of ^{1}H/^{13}C DOSY with D-FW analysis.[14] Hence the LDA-*d*/THF/Tol system represents an ideal case to verify the reliability of isotopic ^{2}H DOSY/D-FW analysis. Preparation of LDA-*d* is already well established in previous literature.[15] The importance of LDA and related alkali metal amides to preparative organic and inorganic chemistry is noted in several recent comprehensive reviews.[16]

Considering that the molecular weight of the target complex, di-THF solvated LDA-*d* dimer, is 360 g/mol, four internal references were selected within a molecular weight spanning 100 to 371 g/mol. They remain inert to organolithium reagents such as LDA. As shown in Figure 4, the D-FW measured molecular weight of LDA-*d* is 366 g/mol (error 2%) in the presence of 10 equiv of THF (observed MW 104 g/mol; see Supporting Information (SI)) in toluene solution. This result is entirely consistent with the fact that LDA exists as a disolvated dimer with THF. Moreover, observed MWs of both LDA-*d* and THF-d_8 were measured in the presense of various amounts of THF; see SI and Scheme 1. We suggest that the results in

Scheme 1. Results of ^{2}H DOSY of LDA-*d* in Toluene with 1−20 equiv of THF/THF-d_8 at Room Temperature



LDA : THF	Obs. MW_{LDA}	Obs. MW_{THF}	D_1/%	D_2/%
1 : 1	316	261	~75	~25
1 : 2	323	146	~60	~40
1 : 10	366	104	<5	>95
1 : 20	360	--	<5	>95

Mono-solvated dimer (D1) **Di-solvated dimer (D2)**

Scheme 1 are consistent with an equilibrium between the mono-THF solvated LDA dimer (D_1) and di-THF solvated LDA dimer (D_2) with the exclusion of the LDA monomer. Hence, only THF solvated LDA dimer exists in hydrocarbon

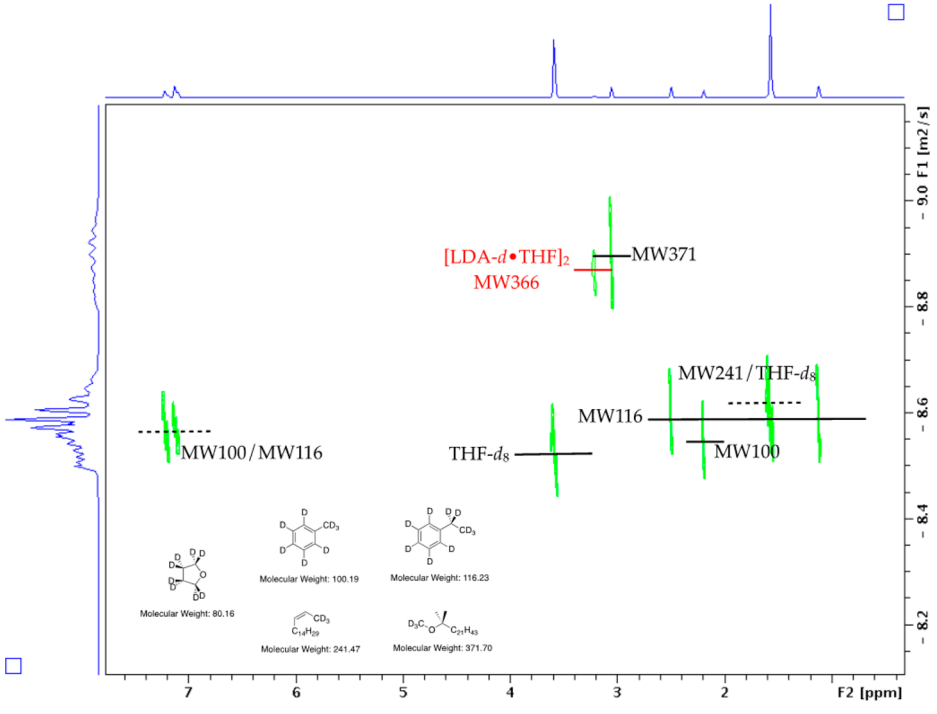


Figure 4. ^{2}H DOSY NMR of LDA-*d* in toluene with 1 equiv of THF-d_8 and 9 equiv of THF.

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solvent at room temperature. Thus, this representative example demonstrates that ^{2}H DOSY/D-FW analysis is feasible and is entirely consistent with ^{1}H DOSY/D-FW experiments.

Application on Amide via Hydrogen−Deuterium Exchange Labeling. The most synthetically convenient method of deuterium labeling is direct hydrogen−deuterium exchange. This method is routinely applied to amides in the backbone of a protein in order to study the structure and dynamic properties of proteins. Therefore, it is intriguing to determine whether ^{2}H DOSY based upon this simple amide-exchange reaction can be utilized with the ^{2}H DOSY/D-FW methodology. Hence, in an initial experiment, 10 μL of D_2O were added to 0.5 mL of a 0.4 M acetanilide/acetone-d_6 solution and the molecular weight of acetanilide as determined by monitoring the nonexchangeable protons was determined by ^{1}H DOSY as 181 g/mol (Figure 5). This is larger than its FW

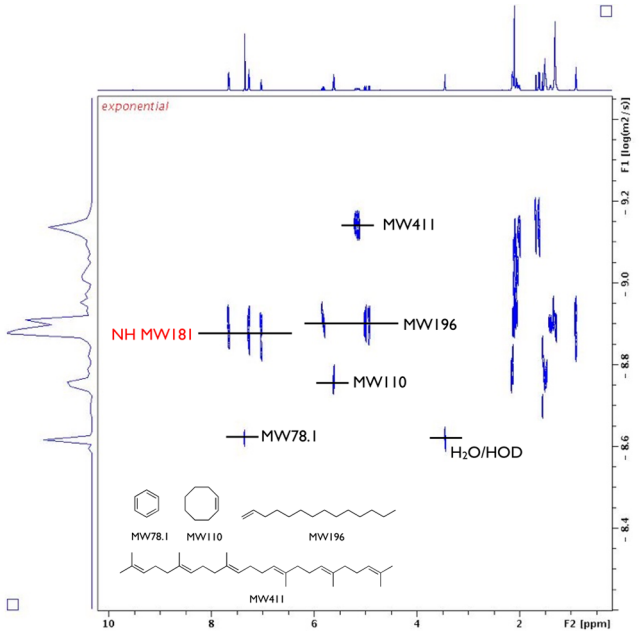

Figure 5. ^{1}H DOSY NMR of 0.4 M acetanilide in acetone-d6 with 10 μL of D_2O (2.5 equiv).

135 g/mol due to self-dimerization and solvation by water in the solution. We prepared another sample identical to the one in the first experiment, but we used nondeuterated acetone as the solvent instead of acetone-d_6. Before analysis in the ^{2}H DOSY experiment, this second sample was allowed to equilibrate for 1 h to allow the H−D exchange to achieve equilibrium. The only observable peak of acetanilide in ^{2}H NMR is from the N−D group with T_1 relaxation time 0.5 s. This relaxation time is long enough for ^{2}H DOSY analysis with the appropriate experimental diffusion time (d20) of 0.1 s. As shown in Figure 6, the measured molecular weight of acetanilide-*d* by ^{2}H D-FW analysis is 197 g/mol. This value is within 10% error of the result observed in the ^{1}H DOSY experiment. Therefore, we suggest that compounds with exchangeable protons such as peptides and also with a relatively long deuterium relaxation time are suitable for ^{2}H DOSY/D-FW analysis via an experimentally straightforward H−D exchange.

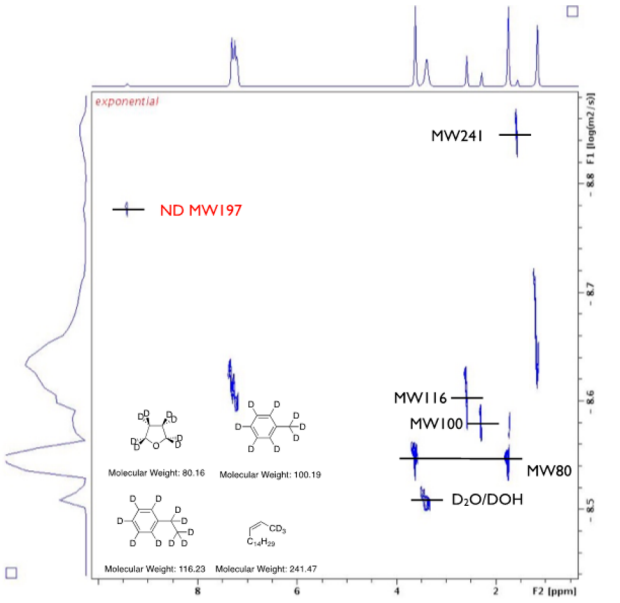

Figure 6. ^{2}H DOSY NMR of 0.4 M acetanilide in acetone with 10 μL of H_2O (2.5 equiv).

CONCLUSION

An internally referenced ^{2}H DOSY method is described with both partially deuterated and perdeuterated internal references. The correlation between log *D* and log FW yields a linear relationship (R^2 > 0.99) in all ^{2}H DOSY experiments we performed. Thus, the solution state structure of THF solvated LDA was studied in hydrocarbon solvent via ^{2}H DOSY and an equilibrium between monosolvated and disolvated dimer is observed at room temperature consistent with the results obtained in other analysis. Significantly, a nondeuterated compound with an exchangeable proton is labeled by deuterium through a proton−deuterium exchange process and this compound was analyzed by both ^{1}H and ^{2}H DOSY experiments with compatible MW results. Hence, we suggest that the use of ^{2}H labeling significantly extends the applicability of D-FW analysis by overcoming the limitation imposed by overlapping and nonresolvable ^{1}H NMR signals.

EXPERIMENTAL SECTION

Procedures for NMR Experiments. ^{1}H chemical shifts were referenced to TMS (from $CDCl_3$) at 0.00 ppm, and ^{13}C chemical shifts were referenced to $CDCl_3$ at 77.2 ppm. All NMR experiments were acquired on a 400 MHz spectrometer equipped with a *z*-axis gradient ATMA BBO probe. For DOSY experiments, a *z*-axis gradient amplifier was employed, with a maximum gradient strength of 0.214 T/m. The spin−lattice relaxation time (T_1) was estimated by the zero-crossing/null-time obtained using the standard T_1 inversion recovery experiment (t1ir1d) after calibration of a 90° pulse (P_1). ^{1}H and ^{2}H DOSY was performed using the standard ledbpgp2s pulse program, employing a bipolar gradient pulses for diffusion, and two spoil gradients. The diffusion time (d20) was 100 ms, and the rectangular gradient pulse duration (P30) was 1000 μs for ^{1}H DOSY and 3000 μs for ^{2}H DOSY. ^{2}H was observed on the broad-band channel, but could also be routed to the lock channel. Gradient recovery delays (d16) were 200 μs. Individual rows of the quasi-2-D diffusion databases were phased and baseline corrected. Actual diffusion coefficients used for D-FW analysis were obtained using the T1/T2 analysis module in commercially available software.

Synthesis of 2,2,2-^{2}H-4′-*tert*-Butylacetophenone. Gibson's method[17] has been applied here to label the α-position of ketones by deuterium. 0.88 g of 4′-*tert*-butylacetophenone (5 mmol, 1.0 equiv)

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was added to a solution containing 3 mL of methanol-d (75 mmol, 15 equiv), 0.9 mL of D_2O (50 mmol, 10 equiv), and 30 mg of sodium metal (1.3 mmol, 0.26 equiv) in a flamed-dried flask under an argon atmosphere. The mixture was heated to reflux for 3 h, cooled, and diluted with 20 mL of diethyl ether. The organic phase was washed with 10 mL of water twice and brine once and dried over anhydrous Na_2SO_4. After removal of solvent by rotary evaporation, 0.82 g of 2,2,2-^{2}H-4′-*tert*-butylacetophenone (92%) was gained as a colorless oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.34 (s, 9H), 7.48 (d, 2H, J = 8.5 Hz), 7.95 (d, 2H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 31.1, 35.1, 125.5, 128.3, 134.6, 156.8, 198.0; HRMS-ESI-TOF m/z: $[M+H]^+$ Calcd for $C_{12}H_{14}D_3O$: 180.1468. Found: $[M+H]^+$ 180.1458.

Synthesis of *cis*-(Methyl-^{2}H)-oleate.[18] 0.113 g of oleic acid (0.4 mmol) was dissolved in 1 mL of chloroform. 0.02 g of methanol-d4 (0.6 mmol, 1.5 equiv) and 0.023 g of trimethylsilyl chloride (0.2 mmol, 0.5 equiv) have been slowly added to the solution. After stirring at room temperature for 12 h, the reaction mixture was quenched and washed with 1 mL of 0.5 M $NaHCO_3$, then washed with 1 mL of brine, and dried over by anhydrous Na_2SO_4. After removal of solvent by rotary evaporation, 96 mg of ester (80%) were obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.88 (t, 3H, J = 6.7 Hz), 1.15−1.40 (m, 20H), 1.62 (m, 2H), 2.01 (m, 4H), 2.30 (t, 3H, J = 7.6 Hz), 5.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.1, 22.7, 24.9, 27.1, 27.2, 29.1, 29.1, 29.1, 29.3, 29.5, 29.6, 29.7, 31.9, 34.1, 129.7, 129.9, 174.2.

Synthesis of (*Z*)-Heptadec-2-ene-1,1,1-^{2}H. 0.55 g of 1-hexadecyne (2.5 mmol, 1.0 equiv) was dissolved in 20 mL of dried THF in a flame-dried flask under an argon atmosphere. 1.4 mL of 2.2 M *n*-BuLi (3.0 mmol, 1.2 equiv) was added slowly at −78 °C. After 10 min, the mixture was warmed up to 0 °C and stirred for 0.5 h. Then 0.54 g of CD_3I (3.75 mmol, 1.5 equiv) was added and stirred at room temperature for 3 h. The resulting solution was quenched with 5 mL of saturated ammonium chloride and extracted with 20 mL of hexanes three times. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After removal of solvent by rotary evaporation, heptadec-2-yne-1,1,1-^{2}H was gained and used in the next step without purification. Heptadec-2-yne-1,1,1-^{2}H was reduced to (*Z*)-heptadec-2-ene-1,1,1-^{2}H by Ashby's method.[19] Under an atmosphere of nitrogen, 0.05 equiv of Cp_2TiCl_2 was dissolved in THF. Crude heptadec-2-yne-1,1,1-^{2}H was added at 0 °C, and then 1.2 equiv of $LiAlH_4$ was added. After stirring at room temperature for 3 h, the reaction was quenched by the successive addition of water, 5% NaOH (aq), and water. The mixture was filtered and then concentrated under reduced pressure. The crude product was purified via silica gel chromatography (100% hexanes) to gain a transparent oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.88 (t, 3H, J = 6.8 Hz), 1.10−1.60 (m, 24H), 2.02 (m, 2H), 5.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.1, 22.7, 26.9, 29.3, 29.4, 29.6, 29.6, 29.7, 29.7, 31.9, 123.5, 131.0; MS m/z 241 $[M]^+$, 241, 213, 196, 171, 154, 128, 111, 83, 57.

Synthesis of 2-Methyl-2-(methoxy-^{2}H)-tricosane. 2-Methyltricosan-2-ol was prepared by following the previously reported method.[20] 0.23 g of 60% sodium hydride in mineral oil (5.7 mmol, 4 equiv) was placed in a flame-dried flask under an argon atmosphere. The gray mixture was washed with 3 mL of dry pentane three times in order to remove mineral oil. Then 10 mL of dried THF and 0.50 g of 2-methyltricosan-2-ol (1.4 mmol, 1.0 equiv) were added, and the resulting solution was refluxed for 4 h. 0.30 g of CD_3I (2.1 mmol, 1.5 equiv) has been added at 0 °C into the solution, before another 3 h of reflux. The reaction mixture was quenched with 5 mL of saturated ammonium chloride at 0 °C and then extracted with 10 mL of hexanes three times. The combined organic phase was washed with 30 mL of brine and dried over anhydrous Na_2SO_4. After removal of solvent by rotary evaporation, the residue was purified chromatographically on a flash column by hexanes. After the removal of solvent, 0.38 g of ether (1.0 mmol, 72%) was obtained as a white solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.88 (t, 3H, J = 6.8 Hz), 1.13 (s, 6H), 1.24−1.30 (br, 40H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.1, 22.7, 23.9, 25.0, 29.4, 29.7, 29.7, 29.8, 29.8, 30.3, 32.0, 39.9, 74.6.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01457.

NMR data (PDF)

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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