Ligand Binding Constants to Lithium Hexamethyldisilazide (LiHMDS) Determined by Diffusion-ordered NMR Spectroscopy (DOSY)

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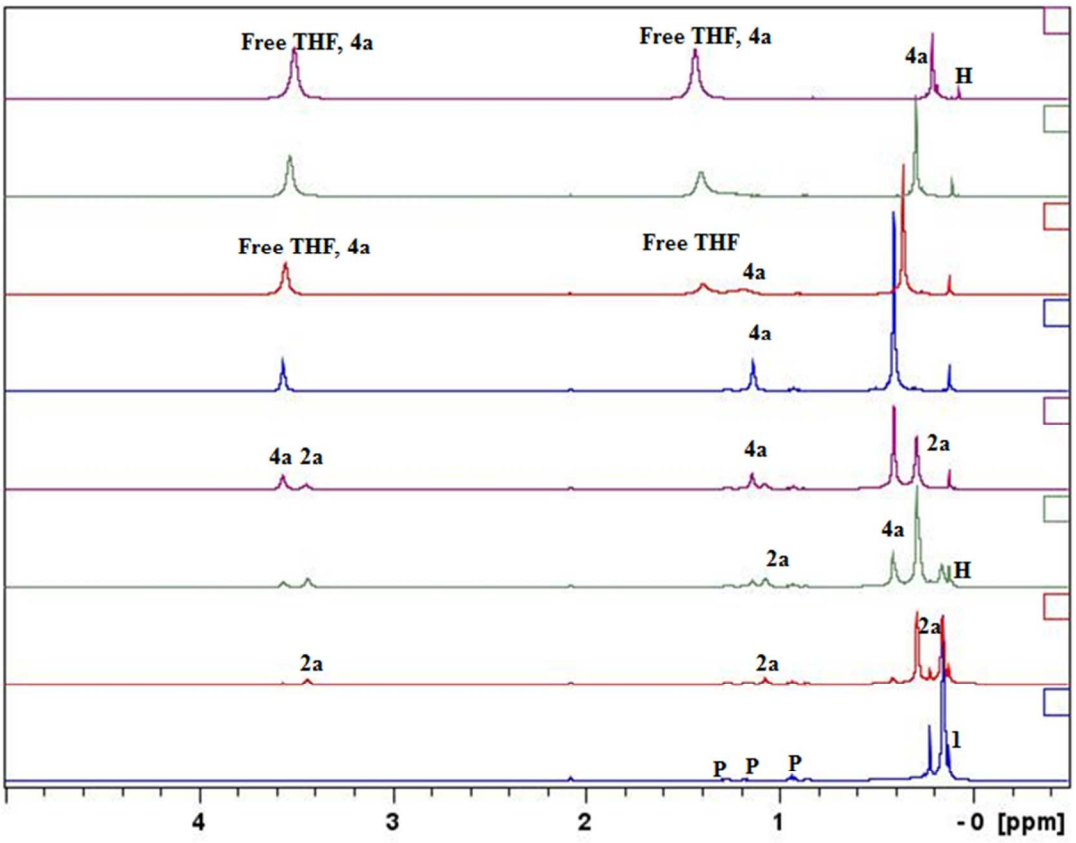


Figure S1. ^{1}*H NMR titration of THF into a solution of un-solvated LiHMDS in tol-d8* at -60°C. *From bottom to top,* ^{1}*H NMR of addition of 0, 0.25, 0.5, 0.75, 1,2.5, 4.5 and 10 eq. of THF into 1 eq.* ***1*** *in tol-d8.* P and H denotes pentane and HMDS, respectively.

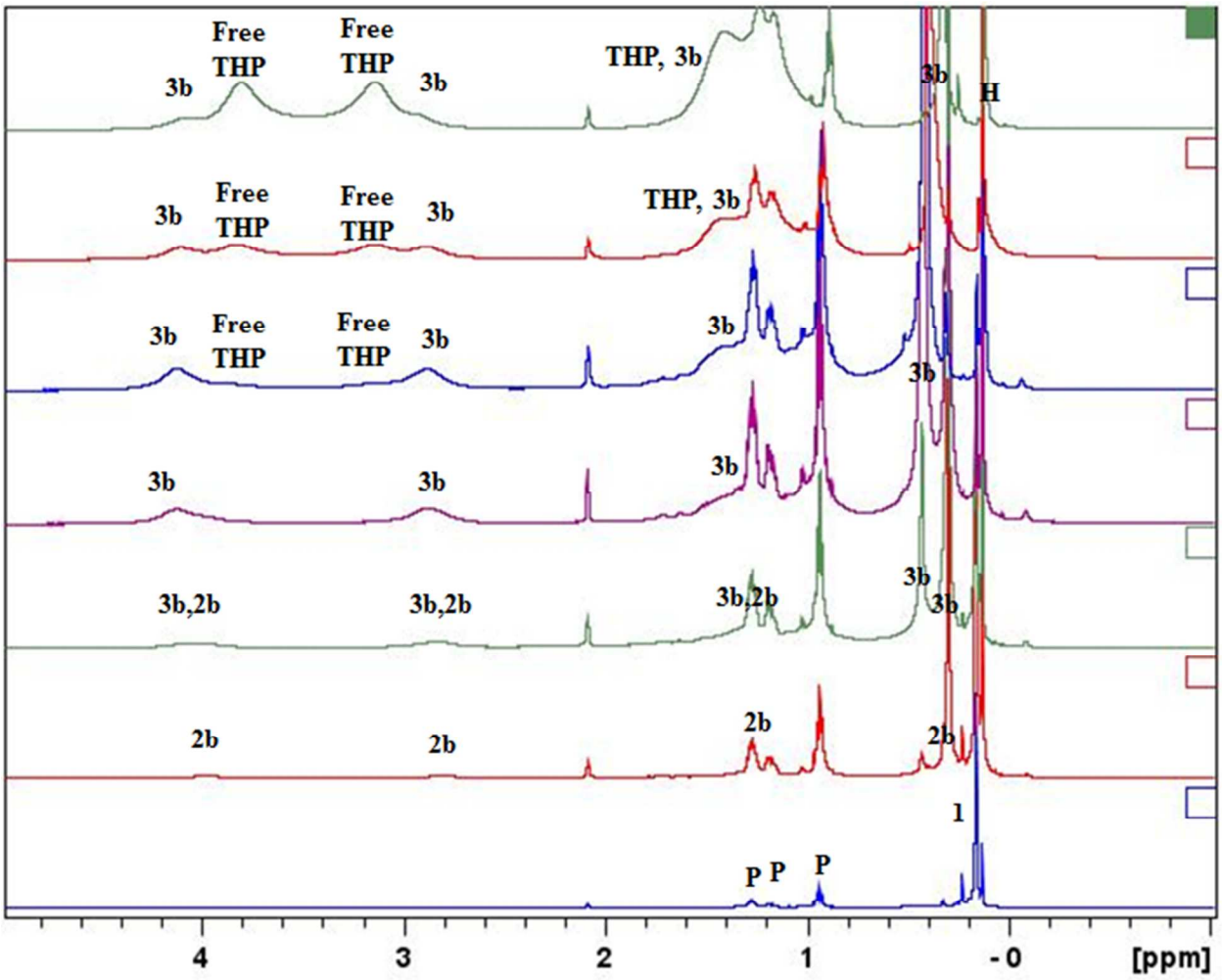


*Figure S2. [1]H NMR titration of THP into a solution of un-solvated LiHMDS **1** in tol-d8* at -60°C. *From bottom to top, 1H NMR of addition of 0, 0.34, 0.45, 0.76, 1.25, 3, and 5 eq. of THP into 1 eq. **1** in tol-d8*. P and H denotes pentane and HMDS, respectively.

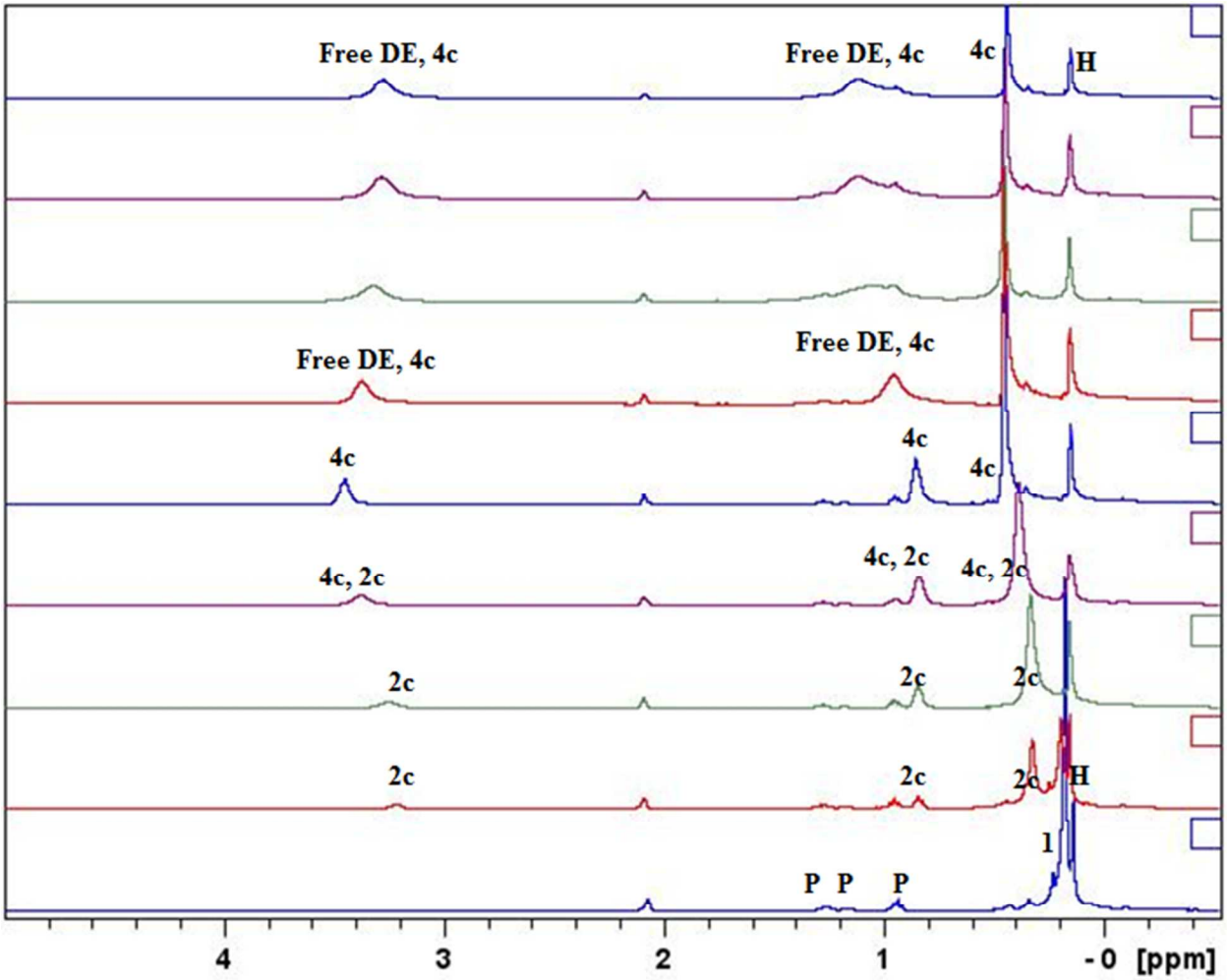


Figure S3. ^{1}*H NMR titration of diethyl ether into a solution of unsolvated LiHMDS in tol-d8* at -60°C. *From bottom to top, 1H NMR of addition of 0, 0.16, 0.42, 0.57, 0.93, 1.7, 2.5 and 2.7 eq. of diethyl ether into 1 eq.* ***1*** *in tol-d8.* P and H denotes pentane and HMDS, respectively.

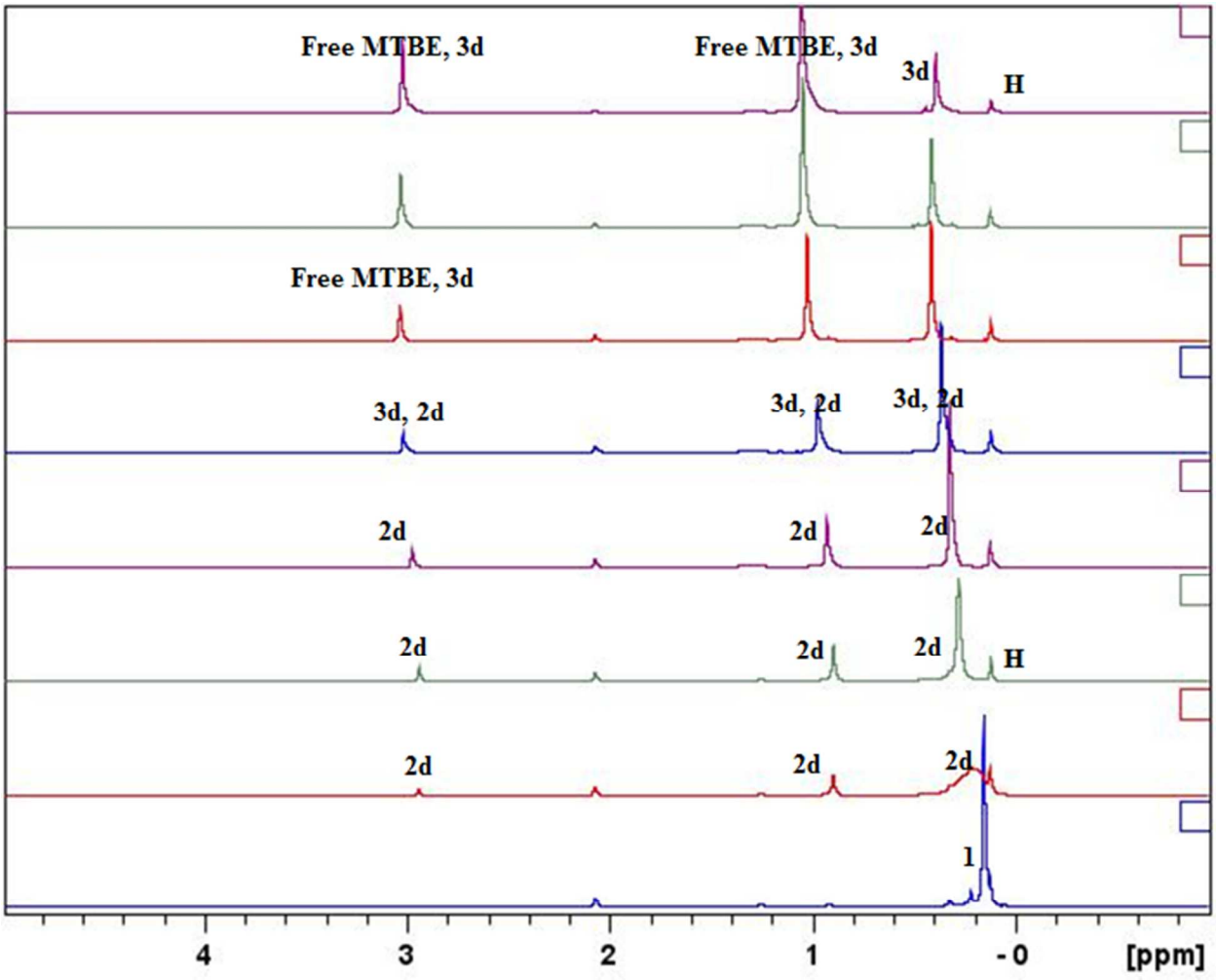


Figure S4. ^{1}*H NMR titration of MTBE into a solution of unsolvated LiHMDS in tol-d8* at -60°C. *From bottom to top, 1H NMR of addition of 0, 0.19, 0.57, 0.78, 1.8, 3.5, and 7.7 eq. of MTBE into 1 eq.* ***1*** *in tol-d8.* P and H denotes pentane and HMDS, respectively.

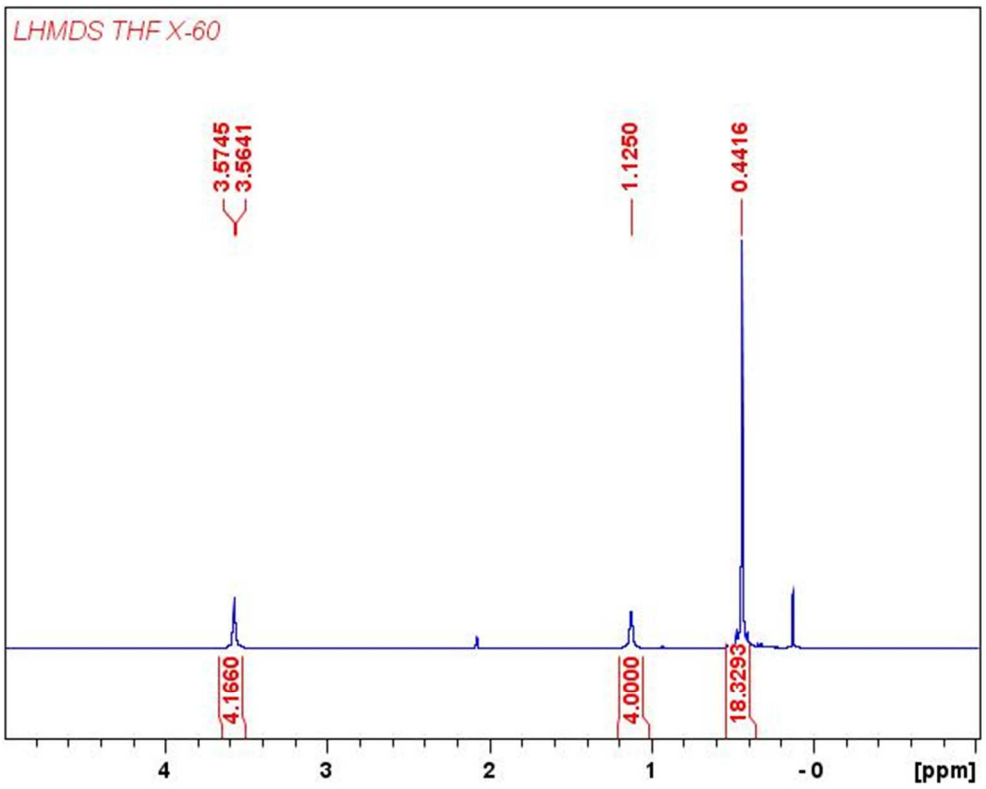


*Figure S5. [1]H NMR of [(LiHMDS)·THF]2 complex **3a** crystals dissolved in tol-d8* at -60°C.

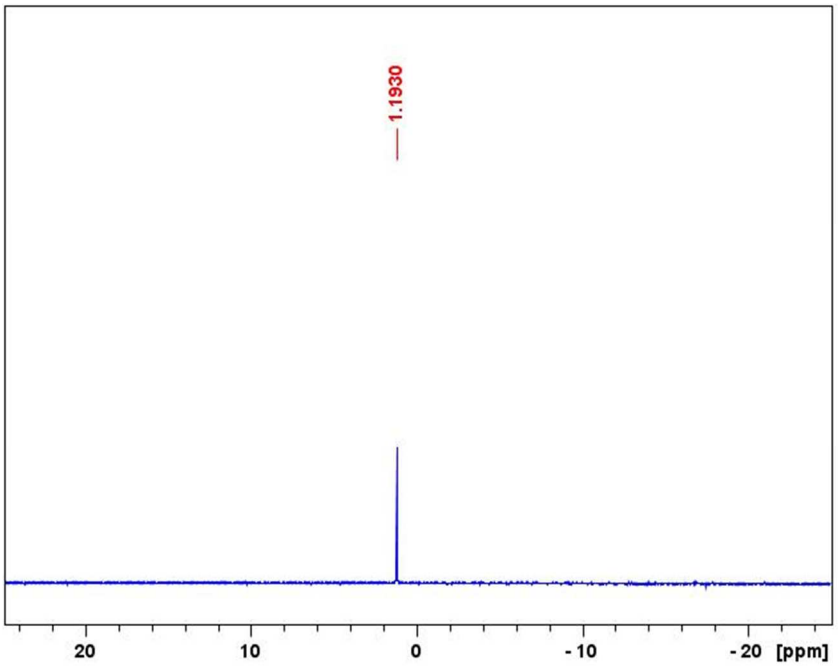


*Figure S6.[6]Li NMR of [(LiHMDS)·THF]2 complex **3a** crystals dissolved in tol-d8* at -60°C.

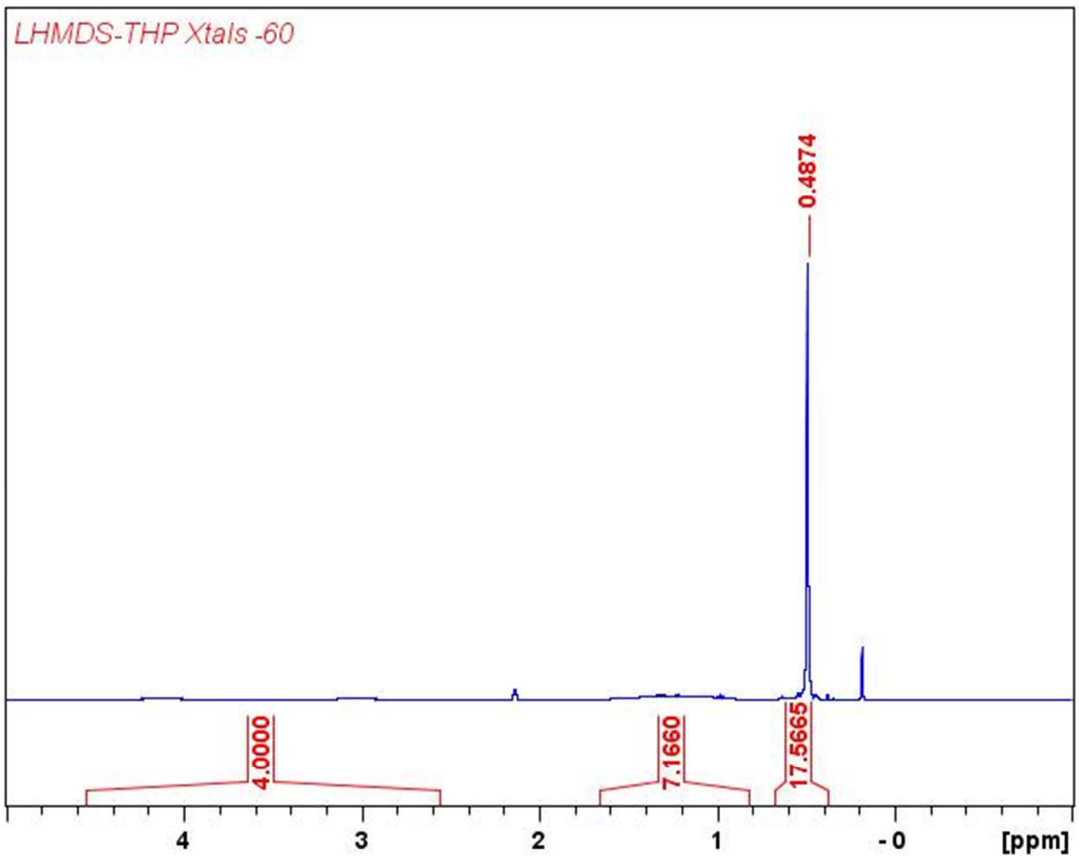


Figure S7. ^{1}*H NMR (500 MHz) of [(LiHMDS)·THP]2 complex* ***3b*** *crystals dissolved in tol-d8* at -60°C .

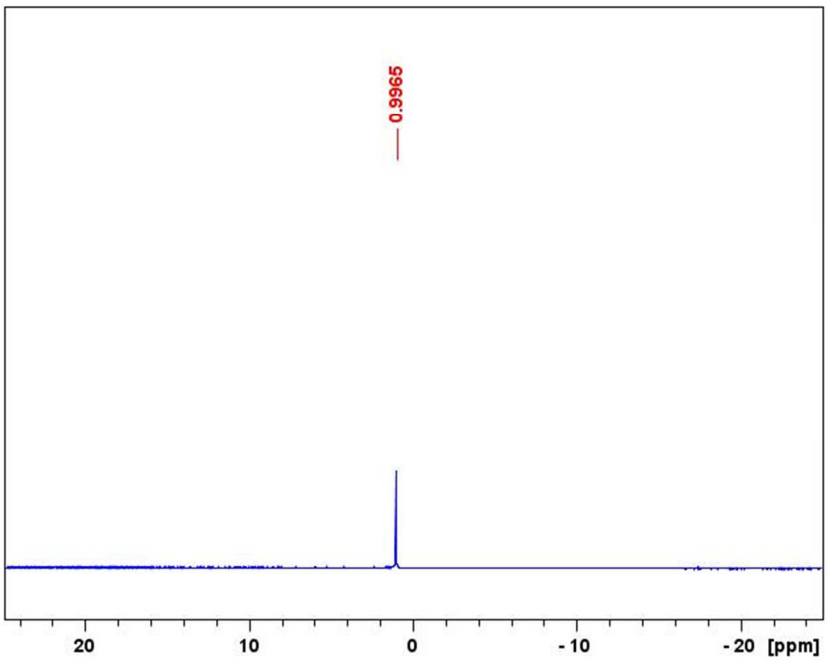


Figure S8. ^{6}*Li NMR of [(LiHMDS)·THP]2 complex* ***3b*** *crystals dissolved in tol-d8* at -60°C.

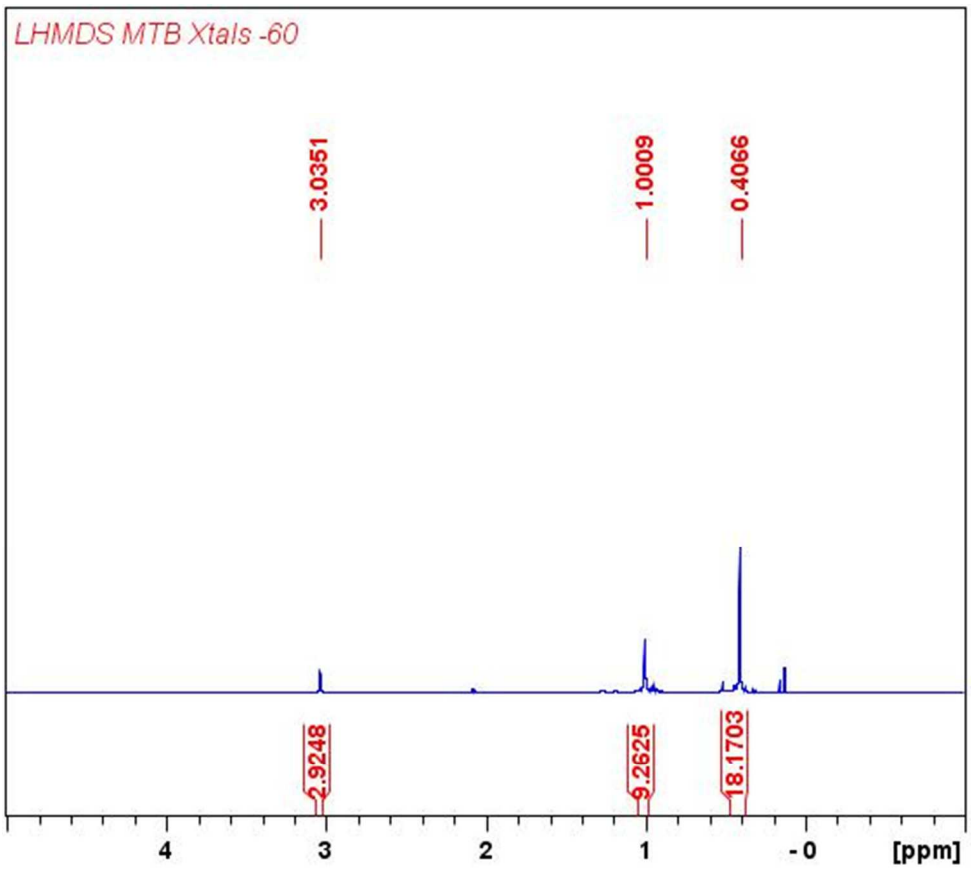


*Figure S9. [1]H NMR of [(LiHMDS)·MTBE]2 complex **3d** crystals dissolved in tol-d8* at -60°C .

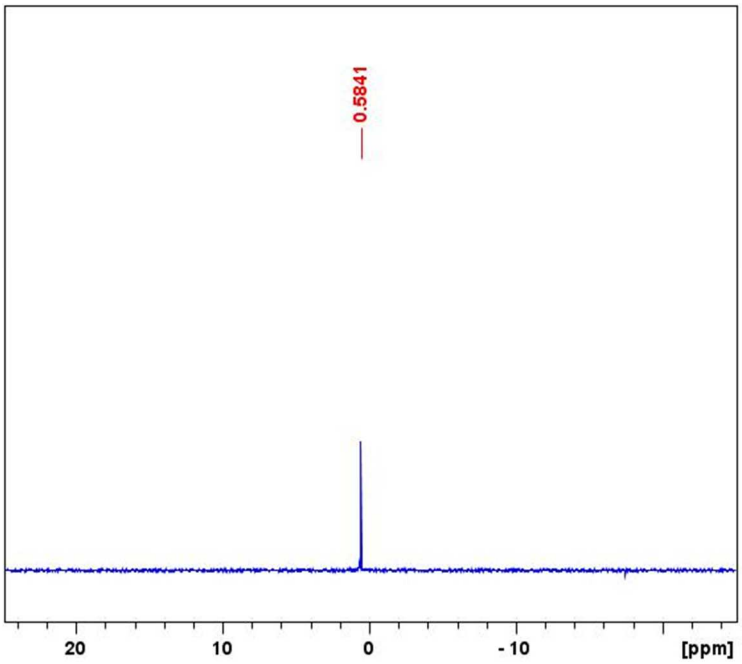


*Figure S10.[6]Li NMR of [(LiHMDS)·MTBE]2 complex **3d** crystals dissolved in tol-d8* at -60°C.

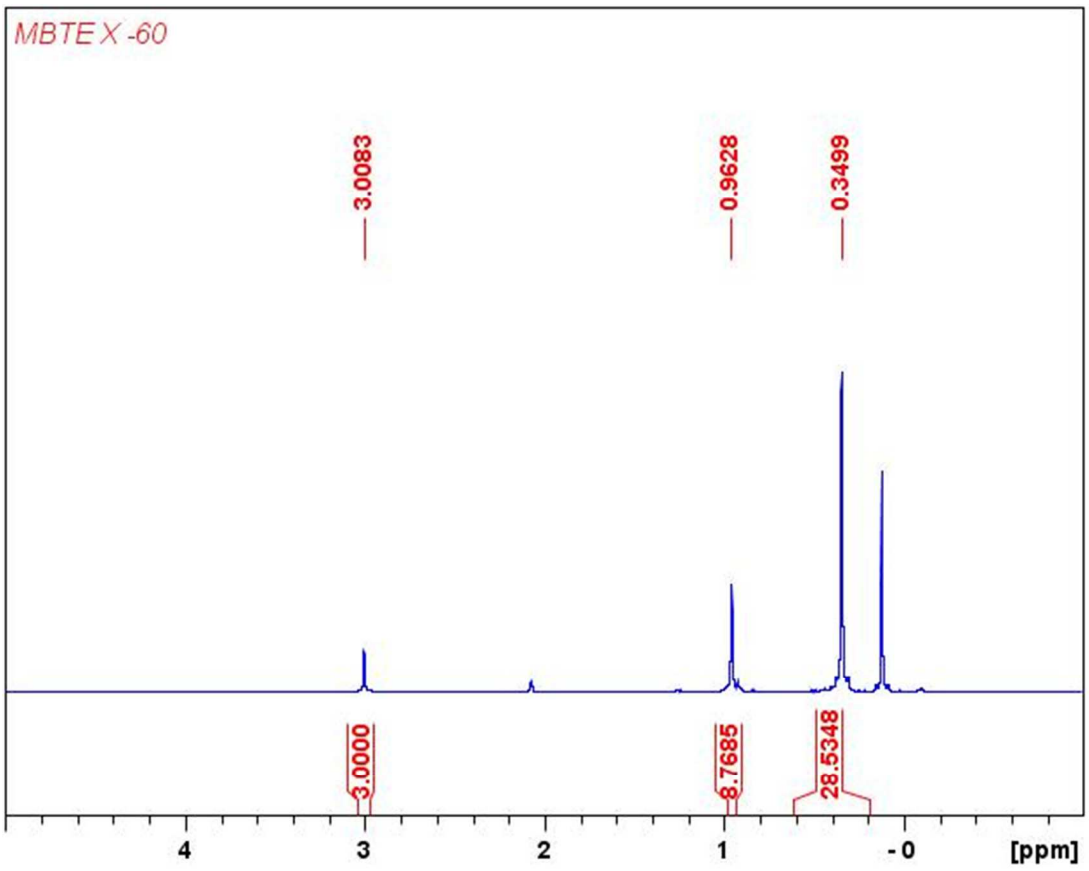


Figure S11. [1]*H NMR of (LiHMDS)2·(MTBE) complex* ***2d*** *crystals (containing slight excess MTBE) dissolved in tol-d8* at -60°C .

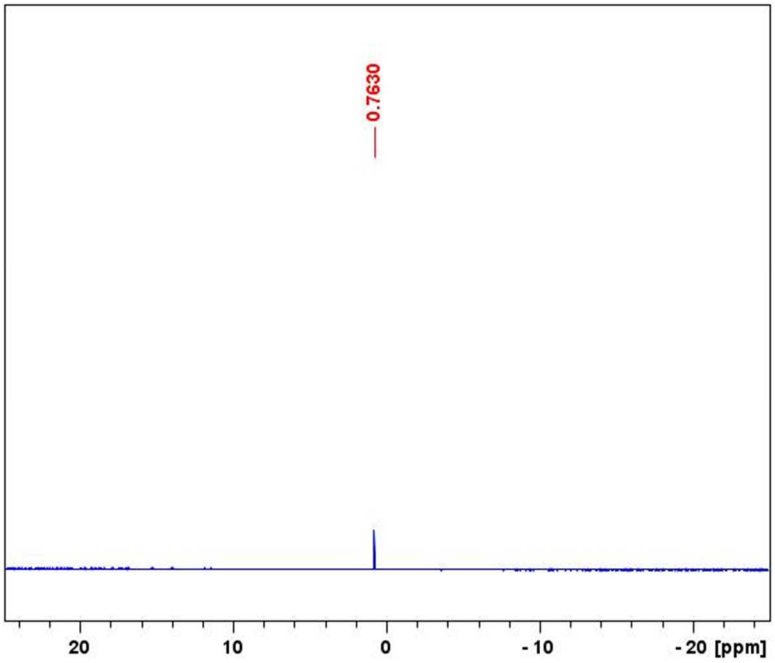
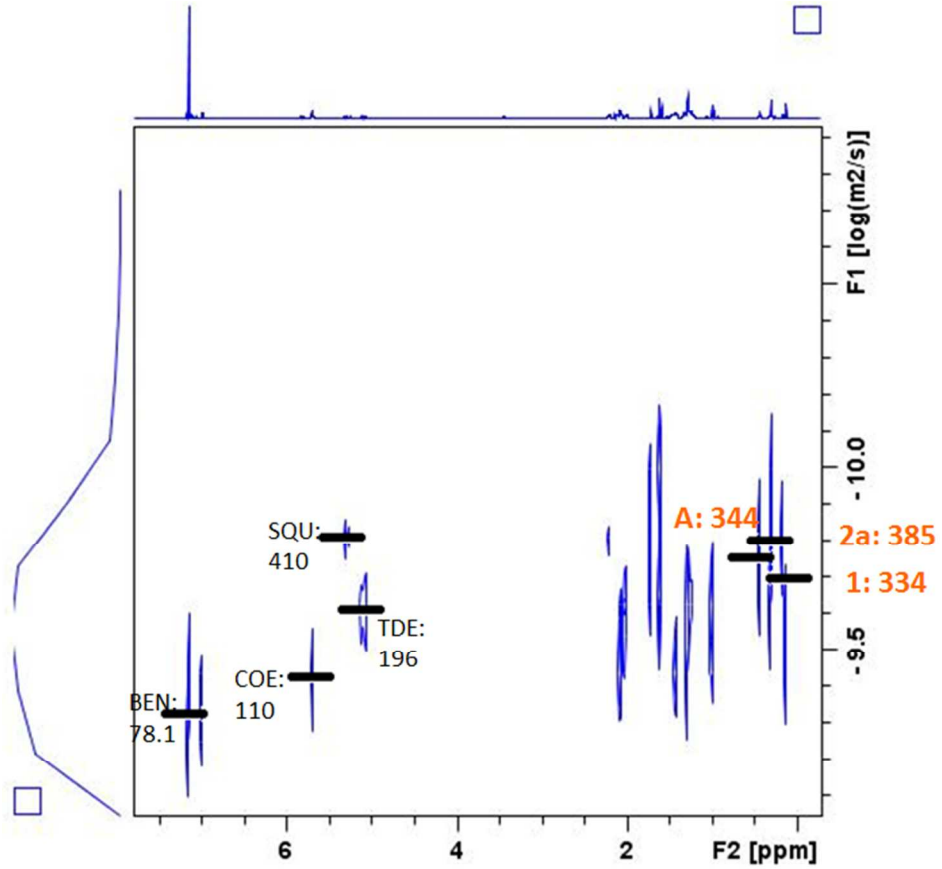


Figure S12.[6]*Li NMR of (LiHMDS)2·(MTBE) complex* ***2d*** *crystals dissolved in tol-d8* at -60°C.

Figure S13. [1]H DOSY spectra of of LiHMDS solution with 0.4 eq. THF in Tol-d8 at -60 °C.



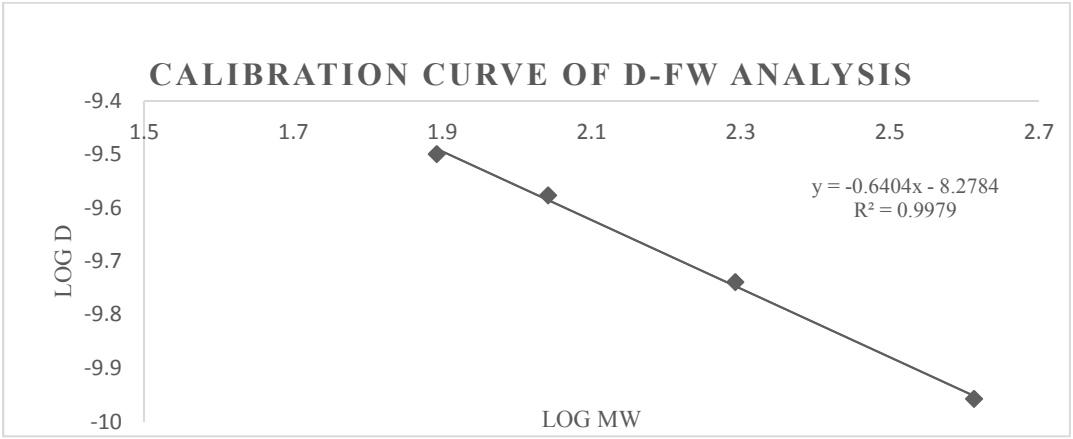


Figure S14. Calibration curve of D-FW Analysis of Table 1.

Figure S15. ^{1}H DOSY spectra of of LiHMDS solution with 1 eq. THF in Tol-d8 at -60 °C.

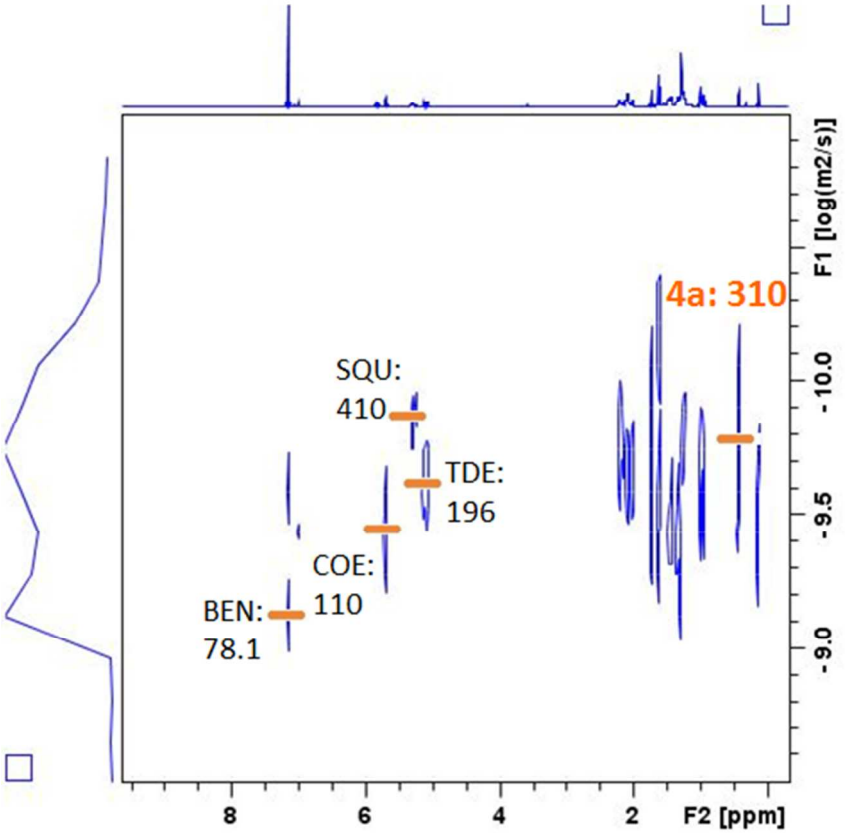


Figure S16. Calibration curve of D-FW Analysis of Table 2.

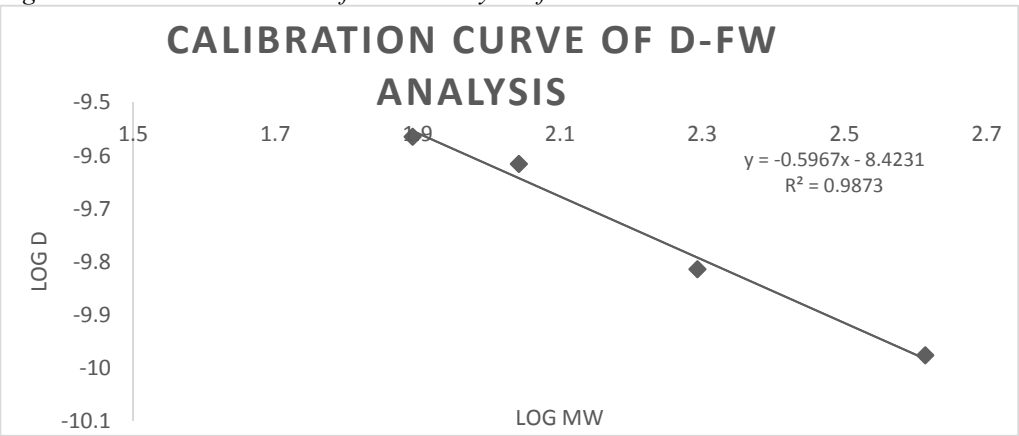


*Table S1. D-FW Analysis of ^{1}H DOSY of **3a** crystals dissolved in toluene-d_8 at −60 °C.*

Entry	Compound	FW g/mol	D m_2/s	Predicted FW g/mol	% Error
1	BEN	78.1	2.73E-10	80	3
2	COE	110	2.36E-10	104	-4
3	SQU	410.	9.83E-11	408	-0.4
4	TDE	196	1.67E-10	201	3
5	**THF**	**472**	**1.04E-10**	**352**	
6	**3a**	**472**	**9.02E-11**	**446**	5

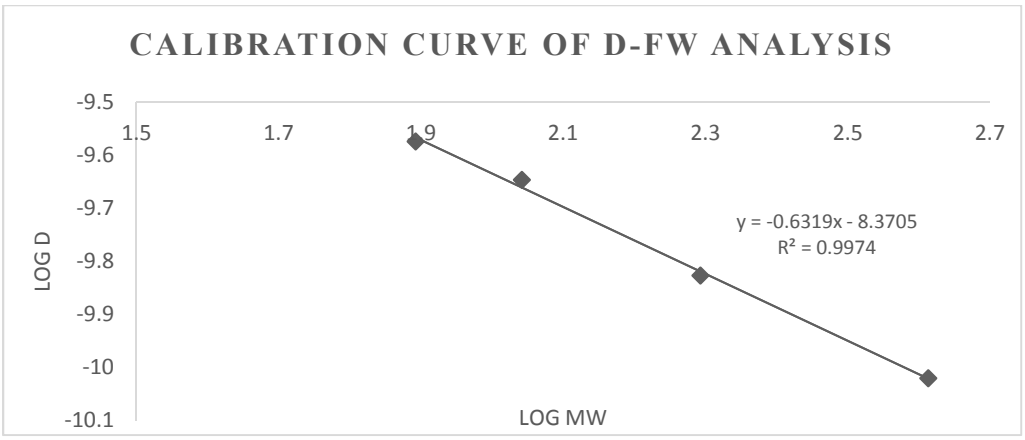
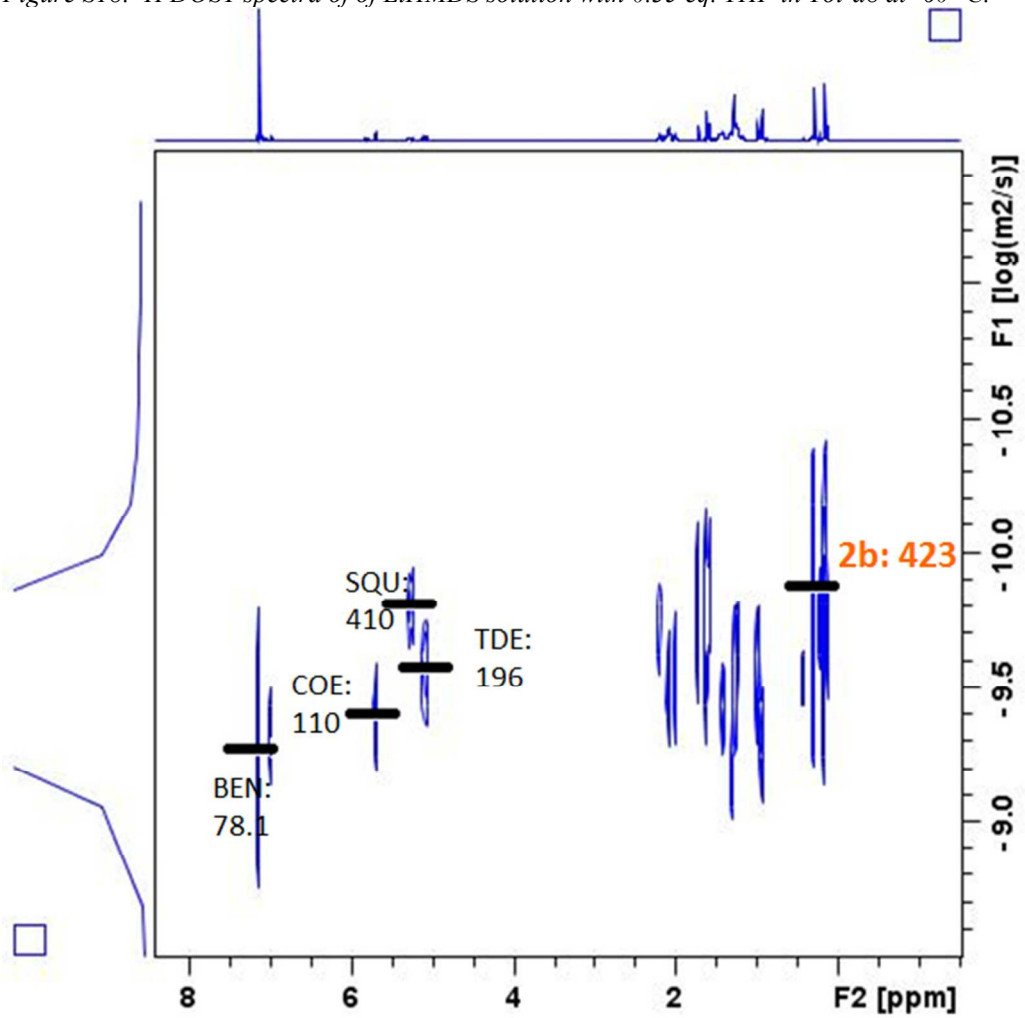


Figure S17. Calibration curve of D-FW Analysis of Table S1.

Figure S18. ^{1}H DOSY spectra of of LiHMDS solution with 0.35 eq. THP in Tol-d8 at -60 °C.



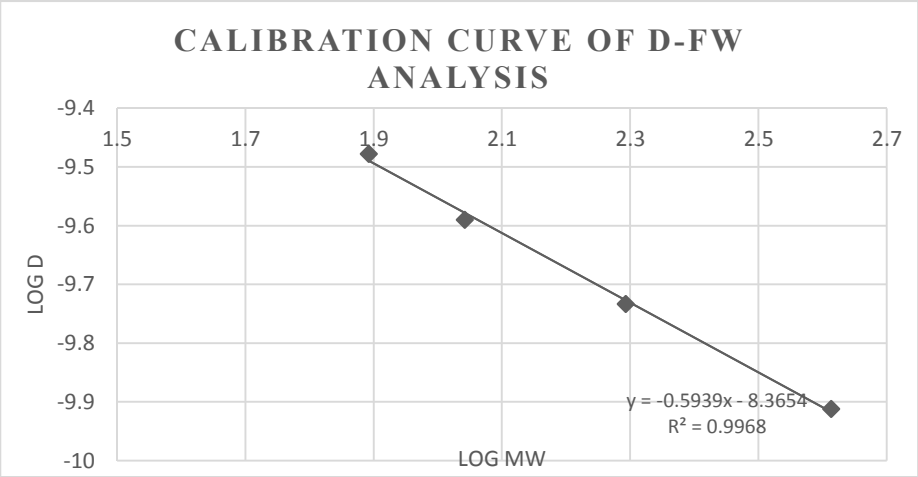
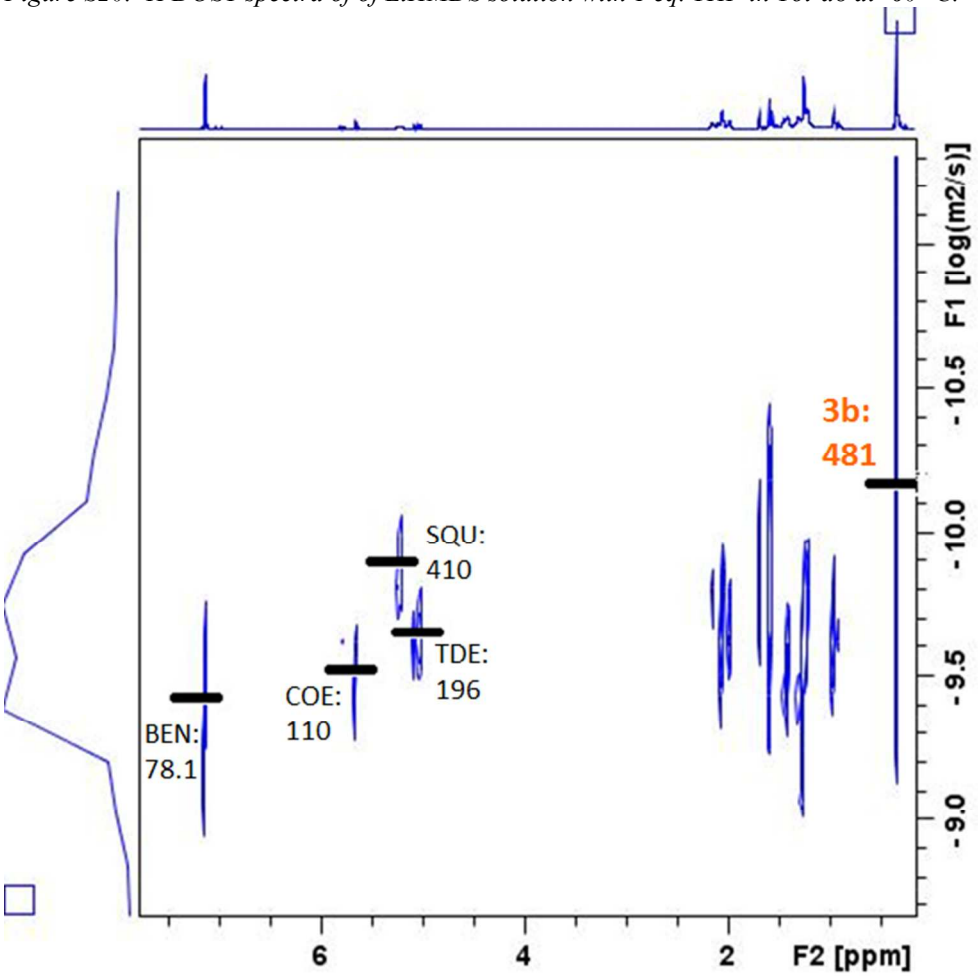


Figure S19. Calibration curve of D-FW Analysis of Table 3.

Figure S20. ^{1}H DOSY spectra of of LiHMDS solution with 1 eq. THP in Tol-d8 at -60 °C.



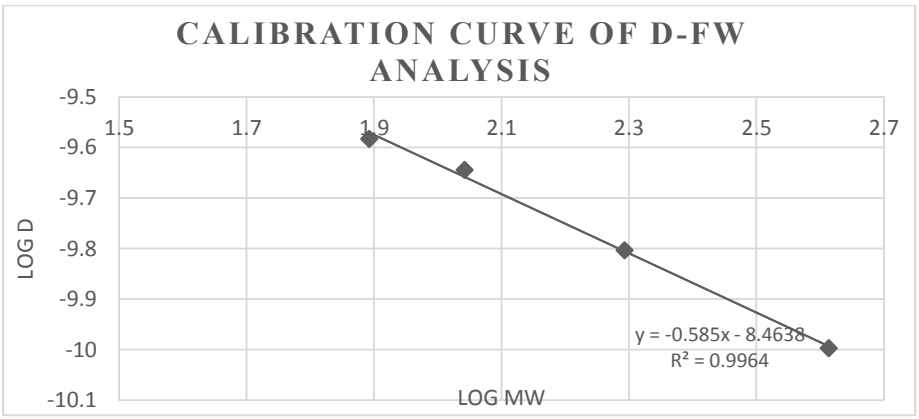


Figure S21. Calibration curve of D-FW Analysis of Table 4

*Figure S22. ^{1}H DOSY of **3b** crystals dissolved in toluene-d_8 at −60 °C.*

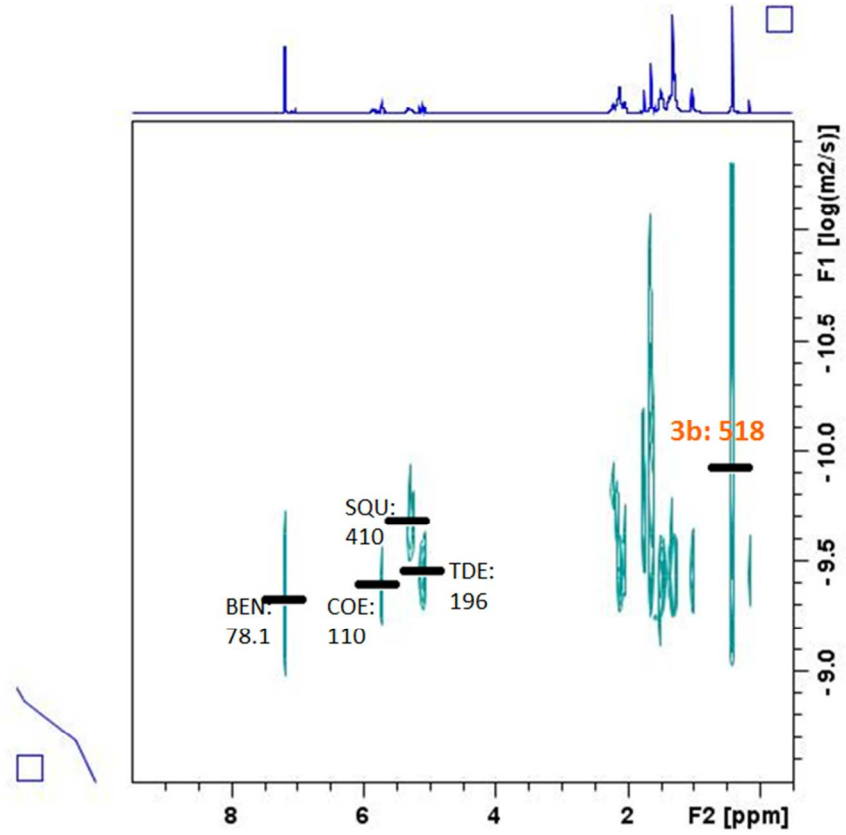


*Table S2. D-FW Analysis of ^{1}H DOSY of **3b** crystals dissolved in toluene-d_8 at −60 °C.*

Entry	Compound	FW g/mol	D m_2/s	Predicted FW g/mol	% Error
1	BEN	78.1	3.53E-10	79	2
2	COE	110	2.99E-10	108	-1
3	SQU	410.	1.43E-10	416	1
4	TDE	196	2.18E-10	192	1
5	**3b**	**506**	1.27E-10	**518**	2

Figure S23. Calibration curve of D-FW Analysis of Table S2.

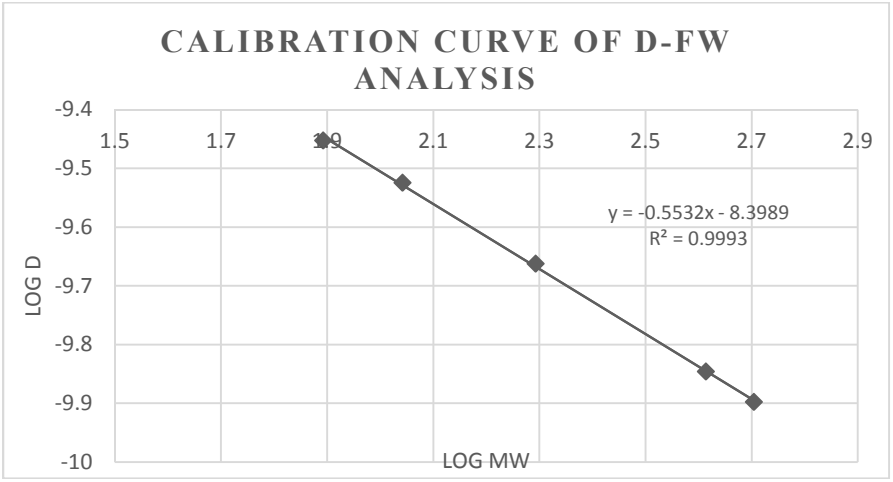


Figure S24. ^{1}H DOSY spectra of LiHMDS solution with 0.5 eq. DE in Tol-d8 at -60 °C.

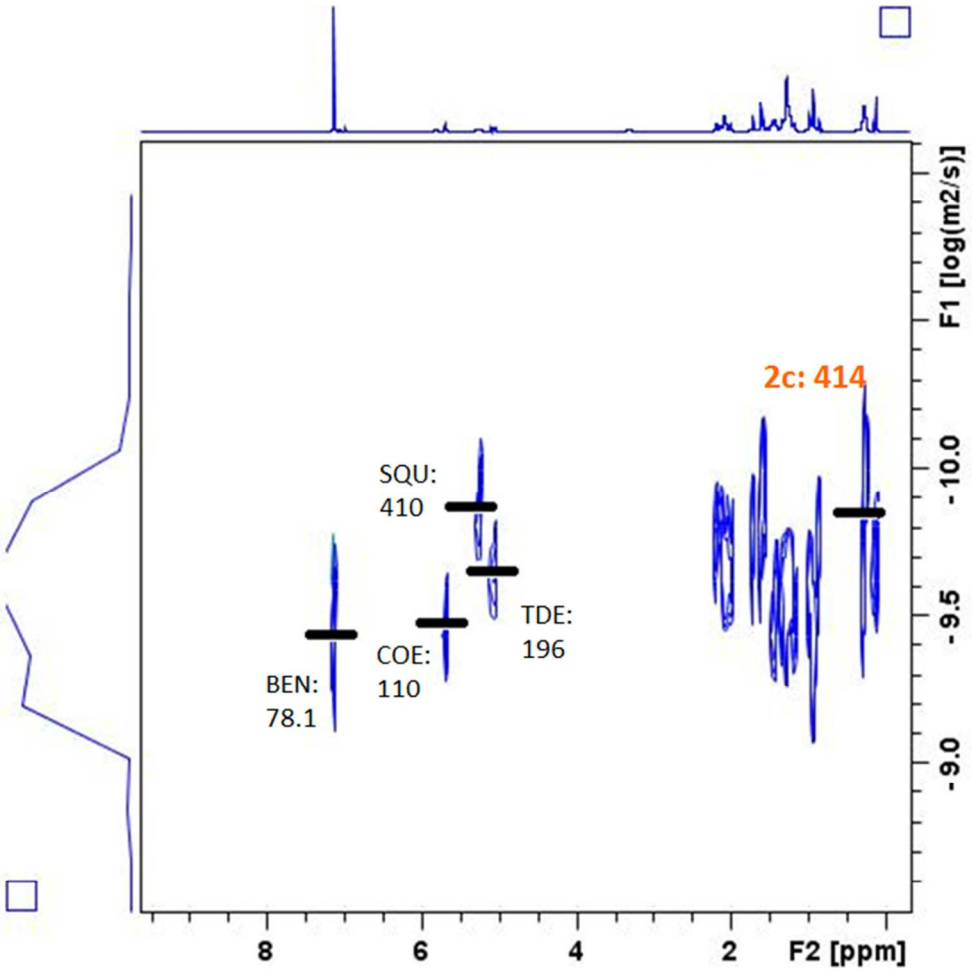


Table S3. D-FW Analysis of ^{1}H DOSY of LiHMDS solution with 0.5 eq. DE in toluene-d_8 at −60 °C.

Entry	Compound	FW g/mol	D m_2/s	Predicted FW g/mol	% Error
1	BEN	78.1	2.4850E-10	79	2
2	COE	110	2.0390E-10	109	-0.3
3	SQU	410.	8.8900E-11	420	2
4	TDE	196	1.4610E-10	188	-4
5	**2c**	**409**	8.9730E-11	**414**	1

Figure S25. Calibration curve of D-FW Analysis of Table S3.

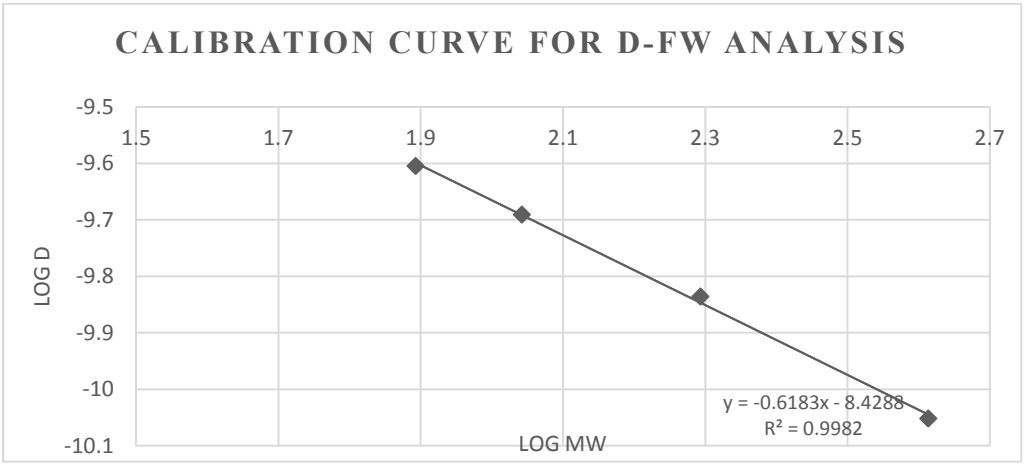


Figure S26. ^{1}H DOSY spectra of LiHMDS solution with 1 eq. DE in Tol-d8 at -60 °C.

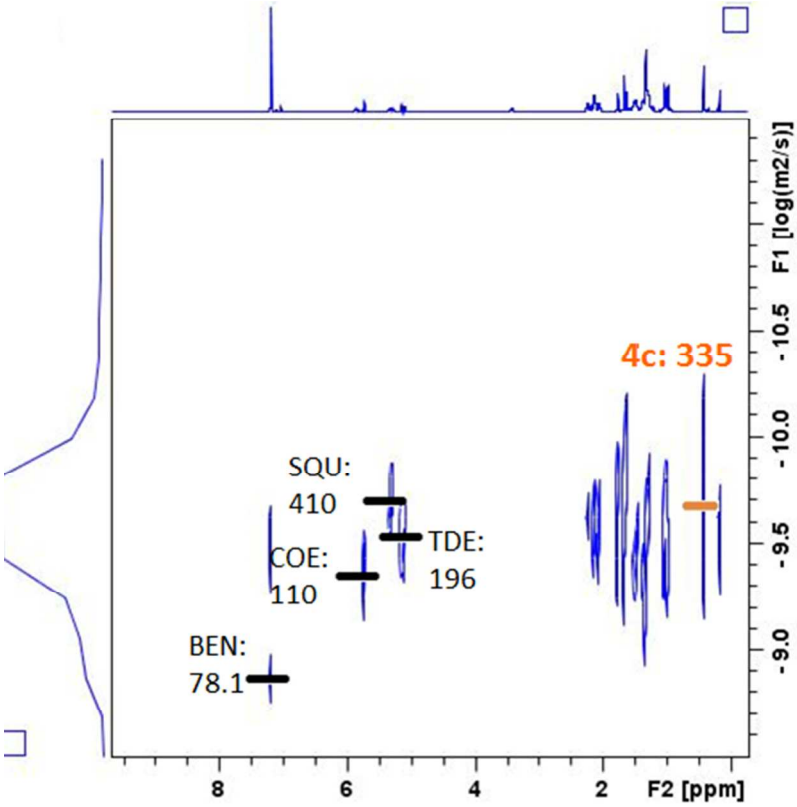


Table S4. D-FW Analysis of ^{1}H DOSY of LiHMDS solution with 1 eq. DE in Tol-d8 at -60 °C.

Entry	Compound	FW g/mol	D m_2/s	Predicted FW g/mol	% Error
1	BEN	78.1	3.10E-10	80	2
2	COE	110	2.67E-10	105	-4
3	SQU	410.	1.27E-10	410	-0.1
4	TDE	196	1.88E-10	200	1
5	**4c**	**315**	1.42E-10	**335**	6

Figure S27. Calibration curve of D-FW Analysis of Table S4.

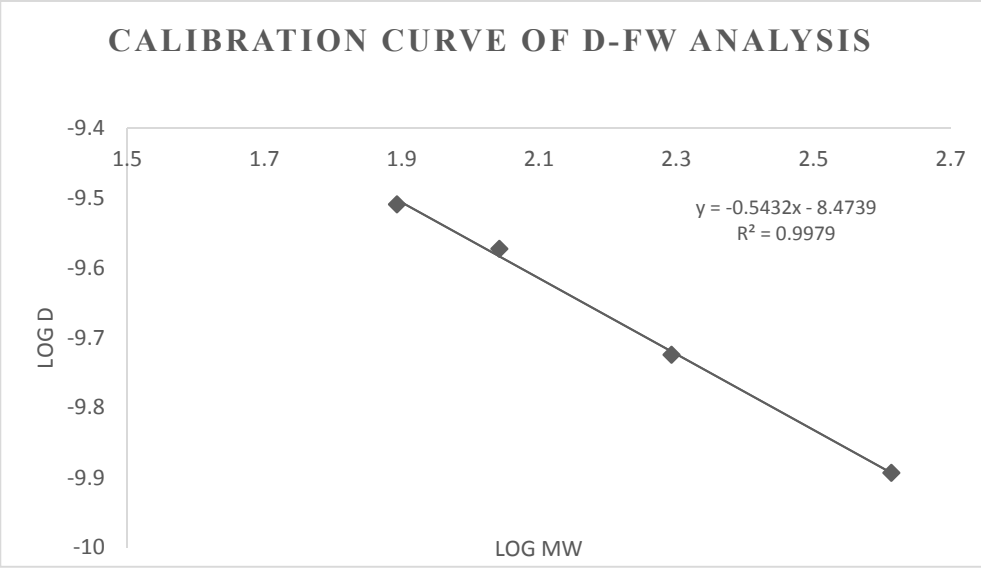


Figure S28. ^{1}H DOSY spectra of of LiHMDS solution with 1 eq. MTBE in Tol-d8 at -60 °C.

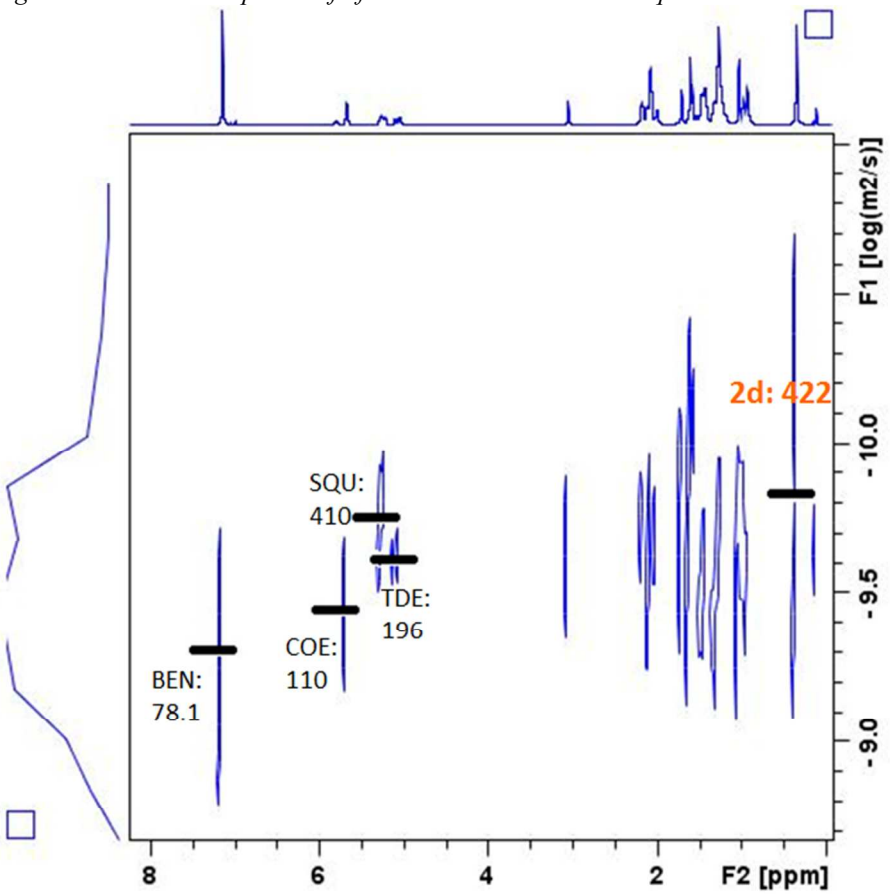


Table S5. D-FW Analysis of ^{1}H DOSY of LiHMDS solution with 1 eq. MTBE in toluene-d_8 at −60 °C.

Entry	Compound	FW g/mol	D m_2/s	Predicted FW g/mol	% Error
1	BEN	78.1	2.96E-10	71	-8
2	COE	110	2.34E-10	108	-1
3	SQU	410.	1.18E-10	360	-12
4	TDE	196	1.46E-10	250	27
5	**2d**	**422**	1.08E-10	**422**	0.1

Figure S29. Calibration curve of D-FW Analysis of Table S5.

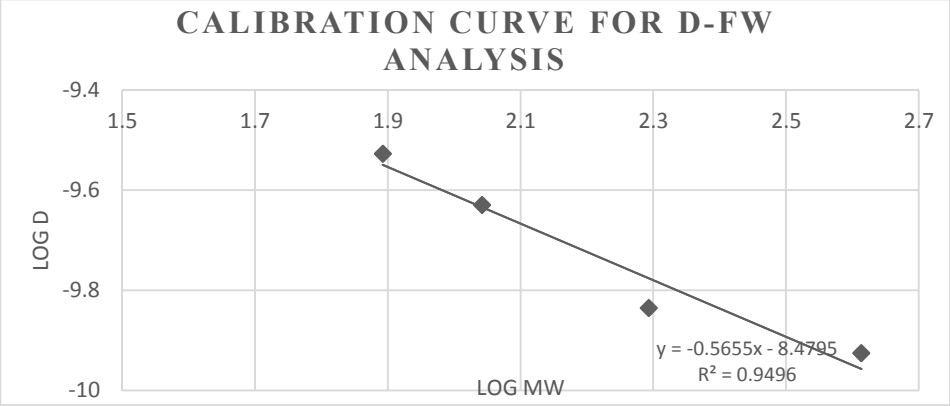


Figure S30. ^{1}H DOSY spectra of of LiHMDS solution with 2 eq. MTBE in Tol-d8 at -60 °C.

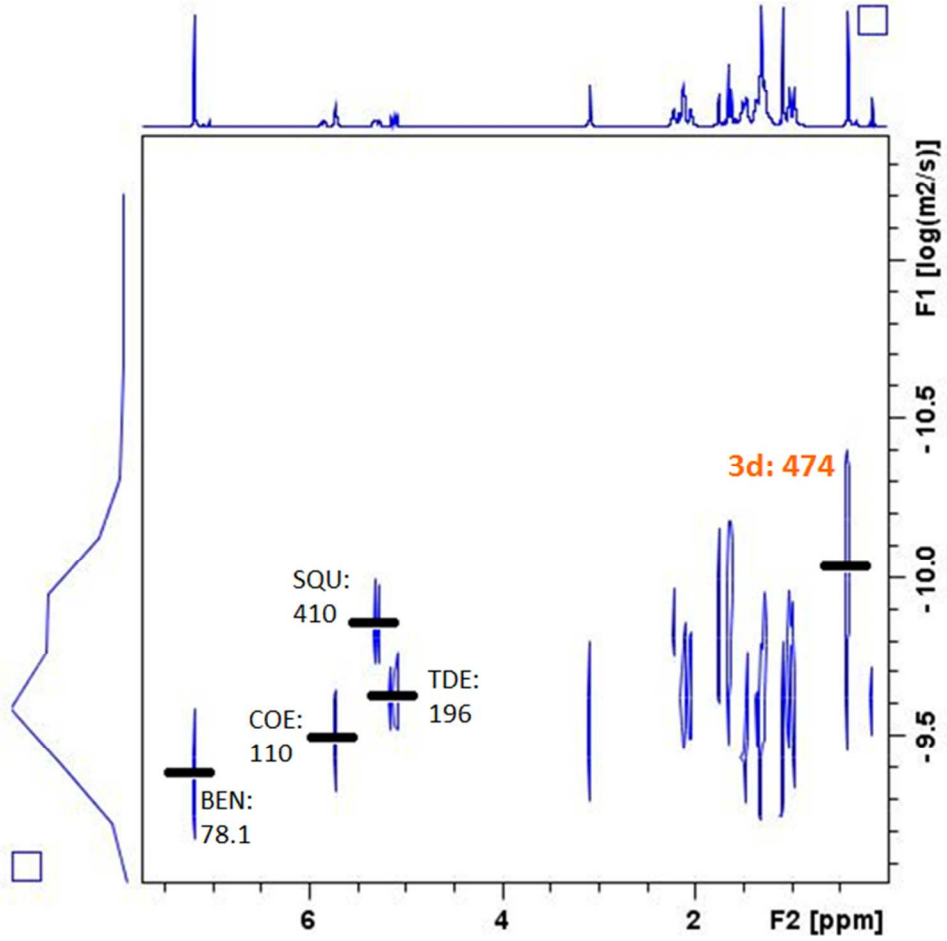


Table S6. D-FW Analysis of ^{1}H DOSY of LiHMDS solution with 2 eq. MTBE in toluene-d_8 at −60 °C.

Entry	Compound	FW g/mol	D m_2/s	Predicted FW g/mol	% Error
1	BEN	78.1	2.96E-10	80	2
2	COE	110	2.34E-10	104	-5
3	SQU	410.	1.18E-10	408	-0.5
4	TDE	196	1.46E-10	202	3
5	**3d**	**494**	1.08E-10	**474**	-4

Figure S31. Calibration curve of D-FW Analysis of Table S6.

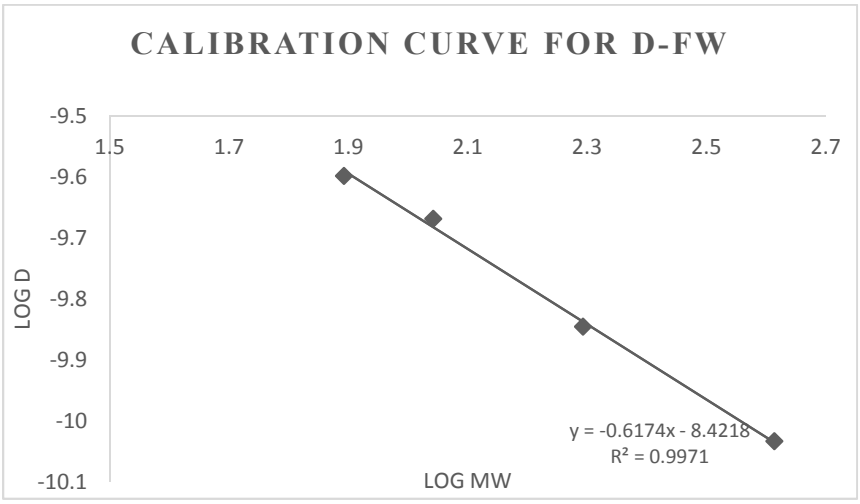


*Figure S32. ^{1}H DOSY of **2d** crystals dissolved in toluene-d_8 at −60 °C.*

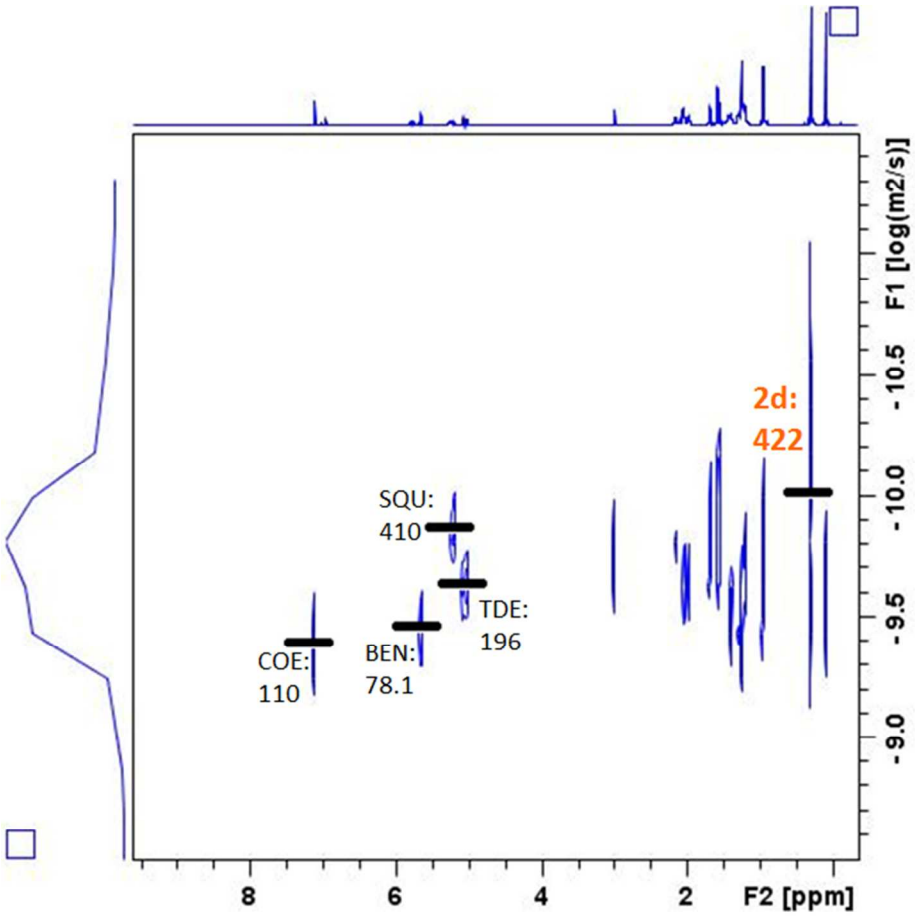


*Table S7. D-FW Analysis of ^{1}H DOSY of **2d** crystals dissolved in toluene-d_8 at −60 °C.*

Entry	Compound	FW g/mol	D m_2/s	Predicted FW g/mol	% Error
1	BEN	78.1	2.52E-10	80	3
2	COE	110	2.20E-10	106	-6
3	SQU	410.	1.04E-10	406	-1
4	TDE	196	1.53E-10	205	4.6
5	**2d**	**422**	1.00E-10	**422**	0.1

Figure S33. Calibration curve of D-FW Analysis of Table S7.

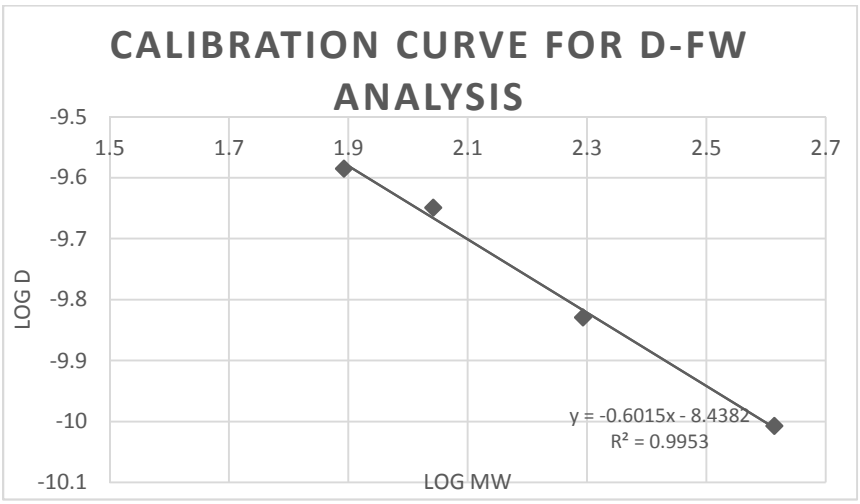


*Figure S34. ^{1}H DOSY of **3d** crystals dissolved in toluene-d_8 at −60 °C.*

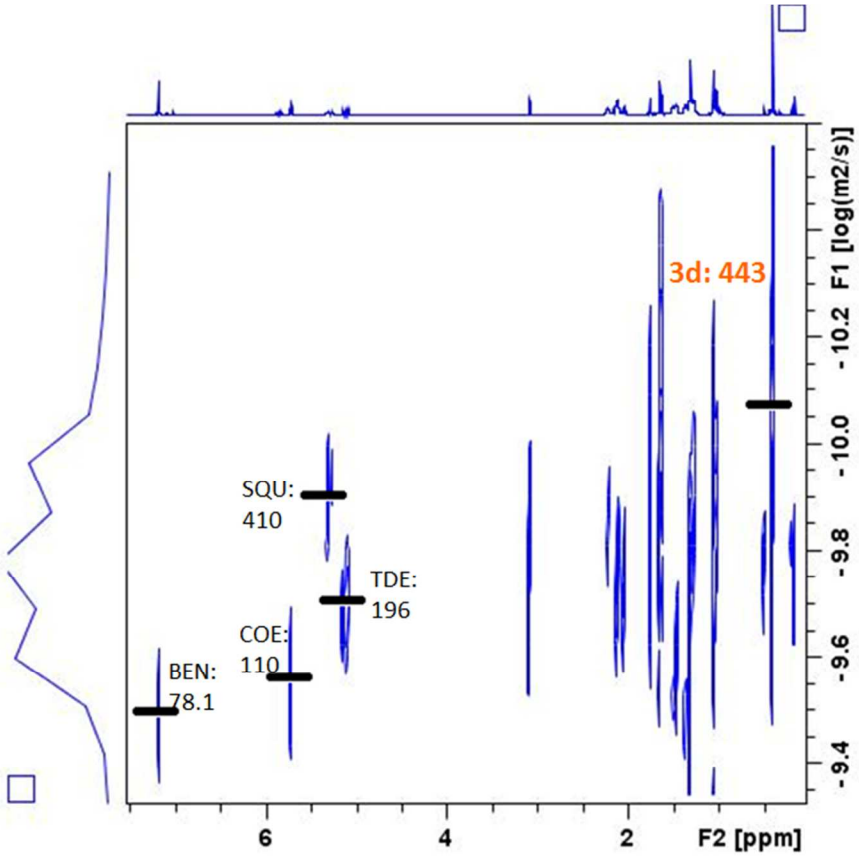


*Table S8. D-FW Analysis of ^{1}H DOSY of **3d** crystals dissolved in toluene-d_8 at −60 °C. *A lower molecular weight predicted, most likely due to a slight amount of mono-solvated dimer crystals **2d**.*

Entry	Compound	FW g/mol	D m_2/s	Predicted FW g/mol	% Error
1	BEN	78.1	2.52E-10	80	3
2	COE	110	2.20E-10	104	-6
3	SQU	410.	1.04E-10	408	-0.3
4	TDE	196	1.53E-10	202	3
5	**3d**	**494**	1.00E-10	**443**	-10*

Figure S35. Calibration curve of D-FW Analysis of Table S8.

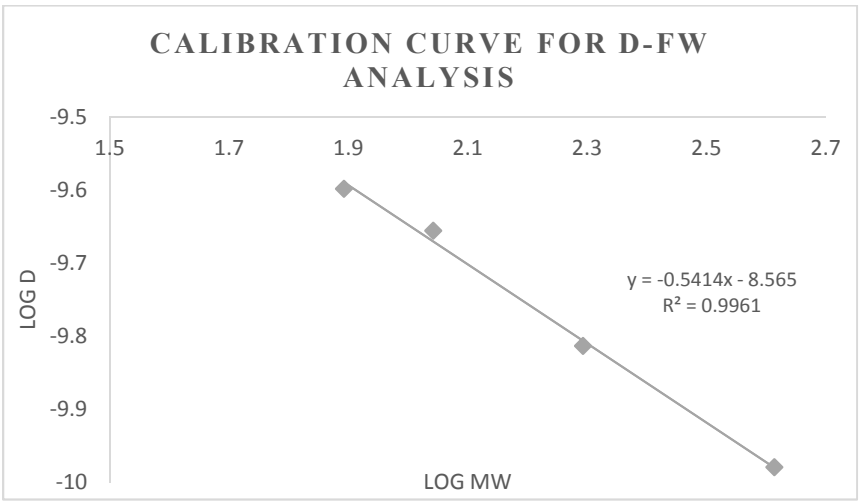


Figure S36. ^{1}H DOSY spectra of of LiHMDS solution with 0.35 eq. *t*-butyl acetate in tol-d8 at -60 °C.

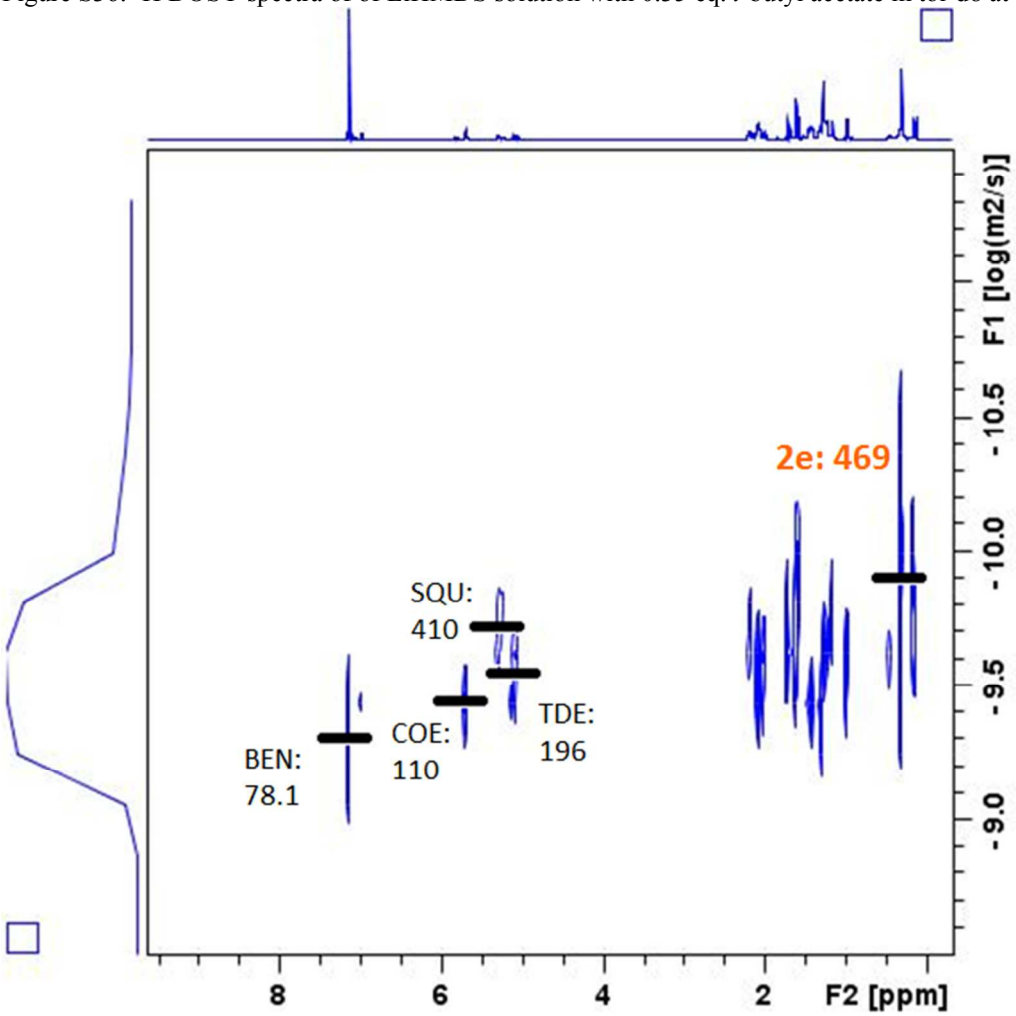


Figure S37. Calibration curve of D-FW Analysis of Table 5.

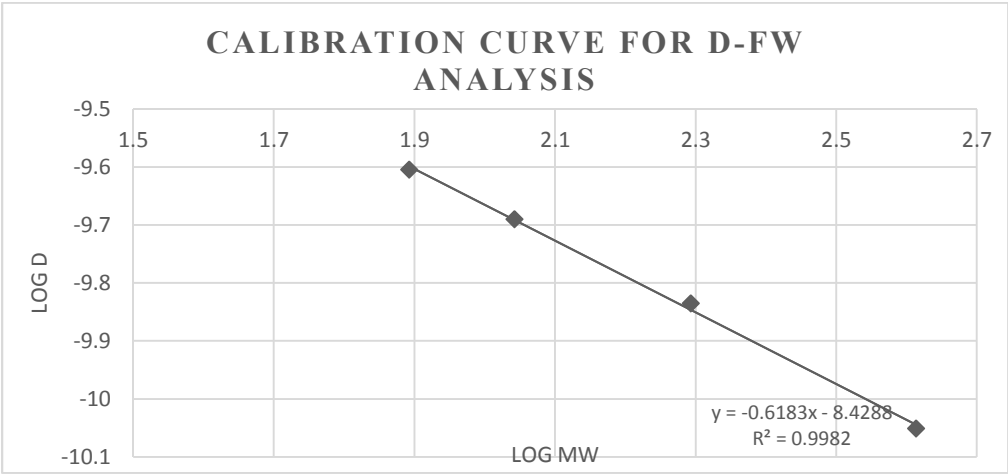


Figure S38. ^{1}H DOSY spectra of of LiHMDS solution with 1 eq. *t*-butyl acetate in tol-d8 at -60 °C.

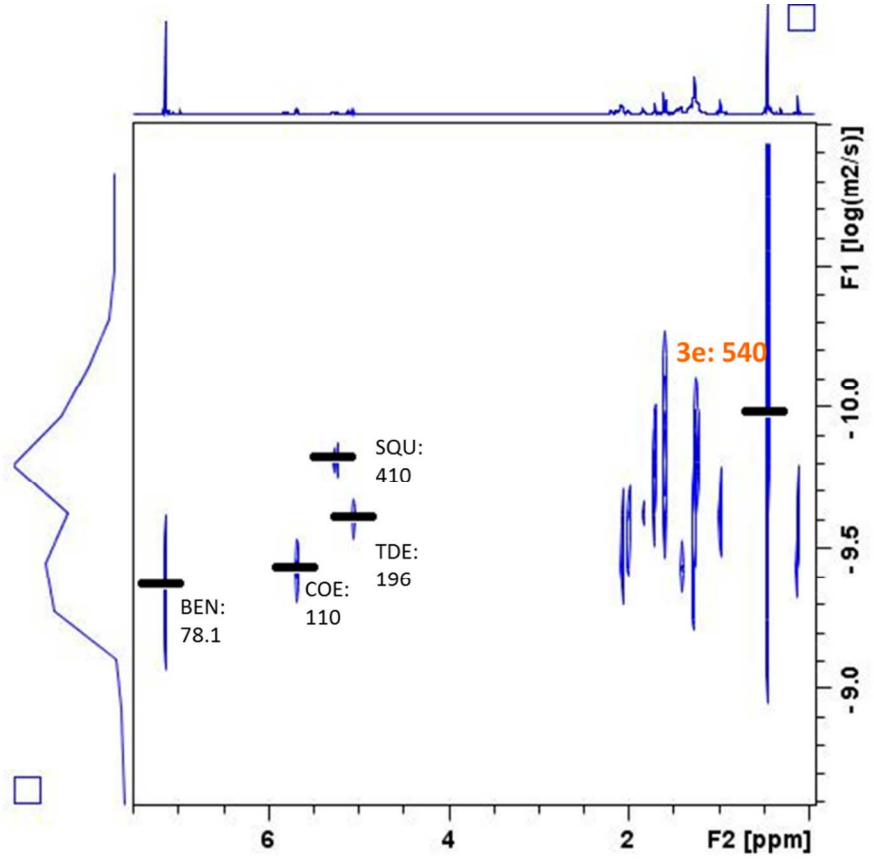
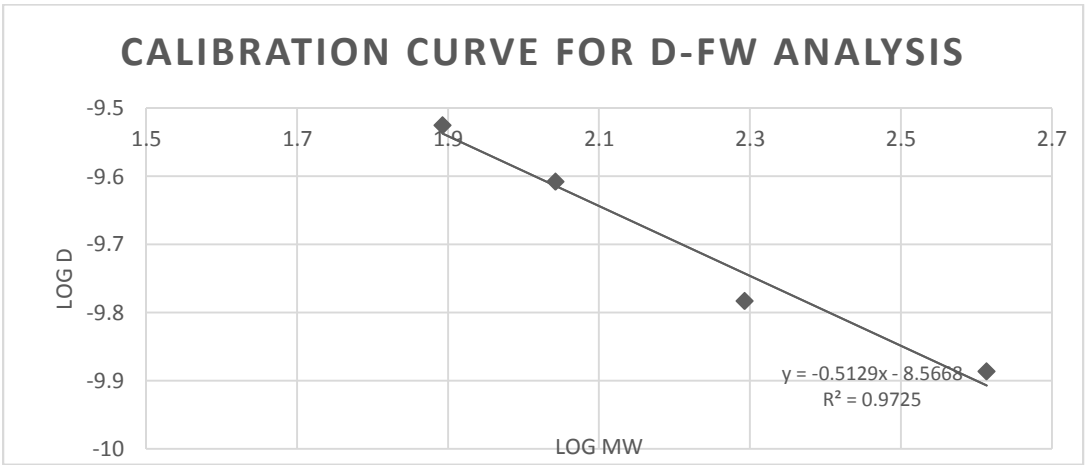


Figure S39. Calibration curve of D-FW Analysis of Table 6.



Determination of Binding Constants

The general equilibrium binding constants between a LiHMDS molecule and ligand is expressed by:

$$a[H] + b[L] \rightleftharpoons c[H_a \cdot L_b] \quad (1)$$

$$K_a = \frac{[H_a \cdot L_b]^c}{[H]^a[L]^b} \quad (2)$$

Diffusion coefficient is the weighted average of bound and unbound ligands, where ρ represents fraction of bound ligands

The fraction of bound ligands can be calculated using D_{obs}, the observed weighted average diffusion coefficient of the ligand, D_{free}, the diffusion coefficient of the free ligand, and $D_{complex}$, the diffusion coefficient of the complex.

$$Dobs = \rho Dcomplex + (1 - \rho)Dfree$$

$$\rho = \frac{Dobs - Dfree}{Dcomplex - Dfree}$$

For 1:1 binding model, a=b=c=1

$$[H] + [L] \rightleftharpoons [H \cdot L] \quad (1)$$

$$K_a = \frac{[H \cdot L]}{[H][L]} \quad (2)$$

Since ρ represents fraction of bound ligands

$$\rho = \frac{[H \cdot L]}{[H] + [H \cdot L]} \quad (7)$$

Eq. 2 and Eq. 3 can be combined and a non-linear regression of titration data using equation 6 will give binding constant K_a (M^{-1}):

$$\rho = \frac{Ka[H]}{1 + Ka[H]} \quad (5)$$

For 2:1 binding model, a= c=1, b=2

$$[H] + 2[L] \rightleftharpoons [H \cdot L_2] \quad (1)$$

$$K_a = \frac{[H \cdot L_2]}{[H][L]^2} \quad (2)$$

Since ρ represents fraction of bound ligands

$$\rho = \frac{[H \cdot L_2]}{[H] + [H \cdot L_2]} \quad (8)$$

Eq. 2 and Eq. 3 can be combined and a non-linear regression of titration data using Eq. 8 will give overall binding constant K_a (M^{-2}):

$$\rho = \frac{2K_a[H][L]}{1 + 2K_a[H][L]} \quad (6)$$

H-DOSY/Titration Experiments

The stock solutions of **1** for titration experiment were prepared in tol-d_8 and kept at -70°C. The LiHMDS-ether systems for NMR measurements were prepared by titrating the appropriate volumes of stock solutions of **1** into 0.1-0.2 M of ligand in tol-d_8 at -70°C and allowed to equilibrate for 10 minutes before NMR measurement at -60°C. The volume of each addition and the total concentration of complex [H_t] at each titration point was estimated via NMR integrations using TMS and benzene as internal reference. [H] and [L] were estimated via experimentally determined fraction of bound ligands from diffusion experiments/NMR integrations and non-linear regression fitting of measured values using Excel/Matlab. Regression analyses use data points $0.2 \leq \rho \leq 0.8$ to minimize errors. Replication of titration experiments within 0.1-0.2M were conducted to obtain errors.

Figure S40. Fraction of Bound THP vs. [LiHMDS} estimated using NMR Integration at -60°C in a titration of LiHMDS into 0.1M of THP.

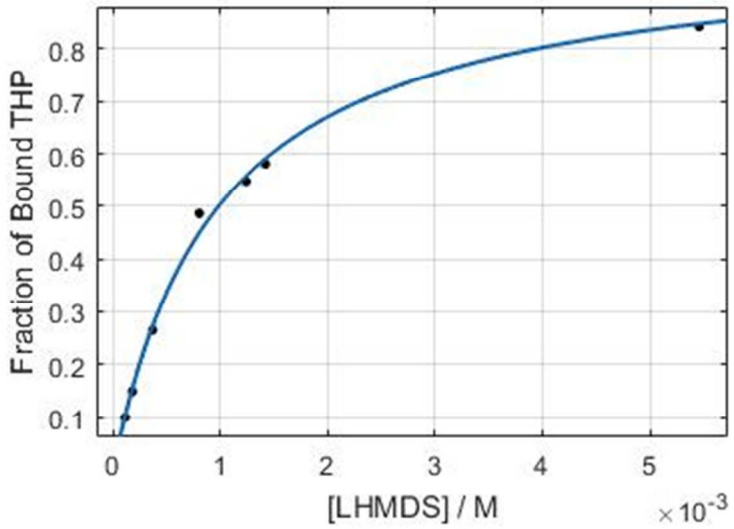


Figure S41. Fraction of Bound Acetate vs. [LiHMDS} estimated using NMR Integration at -60°C in a titration of LiHMDS into 0.1M of tert-butyl Acetate.

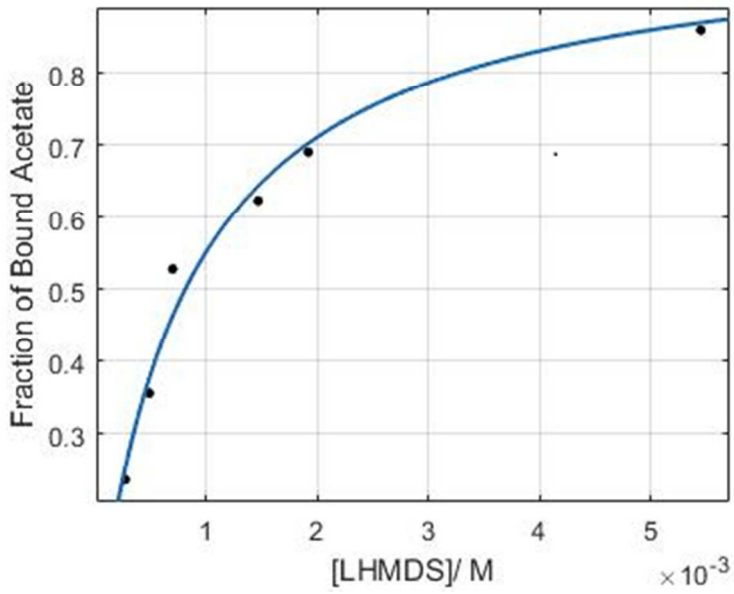


Figure S42. Diffusion Coefficients of THF vs. estimated [THF][LiHMDS] at -60°C in a titration of LiHMDS into 0.1M of THF. Measured $D_{complex}$ 4a is 9.72±0.8x10^{-11} m^2/s and D_{free} is 3.42x10^{-10} m^2/s.

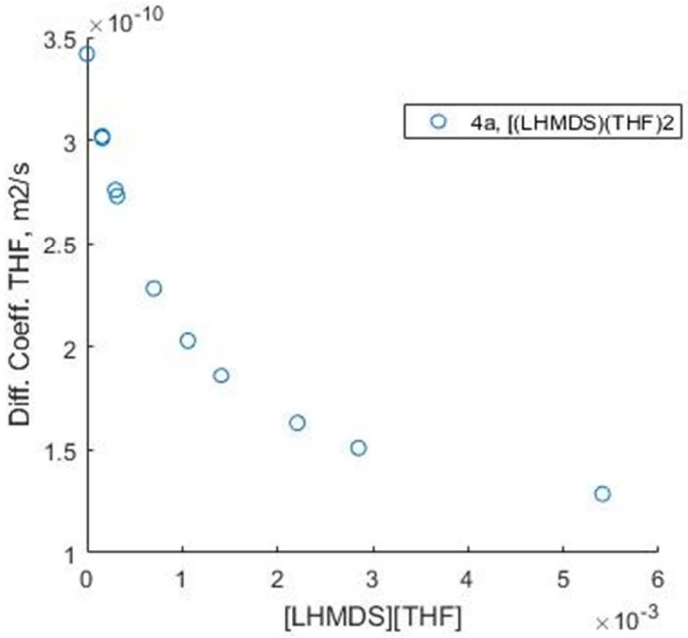


Figure S43. Estimated fraction of Bound THF vs. [THF][LiHMDS] at -60°C in a titration of LiHMDS into 0.1M of THF.

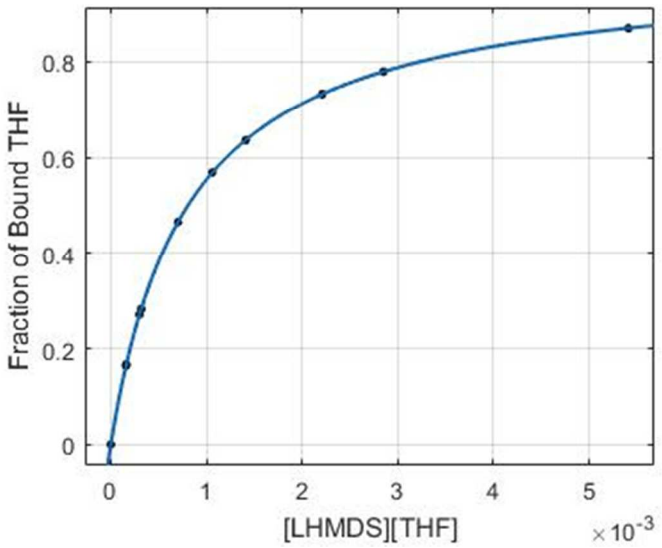


Figure S44. Diffusion Coefficients of DE vs. estimated [DE][LiHMDS] at -60°C in a titration of LiHMDS into 0.1M of DE. Measured $D_{complex}$ 4c is 1.07±0.04x10^{-10}m^2/s and D_{free} is 3.96x10^{-10} m^2/s.

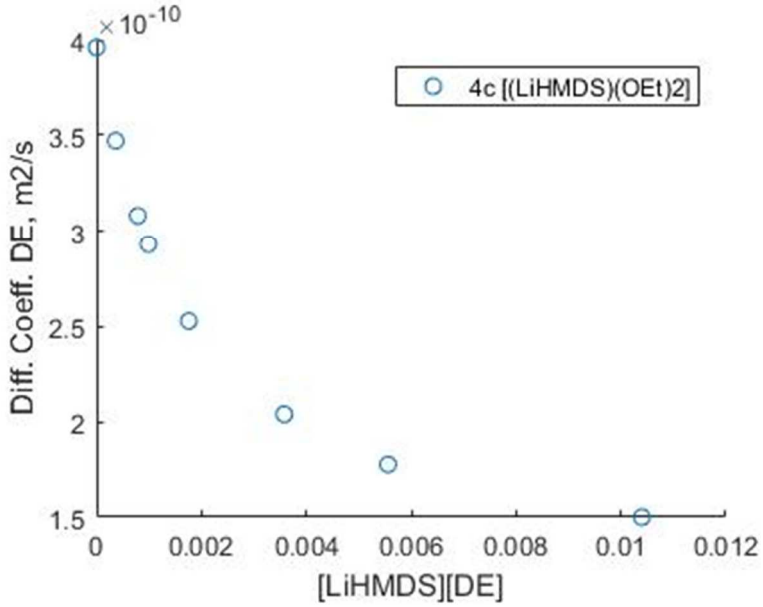
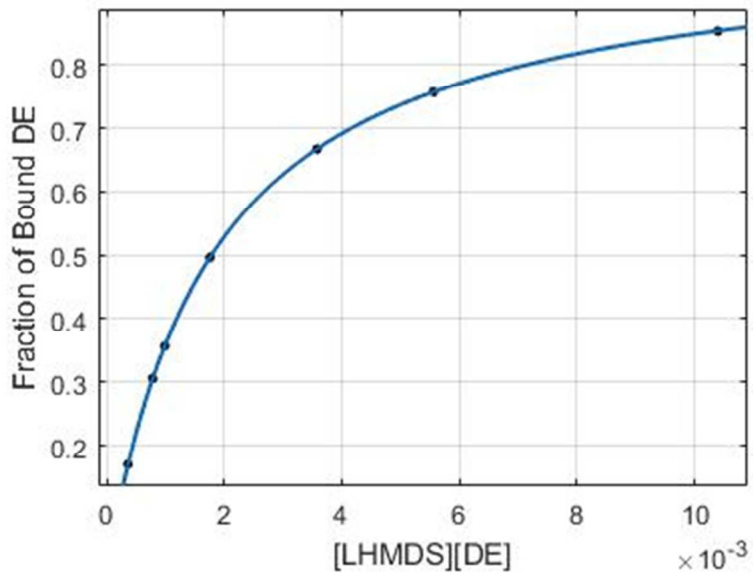
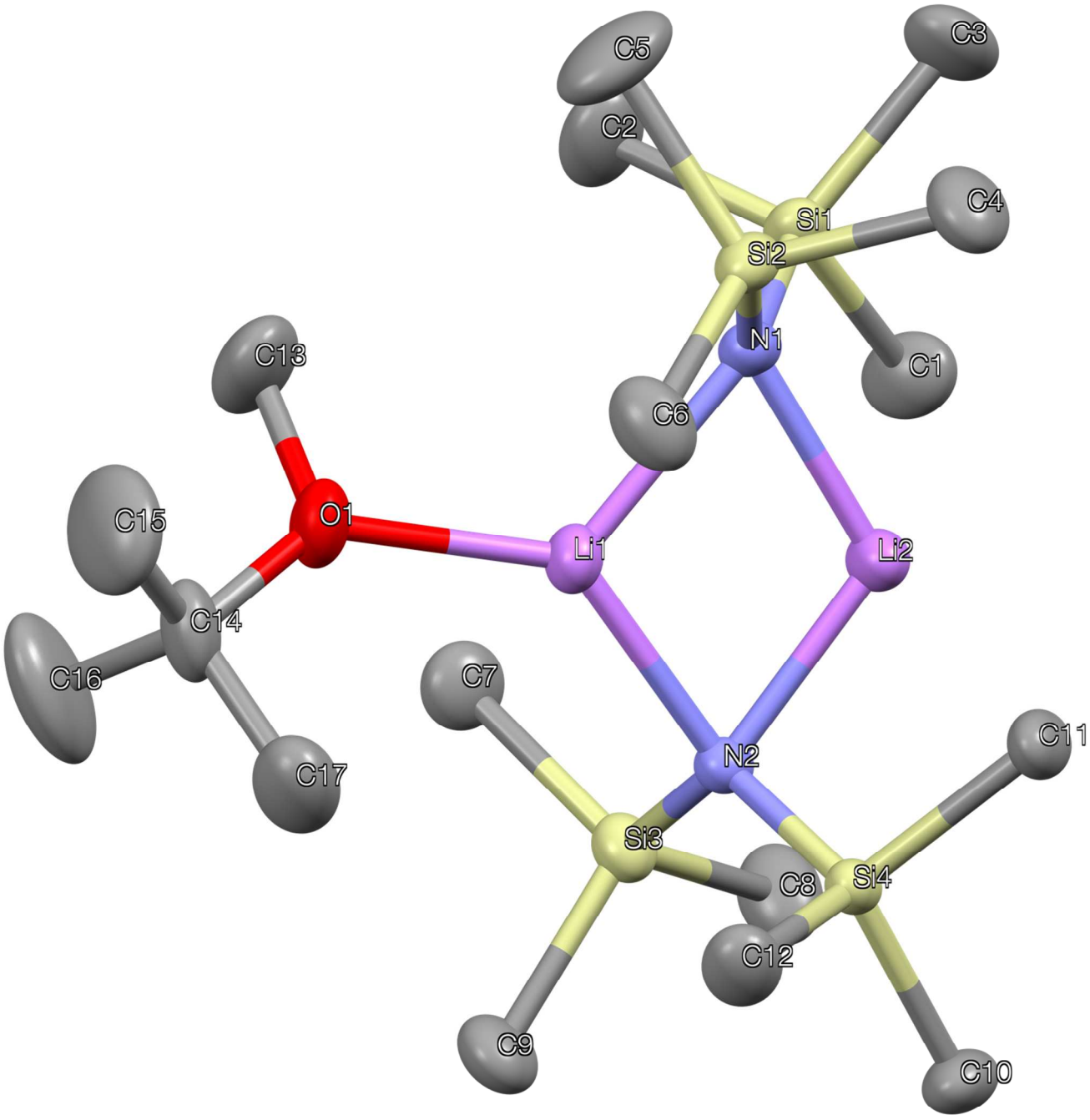


Figure S45. Estimated fraction of Bound DE vs. [DE][LiHMDS] at -60°C in a titration of LiHMDS into 0.1M of DE.



Crystal data and structure refinement for compound 2d, $[LiHMDS]_2$ • t-Bu-O-Me

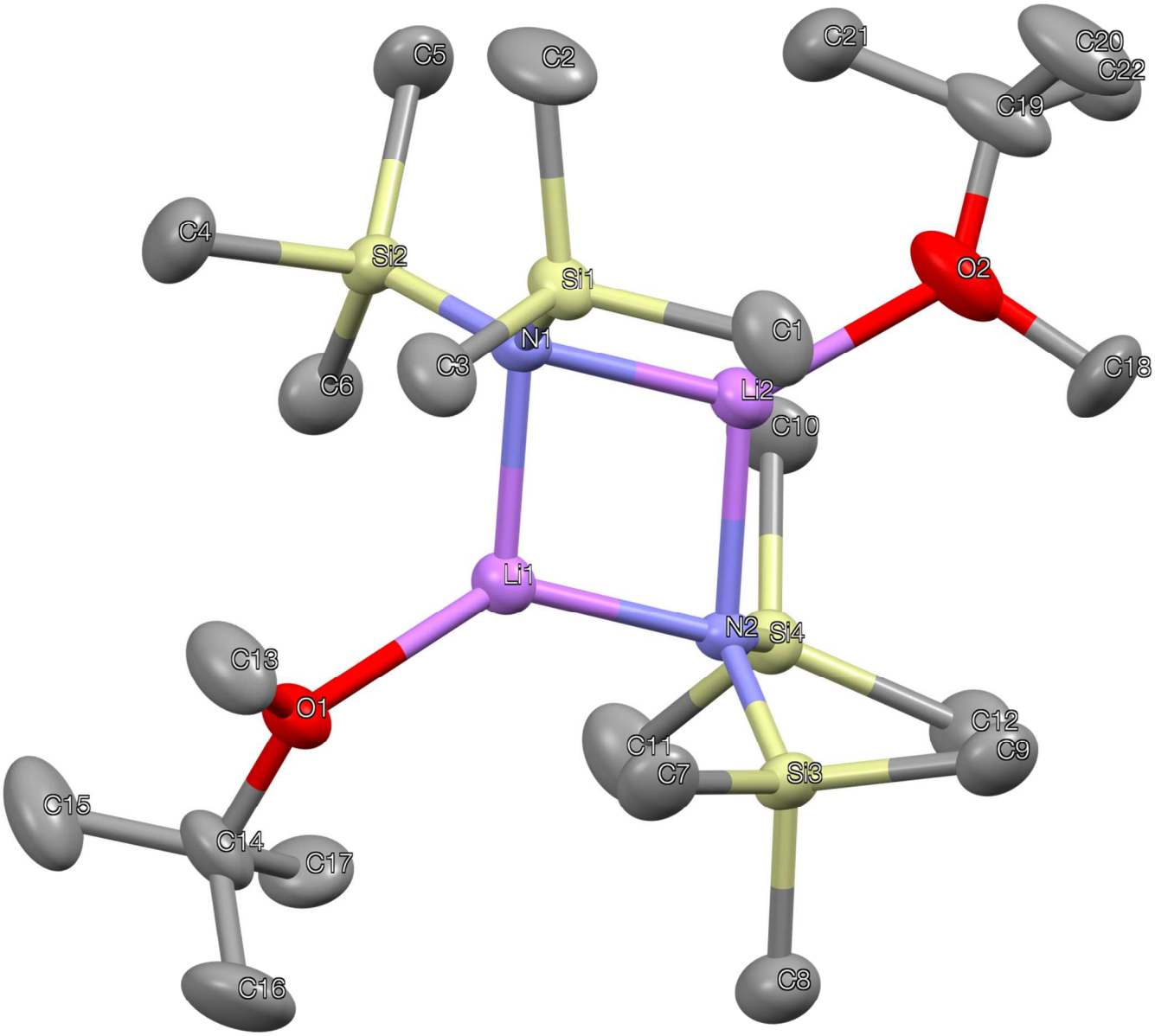
Identification code	ot29jun16_0m
Empirical formula	$C_{17}H_{48}Li_2N_2OSi_4$
Formula weight	422.81
Temperature/K	173.21
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	10.3402(9)
b/Å	12.5483(10)
c/Å	22.5384(19)
α/°	90
β/°	100.789(3)
γ/°	90
Volume/$Å^3$	2872.7(4)
Z	4
$\rho_{calc}g/cm^3$	0.9775
μ/mm^{-1}	0.215
F(000)	937.5
Crystal size/mm^3	0.34 × 0.3 × 0.28
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.9 to 49.5
Index ranges	$-12 \leq h \leq 12$, $-14 \leq k \leq 14$, $-26 \leq l \leq 26$
Reflections collected	29411
Independent reflections	4893 [R_{int} = 0.0236, R_{sigma} = 0.0152]
Data/restraints/parameters	4893/0/250
Goodness-of-fit on F^2	1.024
Final R indexes [I>=2σ (I)]	R_1 = 0.0339, wR_2 = 0.0924
Final R indexes [all data]	R_1 = 0.0383, wR_2 = 0.1020
Largest diff. peak/hole / e $Å^{-3}$	0.53/-0.30



Thermal ellipsoid plot (50% probability) for compound 2d, $[LiHMDS]_2$ • t-Bu-O-Me

Crystal data and structure refinement for 3d, [LiHMDS • t-Bu-O-Me]$_2$

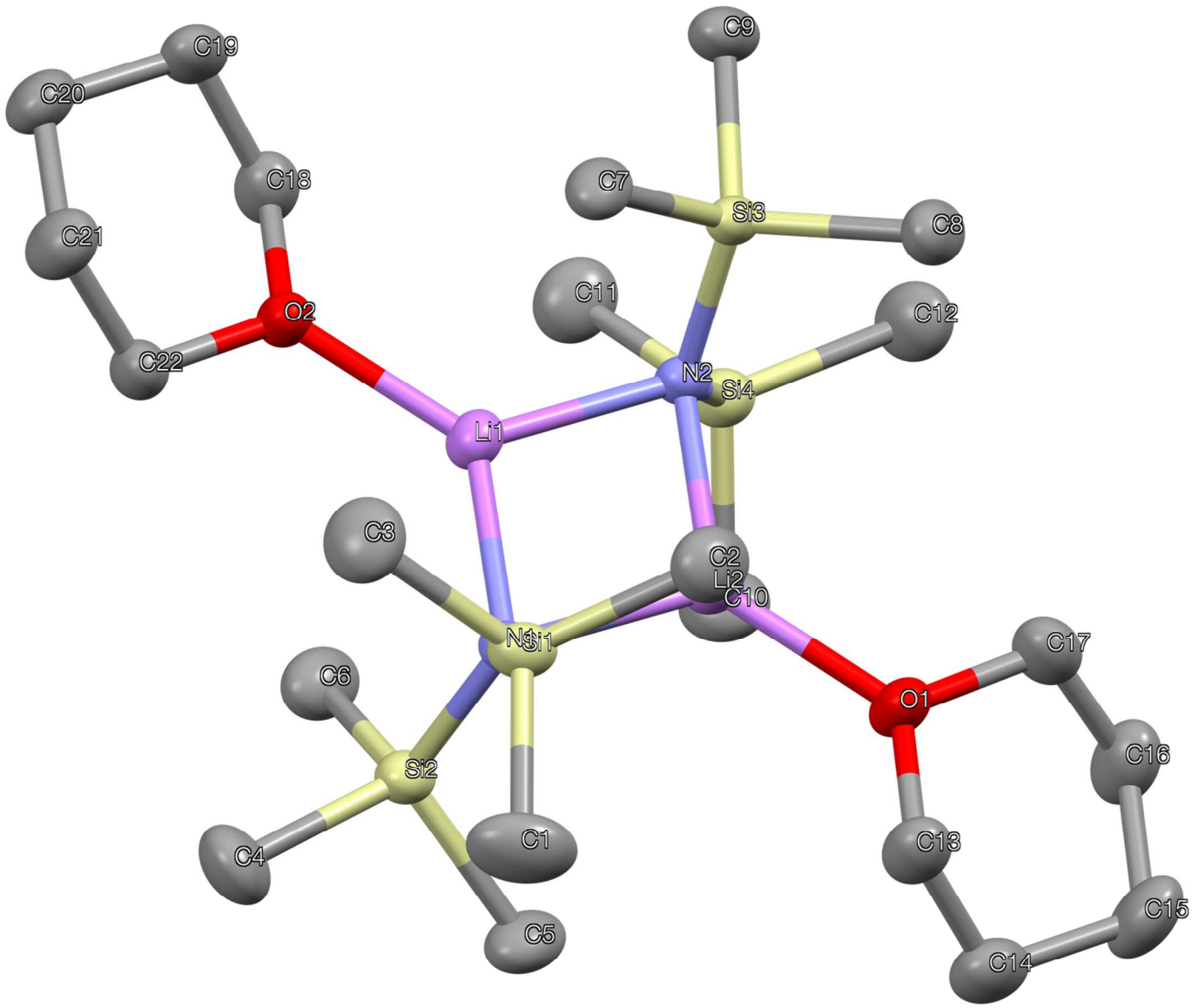
Identification code	ot06jul16_0ma_a
Empirical formula	$C_{11}H_{30}LiNOSi_2$
Formula weight	255.48
Temperature/K	173.21
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	20.3799(19)
b/Å	9.2500(9)
c/Å	19.8691(19)
α/°	90
β/°	112.675(2)
γ/°	90
Volume/Å^3	3456.1(6)
Z	8
ρ_{calc}g/cm^3	0.9819
μ/mm^{-1}	0.190
F(000)	1137.6
Crystal size/mm^3	0.24 × 0.22 × 0.18
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.12 to 44.5
Index ranges	$-21 \leq h \leq 21$, $-9 \leq k \leq 9$, $-21 \leq l \leq 21$
Reflections collected	20884
Independent reflections	4346 [R_{int} = 0.0603, R_{sigma} = 0.0505]
Data/restraints/parameters	4346/0/308
Goodness-of-fit on F^2	1.063
Final R indexes [I>=2σ (I)]	R_1 = 0.0922, wR_2 = 0.2288
Final R indexes [all data]	R_1 = 0.1155, wR_2 = 0.2414
Largest diff. peak/hole / e Å^{-3}	0.96/-0.62



Thermal ellipsoid plot (50% probability) for compound 3d, [LiHMDS • t-Bu-O-Me]$_2$

Crystal data and structure refinement for compound 3b, $[LiHMDS \bullet DHP]_2$

Identification code	ot08jul16_0m_a
Empirical formula	$C_{11}H_{28}LiNOSi_2$
Formula weight	253.46
Temperature/K	173.2
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	9.2754(5)
b/Å	20.029(1)
c/Å	17.8817(9)
α/°	90
β/°	99.343(2)
γ/°	90
Volume/Å^3	3277.9(3)
Z	8
ρ_{calc}g/cm^3	1.0271
μ/mm^{-1}	0.200
F(000)	1121.6
Crystal size/mm^3	0.2 × 0.19 × 0.18
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.46 to 49.18
Index ranges	$-10 \le h \le 10$, $-22 \le k \le 23$, $-20 \le l \le 20$
Reflections collected	22793
Independent reflections	5445 [R_{int} = 0.0454, R_{sigma} = 0.0490]
Data/restraints/parameters	5445/0/300
Goodness-of-fit on F^2	1.060
Final R indexes [I>=2σ (I)]	R_1 = 0.0473, wR_2 = 0.0963
Final R indexes [all data]	R_1 = 0.0794, wR_2 = 0.1091
Largest diff. peak/hole / e Å^{-3}	0.51/-0.37



Thermal ellipsoid plot (50% probability) for compound 3b, $[LiHMDS \bullet DHP]_2$