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Synthesis and Structures of α-Lithiated Vinyl Ethers

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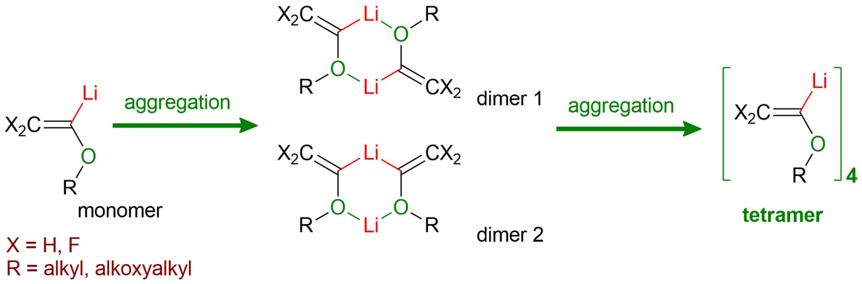

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Synthesis and Structures of α-Lithiated Vinyl Ethers

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The structures of α-lithiated vinyl ethers were explored on the basis of a combined computational and NMR study. Calculations (M06/6-31+G(d)) on free energies of aggregate formation for a series of α-lithiated vinyl ethers indicated that the tetramer is generated preferentially in both the gas phase and THF solution, except for cyclohexylidene derivatives. (1-(Methoxymethoxy)vinyl)lithium, (2,2-difluoro-1-(methoxymethoxy)vinyl)lithium, and (1-butoxyvinyl)lithium were prepared in NMR tubes by the deprotonation of alkyl/alkoxylalkyl vinyl ethers or by the transmetalation of tin compounds. The NMR spectra of these lithium species in THF solution showed that in each species one aggregate is primarily present at 173 K, which is consistent with the preference of the tetramer.

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1. Introduction

α-Alkoxyvinyllithiums, initially developed by Schöllkopf[1] and Baldwin,[2] are useful acyl anion equivalents since their reactions with electrophiles lead to adducts that can be hydrolyzed to acetyl derivatives.[3] These strong nucleophiles readily undergo 1,2-addition to a wide range of carbonyl compounds,[2,4a–4e] reaction with alkyl halides[2,4f] and silyl chlorides,[4g] transmetalation into corresponding metallated analogs including vinyl-magnesium,[4h] -tin,[4i] -zinc,[4j] -cerium,[4k] and -cuprate reagents,[4l] and in certain cases conjugate addition to activated electrophiles such as unsaturated acyl ylides,[4m] vinyl sulfones,[4n,4o] vinylbenzothiazoles,[4p] and unsaturated oxazolines.[4q] α-Alkoxyvinyllithiums and 1-alkoxyallenyllithiums were used in the synthesis of natural products including nicandrenones by Corey,[5a] OSW-1 by Jin,[5b] crotophorbolone by Inoue,[5c] rishirilide B by Pettus,[5d] nikkomycin by Barrett,[5e] calcimycin by Boeckman,[5f] phyllanthoside by Smith,[5g] pederin by Kocienski,[5h] roseophilin by our group,[5i] and others. It is generally known that alkyllithium reagents exist as oligomeric species in solution,[6] in which the state of aggregation depends on solvent, concentration, temperature, as well as additives, typically a coordinating cation (Lewis acid) such as LiCl or a metal-coordinating solvent such as HMPA. Understanding the state of aggregation of organolithium compounds can help to better understand their structure – activity relationships.[7] As an illustration, aggregates do not always dissociate to monomers before reacting with a substrate, and the monomer is not necessarily more reactive than an aggregated species.[8] In an earlier report,[9] our group described that 1-methoxyallenyllithium exists in a dimer–tetramer equilibrium in THF solution (NMR experiments) while in the gas phase this species is aggregated as a hexamer (computational results). In this work we describe the synthesis and structures of α-lithiated vinyl ethers on the basis of a combined computational and NMR study. In the context of a wide range of α-lithiated vinyl ethers varying from simple species such as 1-methoxy and 1-ethoxyvinyllithium to more complicated species like α-lithiated enol carbamates,[10a–10d] α-lithiated β-substituted vinyl ethers,[10e–10l] as well as α-lithiated cyclic vinyl ethers[10m–10u] including α-lithiodihydrofurans, α-lithiodihydropyrans and others, our work focus on several simple α-lithiated vinyl ethers.

2. Results and discussion

2.1. Synthesis

The first challenge was to prepare the precursors for the vinyllithiums in sufficient purity and in the absence of contaminants that would render their NMR spectra difficult to interpret. The most straightforward method to prepare α-lithiated vinyl ethers is through deprotonation with strong base. The high regioselectivity of this process is due to the higher thermodynamic acidity of the α- compared to the β-vinyl hydrogen atom due to the proximity of the electronegative oxygen atom. The kinetic acidity of the α-vinyl hydrogen atom is also enhanced because the oxygen atom can precoordinate an alkyllithium base and direct it to the adjacent α-hydrogen atom rather than β.[3] For example, it is known that alkyl vinyl ethers such as methyl vinyl ether or ethyl vinyl ether, are most readily metallated with *t*-BuLi, while the methoxymethyl vinyl ethers can be deprotonated with less basic *s*-BuLi or *n*-BuLi. This is due to chelation of the methoxy oxygen atom of the methoxymethyl group to lithium.[11] Our syntheses of (1-(methoxymethoxy)vinyl)lithium **4**, (2,2-difluoro-1-(methoxymethoxy)vinyl)lithium **9**, and (1-butoxyvinyl)lithium **12** are summarized in Scheme 1.

*(1-(Methoxymethoxy)vinyl)lithium (**4**)*

The immediate precursor of vinyllithium **4**, (methoxymethoxy)ethene **3**, was prepared from commercially available 2-bromoethanol **1** in two steps, following the procedure of Tamao and co-workers.[11] Methoxymethylation of 2-bromoethanol **1** with 6.0 equiv of dimethoxymethane in the presence of 0.5 equiv of phosphorous pentoxide at room temperature led to 1-bromo-2-(methoxymethoxy)ethane **2** in 63% yield following distillation. Dehydrobromination of **2** with one pellet of KOH in the presence of catalytic tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) provided (methoxymethoxy)ethene **3** in 61% yield following distillation.

The conditions for α-deprotonation of **3** were optimized in a series of experiments in which the lithiated species was trapped with stoichiometric benzaldehyde. The reaction with *s*-BuLi/cyclohexane was cleaner than with *n*-BuLi/hexane or with *t*-BuLi/pentane. Accordingly, NMR spectra (^{1}H, ^{13}C, ^{6}Li) of (1-(methoxymethoxy)vinyl)lithium **4** were recorded at –100, –90, –80, –60, –40 °C after treatment of **3** with a stoichiometric amount of *s*-BuLi/cyclohexane in THF-d_8 in a flame-sealed NMR tube. The ^{1}H NMR indicated complete α-lithiation after storage at –78 °C for 2.5 h.

*(2,2-Difluoro-1-(methoxymethoxy)vinyl)lithium (**9**)*

Several factors rendered the synthesis of **9** unexpectedly challenging. We first prepared 1,1,1-trifluoro-2-(methoxymethoxy)ethane **6** by following the same procedure that we had used for **2**. The reaction mixture from treatment of 2,2,2-trifluoroethanol **5** with 6.0 equiv of dimethoxymethane in the presence of 0.5 equiv of phosphorus pentoxide was highly viscous and very difficult to stir. Conversion to **6** was only 56% complete after 18 h as determined by ^{1}H NMR spectroscopy of the crude reaction mixture, leading to 23% product yield following fractional distillation. We were unable to completely separate **6** (b.p. *ca.* 57 °C, 760 mmHg) from unreacted dimethoxymethane (b.p. 42 °C, 760 mmHg). Using a smaller excess of dimethoxymethane addressed this problem but increased the viscosity and led to lower conversion even after much longer reaction times. This problem was solved by using Celite in combination with phosphorus pentoxide (1:1 wt) which made the reaction mixture less viscous and much easier to stir. The reaction was complete in 6 h with 3.0 equiv of dimethoxymethane and led to pure product **6** in 42% yield after fractional distillation. It should be mentioned that other methods for methoxymethylation of alcohols, for example by treatment with methoxymethyl chloride and bases, such as DIPEA, NaH, or even *n*-BuLi, in solution or neat with a Lewis acid such as Al_2O_3 did not lead to a satisfactory result due to the weak nucleophilicity of **5**. Less than 55% conversion was observed in all cases and separation of the product from solvents was in all cases very difficult.

(2,2-Difluoro-1-(methoxymethoxy)vinyl)lithium **9** was obtained quantitatively by treatment of **6** with 2.0 equiv of *n*-BuLi/hexane in THF-d_8 at –78 °C for 2 h in a flame-sealed NMR tube. However, this reaction generates LiF, and the lithium cation can affect the state of the aggregation of the vinyllithium.[12] To prepare **9** in the absence of LiF, it would be preferable to deprotonate 1,1-difluoro-2-(methoxymethoxy)ethene **7** with stoichiometric *n*-BuLi/hexane. The preparation of difluorovinyl ethers is well-precedented.[13] However, it was challenging to obtain pure **7** because its boiling point was very close to that of its precursor **6** (57 °C at 760 mmHg) and also close to the boiling points of solvents that are typically used for the elimination, such

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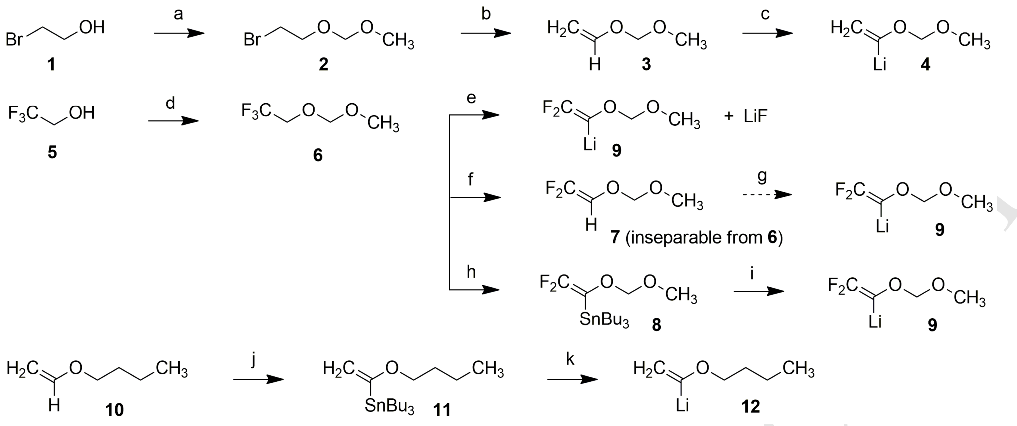
as THF, or to the hexane that is present in commercially available *n*-BuLi. We were never successful in our attempts to convert **6** into **7** quantitatively. Neat or in ethylene glycol, solid KOH or *t*-BuOK did not completely consume the starting material. Alkyllithiums such as MeLi/Et_2O or *t*-BuLi/pentane led to either no reaction (MeLi) or formed 1-fluoro-2-(methoxymethoxy)ethyne (MeLi in the presence of catalytic *i*-Pr_2NH, or *t*-BuLi). We were unable to use neat dioxane (m.p. 10–12 °C) or diglyme (m.p. –64 °C) because of the thermal instability of **9**: Its analog (2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)lithium decomposes at –65 °C.[13c] Toluene or heptane could be used as co-solvents making it possible to conduct the reaction at –78 °C but this resulted in low conversion to product. To circumvent all these problems (2,2-difluoro-1-(methoxymethoxy)vinyl)lithium **9** was prepared by transmetalation of tributyl(2,2-difluoro-1-(methoxymethoxy)vinyl)stannane **8** with stoichiometric *n*-BuLi/hexane. The prepared NMR solution of (methoxymethoxy)vinyl)lithium **9** contained stoichiometric tetrabutyltin, which was not reported to have effects on the state of aggregation of vinyllithiums. Tributyl(2,2-difluoro-1-(methoxymethoxy)vinyl)stannane **8** was prepared in 77% isolated yield by treatment of **6** with 2.2 equiv of *n*-BuLi/hexane in THF at –78 °C, followed by trapping with tributyltin chloride. The NMR spectra (^1H, ^{13}C, ^6Li, ^{19}F) of **9** were recorded at –100, –90, –80, –70 °C after treatment of **8** with stoichiometric *n*-BuLi/hexane in THF-d_8 in a flame-sealed NMR tube. The ^1H NMR spectrum showed that α-lithiation was complete after storage at –78 °C for 30 min.

Scheme 1. Preparation of vinyllithiums[a]



[a] Reagents and conditions: (a) $CH_3OCH_2OCH_3$, P_2O_5, 0 °C, 10 min, rt, 12 h, 63%; (b) pellet KOH, TDA-1, 140 °C, 27 h, 61%; (c) *s*-BuLi/cyclohexane (1.0 eq), THF-d_8, –78 °C, 2.5 h, NMR exp.; (d) $CH_3OCH_2OCH_3$, P_2O_5/Celite (1/1 wt.), 0 °C, 15 min, rt, 6 h, 42%; (e) *n*-BuLi/hexane (2.0 eq), THF-d_8, –78 °C, 2 h, NMR exp.; (f) KOH, *t*-BuOK, or alkyllithiums with/without *i*-Pr_2NH then work up; (g) *n*-BuLi/hexane (1.0 eq), THF; (h) i. *n*-BuLi/hexane (2.2 eq), THF, –78 °C, 2 h, ii. *n*-Bu_3SnCl, –78 °C to rt, 2 h, 77%; (i) *n*-BuLi/hexane (1.0 eq), THF-d_8, –78 °C, 30 min, NMR exp.; (j) i. *t*-BuLi/pentane (1.0 eq), Et_2O, –78 °C, 0 °C, 3 min, ii. *n*-Bu_3SnCl, –78 °C to rt, 2 h, 68%; (k) *n*-BuLi/hexane (1.0 eq), THF-d_8, –40 °C, 45 min, NMR exp.

(1-Butoxyvinyl)lithium (12)

Our first attempt to prepare **12** from commercially available 1-(vinyloxy)butane **10** by treatment with stoichiometric *t*-BuLi/pentane in THF-d_8 showed that the reaction did not occur at temperatures lower than –40 °C while at –20 °C to 0 °C, along with the major product **12**, small amounts (*ca.* 20%) of several undesired byproducts were detected whose structures were not determined. This result is consistent with an earlier report by Soderquist and co-workers who found that the deprotonation of methyl vinyl ether or of ethyl vinyl ether with *t*-BuLi generated small amounts (*ca.* 7%) of dilithioacetylene from β-deprotonation followed by the elimination of alkoxide.[4i] To overcome this problem the same strategy that was used to prepare **9** was followed. (1-Butoxyvinyl)tributylstannane **11** was prepared in 68% yield by treatment of **10** with *t*-BuLi/pentane in Et_2O followed by trapping with tributyltin chloride.[14] Transmetalation of **11** with *n*-BuLi/hexane led to **12**, accompanied by tetrabutyltin. The NMR spectra (^1H, ^{13}C, ^6Li) of (1-butoxyvinyl)lithium **12** were recorded at –100, –90, –80, –70 °C after treatment of (1-butoxyvinyl)tributylstannane **11** with a stoichiometric amount of *n*-BuLi/hexane in THF-d_8 in a flame-sealed NMR tube. The ^1H NMR showed that α-lithiation was complete after storage at –40 °C for 45 min.

2.2. Computational results

Calculations were performed on gas phase and THF solvated monomer, two isomeric dimers and the tetramer of α-lithiated vinyl ethers (Figure 1). The optimized gas phase geometries of 1-lithio-1-methoxyethene and its derivatives are shown in Figure 2. In 1-lithio-1-methoxyethene, the lithium and two carbon atoms are in a nearly linear arrangement, with the lithium atom also coordinated to oxygen in a 3-membered ring. A similar geometry was found for the *Z*-fluoro derivative, but in the *E*-fluoro- and difluoro derivatives, the lithium atom also coordinates to fluorine, resulting in a non-linear Li-C-C arrangement. In the cyclohexylidene derivative, the cyclohexane ring constrains the vinylidine group to an approximately sp^2 geometry. Thus, small structural changes can perturb the geometry of substituted 1-lithio-1-methoxyethenes. All of the 1-lithio-1-methoxymethoxyethenes optimized to similar geometries with the MOM group coordinating to the lithium atoms, as shown in Figure 3.

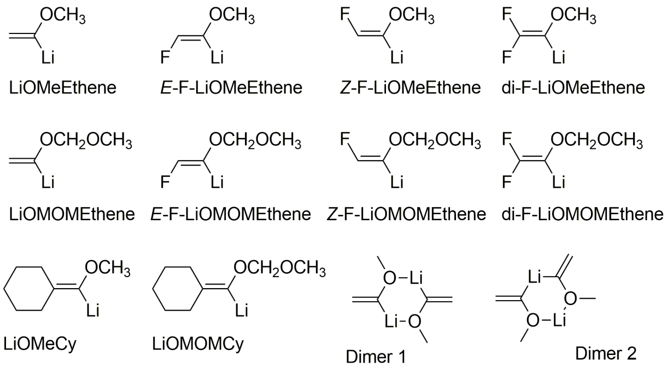


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Figure 1. Structures of α-lithiated vinyl ethers.

The gas phase dimers of 1-methoxyvinyllithium and its derivatives consisted of two regioisomers, as shown in Figure 4. The first, designated Dimer 1, has a C2 axis of rotation, and Dimer 2 has a mirror plane bisecting the two lithium atoms. The parent compound and its fluoro derivatives optimized to similar geometries which were nearly planar. Non-planar geometries were found for the two cyclohexylidene isomers. The analogous methoxymethoxy derivatives are shown in Figure 5. In each of those gas phase structures, some or all of the MOM oxygen atoms were coordinated to lithium, and Li-F coordination was also observed in Dimer 2 of *E*-fluoro- and difluoro- derivatives.

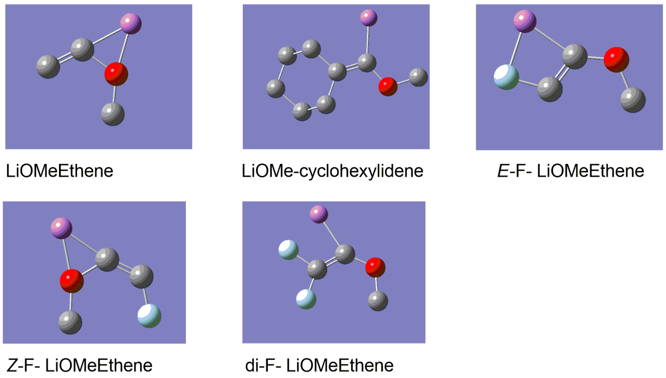
LiOMeEthene
LiOMe-cyclohexylidene
E-F- LiOMeEthene
Z-F- LiOMeEthene
di-F- LiOMeEthene

Figure 2. Optimized gas phase geometries of 1-methoxyvinyllithium monomers. Grey carbon; Red oxygen; violet lithium; light blue fluorine. Hydrogens omitted for clarity.

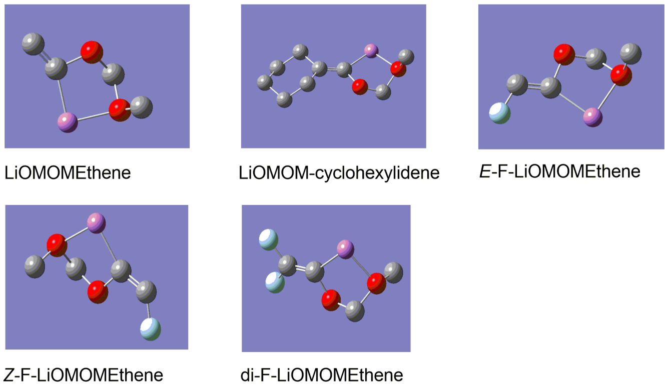
LiOMOMEthene
LiOMOM-cyclohexylidene
E-F-LiOMOMEthene
Z-F-LiOMOMEthene
di-F-LiOMOMEthene

Figure 3. Optimized gas phase geometries of 1-methoxymethoxyvinyllithium monomers.

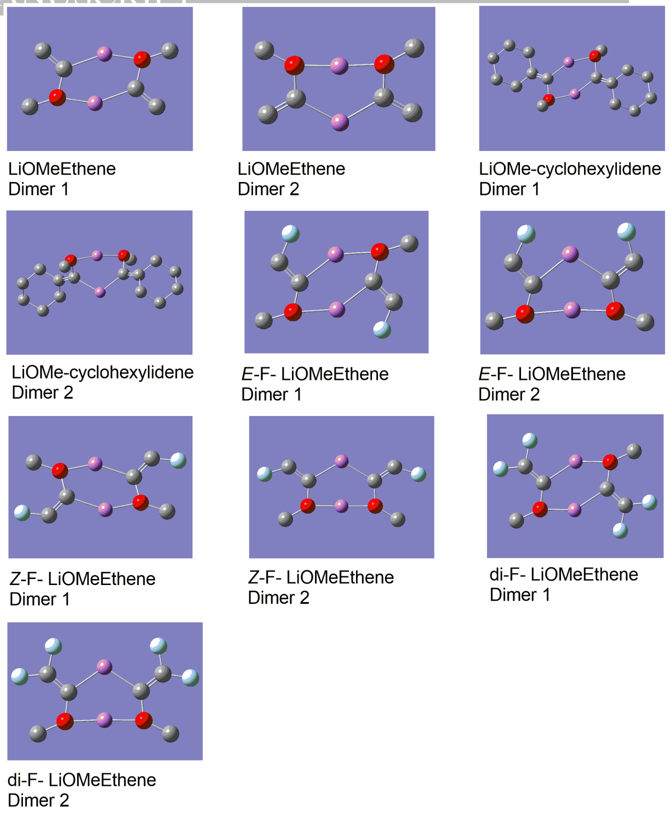
LiOMeEthene Dimer 1
LiOMeEthene Dimer 2
LiOMe-cyclohexylidene Dimer 1
LiOMe-cyclohexylidene Dimer 2
E-F- LiOMeEthene Dimer 1
E-F- LiOMeEthene Dimer 2
Z-F- LiOMeEthene Dimer 1
Z-F- LiOMeEthene Dimer 2
di-F- LiOMeEthene Dimer 1
di-F- LiOMeEthene Dimer 2

Figure 4. Optimized gas phase geometries of 1-methoxyvinyllithium dimers.

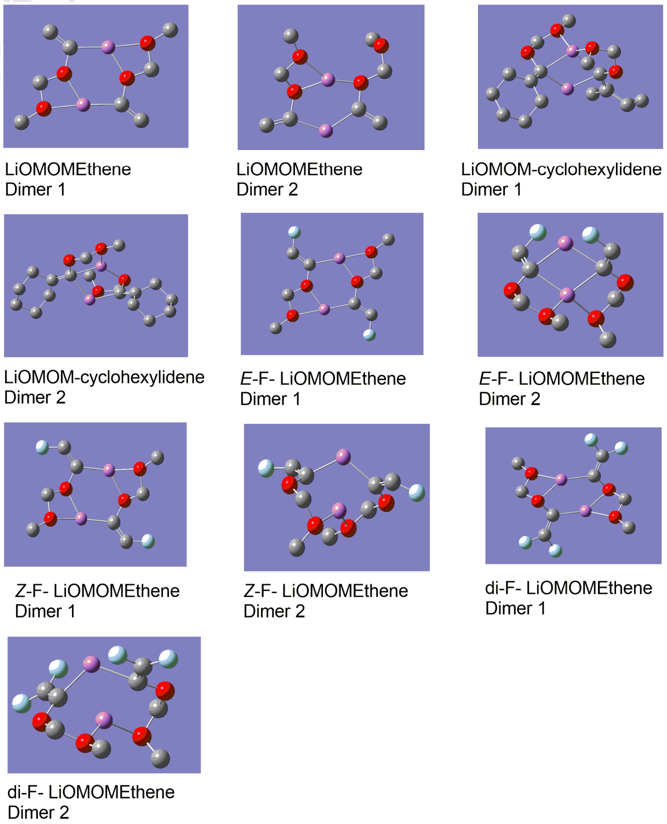
LiOMOMEthene Dimer 1
LiOMOMEthene Dimer 2
LiOMOM-cyclohexylidene Dimer 1
LiOMOM-cyclohexylidene Dimer 2
E-F- LiOMOMEthene Dimer 1
E-F- LiOMOMEthene Dimer 2
Z-F- LiOMOMEthene Dimer 1
Z-F- LiOMOMEthene Dimer 2
di-F- LiOMOMEthene Dimer 1
di-F- LiOMOMEthene Dimer 2

Figure 5. Optimized gas phase geometries of 1-methoxymethoxyvinyllithium dimers.

The calculated relative energies of the two gas phase dimers are shown in Table 1. With the 1-methoxyvinyllithiums, there is a slight energetic preference for Dimer 1, except for the *E*-

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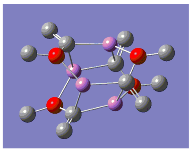
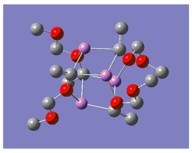
fluoroderivative, where there is a slight preference for Dimer 2. That is possibly due to stronger Li-F coordination in that compound. The preference for Dimer 1 is retained in the 1-MOMvinyllithium and 1-MOMcyclohexylidenelithiums, but the 1-fluoro- and difluoro- derivatives strongly favor Dimer 2. Close examination of the optimized geometries show structures resembling solvent separated ion pairs with MOM-coordinated lithium ions, perhaps as a result of fluorine stabilization of the negative charge on the anionic fragments.

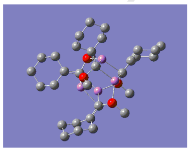
Table 1. Relative stability of dimers in the gas phase (kcal/mol)

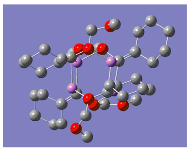
Molecule	Dimer 1 → Dimer 2
LiOMeEthene	0.3
E-F_LiOMeEthene	–0.3
Z-F_LiOMeEthene	0.6
di-F_LiOMeEthene	0.6
LiOMeCy	1.3
LiOMOMEthene	1.9
E-F_LiOMOMEthene	–12.8
Z-F_LiOMOMEthene	–4.9
di-F_LiOMOMEthene	–7.8
LiOMOMCy	5.2

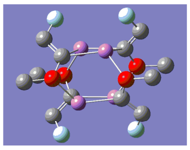
The dimers can further aggregate to tetramers as shown in Figure 6. In both the 1-methoxy- and 1-MOM-vinyllithiums and derivatives, the tetramers adopted geometries that maximized Li-O coordination, and which favored Li-O over Li-F coordination.

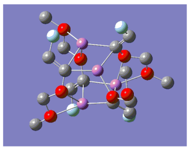

LiOMeEthene Tetramer

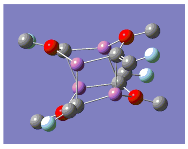

LiOMOMEthene Tetramer

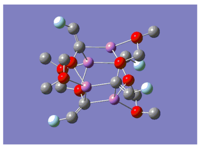

LiOMe-cyclohexylidene Tetramer

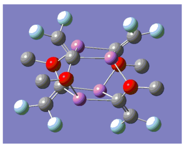

LiOMOM-cyclohexylidene Tetramer


E-F- LiOMeEthene Tetramer


E-F- LiOMOMEthene Tetramer


Z-F- LiOMeEthene Tetramer


Z-F- LiOMOMEthene Tetramer


di-F- LiOMeEthene Tetramer

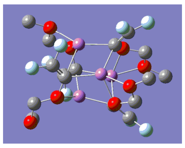

di-F- LiOMOMEthene Tetramer

Figure 6. Optimized gas phase geometries of 1-methoxy- and 1-methoxymethoxyvinyllithium tetramers.

The energies of aggregate formation for the gas phase compounds are shown in Table 2. For the 1-methoxyvinyllithiums, the tetramers were all strongly favored over the dimers. That was also the case for the 1-MOM-vinyllithium, 1-MOM-cyclohexylidenelithium, and *Z*-fluoro-1-MOM-vinyllithium molecules. The *E*-fluoro-1-MOM-vinyllithium showed a slight preference for Dimer 2 over the tetramer, while the di-fluoro-1-MOM-vinyllithium had a slight preference for the tetramer. This can be understood by the relatively strong Li-F coordination in Dimer 2 of the latter two compounds.

Table 2. Free energies (kcal/mol) of gas phase dimer and tetramer formation

Molecule	2 monomer → Dimer 1	2 monomer → Dimer 2	2 Dimer 1 → Tetramer	2 Dimer 2 → Tetramer
LiOMe Ethene	–38.9	–38.7	–31.3	–31.9
E-F-LiOMe Ethene	–34.8	–35.1	–25.0	–24.3
Z-F-LiOMe Ethene	–37.6	–37.0	–28.4	–29.5
di-F-LiOMe Ethene	–40.4	–39.7	–18.6	–19.8
LiOMeCy	–40.5	–39.2	–22.6	–25.3
LiOMOM Ethene	–24.7	–22.7	–25.0	–28.9
E-F-LiOMOM Ethene	–22.7	–35.5	–22.4	3.19
Z-F-LiOMOM Ethene	–24.6	–29.5	–26.0	–16.2
di-F-LiOMOM Ethene	–26.1	–30.9	–10.7	–1.1
LiOMOMCy	–29.6	–24.4	–6.02	–16.5

The second part of the computational work involves solvated species, and the microsolvation model was used for this purpose. In this case, one or more explicit THF ligands were placed on each lithium atom, as was done by Collum and coworkers in the early days of computational studies of lithium amides.[15] The justification for this approach is that polar ligands such as THF, HMPA, and others, act as part of a "supermolecule", and in the case of HMPA, Li-P NMR coupling is observed.[16] This cannot be correctly modeled by existing continuum solvent models, and our earlier work showed no advantage of using a combination of explicit and continuum solvent models over the explicit solvent model alone.[17] Different conformations of attached ligands were examined when it appeared that a lower energy conformation was possible, in an attempt to find the global energy minimum.

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However, in some cases the potential energy surface is relatively flat, with numerous possible confirmations. In these cases the calculated free energies should be taken as qualitative rather than as quantitatively correct.

The optimized geometries of all THF solvated species are presented in the supporting material. The solvated structures were generally similar to those in the gas phase, except that the strongly coordinating THF ligand sometimes caused changes in the Li-OMe or Li-OMOM coordination found in the gas phase. Table 3 shows the third solvation energies of the monomers. The 1-methoxyvinyllithiums readily accepted a third THF ligand, while the 1-MOMvinyllithiums showed a slight preference for the THF disolvate.

Table 3. Third solvation free energies of the monomer (kcal/mol)

LiORC=CXY	R=Me	R=MOM
LiOREthene	–4.3	1.8
E-F- LiOREthene	–8.0	0.7
Z-F- LiOREthene	–5.8	1.1
di-F- LiOREthene	–5.6	0.5

The 1-methoxyvinyllithium dimers can potentially exist as two regioisomers, shown in the supporting material, and different types of THF coordination are possible. These can sometimes accommodate 4 THF ligands per dimer, or 2 THF ligands per dimer. The latter may have one THF ligand per lithium atom or both THF ligands on the same lithium atom. The latter is likely a short-lived intermediate that may be a reactive species.

The calculated free energies of tetrasolvated dimers from the disolvated dimer and two additional THF ligands are shown in Table 4. For the 1-methoxyvinyllithiums, the calculations predict the tetrasolvate to form quantitatively for both isomers. For the 1-methoxymethoxyvinyllithiums, Dimer 1 has an energetic preference for the tetrasolvate, except for the more hindered cyclohexylidene derivative, which will exist primarily as the disolvate. Dimer 2 of the cyclohexylidene derivative will also exist primarily as a mixture of the two disolvated forms. Most of the other methoxymethoxyvinyllithiums will exist as a mixture of solvation states.

Table 4. Free energies of tetrasolvation of the dimers from the disolvates (kcal/mol)

Dimer•2THF + 2THF → Dimer•4THF

Molecule	Dimer 1	Dimer 2-Solv 1 [Solv 2]
LiOMeEthene	–3.6	–9.8 [–5.0]
E-F-LiOMeEthene	–4.9	–4.0 [–7.6]
Z-F-LiOMeEthene	–4.9	–10.6 [–6.3]
di-F-LiOMeEthene	–7.1	–11.1 [–10.4]
LiOMeCyclohexylidene	–4.1	–4.5 [–7.6]
LiOMOMEthene	–3.9	–3.3 [–1.4]
E-F-LiOMOMEthene	–3.7	0.2 [0.1]
Z-F-LiOMOMEthene	–3.7	–2.3 [1.1]
di-F-LiOMOMEthene	–5.0	–1.7 [3.3]
LiOMOMCyclohexylidene	5.2	4.2 [3.9]

The two isomeric dimers can exist in more than one solvation state, and the structures are often comparable in stability. The calculated energies are presented in the supporting material as Table S124. For the 1-methoxyvinyllithiums, the two tetrasolvated dimers are comparable in energy, and are expected to coexist in solution. THF-disolvated Dimer 1 is generally energetically favored over Dimer 2. The tetrasolvated methoxymethoxyvinyllithiums also favor Dimer 1, except for the cyclohexylidene derivative. The relative energies of the disolvated dimers are sensitive to small changes in structure and solvation state.

Tables 5 and 6 show the dimerization energies of the THF solvated monomer to tetrasolvated Dimer 1. For the 1-methoxyvinyllithiums, these energies are based on the trisolvated monomer, while the disolvated monomer was used for the methoxymethoxyvinyllithiums, as the disolvated form is more stable in these more hindered molecules. The calculations show that the dimers of the 1-methoxyvinyllithiums are formed quantitatively, and the methoxymethoxyvinyllithiums also exist primarily as the dimers.

Table 5. Dimerization free energies of methoxyvinyllithiums in THF (kcal/mol) Energies based on Dimer 1•4THF

2 Monomer•3THF → Dimer•4THF + 2 THF

Molecule	ΔG Dimerization
LiOMeEthene	–9.7
E-F-LiOMeEthene	–6.2
Z-F-LiOMeEthene	–5.4
di-F-LiOMeEthene	–9.5
LiOMeCyclohexylidene	–11.7

Table 6. Dimerization free energies of MOMOvinyllithiums in THF (kcal/mol). Energies based on Dimer 1•4THF

2 Monomer•2THF → Dimer•4THF

Molecule	ΔG Dimerization
LiOMOMEthene	–4.0
E-F-LiOMOMEthene	–1.6
Z-F-LiOMOMEthene	–4.8
di-F-LiOMOMEthene	–1.7
LiOMOMCyclohexylidene	–4.2

The calculated free energies of tetramer formation are shown in Table 7. The 1-methoxyvinyllithiums strongly favor tetramer formation from the solvated dimers, except for the cyclohexylidene derivative. The latter will also exist largely as the tetramer in THF solution, possibly in equilibrium with the dimers. The 1-methoxymethoxyvinyllithiums are also expected to form the tetramer quantitatively, except for the cyclohexylidene derivative, which will exist primarily as dimers.

Table 7. Free energies of THF solvated tetramer formation from Dimer 1 [Dimer 2] (kcal/mol)

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2 Dimer1•4THF → Tetramer•4THF + 4THF (2 Dimer2•4THF → Tetramer•4THF + 4THF)

Molecule	ΔG Tetramerization
LiOMeEthene	–13.6 [–13.8]
E-F-LiOMeEthene	–17.9 [–12.0]
Z-F-LiOMeEthene	–14.9 [–9.0]
di-F-LiOMeEthene	–10.0 [–4.0]
LiOMeCyclohexylidene	–2.4 [3.6]
LiOMOMEthene	–18.6 [–12.6]
E-F-LiOMOMEthene	–17.1 [–11.1]
Z-F-LiOMOMEthene	–18.7 [–12.7]
di-F-LiOMOMEthene	–12.2 [–6.3]
LiOMOMCyclohexylidene	6.0 [11.9]

2.3. Discussion

(1-(methoxymethoxy)vinyl)lithium ***(4)***

The ^{1}H, ^{13}C, and ^{6}Li NMR spectra of (1-(methoxymethoxy)vinyl)lithium **4** at 233 , 213, 193, 183, and 173 K are shown in Figures 7–9. The peak corresponding to the C-1 carbon atom at approximately 216.0 ppm in the ^{13}C NMR provides the most information about the aggregation state. At 173 K there is one dominant peak at 216.0 ppm corresponding to the C-1 carbon atom, suggesting that primarily one aggregate of **4** exists. However, in some certain cases it is possible that more than one aggregate of **4** has overlapping peaks at 216.0 ppm, in which case further experiments such as using labeled lithium species, 2D-, HOESY, or DOSY NMR spectra are required to distinguish them.[18] The aggregation states of α-lithiated vinyl ethers **4**, **9**, and **12** are described below in the case that observed signals corresponding to the C-1 carbon of aggregates in the ^{13}C NMR spectra do not contain a group of unresolved peaks or signals. Based on the calculation result, it is likely that the aggregate of **4** at 173 K is the tetramer, which is the most thermodynamically stable species. The C-1 peak in the ^{13}C NMR spectra appeared broad (line width 113.1 Hz) at 173 K indicating carbon–lithium spin-spin coupling.[19] Unfortunately, this peak was not fully resolved even when resolution enhancement was applied, and the identification of carbon–lithium spin-spin coupling constants was rendered more difficult by the presence of lithium isotopes in **4**, which was prepared from normal *n*-BuLi (Sigma–Aldrich) containing 92% natural abundance of ^{7}Li (nuclear spin I = 3/2) and 7.5% natural abundance of ^{6}Li (I = 1). At 173 K, the multiplet at the base of the Li peak in the ^{6}Li NMR and the broad peaks corresponding to the vinyl protons at 4.99 and 3.83 ppm in the ^{1}H NMR are also associated with the carbon–lithium and proton–lithium couplings.[18a] At 183 K, a small peak at 218.4 ppm (line width 93.6 Hz) in the ^{13}C NMR appeared, in which its chemical shift is downfield of that of the major peak at 216.5 ppm (line width 96.3 Hz), suggesting a minor amount of the dimer 2, the second thermodynamically stable species. The trend in chemical shifts is similar to that of 1-methoxyallenyllithium in our earlier work.[9] At 193 K, these two peaks unite to a single broad peak at 216.9 ppm (line width 132.4 Hz) that can be explained by interaggregate carbon–lithium bond exchange that occurred when the temperature raised. At temperatures above 213 K, the peak of the C-1 carbon became fully sharp due to rapid exchange processes including inversion at the C-1 carbon, intra-aggregate carbon–lithium bond exchange, and interaggregate carbon–lithium bond exchange.[20] In addition to the major peaks of the tetramer, trace peaks from 113.6 ppm to 140.9 ppm in the ^{13}C NMR spectra increased at low temperatures, suggesting that there are minor amounts of other species, presumably the hexamer, favored at lower temperatures. Similar peaks were observed on 1-methoxyallenyllithium at 173 K.[9,21]

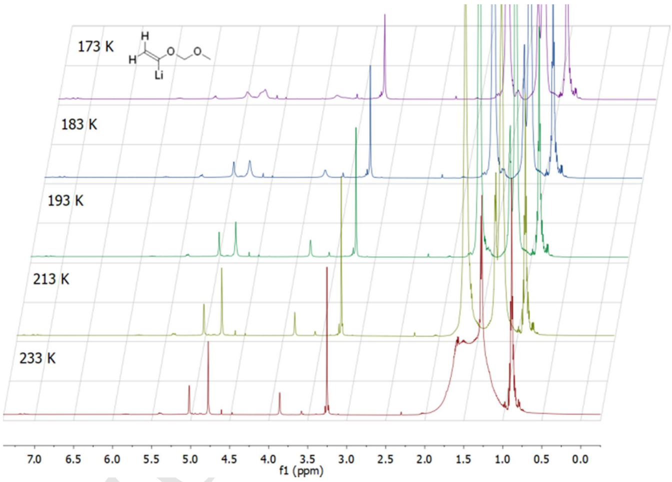

Figure 7. Stacked plot of ^{1}H NMR spectra of (1-(methoxymethoxy)vinyl)lithium **4** in THF-d_8 at 173–233 K. ^{1}H NMR (500 MHz, THF-d_8, 233 K) δ (ppm) 5.02 (d, *J* = 2.4 Hz, 1H), 4.78 (s, 2H), 3.86 (d, *J* = 2.4 Hz, 1H), 3.25 (s, 3H).

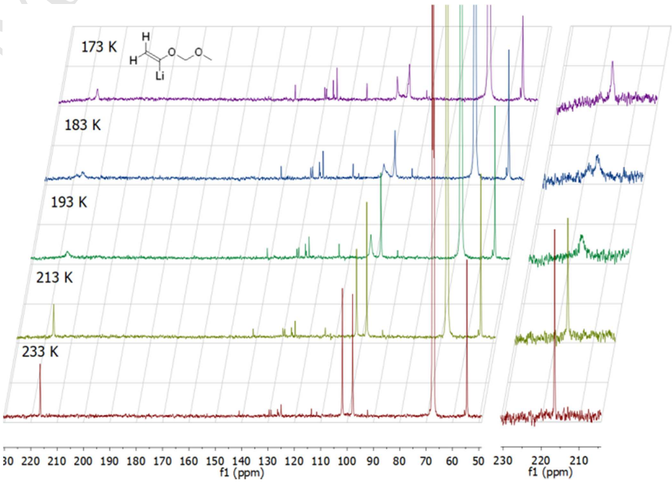

Figure 8. Stacked plot of ^{13}C NMR spectra of (1-(methoxymethoxy)vinyl)lithium **4** in THF-d_8 at 173–233 K. ^{13}C NMR (126 MHz, THF-d_8, 233 K) δ (ppm) 216.4 (C-1), 101.8 (CH_2O), 97.9 (C-2), 54.5 (CH_3).

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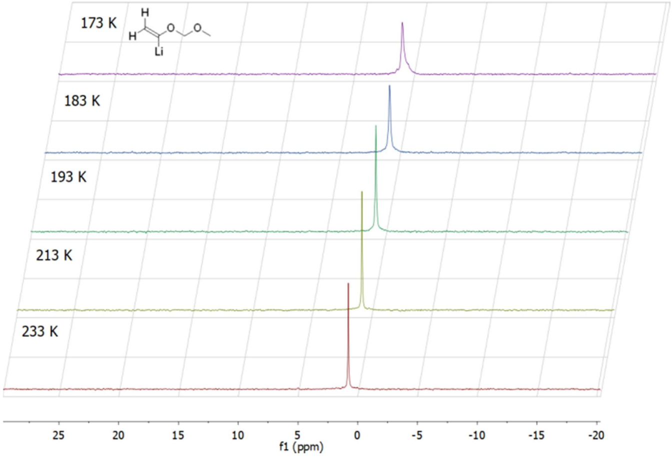

Figure 9. Stacked plot of ^{6}Li NMR spectra of (1-(methoxymethoxy)vinyl)lithium **4** in THF-d_8 at 173–233 K.

*(1-Butoxyvinyl)lithium (**12**)*

The ^{1}H, ^{13}C, and ^{6}Li NMR spectra of **12** at 203, 193, 183, and 173 K are shown in Figures 10–12. The three peaks of the C-1 carbon at about 212 ppm in the ^{13}C NMR spectra suggest that at least three aggregates of (1-butoxyvinyl)lithium are in equilibrium at these temperatures. At 203 K, at least two aggregates, corresponding to the two partially overlapping peaks of the C-1 carbon at about 211.2–212.4 ppm were observed. At 193 K, these two peaks are well separated (212.4 ppm with line width 74.3 Hz and 211.6 ppm with line width 71.1 Hz), which can be explained by the slow interaggregate carbon–lithium bond exchange at this temperature. At 193 K, a small downfield peak appeared at about 213.3 ppm and became one of the major peaks at 173 K (213.5 ppm with line width 79.8 Hz). Because there are no unresolved peaks in the ^{13}C NMR spectra at 212 ppm it is possible that three aggregates of **12** exist at 173–203 K. Based on our calculation results on the aggregates of (1-methoxyvinyl)lithium, a derivative of **12**, it is likely that the tetramer and one of either the dimer 1 or the dimer 2 are the main aggregates at 203 K while the other dimer, which is favored at lower temperatures, appears at 193 K and is one of the three major lithium species at 173 K. The chemical shift of the peak corresponding to the C-1 carbon in the ^{13}C NMR spectra of the dimer appearing at 193K (213.3 ppm) is slightly downfield of that of the tetramer (212.4 ppm or 211.6 ppm). All peaks corresponding to the C-1 carbon were broadened due to the carbon–lithium couplings. The ^{6}Li NMR does not provide clear evidence about the aggregation state at these temperatures due to rapid relaxation of the ^{6}Li nuclei. The appearance of the *Z*-vinyl proton at 4.84 ppm in the ^{1}H NMR at 203 K like an arrow with two small outer lines and two clear central lines of the major quartet would clearly indicate the spin–spin coupling between this proton and a mixture of ^{6}Li and ^{7}Li isotopes.[22]

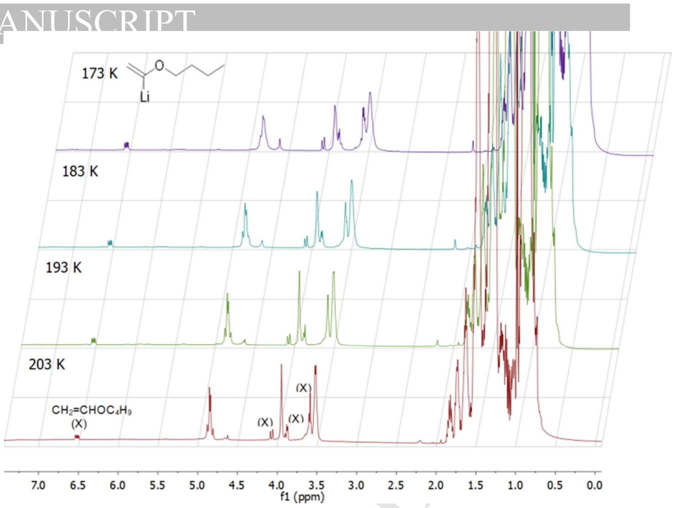

Figure 10. Stacked plot of ^{1}H NMR spectra of (1-butoxyvinyl)lithium **12** in THF-d_8 at 173–203 K. ^{1}H NMR (500 MHz, THF-d_8, 203 K) δ (ppm) 4.84 (br, 1H), 3.94 (br, 1H), 3.51 (s, 2H).

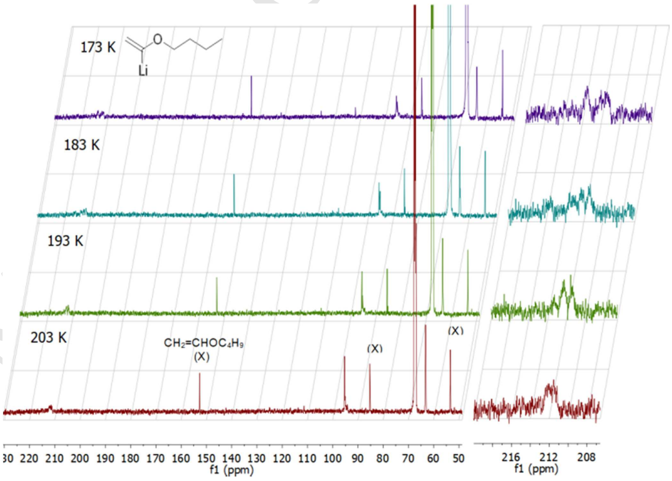

Figure 11. Stacked plot of ^{13}C NMR spectra of (1-butoxyvinyl)lithium **12** in THF-d_8 at 173–203 K. ^{13}C NMR (126 MHz, THF-d_8, 203 K) δ (ppm) 211.8 (C-1), 95.3 (C-2), 63.3 (CH_2O).

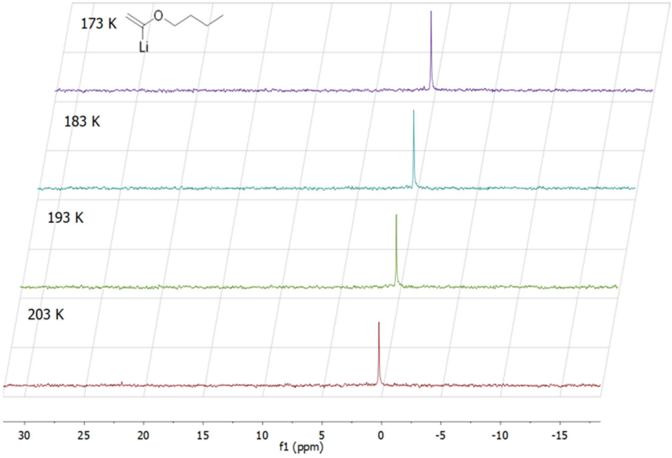

Figure 12. Stacked plot of ^{6}Li NMR spectra of (1-butoxyvinyl)lithium **12** in THF-d_8 at 173–203 K.

*(2,2-Difluoro-1-(methoxymethoxy)vinyl)lithium (**9**)*

The ^{1}H, ^{13}C, ^{6}Li, and ^{19}F NMR spectra of **9** at 203, 193, 183, and 173 K are shown in Figures 13–16. At 173 and 183 K one

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peak at 144.6 ppm in the ^{13}C NMR corresponding to the C-1 carbon atom and two peaks at 128.6 and 92.8 ppm in the ^{19}F NMR corresponding to the two geminal fluorine atoms were observed. At 193 and 203 K a smaller peak at 144.8 ppm in the ^{13}C NMR and two smaller peaks at 128.8 and 92.9 ppm in the ^{19}F NMR appeared. In the case of no unresolved peaks, it is possible that at 173 and 183 K one aggregate of (2,2-difluoro-1-(methoxymethoxy)vinyl)lithium is the major species while at 193 and 203 K a smaller amount of the other aggregate is present. Based on the calculation results, it is likely that the tetramer, the most thermodynamically stable species, dominates at 173 and 183 K, and the dimer 2, the second thermodynamically stable one, is present at 193 and 203 K. At 203 K, the peaks of the C-1 carbon of the dimer 2 (144.8 ppm) have chemical shift downfield of those of the tetramer (144.6 ppm) and the peaks of the two geminal fluorine atoms of the dimer 2 (–128.8 and –92.9 ppm) have chemical shifts upfield of that of the tetramer (–128.6 and 92.8 ppm). The trend in chemical shifts is similar to that of (1-(methoxymethoxy)vinyl)lithium **4**. At all temperatures examined, the ^{1}H NMR of **9** does not provide useful information about the aggregation states. The ^{6}Li NMR shows only one peak (0.53 ppm) at 203 K because of rapid relaxation of the ^{6}Li nuclei, however, at 173 K, a tiny peak at 1.58 ppm beside the major one at 0.51 ppm appeared, confirming trace amounts of a second species, presumed to be dimer 2, at this temperature, although it was not enough to be observed clearly in the ^{13}C and ^{19}F NMR.

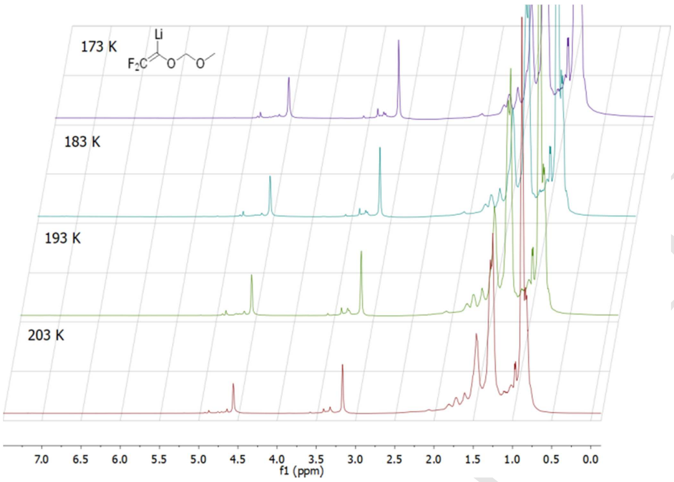

Figure 13. Stacked plot of ^{1}H NMR spectra of (2,2-difluoro-1-(methoxymethoxy)vinyl)lithium **9** in THF-d_8 at 173–203 K. ^{1}H NMR (500 MHz, THF-d_8, 173 K) δ (ppm) 4.52 (s, 2H), 3.12 (s, 3H).

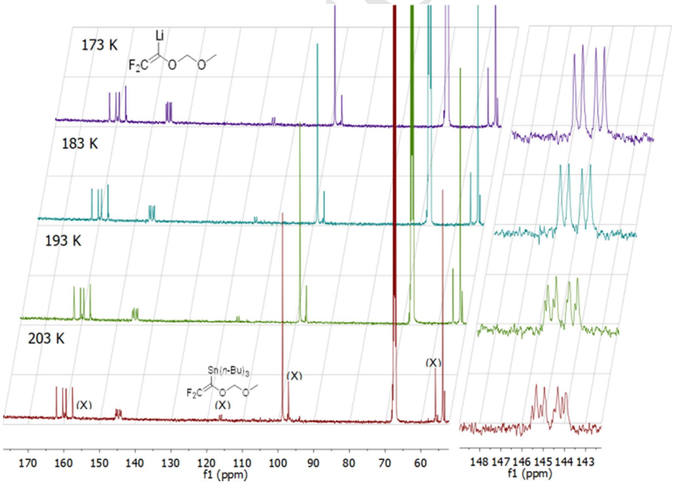

Figure 14. Stacked plot of ^{13}C NMR spectra of (2,2-difluoro-1-(methoxymethoxy)vinyl)lithium **9** in THF-d_8 at 173–203 K. ^{13}C NMR (126 MHz, THF-d_8, 173 K) δ (ppm) 159.6 (dd, $^{1}J_{C,F}$ = 342.3, 223.6 Hz) (C-2), 145.3 (dd, $^{2}J_{C,F}$ = 128.1, 49.8 Hz) (C-1), 98.8 (CH$_2$O), 53.8 (CH$_3$).

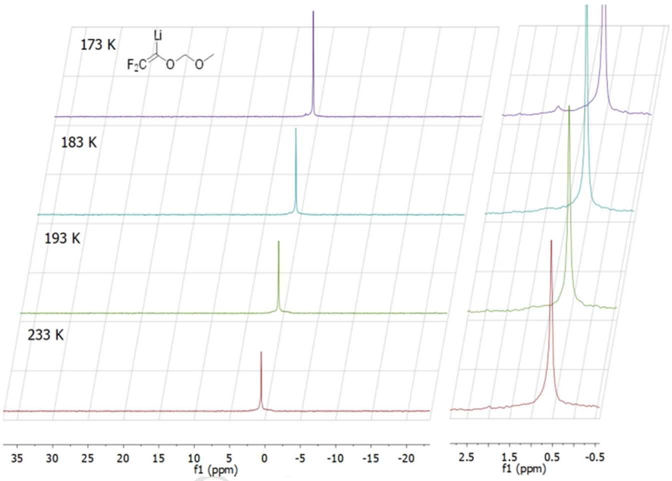

Figure 15. Stacked plot of ^{6}Li NMR spectra of (2,2-difluoro-1-(methoxymethoxy)vinyl)lithium **9** in THF-d_8 at 173–203 K. ^{6}Li NMR (74 MHz, THF-d_8, 173 K) δ (ppm) 1.58, 0.51.

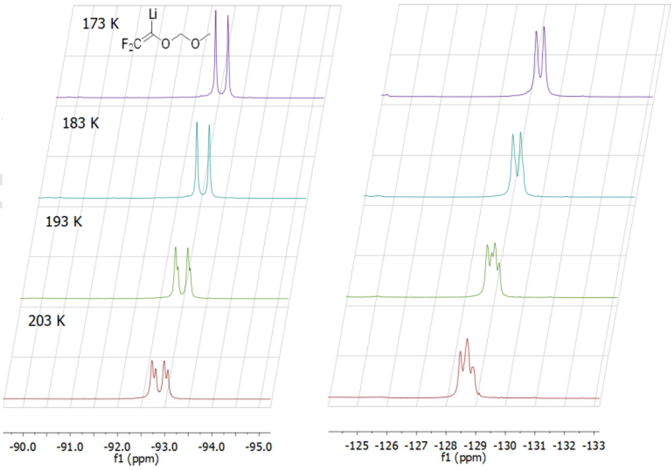

Figure 16. Stacked plot of ^{19}F NMR spectra of (2,2-difluoro-1-(methoxymethoxy)vinyl)lithium **9** in THF-d_8 at 173–203 K. ^{19}F NMR (471 MHz, THF-d_8, 173 K) δ (ppm) –93.1 (d, $^{2}J_{F,F}$ = 123.2 Hz), –129.4 (d, $^{2}J_{F,F}$ = 123.2 Hz).

3. Conclusion

(1-(Methoxymethoxy)vinyl)lithium was prepared by regioselective deprotonation of (methoxymethoxy)ethene. The synthesis of (2,2-difluoro-1-(methoxymethoxy)vinyl)lithium and (1-butoxyvinyl)lithium by deprotonation led to impurities, therefore these α-lithiated vinyl ethers were prepared via Li/Sn exchange reactions. The calculated free energies of aggregate formation for α-lithiated vinyl ethers indicated that the tetramer in each species was favored over the dimers and the monomer in both the gas phase and THF solution, except for (cyclohexylidene(methoxymethoxy)methyl)lithium, where the dimers are mainly present in THF. In all other cases, the NMR spectra in THF solution, together with the calculation results, are consistent with the preference for the tetramer. In addition, a trace of higher aggregates of (1-(methoxymethoxy)vinyl)lithium was observed at 173 K, a minor amount of the dimer 2 of (1-(methoxymethoxy)vinyl)lithium was observed at 183 K, a small

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amount of the dimer 2 of (2,2-difluoro-1-(methoxymethoxy)vinyl)lithium was observed at 193–203 K, and a significant amount of one dimer (203 K) or two dimers (173 K) of (1-butoxyvinyl)lithium was detected. These imply that the reactivity as well as the reaction pathways of these α-lithiated vinyl ethers, particularly those of (1-butoxyvinyl)lithium, slightly depend on temperature. We conclude that this study adds to earlier work in which we focused on the aggregation state of alkoxyallenyllithium.[9,21] The dimer 1 is in equilibrium with the tetramer in THF solution of 1-alkoxyallenyllithium, but the tetramer of 1-alkoxy/1-(alkoxyalkoxy)vinyllithium is the major species. Accordingly, the reactivity as well as the reaction pathways of 1-alkoxyallenyllithium and those of 1-alkoxy/1-(alkoxyalkoxy)vinyllithium are presumably not identical. Our work also demonstrates versatile strategies for the synthesis of 1-alkoxy/1-(alkoxyalkoxy)vinyllithiums that can be used for nucleophilic addition reactions.

4. Experimental section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz (^{1}H) and 126 MHz (^{13}C). ^{19}F NMR chemical shifts were referenced to a CF_3COOH (in THF) external standard (–76.5 ppm). ^{6}Li NMR chemical shifts were referenced to a LiCl (in THF) external standard (0 ppm). Chemical shifts are reported in parts per million (δ) and are referenced to the solvent, i.e. 7.26/77.0 for $CDCl_3$. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), or m (multiplet). Coupling constants (J) are reported in Hertz (Hz). Thin layer chromatography (TLC) was performed on glass plates 250 μm, particle size 5–17 μm, pore size 60 Å. Flash column chromatography was performed on silica gel, 200–400 mesh or premium silica gel, 60 Å, 40–75 μm. All moisture sensitive reactions were performed under a static atmosphere of nitrogen or argon in oven dried or flame-dried glassware. Purity and homogeneity of all materials was determined to be at least 95% from TLC, ^{1}H NMR and ^{13}C NMR. Purity and homogeneity of final products was determined to be at least 95% from TLC, ^{1}H NMR and ^{13}C NMR.

Preparation of α-lithiated vinyl ethers in NMR tube reactions

*(1-(Methoxymethoxy)vinyl)lithium (**4**)*

To a 1.08 M solution of *s*-BuLi in cyclohexane (200 µL, 0.216 mmol) in an oven dried NMR tube connected to an ampule-sealing apparatus under an argon atmosphere at –78 °C was added a solution of (methoxymethoxy)ethene **3** (19 mg, 0.215 mmol) in THF-d_8 (600 µL) dropwise via syringe. The reaction was allowed to proceed for 30 min at –78 °C before being flame-sealed under vacuum. The ^{1}H NMR spectrum showed that lithiation was complete after storage at –78 °C for an additional 2 h. The ^{1}H NMR (500 MHz), ^{6}Li NMR (74 MHz), and ^{13}C NMR (126 MHz) spectra of **4** were recorded at 173, 183, 193, 213, and 233 K. ^{6}Li NMR spectra and ^{13}C NMR spectra were broadband, proton decoupled.

*(2,2-Difluoro-1-(methoxymethoxy)vinyl)lithium (**9**)*

To a 1.15 M solution of *n*-BuLi in hexane (200 µL, 0.23 mmol) in an oven-dried NMR tube connected to an ampule-sealing apparatus under an argon atmosphere at –78 °C was added a solution of tributyl(2,2-difluoro-1-(methoxymethoxy)vinyl)stannane **8** (95 mg, 0.23 mmol) in THF-d8 (600 µL) dropwise via syringe, then the NMR tube was flame-sealed under vacuum. The ^{1}H NMR spectrum showed that lithiation was complete after storage at –78 °C for 30 min. The ^{1}H NMR (500 MHz), ^{6}Li NMR (74 MHz), ^{19}F NMR (471 MHz), and ^{13}C NMR (126 MHz) spectra of **9** were recorded at 173, 183, 193, and 203 K. ^{6}Li NMR spectra and ^{13}C NMR spectra were broadband, proton decoupled.

*(1-Butoxyvinyl)lithium (**12**)*

To a 1.10 M solution of *n*-BuLi in hexane (200 µL, 0.22 mmol) in an oven-dried NMR tube connected to an ampule-sealing apparatus under an argon atmosphere at –78 °C was added a solution of (1-butoxyvinyl)tributylstannane **11** (78 mg, 0.20 mmol) in THF-d_8 (600 µL) dropwise via syringe, then the NMR tube was flame-sealed under vacuum. The ^{1}H NMR showed that lithiation was complete after storage at –40 °C for 45 min. The ^{1}H NMR (500 MHz), ^{6}Li NMR (74 MHz), and ^{13}C NMR (126 MHz) spectra of **12** were recorded at 173, 183, 193, and 203 K. ^{6}Li NMR spectra and ^{13}C NMR spectra were broadband, proton decoupled.

Preparation of starting materials

*(Methoxymethoxy)ethene (**3**)*

To a solution of 2-bromoethanol **1** (12.5 g, 0.10 mol) in dimethoxymethane (53 mL, 0.60 mol) under an argon atmosphere at 0 °C was added P_2O_5 (7.12 g, 0.05 mol) in one portion with vigorous stirring. The reaction mixture was stirred at 0 °C for 10 min, then at room temperature for 12 h during which time the viscosity of the mixture decreased. The reaction was quenched with water, and the organic material was extracted with Et_2O. The combined organic layer was washed again with water, then saturated aqueous Na_2CO_3, dried over $MgSO_4$, filtered, and carefully concentrated under reduced pressure (20–30 mmHg) at room temperature. The residue was distilled under reduced pressure (40 mmHg) at 80 °C to give 1-bromo-2-(methoxymethoxy)ethane **2** (10.6 g, 63% yield) as a colorless liquid.

A round-bottomed flask containing **2** (8.40 g, 0.05 mol), KOH pellets (5.61 g, 0.1 mol), and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) (0.81 g, 0.25 mmol) was equipped with a reflux condenser that was attached through a rubber tube to a clean cold trap (–78 °C), whose outlet was equipped with a $CaCl_2$ drying tube. The reaction mixture was heated to reflux at 140 °C for 27 h. The crude product containing water was collected in the cold trap. Water was removed by a syringe. The crude product was distilled at atmospheric pressure into an ice-cooled receiver to give pure *(methoxymethoxy)ethene* **3** (2.68 g, 61% yield, bp 68 °C) as a colorless oil. Traces of water were then removed using 4Å molecular sieves.

Spectral data of 1-bromo-2-(methoxymethoxy)ethane and of methoxymethyl vinyl ether were identical to those reported in the literature.[23]

*(1-Butoxyvinyl)tributylstannane (**11**)*

To a 0.9 M solution of *t*-BuLi in pentane (3.1 mL, 2.80 mmol) diluted with Et_2O (3 mL) under an argon atmosphere at –78 °C was added a solution of 1-(vinyloxy)butane **10** (0.28 g, 2.80 mmol) in Et_2O (2 mL) dropwise over 3 min. After completion of addition, the reaction mixture was warmed to 0 °C for 3 min, then cooled back to –78ºC. Tributyltin chloride (0.7 mL, 2.50 mmol) was added, and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction was quenched with aqueous saturated NH_4Cl, and the organic material was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane as eluent to afford *(1-*

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butoxyvinyl)tributylstannane **11** (0.74 g, 68% yield) as a viscous colorless oil. Spectral data were identical to those reported in the literature.[24]

*1,1,1-Trifluoro-2-(methoxymethoxy)ethane (**6**)*

To a solution of 2,2,2-trifluoroethanol (20 g, 0.20 mol) in dimethoxymethane (53 mL, 0.60 mol) under an argon atmosphere at 0 ^{o}C was added a mixture of P_2O_5 (14.2 g, 0.10 mol) and Celite (14.0 g) in one portion with vigorous stirring. The reaction mixture was stirred at 0 ^{o}C for 15 min, then at room temperature until the ^{1}H NMR showed that most of starting material was converted to product (*ca.* 6 h). The reaction was quenched with water, and the organic material was extracted with Et_2O. The combined organic layer was washed again with water, then saturated aqueous Na_2CO_3, dried over $MgSO_4$, filtered, and carefully concentrated with a rotary evaporator under reduced pressure (180 mmHg) at room temperature. The residue was fractionally distilled at atmospheric pressure using a Vigreux column to give *1,1,1-trifluoro-2-(methoxymethoxy)ethane* **6** (12.2 g, 42%, bp 57 ^{o}C) as a colorless liquid. Traces of water were then removed using 4Å molecular sieves.

^{1}H NMR (500 MHz, THF-d_8) δ 4.65 (s, 2H), 3.94 (q, $^{3}J_{H,F}$ = 9.1 Hz, 2H), 3.33 (s, 3H). ^{13}C NMR (126 MHz, THF-d_8) δ 125.4 (q, $^{1}J_{C,F}$ = 278 Hz, CF_3), 97.4 (s, CH_2), 64.8 (q, $^{2}J_{C,F}$ = 34 Hz, CH_2), 55.6 (s, CH_3). ^{19}F NMR (471 MHz, THF-d_8) δ –75.1 (t, $^{3}J_{H,F}$ = 9.1 Hz).

*Tributyl(2,2-difluoro-1-(methoxymethoxy)vinyl)stannane (**8**)*

To a 2.5 M solution of *n*-BuLi in hexane (8.8 mL, 22.0 mmol) diluted with THF (30 mL) under an argon atmosphere at –78 ^{o}C was added a solution of 1,1,1-trifluoro-2-(methoxymethoxy)ethane **6** (1.44 g, 10.0 mmol) in THF (10 mL) dropwise over 10 min. After completion of addition, the reaction mixture was stirred at –78 ºC for 2 h. Tributyltin chloride (2.6 mL, 9.50 mmol) was added, and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction was quenched with aqueous saturated NH_4Cl, and the organic material was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane as eluent to afford *tributyl(2,2-difluoro-1-(methoxymethoxy)vinyl)stannane* **8** (3.19 g, 77% yield) as a viscous colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (s, 2H), 3.41 (s, 3H), 1.57–1.45 (m, 6H), 1.36–1.29 (m, 6H), 1.09–0.97 (m, 6H), 0.89 (t, *J* = 7.4 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6 (dd, $^{1}J_{C,F}$ = 317 Hz, $^{1}J_{C,F}$ = 267 Hz, CF_2), 115.8 (dd, $^{2}J_{C,F}$ = 72 Hz, $^{2}J_{C,F}$ = 11 Hz), 97.2, 56.0, 28.8, 27.2, 13.5, 10.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ –85.1 (d, $^{2}J_{F,F}$ = 67 Hz), δ –110.0 (d, $^{2}J_{F,F}$ = 67 Hz).

Computational Methods

Geometry optimizations and frequency calculations for each structure were performed with the Gaussian 09 program,[25] at the M06/6-31+G(d)[26] level of theory. A frequency calculation at the optimized geometry followed each geometry optimization. Vibrational frequencies calculated at 298.15 K and the thermal energies to the free energies, obtained from the frequencies, were added to the electronic energies, to obtain approximate free energies of each species.

Solvent effects were modeled by placing explicit THF ligands on the lithium atoms and optimizing the geometry of this solvated "supermolecule". One or two THF ligands were placed on each lithium atom according to the structure and the number of ligands that fit without causing excessive steric strain. Special care was taken to ensure consistent handling of standard states.[27,28] Specifically, a correction term $RT\ln(c°RT/P°)$ must be added per mole of each species in the reaction under consideration, which represents the change in free energy involved in compressing the system from standard pressure $P°$ (or a concentration of $P°/RT$) used in gas phase calculations to the standard concentration of $c°$ = 1 mol/L commonly used for solutions. This term is numerically equal to +1.8900 kcal/mol at 298.15 K. While it cancels from both sides when the net change in the number of moles due to reaction Δn = 0, it is a non-negligible correction in cases where $\Delta n \neq$ 0. Yet another correction is required for cases where a THF or ether ligand dissociates, illustrated for THF by:

$$\mathrm{RLi}\cdot n\mathrm{THF} \rightleftarrows \mathrm{RLi}\cdot m\mathrm{THF} + (n-m)\mathrm{THF}$$

for which

$$\Delta G^{o} = -RT\ln\frac{[\mathrm{RLi}\cdot m\mathrm{THF}]}{[\mathrm{RLi}\cdot n\mathrm{THF}]} - (n-m)RT\ln\frac{[\mathrm{THF}]}{c^{o}} \qquad (1)$$

Since the concentration of pure THF or ether is different from the one M standard concentration $c°$, it was evaluated from its molar volume at 1 atm and 298.15 K using the empirical expression provided by Govender and coworkers,[29] and incorporated into the second term of Eq. (1). Numerically, this correction to $\Delta G°$ amounts to –1.4883 kcal/mol per THF at 298.15 K. This approach to modeling solvation effects on organolithium compounds has been used previously,[30–35] and has been found to give results in good agreement with available experimental results.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:…

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