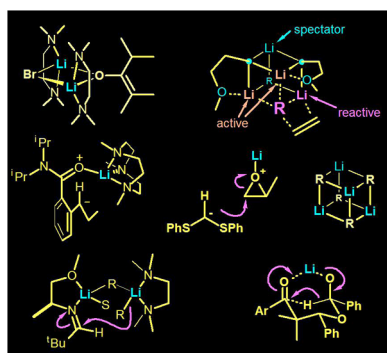


Role of Organolithium Aggregates and Mixed Aggregates in Organolithium Mechanisms

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1. INTRODUCTION

Organolithium reagents were first prepared in 1917 by Schlenk^{1a} and developed in the following three decades by major contributions from Ziegler (who first prepared *n*-BuLi and other alkylolithiums from alkyl chlorides^{1b}) and Gilman and Wittig (who independently discovered aromatic metalation and the lithium–halogen exchange). After a significant gestation period they eventually exceeded in range and number of applications even the previously discovered very popular Grignard reagents. Although the air and moisture sensitivity of organolithium reagents had previously presented challenges to nonexperts, the wider range of reactivities exhibited and the improvement in laboratory facilities and techniques, which enabled safe and effective utilization, led to a significant increase in their appeal. Most importantly, it was the availability of cheap commercial *n*-BuLi (and eventually several others) which allowed the easy preparation of many hundreds of organolithium reagents by the metalation (Li/H exchange), metal halogen (Li/X), and transmetalation (Li/M) methods, which are not as generally available for Grignard reagents.

The use of organolithium reagents as initiators for some economically important polymerizations (styrene, isoprene, butadiene, methyl methacrylate),² the very wide adoption of organolithium reagents for small-scale organic synthesis (because of their much lower cost and greater ease of handling, Grignard reagents are often the reagents of choice for large-scale manufacturing), and the quite contrary physical properties of organolithium reagents (apparently ionic materials, some miscible with pentane that could be distilled) naturally led to an interest in their structure and in the mechanisms for their formation and reactions.

Because of the vast scope of the literature on carbanions and lithium reagents in particular and the many reviews that have already been published (including three books in the past decade),³ some (occasionally arbitrary) exclusions of coverage to minimize repetition and keep this review to a reasonable size were made. We have focused on structures and reactions of organolithium species where mechanistic studies implicated specific aggregates as reactive species. The coverage is restricted to reactions of monolithium reagents where a significant charge resides on a carbanion. This includes enolates, lithiated imines, and lithiated sulfones, even though the lithium may be primarily localized on oxygen or nitrogen since these are commonly considered as carbanion species and usually react as such. However, the considerable literature of metalated β -dicarbonyl compounds and their analogues (ketophosphonates, ketosulfonates, ketosulfones) is considered outside our scope, as are the many classical “carbanion” studies focused on ion-pair behavior and stereochemistry where aggregation was not an issue or was avoided by the use of polar solvents and where a proper discussion would need to include the other alkali metals and counterions.⁴ Various N–Li, O–Li, S–Li, Se–Li, P–Li, Si–Li, and related species are also excluded. In particular, the chemistry of lithium amides (especially LiN(*i*-Pr)₂) has been very thoroughly explored by the Collum group (far more than any other lithium species) and has been reviewed at intervals.⁵ We will also exclude (unless aggregates are specifically involved in a mechanistic context) the very sizable literature on the stereochemistry of organolithium species as well as the mixed aggregates between lithium amides and alkoxides and alkylolithium reagents formed for the purpose of asymmetric reactions (industrial applications have been reviewed recently⁶).

Stereochemical aspects of chiral organolithium species have been reviewed several times.^{3c,7} We will also omit discussions of mixed-metal “superbases” (Li/Na, Li/K, Li/Mg, Li/Zn, etc.),⁸ as well as lithium reagent catalyzed polymerization reactions.²

The complexity of organolithium structures and reactions has led to many computational studies. These will not be directly addressed, although the results of such studies often informed the mechanistic proposals that were made to rationalize experimental findings.

In this review we will first summarize (in a comprehensive but not exhaustive way) common structure types found in the solid state by single-crystal X-ray crystallography. We then offer a brief account of the methods for determining solution structure and a summary of what is known about solution structures of the principal classes of organolithium reagents. The main part of the review is a summary and discussion of organolithium reactions where significant experimental studies have provided mechanistic insights.

2. STRUCTURES OF ORGANOLITHIUM REAGENTS

The first obtained single-crystal X-ray structure of a lithium reagent was that of ethyllithium in 1963,^{9a,b} which turned out to be a cubic tetramer with strong associations between tetramer units, as did the structure of methyllithium reported a year later.^{9c} Since then, many hundreds of solid-state organolithium structures have been reported,¹⁰ with aggregation states ranging from monomeric to polymeric. The information about structures in solution is inherently less precise, but does closely follow the trends established for the solid state. Figure 1 presents the principal structural types that have been established for organolithium species.

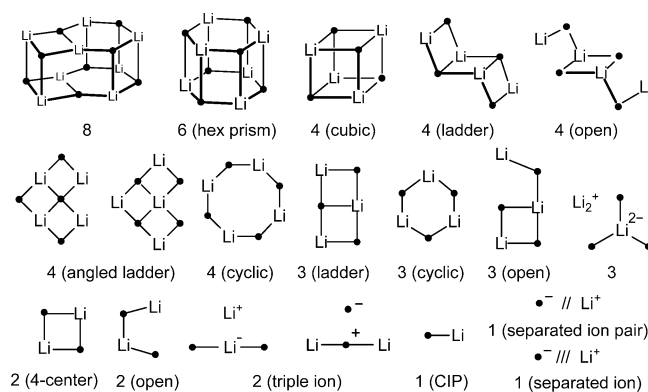
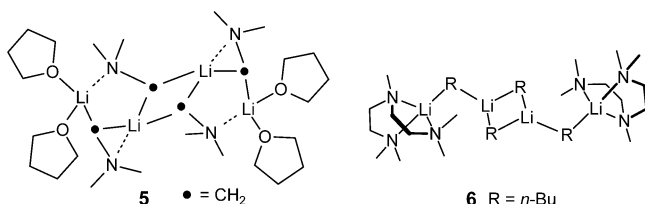


Figure 1. Structural types of organolithium reagents that have been characterized in the solid state or in solution. Numbers refer to the aggregation state. The structures are idealized, since in the actual structures the various polyhedra are not regular. “Dangling” (monocoordinated) lithiums in open structures are typically solvated by a tridentate ligand.

Most of these structures can be understood in terms of Mulvey’s “ring stacking and laddering principle”,^{10d} in which the strongly dipolar RLi units pair up to form dimers to cancel the dipoles. More dipoles can be added to form ladders, or rings can stack to cancel the quadrupole of the dimers, and so on. Special solvation and structural features can also result in a number of open structures, usually resulting from especially strong polydentate coordination of a lithium (2-, 3-, or 4-open structures). The lithium usually surrounds itself with basic ligands, most commonly four, but sometimes three and

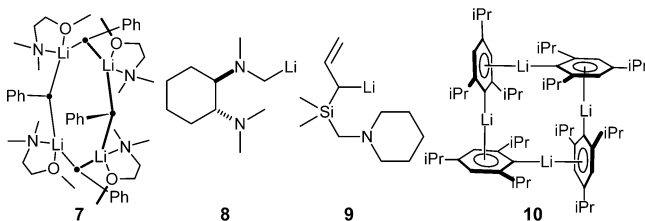
membered rings will occupy some of the coordination sites, as in 3-lithio-1-methoxybutane,^{33b} 3-lithio-1-(dimethylamino)propane,^{33c} or [2-[(dimethylamino)methyl]phenyl]lithium.³⁴

There are a variety of open tetramers known in which several of the lithium contacts to the carbanion center have been cleaved and replaced by chelating groups or a polydentate cosolvent. These open structures represent possible glimpses of what reactive forms of cubic tetramers may look like. For example, *n*-BuLi complexed with TMEDA forms two stereoisomeric four-center ladder tetramers, the step-ladder **4a** and the bowl-ladder **4b**, in which one face of the cubic tetramer has been expanded.³⁵ Phenyllithium forms a similar ladder structure with sparteine³⁶ and a sparteine surrogate.³⁷ A more unusual ladder, **5**, is formed by LiCH₂NMe₂, which involves both normal four-center C–Li–C–Li and less common five-center C–Li–C–Li–N rings.³⁸ The sulfoximine PhS(=O)(=NMe)·CH₂Li·TMEDA forms a complex ladder in which all three basic sites (O, N, C) contact the lithium atoms.³⁹



Even more unusual is the open tetramer **6**, in which a 1/2 equiv of PMDTA creates a structure that can be thought of as a cyclic four-center dimer, coordinated on each lithium to PMDTA–*n*-BuLi monomers.⁴⁰ PMDTA as a ligand usually does not permit more than one C–Li contact, although chelating groups can lead to formally pentacoordinate lithiums, as for [2-fluoro-6-(phenylsulfonyl)phenyl]lithium–PMDTA.⁴¹ It is easy to imagine that some of the *n*-butyl groups in **4** and **6** have the characteristic steric and electronic environment and hence much higher reactivity of dimers rather than that of the parent cubic tetramers, accounting for the activating effect of polyamine additives. A sterically encumbered ortho-metalated benzamide forms a complex open tetramer structurally related to **6**.⁴²

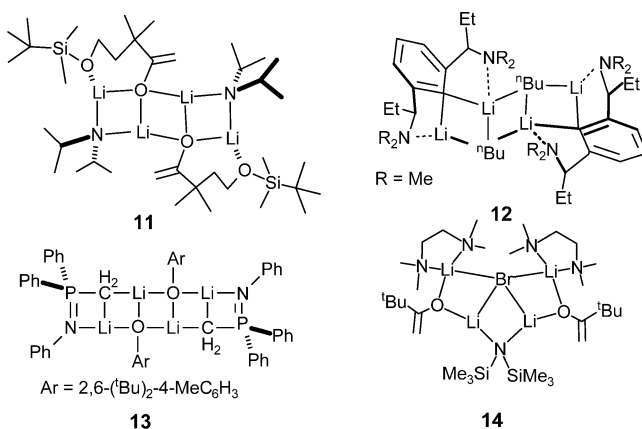
Monocyclic tetramers are also known. Thus, eight-membered rings with a (Li–C)₄ framework are formed by benzylolithium coordinated to an amino ether (**7**),⁴³ metalated 1,2-bis-(dimethylamino)cyclohexane **8**,^{44a} the analogous metalated TMEDA,^{44b} and the substituted allyllithium **9**.^{44c} A 12-membered cyclic tetramer with a (C–Li–P)₄ framework is formed by Ar₂PCH₂Li (Ar = 2-[(dimethylamino)methyl]phenyl).⁴⁵ An alternate mode of tetramerization is shown by unsolvated 2,4,6-trisubstituted phenyllithiums, which crystallize in a macrocyclic π -complex, **10**.⁴⁶



Mixed tetramers of two different lithium reagents (such as (*n*-BuLi)₂·(ArLi)₂)^{46,47} or lithium reagents and lithium halides (such as (PhLi)₃·(LiBr)₁·(Et₂O)₃^{30a} and (cyclopropyl-Li)₂·

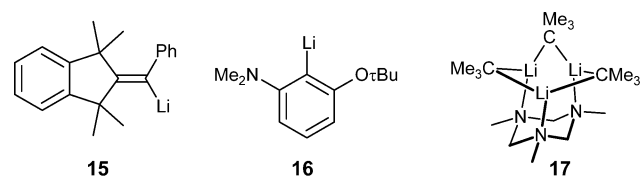
(LiBr)₂·(Et₂O)₄)⁴⁸ where bromides replace a carbanion in a cubic tetramer closely resemble the homotetramers.

Mixed ladder structures, such as the mixed tetramer **11** between LDA and a chelated enolate, are also known.⁴⁹ This can be considered as basically a normal four-center dimer, with an LDA coordinated to each side. A chelated 2:2 ArLi–*n*-BuLi mixed tetramer forms a ladder structure, **12**.⁵⁰ Other similar mixed tetrameric ladders involving *n*-BuLi⁵¹ and *t*-BuLi^{44a,52} have been reported. A more extended ladder structure is found for the lithiophosphazene–lithium phenoxide 2:2 mixed tetramer **13**.⁵³

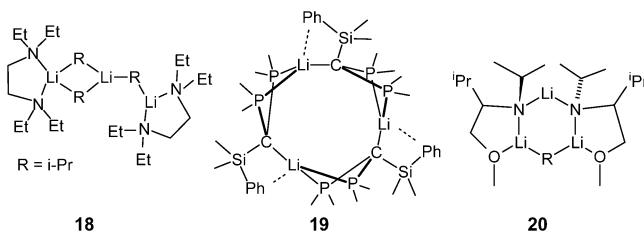


Even a mixed tetramer, **14**, consisting of three different lithium species, one LiBr, one (Me₃Si)₂NLi, and two lithium enolates of pinacolone, has been crystallized.^{54a}

2.1.3. Trimers. Relatively few trimeric organolithium species have been characterized in the solid state. Most are six-membered rings with alternating C and Li atoms. For example, a hindered (α -phenylvinyl)lithium reagent, **15**, crystallizes as an unsolvated cyclic trimer,⁵⁵ as do several 2,6-disubstituted phenyllithiums **16** (bis-*t*-BuO,^{56a} bis-Me₂N,^{56b} and Me₂N and *t*-BuO^{56c}). A very unusual chelation-framework-induced trimer structure is provided by the triamine complex of *t*-BuLi, **17**.⁵⁷



Metalated *trans*-1,2-bis(dimethylamino)cyclohexane also forms a cyclic trimer in which each lithium is coordinated to two carbons and two amino groups.^{58a} A rare example of an open trimer is provided by the tetraethylethylenediamine complex of isopropyllithium **18**.⁵⁹

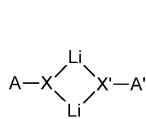


Like tetramers and dimers, trimers can also form larger cyclic structures by coordination to a basic group on the lithiated

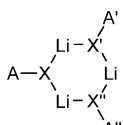
carbon, as in the nine-membered phosphine-chelated structure **19**.⁶⁰

Several mixed trimers between chiral lithium amides and RLi species have been characterized, such as compound **20**.⁶¹

The rare occurrence of trimers is in a way fortunate. Simple NMR methods which rely on C–Li connectivity, or more generally Li–X connectivity, to identify aggregates cannot distinguish dimers from cyclic trimers. For each, Li has two X contacts, and each X has two Li contacts. In cases where the lithium-bearing X nucleus is NMR active, as in a ¹³C-enriched compound, a ¹⁵N-enriched lithium amide,^{62a} or a ³¹P–Li^{62b} species such as Ph₂PLi,^{62b} the NMR spectra will show predictable differences in the appearance of any nucleus A coupled to the X nucleus (e.g., the ipso phenyl carbon in Ph₂PLi), provided there is substantial coupling between X and X'. In a dimer the X nucleus will be coupled to only one other X nucleus, forming an AA'XX' system, whereas in a trimer the X nucleus will be coupled to two others (forming an AA'A"XX'X" system). For the much more common situation of a C–Li species with ¹³C at natural abundance, a ⁶Li{¹³C} HMQC-TOCSY experiment on the ⁶Li-enriched compound can distinguish a dimer from a trimer by the observation of an additional cross peak in the latter (i.e., the remote lithium in the trimer is not coupled (or coupled by a much smaller coupling constant) to the ¹³C, whereas the other two lithiums are strongly coupled).^{62c} Since such techniques are not routinely applied, it does seem probable that a small fraction of the aggregates casually identified as dimers may in fact be trimers.

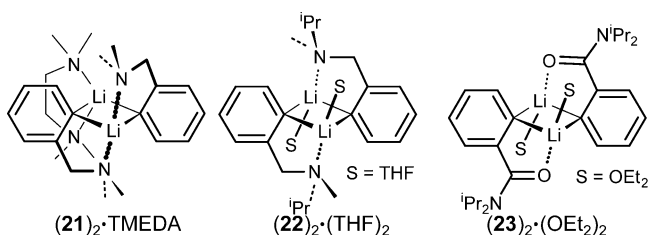


Dimer: AA'XX' spin system

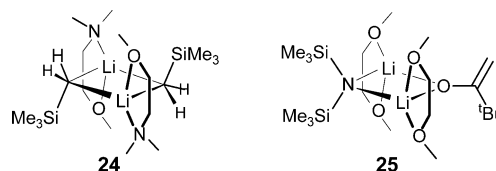


Trimer: AA'A"XX'X" spin system

2.1.4. Dimers. Cyclic four-center structures are by far the most common motif found for dimers in the solid state. Here each lithium contacts two carbons, leaving two coordination sites vacant. In the absence of basic solvents, these sites are weakly coordinated to neighboring dimers (e.g., PhLi⁶³) or to other parts of the carbanion fragment (e.g., (Me₂PhSi)₂CHLi^{64a}). More typically, depending on steric effects, the open sites can be filled by from two to four basic ligands, either chelating groups (e.g., in (1,5-bismethoxy-3-pentyl)lithium^{65a} and [2,6-bis(oxazolynyl)phenyl]lithium^{65b}) or solvent molecules (e.g., (t-BuLi)₂·(OEt)₂,¹⁶ (Ph₂NCH₂Li)₂·(THF)₃,^{66a} and (PhSCH₂Li)₂·(THF)₄,^{66b} (mesityl-Li)₂·(THF)₄,^{66c}) or a combination of both (e.g., (**21**)₂·TMEDA,⁶⁷ (**22**)₂·(OEt)₂,⁶⁷ (**22**)₂·(THF)₂,^{68a} [2-(diphenylphosphino)phenyl]lithium,^{68b} [(methoxymethyl)phenyl]lithium,^{68c} (8-methoxy-1-naphthyl)lithium^{68d} and (triphenylallenyl)lithium⁶⁹). Occasionally 5-coordinated lithiums are seen, as in a trischelated dimeric allyllithium reagent.⁷⁰

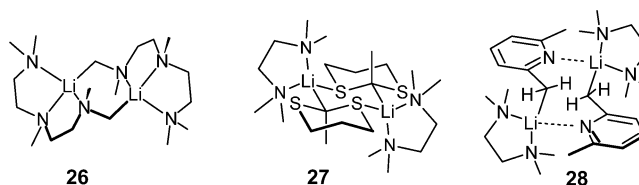


Bidentate amines such as TMEDA, TMEDA, or sparteine are very effective at stabilizing cyclic dimers, and many structures have been determined: PhLi,⁷¹ benzofuran and the S and Se analogues,⁷² [2-(ethylthio)phenyl]lithium,⁷³ lithio-phenylacetylide,^{31b} n-BuLi,^{74,28} [(methylthio)methyl]lithium,^{35,75} s-BuLi,⁷⁶ MeLi,^{36,37} i-PrLi,^{74,76} and bicyclobutyl-lithium.⁷⁷ Alkoxyamines or DME can also play this role, as in the dimers (Me₃SiCH₂Li·DME)₂,²⁶ and **24**,⁴³ or the mixed dimer **25**.⁷⁸

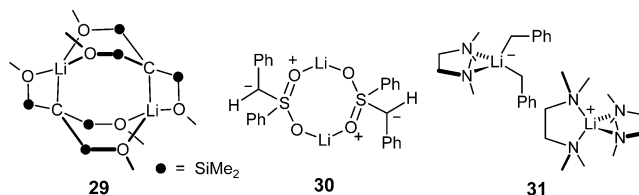


Four-center dimers with Li–O contacts are formed by enolates (those of 2,4,6-trimethylacetophenone–TMEDA,⁷⁹ dibenzyl ketone^{80a} phenyl methyl ketone^{80b} 2-carbomethoxycyclohexanone dimethylhydrazone⁸¹) as well as by lithiophosphonamides,⁸² and lithio sulfoxides.⁸³

A variety of larger-ring cyclic dimers are also known, where a basic group that is part of the lithium reagent coordinates to a lithium of the other component of the dimer. Structures involving six-membered ring chelates have been reported for α-N (e.g., α-lithiated benzylamine,⁸⁴ lithiated PMDTA **26**⁴⁰), metalated TMTAN⁵²) α-S (lithiodithiane **27**,⁸⁵ PhSCH₂Li–TMEDA⁷⁵ and α-P (Ph₂PCH₂Li–TMEDA⁸⁶) substituted lithium reagents. The six-membered ring can be in either a chair or, more rarely, in a twist-boat.^{86b} An infinite ladder of alternating four- and six-ring structures is formed by both PhSCH₂Li^{66b} and Ph₂PCH₂Li⁸⁷ when crystallized from a deficiency of THF.

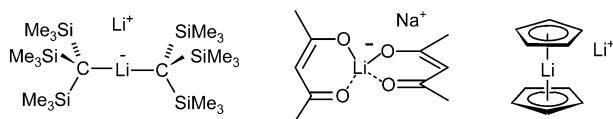


Chelated eight-membered ring dimers are formed by several (pyridylmethyl)lithium structures: [(6-methylpyridyl)methyl]lithium (**28**),^{88a} [[α,α-bis(trimethylsilyl)pyridyl]methyl]lithium,^{88b} and (MeOMe₂Si)₃CLi (**29**).⁸⁹ Eight-membered cyclic structures with no C–Li contacts are formed by several lithio sulfones (e.g., **30**)⁹⁰ and sulfoximines.⁹¹ A macrocyclic dimer involving both CH₂–Li contacts and cyclopentadienyl π-contacts is formed by a lithiated cyclopentadienylphosphonium ylide.⁹²

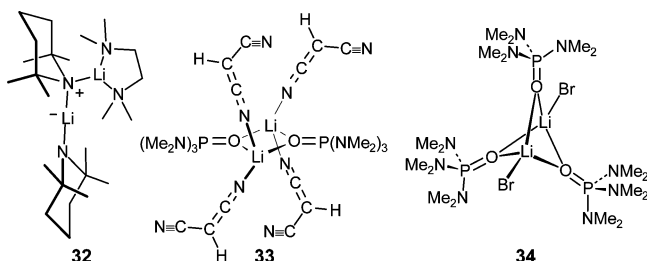


Although more rare, several dimers of the triple ion type (R–Li–R[–]–Li⁺) have been characterized, including sterically hindered systems such as [tris(trimethylsilyl)methyl]lithium,⁹³ β-dicarbonyl enolates such as lithium ethyl acetoacetate,⁹⁴ and lithium biscoordinated to anionic π-systems such as cyclohexadienide,⁹⁵ cyclopentadienide,⁹⁶ and boratabenzene.^{97a} (3,5-

Dimethylbenzyl)lithium–TMEDA **31**⁹⁸ and bis[(2-pyridylmethyl)lithium]–(12-Cr-4)₂⁹⁹ also form triple ions. Dimers form triple ions as a consequence of a significant energetic advantage of unequal solvation of the two lithiums. For example, in (Me₃Si)₃CLi a normal four-center dimer may have room to coordinate only two THF molecules, if that (the phenyl analogues (PhMe₂Si)₃CLi^{64b} and PhMe₂Si-(Me₃Si)₂CLi^{64a} crystallize as mono-THF-solvated monomers). The triple ion, on the other hand, can coordinate four THFs on the ionic lithium, two more than the cyclic dimer, even if the internal lithium is unsolvated.

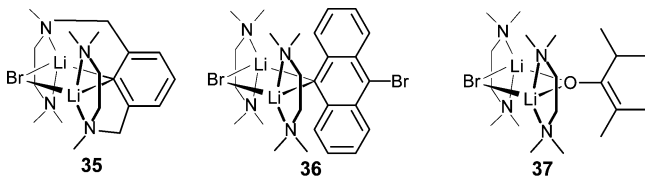


Open dimers (R–Li–R–Li) have been frequently proposed as intermediates in the reactions of cyclic dimers, as a way of exposing both a carbanion carbon and a coordinatively unsaturated lithium which may function as a Lewis acid toward the substrate. Solid-state structures are rare, e.g., the lithium tetramethylpiperidide structure **32**¹⁰⁰ (analogues of **32** were also characterized in solution¹⁰¹).



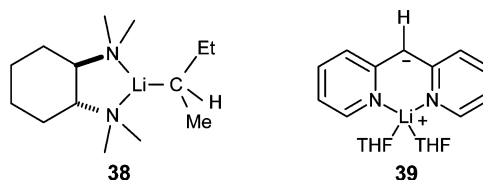
There are two more types of dimers which have been found in the solid state, in which HMPA rather than the anionic fragment bridges the lithiums. Lithiated malononitrile–HMPA forms a network polymer, **33**, with a four-membered O–Li–O–Li ring at the core,^{102a} and LiBr forms a triple-bridged structure represented by **34**.^{102b} No solid-state structure of this type for an organolithium reagent has been reported, but such species have been detected in solutions of PhLi¹⁰³ and *n*-Bu₃SnLi¹⁰⁴ in Et₂O containing 1.5 equiv of HMPA.

Mixed dimers follow the patterns for the homodimers, with four-center structures predominating. Thus, a chelated aryllithium forms the mixed dimer **35** with LiBr.¹⁰⁵ (10-Bromo-9-anthracenyl)lithium forms similar mixed dimers with LiBr coordinated by TMEDA (**36**) or DME.¹⁰⁶ The lithium enolates of 2,4-dimethyl-3-pentanone and pinacolone form mixed dimers **37**^{54b} and **25**⁷⁸ with LiBr and (Me₃Si)₂NLi.

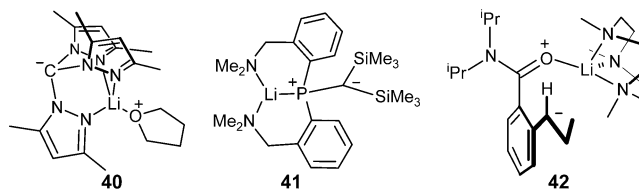


2.1.5. Monomers. Monomers typically have only one carbon–Li contact, leaving up to three solvation sites, although delocalized anions such as allyl or cyclopentadienyl will often effectively occupy more than one site. The factors that favor monomer formation are charge delocalization in the carbanion (as in various benzylolithiums¹⁰⁷), situations of high steric

crowding of the carbanion carbon (as in (2,4,6-*tert*-butylphenyl)lithium^{108a} and other 2,6-disubstituted aryllithiums^{108b–e}), and strongly donating solvents (especially THF and HMPA). Tridentate ligands such as PMDTA and TMTAN are very effective at forming monomers. Crystal structures include phenyllithium–PMDTA,¹⁰⁹ (2-methoxyphenyl)lithium–PMDTA,^{30d} [2-fluoro-6-(phenylsulfonyl)phenyl]lithium–PMDTA,⁴¹ BnLi–TMTAN,⁵² Me₃SiCH₂Li–PMDTA,¹¹⁰ and Me₂P(Me₃Si)–CHLi–PMDTA.^{86c} In sterically encumbered situations or when the anion is delocalized, bidentate ligands such as TMCDA (*t*-BuLi^{58a} and *s*-BuLi (**38**)⁷⁶), sparteine (*t*-BuLi,¹¹¹ indenyllithium,¹¹² and allyllithium¹¹³), and TMEDA (CpLi,^{96b,d,114} BnLi,¹¹⁵ and allyllithium^{116a}) can form monomers.



Even with monomers there are structural complexities concerning the site of lithium coordination. If there are other basic sites, the lithium may coordinate there instead of at (or in addition to) the carbanion center. Not surprisingly, this is the case for monomeric enolate–PMDTA complexes.⁸⁰ It also happens when charge is delocalized and the lithium is well-coordinated elsewhere in the molecule, as for compounds such as **39**,⁹⁹ **40**,¹¹⁷ **41**,¹¹⁸ and **42**.¹¹⁹ There is also the CIP/SIP dichotomy: if the carbanion fragment has extensive charge delocalization and there is effective solvation for lithium, the carbon–lithium contact can be broken and solvent-separated ion pairs (SIPs) are formed, where the cation and anion are still associated, but the lithium is fully coordinated by solvent or cosolvent. Even trace amounts of SIPs may dominate the chemistry of such species because of their extremely high reactivity relative to that of contact ion pairs (CIPs).^{4,120} Significant conversion to SIPs in THF occurs only with strongly delocalized carbanions. The cosolvent HMPA is very effective at causing ion separation. In the sorts of lithium species and media we are concerned with here, the formation of truly separated ions is not typically detected.



2.1.6. Substrate Complexes. In mechanistic discussions of organolithium reagents the question of complex formation between the RLi aggregate and the substrate is almost ubiquitous. Although such complexes have been detected by spectroscopic methods, or by the kinetic behavior of the reaction, actual X-ray structures provide more specific information. Several have been found: a bis(ethylene oxide) complex of (2-methoxyphenyl)lithium tetramer^{121a} and a ketone complex of a lithiated cyclopentadienide.^{121b}

2.2. Solution Structures of Organolithium Reagents

Solid-state X-ray crystal structures provide detailed information about the exact coordination environment at lithium in carbanions, but provide only a strong hint as to the structures adopted in typical solvents such as hexane, toluene, ether, and tetrahydrofuran. There are a number of methods that have been employed to establish the solution aggregation state and other structural features of organolithium reagents. Since all methods are to some extent subject to error or alternative interpretations, it is usually prudent to use more than one technique to securely establish aggregation in solution.

2.2.1. Colligative Properties. The earliest methods for determination of aggregation were physical methods such as cryoscopy (freezing point depression) measured in solvents such as benzene, cyclohexane, and even THF,¹²² vapor pressure osmometry in pentane, ether, and THF, and ebullioscopy (boiling point elevation) in solvents such as diethyl ether and dimethyl ether. Unfortunately, these methods are restricted to solvents with suitable physical properties, provide only an average molecular weight distribution, and are very sensitive to impurities that are formed by contamination from reactions with oxygen and moisture or by attack of the lithium reagent on ether solvents (particularly a problem for vapor-pressure-based methods). Nevertheless, the results supported the notion that most lithium reagents were aggregated, although the precise numbers should be viewed with some skepticism, and sometimes varied considerably between researchers.

2.2.2. NMR Spectroscopy. The advent of multinuclear low-temperature NMR spectroscopy provided remarkably informative techniques for determination of organolithium solution structures.^{123–125} For reagents where the lithium is bound to carbon, the number of C–Li contacts can often be determined from the detection of lithium–carbon J coupling, first observed in the ^7Li NMR spectrum of 57% ^{13}C -enriched MeLi-LiLi ,¹²⁴ in THF at -60°C . This study demonstrated that the solid-state tetramer structure was also maintained in solution. An important advance was the recognition by the Fraenkel group that ^6Li was superior to ^7Li for the detection of small coupling constants to ^{13}C .¹²⁶ Both ^6Li ($I = 1$, 7.4% abundance) and ^7Li ($I = 3/2$, 92.7% abundance) are quadrupolar nuclei, but ^6Li has such a small quadrupole moment that its T_1 relaxation behavior is almost like that of a spin $1/2$ nucleus. Thus, the lines are sharper, allowing the detection of small couplings to other nuclei (^{13}C , ^{15}N , ^{31}P), even though the $^6\text{Li-X}$ couplings are smaller by a factor of 2.6 than the $^7\text{Li-X}$ couplings.^{126,127} The long T_1 values also mean that NOE experiments (HOESY) can be carried out to detect the proximity of lithium to protons.^{123b} Since both ^6Li and ^{13}C are low-abundance nuclei, coupling between them at natural abundance can only be detected by the observation of satellite signals, so usually one of them has to be enriched to conveniently observe coupling. It is common practice to prepare ^6Li -enriched materials, which allows detection of J_{CLi} in the ^{13}C NMR spectra. Doubly enriched materials with ^{13}C at the carbanion carbon are sometimes prepared to allow high-sensitivity observation of coupling in both the ^6Li and ^{13}C NMR spectra.¹²⁷ Natural-abundance ^{13}C satellites have been occasionally detected in the ^6Li NMR spectra, bypassing the need for ^{13}C enrichment.¹²⁵

The natural line width of ^7Li signals is quite variable as a result of coupling between quadrupolar T_1 relaxation and molecular dipoles, but is typically at least several Hertz,¹²⁸ so only relatively large couplings (say >5 Hz or so) can be

routinely resolved with ^7Li at natural abundance. T_1 relaxation is not the only source of the line broadening which so frequently obscures C–Li coupling. There can also be intermolecular lithium exchange events (T_2 broadening). For such systems ^7Li can provide a better view of coupling because the larger line separation means higher exchange rates can be tolerated while line splitting is still observed. Basically, for carbons bound to one lithium (monomers), J_{LiC} values range from 15 to almost 40 Hz. ^7Li observation at natural abundance will usually give adequate resolution to detect the 1:1:1:1 quartet. For carbons coupled to two or more lithiums, the couplings are substantially smaller (the coupling is roughly inversely proportional to the number of C–Li contacts^{129,130}) and ^6Li enrichment is often required to observe coupling in the ^{13}C NMR spectra.

For trimers and higher aggregates, coupling between lithium and carbon can be either static or dynamic. Thus, for a cubic tetramer the static structure will have lithium coupled to three carbons and vice versa, whereas the dynamic structure will have each nucleus coupled to four others because of rapid intramolecular rearrangement of the C–Li bonds. For $t\text{-BuLi}$ in pentane a static tetramer is observed below -22°C and a dynamic one above -5°C .¹²⁸ Cyclic dimers and trimers have the same static coupling pattern (Li and C each have two coupling partners), but a trimer can become dynamic at higher temperature, with each nucleus having three coupling partners, whereas a dimer cannot, allowing a distinction to be made.¹³⁰

If more than one aggregate is present, separate NMR signals for the two (occasionally even three) aggregates can almost always be resolved at sufficiently low temperatures, as in the ^{13}C NMR spectra of PhLi in Et_2O and THF in Figure 5.¹⁰³ The

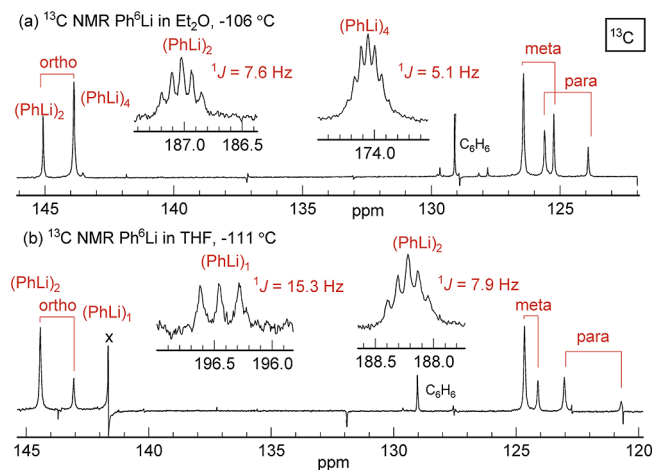


Figure 5. ^{13}C NMR spectra of Ph_6Li : (a) 0.16 M in Et_2O at -106°C , (b) 0.08 M in THF at -111°C . Adapted from ref 103. Copyright 1998 American Chemical Society.

relative aggregation state of the two species can be determined by measurement of their ratio as a function of concentration. The identification of hexamers, octamers, and nonamers for propyllithium in cyclopentane was an early successful application of this technique.¹³¹

The rate of interaggregate exchange, and hence the temperature needed to observe distinct aggregate signals, varies widely, but typically falls within the range of DNMR experiments (ΔG^\ddagger between 7 and 17 kcal/mol). For alkylolithiums in hydrocarbon solvents, intermolecular exchange

rates are slower than in ether solvents, and there are large steric effects. Thus, the C–Li coupling in $(t\text{-BuLi})_4$ in cyclopentane can be observed even at room temperature ($\Delta G^\ddagger > 16$ kcal/mol). For the tetramer–hexamer mixture of $i\text{-PrLi}^{125d}$ and $s\text{-BuLi}^{132a}$ coupling and distinct aggregate signals can be resolved below 0°C ($\Delta G^\ddagger > 14.5$ kcal/mol), and for EtLi^{125d} and $n\text{-PrLi}$ (both mixtures of hexamers and octamers), temperatures below -30°C are required ($\Delta G^\ddagger > 13$ kcal/mol).^{126,131} In ethereal solvents exchange rates are generally much faster, although it is unusual for an intermolecular aggregate exchange to still be fast on the NMR time scale below -100°C . Thus, for the tetramer–dimer mixture of PhLi in Et_2O , separate NMR signals are observable below -80°C ,¹⁰³ whereas in THF the monomer and dimer signals¹²⁹ decoalesce at ca. -100°C ($\Delta G^\ddagger = 8$ kcal/mol¹⁰³). The tetramer and dimer signals of vinyl lithium in THF decoalesce below -60°C .²⁹

In the absence of C–Li contacts, or if coupling is not resolvable for some reason (T_2 broadening due to rapid intermolecular Li–Li exchange, T_1 line broadening due to quadrupolar relaxation, and other less well-defined causes of line broadening), a very effective method involves the low-temperature observation of mixed aggregates formed by placing two related lithium reagents (A and B) together in defined ratios, where the aggregation state defines the number of mixed species obtained. Often separate spectroscopic signals are seen for each mixed aggregate, precisely defining the aggregation state. NMR signals of any of the nuclei can be used. In favorable cases IR absorptions are also effective.¹³³ This technique (the method of continuous variation, Job plot¹³⁴) requires that the mixed species have one or more NMR signals that are different for the homoaggregates and each of the mixed aggregates and that exchange between them is slow on the NMR time scale. Monomers will give no new signals. Dimers will ideally give a 1:2:1 ratio of signals for species AA, AB, and BB (an early example of the technique was used to characterize triple ions¹³⁵), trimers a 1:3:3:1 ratio, tetramers a 1:4:6:4:1 ratio for the A_4 , A_3B , A_2B_2 , AB_3 , and B_4 species, and so on. Figure 6

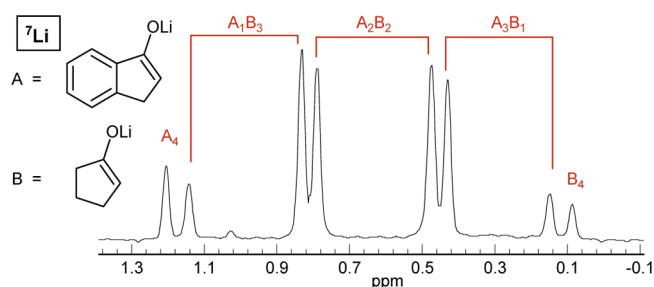


Figure 6. ^6Li NMR spectrum of a 1:1 mixture of indanone and cyclopentanone lithium enolates in 2 M THF–toluene at -30°C . Reprinted from ref 134b. Copyright 2008 American Chemical Society.

illustrates a nice example of the technique for showing that the enolates are tetramers. Each mixed aggregate gives two signals because the tetramers are static (intramolecular exchange of lithium nuclei is slow). It is interesting that at this temperature in DME solvent the intramolecular exchange is fast and a single peak is observed for each mixed aggregate.^{134b}

For the method to be reliable, the A and B species must be as alike as possible, so each can be shown (or assumed) to have the same aggregation state; otherwise ambiguous results will be obtained. This also assures that the mixed aggregates will be formed in close to statistical ratios. Of course, the more alike

the two lithium species are, the more similar their NMR properties will be, leading to situations where the various environments cannot be resolved. The absence of new signals in mixtures suggests monomers, but the experiments are less definitive since rapid exchange or insufficient chemical shifts could be masking the A_nB_m species.¹³⁶

One of the earliest proofs of the tetrameric nature of methyllithium in ether solution was of this type.¹³⁷ Solutions of defined mixtures of methyl- and ethyllithium gave appropriate ^7Li NMR signals corresponding to the different local environments of a lithium in a static tetrahedral tetramer (i.e., the nearest neighbors of a lithium could be Me_3 , Me_2Et , MeEt_2 , or Et_3).

The most refined version of this method involves isotopically perturbed mixed aggregates, for example, CH_3Li and CD_3Li , where isotope shifts provide a 1:4:6:4:1 ratio of ^6Li signals for the various isotopomers of the tetramer.^{125b,138}

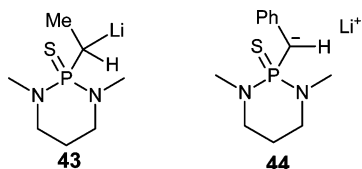
The method has been especially useful in cases where NMR coupling is not available, such as lithium enolates^{80,134a,b,139} and phenoxides,^{134d} or when ^{13}C enrichment is difficult, as in aryllithium triple ions.¹³⁵ Of course, E/Z isomers^{80a} or RR/RS pairs, either at the lithium center or elsewhere in the molecule,¹⁴⁰ can also play the role of providing mixed aggregates which code for the aggregation state. It is important to note that there are other sources of signal doubling (or multiplication) in *chelated* lithium reagents involving the relative arrangement or stereochemistry of chelating groups among the lithium binding sites.^{67,141–143}

A similar but less directly reliable method involves the use of various cosolvents, of which HMPA, TMEDA, PMDTA, and TMTAN (Figure 4) are especially useful. In this technique the low-temperature NMR spectra of one or more nuclei are observed as small increments of one of these cosolvents is added. The behavior of such solutions (both chemical shifts and number of species formed) can provide strong hints as to the aggregates present. Thus, addition of HMPA to solutions of the tetramer MeLi^{144} or acetophenone lithium enolate^{80a} provides a series of HMPA complexes readily identified by characteristic ^7Li chemical shifts and Li–P couplings. Four species are observed in addition to the THF-solvated tetramer, $(\text{RLi})_4\cdot(\text{HMPA})_1$ (1:3 ratio of ^7Li NMR signals), $(\text{RLi})_4\cdot(\text{HMPA})_2$ (2:2 ratio of signals), $(\text{RLi})_4\cdot(\text{HMPA})_3$ (3:1 ratio of signals), and $(\text{RLi})_4\cdot(\text{HMPA})_4$ (one signal), which could only form if the species was tetrameric. For a dimer, only two new species are observed, $(\text{RLi})_2\cdot(\text{HMPA})_1$ (1:1 ratio of ^7Li NMR signals) and $(\text{RLi})_2\cdot(\text{HMPA})_2$ (one ^7Li NMR signal, a doublet). Additional HMPA usually results in dissociation to monomers, which give only two new signals, $(\text{RLi})_1\cdot(\text{HMPA})_1$ (a doublet in the ^7Li NMR spectrum) and $(\text{RLi})_1\cdot(\text{HMPA})_2$ (a triplet).

Of course, the addition of cosolvents can also change the aggregation state, so chemical shifts of all pertinent nuclei have to be carefully monitored to check for signs of deaggregation (or occasionally even increased aggregation^{135,145}) during such experiments. Almost invariably a change in aggregation state will have much larger effects on the chemical shifts of nearby nuclei than replacement of one coordinating solvent or ligand by another. For example, the para carbon of the PhLi monomer changes by less than 0.1 ppm on replacement of THF by PMDTA or by HMPA, but moves 2.3 ppm upfield in the dimer and another 2 ppm in the tetramer.¹⁰³

The HMPA titration technique is especially useful in detecting the ion pair status for monomeric species, clearly showing, for example, that lithiated phenylacetonitrile is a

monomeric CIP in THF, which undergoes ion pair separation with HMPA,¹⁴⁶ that the lithiothiophosphonamide **43** is a CIP, and that the benzyl system **44** is an SIP.¹⁴⁷ Lithiated sulfone monomers and dimers in THF are converted to SIPs with HMPA.¹⁴⁸ This technique and others have been used to show that numerous methyllithium species with two anion-stabilizing groups (e.g., SR, SeR, SiR₃, Ph, vinyl, and alkynyl¹⁴⁹) are monomers in THF (CIP) and undergo ion pair separation with the addition of HMPA. The number of equivalents of HMPA required to cause ion separation is a sensitive measure of the strength of the ion pairing in the monomer CIP.



TMEDA also elicits characteristic behavior. Tetramers will typically show no interaction with TMEDA in THF solution, but if we are dealing with a dimer such as PhLi or dibenzyl ketone lithium enolate, TMEDA will often form two (and only two) new species, namely, (RLi)₂·(TMEDA)₁ and (RLi)₂·(TMEDA)₂.^{103,150}

Typically the tridentate ligands, such as PMDTA and TMTAN, will tend to form monomers, or they will interact weakly or not at all with RLi species. If the dimer association equilibrium is high, PMDTA can occasionally act as a bidentate ligand (weaker than TMEDA), leaving one amino group dangling. This is the case for vinylithium²⁹ and for [2-[(dimethylamino)methyl]phenyl]lithium (**21**)⁶⁷ and has also been seen in the solid state when a third coordination site is not available.¹⁵¹ Such behavior is readily recognized in the NMR spectrum at low temperatures, so these cosolvents are useful for characterization of RLi compounds at the monomer–dimer interface.

Another potent NMR technique involves diffusion experiments (DOSY, PGSE) in which molecular weight estimates for individual species in a solution can be made by NMR measurement of the rates of molecular diffusion.^{152,153} There is typically enough difference in diffusion rates to allow strong inferences about the aggregation state to be made and even some hints about the level of solvation.¹⁵⁴

An NMR parameter with the potential of providing information about structures in solution is the ⁷Li quadrupolar coupling constant (QCC), which is sensitive to both aggregation and solvation. Determination of the QCC requires measurement of the ⁷Li T₁, some estimate of the effective rotational correlation times, which can be obtained from ¹³C relaxation, and some estimate of molecular asymmetry.¹⁵⁵ The method has been used only occasionally,¹⁵⁶ and not in situations where an unknown aggregation state was established de novo, presumably because of the difficulty in both measuring the QCC and interpreting the data.

Finally, the electron density in the carbanion fragment varies significantly with the aggregation state, since the negative charge is substantially reduced for each C–Li contact, leading to the largest shift effects for separated ion pairs and sequentially smaller shifts for monomers (contact ion pairs), dimers (with two C–Li or O–Li contacts), and tetramers or higher aggregates (with three Li contacts). The chemical shifts of lithiated sp² and sp carbons are especially sensitive to aggregation.¹⁵⁷ Thus, there are often quite reliable empirical

correlations that can provide strong hints as to the aggregation state once the NMR properties of several aggregates of an RLi species have been established.^{67,158,159} A very nice example is provided by the carbon shifts of lithium enolates. When compared to a model, the trimethylsilyl enol ether, the ¹³C Δδ values of the enolate carbons are almost linear with the aggregation state (more specifically, with the number of O–Li contacts).¹⁶⁰

2.3. Aggregates and Mixed Aggregates of Principal Classes of Organolithium Reagents

2.3.1. Alkylolithiums. *Methyllithium* is a special case. Unsolvated MeLi in the solid state forms cubic tetrameric clusters with strong coordination of each lithium to the methyl of a neighboring cluster.^{9c} A tetrasolvated cubic tetramer crystallizes from THF.²⁷ It is also a tetramer in ether^{124b,161} and THF^{125b} solutions. Even the very polar cosolvent HMPA causes no detectable deaggregation, but sequentially replaces the coordinated ethers by HMPA.^{144a} Only strong chelating diamines can reduce the aggregation state to dimeric in the solid state.⁷⁶

The mixed aggregates between MeLi, LiI, and LiBr were identified by the earliest researchers in the area soon after NMR spectroscopy became available,¹⁶² and they have been carefully studied since then. In toluene all possible LiBr–MeLi homo- and heterotetramers have been characterized. They form in a close to statistical ratio.¹⁶³ A detailed NMR study in THF of 1:1 mixtures of MeLi–LiBr and MeLi–LiI using the isotope perturbation method^{125b,138b} showed that for LiBr (monomer in THF¹⁶⁴) a 66:17 ratio of (MeLi)₄ to (MeLi)₃·(LiBr) was present, in addition to 17% mixed dimer. Higher mixed aggregates were absent. For LiI (less aggregated than LiBr) a 9:1 ratio of (MeLi)₄ to (MeLi)₃·(LiI) was seen, in addition to trace amounts of the 2:2 mixed tetramer. Amazingly, addition of LiCl to MeLi in THF forms exclusively a well-characterized mixed dimer, suggested to be trisolated from DOSY measurements.¹⁵⁴

Several mixed aggregates of MeLi with amide ligands are known.^{7e,165,166} Methyllithium forms nearly statistical mixtures of mixed tetramers with *n*-BuLi in THF.¹⁶⁷

Ethyllithium is hexameric by cryoscopy in benzene and cyclohexane.¹⁶⁸ NMR studies show it to be a mixture of three higher aggregates in cyclopentane. Although precise assignments could not be made, they are probably hexamer, octamer, and nonamer in analogy with the more thoroughly characterized *n*-PrLi aggregates.^{125d}

n-Propyllithium has been used as a model for solution studies of *n*-BuLi, since it gives better resolved NMR signals. One of the earliest studies to use ⁶Li-enriched material to observe C–Li coupling was a detailed examination of *n*-PrLi in cyclopentane which showed it to be a mixture of hexamers, octamers, and nonamers.¹³¹ A well-defined mixed dodecamer of (*n*-PrLi)₈·(*n*-PrOLi)₄ was characterized in cyclopentane.¹⁶⁹

n-Butyllithium is by far the best studied of all organolithium reagents. A hexamer crystallizes from pentane,¹⁶ and it is mainly hexameric in hydrocarbon solvents,^{125d,170} tetrameric in diethyl ether,¹⁷⁰ and a tetramer–dimer mixture in THF (see Figure 7),¹⁷¹ with ΔG[‡] for interconversion of around 11 kcal/mol. Chelating diamines such as TMEDA^{28,127,150a,158,172} or TMCDA⁵ convert the tetramers and hexamers to biscomplexed dimers in hydrocarbon solution (although not necessarily in THF). No monomeric forms are known, although there is a suggestion, based on residual ⁷Li

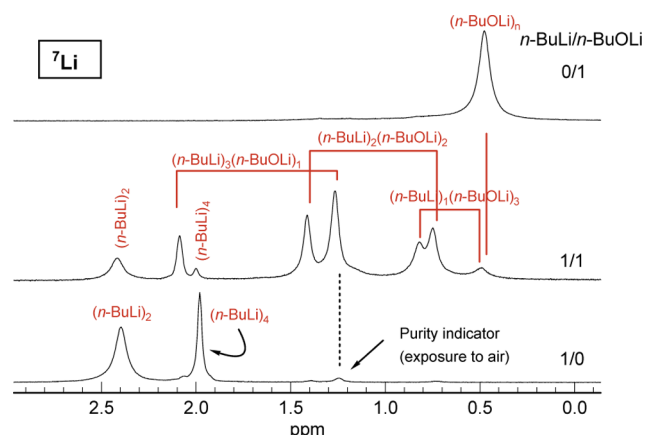
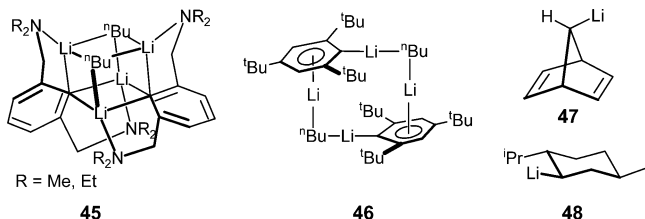


Figure 7. ^7Li NMR spectra of $n\text{-BuLi}$ and the mixed tetramers between $n\text{-BuLi}$ and $n\text{-BuOLi}$ in 1:3 THF– Me_2O solution (0.03 M) at -130°C . Reprinted with permission from ref 301a. Copyright 2007 Amanda C. Jones.

quadrupolar couplings, that $n\text{-BuLi}$ forms a monomeric complex with PMDTA.^{156e} Chelating triamines such as TMTAN and PMDTA, which will often produce monomeric structures with less tightly aggregated RLi species, form a variety of open tetramers (6).⁴⁰

The more hindered primary reagents, such as neopentyllithium, are less aggregated, being dimeric in diethyl ether and a mixture of monomer and dimer in THF. Well-characterized monomer complexes are formed with PMDTA and TMTAN.¹⁷³

Because of the extensive use of $n\text{-BuLi}$ for metalation reactions and as a model lithium reagent for asymmetric synthesis, numerous mixed aggregates have been detected, both in the solid state and in solution. Solid-state mixed cubic tetramers (2:2 RLi– $n\text{-BuLi}$) include the bischelated 2:2 $n\text{-BuLi}$ – ArLi cubic tetramer **45** (in toluene solution a mixture of 3:1 and 2:2 tetramers as well as the homodimer was characterized)⁵⁰ and a 2:2 $n\text{-BuLi}$ –chelated benzyl lithium system.^{125a,174} Mixed ladder tetramer **12** is formed by a bischelated ArLi. Similar ladders are formed by $n\text{-BuLi}$ and an α -(trimethylsilyl)benzyl system,^{51a} by $n\text{-BuLi}$ and two $\text{R}_3\text{SiCH}_2\text{Li}$ units,^{51b} between $t\text{-BuLi}$ and lithiated TMEDA,^{10h} and between $t\text{-BuLi}$ and metalated TMTAN.⁵² A hindered ArLi forms a 2:2 $n\text{-BuLi}$ π -complexed mixed tetramer, **46** (analogous to the homotetramer **10**).⁴⁶



Secondary allyllithiums are less aggregated than primary ones. $s\text{-BuLi}$ is a mixture of hexamer and tetramer in hydrocarbon solvents,¹³² as is $i\text{-PrLi}$.^{125d} In THF a mixture of dimer and monomer is seen for $s\text{-BuLi}$, which is converted entirely to monomers with PMDTA.¹²⁹ Several dimeric solid-state structures of $i\text{-PrLi}$ coordinated to diamines have been reported, as well as the interesting and unusual trimeric structure **18**, consisting of an $i\text{-PrLi}$ unit coordinated to a cyclic dimer.⁵⁹ Other secondary allyllithiums have also been

characterized in THF solution. 7-Norbornadienyllithium **47** is a mixture of mainly dimer and small amounts of monomer in THF.¹⁷⁵ The aggregation state of menthyl lithium (**48**) was not determined, but its unusually high reactivity (compared to $n\text{-BuLi}$ or $s\text{-BuLi}$) toward a number of electrophiles was attributed to steric inhibition of aggregation.¹⁷⁶

tert-Butyllithium crystallizes as a tetramer from pentane¹⁶ and is tetrameric in hydrocarbon solvents.^{125c,177} A disolvated dimer crystallizes from Et_2O ,¹⁶ and a dimer is seen in solution.¹²⁹ In THF $t\text{-BuLi}$ is exclusively monomeric.¹²⁹ A series of mixed tetramers and hexamers of $t\text{-BuLi}$ and $t\text{-BuOLi}$ have been characterized and their fluxional properties examined by DNMR spectroscopy.¹⁷⁸

The structure of an interesting mixed crystal consisting of one $(t\text{-BuLi})_4$ and four [2-(dimethylamino)phenyl]lithium homoaggregated tetramers was determined. On the mixed crystals being dissolved in toluene, the three possible mixed tetramers, as well as the two homotetramers, were characterized. Their equilibrium ratio was nonstatistical, significantly favoring the homotetramers. Exchange rates between the mixed aggregates were measured by ^7Li EXSY experiments.^{125e}

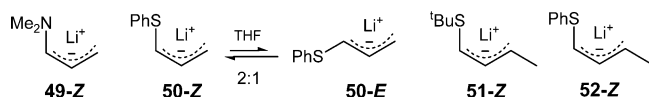
Lithium Amide Mixed Aggregates. Although out of scope for this paper, a number of mixed aggregates of MeLi , $n\text{-BuLi}$, $s\text{-BuLi}$, $t\text{-BuLi}$, and others with chiral lithium alkoxides,^{143c,179} alkoxy-substituted lithium amides,¹⁸⁰ amino-substituted lithium amides,^{7b,165b,181} and phosphino-substituted amides¹⁸² have been characterized in solution and in the solid state with the intent of understanding and optimizing asymmetric synthetic applications.

2.3.2. Allyllithiums. Lithium reagents with π -delocalized charge are typically less aggregated, with the π -system often occupying more than a single coordination site on lithium. Early colligative property measurements suggested allyllithium was polymeric in Et_2O (the TMEDA complex was found to be polymeric in the solid state¹⁸³) and approximately dimeric in THF on the basis of colligative property measurements,¹⁸⁴ including cryoscopy in THF.^{185a} The crystal structure of a monomeric PMDTA complex was reported.^{185b} Saunders's isotope perturbation experiments¹⁸⁶ suggest an asymmetric π -bonded structure.^{136,185a}

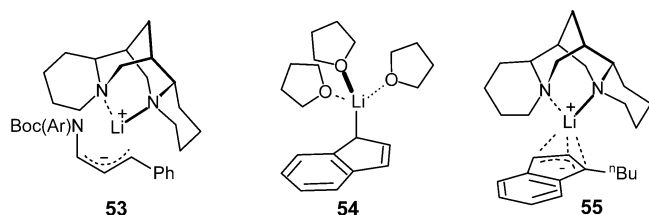
Allyllithium compounds substituted at the 1-position have the interesting property that the *Z* isomer is often preferred. This is true for simple alkyl substituents, with crotyllithium favoring the *Z* isomer 85:15 in THF.¹⁸⁷ Larger substituents than methyl, such as isopropyl (14:86) and *tert*-butyl (3:97), favor the *E* isomer. These numbers were determined from trapping studies, but NMR investigations confirmed the *Z* preference.¹⁸⁸ The preferences for the *Z* isomer are higher for less coordinating metals. With cesium as a counterion, even the isopropyl compound favors the *Z* isomer by 66:34.

Alkoxy-substituted allyllithium reagents (metalated allyl ethers) give only *cis* products when they react at the γ -position.¹⁸⁹ [1-(Dimethylamino)allyl]lithium **49** (mixture of monomer and dimer by NMR and cryoscopy) is all *Z* in THF.¹⁹⁰ [1-(Phenylthio)allyl]lithium **50** is monomeric in THF (cryoscopy¹⁹¹), and a 2:1 mixture of the *Z* and *E* isomers is seen in the ^1H and ^{13}C NMR spectra at -120°C in 3:2 THF– Et_2O . The signals coalesce above -70°C . When HMPA was added to form the SIP, a similar ratio of isomers was seen. [2-(Pyridylthio)allyl]lithium is also a 3:2 mixture of *Z* and *E* isomers.¹⁹² An X-ray structure of **51**–TMEDA showed the *Z* isomer.^{116a} Solution NMR studies suggested mainly the *E* isomer for **51** and the *Z* isomer for **52**. However, NMR spectra

were taken at 220 K, which may not have been low enough to decoalesce the rotamers.¹⁹³ Trialkylsilyl-substituted allyllithiums are exclusively in the *E* geometry,¹⁹⁴ although chelating substituents can force conversion to *Z* isomers to improve internal ion pairing.¹⁹⁵

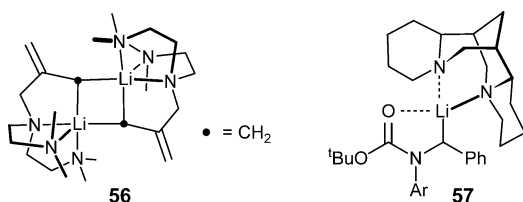


More complex allyllithiums such as the sparteine complex **53** also show a preference for the *Z* geometry.^{113a} However, strongly conjugating substituents generally prefer the *E* geometry, as in the X-ray structure of (1,3-diphenylallyl)-lithium.¹⁹⁶



Interesting insights into coordination and solvation of allyl systems is provided by the X-ray structures of **54** and **55**.¹¹² In the former, the Li is trisolated and the indenyl allyl system is monocoordinated to lithium. In **55**, the lithium is bicoordinated by the sparteine ligand and the allyl fragment is π -coordinated to lithium, in spite of the increased hindrance due to the butyl group. The π -coordinated allyl occupies two sites on lithium.

NMR studies of a series of allyllithiums with chelating substituents provided insight into the fine details of ion pair structures, localization of the lithium, and the dynamics of ion pair reorganization (e.g., **56**, which is dimeric in the solid state and in benzene).^{70,197,198,199}

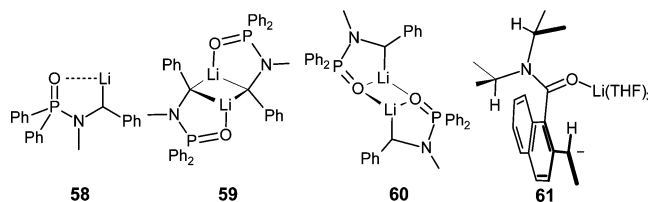


2.3.3. Benzylolithiums. Several crystal structures have been reported for benzylolithium. A polymer crystallizes from ether,^{66c} and an eight-ring tetramer complexed with $\text{MeOCH}_2\text{CH}_2\text{NMe}_2$ crystallizes from toluene.⁴³ This complex is dimeric in toluene solution. Monomeric benzylolithiums coordinated to TMEDA-THF,^{107a} quinuclidine,^{107c} and PMDTA have been crystallized.⁴³ Benzylolithium is also monomeric in THF solution.¹⁶¹ Examination of ^{13}C chemical shifts suggests weak C–Li bonding and extensive delocalization of the negative charge. This is also indicated by the unusually small and difficult to resolve (due to fast dynamics of C–Li bond exchange) ^6Li –C coupling of 3.8 Hz in THF for BnLi –TMEDA, compared to 17 Hz¹²⁹ for typical monomers.²⁰⁰ A similar small coupling was observed for a crown-belted BnLi .²⁰¹

$[\alpha\text{-(Dimethylamino)benzyl}]$ lithium solvated by Et_2O is dimeric in the solid state.⁸⁴ In THF solution it is monomeric and shows an interesting conversion from η^1 at low temperature to η^3 at high temperature, presumably associated with a thermal desolvation event (similar to **54** and **55**). The η^1

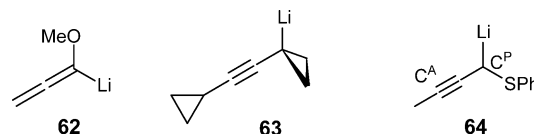
structure is also formed when PMDTA is added.²⁰² Other substituted benzylolithiums, such as $\text{Ph}(\text{PhS})\text{CHLi}\cdot(\text{THF})_3$ and $\text{Ph}(\text{Me}_3\text{Si})\text{CHLi}\cdot(\text{TMEDA})$, are monomeric in the solid state¹¹⁵ and in THF solution.^{203,204}

More complex benzylolithium species are also monomeric in THF solution, e.g., the sparteine complex **57**, as shown by the 1:1:1 triplet of C to ^6Li ($J = 3.9$ Hz).²⁰⁵ A lithiated *N*-benzylphosphinamide in Et_2O solution is a mixture of a monomer (**58**) and two isomeric dimers (**59** and **60**).²⁰⁶

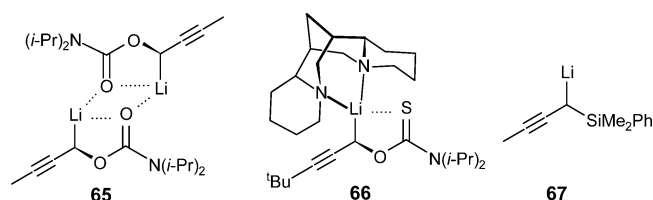


The laterally metalated naphthylcarboxamide **61** is monomeric, and the lithium is bonded not to the benzylic carbon but to the amide oxygen.²⁰⁷ The same type of structure was found for analogous lithiated benzamides complexed to PMDTA (e.g., **42**) or diethylene glycol dimethyl ether, although in the latter there was weak secondary bonding between lithium and the carbanion center.^{119,208}

2.3.4. Allenyllithiums and Propargyllithiums. The parent compound is unambiguously allenic, on the basis of the ^{13}C chemical shift of the central carbon at δ 196.4.²⁰⁹ Propargyllithiums have this carbon between δ 90 and δ 100. Allenyllithium is a mixture of dimer and monomer in THF solution.²¹⁰ (1-Methoxyallenyl)lithium **62** is a dimer in THF and a tetramer in Et_2O .²¹¹ All other simple alkylated allenyllithiums examined also have allenyl structures and are monomeric in THF.²¹⁰ An exception is the (1-alkynylcyclopropyl)lithium **63**, which is propargylic, presumably as a result of angle strain.²¹²

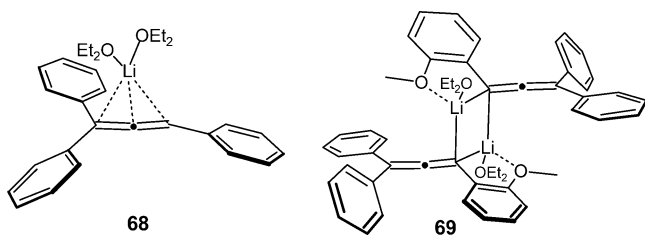


Propargyllithium reagents are formed when there is a carbanion-stabilizing group at the propargyl carbon, such as PhS (**64**), PhSe , or Ph (silyl does not quite do it) or a strong chelating group to fix the position of the lithium (as in **65**).^{210,213} An X-ray structure of a thiocarbonyl-substituted sparteine complex **66** showed localized bonding of lithium to the propargyl carbon.²¹⁴

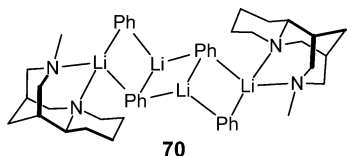


Saunders's isotope perturbation experiments¹⁸⁶ with deuterium-labeled allenyllithiums whose NMR properties are intermediate between those of allenyl and propargyl (phenyl and silyl at the propargyl carbon, as in **67**) show that there is a close balance between π -type bonding and localized bonding of lithium to either the allenyl or propargyl terminus of the anion.²¹⁵ This is also seen in a pair of X-ray structures. The

triphenyl compound **68** is a disolvated π -complex in which the allenyl anion takes up two coordination sites, whereas the *o*-methoxy analogue **69** is a four-center dimer with localized bonding at the allenyl carbon, presumably the result of favorable chelation.⁶⁹



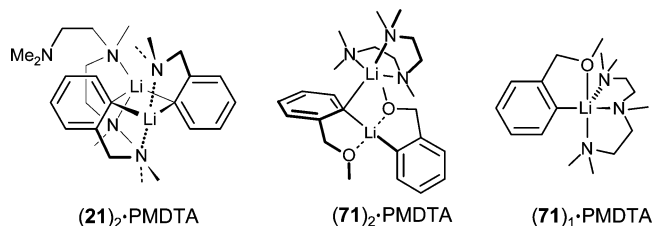
2.3.5. Aryllithiums. Numerous aryllithium reagents have been characterized in the solid state and in solution. Most intensively studied is the parent PhLi. A cubic tetramer crystallizes from diethyl ether,^{30a} and a mixture of tetramer and dimer is seen in diethyl ether solution. In THF a mixture of dimer and monomer is found (Figure 5).^{103,129} In toluene or ether, TMEDA converts PhLi to a biscomplexed dimer,⁷¹ whereas in THF, TMEDA complexes the monomer and dimer nearly equally and the net aggregation state is unaffected. 12-Crown-4 does not detectably complex PhLi in THF, but does increase the reactivity.¹⁰³ PMDTA causes nearly quantitative conversion to a monomeric PMDTA complex.^{103,129} A chiral diamine related to sparteine forms the ladder tetramer **70** with PhLi.³⁷ Sparteine itself also forms such structures.³⁶



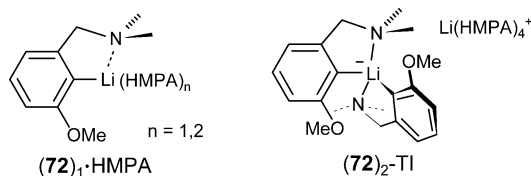
Substituted aryllithium reagents follow a similar pattern. Steric effects are pronounced as illustrated in Figure 2. Mesityllithium is monomeric in dilute solution in THF¹³⁵ (although it crystallizes as a THF-solvated dimer¹⁹⁸) and dimer is present in THF–toluene solution.²¹⁶ PMDTA forms a monomeric complex.^{129,195} (2,4,6-Tri-*tert*-butylphenyl)lithium is entirely monomeric in THF.^{129,195} An unprecedented series of solvates for the dimer of 9-lithioanthracenes were characterized by single-crystal X-ray analysis. The series included the (OEt₂)₂ complex, as well as the (OEt₂)₂·THF, (OEt₂)₂·(THF)₂, (OEt₂)₁·(THF)₃, and (THF)₄ solvates. The structures reveal in a direct way the better solvating power of THF over Et₂O and illustrate subtle changes in geometry to allow better interactions between carbanion carbons and lithium as the level and strength of solvation change.¹¹

In contrast to PhLi and alkyl-substituted phenyllithiums, which are substantially or entirely monomeric in THF, aryllithiums with chelating substituents tend to be more dimerized. Thus, for [2-[(dimethylamino)methyl]phenyl]lithium (**21**)⁶⁷ and [2-(methoxymethyl)phenyl]lithium (**71**)¹² only dimers are detectable, with $K_{MD} > 20\,000\text{ M}^{-1}$ in 3:2 THF–ether, compared to PhLi, with $K_{MD} = 210\text{ M}^{-1}$. The chelated RLi also have higher kinetic barriers for dissociation of dimer to monomer ($\Delta G^\ddagger = 8.3\text{ kcal/mol}$ for PhLi at -101°C and $>12.5\text{ kcal/mol}$ for (**21**)₂ at -36°C). These chelated dimers are “sturdy” enough that PMDTA does not convert them fully to monomers, unusual for dimers. PMDTA behaves as a bidentate ligand, forming (**21**)₂·PMDTA and leaving the

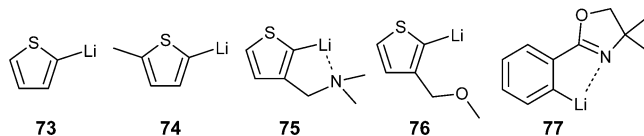
four-center core intact. With the chelated ether **71**, PMDTA forms a mixture of a rare open dimer structure, (**71**)₂·PMDTA, as well as the PMDTA monomer pentacoordinate at lithium.¹² Even a single chelating group favors dimerization: mixtures of PhLi and **21** as well as PhLi and **71** form monochelated mixed dimers with more favorable equilibrium constants and a higher barrier to dissociation than PhLi homodimer.



PhLi and virtually all other substituted aryllithiums examined form significant fractions of triple ions (ArLiAr[−]·Li(HMPA)₄⁺) in THF–HMPA solutions.^{12,67,103,135} For several 2,6-disubstituted phenyllithiums (Me₂, *i*-Pr₂, (MeO)₂) more than half of the lithium species were triple ions in THF at 2 equiv of HMPA.¹³⁵ [6-Methoxy-2-[(dimethylamino)methyl]phenyl]lithium **72** is a mixture of dimer and monomer in THF. The addition of HMPA leads to 15% (**72**)₂·TI triple ion, with the rest a mixture of the mono- and bis-HMPA complexes of the monomer (**72**)₁·HMPA. In the triple ion the central lithium is coupled to both nitrogens in the ⁶Li–¹⁵N doubly enriched compound, showing that even the presumably very electron rich central lithium of a triple ion retains some electrophilic properties.⁶⁷



2-Lithiothiophene (**73**) and 5-methyl-2-lithiothiophene (**74**) have aggregation behavior very much like that of PhLi. X-ray structures have been obtained of ether-solvated tetramers^{30e,217} of THF-, DME-, and TMEDA-solvated dimers and of a PMDTA-solvated monomer.²¹⁷ In THF solution, both **73** and **74** are mixtures of monomer and dimer.²¹⁸ Like the phenyl analogues, the amine-chelated compound **75** also showed an enhanced aggregation due to a chelation effect. The model compound **74** had $K_{MD} = [D]/[M]^2 = 2.1\text{ M}^{-1}$ at -136°C in 3:2:1 THF–Me₂O–Et₂O and was much less aggregated than **75** ($K_{MD} = 15\,900\text{ M}^{-1}$). However, in contrast to **71**, the ether-chelated thiophene **76** was comparably aggregated to the unchelated models ($K_{MD} = 3.3\text{ M}^{-1}$).¹⁴²

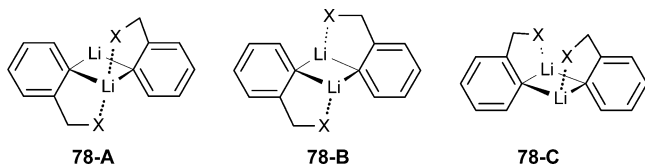


The chelation–aggregation correlation is seen elsewhere as well. 8-Lithio-1-methoxynaphthalene is dimeric in THF (no monomer seen),^{68d} even though it is more sterically hindered and probably has better charge delocalization than PhLi. (2-Oxazolinyphenyl)lithium **77** crystallizes as a chelated dimer from THF and in solution is slightly more aggregated than is *o*-tolyllithium, in spite of the steric demand and electronic

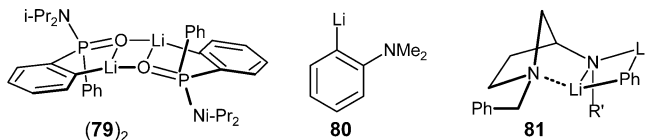
stabilization of the substituent.¹³ [2,6-Bis(oxazolynil)phenyl]-lithium is dimeric in the solid state and remains dimeric with THF present.^{65b}

This effect also seems to be operative in other types of lithium reagents. (Triphenylallenyl)lithium **68** is a monomeric dietherate in the solid state. Replacing one of the phenyls by a 2-methoxyphenyl produced a chelated dimeric structure, **69**.⁶⁹ Although aggregation effects are complicated, it may be that a chelating group uses the coordination space around lithium more efficiently, leaving room for dimerization and additional solvation.

Chelated aryllithium reagents can exist as mixtures of chelation isomers (**78**), which are often in slow exchange on the NMR time scale at low temperature. Isomer **A** has two different lithium environments and so can be distinguished from **B** and **C**, which are hard to differentiate. Most commonly seen is isomer **B**,^{13,68,208} but several type **A** crystal structures have been reported^{67,219} (especially diamine complexes²²⁰ as in (**21**)₂·TMEDA⁶⁷). In solution, mixtures of two²²¹ or even all three^{67,142} isomers have been detected. Such isomerism has also been seen for chelated alkylolithium reagents.^{65a,141}



Although ArLi dimers almost always have a four-center C–Li–C–Li core, alternate modes of dimerization are seen when other basic sites are present. For an ortho-lithiated phosphinamide **79** three components were characterized by NMR spectroscopy in THF, a chelated monomer and a Li–O–Li–O-coordinated dimer (**79**)₂ and its stereoisomer (inversion at one P-center).²²² Note that such dimers can be mistaken for monomers in NMR studies because the C–Li carbon shows coupling to only a single lithium.

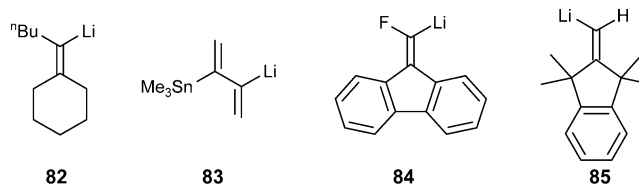


[2-(Dimethylamino)phenyl]lithium **80** forms mixed tetramers with *t*-BuLi in toluene, but the homotetramers are thermodynamically favored.^{125e} A mixed dimer, **81**, between PhLi and a chiral amide has been spectroscopically characterized in THF solution,²²³ as has the mixed dimer between **71** and PhLi.¹²

2.3.6. Vinyllithiums. Vinyllithium reagents are readily prepared by direct lithiation of halides, by the Li/I, Li/Br, or Li/Sn exchanges, by metalations,²²⁴ and by more indirect methods such as carbolithiation of acetylenes or metalation of tosylhydrazones (Shapiro reaction).²²⁵ They have been widely used as synthetic reagents.²²⁶

Vinyllithium itself has been crystallized as a tetra-THF-solvated tetramer, and it is a mixture of mostly tetramer and some dimer in THF (by NMR spectroscopy²⁹ and vapor pressure osmometry²²⁷). TMEDA in THF causes some increase in the fraction of dimer, but complete dimer formation occurs in toluene. PMDTA does not form monomer, but behaves as a bidentate ligand.²⁹

Any increase in steric effects or electronic stabilization will tend to lower the level of aggregation, but few systems have been studied in detail. (α -Ethoxyvinyl)lithium in THF is a cubic tetramer.²²⁸ The trisubstituted vinyllithium **82** is a dimer in THF.¹²⁷ Proton NMR studies of the interaction of THF with 1-lithio-1-phenyl-1-butene (formed in hexane) suggested a monomeric structure.²²⁹ The dienyllithium reagent **83** is monomeric in THF (NMR C–Li coupling), as is the PhMe₂Si analogue.²³⁰ The fluorenyl derivative **84**²³¹ and several other (α -halovinyl)lithiums are also monomeric in THF.¹²⁷

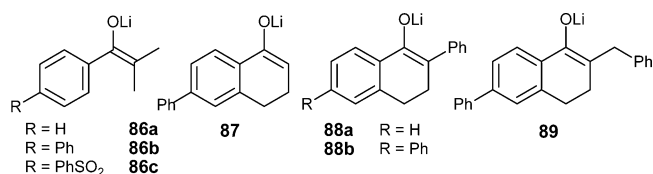


The hindered vinyllithium **85** has been studied carefully. It is a mixture of dimer and monomer in THF solution and exclusively a dimer in *t*-BuOMe. A disolvated dimer crystallizes from ether.^{232a} The more hindered and more delocalized reagent **15** crystallizes as a trimer from hydrocarbons.⁵⁵ A trimer is formed in toluene solution, as shown by the ingenious technique of comparing the low-temperature C–Li signal (coupling to two lithiums) with the higher temperature one when fast intramolecular exchange occurs (coupling to three lithiums), which gave a pattern unique for a trimer.¹³⁰ With 1 equiv of the donor solvent Et₂O, THF, or *t*-BuOMe added to a toluene solution of **15**, disolvated dimers form (also seen in X-ray structures), whereas with excess donor solvent monomers are formed, with the rare property that solvent exchange is slow on the NMR time scale. The lithium in the monomers is only disolvated, presumably for steric reasons. A few other cases with slow solvent exchange in organolithium reagents have been reported (see section 3.2.2).

2.3.7. Lithium Acetylides. Lithium *tert*-butylacetylide crystallizes as a THF-solvated cubic tetramer^{31c} and is mostly a tetramer in THF,^{31a} with Li–C coupling resolvable below –80 °C. Some dimer may be present, as cryoscopic measurements show $n = 2.88$.¹²² Cyclopropylacetylide is a tetramer–dimer mixture in THF.²³³ Lithium acetylides with carbanion-stabilizing substituents (biphenyl,²³⁴ Ph,^{122,235–237} Me₃Si,²³⁸ Ph₃Si,²³⁸ PhS²³⁸) are dimeric or even monomeric (PhSO₂²³⁸) in THF solution. A diamine-complexed dimer of phenylacetylide has been crystallized.^{31b} A series of mixed alkoxide–acetylide tetramers have been characterized in connection with asymmetric additions of acetylides to ketones and aldehydes.^{143b,d}

2.3.8. Lithium Enolates. *Ketone Enolates.* The first thorough NMR investigation of the aggregation state of a lithium enolate solution was reported in a series of papers on lithioisobutyrophenone **86a** by the Jackman group.^{159,239,240} They concluded that in dioxolane and THF **86a** was tetrameric, and they detected two solvation states, probably the tetrasolvate and trisolvate.^{33a} In DME some tetramer was observed, but the major species was a dimer. A mixed tetramer, (**86a**)₃·(LiCl)₁, was also characterized, and it was shown that the rate-determining step for exchange between this species and (**86a**)₄ was dissociation of the former, probably to dimers.

X-ray structures soon confirmed the aggregated nature of lithium enolates. All have lithium coordinated only to oxygen. In the absence of solvents, pinacolone¹⁹ and isobutyrophen-



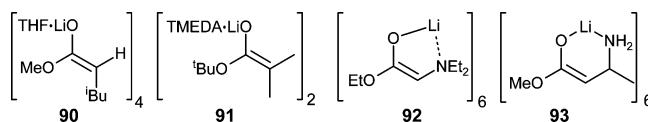
none²⁰ enolates crystallize as hexamers, whereas cubic tetramers crystallize from THF, with one THF coordinated to each lithium.³² A number of additional X-ray structures of TMEDA- and ether-complexed dimers^{20,79,241} and PMDTA-complexed monomers⁸⁰ have been determined. In solution NMR methods are less effective than for C-bound lithium species because of the absence of Li–O coupling information, but the structures of a number of enolates are now known with some assurance. The lithium enolate of acetaldehyde is tetrameric in THF, as judged from detailed NMR studies. A second species, suggested to be a different solvate, was detected, but is more likely a mixed aggregate or possibly a hexamer, since solvent exchange is now known to be much faster than observed.^{242b} Within the limits of NMR detection, unconjugated unhindered enolates such as cyclopentanone, cyclohexanone,^{80a,134b,243} acetophenone,^{80a,243} and pinacolone²⁴⁴ are all tetramers in THF. With more sensitive UV detection, more dilute solutions could be examined, and enolates of *p*-phenylisobutyrophenone **86b**²⁴⁵ and 6-phenyltetralone **87**²⁴⁶ were shown to be tetramer–monomer mixtures in THF.

The ketone enolates of cyclopentanone, cyclohexanone, acetophenone, and isobutyrophenone, all tetrameric in THF, form dimers with TMEDA in hydrocarbon solution,^{134c} and such dimers have also been seen in the solid state for isobutyrophenone²⁰ and pinacolone.²⁴¹ Interestingly, addition of TMEDA to the tetramer solution of, for example, lithio-*p*-fluoroacetophenone in THF does not form dimers.^{80a} A metastable dimer can be observed in RINMR experiments if the TMEDA complex is injected into THF at $-120\text{ }^{\circ}\text{C}$, where its dimerization to tetramer in the presence of TMEDA can then be readily followed.¹⁶⁰ Even PMDTA or TMTAN does not convert several of the tetrameric ketone enolates to lower aggregates.^{80a}

More hindered, inductively stabilized or conjugatively stabilized enolates tend to be dimeric in THF, with monomer sometimes an observable minor component: the enolates of 1,2-diphenyl-2-ethanone (also X-ray),^{80b} 1,3-diphenyl-2-propanone,^{80b,247} 2-phenyltetralone **88a**,²⁴⁸ and 6-phenyl-2-benzyltetralone **89**.²⁴⁶ In several cases (dibenzyl ketone, phenyl benzyl ketone) dimeric enolates were converted to monomeric PMDTA or TMTAN complexes in solution and also in the solid state.^{80b} HMPA converted the enolate of bis(*p*-fluorobenzyl) ketone (dimeric in THF) to HMPA-complexed monomers, triple ions $(RO)_2Li^-\cdot Li^+$, and a higher lithiate, $(RO)_3Li^{2-}\cdot (Li^+)_2$.^{80a}

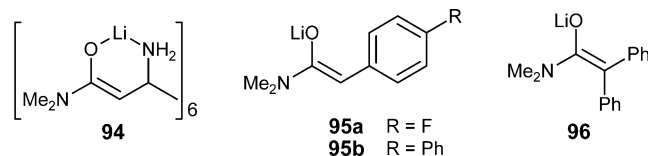
Ester enolates follow a pattern similar to that of the ketone enolates, although far fewer structures are known. Methyl α -*tert*-butylacetate enolate (**90**) forms a THF-solvated tetramer in the solid state, and *tert*-butyl isobutyrate (**91**) and *tert*-butyl propionate enolates form dimeric TMEDA complexes.²⁴⁹ *tert*-Butyl propionate is dimeric in THF from cryoscopic measurements.¹²² Like ketone enolates, several esters and lactone enolates were shown to form dimers in TMEDA–toluene solutions.^{134c} The enolate of methyl isobutyrate has been studied as a model for the living end during the anionic

polymerization of methyl methacrylate. In THF solution a dimer–tetramer mixture was found.²⁵⁰ A later study²⁵¹ detected in addition two isomeric trimers. No proposal was made for the nature of the isomerism of the trimers. *tert*-Butyl isobutyrate is tetrameric in THF and forms mixed tetramers with *t*-BuOLi.²⁵²



Two chelated ester enolates, ethyl α -(diethylamino)acetate (**92**)²⁵³ and the β -amino enolate **93**^{254a,140} are hexameric in the crystal. The latter is also hexameric in THF solution. It is possible that these higher aggregation states represent additional examples of the chelation effect noted in the section on ArLi structures (Section 2.3.5).

Amide Enolates. The chelated β -amino amide enolate **94** forms hexamers in THF.^{254b} The *N,N*-dimethylarylacetonide enolates **95a** and **95b** are mainly dimers in THF, with monomer detectable for the latter ($K_{MD} = 450\text{ M}^{-1}$).^{255a} PMDTA forms monomeric PMDTA and HMPA complexes with **95a**. HMPA in addition forms triple ions and a higher lithiate, $(RO)_3Li^{2-}\cdot (Li^+)_2$.^{80b} The more hindered and conjugated **96** is less aggregated, with $K_{MD} = 40\text{ M}^{-1}$.^{255b}

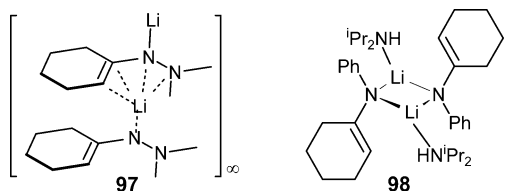


N-Methylpyrrolidinone, *N,N*-dimethylacetamide, and *N,N*-dimethylpropionamide enolates form dimeric TMEDA complexes in toluene solution^{134c} and in the solid state.²⁴¹ Their structures in THF have not been reported. More complicated lactams also crystallize as TMEDA dimers.²⁵⁶

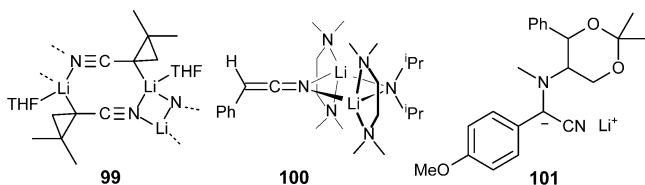
Mixed aggregates have been detected between ketone, ester, and amide enolates and lithium amides,^{49,78,160,254b,257–259} lithium halides,^{54b,159,260} or even both halide and amide (compound **14**)^{54a}.

2.3.9. Lithiated Imines. The nitrogen analogues of enolates have found important applications in organic synthesis,²⁶¹ but their structures have been studied to a much lesser extent than those of enolates. Lithium is typically primarily bonded to nitrogen, but there is a larger tendency to bond to the π -system as well compared to enolates. Lithiated cyclohexanone *N,N*-dimethylhydrazone (**97**) forms an unsolvated polymeric structure when crystallized from THF in which lithium is η^4 -coordinated to one enamine anion, as well as η^1 -coordinated to the enamine nitrogen of another one. In THF solution the osmometric molecular weight indicated a predominantly tetrameric structure.¹⁴⁰ A bis(diisopropylamine) solvate of lithiated *N*-phenylimine **98** has a normal four-center dimer structure.⁸¹ In THF solution a mixture of dimer (*cis* and *trans* stereoisomers) and monomer was detected.²⁶² The *N*-cyclohexylimine showed more complicated behavior with monomers, monosolvated and bis-solvated dimers, and stereoisomeric trimers detected in THF or THP solution.²⁶³

2.3.10. Lithiated Nitriles. Considering their extensive use in synthesis,²⁶⁴ relatively little is known about this class of lithium reagents. Lithiated acetonitrile is not very soluble in common solvents, but a molecular weight determination by



cryoscopy in DMSO indicated tetramers.^{265a} Cryoscopy in THF suggested a nearly monomeric aggregation state,¹²² but some caution is in order about this assignment since LiCH_2CN forms both mixed dimers (in THF) and trimers (in Et_2O) with chiral chelated lithium amides in which both C–Li and N–Li contacts are detected.^{265b,c} Both N–Li and C–Li contacts were also present in the polymeric solid-state structure of (cyanocyclopropyl)lithium **99**.²⁶⁶

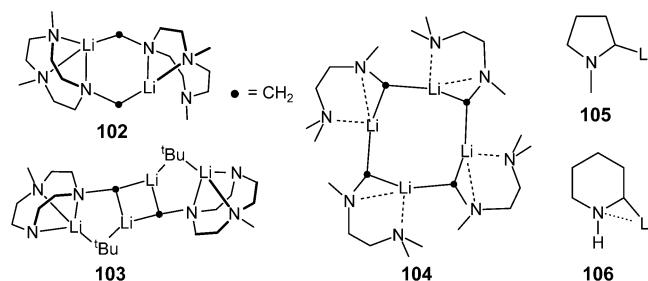


The X-ray crystal structure of lithiophenylacetonitrile–TMEDA shows an N–Li four-center dimer structure,²⁶⁷ as does a mixed dimer with LDA (**100**).²⁶⁸ In solution the TMEDA and Et_2O complexes are also N-coordinated four-center dimers, as shown by observation of Li–N coupling in the NMR spectra and no detectable C–Li coupling. A mixed dimer with $\text{LiN}(\text{SiMe}_3)_2$ was characterized in toluene solution. In THF lithiophenylacetonitrile is nearly monomeric by cryoscopy;¹²² no Li–N coupling could be observed, and no mixed aggregates with $\text{LiN}(\text{SiMe}_3)_2$ were detected.²⁶⁹ HMPA causes ion separation.¹⁴⁶ Several (α -aminocyanobenzyl)lithiums solvated by THF and Et_2O also show four-center NLi dimers in the solid state. One (**101**) was shown to be monomeric in THF by low-temperature cryoscopy.²⁷⁰

2.3.11. Lithiated Amines. X-ray structures of simple (aminomethyl)lithiums have shown that $\text{Me}_2\text{NCH}_2\text{Li}$ forms a THF-tetrasolvated ladder tetramer, **5**,³⁹ and $(\text{CH}_2)_4\text{NCH}_2\text{Li}$ a THF-disolvated cubic tetramer.^{66a} $\text{Ph}_2\text{NCH}_2\text{Li}$ forms a THF-trisolvated four-center dimer.^{66a} The lower levels of solvation are a consequence of the routinely observed coordination of not just carbon but also the nitrogen to the lithium.

The common polyamine ligands are often used with $n\text{-BuLi}$ and other alkylolithiums. This has led to the formation of a series of lithiated amines. PMDTA is readily metalated at a terminal methyl group. The carbanion carbon showed coupling to only one lithium in pentane solution. This, together with cryoscopic measurements in benzene ($n = 1.06$), suggested a monomeric structure.²⁷¹ A later crystal structure of the six-center dimer **26** led these workers to suggest that dimer might also be present in solution, which would explain the coupling and the unexplained signal doubling observed.⁴⁰ Lithiated TMTAN²⁷² forms an analogous six-center dimer, **102**, as well as a 2:2 mixed ladder tetramer, **103**, with $t\text{-BuLi}$.⁵² Metalated TMCDA **8** forms a six-center trimer,^{58a} an eight-center tetramer, and a 2:2 mixed tetramer^{44a} with $t\text{-BuLi}$. Metalated TMEDA forms an eight-center tetramer, **104**.^{44b}

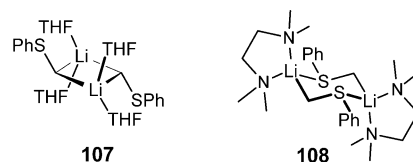
Metalated amines and amides have been of considerable interest in asymmetric synthesis. In this context the solution structures of lithium reagents **105** and **106** have been examined.²⁷³ The pyrrolidine **105** appears to be a four-center



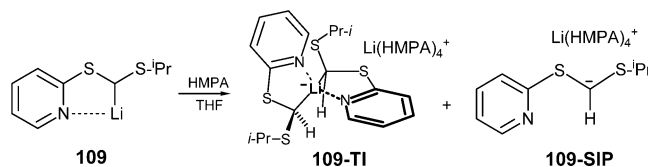
dimer in THF from the coupling to two lithiums observed for the C–Li carbon in the ^{13}C NMR spectrum. No sign of *meso* and *dl* diastereomers was detected, so either the dimers are homochiral or the diastereomers have identical NMR signals. The *N*-ethyl analogue of **105** is a mixture of monomer and dimer.²⁷⁴ Lithiated piperidine **106**, on the other hand, shows coupling of lithium to only one carbon, as well as to nitrogen (in the ^{15}N -enriched compound), so a monomeric structure with N–Li coordination is indicated, although a six-center dimer (analogous to **102**) was not ruled out. There is certainly precedent for closely related structures forming four- and six-centered dimers, as in the TMEDA-complexed RSCH_2Li in section 2.3.12.⁷⁵

2.3.12. Lithiated Sulfides. A variety of lithio sulfides have been used in organic synthesis, most prominently 2-lithio-1,3-dithiane and related compounds. Lithiodithiane itself is monomeric in THF.^{149c,275} The 2-methyl analogue crystallizes as a TMEDA-complexed six-center dimer (**27**),⁸⁵ but in THF solution it is a monomer by cryoscopy¹²² and NMR spectroscopy.^{149c} 2-Phenyldithiane crystallizes as a solvated monomer²⁷⁶ and is also monomeric in THF.²⁷⁷ Several lithiodithianes investigated gave SIPs on treatment with HMPA.^{149c,277}

Crystal structures of PhSCH_2Li have included a monomeric PMDTA complex,²⁷⁸ a polymeric alternating four-ring, six-ring THF-solvated ladder polymer, a four-center THF-solvated dimer, **107**,^{66b} and a six-center dimeric TMEDA complex, **108**.⁷⁵ These results, and the observation that MeSCH_2Li forms a four-center TMEDA-complexed dimer, shows how close the balance is between the four- and six-ring dimers.



In THF (cryoscopy)¹²² and Me_2O solutions (J_{CLi}),⁷⁵ PhSCH_2Li seems to be monomeric. Several (bisthiomethyl)-lithium reagents, such as **109**, are monomeric in THF, but when HMPA is added, they partially dimerize to the triple ion **109-TI**, before forming the SIP **109-SIP**.¹³⁵



A characteristic feature of solid-state and solution structures of S-substituted (as well as Se-, Si-, and P-substituted) alkylolithiums is the strong preference for close alignment of the C–Li bond (or carbanion lone pair orbital) with the C–S

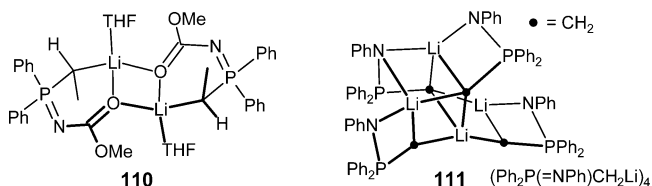
bond. This lone pair σ^* -interaction is strong enough that pronounced conformational preferences are seen^{149b,279} and that rotation around the C–S bond rather than pyramidal inversion at carbon is the principal barrier to enantiomerization of such compounds.^{149a,280}

2.3.13. Lithiated Sulfones. These typically have lithium bonded to oxygen in the solid state, either in monomeric structures²⁸¹ or in eight-membered ring dimers (30),^{90a,c,282} leaving a bare or weakly coordinated carbanion carbon.^{90b,148} The carbanion is sufficiently stabilized that [2.1.1]crypt causes ion separation in the solid state for lithiated isopropyl phenyl sulfone.²⁸³ Solution structures are less well-defined, but sulfones seem to be minimally aggregated in THF (mostly dimers and monomers).^{148,281,284} Much is known about the stereochemistry of the lithio sulfones, which can even be prepared in optically active form at low temperature.²⁸⁵ Like the lithiated sulfides, their chirality is a consequence of restricted rotation rather than inversion at carbon.

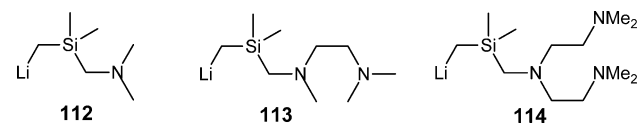
2.3.14. Lithiated Phosphines. The TMEDA complex of $\text{Ph}_2\text{PCH}_2\text{Li}$ crystallizes as a monomer, and it is probably monomeric in THF as well.²⁸⁶ An infinite chain of four- and six-ring ladders crystallizes from THF.⁸⁷ Several other lithiated phosphines crystallize as six-center dimers, including $\text{Me}_2\text{PCH}_2\text{Li}$ –TMEDA,^{86a} $\text{MePhPCH}_2\text{Li}$ –TMEDA,²⁸⁷ $\text{Me}_2\text{PCH}(\text{SiMe}_3)\text{Li}$ –TMEDA, $\text{Me}_2\text{PC}(\text{SiMe}_3)_2\text{Li}$,^{86c} and $(\text{Me}_2\text{P})_3\text{CLi}$ –THF.²⁸⁸ A 9-membered ring cyclic trimer (19)⁶⁰ and a 12-membered chelated open tetramer of $(2-(\text{Me}_2\text{NCH}_2)\text{C}_6\text{H}_4)_2\text{PCH}_2\text{Li}$ are also known.⁴⁵

2.3.15. Lithio Phosphine Oxides. Like enolates, sulfones, and sulfones, lithiated phosphine oxides,²⁸⁹ phosphonates,^{107b} and phosphonamides⁸² are often O-lithiated in the solid state. A solid-state tetramer in which Li–O links form the central cube, with each lithium chelated by the carbanion carbon, has been reported.²⁹⁰ Solution structures appear to be similar.^{206,222}

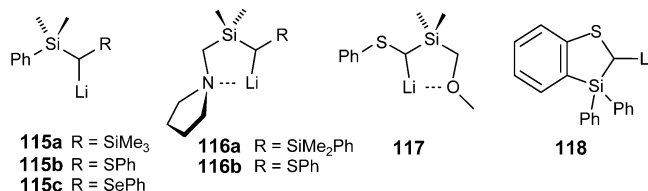
The related phosphine imines (phosphazenes) tend to have both N and C coordinated to Li in monomeric,²⁹¹ dimeric (110),²⁹² or open tetramer (111)^{53,293} structures.



2.3.16. Lithiated Silanes. Lithiated silanes follow the structural pattern of hindered alkyl lithium reagents. Thus, $\text{Me}_3\text{SiCH}_2\text{Li}$ has been crystallized as an unsolvated hexamer,¹⁸ a tetrameric bis- Et_2O complex,²⁶ and a four-center dimer complexed to DME,²⁶ TMEDA,¹¹⁰ $\text{Me}_3\text{NCH}_2\text{CH}_2\text{OMe}$,⁴³ and sparteine.¹¹⁰ A monomeric PMDTA complex is also known.^{110,294} In cyclohexane solution $\text{Me}_3\text{SiCH}_2\text{Li}$ is a hexamer and in benzene a tetramer, with higher aggregates appearing at molar concentration.¹⁷⁰ As usual, chelated, more hindered or more stabilized α -lithiosilanes are less aggregated. Thus, 112 forms a tetramer in benzene solution, 113 a dimer, and 114 a monomer.²⁹⁵



A variety of lithiosilanes with an additional anion-stabilizing group, such as R_3Si (115a, 116a^{149d}), PhS (115b,^{149a} 117,^{149d} 116b,^{149d} 118^{149b}), and PhSe (115c^{149a}), are all monomeric in THF, and all readily form SIPs (as well as some triple ions) on addition of HMPA. The chelated compounds (116, 117) require substantially higher HMPA concentration to undergo ion separation.



Silanes with two additional carbanion-stabilizing groups, such as $(\text{PhS})_2(\text{PhMe}_2\text{Si})\text{CLi}$, are SIPs in THF solution and have quite high barriers to enantiomerization as a result of high rotation barriers.^{149a} Lithium reagents with three silyl groups on the anionic carbon form several unusual structures as a result of extreme steric effects. Most notably, $(\text{Me}_3\text{Si})_3\text{CLi}$ is a mixture of the SIP, the CIP, and the triple ion in THF solution (see section 3.5.3).^{93,296,297} X-ray structures of $(\text{PhMe}_2\text{Si})_3\text{CLi}$ show a mono-THF-solvated monomer^{64b} and $(\text{MeOMe}_2\text{Si})_3\text{CLi}$, a complex eight-ring cyclic dimer in the solid state.⁸⁹

Table 1 summarizes the aggregation states of representative simple lithium reagents in hydrocarbon, Et_2O , and THF solution.

3. ORGANOLITHIUM REACTION MECHANISMS

3.1. Mixed Aggregates

As soon as the aggregated nature of lithium reagents was established, it became clear that mixed aggregates must form²⁹⁸ and that they might well play crucial roles in the chemistry. Indeed, early workers noticed significant reduction in reactivity of $n\text{-BuLi}$ when LiBr or LiCl was present.²⁹⁹ Virtually all organolithium reagents produce new lithium species when they react with substrates, and if the product and starting materials are aggregated, then mixed aggregates will almost inevitably be formed during the reaction, and these will get involved in the chemistry. Indeed, during the first observation of C–Li J coupling in MeLi ,^{124a} a mixed aggregate with LiI was observed, left over from formation of MeLi from MeI , later shown to be $(\text{MeLi})_3\cdot(\text{LiI})_1$. Kinetic studies of organolithium reactions thus routinely use the method of initial rates to minimize interference from mixed aggregates formed during a reaction.

Mixed aggregates may be deliberately formed in attempts to modify the behavior of organolithium reagents, for example, by the addition of lithium halides (especially LiCl , which affects solubility and reactivity profiles³⁰⁰) or by the addition of chiral additives to induce asymmetric behavior. They can also be inadvertently introduced into reaction mixtures through the presence of impurities. For example, $n\text{-BuLi}$ solutions will almost invariably contain small amounts of the mixed tetramer $(n\text{-BuLi})_3\cdot(n\text{-BuOLi})_1$ from reaction with oxygen.^{171b} See Figure 7 for ^7Li NMR spectra of $n\text{-BuLi}$ and the mixed alkoxides formed when $n\text{-BuOH}$ is added to $n\text{-BuLi}$.

The physical methods using colligative properties for determination of the aggregation state were poorly suited for dealing with mixed aggregates, and only the spectroscopic methods (especially NMR) are available to provide insight into solution behavior. Indeed, mixed aggregates are almost

Table 1. Solution Aggregation Levels of Representative Organolithium Reagents in Several Solvents^a

RLi	hydrocarbon ^b	Et ₂ O	THF ^c
MeLi		4 ^{d,e}	4 ^f
EtLi	9/8/6 ^{g,h}	4 ^h	
PrLi	9/8/6 ⁱ		
<i>n</i> -BuLi	9/8/6 ^{g,h}	4 ^{d,h}	4/2 ^{j,k,l}
<i>i</i> -PrLi	6/4 ^{g,h}		
<i>s</i> -BuLi	6/4 ^{g,m}		2/1 ^o
<i>t</i> -BuLi	4 ^{p,q}	2 ^{m,r}	1 ^o
Me ₃ SiCH ₂ Li	6/4 ^h	4 ^h	
Ph ₂ PCH ₂ Li			1 ^s
PhSCH ₂ Li			1 ^k
CH ₂ =CHLi			4/2 ^{t,u}
PhLi		4/2 ^{j,v}	2/1 ^{d,k,o,v}
PhC≡CLi			2 ^k
<i>t</i> -BuC≡CLi			4/2 ^{k,w}
<i>c</i> -PrC≡CLi			4/2 ^x
Me ₃ SiC≡CLi			2 ^y
PhSO ₂ C≡CLi			1 ^y
Allyl-Li		>10 ^z	2/1 ^{t,z,aa}
BnLi			1 ^d
H ₂ C=C=CHLi			2/1 ^{bb}

^aConcentrations are 0.1–1 M. ^bThis includes solvents such as cyclopentane, pentane, hexane, benzene, and toluene (sometimes slightly lower levels of aggregation are seen in the aromatic solvents).

^cThis includes solutions containing, in addition to mostly THF, less polar cosolvents such as pentane, Et₂O, or Me₂O added to lower the viscosity and freezing point. ^dReference 161. ^eReference 124b.

^fReference 125b. ^gReference 125d. ^hReference 170. ⁱReference 131.

^jReference 127. ^kReference 122. ^lReference 171b. ^mReference 138c.

ⁿReference 132a. ^oReference 129. ^pReference 177. ^qReference 125c.

^rReference 125f. ^sReference 286. ^tReference 227. ^uReference 29.

^vReference 103. ^wReference 31a. ^xReference 233. ^yReference 238.

^zReference 184. ^{aa}Reference 185. ^{bb}Reference 210.

invariably observed in NMR spectra of solutions when different aggregated lithium reagents are mixed and temperatures are low enough to stop intermolecular exchange (often –80 or –100 °C or even lower is required).^{178,257b} The principal exception is when one of the species is inherently monomeric. Such species show less tendency to form mixed aggregates with other aggregated lithium reagents. Thus, addition of tetrameric *n*-BuLi to THF solutions of monomeric Ph₂CHLi causes no change in the UV spectrum of the latter, indicating no mixed aggregation.³⁰² Similarly, when LiBr (monomer in THF¹⁶⁴) is added to PhLi solutions (mixture of monomer and dimer), no mixed aggregates are detected.³⁰³

Although the effect of lithium halides and alkoxides on organolithium reactivity has been noticed since the very beginning of systematic studies, only in a few cases do we have anything approaching a full understanding of the processes involved. These will be discussed in subsequent sections.

3.2. Curtin–Hammett Principle

As illustrated for many examples above, organolithium reagents in solution are often mixtures of different aggregates. In donor solvents there are also different solvation states of each aggregate. The Curtin–Hammett principle states that when such species are in rapid equilibrium, the products formed from each species depend on the product of their relative reactivities and concentrations. However, many organolithium reactions are fast enough that reactions can be competitive with, or faster

than, interconversion of such species, leading to rather complex behavior.

3.2.1. Aggregate Exchange. Crucial to understanding the role that aggregates might play in organolithium interactions is the rate of interconversion of various aggregates compared to the rate of reactions being studied. That is, is the kinetic study being done under conditions where the Curtin–Hammett principle applies, where all reactive species are at equilibrium throughout the reaction, or are the rates of aggregate interconversions playing a crucial role? The actual barriers for aggregate exchange are not known in many cases, and those that have been measured vary quite widely.

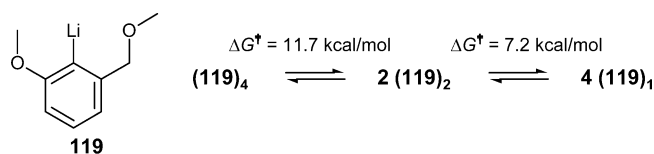
In general, the highest barriers (used here as a synonym for the free energy of activation, ΔG^\ddagger) are seen in hydrocarbon solvents. Steric effects can increase barriers, chelating groups can stabilize aggregates kinetically, and very lithophilic anions such as alkoxides seem to often give very kinetically stable aggregate structures. We will discuss some sample systems in terms of the free energies of activation (ΔG^\ddagger) since ΔH^\ddagger and ΔS^\ddagger are often not known, are much harder to obtain, and are more prone to error. One of highest barriers reported was that of (*t*-BuLi)₄, which was shown to dissociate slowly (presumably to dimers) on the laboratory time scale with $\Delta G^\ddagger_{20} = 23.9$ kcal/mol by observing by ⁷Li NMR spectroscopy the formation of mixed aggregates with (Me₃SiCH₂Li)₆, a process first-order in [*t*-BuLi] and zeroth-order in [Me₃SiCH₂Li].^{304a} The situation is complicated by the observation that the rate of *t*-BuLi dissociation was 20 times faster in toluene than in pentane and that addition of small amounts of triethylamine greatly accelerated the equilibration. Thus, substrates, products, or impurities might accelerate aggregate interconversion, leading to complex kinetics at the Curtin–Hammett boundary.

Nevertheless, it is certain that some studies with *t*-BuLi were carried out below the Curtin–Hammett limit. One such example is a study of indene metalation.^{304b} The *t*-BuLi in nonequilibrium mixtures of (*t*-BuLi)₄ and (*i*-PrLi)₄ in pentane solution was shown to metalate indene more slowly by a factor of 10 than equilibrated solutions, where the *t*-BuLi was incorporated into various *t*-Bu–*i*-Pr mixed aggregates. They conclude that a mixed aggregate such as (*t*-BuLi)₂·(*i*-PrLi)₂ is substantially more reactive than either (*t*-BuLi)₄ or (*i*-PrLi)₄.

The interconversion of organolithium aggregates in ether solvents will typically have free energies of activation that are under 14 kcal/mol, although there are certainly exceptions. As a frame of reference, this corresponds to a half-life of under 1000 s at –78 °C. There is not a great deal of information available on aggregate interconversion barriers, and virtually all of it comes from DNMR studies. It is important to note that the observed line shape changes in DNMR experiments are rarely securely assigned to aggregate dissociations, since there may be associative or impurity-catalyzed processes involved that were not or cannot be distinguished. A dramatic well-characterized example is provided by the LiCl-catalyzed dissociation of LDA³⁰⁵ which comes into play for reactions at the Curtin–Hammett borderline. Most reliable are experiments where both aggregates are detectable and coalescence between their NMR signals or mixed aggregates is studied, which must involve either dissociation to lower aggregates or associative processes (in principle distinguishable by appropriate experiments).^{103,171,297} Less reliable is the coalescence of C–Li coupling,^{12,67} for which other mechanisms exist. Brown et al. estimated the barrier for (MeLi)₄ dissociation to (MeLi)₂ in ether at 11–12 kcal/mol at –20 °C from DNMR exchange

rates of $(\text{MeLi})_4$ with $\text{Me}_4\text{AlLi}^{306}$ or with mixed halide complexes.¹⁶² The $n\text{-BuLi}$ tetramer–dimer exchange has barriers near 10 kcal/mol, measured by DNMR methods.^{171a} Although analysis of the concentration dependence suggested that the exchange might proceed by an associative process,^{171a} the very similar values obtained by an unambiguous method, the rate of reaction of $(n\text{-BuLi})_4$ by RINMR under conditions where dissociation is the rate-determining step, show that the DNMR experiments were also measuring dissociation.²³⁸

The PhLi tetramer–dimer exchange in Et_2O has a ΔG^\ddagger of 10 kcal/mol at -84°C , and the dimer–monomer exchange in THF is around 8 kcal/mol at -93°C .¹⁰³ Other dimer dissociations in THF have quite variable free energy barriers, ranging from 7.0 kcal/mol for 4-methyl-2-lithiothiophene (74)¹⁴² to 9.4 kcal/mol for [2-[2-(dimethylamino)ethyl]phenyl]lithium⁶⁷ and ≥ 12.5 kcal/mol for [2-[(dimethylamino)methyl]phenyl]lithium (21).⁶⁷ From the reported data,³⁴ it can be estimated that for the latter in toluene the barrier is at least 17.5 kcal/mol. The chelated tetrameric ArLi 119 has a dissociation free energy of activation of 11.7 kcal/mol in THF at -29°C . It is interesting that the barrier for dimer–monomer interconversion of 119 (which both coexist with the tetramer) is much lower, ca. 7.2 kcal/mol at -132°C .²³⁸



A DNMR study of the dimers and monomers of the lithium enolate of N,N -dimethyldiphenylacetamide 96 in THF gave a free energy of activation of 10.7 kcal/mol for dimer dissociation.^{255b} The tetramers of 4-fluoroacetophenone lithium enolate dissociate to dimers with a barrier of ca. 16 kcal/mol.¹⁶⁰

Figure 8 shows a graphical representation of some sample measured aggregate interconversion barriers and their relationship to typical time scales of kinetic studies. At room temperature only the fastest techniques (0.01 s time scale) and the highest aggregate exchange barriers could conceivably result in a non-Curtin–Hammett situation. Even at -78°C aggregate lifetimes will be under 5 s for a ΔG^\ddagger of 12 kcal/mol, although with 15 kcal/mol barriers the lifetimes extend into the laboratory time scale (half-life of hours). As a consequence, the vast majority of all kinetic studies of organolithium reactions are carried out under Curtin–Hammett conditions. Some early fast kinetic studies in hydrocarbon solvents may have been close to this limit, judging from observations made during a study of the reaction of $n\text{-BuLi}$ with 4-methylthioacetophenone in benzene (see section 3.5.1 for details).³⁰⁷ Similarly, fast kinetic studies by Holm of $n\text{-BuLi}$ reactions with methyl trifluoroacetate (see section 3.5.5) and PhCN (see section 3.5.8)³⁰⁸ were probably under the Curtin–Hammett limit. The RINMR technique, pioneered by McGarrrity and Ogle,³⁰⁹ allows study of some organolithium aggregates below the Curtin–Hammett lines.^{160,238}

3.2.2. Solvent Exchange. There is another Curtin–Hammett situation with organolithium species in ether and amine solvents involving the rate of solvent dissociation versus reaction rates. Mostly these rates are faster than the NMR time scale ($\Delta G^\ddagger < 6$ kcal/mol). However, there are some notable cases where slow solvent exchange has been detected, allowing a more specific evaluation of the solvation state, equilibria, and

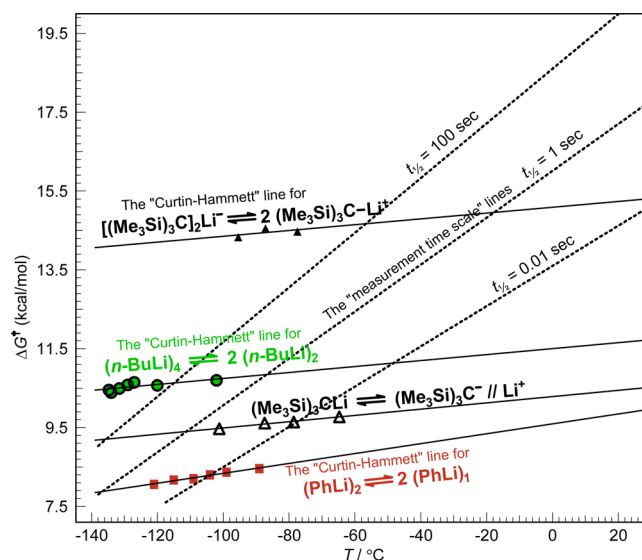
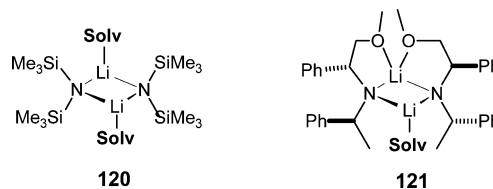


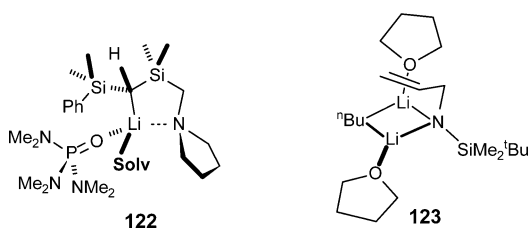
Figure 8. Graphical representation of the Curtin–Hammett principle. Experiments can only be carried out on reactions that are above the measurement time scale lines (dashed) of 0.01 s half-life (accessible by UV or IR stopped-flow methods), the 1 s time scale (lower limit for RINMR methods), and the 100 s time scale (lower limit for classic sampling methods). If the reaction being studied is below the “Curtin–Hammett line”^{120b,297} for a particular aggregate interconversion, then measurements can be made on individual aggregates or mixed aggregates, if above, then ensemble kinetics apply where fractional orders or line curvatures are the only hints about the reactivities of individual aggregates.

dynamics. The first observations involved hindered lithium amides: exchange between free and coordinated ethers in disolvated bis(trimethylsilyl)amide 120 ($\Delta G^\ddagger_{-50} = 8.6$ kcal/mol for Et_2O , $\Delta G^\ddagger_{-28} = 10.8$ kcal/mol for THF)³¹⁰ and in monosolvated 121 (slow at -80°C , $\Delta G^\ddagger_{-50} = 8.5$ kcal/mol for Et_2O , $\Delta G^\ddagger_{-28} = 10.9$ kcal/mol for THF).³¹¹



For organolithium reagents, the first observation in ether solvents was the detection of diastereomeric solvates and a slow exchange between Me_2O and other solvents in 122 ($\Delta G^\ddagger_{-130} = 6.5$ kcal/mol).³¹² Two different coordinated THF signals were observed in the mixed aggregate 123 below -90°C .³¹³ Slow exchange between coordinated and free solvent has been observed for the hindered vinyl lithium reagent 15.¹³⁰ It is likely that the key to a relatively slow solvent exchange is the inhibition of associative processes by steric effects, since the dissociative routes (which have been proven for the amide cases) seem to have significant barriers.

It should be noted here that, in contrast to the ethers, exchange rates for HMPA and for the chelating amines TMEDA, PMDTA, and TMTAN are generally slow enough that individual solvates can be routinely observed in NMR spectra below -100°C . Thus, exchange barriers for free and coordinated HMPA are ca. 8 kcal/mol.^{144a} In enolate complexes the barrier for PMDTA exchange was ca. 10 kcal/mol and for TMTAN ca. 13 kcal/mol. In the latter case, the



exchange occurred by a mechanism in which the TMTAN–Li⁺ unit exchanged enolate partners, rather than the enolate–Li unit exchanging TMTAN partners.^{80b}

The interconversion between contact and solvent-separated ion pairs (CIP, SIP) is also closely related to barriers for solvent exchange, since a single coordinated solvent molecule may be all that stands between the two species. Such barriers can be measured for radical anions by ESR methods, with barriers of ca. 3.5 kcal/mol in THF.³¹⁴ Two such barriers have been measured for lithium species by NMR coalescence, the interconversion between the CIP and SIP of [bis[[3,5-bis(trifluoromethyl)phenyl]thio]methyl]lithium with $\Delta G^\ddagger_{-155} = 5.3$ kcal/mol and that of (Me₃Si)₃CLi in THF–Me₂O mixtures with $\Delta G^\ddagger_{-87} = 9.6$ kcal/mol.³¹⁵ The former probably represents the barrier for dissociation of a single THF. The much higher barrier for the latter is probably because more than one THF has to be removed from the SIP Li(THF)₄⁺ species before the sterically congested CIP can be formed.

The higher reactivity of lower aggregates is almost axiomatic and was recognized soon after the aggregated nature of lithium reagents was established. The frequent observation of fractional orders (assuming these are always correctly interpreted as predissociation to a lower aggregate) requires that the lower aggregates be very much more reactive, since they are present at undetectable concentrations, yet out-compete high concentrations of the principal aggregate. Less direct information was obtained from comparisons of the reactivity of structurally related alkylolithiums. Thus, in addition to 1,1-diphenylethylene in benzene at 30 °C, dimeric menthyllithium (**Q188**) is at least 70 times as reactive as tetrameric *s*-BuLi, in spite of steric effects which might be expected to reduce its reactivity. It is at least 5000 times as reactive as hexameric *n*-BuLi.¹⁷⁶ There have been a few direct measurements of the relative reactivity of higher and lower aggregates which have provided a more quantitative picture of this effect.^{120b,160,238,315} These will be discussed below.

3.3. Metalation Reactions

Metalation reactions (lithium–hydrogen exchange) are among the most useful and most used of organolithium reactions,^{224,316–320} and they were among the earliest to be studied mechanistically. Figure 9 shows an assortment of organolithium reagents that are best prepared by metalation.

3.3.1. Fluorene and Triphenylmethane. The utility and importance of the reactions studied in the early work was often a secondary consideration, and the choice of substrates was dictated by experimental factors: reaction rates that were slow enough to be followed (preferably near room temperature) and products whose concentration could be easily measured by a noninvasive technique to protect the very sensitive reagents and products from air and water (usually by in situ UV–vis or IR spectroscopy). The earliest metalation reactions studied typically produced highly conjugated benzyllithium species. Indeed, the first reported example of a metalation, that of fluorene by ethyllithium in 1928, was of this type.³²¹ In

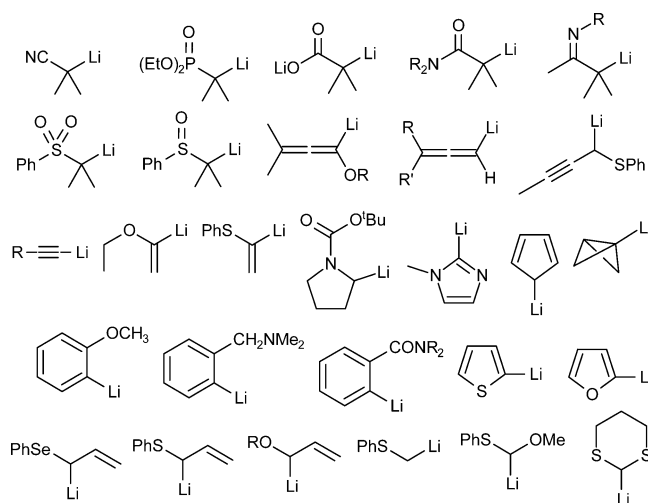


Figure 9. Organolithium reagents commonly prepared by metalation.

pioneering studies, the Evans group showed that in benzene the metalations of fluorene were always first-order in [substrate], but showed fractional orders in [RLi]. The reaction was 0.11-order in [EtLi],^{322a} 0.18-order in [*n*-BuLi],^{322b} and 0.28-order in [*t*-BuLi].^{322c} This behavior is fully consistent with a mechanism in which the principal aggregate underwent predissociation to a monomer, which was the reactive species. Much subsequent work confirmed that in benzene the aggregation state of ethyllithium was greater than 6, that of *n*-BuLi hexameric, and that of *t*-BuLi tetrameric.

Although the numerous cases where fractional orders were close to the inverse of the aggregation state provide some confidence that reactions of monomers was the correct explanation, Brown made qualitative arguments early in the study of lithium reagents that the activation barriers to dissociation of a hexamer or tetramer to monomers in hydrocarbon solvents is too high to allow the process to be a fast pre-equilibrium.³²³ An alternative explanation, extensively explored by Klumpp and co-workers involves complex formation between RLi and the substrate.^{14,295} Such complexes have been observed in the solid state.^{121b} If the substrate first forms a complex with RLi with a significant association constant ($K_{eq} = [\text{RLi} \cdot \text{substrate}] / [\text{substrate}][\text{RLi}]$), then apparent fractional orders can arise. If K_{eq} is large, then the reaction will be zeroth-order in [RLi], but any other fractional order between 1 and 0 can result with appropriate values of K_{eq} .¹⁴

In a very extensive series of studies on the metalation of triphenylmethane in benzene, fractional orders were found for several lithium reagents, including the monomeric compound **114** (0.59-order), the dimer **113** (0.83-order), and the tetramer **112** (0.34-order), with relative reactivities of 20 000, 3000, and 1 at 23 °C. While the fractional orders for the dimer and tetramer can be explained by aggregate predissociation, this cannot be the case for the monomer **114**.²⁹⁵ For metalation with **114** a reasonable fit with the rate data is obtained with $K_{eq} = 40$. This, of course, raises the question of what the nature of the association between **114** and triphenylmethane might be in a sea of benzene, which is a Lewis base comparable to the substrate.

In ether solvents complex formation between RLi and hydrocarbon substrates is unlikely, since the substrates cannot significantly displace ether solvents from lithium. Nevertheless,

fractional orders were also typically found. The kinetics of metalation of Ph_3CH in THF with $n\text{-BuLi}$ (a very difficult experiment because of the high rates) gave orders of 0.25²²⁷ and 0.53³²⁴ in $[n\text{-BuLi}]$. The latter value seems much more consistent with what is now known about $n\text{-BuLi}$ in THF—that it is a mixture of dimer and tetramer under these conditions and that the tetramer is very unreactive and the dimer is at least 4 orders of magnitude more reactive toward all substrates tested.²³⁸ These researchers also measured the activation parameters, which gave $\Delta G^\ddagger_{-30} = 20.6$ kcal/mol, $\Delta H^\ddagger = 9.9$ kcal/mol, and $\Delta S^\ddagger = -32.5$ eu. The large negative entropy is consistent with the extra solvation required to dissociate a tetramer to dimers; as many as four additional THF molecules can coordinate to two dimers than to one tetramer. ΔS^\ddagger for tetramer dissociation to dimer in THF was reported by DNMR methods to be -31.3 eu^{171a} and -7 eu^{171b} and by RINMR to be -7.6 eu.^{301b}

Metalation of Ph_3CH in THF was found to be have an order of 0.28 in $[\text{MeLi}]$ (tetramer) and 0.24 in $[\text{vinylolithium}]$ (largely tetramer in THF, with about 10% dimer at 1.6 M)²²⁷. These fractional orders imply that the monomer is the active metalating agent. Even now nothing is known about the rates or equilibrium constants for monomer formation of these reagents, although there are a few lithium species where monomers and tetramers detectably coexist, including the ArLi **119**²³⁸ and several enolates,^{245,246,325} so dissociation of tetramers to monomers in ether solvents is not unreasonable.

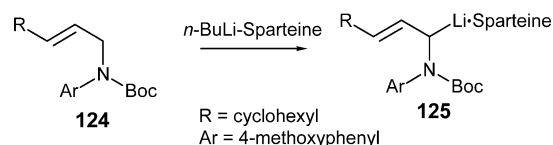
Phenyllithium gave an order of 0.64 in reaction with Ph_3CH ,²²⁷ consistent with later findings that PhLi was a mixture of dimer and monomer in THF (Figure 5).^{103,129} The fractional order and other kinetic behavior of PhLi in THF were fitted to a monomer–dimer $K_{\text{MD}} = [\text{D}]/[\text{M}]^2 = 100 \text{ M}^{-1}$ at 25°C . This is in modest agreement with values later found of 30 M^{-1} at -109°C by cryoscopy¹²² and 40 M^{-1} by NMR spectroscopy at -75°C .¹⁰³ According to their analysis, PhLi dimer is 17 times as reactive as monomer,²²⁷ a questionable conclusion in view of the many kinetic studies where lower aggregates are more reactive.

The reaction of BnLi with triphenylmethane in THF is 0.9-order in $[\text{BnLi}]$. Since BnLi is monomeric in THF, the monomer must be the metalating species. This may explain why BnLi is the most reactive of the reagents examined: at 0.1 M concentration BnLi is 450 times as reactive as MeLi and 20 times as reactive as $n\text{-BuLi}$, both mainly tetramers. The reaction of allyllithium with Ph_3CH in THF is also first-order in $[\text{RLi}]$. The aggregation state of allyllithium in THF has been examined several times. Vapor pressure osmometry gave values of ca. 1.3.²²⁷ Later cryoscopic measurements indicated that it was dimeric, so possibly the dimer is the reactive species in this metalation. Allylic organometallics generally show very special reactivity because the anionic carbon is not necessarily blocked by the metal.

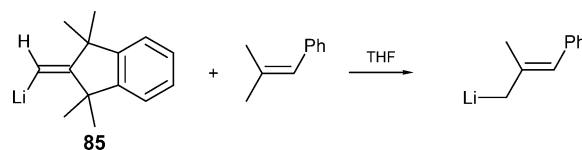
3.3.2. Allylic and Benzylic Metalations. Side chain metalations of aromatic compounds and allylic metalations have an extensive history as routes to synthetically valuable RLi species.³¹⁷

A mechanistic study was performed of the metalation of the allylamide **124** to form **125** in toluene using the $n\text{-BuLi}$ –sparteine complex,³²⁶ whose structure was not determined, but is likely a biscomplexed dimer, $(n\text{-BuLi})_2 \cdot (\text{sparteine})_2$, judging from several X-ray structures of related compounds determined subsequently.^{35–37,110} The metalation reaction shows a large isotope effect ($k_{\text{H}}/k_{\text{D}} = 86$ at -75°C) and is first-order in

[124] and zeroth-order in $[n\text{-BuLi}\text{--}\text{sparteine}]$. A complex between the amine and the metalating agent was detected by the appearance of a new IR signal, but its structure was not determined. Thus, the rate-determining step was the proton transfer within this **124**– $n\text{-BuLi}$ –sparteine complex. An unusual and interesting feature of this deprotonation is that it is strongly inhibited by an excess of $n\text{-BuLi}$ over the amount of sparteine. There must be competitive complexation of free $n\text{-BuLi}$ with **124** to form an unreactive complex with K_{eq} larger than the $n\text{-BuLi}$ –sparteine K_{eq} , and indeed, it was confirmed that $n\text{-BuLi}$ formed such a complex, but did not significantly metalate the substrate under these conditions.



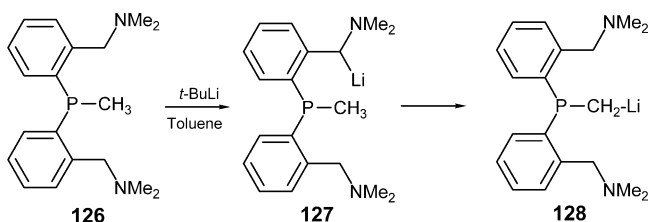
The vinylolithium **85** is a mixture of dimer and monomer in THF, with dimer predominating at room temperature and monomer at -78°C . From the positive entropy of dimerization (16.9 eu) the authors concluded that the release of two THF molecules is probably involved. A rate study of the metalation of β,β -dimethylstyrene by **85** gave 0.5-order in **[85]**, indicating that the monomer is the active species. Since the barrier for interconversion of monomer and dimer (measured by DNMR) is only 9.2 kcal/mol, and the barrier to metalation was 23.7 kcal/mol, the reaction is clearly under Curtin–Hammett conditions.^{232a}



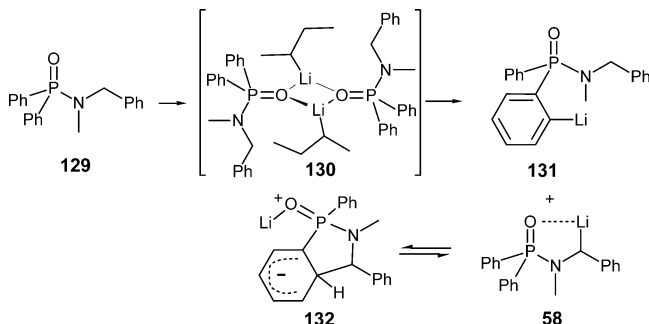
In $t\text{-BuOMe}$ solution, the dissociation to monomer is much less favorable and no metalation could be detected. From the data provided, it can be estimated that the THF-solvated monomer of **85** was at least 100 times as reactive as the $t\text{-BuOMe}$ -solvated dimer at 30°C . The data also showed that **85** is ca. 60 times as reactive as vinylolithium (mainly tetramer²⁹ in this solvent) and that $n\text{-BuLi}$ (mixture of dimer and tetramer¹⁷¹) is only 7 times as reactive as **85**.^{232b} The reactive aggregate in each of these comparisons is unknown.

The kinetic product of the metalation of the aminophosphine **126** is the benzyllithium reagent **127**, which is a dimer in the solid state and retains the dimer structure in toluene solution.³²⁷ This compound rearranges to the more stable (phosphinomethyl)lithium **128** in toluene above room temperature. The rearrangement is first-order in $[(\text{127})_2]$ and is unaffected by the presence of starting phosphine **126**. This suggests that a proton transfer within the dimer is involved. It was not established whether the transfer was intramolecular (six-center) or intermolecular but intra-aggregate. One complication is that the activation parameters ($\Delta H^\ddagger = 16.3$ kcal/mol, $\Delta S^\ddagger = -30$ eu) point to a more structured transition state than a simple intramolecular proton transfer.⁴⁵

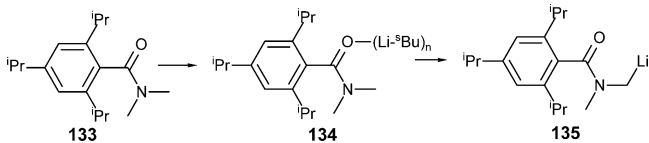
A very detailed NMR study was carried out of the metalation of the N -benzylphosphinamide **129** with $s\text{-BuLi}$ in THF. At low temperature a set of four diastereomeric precomplexes, characterized as **130**, were detected. These then formed either the ortho-metalated product **131**, formed irreversibly, or the benzyllithium **58**, which cyclized reversibly to four diaster-



omers of a dearomatized cyclohexadienyl anion, **132**. The equilibrium was toward **132** at low temperature and **58** at high temperature. The three anionic products could be trapped with electrophiles such as aldehydes or proton sources.³²⁸

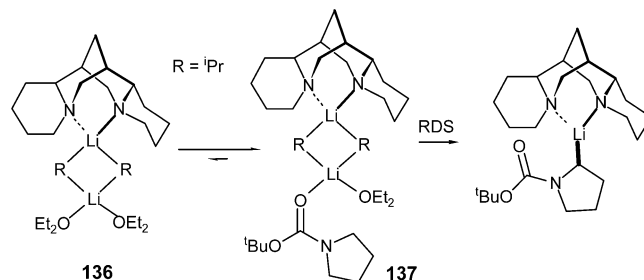


3.3.3. Dipole-Stabilized Metalations. During metalation of hydrocarbons in ether solvents, kinetic complications from complex formation with the substrate are unlikely, since the substrates cannot significantly displace ether solvents from lithium. Such complexation is much more likely, however, with more basic substrates, especially in hydrocarbon solvents. In an extensive stopped-flow IR spectroscopy kinetic study of the N-CH₃ metalation of benzamide **133** with *s*-BuLi in cyclohexane, it was shown that a complex, **134**, forms first in a pre-equilibrium, which was then converted exclusively to the *cis*-lithiated amide **135**.³²⁹ A similar complex was detected in a related formamidene metalation.³³⁰ Only one rather complicated mechanistic scenario was found that fit all the rate data for this metalation.³³¹ The *s*-BuLi tetramer becomes progressively complexed to 1–3 molecules of the amide, with each association constant smaller than the previous one ($K_{\text{eq}} = [(s\text{-BuLi})_4 \cdot \text{133}] / [(s\text{-BuLi})_4][\text{133}] = 2000 \text{ M}^{-1}$, down to $K_{\text{eq}} = 50 \text{ M}^{-1}$ for $[(s\text{-BuLi})_4 \cdot (\text{133})_4] / [(s\text{-BuLi})_4][(\text{133})_3][\text{133}]$), but with each complex having progressively higher reactivity ($k = 0.001\text{--}15 \text{ s}^{-1}$). In this scenario other aggregates were not detectably involved. The presumption is that each amide complexed to the tetramer increases the electron density and availability of the *s*-Bu anionic base in the activated complex.



A complex of *i*-PrLi with sparteine in ether was spectroscopically characterized as the dimer **136**.³³² A crystal structure of the monoetherate was later obtained.⁷⁴ A kinetic study of the metalation of *N*-Boc-pyrrolidine showed that the metalation was essentially zeroth-order (<0.20) in the [RLi] complex, consistent with near-quantitative precomplex formation ($K_{\text{eq}} > 300 \text{ M}^{-1}$) to form **137**. The order in amide was not determined. A large intermolecular isotope effect (>30 at -78°C) was measured. Thus, the mechanistic pathway

involves a reversible precomplex formation followed by rate-determining intramolecular deprotonation to form the lithiated pyrrolidine.³³³ Details of the deprotonation are unknown, but an open dimer transition state was suggested, consistent with other reactions which have been more completely characterized³³⁴ and the results of high-level computations.³³⁵



3.3.4. Silane Metalation. In an NMR study with some qualitative rate observations, Thomas showed that addition of MeOSiMe₃ to (*t*-BuLi)₄ in cyclopentane resulted in partial conversion to the alkoxy-complexed dimer (*t*-BuLi)₂·(MeO-SiMe₃)₂, which was fully characterized by ¹H, ⁶Li, and ¹³C NMR (the two species were in slow exchange at -90°C).³³⁶ Metalation of the SiCH₃ group proceeded at -60°C over a period of hours to form a mixed tetramer, (*t*-BuLi)₁·(MeOMe₂SiCH₂Li)₃, also characterized by NMR spectroscopy. As this tetramer builds up and the dimer is depleted, the rate of metalation drastically slows, and warming to 25°C is required to complete the reaction. Thus, the mixed tetramer intermediate is substantially less reactive than the dimer. This tendency for metalation reactions to “stall out”²³⁷ or at least slow down has been observed repeatedly^{233,337,338} and can probably be generally attributed to mixed aggregates that are of higher order than the active species, and thus inherently less reactive (as in this case), or to mixed aggregates of the same order, but which are much less reactive than the starting homoaggregate.

3.3.5. Acetylene Metalations. Acetylenes are too acidic for normal kinetic studies of deprotonations with common RLi species, but are within range for the RINMR technique. Moreover, the rates are high enough that for *n*-BuLi these deprotonations occur under the Curtin–Hammett limit: rates can be faster than the rates of interconversion of *n*-BuLi dimer and tetramer. In an RINMR study of the metalation of (trimethylsilyl)acetylene with *n*-BuLi in 1:3 THF–Me₂O at -130°C , (*n*-BuLi)₂ reacted in less than 1 s and (*n*-BuLi)₄ required several hours.²³⁸ Although the dimer is too reactive to measure directly ($t_{1/2} < 1 \text{ s}$), its rate could be easily estimated from the rate of deprotonation of deuterated (trimethylsilyl)acetylene (which had a half-life of several seconds) and from the isotope effect $k_{\text{H}}/k_{\text{D}}$ of 52 measured by competition experiments. The dimer reaction formed an intermediate species, characterized as the *n*-BuLi–acetylide mixed dimer **138**, which reacted with another equivalent of acetylene to form the acetylide homodimer **139**. The mixed dimer was 1/42 as reactive as the homodimer. This is one of the few direct measurements of the reactivity of a mixed aggregate of a lithium reagent in comparison with a homoaggregate (Figure 10).

The reaction of (*n*-BuLi)₄ with (trimethylsilyl)acetylene was zeroth-order in [acetylene] and was identical to the rate of dissociation of the tetramer measured by several other techniques. Such experiments showed that (*n*-BuLi)₂ is at least 40 000 times as reactive as (*n*-BuLi)₄. Several more

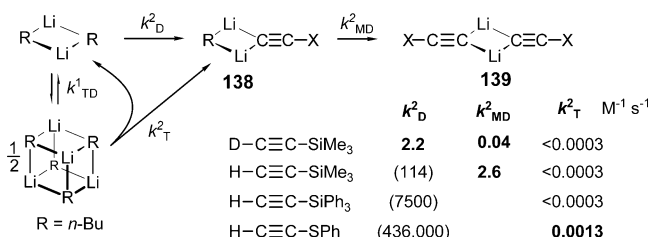


Figure 10. RINMR rate study of the reaction of *n*-BuLi aggregates with several acetylenes at -135°C in 3:1 Me₂O–THF. The bold rate constants were measured directly; the ones in parentheses were estimated from appropriate competition experiments. The relative reactivity of (*n*-BuLi)₄ and (*n*-BuLi)₂ toward (phenylthio)acetylene is 1:(3.2 × 10¹⁰). The relative reactivity of (*n*-BuLi)₂ and **138** (X = SiMe₃) toward deuterio(trimethylsilyl)acetylene is 42:1.²³⁸

reactive acetylenes were examined, and (phenylthio)acetylene was found to react with (*n*-BuLi)₄ slightly faster than dissociation to dimers. From a series of competition experiments, the (phenylthio)acetylene rate with (*n*-BuLi)₂ could be measured, leading to an estimate that (*n*-BuLi)₂ is 3 × 10⁸ times as reactive as (*n*-BuLi)₄ in this deprotonation (Figure 10).²³⁸

A more limited study of the deprotonation of several acetylenes with the aryllithium reagent **119** showed similar very large differences in aggregate reactivity. This compound in THF–Me₂O solution is a mixture of monomer, dimer, and tetramer, with the monomer and dimer in fast equilibrium even on the DNMR time scale at -130°C ($\Delta G^\ddagger_{-132} = 7.2$ kcal/mol) and certainly on any time scale currently achievable by RINMR (the practical lower limit on ΔG^\ddagger on a 5 s time scale at -130°C is about 8.6 kcal/mol). However, the interconversion of (**119**)₄ with the lower aggregates is much slower ($\Delta G^\ddagger_{-29} = 11.7$ kcal/mol). It was shown by extrapolations using the relatively acidic (phenylsulfonyl)acetylene that (**119**)₄ was at least 10¹⁴ times as reactive as (**119**)₁ toward this acetylene, presuming that the monomer is the reactive species.²³⁸

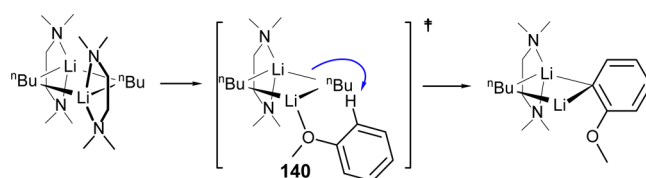
3.3.6. Aromatic Ortho-Metalations. Among the most important applications of organolithium species in synthetic chemistry is the ortho-metalation reaction.^{316a,c,320,339} There have been many empirical studies seeking to control the chemoselectivity (addition vs metalation) or regioselectivity (positional, ring vs lateral) of the metalation of benzenes or aromatic heterocycles, as well as efforts to measure the relative acidities of the protons at potential sites of metalation.^{340,339a,341} The metalation site can be sensitive to the nature of the base, the solvent, and/or the presence of strongly coordinating cosolvents (TMEDA,^{342,343} PMDTA³⁴⁰) or other additives, such as potassium alkoxides³⁴⁴ or lithium aminoalkoxides.³⁴⁵ It is clear that, in addition to CIPE and local steric effects, aggregation effects and mixed aggregates play important, if at best vaguely known, roles in these reactions. Coverage of ortho-metalations in this review is limited to those where the role of aggregates is clearly defined.



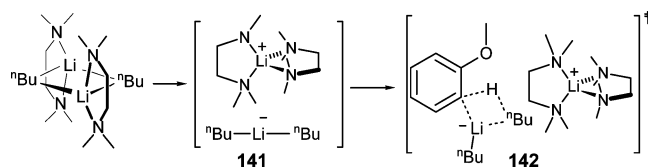
As one of the earliest ortho-metalations to be discovered, the mechanism of the reaction of anisole (X = OMe) with *n*-BuLi has been examined repeatedly.^{158,334,346,347} Much discussion has centered around the role of precomplexes and the CIPE effects, first suggested by Roberts and Curtin.^{348a} Indeed, addition of anisole to hexameric *n*-BuLi in toluene solutions

forms a tetrameric 1:1 complex, but no metalation occurs at room temperature. Addition of TMEDA forms the dimeric *n*-BuLi–TMEDA complex, anisole is released, and rapid metalation ensues.¹⁵⁸ Thus, complex formation is not necessarily an essential prerequisite for metalation. Other basic cosolvents, such as THF or ether, also result in useful metalation rates.^{346b} Primary H/D isotope effects ($k_H/k_D = 2.5$ – 3.5) are found in the TMEDA-assisted reaction by both intramolecular and intermolecular competition. Thus, any precomplexation steps are rapid and reversible, and the rate-determining step is proton transfer.³⁴⁷

The above workers suggested transition states based on computations which involved dissociation of one TMEDA from (*n*-BuLi)₂·(TMEDA)₂ and complexation of anisole to form the complex **140**. Intramolecular proton transfer facilitated by agostic interactions of lithium with the ortho-hydrogen completed the metalation.¹⁵⁸

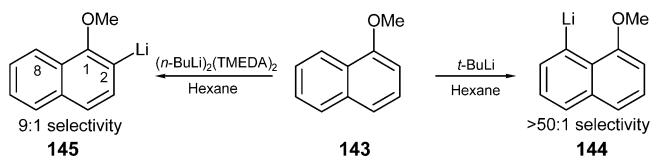


Kinetic studies of a series of alkoxybenzenes provided a more detailed picture.³³⁴ The metalation in pentane showed first-order kinetics in [(*n*-BuLi)₂·(TMEDA)₂] and zeroth-order kinetics in excess [TMEDA]; thus, the dimer is the reactive species, but prior dissociation of TMEDA, as required by the mechanism shown in **140**, does not occur. Collum suggests, supported by computational studies, that the key metalating species is an isomer of the four-center dimer, the triple ion **141**, and his evidence suggests transition state **142**. This explains the weak indications of chelating effects (Ph–O–CH₂CH₂NMe₂ is only 1.3 times as reactive as Ph–O–Me), since the central lithium of the triple ion would not be expected to be particularly electrophilic and thus would participate poorly in CIPE^{316c} effects, although internal lithiums in triple ions have been shown to be capable of forming chelates (see **72**¹² and **31**⁹⁸).



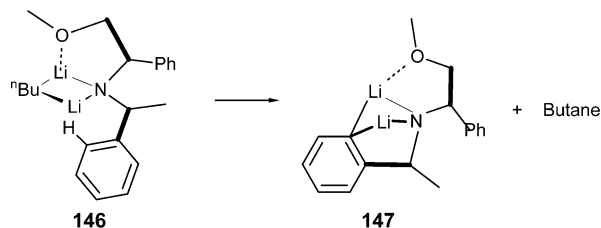
1-Methoxynaphthalene (**143**) shows interesting selectivity in metalation at the 2- and 8-positions.^{339b,342} *t*-BuLi in hexane gave >99% 8-metalation (**144**), whereas *n*-BuLi–TMEDA gave predominantly metalation at the 2-position (**145**). As with anisole, addition of **143** to solutions of *n*-BuLi formed a complex, but metalation did not occur. Addition of TMEDA freed **143**, and metalation to give **145** occurred. A large isotope effect k_H/k_D of 15 was observed. This is consistent with a mechanism similar to that found for anisole (see **142**).^{334b} Calculations predicted a more favorable transition state for 2-metalation. Similar addition of **143** to solutions of (*t*-BuLi)₄ in hexane showed no sign of complexation, and no isotope effect was detectable for the formation of **144**. Thus, here the rate-determining step is proposed to be disruption of (*t*-BuLi)₄ to form a reactive aggregate (presumably monomer or dimer), which then interacts with **143**. It was suggested that the

metalation at the 8-position is the result of thermodynamic control (**144** is the more stable isomer), although the mechanism for equilibration is not clear. It is unfortunate that these authors did not report any of their rate data,³⁴² since the rate of interaggregate exchange for $(t\text{-BuLi})_4$ has been estimated (this is presumably the rate of dissociation to dimers).^{304a} Qualitatively, the metalation rates do seem to be comparable to the rates of $t\text{-BuLi}$ dissociation.

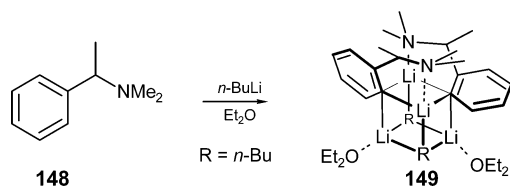


In an NMR study of the metalation of the peri-position of naphthol with $(n\text{-BuLi})_2(\text{TMEDA})_2$, in addition to the homodimers $(n\text{-BuLi})_2$ and $(1\text{-naphthyl-OLi})_2$, a 1:1 mixed aggregate was detected by NMR, shown to be $(1\text{-naphthoxide})\cdot(n\text{-BuLi})\cdot(\text{TMEDA})$, characterized by J_{CLi} , $^1\text{H}-^7\text{Li}$ HOESY, and QCC.³⁴⁹ The hydrogen at the 8-position showed the strongest NOE interaction with lithium, and that is where metalation occurred.

In connection with studies on complexes of $n\text{-BuLi}$ with the chiral lithium amide **146**, an ortho-metalation was observed to form **147**. The reaction was first-order in **146** and showed saturation kinetics (an increase in $[n\text{-BuLi}]$ by a factor of 15 gave an increase in rate by a factor of 2), leading to the conclusion that the metalation occurred within the complex **146** and not by attack of an external $n\text{-BuLi}$ aggregate on **146**.³⁵⁰



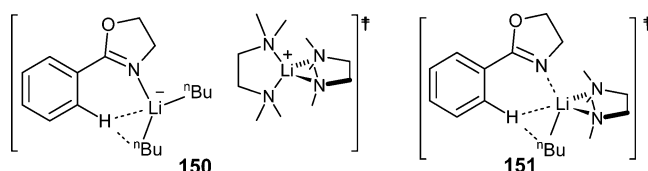
It is not uncommon for difficult metalations to require excess metalating agent, and the involvement of mixed aggregates of lower reactivity is often suggested as the reason. A specific example is the ortho-metalation of [1-(dimethylamino)ethyl]benzene (**148**) in diethyl ether with $n\text{-BuLi}$, which cannot be pushed past 50% reaction.³³⁷ This was subsequently traced to the formation of a 2:2 mixed aggregate, **149** (X-ray structure⁴⁶), in which the butyl groups are apparently very unreactive in further metalations. It was not determined whether the mixed tetramer is itself much less reactive or whether the lower reactivity was due to a much less favorable tetramer-dimer or tetramer-monomer equilibrium. In this case $t\text{-BuLi}$, which does not form such mixed aggregates, performed a rapid and complete metalation.³⁵¹



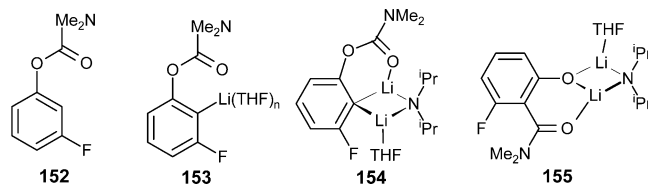
An isotope effect study of the ortho-metalation of N,N -diisopropylbenzamide with $s\text{-BuLi}$ -TMEDA in THF gave $k_{\text{H}}/$

$k_{\text{D}} > 20$ both for the intramolecular (2-deuterio compound) and for the intermolecular (dideuterio vs diprotio) competition. Thus, the deprotonation itself is rate limiting. Any precomplexes are formed reversibly.³⁵²

A kinetic study of the metalation of a series of oxazolines by $(n\text{-BuLi})_2(\text{TMEDA})_2$ in pentane gave first-order kinetics in the metalating agent and zeroth-order kinetics in excess $[\text{TMEDA}]$. This suggests a triple ion mechanism similar to that of **142**, except that there are strong indications (both experimentally and computationally) of coordination between the triple ion lithium and the oxazoline nitrogen (**150**). For the less reactive substrates the order in metalating agent approached 0.5, indicating a monomer-based mechanism (**151**) competing with dimer.³⁵³



Lithium diisopropylamide ortho-metalations of phenyl carbamates (e.g., **152**) have also been subjected to detailed mechanistic investigation.³⁵⁴ We will briefly discuss here the findings on the subsequent Fries rearrangement of the *o*-lithio carbamates, which were formed as THF-solvated monomers **153** or as mixed dimers **154** (if excess LDA was present). The dimer **154** rearranged to **155** by two pathways, either directly, in a reaction that was first-order in $[\text{THF}]$, or in a reaction that was inhibited by excess LDA and second-order in $[\text{THF}]$ and thus involved THF-assisted dissociation to the much more reactive monomer. Interestingly, in $t\text{-BuOMe}$ as the solvent a component of the reaction was accelerated by excess LDA. This can be assigned to a mechanism where **154** is coordinated by a second LDA monomer to form a 1:2 mixed trimer, which rearranged more rapidly than the mixed dimer. This is one of the rare cases with some experimental support for a higher aggregate more reactive than a lower one.³⁵⁵



Included here is a brief description of one of the most interesting ortho-metalations whose mechanism has been elucidated in detail, the deprotonation of the amide **156** in THF. LDA reactions are not in the scope of this review, but an RLi-LDA mixed aggregate plays a surprising and previously undetected role, resulting in a kinetic scheme of almost nightmarish complexity. An initial deprotonation of **156** by LDA dimer forms the four-center mixed dimer **157**, which is quite unreactive and slows the metalation process. It, however, slowly isomerizes to a second much more reactive dimer, shown to be **158**. An outline of the mechanism is given in Figure 11.³⁵⁶

Related to these ortho-lithiations is an interesting observation on the behavior of aryl triflates. When **159** was treated with $n\text{-BuLi}$ in THF (Li/Br exchange), the observed products were derived from the chlorobenzynes **160**. On the other hand, LDA deprotonation of **161** under the same conditions gave the

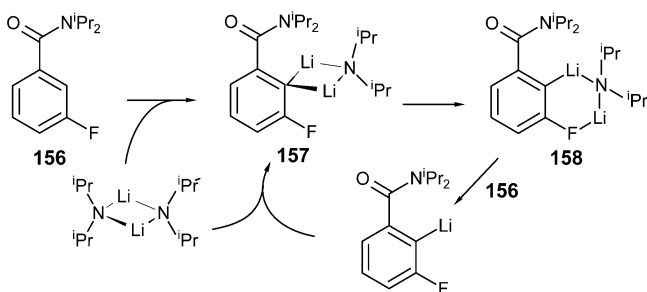
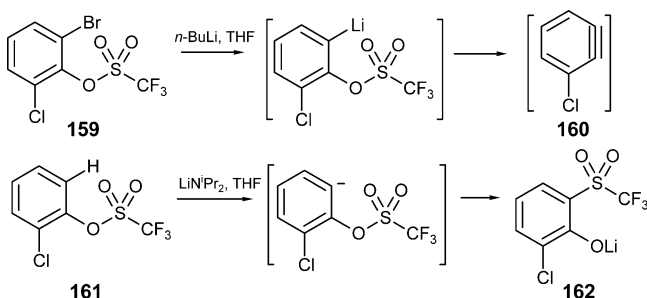


Figure 11. Mechanism of ortho-metalation of a fluorobenzamide. Reprinted from ref 356. Copyright 2008 American Chemical Society.

sulfonyl migrated product **162**. Thus, different intermediates must be involved. The authors suggested that the aryllithium reagent gives benzyne, but that the free aryl anion (perhaps formed by deprotonation by an LDA triple ion) undergoes the O to C migration of the sulfonyl group.³⁵⁷ Such carbanion intermediates on the path to the formation of lithium reagents (or Grignard reagents³⁵⁸) have been proposed in other contexts as well.³⁵⁹



3.3.7. Solvent Metalations. A persistent problem with the use of organolithium reagents is the tendency for the more aggressive alkylolithiums to attack ether solvents. THF is especially reactive; it usually forms acetaldehyde lithium enolate and ethylene, although an alternative mode of decomposition, which forms but-3-en-1-ol, occurs in THF–HMPA mixtures.³⁶⁰ There have been several mechanistic studies of these reactions.

In the course of metalation studies of Ph_3CH by $n\text{-BuLi}$ in THF discussed above,³²⁴ it was observed that the formed Ph_3CLi decayed in a kinetically well behaved way in a reaction with the solvent. The process was strictly first-order in $[\text{Ph}_3\text{CLi}]$. Since these experiments were run in a time period where virtually all kinetic studies with lithium reagents were giving small fractional orders, this result with a lithium reagent known to be monomeric was reassuring.

A detailed kinetic study of the reaction of $n\text{-BuLi}$ with Et_2O and THF gave the following results. In Et_2O the order in $[n\text{-BuLi}]$ was 0.3 throughout the range of concentrations from 0.0001 to 2 M. For THF, the order was 0.3 above 0.1 M, but went to nearly 1 below 0.02 M.³⁰⁸ This result was interpreted in terms of a dissociation of tetramer to a reactive monomer. With the information now available about $n\text{-BuLi}$,¹⁷¹ it seems that the change from 0.3-order to first-order was more likely a transition from tetramer to reaction of the dimer, which becomes the dominant species at low concentrations.

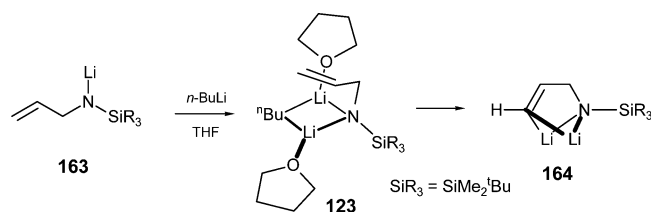
$t\text{-BuLi}$ is the most aggressive of all commonly used lithium reagents and reacts with most ether solvents below room temperature. Addition of Et_2O to $(t\text{-BuLi})_4$ solutions in cyclopentane forms a tetrasolvated dimer, $(t\text{-BuLi})_2 \cdot (\text{Et}_2\text{O})_4$, in a nearly stoichiometric reaction at -80°C , but with an

equilibrium which increasingly favors the unsolvated tetramer at higher temperatures.^{125f} No complexation of Et_2O to $(t\text{-BuLi})_4$ could be detected. Interestingly, a subsequent crystal structure showed a disolvated dimer, $(t\text{-BuLi})_2 \cdot (\text{Et}_2\text{O})_2$.¹⁶ Solutions having a <2:1 ratio of Et_2O to $t\text{-BuLi}$ were stable at -80°C , but when there was excess Et_2O decomposition became increasingly rapid in a reaction that was first-order in $[(t\text{-BuLi})_2(\text{Et}_2\text{O})_4]$ and first-order in $[\text{Et}_2\text{O}]$, so the decomposition involves reaction of the solvated dimer with free ether, and not intra-aggregate attack on a coordinated ether. The product of the reaction was identified as the mixed tetramer $(t\text{-BuLi})_3 \cdot (\text{EtOLi})_1$ by ^6Li , ^1H , and ^{13}C NMR spectroscopy. The formation of $t\text{-BuCH}_2\text{CH}_2\text{Li}$ from addition of $t\text{-BuLi}$ to ethylene was confirmed by product analysis.^{125f}

In an IR and Raman spectroscopy study of the reaction of $n\text{-BuLi}$ with THF at 25°C , Corset and co-workers showed that the decomposition was first-order in $[(n\text{-BuLi})_2]$.³⁶¹ They identified the three species formed during the reaction by vibrational signatures (using computed IR spectra) as the mixed dimer $(\text{BuLi})_1 \cdot (\text{CH}_2=\text{CHOLi})_1$, a lithium enolate dimer, and a lithium enolate tetramer. They proposed a mechanism in which one of the coordinated THF molecules undergoes intramolecular deprotonation and fragmentation to form the mixed aggregate. Recent work has shown that 4-fluoroacetophenone lithium enolate had a dimer–tetramer association constant in THF, $K_{\text{eq}} = [\text{T}]/[\text{D}]^2 \geq 2 \times 10^6 \text{ M}^{-1}$, and that the dimer had a half-life of only minutes at -120°C .¹⁶⁰ Since acetaldehyde enolate is less sterically encumbered, and less inductively stabilized, it is unlikely that an acetaldehyde enolate dimer was being observed at room temperature. Probably several mixed tetramers were detected. An NMR study of acetaldehyde lithium enolate indicated a tetrameric structure.^{242b}

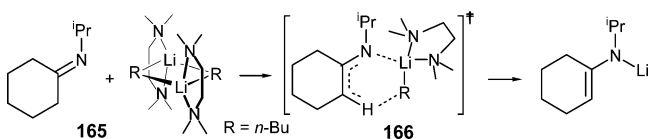
Another reaction of $n\text{-BuLi}$ that is of some importance is the thermal decomposition to form LiH and butene. A kinetic study of this reaction in hexane showed the elimination was first-order in $[(n\text{-BuLi})_6]$ and showed an isotope effect $k_{\text{H}}/k_{\text{D}}$ of 3–4, so a simple four-center unimolecular elimination within the aggregate was proposed. Deliberate addition of $n\text{-BuOLi}$ caused small rate increases (a factor of 2 with 22% $n\text{-BuLi}$ replaced by $n\text{-BuOLi}$).³⁶²

3.3.8. Miscellaneous Metalations. A detailed NMR investigation, including DOSY molecular size measurements, of the vinyl metalation in THF of **163** to form **164** showed that the starting lithium amide was a mixture of monomer and two stereoisomeric dimers. A likely intermediate mixed dimer with $n\text{-BuLi}$ **123** was characterized, and the product dilithium species was shown to be a mixture of monomer, dimer, and tetramer. The intermediate **123** had the vinyl group coordinated to one lithium as indicated by NOE experiments and two distinct THF signals in the low-temperature NMR spectra (a rare slow exchange of solvent).³¹³

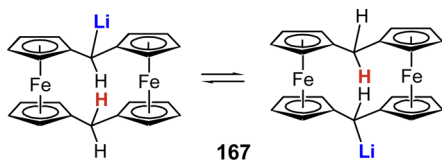


The metalation of a ketimine, **165**, by $(n\text{-BuLi})_2 \cdot (\text{TMEDA})_2$ was first-order in substrate and 0.5-order in $[(n\text{-BuLi})_2]$. Similar results were found for $(\text{PhLi})_2 \cdot (\text{TMEDA})_2$. The reaction was zeroth-order in excess TMEDA, so the reactive nucleophile was

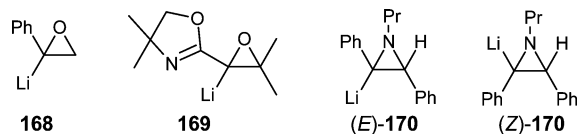
(RLi)₁·(TMEDA)₁. Neither ligand dissociation nor ligand-assisted deaggregation was involved. The authors concluded that the reaction involved the transition state **166**.^{363a}



A somewhat unusual metalation studied in some detail is the intramolecular proton transfer in the ferrocenophane **167**.³⁶⁴ The solid-state structure was monomeric and had an exo-bonded lithium cation.³⁶⁵ This was also the solution structure in ether, 2,5-dimethyltetrahydrofuran, and THF. DNMR studies of the degenerate proton transfer showed a modest isotope effect ($k_H/k_D = 7.4$ at 320 K) and a significant Saunders isotope perturbation¹⁸⁶ in the monodeuterio compound. The solvent dependence (proton transfer was 4000 times as fast in THF as in Me₂THF) and relatively high negative entropy of activation ($\Delta H^\ddagger = 4.5$ kcal/mol, $\Delta S^\ddagger = -22$ eu) was consistent with one additional THF molecule in the transition state. Since the ground state is probably doubly solvated, judging from the X-ray structure of the bis(2,3-dimethyltetrahydrofuran) solvate, the authors suggest that the additional solvent molecule loosens the coordination of lithium or produces an SIP, which then transfers the proton.



The deprotonation of styrene oxide with *s*-BuLi in THF gave solutions of the α -lithio derivative **168**, which is a complex mixture of species in solution, further complicated by decompositions to give several alkoxide species, as well as small amounts of β -lithiation. Careful NMR investigation of the natural abundance as well as the doubly ¹³C-enriched compound showed that **168** was a mixture of monomer and four stereoisomeric dimers (presumably diastereomers at carbon as well as chelation isomers).³⁶⁶

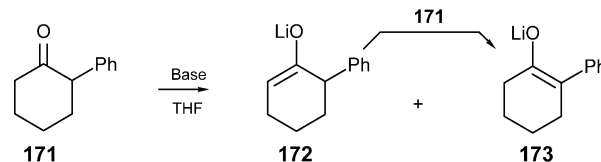


The metalation of an oxaziridinyl epoxide to form **169** was very rapid in THF even at the lowest temperatures. This compound also appeared to be mainly monomeric, with small amounts of several diastereomeric dimers present. Unlike that of lithiated styrene oxide **168**,³⁶⁷ configurational isomerization of **169** was rapid.³⁶⁸

Metalation of related aziridines has also been studied. *trans*-1,2-Diphenyl-*N*-propylaziridine is metalated rapidly in THF to form a lithium species, **170**, in which the C–Li carbon is coupled to one lithium, hence probably a monomer. The kinetic product (*E*)-**170** rapidly isomerized to form (*Z*)-**170**. Deprotonation in toluene–TMEDA gave (*E*)-**170**, which was dimeric and configurationally stable and could be trapped stereospecifically with electrophiles.³⁶⁹

Several enolate proton transfers have also been studied. The deprotonation of 2-phenylcyclohexanone **171** with 9-lithio-

9,9,10-trimethyl-9,10-dihydroanthracene as the base gave a 6:1 ratio of the enolates **172** and **173**. In the presence of excess ketone, **172** isomerized to **173** in a reaction that was first-order in [**171**] and 0.25-order in [**172**]. Thus, the isomerization mechanism involves a pre-equilibrium dissociation of (**172**)₄ to the monomer, followed by proton transfer to form **173**.³⁷⁰

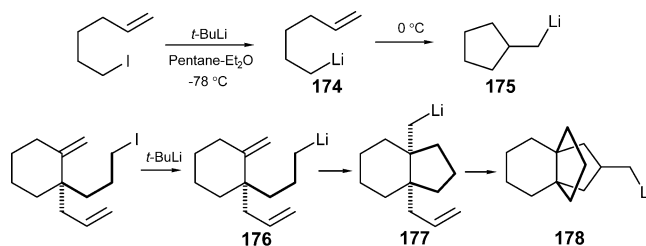


A study of the proton transfer between cyclopentanone lithium enolate and 2-methylcyclopentanone in THF–HMPA showed that addition of HMPA causes only a factor of 5 rate increase at -50°C (alkylation with MeI increases by a factor of 7500). The reaction was first-order in [enolate] and zeroth-order in excess [HMPA].³⁷¹ Thus, the transition state for proton transfer had the same number of coordinated HMPA molecules as the predominant species, known to be (ROLi)₄·(HMPA)₄.^{80a}

3.4. Alkene Addition (Carbolithiation)

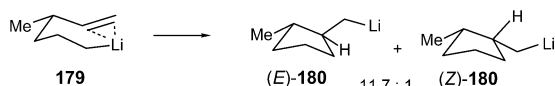
Addition of lithium reagents to weakly activated double bonds such as styrene or butadiene was an early focus of mechanistic studies in organolithium chemistry because of the interest in understanding the industrially important anionic polymerizations to form polystyrene, polybutadiene, and polyisoprene. The studies related to polymerization are not in the scope of this review,^{2,372} nor are those whose primary focus is the synthetic aspects of the reaction.^{373–381} Some model studies in nonpolymerizing systems are summarized below.

Intramolecular cyclizations occur with greater facility than intermolecular ones, and many examples have been reported. The observation by Bailey and co-workers that 5-hexenyl-lithium **174** cyclizes to form (cyclopentylmethyl)lithium **175** under mild conditions (0°C in pentane–Et₂O)^{374a,b} helped to clarify the mechanism of the Li/I exchange, where the formation of cyclized products had been interpreted in terms of radical intermediates and an SET mechanism (see section 3.7). In some cases anionic rather than radical cyclizations were involved. Cyclizations are fairly general provided that additions are exocyclic, form primary alkylolithiums, and give five-membered rings, although cyclobutanes can be formed in favorable situations.³⁷⁶ These effects are illustrated in the tandem cyclization of the lithium reagent **176** to form **177** and then **178**.^{374c}



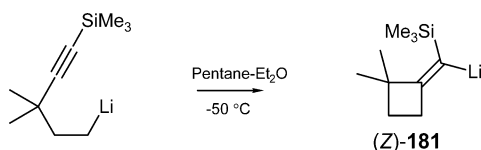
Alkylolithiums,^{319,374–378} aryllithiums,^{374d,379} and vinyl-lithiums^{376,380} undergo such cyclizations. The mechanism of these reactions has been minimally investigated. Activation parameters for the cyclization in pentane–Et₂O solution of **174** ($\Delta H^\ddagger = 11.8$ kcal/mol, $\Delta S^\ddagger = -30$ eu)^{374a} and a related acetylene ($\Delta H^\ddagger = 23.0$ kcal/mol, $\Delta S^\ddagger = 4.8$ eu)³⁸¹ have been

determined, and Lewis basic solvents or additives such as TMEDA facilitate the additions. However, neither the aggregation state of the precursor lithium reagent nor the reactive aggregate is known for these cyclizations. Computations and the often high stereochemical preferences support the intervention of lithium–alkene complexes as intermediates,^{374g,380} and such complexation has been experimentally detected in a noncyclizing system.³⁸² The substituted hexenyllithium **179** cyclizes to the products (*E*)-**180** and (*Z*)-**180** in an 11.7:1 ratio, suggesting the ordered transition state shown.^{374g}

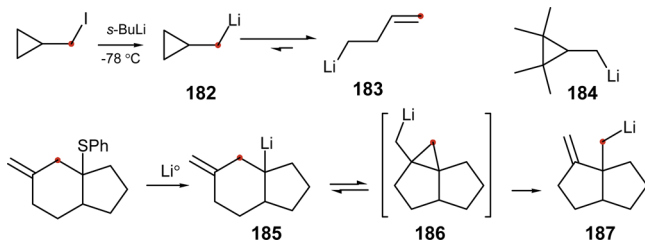


Except for additions to ethylene (section 3.4.4), *intermolecular* additions to double bonds are usually successful only with alkenes bearing activating substituents such as vinyl,⁹⁵ aryl,^{383,384} thio,^{385,386} or silyl,³⁸⁷ which form a stabilized anion during the addition. Studies of these reactions include detailed consideration of the stereochemistry of the addition at both the C–C and the C–Li termini.³⁸⁸ Additions of this type with principally a synthetic (rather than a mechanistic) objective, often with asymmetric reactions in mind, are not in the scope of this review.³⁸⁹

Intramolecular carbolithiation of acetylenes has also been examined.³⁸¹ Usually strict *syn*-addition of carbon and lithium to the triple bond is seen, as in the formation of (*Z*)-**181**.³⁹⁰ In a special case a *trans*-addition occurs, apparently mediated by a chelation effect.³⁹¹

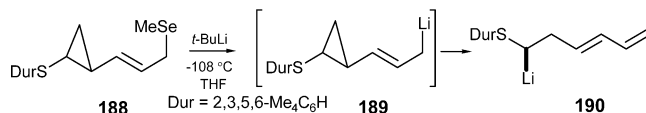


3.4.1. (Cyclopropylmethyl)lithium. A special case of intramolecular carbolithiation is the cyclopropylmethyl–homoallyl system (**182**, **183**), where the former is stable for only a short time at $-78\text{ }^{\circ}\text{C}$ in pentane– Et_2O before retrocarbolithiation to the homoallyl system occurs.³⁹² The equilibrium can be moved entirely to the side of the cyclopropyl system with suitable alkyl substitution, as in **184** (X-ray structure³⁹³). The rearrangement is reversible, as shown by a number of isomerizations of secondary and tertiary homoallyllithium reagents to primary ones, e.g., conversion of **185** to **187**, presumably via **186**.³⁹⁴



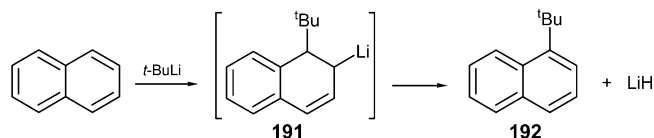
In a suitably designed system, it was possible to determine the stereochemistry of the retrocarbolithiation. The optically active selenide **188** was converted to the lithium reagent **189** by Li–Se exchange, which underwent ring-opening to the α -ArS lithium reagent **190**. Trapping with either R_3SnBr or MeI gave optically active products which showed that ring-opening had

occurred with >90% retention of configuration at the lithiated carbon in **190**. Durylthio compounds were shown to be configurationally stable under these conditions.³⁹⁵



3.4.2. Addition to Aromatic Rings. In favorable situations additions of organolithium reagents to suitably activated aromatic rings can be observed,^{328,396} including fullerenes³⁹⁷ and nanotubes.³⁹⁸

In an early kinetic study of the addition of *t*-BuLi to naphthalene (forming **191** and then **192**) in decalin solution, a reaction 0.5-order in $[\text{t-BuLi}]$ was found.³⁹⁹ This was interpreted in terms of dissociation of the $(\text{t-BuLi})_4$ to dimers, followed by addition to the aromatic ring. The reaction was inhibited by *t*-BuOLi (inverse 0.25-order), ascribed to formation of unreactive mixed aggregates (presumably the mixed aggregates characterized later¹⁷⁸), which had a lower dissociation constant than the homotetramer. This is a reasonable assumption, considering the much smaller steric effect of an alkoxide versus a *tert*-butyl carbon.



3.4.3. Addition to 1,1-Diphenylethylene. The addition of RLi to styrene forms a benzyl anion. Although systems are known where addition can be stopped,^{383,384} typically the benzyl anion then adds to additional styrene molecules to form a polymer.^{2,132b,372} Alkyl lithium reagents add readily to 1,1-diphenylethylene, but the more stabilized product anion does not add again, so this reaction was used as a model for the styrene addition. Studies of the addition of several RLi reagents to 1,1-diphenylethylene in benzene found the reaction to be 0.18-order in $[\text{n-BuLi}]$,⁴⁰⁰ 0.11-order in $[\text{EtLi}]$,^{322a} and 0.25-order in $[\text{t-BuLi}]$,^{322c} all reasonably consistent with a monomer-based mechanism. In 0.4% Et_2O –benzene somewhat higher orders were found for EtLi (0.28), *n*-BuLi (0.5), and PhLi (0.41), probably better rationalized by dimer reactions, since both *n*-BuLi and PhLi are mostly tetrameric in Et_2O .⁴⁰¹ A study of the effect of added lithium alkoxide on the addition of *n*-BuLi in benzene gave modest increases in rate at a 1:1 ratio of *n*-BuLi to ROLi : a factor of 1.4 for *n*-BuOLi, 1.7 for *t*-BuOLi, and 4.6 for lithium menthoxide.⁴⁰² Therefore, the mixed alkoxide aggregates present in these solutions are only marginally more reactive than *n*-BuLi itself.

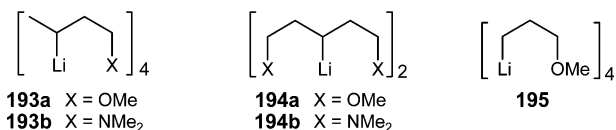
In an extensive study of the reaction of 1,1-diphenylethylene in THF at $22\text{ }^{\circ}\text{C}$, the orders in RLi were measured for benzyl lithium (1.1), allyllithium (1), phenyllithium (0.66), vinyl lithium (0.34), and methyl lithium (0.27). The rates of the *n*-BuLi reaction were too fast for accurate measurements, but 0.4-order was estimated.³⁰² Another study at $-40\text{ }^{\circ}\text{C}$ using a stopped-flow technique gave 0.5-order in $[\text{n-BuLi}]$.⁴⁰¹ Except for allyllithium, which is now believed to be dimeric in THF,^{185a} these orders are consistent with monomers being the reactive species in all cases. *n*-BuLi is largely dimer with some tetramer under the conditions of this experiment,¹⁷¹ so the 0.4–0.5-order is appropriate. PhLi is monomer with some dimer (Figure 5),^{103,129} so 0.66-order could be consistent.

Vinylolithium is mostly tetramer, but with a significant fraction of dimer,²⁹ so the 0.34-order is that expected for monomer reactivity.

3.4.4. Addition to Ethylene. A pioneering study of the addition of *s*-BuLi, *i*-PrLi, and *t*-BuLi (*n*-BuLi did not react) to ethylene in pentane included specific consideration of coordinating solvent. No ethylenation occurred without added ethers, but Et₂O, THF, 1,4-dimethoxybutane, and triethylamine were all effective catalysts. In reactions with >5 equiv of Et₂O, the reaction with *s*-BuLi and *i*-PrLi was first-order in [ethylene], first-order in [RLi], and second-order in [Et₂O]. Thus, the principal aggregate (tetramer) was the reactive one, and the transition state has two more molecules of Et₂O than the prevailing solvated form. Unfortunately, the degree of solvation with Et₂O was not known, but the level could be measured with Me₂O using vapor pressure measurements in heptane solution and was found to be a little above 2 (main species (*s*-BuLi)₄·(Me₂O)₂). The authors hypothesize that the more hindered Et₂O perhaps forms only (*s*-BuLi)₄·(Et₂O)₁ and that the transition state consists of the trisolvated tetramer, coordinated to ethylene at the remaining vacant site: (*s*-BuLi)₄·(Et₂O)₃·CH₂=CH₂.⁴⁰³ Alternatively, if Et₂O also disolvates (*s*-BuLi)₄, then ladder tetramers related to **4** or **70** would be implicated.

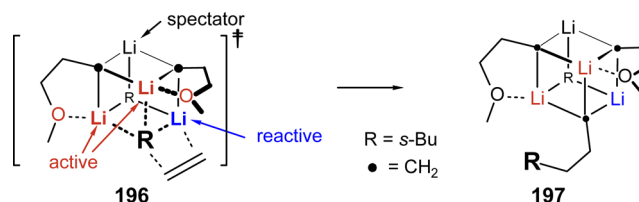
The interesting observation was made that small increments of THF greatly accelerated the addition of *t*-BuLi, whereas larger amounts (>10 equiv) caused a rate decline, with the reaction rate becoming inversely dependent on [THF]. This was interpreted in terms of a mechanism where the reactivity of the tetramer is increased by successive coordination to THF, with the optimum species being the trisolvated tetramer having one coordination site vacant (presumably the ethylene coordinates here). Excess THF eventually blocked all four lithium sites, requiring decooordination before carbometallation can occur.⁴⁰³ However, *t*-BuLi is now known to be dimeric in Et₂O^{125f} and monomeric in THF,¹²⁹ so the biphasic behavior with THF would have to be reinterpreted in terms of dimers or monomers.

In a series of studies directly aimed at probing the role of ether solvents on the often great increases in the reactivity of aggregated lithium reagents, Klumpp et al. used internal coordination by suitable chelating groups to provide a controllable analogue of a solvation environment. The tetrameric chelates **193a** and **193b** reacted readily with ethylene in pentane solvent, under conditions where *s*-BuLi was unreactive. The amine-chelated tetramer **193b** was at least 3 times as reactive as the ether chelate **193a**. It is interesting that the bischelated dimers **194** were 1 or 2 orders of magnitude less reactive than the tetramers **193**.⁴⁰⁴



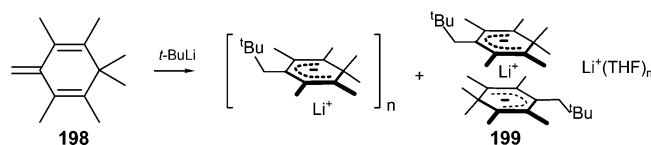
In benzene solution neither tetrameric *s*-BuLi (ether cosolvent is required for reactivity) nor tetrameric (3-methoxypropyl)lithium (**195**) (primary alkylolithiums are poorly reactive) adds to ethylene at an appreciable rate. Remarkably, mixtures of the two were quite reactive toward ethylene to form (3-methylpentyl)lithium. NMR spectroscopic studies showed that the expected series of mixed tetramers (*s*-BuLi)₃·(**195**)₁, (*s*-BuLi)₂·(**195**)₂, and (*s*-BuLi)₁·(**195**)₃ were formed. The

addition reaction was first-order in [ethylene] and 0.74-order in [RLi] for a 1:1 ratio of the two reagents. The fractional order was explained by some precomplex formation. The rate of ethylenation maximized at ratios of **195** to *s*-BuLi where the concentration of the (*s*-BuLi)₂·(**195**)₂ mixed aggregate was maximal and was reduced significantly at lower or higher ratios of **195** to *s*-BuLi. The authors conclude that two chelating methoxy ligands are optimal to activate a tetramer and suggested an appealing model for the transition state shown in **196**, which leads to the mixed tetramer **197**.⁴⁰⁵

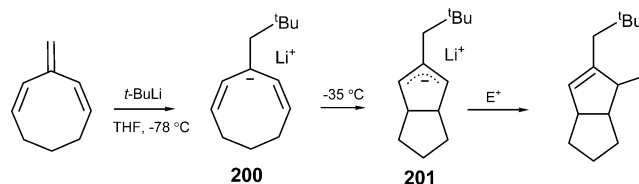


It was proposed that of the four lithiums in the tetrameric transition state, one is a spectator (it is coordinated only to the nonreacting RLi species), one is the reactive Li which will become coordinated to the substrate ethylene (blue), and the remaining two are active (red): they are bonded to the *s*-Bu group undergoing addition. It is the two essential chelating methoxy groups which provide electron density to the two active lithiums to aid release of the *s*-Bu group so the ethylenation can proceed. Note that the presence of a third chelating group in the (*s*-BuLi)₁·(**195**)₃ complex would only provide electron density for the spectator lithium, which is insulated from the reaction center.⁴⁰⁵

3.4.5. Polyene Addition. The earliest organolithium triple ion to be characterized was **199** formed by addition of *t*-BuLi in THF to the methylenecyclohexadiene **198**.⁹⁵

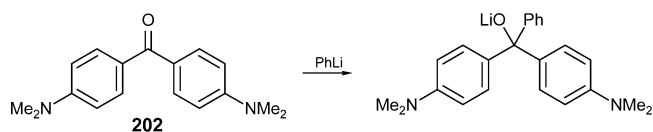


Additions of RLi to a variety of 3-methylene-1,4-cycloalkadienes proceed smoothly, producing pentadienyl anions, e.g., **200**. In this case, electrocyclic closure led to the bicyclo[3.3.0] allyllithium **201**.⁴⁰⁶

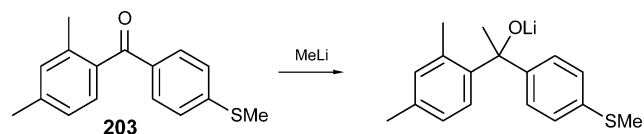


3.5. Additions to Carbonyl Compounds

3.5.1. Ketones. The first kinetic study of carbonyl addition involved the reaction of PhLi with Michler's ketone (**202**) using an interesting stopped-flow analytic method. A crossed stream of ketone (in toluene) and PhLi (in ether) was injected into methanol, and the fraction of reacted ketone was measured. With the assumption that the contact time (although unknown) was constant as concentrations were changed, the authors concluded that the reaction was first-order in [PhLi] and first-order in [ketone].⁴⁰⁷ This would be consistent with (PhLi)₂ being the reactive species.



The first real kinetic study of a ketone addition was a UV-detected stopped-flow examination of the reaction of MeLi with 2,4-dimethyl-4'-(methylthio)benzophenone (**203**) at 25 °C in Et₂O.^{299c} The reactions were very fast, with k_{obsd} values between 20 and 100 s⁻¹ (ΔG^\ddagger of ca. 15 kcal/mol). Since the barrier for dissociation of (MeLi)₄ in Et₂O has been estimated at around 11 kcal/mol,³⁰⁶ it is probable that these experiments were under Curtin–Hammett conditions. The course of the reaction followed the rate law $\text{rate} = [\text{MeLi}]^{0.25}[\text{ketone}]^{1.0}$, consistent with a pre-equilibrium dissociation of MeLi to monomers, which then reacted with ketone. The fractional orders can also arise if the ketone forms a complex with (MeLi)₄, which then continues to product. However, no complex formation could be detected in the rapid-scan UV spectra used for the kinetic measurements. Such complexes were detected in similar Grignard additions in Et₂O⁴⁰⁸ and *n*-BuLi additions in benzene.



The effect of halides was also probed. Reduction in rates was observed with both LiBr and LiI. One equivalent of LiBr caused an approximately 2-fold reduction in rate, a 5-fold excess about a factor of 5 reduction in rate. The rate law was still 0.25-order in [MeLi].^{299c} The origin of these rate reductions is not known; perhaps the halide mixed aggregates have a lower equilibrium constant for dissociation to monomer.

A similar study of the reaction of *n*-BuLi with 4-(methylthio)acetophenone in benzene showed some indications of precomplexes between ketone and *n*-BuLi—broadening of the *n*-to- π^* transition in the UV spectrum—but the IR spectrum was not affected.³⁰⁷ The rate data could be fit either to a mechanism involving dissociation of (*n*-BuLi)₆ to monomers, followed by addition, or to a mechanism in which a precomplex was formed between (*n*-BuLi)₆ and ketone, with $K_{\text{eq}} = 600 \text{ M}^{-1}$, followed by reaction.

An interesting effect of alkoxides was noted. It was shown that when 1% alcohol product was deliberately added to the *n*-BuLi, the reaction rate was doubled. However, the reaction was not autocatalytic, nor did the addition of alcohol to the ketone before the reaction have any effect on the rate. The authors concluded that the formation of the *n*-BuLi mixed aggregate responsible for the rate acceleration was slower than addition of *n*-BuLi to the ketone. The ΔG^\ddagger for the ketone addition was ca. 14.7 kcal/mol. It is conceivable, and even likely, that aggregate interconversion barriers could be this high. An estimate can be made from the loss of Li–C coupling in a dodecameric *n*-PrLi–*n*-PrOLi mixed aggregate in cyclopentane,¹⁶⁹ which occurred well above –25 °C. Assuming a coalescence temperature of 0 °C, with $J = 2.3 \text{ Hz}$, we can estimate $\Delta G^\ddagger = 15.0 \text{ kcal/mol}$ for interaggregate exchange.

In a stopped-flow kinetic study of the reaction of *s*-BuLi with several *s*-butyl aryl ketones in cyclohexane at 25 °C, rather complicated kinetic behavior was found. The data could be consistently explained using curve-fitting procedures by a

combination of two mechanisms: (1) the association of the (*s*-BuLi)₄ with ketone (detected by IR), followed by addition, and (2) dissociation to (*s*-BuLi)₁, followed by reaction. Although this paper does not report much detailed kinetic data, the kinetic analysis gave estimates of the relative reactivity of monomers and tetramers, 1500:9 for methyl *s*-butyl ketone. Electron-deficient ketones complexed less strongly with (*s*-BuLi)₄, and a larger proportion of the reaction went through monomer pathway 2.⁴⁰⁹

Although such studies are not directly germane to the focus of this review, which is aggregate reactivity, the Yamataka group has examined isotope effects on the addition of MeLi,^{410a} PhLi,^{410b} allyllithium,^{410b} and PhSCH₂Li^{410c} with benzophenones in ether at 0 °C. They found no detectable ¹⁴C–¹²C kinetic isotope effect at the carbonyl group. Hammett correlations were also done and gave ρ values from 0.17 to 0.26. This is in contrast to Grignard additions, which gave significant isotope effects and ρ values of 0.5–0.9. The KIE and small ρ values were considered as supporting an SET mechanism, although it is not clear why formation of a negatively charge radical anion should not have a substantial Hammett ρ . Other possibilities, such as rate-determining precomplex formation or a very early transition state, were considered less likely, but hard to rule out.

These isotope effects and Hammett $\sigma\rho$ experiments were done by competition methods. This technique suffers from the potential problem of mixing-controlled processes in these very fast reactions, which would suppress both isotope and substituent effects. Studies of Grignard reactions, which are much slower, typically give more normal KIE and ρ values. A Hammett study of the reaction of MeLi with benzophenones using carefully controlled continuous slow addition gave a ρ value that was larger (0.94) than that obtained earlier (0.26).⁴¹¹

Responding to this, the Yamataka group performed a stopped-flow rate study of the reaction of MeLi with benzophenones, which gave a ρ of 0.4. The order in [MeLi] was between 0.27 and 0.46, indicating that (MeLi)₄ has to dissociate to (MeLi)₂ or (MeLi)₁ before reaction with the ketone.⁴¹² Together these studies of the ketone reaction leave some question as to whether SET reactions are involved, especially for the very fast reactions of aldehydes where the rate-leveling effect of insufficient mixing would be most severe.

Support for polar mechanisms for carbonyl additions is provided by the stereochemistry at the lithium center. The reaction of (*S*)-2-lithio-*N*-methylpyrrolidine (**105**, dimer in THF²⁷⁴) with benzophenone gives racemic products, as expected for an SET mechanism. However, the reactions with benzaldehyde, acetone, and cyclohexanone all proceed with complete retention of configurations. Thus, these additions proceed by a polar mechanism.⁴¹³

Deuterium isotope effects have also been measured for the addition of alkyllithium reagents CD₃Li and CH₃CD₂Li to ketones in Et₂O. Significant positive isotope effects were observed, with $k_{\text{H}}/k_{\text{D}} = 1.06$ –1.14. Two explanations were considered. An SET process should involve significant rehybridization of the carbanion carbon during formation of methyl radical (hence a significant isotope effect), whereas a polar mechanism should involve little change in structure during the addition, so the results could be interpreted as favoring an SET mechanism for the carbonyl addition.⁴¹⁴ However, a steric effect could also be the source of an isotope effect, where the smaller size of the CD₃ group results in a less crowded aggregate and hence a smaller aggregate dissociation

constant. Since lower aggregates are typically the reactive species, a lower rate for CD_3Li than for CH_3Li is expected. This would also explain the observation that isotope effects were observed both for ketones that would be expected to be poor electron acceptors, such as 2-octanone, and for those that are good ones, such as benzophenone and 1,3-diphenyl-2-buten-1-one. This effect also rationalizes the consistently smaller isotope effects found for Grignard additions, where such a steric effect would be smaller or absent.⁴¹⁵

Competing deprotonation to form enolates is regularly observed during addition of lithium reagents to ketones. Some qualitative trends have been identified. Steric effects in either the lithium reagent or the ketone promote enolization, as do polar solvents. The Klumpp group performed interesting experiments using a series of lithiated silanes which all have the same local structure at the lithium center, but with different pendant amino groups which change the aggregation state ("internal solvation").⁴¹⁶ In pentane solution, the tetramer **112** gave mostly carbonyl addition, the dimeric **113** gave approximately equal amounts, and the monomer **114** gave mostly enolization (Figure 12). These results suggest that

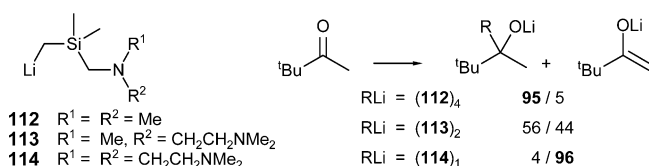
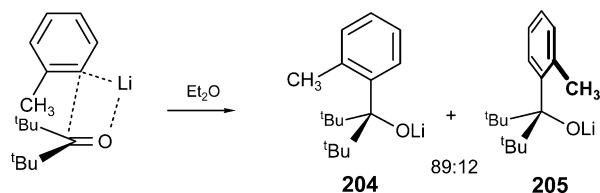


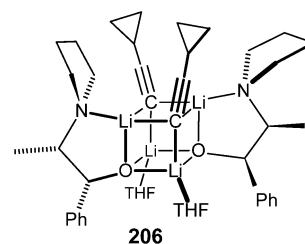
Figure 12. Ratios of addition to enolization in pentane at -70°C for different aggregated chelated (α -silylmethyl)lithiums.⁴¹⁶

aggregation and/or basic coordination to lithium play key roles. Unfortunately, it is not known whether the prevailing aggregate or a lower one is the reactive species in these reactions, so it is unclear whether the changes result from the various levels of amine coordination on a reactive monomer or the consequences of various aggregates as nucleophiles.

In a study which does not address aggregate issues, but does provide some details about the geometry of ArLi addition to ketones, Dubois and co-workers showed that the addition of *o*-tolyl lithium to di-*tert*-butyl ketone produces predominantly the *anti*-conformation **204** (interconversion of the conformational isomers is slow), even though the *syn*-isomer **205** is more stable. The authors conclude that at the transition state for addition the phenyl group must lie in the plane which contains the carbonyl group, and not perpendicular to it.⁴¹⁷

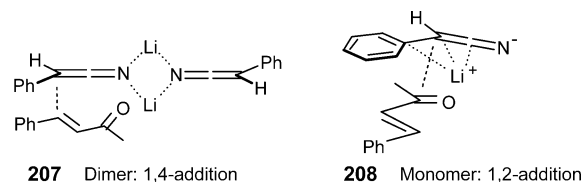


A study of the mixed aggregate between a lithium acetylide and a β -amino alkoxide showed a number of very interesting properties. The kinetically formed aggregates were relatively ineffective in promoting asymmetric addition of the acetylide to ketones, but if a 1:1 solution was warmed to room temperature, a single mixed aggregate formed, which was characterized using ^6Li -, ^{15}N -, and ^{13}C -enriched materials as the C_2 -symmetric 2:2 adduct **206**. This aggregate gave high levels of asymmetric induction in ketone additions.²³³



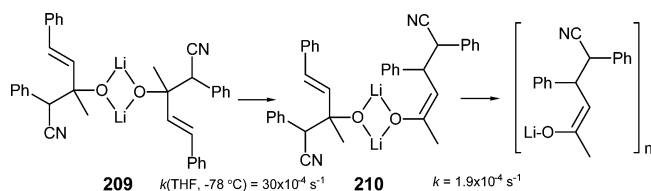
3.5.2. Enones. Many studies of the addition of organolithium reagents to enones^{373a} have focused on the factors governing direct (1,2) versus conjugate (1,4) additions. A variety of explanations have been advanced, including HSAB considerations, SET vs ionic processes, and, of interest in this context, the possibly different behavior of aggregates.

A detailed study of the IR spectra of lithiophenylacetonitrile in a series of THF–toluene mixtures showed a strong correlation between the measured ratios of dimer and monomer and the ratio of 1,2- to 1,4-addition to benzalacetone. The authors suggested that the 1,4-addition proceeded through an extended transition state, **197**, involving a dimer and that 1,2-addition occurred through a compact transition state, **198**, involving a monomer.⁴¹⁸ Inherent in this proposal is the requirement that the products are formed under kinetic control and also that both additions are faster than monomer–dimer equilibration, since otherwise the dimer and monomer would have to exhibit comparable reactivity, an unlikely scenario.



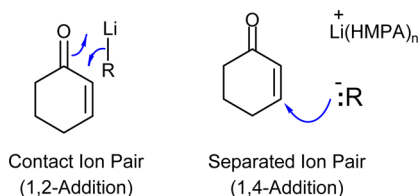
A reinvestigation of this and other lithionitrile reactions⁴¹⁹ showed that the correlation was not direct (as implied by the structures **207** and **208**), but was a case of two observables having a common cause, rather than by a direct cause and effect relationship between the observables. The very different reactivity of a mixed aggregate was probably a major cause of this misinterpretation. Irrespective of the solvent mixture, the kinetic product was always the 1,2-adduct (>97%) if the reaction was sampled quickly enough. However, there was an initial very fast isomerization of half of the 1,2-adduct to the 1,4-isomer (by reversal to enone and a slower 1,4-addition), followed by a second phase of 1,2- to 1,4- isomerization approximately 20 times slower. The tests performed by the earlier authors to demonstrate kinetic addition were after the fast phase and during the slow phase, leading them to conclude that the kinetic ratio was being detected. A likely explanation for the biphasic behavior is that during the isomerization the initial homodimer **209** (or a higher aggregate) of the 1,2-adduct is converted (at 50% reaction) to the enolate–alkoxide heterodimer **210**. This heterodimer, for unknown reasons, is much slower to undergo the retro-1,2-addition to form the final enolate aggregate.

The correlation between the monomer:dimer ratio and the 1,2-addition:1,4-addition ratio is thus due to a common cause: the less polar solvent mixtures cause an increase in the fraction of dimer and also slow the 1,2-to-1,4 isomerization, leading to an apparent correlation.⁴¹⁹ Other examples of medium and structure effects on the ratio of 1,2-addition to 1,4-addition of metalated nitriles can also be ascribed to variations in the 1,2-



to-1,4 isomerization rate rather than the claimed variations in the kinetic ratio of 1,2-addition to 1,4-addition.⁴²⁰

An interesting observation was made in 1979 by several researchers⁴²¹ that the kinetic product of addition of several thio-substituted organolithium reagents (such as 2-lithio-1,3-dithiane) switched from 1,2-addition to 1,4-addition when the solvent was switched from Et₂O or THF to mixtures with HMPA. Careful study of the temperature and solvent dependence of this effect for [bis(phenylthio)methyl]lithium led to the suggestion that it was the conversion of monomeric contact ion pairs (proposed to give 1,2-addition) to separated ion pairs (which gave 1,4-addition) that was responsible.⁴²² The development of the low-temperature HMPA titration technique^{144a} allowed a quantitative evaluation of the CIP/SIP composition for a variety of S-substituted lithium reagents, and comparison with the 1,2-addition to 1,4-addition ratio. These reactions appeared to be under Curtin–Hammett control (i.e., CIP–SIP interconversion was faster than addition to enone), but the strong correlation between the fraction of SIP and the 1,4-addition supported the ion pair hypothesis. In addition, there were stereochemical effects which showed that the 1,4-addition had two components, one a lithium-assisted process at low levels of HMPA (Li⁺ complexed to enone) and an unassisted one (Li⁺ complexed only to HMPA).^{149f}



Although lithium amide additions are not in the scope of this review, we do want to note that a detailed kinetic study by the Collum group of the addition of LiN(*i*-Pr)₂ to an enoate ester revealed complex behavior, including rate-limiting reorganization of the LDA aggregate and autocatalysis.⁴²³

3.5.3. Aldehydes. The reaction of aldehydes with organolithium reagents is too fast for kinetic studies at easily accessible temperatures, so a number of studies have been performed that used less direct methods, including Hammett correlations and ¹²C/¹⁴C, ¹²C/¹³C, and H/D isotope effects. In a study of the reaction of PhLi with benzaldehydes, the Yamataka group using competition experiments at 0 °C in 7:3 cyclohexane–ether found a very small Hammett ρ value of 0.18 and a ¹²C/¹⁴C isotope effect of 0.998. They concluded that this was an electron-transfer reaction.^{410b} Since organolithium additions to aldehydes are extremely fast reactions, especially at such high temperatures, there is a real question of whether mixing is sufficiently fast to avoid the local depletion problem and the attendant reduction in relative rates of additions.

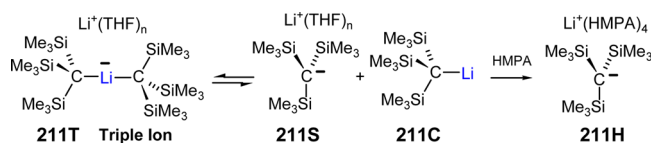
Gajewski measured H/D isotope effects for PhCOH–PhCOD with MeLi, PhLi, *n*-BuLi, *t*-BuLi, and allyl-Li at –78 °C in Et₂O solution using competition experiments.⁴²⁴ No special precautions were reported for efficient mixing of the reagents. Taking into consideration the electrochemical proper-

ties of the reactants, they concluded that allyl-Li ($k_{\text{H}}/k_{\text{D}} = 1.095$) reacted by an SET process, whereas MeLi ($k_{\text{H}}/k_{\text{D}} = 0.88$) reacted by polar addition, as did PhLi ($k_{\text{H}}/k_{\text{D}} = 0.95$). *n*-BuLi and *t*-BuLi showed $k_{\text{H}}/k_{\text{D}} = 0.99$; the authors suggest that these are also polar additions and that the high exothermicity resulted in a very early transition state and negligible isotope effects. We note again that mixing issues could also be contributing to the small isotope effects for these reactants.

MacGarrity and Ogle³¹⁵ developed an RINMR apparatus that allowed them to measure the kinetics of an aldehyde–RLi reaction for the first time. In THF *n*-BuLi is a nearly equimolar mixture of dimer and tetramer. They measured the kinetics at –85 °C on a time scale of a few seconds and were able to show that (*n*-BuLi)₂ was more reactive than (*n*-BuLi)₄, they estimated by a factor of 10 (later shown to be a large underestimate²³⁸), and that there were some interesting complications in the process, including the transient addition of the initially formed alkoxide to unreacted aldehyde to reversibly form lithiohemiacetal structures, which then reverted to aldehyde over a few seconds. It was proposed that the kinetically formed nonequilibrium alkoxides were unusually reactive and added to the aldehyde before they formed the thermodynamically more stable higher aggregates present at equilibrium.

McGarrity and Ogle also made some qualitative observations on the reaction of *n*-BuLi–*n*-BuOLi mixed tetramers. Each of the mixed tetramers was found to be more reactive than (*n*-BuLi)₄, with (*n*-BuLi)₂·(*n*-BuOLi)₂ having a reactivity similar to that of (*n*-BuLi)₂, being about 7 times as reactive as (*n*-BuLi)₄.³¹⁵ These results have to be taken as very approximate.

Using an RINMR apparatus that allowed operation at temperatures down to –135 °C, which resulted in much slower rates, Reich et al.²³⁸ showed that the (*n*-BuLi)₂ reaction with benzaldehyde in THF was complete in under 1 s at –131 °C, whereas (*n*-BuLi)₄ reacted over several hours. Thus the reactivity difference was at least a factor of 4000 between dimer and tetramer. With the less reactive *p*-(diethylamino)-benzaldehyde, (*n*-BuLi)₄ no longer reacted (the rate was zeroth-order in [aldehyde] and identical to the measured rate of tetramer dissociation). This observation has the interesting corollaries that even this relatively basic aldehyde was not effective at converting (*n*-BuLi)₄ to more reactive species or providing assistance in tetramer dissociation (see below for a contrasting observation with the triple ion **211T**). The aldehyde still reacted with (*n*-BuLi)₂ in under 1 s at –131 °C, so the dimer is at least a factor of 20 000 more reactive than the tetramer. Since the dimer was too fast to measure, and the tetramer too slow, it is certain that these relative rates are substantial (perhaps huge) underestimates. The factor of 10 reported by McGarrity,³¹⁵ long the benchmark of aggregate relative reactivity, was presumably the result of operating too close to the “Curtin–Hammett line” (Figure 8), so the dynamic range was very small and the reactivity of the two aggregates was not distinct enough for the detection method.



[Tris(trimethylsilyl)methyl]lithium (**211**)^{93a,120b,296,315} is a most unusual lithium reagent, with relatively high barriers for interconversion of the three species present in THF (CIP

211C, SIP **211S**, and triple ion **211T**), allowing them to be individually studied in THF solutions under non-Curtin–Hammett conditions at low temperatures, for **211T** below $-75\text{ }^{\circ}\text{C}$ ($\Delta G^{\ddagger}_{-90} = 14.3\text{ kcal/mol}$) and for **211C/S** below $-130\text{ }^{\circ}\text{C}$ ($\Delta G^{\ddagger}_{-90} = 9.6\text{ kcal/mol}$).²⁹⁷ Particularly the interconversion of the triple ion with the two monomeric species is slow enough for careful study by RINMR methods below the Curtin–Hammett line (see Figure 8). The reaction of **211S** and **211C** with benzaldehydes was too fast to measure at $-135\text{ }^{\circ}\text{C}$, but that of **211T** was quite slow (monomers were at least 10^7 as reactive as the triple ion at $-130\text{ }^{\circ}\text{C}$) and showed some interesting properties. Solutions of pure **211T** were prepared by scavenging the monomers **211S** and **211C** with MeI (which did not detectably react with **211T**), followed by reaction with aldehydes. The reactivity of **211T** showed an inverse electronic effect: electron-rich aldehydes such as *p*-(diethylamino)-benzaldehyde were more reactive than electron-deficient ones (CF_3 -substituted). A normal reactivity sequence was found when competition experiments between pairs of aldehydes were performed. The reaction of **211T** was first-order in [aldehyde], but this was shown to be the result of a rate-determining aldehyde-catalyzed dissociation of **211T** to form the much more reactive monomers. Since electron-rich aldehydes are more effective at this catalysis, they reacted more rapidly. In competition experiments the more basic aldehyde causes triple ion dissociation, but the electron-deficient aldehyde then out-competed the electron-rich one in reaction with the monomers, leading to the opposite reactivity trend.

A key observation in the studies of **211** was that HMPA did not detectably complex with or accelerate the dissociation of **211T**, probably for steric reasons (the “cone angle” of aldehydes, which did interact, is much smaller than that of HMPA), although it did instantly cause conversion of both monomers to the SIP–HMPA complex **211H**. Remarkably, **211H** was essentially unreactive toward aldehydes, presumably because HMPA coordination suppressed the Lewis acid properties of the lithium cation. **211S** was at least 10^{10} times as reactive **211H**, representing a rare estimate of the activating effect of lithium cation on a carbonyl addition.²⁹⁷

Mixed aggregates play key roles in numerous asymmetric additions, which are not within the scope of this review. However, we mention a particularly interesting example where an understanding of aggregate behavior assisted in development of the first addition of RLi to an aldehyde catalytic in a chiral amide. The mixed dimer **212** is believed to be the active nucleophile. The key observation was that entrapment of the chiral amide by the product lithium alkoxide could be ameliorated by judicious addition of LiCl, which had a higher affinity for the alkoxide than did the amide.⁴²⁵ It may also be that LiCl plays a catalytic role in “shuffling” the mixed aggregates, as has been found in other contexts.³⁰⁵

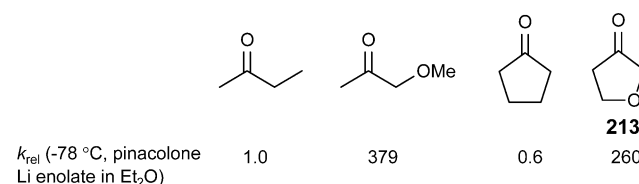


3.5.4. Aldol Condensation. Arguably the most important reaction of aldehydes is the aldol reaction, yet it has been subject to very few kinetic studies. Like most other aldehyde organolithium reactions, this one is too fast to study by classical kinetics. Since enolates are invariably aggregated in ether solvents, the involvement of aggregates and mixed aggregates

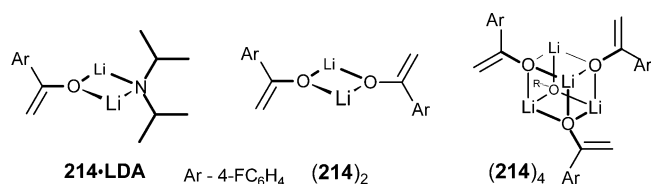
was expected,⁴²⁶ and a lot of qualitative information strongly supported this notion, e.g., from diastereomer ratios that are sensitive to lithium amide or alkoxide additives.⁴²⁷ Thermochemical measurements of the aldol reaction of pinacolone enolate with pivaldehyde provided data on the aggregation state of the enolate (hexamer in hydrocarbons, tetramer in ethers), on the heats of solvation of starting enolate and aldolate products with THF, DME, and TMEDA, and on the substantial exothermicity of the reaction.⁴²⁸

The first actual rate measurement was an RINMR study by Palmer, Ogle, and Arnett.⁴²⁹ They examined the rate of reaction of lithio pinacolone with 4-methylbenzaldehyde in methylcyclohexane at $-80\text{ }^{\circ}\text{C}$ (half-life of 13 s) with the goal of applying the Ebersson analysis for SET reactions to the aldol process. This and other tests, including cyclizable probes, were negative for any SET component. Although the enolate is probably hexameric in this solvent, no direct inferences were made on the role of aggregates. Ashby and Argyropoulos⁴³⁰ had shown that, in the very slow reaction of lithium pinacolone with benzophenone, ketyl radicals were formed.

In this context we mention here the extensive aldol competition studies by Das and Thornton⁴³¹ which, although not directly providing information about aggregation, gave an excellent overview of substituent rate effects in lithium pinacolone aldol reactions, including the interesting and well-supported conclusion that the accelerating effect of α -alkoxy substituents (acetone vs methoxyacetone, 379 \times) was a field effect and not a consequence of chelation, since a similar effect was seen for a cyclic α -alkoxy ketone, **213**, incapable of chelation.



With the availability of an RINMR apparatus capable of operating well below $-120\text{ }^{\circ}\text{C}$,²³⁸ it became possible to actually study the aldol process kinetically. The lithium enolate of 4-fluoroacetophenone is a tetramer in THF, (**214**)₄, with no other aggregates detectable by NMR spectroscopy.^{80a} The aldol reaction with 3-fluorobenzaldehyde is kinetically well behaved, being first-order in both components.¹⁶⁰ Since the interconversion between tetramer and dimer (vide infra) is far slower than the aldol reaction, this means that the tetramer is the reactive species. One intermediate was detected, a 3:1 enolate–aldolate mixed tetramer which builds up to a maximum 1/3 of the reaction mixture. This was the first experimental proof of a proposal in enolate tetramer reactivity made several decades ago.⁴³² Kinetic simulations showed the 3:1 mixed tetramer to be about 2.3 times as reactive as the enolate homotetramer. No other intermediates were detected.¹⁶⁰ Thus, the product of the reaction of the 3:1 mixed tetramer (presumably the 2:2 mixed tetramer) either is substantially more reactive than the 4:0 and 3:1 aggregates or dissociates to more reactive lower aggregates. The latter seems more likely since measurements in THF gave aggregation numbers of 1.7 by vapor pressure osmometry and 0.85 by cryoscopy for the aldolate from pinacolone and benzaldehyde.²⁴⁴ A tetrameric aldolate from pinacolone and pivaldehyde crystallizes from pentane.⁴³³

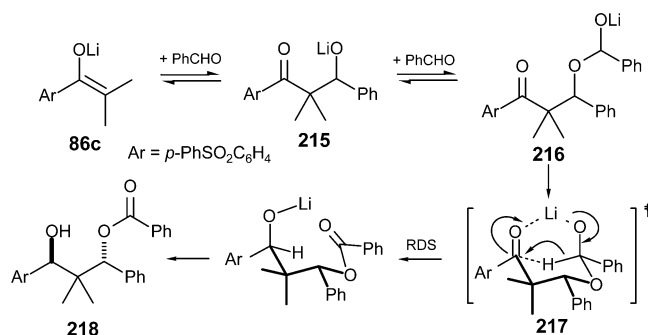


When 4-fluoroacetophenone is deprotonated at $-120\text{ }^{\circ}\text{C}$ with dimeric LDA, the first detected intermediate is a mixed dimer, 214-LDA, which deprotonates a second 1/2 equiv of the acetophenone to form the enolate dimer (214)₂.¹⁶⁰ The mixed aggregate is 1.5 times as reactive as (LDA)₂. The dimer is metastable and over a period of several minutes dimerizes to form the stable tetramer (214)₄. This allows the chemistry of the dimeric enolate to be studied under conditions identical to those of the tetramer. The dimer reacts with aldehydes on a barely measurable time scale with a half-life of 1.5 s at $-120\text{ }^{\circ}\text{C}$ and the tetramer with a half-life 30 s, so (214)₂ is 20 times as reactive as (214)₄. This is in sharp contrast to the (*n*-BuLi)₂ and (*n*-BuLi)₄ reactions, which showed very large rate ratios for reaction with a number substrates, including addition to aldehydes, ketones, amides, and esters and deprotonation of acetylenes (typically $>10^4$ and as high as 10^8).²³⁸ This is perhaps not too surprising, since the nucleophilic carbon in the *n*-BuLi tetramer is protected by coordination to three lithiums, probably requiring opening of the stable tetramer structure before reaction can occur. The nucleophilic carbon of an enolate, on the other hand, is not so encumbered (lithiums are on oxygen), so only the presumably much smaller effect of electronic deactivation by a more highly coordinated lithium is seen. In this context it is interesting that silylation of the two enolate aggregates again showed a large rate difference of at least 10^4 between (214)₂ and (214)₄ (silylation occurs mainly on oxygen).⁴³⁴

A small Hammett $\sigma\rho$ study was also done of the reaction of (214)₄ with benzaldehydes, giving a ρ value of 4.0.¹⁶⁰

The Yamataka group has applied ¹²C/¹³C kinetic isotope effects and a Hammett treatment to the reaction of pinacolone lithium enolate with benzaldehydes in THF at $0\text{ }^{\circ}\text{C}$.^{410d} From the Hammett ρ value of 1.16, and KIE of 1.019, they concluded that the aldol reaction went by a polar rather than the SET mechanism they propose for more basic lithium reagents such as NCCH₂Li (¹²C/¹³C isotope effects 0.992, Hammett ρ of 0.14).^{410c} Unfortunately, both the enolate and lithionitrile aldol studies were done at $0\text{ }^{\circ}\text{C}$. This is quite problematic since lithium aldol reactions are blindingly fast and, in addition, are certainly reversible at such high temperatures, and this explains the much smaller Hammett ρ they obtained compared to the 4-fluoroacetophenone enolate results.¹⁶⁰

The aldol–Tishchenko reaction of 86c (monomer–dimer in THF) with benzaldehyde forms the *anti*-diol monoester 218 as the sole product after quenching. A kinetic study showed the reaction to be second-order in [benzaldehyde] and approximately first-order (0.83) in [86c] and to have an isotope effect $k_{\text{H}}/k_{\text{D}}$ of 2.0 when deuteriobenzaldehyde was used. On this basis, and supported by computational studies, the reaction involved rapid reversible formation of the aldol adduct 215 and then reversible formation of hemiacetal 216, with the rate-determining step being intramolecular proton transfer in transition state 217.⁴³⁵ Adducts related to 216, but with alkoxide added to the carbonyl group to form a 1,3-dioxane ring, have been characterized during aldol reactions of phosphazene enolates.¹³⁹



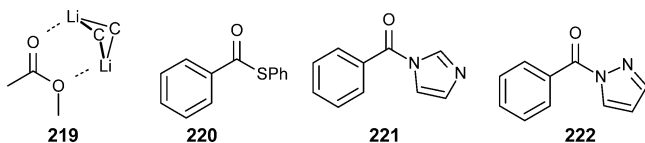
3.5.5. Carboxylic Esters. The first kinetic study of an RLi–ester addition was by Holm,⁴³⁶ who used a thermographic fast-flow method for the rate measurements. In contrast to other reactions of *n*-BuLi studied at the time, which invariably gave <0.5 -order in [*n*-BuLi] and first-order in substrate, they found that the addition to methyl trifluoroacetate in Et₂O was first-order in [*n*-BuLi] but essentially zeroth-order in [ester]. Holm concluded that the rate-determining step was dissociation of (*n*-BuLi)₄ to a lower aggregate. This rate was 18 s^{-1} at $-28\text{ }^{\circ}\text{C}$ and 0.007 s^{-1} at $-80\text{ }^{\circ}\text{C}$,³⁰⁸ which gives a $\Delta G^\ddagger = 12.8\text{ kcal/mol}$. Reference to Figure 8 shows that the predicted barrier to (*n*-BuLi)₄ dissociation in 3:1 Me₂O–THF (a significantly more polar solvent than Et₂O) was 11.5 kcal/mol. Therefore, the Holm results seem quite reasonable in view of the current knowledge of the behavior of *n*-BuLi, including the direct observation^{238,301c,437} that neither ketones nor esters react with (*n*-BuLi)₄.

Holm also made the interesting observation that LiBr, which caused a small reduction in the rate of reaction of *n*-BuLi with benzonitrile in Et₂O (reaction with ketone was also inhibited by LiBr and LiI^{299c}), actually caused a rate increase (3 equiv of LiBr increased the rate 20-fold at $-80\text{ }^{\circ}\text{C}$). Thus, LiBr might catalyze the dissociation of (*n*-BuLi)₄, analogously to the well-documented observations by the Collum group that LiCl can catalyze the rate of dissociation of LiN(*i*-Pr)₂ dimer, leading to large rate increases when dissociation is rate limiting.^{423,438}

An IR stopped-flow kinetic study by the Smith group of the reaction of *s*-BuLi, *n*-BuLi, and *c*-pentyl-Li with several benzoate esters in cyclohexane at $25\text{ }^{\circ}\text{C}$ showed exceedingly complex behavior, but gave several interesting results.⁴³⁹ An ester–(RLi)_{*n*} complex was detected with modest K_{eq} ($27\text{--}138\text{ M}^{-1}$ for *s*-BuLi with various esters). Ketone–(RLi)_{*n*} complexes formed as intermediates in the reaction were also detected. The reactions were first-order in [ester]. The general kinetic dependence on [RLi] was an initial increase, followed by a plateau or an actual decrease, in k_{obsd} as [RLi] was increased. A qualitative kinetic model was proposed involving two competing mechanisms. In the first the ester–RLi aggregate complex reacts to give products. In the second the RLi tetramer dissociates to monomer, which reacts directly with ester. More reactive esters (e.g., ethyl 3,5-bis(trifluoromethyl)benzoate) formed weaker complexes with the RLi aggregate and tended to react more extensively by the monomer pathway, whereas those forming strong complexes (ethyl *p*-phenoxybenzoate) tied up a larger fraction of the ester as a complex and thus became unavailable to react by the monomer pathway. A complicating feature is that the LiOEt which is formed during the reaction increases the rate (a factor of 5 for addition of 0.35 equiv of LiOEt to *c*-pentyl-Li), although an exact kinetic form of this process and the possible intervention of mixed aggregates were not elucidated. Both ether and TMEDA caused large rate

increases in the ester reaction rates (e.g., 2% ether caused a 50-fold rate increase at 25 °C).

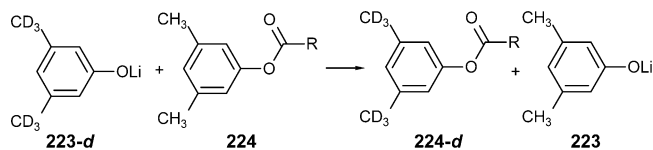
The Claisen reaction of enolates with esters and other acylating agents is slow enough for rate measurements by traditional means. The kinetics of the reaction of the enolate of *p*-(phenylsulfonyl)isobutyrophenone (**86c**, a monomer–dimer mixture in THF) and *p*-phenylisobutyrophenone (**86b**, a monomer–tetramer mixture in THF) with benzoate esters is first-order in [ester].^{325a} Surprisingly, in contrast to the ca. 10³ higher reactivity of monomers compared to dimer or tetramer in alkylation reactions (section 3.8.1),^{248,440} in the acylation process, (**86b**)₁ and (**86b**)₄ have nearly identical reactivity (for phenyl benzoate k_M/k_T was within experimental error of 1.0). For the monomer–dimer mixture of **86c** the monomer was only 11.5 times as reactive as the dimer. Similar ratios were measured for other benzoate esters. Streitwieser hypothesized^{325c} that this unusually small aggregate effect was a consequence of a double coordination of both oxygens of the ester with dimers and higher aggregates (e.g., **219**), an interaction which should activate the ester toward nucleophilic attack and which is not possible with the monomer. Some support for this hypothesis was provided by studies with thioester **220** and benzoylimidazole **221**, which are much less likely to interact in this way because of reduced basicity of the leaving heteroatom. No reactivity of the higher aggregate could be detected; k_M/k_D rate ratios of at least 100 can be estimated for **86c**. In contrast, benzoylpyrazole **222**, where coordination analogous to that in **219** is plausible, gave a more modest k_M/k_D ratio of 5.8.^{325c}



Similar results were obtained for the monomer–tetramer reactivity of **86b**. Here also little or no tetramer reactivity could be detected for **220** and **221**, whereas with **222**, a k_M/k_T value of 1.3 was measured. A coordination analogous to **219** on the face of the tetramer was proposed to explain the high reactivity of **222** toward the tetramer in comparison with the benzimidazole analogue of **221**.^{325c} In *t*-BuOMe, the tetramer of **86b** reacts substantially slower than does the tetramer in THF, suggesting that polar intermediates which require solvent stabilization (possibly open tetramers) are involved.²⁴⁵

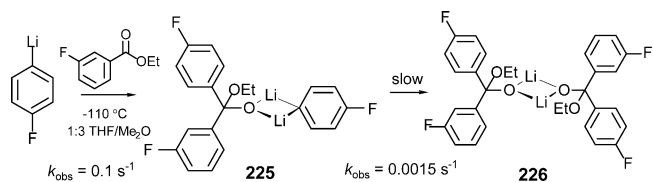
Jackman considered lithium phenoxides as less troublesome analogues of enolates. A description of one of his interesting studies is outlined here,⁴⁴¹ even though technically out of the scope of this review. This involves the degenerate exchange between a deuterium-labeled lithium phenoxide, **223-d**, and the analogous phenyl ester **224**. This sort of exchange is kinetically simpler than most organolithium reactions because no interference from mixed aggregates is possible. In THF (where **223** is a tetramer) the reaction was first-order in both components ($R = n\text{-Pr}$), so the phenoxide tetramer is the reactive species. In pyridine **223** is a mixture of dimer and tetramer. The kinetics could be accurately fit to a scheme where both aggregates were reactive and which fit with the independently measured dimer–tetramer K_{eq} . The dimer was found to be 13 times as reactive as the tetramer. In dioxolane, where **223** is a mixture of tetramer and hexamer,⁴⁴² a pronounced upward drift of the rates with increased [**223**] was noted, which could be fit to a scheme where the hexamer

was of *higher* reactivity than the tetramer by a factor of 5.5! We have found no other case where the rates of hexamers and tetramers were compared.



The kinetic data provided several indicators that the mechanism involves an initial complex formation between the ester and the phenoxide tetramer before alkoxide transfer from Li to the carbonyl group occurs. Most significant was the discovery of a pronounced CIPE effect with esters having substituents capable of coordinating to lithium. For example, **224** ($R = \text{CH}_2(2\text{-pyridyl})$) was over 200 times as reactive as **224** ($R = n\text{-Pr}$). The observation that the transesterification was slower in the more strongly coordinating solvents such as pyridine than in THF or dioxolane suggests that solvent participation at the transition state to form open tetramers such as ladder or ring structures is not occurring.⁴⁴²

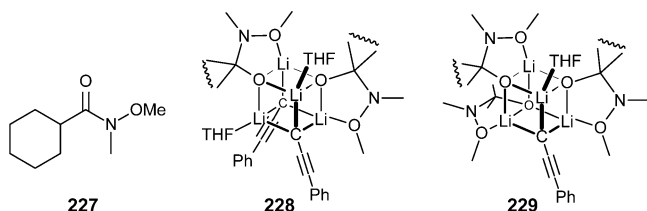
An RINMR study of the reaction of methyl *m*-fluorobenzoate with (*p*-fluorophenyl)lithium (monomer–dimer) shows measurable rates at −110 °C in 1:3 THF–Me₂O. The first intermediate detected was the mixed dimer **225** of the ArLi and the tetrahedral intermediate, which then reacted slowly with more ester to form the alkoxide dimer **226**. The second step was 1/70 as fast as the first.⁴³⁷ It could not be established whether (ArLi)₁ or (ArLi)₂ reacted with the ester, although the Streitwieser work,^{325c} on Claisen reactions, suggests that esters may be unusually reactive toward dimers in competition with monomers. The tetrahedral intermediates **225** and **226** decompose at −90 °C to form ketone and then tertiary alcohol if any ArLi is left.



3.5.6. Carboxylic Amides. Amides are infrequently used as electrophiles. The main exceptions are *N,N*-dimethylformamide (DMF) or other formamides and Weinreb amides (*N*-methoxy-*N*-methyl amides),⁴⁴³ which have been used extensively as acylating agents for the synthesis of aldehydes and ketones.⁴⁴⁴ The additions to DMF are very fast, and so have not been subjected to detailed study. Even using the RINMR technique, DMF reacted with *n*-BuLi dimer too fast to be measured ($t_{1/2} < 2$ s at −130 °C). With *N*-methoxy-*N*-methylbenzamide, reaction with (*n*-BuLi)₂ had a half-life of 5 s, similar to the rate of reaction with acetone, but no detailed studies were performed.²³⁸

With the less reactive lithium phenylacetylide, Weinreb amides become amenable to study at convenient temperatures. An NMR and IR spectroscopic study, using ⁶Li- and ¹³C-enriched lithium reagent, and kinetic study of the addition of lithium phenylacetylide to **227** in hexane–THF mixtures at −50 °C showed that the initial part of the reaction proceeded through dissociation of the dimeric acetylide to a monomer and loss of one solvent molecule to form a mono-THF-solvated transition state (first-order in [**227**], half-order dependence on

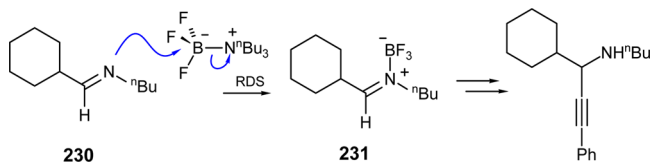
[RLi], inverse first-order dependence on [THF]).²³⁷ The initial phase of the reaction proceeded smoothly at $-50\text{ }^{\circ}\text{C}$ to 50% conversion and then slowed down dramatically. This was traced to formation of a 2:2 mixed tetramer, **228**, with very reduced reactivity. At room temperature this species was slowly converted to the 3:1 mixed tetramer **229**, which was still less reactive.



An interesting observation was made during studies of the reactivity of a series of electrophiles toward $(n\text{-BuLi})_2$ using RINMR. All common ones except for aldehydes and DMF are unreactive toward $(n\text{-BuLi})_4$.²³⁸ The reaction of $(n\text{-BuLi})_2$ with a benzoate ester in 1:3 THF–Me₂O had a $t_{1/2}$ of 24 s at $-131\text{ }^{\circ}\text{C}$. As expected, the reaction with acetone was faster ($t_{1/2} = 2.8$ s), but (somewhat unexpectedly) only by about a factor of 10. Remarkably, the reaction with *N,N*-dimethylbenzamides was comparable to that with acetone and much faster than reaction with ester. The origin of this reactivity reversal (from normal nucleophilic additions toward acyl-X species) is unknown. Phenyllithium reacted slightly faster with esters than with amides.^{301c,437}

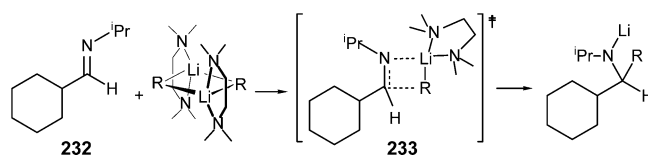
3.5.7. Imines. The addition of nucleophiles to imines constitutes a major synthetic route for the preparation of amines.⁴⁴⁵ Detailed mechanistic studies of the reaction with lithium reagents as nucleophiles are rare.

The relatively low reactivity of *N*-alkyl imines has led to the use of BF₃ to enhance reaction rates. In a study of the mechanism of the addition of lithium phenylacetylide to imine **230** using $n\text{-Bu}_3\text{N}\cdot\text{BF}_3$ as the catalyst, it was found that the reaction was first-order in [230], first-order in [$n\text{-Bu}_3\text{N}\cdot\text{BF}_3$], zeroth-order in [acetylide], and zeroth-order in excess [$n\text{-Bu}_3\text{N}$]. Thus, the mechanism involves a rate-determining nucleophilic attack of the imine on boron to form the imine complex **231**, which then reacts rapidly with the acetylide. No information about the reactive aggregate of the acetylide could be obtained. No reaction occurs in the absence of BF₃.⁴⁴⁶

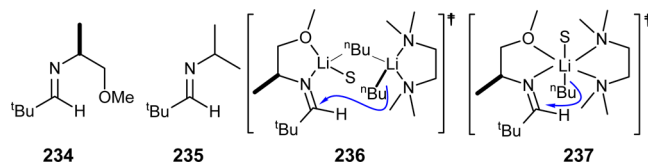


The addition of $(n\text{-BuLi})_2\cdot(\text{TMEDA})_2$ and $(\text{PhLi})_2\cdot(\text{TMEDA})_2$ in pentane to the aldimine **232** was first-order in substrate, 0.5-order in [$(n\text{-BuLi})_2$], and zeroth-order in excess [TMEDA]. $n\text{-BuLi}$ gave no detectable α -metalation; PhLi gave about 5%. The kinetics indicate a simple mechanism in which the RLi dimer dissociates to the monomeric diamine complex, which then adds to the imine, as in **233**. The effect of different diamines on the rate was complex.^{363a}

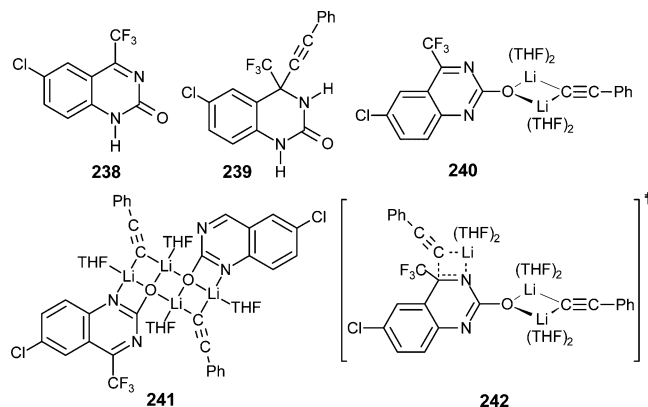
Extension of these studies to an aldimine, **234**, with a potentially chelating group gave much more complicated behavior.^{363b} The addition rate of $(n\text{-BuLi})_2\cdot(\text{TMEDA})_2$ to **234** was about 1000 times faster than to the nonchelated model **235** in toluene-*d*₈ solution. Now both the monomer and the



dimer are reactive, with the dimer pathway inhibited by excess TMEDA, signaling $(n\text{-BuLi})_2\cdot(\text{TMEDA})_1$ as the reactive RLi species. At low [TMEDA] the open dimer transition state **236** ($S = \text{OEt}_2$) was implicated by an additional dependence on the concentration of added diethyl ether, which does not detectably complex to $(n\text{-BuLi})_2\cdot(\text{TMEDA})_2$. At high diamine concentration the dimer pathway is suppressed in favor of a monomer pathway. This pathway also shows a first-order dependence on additional donor solvent with stoichiometry $(n\text{-BuLi})_1\cdot(\text{TMEDA})_1\cdot\text{Solv}\cdot\text{234}$, suggesting the somewhat unusual octahedrally coordinated transition structure **237**. Octahedral coordination of lithium is often seen in $\text{Li}^+\cdot(\text{DME})_3$ species,⁴⁴⁷ but is rare otherwise, especially for relatively sterically demanding ligands such as these. Similar stoichiometry of the transition states was found for imine additions in the presence of the stronger ligand TMCDA and THP as the additional donor ligand ($S = \text{THP}$).^{363c}



A more complex imine addition involves reactions of lithium acetylides with quinazoline **238** to form **239**, a model study related to the synthesis of some promising antiviral drugs. Mixing lithium phenylacetylide with the lithium salt of the quinazoline produced two mixed aggregates, spectroscopically characterized as the dimer **240** and a 2:2 ladder tetramer, **241**. Under conditions where **240** was the main quinazoline species, the reaction was first-order in [240], 0.5-order in excess [LiCCPh] (which is dimeric in THF solutions), and zeroth-order in [THF]. Thus, the conversion of **240** to product is not an intramolecular transfer of carbanion to the electrophilic imine (a reasonable supposition), but rather involves attack of an external solvated monomeric acetylide on **240** (transition state **242**).²³⁶



3.5.8. Nitriles. An early kinetic study by Holm of the reaction of $n\text{-BuLi}$ with benzonitrile in Et₂O at $20\text{ }^{\circ}\text{C}$ gave an order of 0.33 in [$n\text{-BuLi}$],⁴³⁶ similar to studies of $n\text{-BuLi}$ reactions with Ph₃CH^{227,324} and 1,1-diphenylethylene,³⁰² even

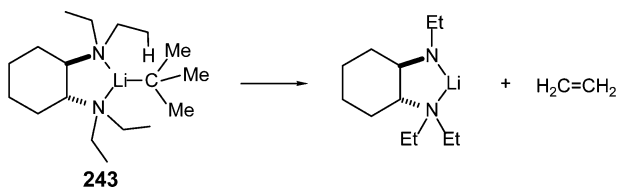
though the nitrile reaction was several orders of magnitude faster. The author argued that benzonitrile should not be able to displace Et₂O from the lithium, so precomplex formation cannot explain the fractional order. The fast rates were measured by a thermographic flow method with half-lives in the millisecond range.⁴³⁶ A free energy barrier of ca. 14.5 kcal/mol at 20 °C for the addition can be calculated from the rates reported. Although the ΔG^\ddagger for dissociation of (*n*-BuLi)₄ in Et₂O is not known, it can be estimated to be between 11 and 12 kcal/mol in THF at this temperature,^{171,238} so these rates are likely to be above the Curtin–Hammett line, as required for a fast pre-equilibrium to form dimers or monomers.

A kinetic study of the reaction of *n*-BuLi with benzonitrile in Et₂O at –80 °C showed saturation kinetics, with the rate becoming independent of substrate concentration above 1 M. The saturation rate had $\Delta G^\ddagger = 12.8$ kcal/mol, very similar to the substrate-independent rate with methyl trifluoroacetate (see section 3.5.5). Therefore, here it appears that the rate-limiting step has also become dissociation of the (*n*-BuLi)₄.³⁰⁸

A similar kinetic study of the reaction of PhLi with benzonitrile in Et₂O gave an order of 0.64 in [PhLi].⁴⁴⁸ Since PhLi is now known to be a nearly 1:1 mixture of tetramer and dimer under the conditions of the experiment,¹⁰³ these data fit better with a dimer-based mechanism than a monomer one. A Hammett study of various ArLi compounds gave an essentially flat plot, with less than a factor of 2 between [4-(dimethylamino)phenyl]lithium and [3-(trifluoromethyl)phenyl]lithium. Grignard additions are predicted to vary by a factor of 10 000 for the same series.⁴⁴⁹ It is possible that here the increase in nucleophilicity in ArLi by an electron-donating group is in part offset by higher aggregation numbers. The substituent effect was larger for substituted benzonitriles, giving a factor of 9 between 4-chloro- and 4-methylbenzonitrile.⁴⁴⁸

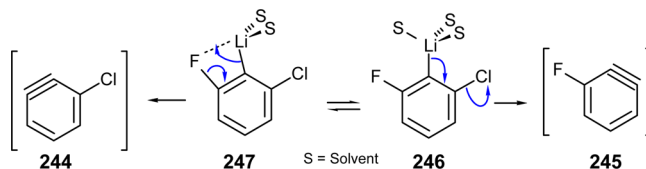
3.6. Elimination Reactions

Organolithium reagents are only occasionally used to deliberately carry out β -elimination reactions. Lithium amide-mediated eliminations are more common and have been studied in some detail.⁴⁵⁰ We mention here an intriguing report of an unusual elimination of an amine. *t*-BuLi forms a monomeric complex, **243**, with trans-1,2-bis(diethylamino)-cyclohexane. On raising the temperature, ethylene is evolved and the de-ethylated lithium amide is formed (crystallizes as a cyclic (Li–N)₃ trimer). The X-ray structure of **243** reveals a close approach of the *t*-BuLi carbanion carbon to the β -H of an ethyl group, so an intramolecular elimination is presumed.^{58b}



A more useful organolithium-promoted elimination is the conversion of lithioaromatics with ortho leaving groups (halide, sulfonate) to benzyne.^{348b,451,452} An interesting observation was reported that the elimination ratio of fluoride vs chloride, bromide, or iodide was strongly solvent dependent, with ratios as high as 10:1 in favor of the fluoride elimination product **244** in toluene solution and 50:1 in favor of the chloride elimination product **245** in THF.⁴⁵³ Kinetic and product studies traced this effect to a difference in the level of solvation of the lithium by THF. Specifically, the LiF elimination in toluene solution is

inhibited by THF (inverse first-order), whereas the LiCl elimination is unaffected by [THF]. Since the likely solvation state of a monomeric aryllithium is the trisolvate, this means the chloride elimination proceeds through **246**, whereas the fluoride elimination requires formation of the disolvate **247**, most likely to free a coordination site on lithium in favor of a Li–F interaction.⁴⁵⁴ The absence of electrophilic assistance in departure of chloride ion has also been noted in S_N2 substitutions (section 3.8.4).^{120c}



3.7. Li/Br, Li/I, and Li/Sn Exchange

The lithium–iodine, lithium–bromine (halophilic reactions⁴⁵⁵), and related lithium–selenium, lithium–tellurium, and lithium–tin^{456a} exchanges are the premier methods for the preparation of complex lithium reagents, especially vinyl- and aryllithiums, but also primary and even secondary alkyllithiums.^{456b,c} Because these reactions are very fast, there are many examples of Li/I exchanges in the presence of various functional groups, including nitriles, amides, esters, nitro groups, ketones,⁴⁵⁷ and even aldehydes.⁴⁵⁸ The Li/Br exchange is slower by several orders of magnitude, but still fast enough to allow preparation of lithium reagents in the presence of esters,⁴⁵⁹ Weinreb amides,⁴⁶⁰ isocyanates,⁴⁶¹ and even anhydrides.⁴⁶² Li/Cl exchanges are again several orders of magnitude slower and are useful only in select situations where the common side reactions are suppressed and a relatively stabilized carbanion is being produced.

Mechanistic efforts⁴⁶³ have focused on the question of possible SET pathways and on the intermediacy of ate complex intermediates, as first suggested by Wittig.⁴⁶⁴ Although radical products are seen, and radicals can sometimes be detected during Li/I exchanges,⁴⁶³ it is now clear that these are side reactions and that the Li/I exchange is a polar reaction, proceeding through iodine ate complexes, which can in favorable cases be structurally⁴⁶⁵ and spectroscopically^{218,466,467} characterized. Primary and secondary iodides with olefinic radical traps can be exchanged without any cyclization,^{374a,b,468} and secondary alkyl iodides⁴⁶⁹ (as well as tellurides⁴⁷⁰) can be exchanged with high retention of stereochemistry, which should not be possible if radicals are intermediates.

The Li/Br exchange in secondary alkyl systems may involve radical intermediates,⁴⁶⁸ but aryl,^{379,471} vinyl, and cyclopropyl⁴⁷² halides do not, by the stereochemical and/or cyclizable probe criteria.

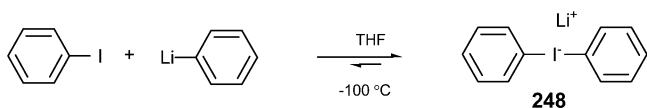
One of the earliest kinetic studies of the Li/Br exchange was the approach to equilibrium between phenyllithium and substituted aryl bromides in Et₂O. The reaction was first-order in [ArBr] and in [(PhLi)_n].⁴⁷³ Although the aggregation state of PhLi was not firmly known at that time, later work showed it to be a mixture of dimer and tetramer in ether at –90 °C,¹⁰³ making the dimer the active nucleophile in the exchange. A Hammett ρ of 4.0 was determined for different aryl bromides. Activation parameters for *p*-bromotoluene were $\Delta G^\ddagger = 23.3$ kcal/mol and $\Delta S^\ddagger = -23.6$ eu. There was a small reduction (2×) in rate when LiBr was added, with a plateau at 0.5 equiv.

The THF reaction was too fast to measure (at least several orders of magnitude faster than in Et₂O), consistent with the lower aggregation of PhLi in THF. These data were considered consistent with either a bimolecular nucleophilic attack mechanism or an ate complex process.

The Li/Br exchange of *n*-BuLi with bromobenzene in hexane is also first-order in [PhBr] and first-order in [(*n*-BuLi)₆], so the reaction involves attack of the intact hexamer on the bromide. The rate was insensitive to small additions of PhLi, LiBr, or *n*-BuOLi. A Hammett plot for a variety of bromobenzenes gave $\rho = 2$, with bromoanisoles having faster rates than expected. This was identified as an ether solvation effect, since addition of PhOMe up to 1 equiv caused a 12-fold increase in rate, attributed to disruption of (*n*-BuLi)₆ to form the anisole-solvated tetramer.⁴⁷⁴

The I, Te, Sn, and Se exchange reactions are too fast for normal kinetic studies, but in a series of competition experiments using *n*-BuLi in THF at -70°C PhI, PhTe(*n*-Bu), PhSn(*n*-Bu)₃, and PhSe(*n*-Bu) gave relative rates of 1500:300:15:1 for PhM(*n*-Bu)_{*n*} substrates. A Hammett treatment of the ArTe(*n*-Bu) exchange gave a ρ of 3.4.^{475a} Since the I and Te exchanges are extremely fast in THF, it is possible that there was some rate compression due to mixing problems. Studies of the PhLi–Ar_{*n*}M exchanges using several DNMR and classical exchange methods gave relative rates as follows (in THF extrapolated to 0°C): I (10⁸), Te (10⁸),^{475b} Sn (10³), Sb (1.7),⁴⁷⁶ Br (0.25), Se (0.025), Cl (10^{−6}), S (10^{−6}).^{475b}

Ate complex intermediates could be spectroscopically characterized for the iodine (**248**),^{218,466a,b} tellurium,^{466b,475b,477–479} and tin⁴⁸⁰ exchanges. The lighter elements form much less stable ate complexes, but a selenium ate complex could be detected in an especially favorable system.^{478,481} Detailed NMR studies showed the role these ate complexes play in the Li/Se, Li/I, Li/Sn, and Li/Te exchanges. Lithium–silicon exchanges are useful only in special situations, but even silicon ate complexes could be characterized.⁴⁸²



From the data available, it is clear that the Li/I exchange is among the fastest of all organolithium reactions, perhaps the fastest of the useful ones (reaction with protic acids is possibly faster), and cannot, in general, be studied by classical kinetic methods, although rates in Et₂O can be measured at low temperature.⁴⁸³ In THF the Li/I exchange rates are fast enough to study by DNMR methods and indeed are almost too fast even for this technique, requiring experiments at the lowest accessible temperatures. Thus, both the Li/I and Li/Te exchanges are fast on the NMR time scale down to below -100°C in THF, as shown by the ⁷Li NMR spectra of PhI and Ph₂Te mixtures with PhLi (Figure 13). At 1 equiv of metalloid, the conversion to ate complex is complete; no PhLi can be detected. At 1/3 equiv of metalloid the signals for (PhLi)₁ and Ph₂ILi (**248**) at -105°C are just past coalescence (k_{exch} of ca. 600 s^{−1}), whereas those of (PhLi)₁ and Ph₃TeLi are just below coalescence (k_{exch} of ca. 300 s^{−1}). Most interesting, the signals for (PhLi)₂ show no broadening, so the dimer exchanges with PhI much more slowly than the monomer.^{466b}

The low reactivity of dimers versus monomers is also indicated by comparisons of the degenerate Li/I exchanges in

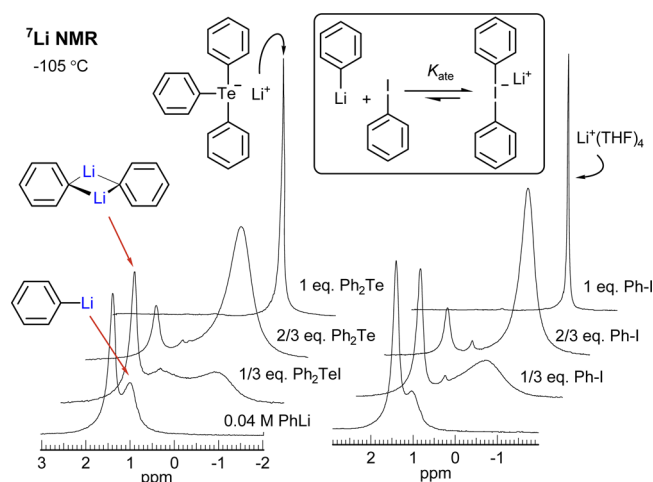
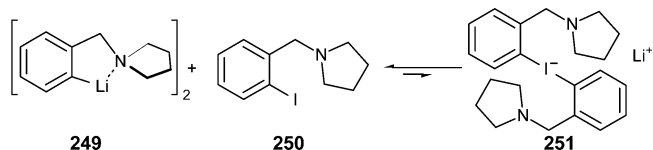
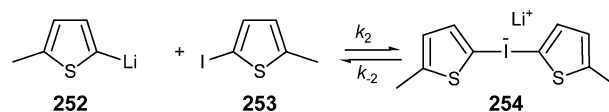


Figure 13. ⁷Li NMR spectra of the titration of PhLi (0.04 M) with Ph₂Te and PhI in THF at -105°C . Reprinted from ref 466b. Copyright 1991 American Chemical Society.

PhLi–PhI and the chelated ArLi **249**. The latter is strongly dimerized, with a barrier to dissociation to monomer that is ca. 5 kcal/mol higher in **249** than in PhLi. By DNMR measurements the Li/I exchange of PhLi–PhI is at least 10⁵ times as fast as for the **249**/**250** exchange at -2°C ($\Delta\Delta G^\ddagger$ of ca. 6 kcal/mol).⁴⁸⁴ This can be ascribed to the much lower concentration and rate of formation of monomers in **249**, since only monomers participate in the exchange (at least for PhLi–PhI^{466b,477}). The ate complex **251** was not detectable, whereas the ate complex Ph₂I[−]Li⁺ is readily observed and forms essentially quantitatively at -105°C (Figure 13).



As part of a detailed DNMR investigation of the degenerate exchange between the thienyllithium **252** and the iodide **253**, it was shown that the lithium reagent was a mixture of dimer and monomer in THF. The two species form a detectable iodine ate complex, **254**, whose formation constant, like that of PhLi–PhI, is highly temperature dependent, going from <10% ate complex at -60°C to >90% ate complex at -120°C . The exchange process involves the ate complex, the iodide, and the monomer and dimer of the lithium reagent, with (**252**)₁ reacting at least 1000 times as fast at -102°C as (**252**)₂. There was also a major contribution from a second exchange process in which the ate complex **254** was the carbanion donor toward the iodide. The ate complex was comparable in reactivity to (**252**)₁.²¹⁸



3.8. Substitution (S_N2) Reactions

The utilization of simple alkyllithium reagents as nucleophiles in S_N2 reactions is somewhat limited, since such reactions are prone to several side reactions, notably α - and β -metalation of halide, tosylate, or epoxide substrates and (especially for alkyl

iodide electrophiles) the metal–halogen exchange reaction. It is more stabilized, less basic, and less aggregated organolithium reagents that have been most successfully used as nucleophiles in S_N2 reactions. Specifically, lithiodithianes and related S-, Si-, and P-substituted lithium reagents (often functioning as acyl anion equivalents⁴⁸⁵), lithium enolates,^{240,426,486} lithium metal-oenamines,^{261,487} various substituted allyllithium reagents,⁴⁸⁸ and aryllithium reagents have seen the most use.

In a very early mechanistic study of the reaction of EtLi in benzene with benzyl chloride to give propylbenzene, first-order kinetics in both components was reported. The main point of the study was a measurement of the $^6\text{Li}/^7\text{Li}$ isotope effect, which was found to be 1.029.⁴⁸⁹ The authors concluded that significant C–Li bond-breaking must be occurring in the transition state, ruling out SET processes as rate determining. It is a testament to the deep-seated effects of solvation and aggregation state for RLi reactions that the reaction of EtLi in ether gives exclusively Li/Cl exchange to form BnLi,⁴⁹⁰ whereas in THF the only process detected is deprotonation to form (α -chlorobenzyl)lithium and products of its further reaction (Figure 14).⁴⁹¹

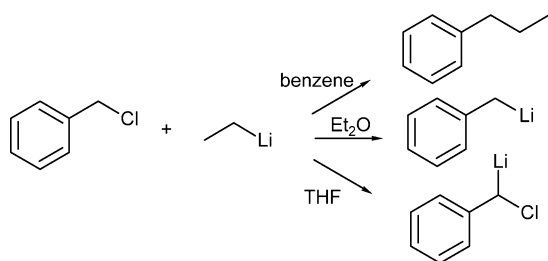


Figure 14. Solvent effects on the reaction of benzyl chloride with EtLi.^{489–491}

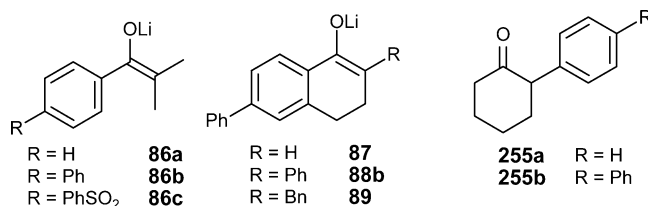
3.8.1. Ketone Enolates. Because of their great synthetic importance, enolate alkylations have been studied intensively by several groups. In his pioneering work on the solution structure and alkylation reactions of lithioisobutyrophenone (**86a**), Jackman provided several lines of qualitative evidence, using kinetics and O-alkylation:C-alkylation ratios as probes, that with enolates the aggregates seemed to be the reactive species, unlike many of the organolithium reactions studied up to that time (*n*-Bu, MeLi, PhLi) which typically showed fractional orders, interpreted as reactions via monomers rather than the higher aggregates present in solution. He noted that the C:O ratios in reactions with MeOTs started at 6 and eventually declined to 1.6 as the reaction proceeded.^{260a} A similar reduction in C:O ratio was seen when LiClO_4 was added. This effect was attributed to the intervention of mixed tetramers, analogous to the 3:1 enolate–LiCl tetramer which was well characterized.¹⁵⁹

Streitwieser applied his single-value decomposition technique, which depends on careful examination of UV spectra of conjugated systems, combined with equilibrium pK_a measurements, to determine the aggregation state of a number of enolates. The UV method requires a chromophore sensitive to the aggregation state, hence the more extended π -system for many of his enolates. For the lithium enolate of *p*-(phenylsulfonyl)isobutyrophenone (**86c**),⁴⁹² he demonstrated the existence of a monomer–dimer equilibrium at 25 °C in THF, substantially favoring the dimer ($K_{\text{MD}} = [\text{D}]/[\text{M}]^2 = 5000 \text{ M}^{-1}$). In a study of alkylation kinetics with 4-tert-

butylbenzyl bromide, the reaction was half-order in [enolate], so the monomer is the reactive species. No dimer reactivity could be detected, leading to estimates that monomers were at least 2 or 3 orders of magnitude more reactive than dimers in these S_N2 reactions. Only C-alkylation products were formed.

Addition of LiBr to the lithium enolate of **86c** in THF formed a mixed dimer ($K_{\text{agg}} = [(\text{86c})_1 \cdot \text{LiBr}]/[(\text{86c})_1][\text{LiBr}] = 3600 \text{ M}^{-1}$). Detailed studies of the alkylation kinetics of this enolate with *p*-tert-butylbenzyl bromide showed contributions from all three species present, with a reactivity ratio $(\text{86c})_1 : (\text{86c}) \cdot (\text{LiBr}) : (\text{86c})_2$ of 2700:7:1 at 25 °C.⁴⁴⁰ A similar mixed aggregate study of **86c** with $\text{LiN}(\text{SiMe}_3)_2$ gave a smaller aggregation constant ($K_{\text{agg}} = [\text{86c} \cdot \text{LiNR}_2]/[(\text{86c})_1][\text{LiNR}_2] = 760 \text{ M}^{-1}$). Kinetic studies of the alkylation process showed that $(\text{86c})_1$ was 100 times as reactive as $\text{86c} \cdot \text{LiN}(\text{SiMe}_3)_2$. Similar results were found for the 2-benzyltetralone **89**.⁴⁹³

The enolates of 2-phenylcyclohexanone (**255a**; $K_{\text{MD}} = [\text{D}]/[\text{M}]^2 = 2800 \text{ M}^{-1}$),³⁷⁰ 2-phenyltetralone (**88a**; $K_{\text{MD}} = 1930 \text{ M}^{-1}$), and 2,6-diphenyltetralone (**88b**; $K_{\text{MD}} = 2650 \text{ M}^{-1}$) behaved analogously.²⁴⁸ For **88a**, the K_{MD} was very similar in DME as the solvent (3700 M^{-1}) and the alkylation rates were comparable to those in THF.²⁴⁵ In *t*-BuOMe, on the other hand, **88a** was a tetramer, no lower aggregates could be detected, and the enolates were unreactive toward benzyl halides.



The solution structure and reactivity of 2-biphenylcyclohexanone (**255b**; $K_{\text{MD}} = 4300 \text{ M}^{-1}$) were similar to those of the other dimers. Activation parameters were measured for reaction with *m*-chlorobenzyl bromide ($\Delta H^\ddagger = 9.6 \text{ kcal/mol}$, $\Delta S^\ddagger = -25.5 \text{ eu}$). The normal activation entropy for a bimolecular substitution suggests that lithium solvation in the transition state is similar to that in the ground state, which argues against lithium participation as a Lewis acid in assisting departure of the leaving group.⁴⁹⁴

In a related study of *p*-phenylisobutyrophenone lithium enolate **86b**, Streitwieser determined that this enolate was predominantly tetramer in THF, with measurable amounts of monomer at low concentrations.^{325b} The alkylation kinetics gave no detectable contribution from reaction of the tetramer; all reaction occurred through the monomer. From the data presented k_{M} is at least 20 times as large as k_{T} . An interesting observation was that $(\text{86c})_1$ was slightly more reactive (a factor of 2.3) toward *p*-tert-butylbenzyl bromide than $(\text{86b})_1$, even though the latter is 1.2 pK_a units more basic. In this reaction several benzyl halides were shown to give exclusively C-alkylation with **86b**. However, with MeOTs significant O-alkylation was seen, ranging from a C:O ratio of 0.95 at low conversion and going to 0.44 at the completion of the reaction. A similar observation made by Jackman with isobutyrophenone was ascribed to the different C:O selectivities of mixed aggregates formed between the enolate and LiOTs.²⁶⁰ Streitwieser stops short of endorsing this, since LiBPh_4 , which arguably cannot form a similar mixed aggregate, similarly affects the O:C ratio.

The structure and reactivity of enolate **86b** were also studied in THF with several cosolvents.⁴⁹⁵ HMPA gave the most profound effects. Addition of 3 equiv converts a 0.1 M THF solution of enolate which is 98% tetramer to one which is 98% monomer. The alkylation rate is also substantially increased, with the reaction being first-order in [HMPA]; that is, the alkylation transition state has one more HMPA than the starting enolate (which probably has the structure **86b**·(HMPA)₂).^{80b} This may signal the intervention of an SIP in the alkylation, since monomeric lithium reagents (contact ion pairs) have never been observed to be coordinated to three HMPA ligands. PMDTA and DMPU had smaller effects on enolate structure and reactivity.

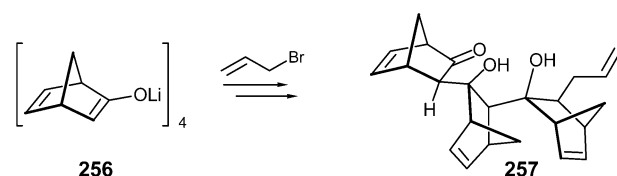
Ketone enolate alkylations are plagued with the problem of dialkylation, and a suggestion was made by House that this was basically an aggregation phenomenon, i.e., that the mono-alkylated product was less aggregated and hence more reactive than the initial enolate. When proton transfers compete with alkylation rates (often the case in synthetic applications), the less aggregated product enolate out-competes the original enolate.^{496a} In a study of this effect, Streitwieser showed that 6-phenyltetralone enolate **87** is a tetramer–monomer mixture in THF ($K_{MT} = [T]/[M]^4 = 4.7 \times 10^{10} \text{ M}^{-3}$), whereas the enolate of the benzylation product **89** is a monomer–dimer mixture ($K_{MD} = [D]/[M]^2 = 3800 \text{ M}^{-1}$). This translates into an equilibrium concentration of 0.001 M (**87**)₁ but a 0.005 M concentration of (**89**)₁ at 0.1 M enolate concentration. In addition, (**89**)₁ is 1.8 times as reactive as (**87**)₁ toward benzyl bromide even though it is slightly less basic. Only the monomers react, so other things being equal, the substituted enolate **89** is 9 times as reactive as the unsubstituted enolate **87** at 0.1 M in THF.²⁴⁶

Lithiated sulfones, particularly the parent $\text{PhSO}_2\text{CH}_2\text{Li}$, also suffer from dialkylation problems. Apparently proton transfer occurs readily during the alkylation process in THF, leading to low concentrations of the less stable product lithio sulfone. This reagent was shown to be much more reactive (e.g., lithiated pentyl phenyl sulfone is 20 times as reactive toward *n*-BuBr as $\text{PhSO}_2\text{CH}_2\text{Li}$), leading to significant dialkylation even though very little of the lithiated product is present at equilibrium.^{496b} It seems likely that factors similar to those involved in enolate bisalkylation may also operate here; i.e., the more hindered lithiated product sulfone is less aggregated and may show a higher SIP/CIP equilibrium and thus be able to compete with the starting reagent.

The kinetics of alkylation of cyclopentanone lithium enolate with MeI showed that excess HMPA accelerated the reaction by a factor of 7500 compared to the reaction in THF. The reaction in THF–HMPA was first-order in [MeI], first-order in [enolate], and first-order in excess [HMPA]. Thus, the HMPA-complexed tetramer is the active species (the authors incorrectly identified the enolate as a dimer).³⁷¹ Since cyclopentanone in THF with excess HMPA is a tetraordinated tetramer,^{80a} this implicates an open tetramer as the reactive species, with one additional HMPA coordinated at the site of the opening.

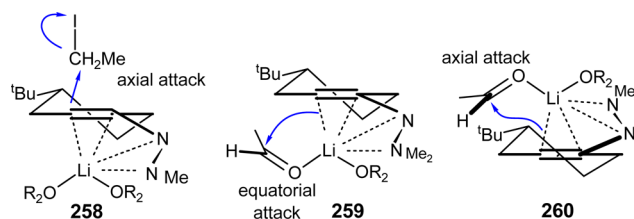
An interesting alkylation bisaldol product, **257**, was isolated from the attempted alkylation of norbornenone enolate **256** with allyl bromide. This stereoselective process could be rationalized by an initial alkylation of the tetrameric enolate, followed by two consecutive intra-aggregate aldol reactions, controlled by the preorganized tetrameric structure.^{242a} No direct evidence for such a sequence was reported, but it is

feasible considering what is now known about the rates of alkylations and aldol processes.



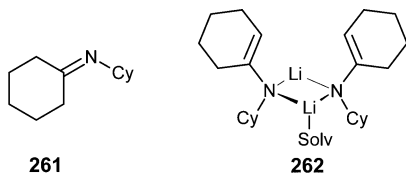
3.8.2. Ester Lithium Enolates. Ester enolates have been structurally much less studied than ketone enolates (presumably in part due to their thermal instability), and mechanistic studies have also been limited. Careful NMR studies of the enolate of methyl β -aminopropionate (**93**) (synthesis of the coronary drug otamixabon) using Job's plots revealed that the hexameric unsolvated structure found in the crystal was also present in THF solution. The alkylation of **93** with benzyl bromide was first-order in [enolate], so the hexamer is the reactive species. The reaction was also first- or second-order in [THF]. Since there are no vacant coordination sites on the intact hexamer, Collum proposed, supported by some computations, that the role of the THF molecules was to produce an open hexameric ladder structure which is the active alkylating agent.¹⁴⁰

3.8.3. Lithiated Hydrazones. Lithiated cyclohexanone *N,N*-dimethylhydrazone **258** is a tetramer–hexane solution. Alkylation with EtI is first-order in [EtI] and approximately 1/3- to 1/4-order in [(**258**)₄], so monomer is the likely reactive species.⁴⁹⁷ This was supported by a number of experiments which tested for aggregate reactivity using the stereochemistry of alkylation as a probe. The stereochemistry of alkylation of 3-methylcyclohexanone imine was unaffected by the addition of other lithiated hydrazones or by the presence of both regioisomers, which would require the presence of different ratios of mixed aggregates. The reaction was second-order in added 2-methyltetrahydrofuran, so a rapid pre-equilibrium in which addition of two solvent molecules dissociates the tetramer leading to a reactive transition state as shown in **258** was proposed in which halide reacts on the face of the anion opposite the lithium cation. The high stereoselectivity (50:1) was rationalized as a matched combination of modest selectivity for bottom coordination and modest selectivity for axial attack. The much lower selectivity for reaction with aldehydes (1.7:1) was explained by these effects being in opposition, since the aldol process is likely to proceed through a cyclic transition state, where the sterically favored lithium species **259** leads to the less favorable equatorial attack and the less sterically favored lithium species **260** results in the more favored axial attack.

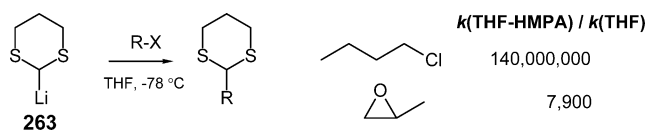


A study of the alkylation of the lithiated cyclohexanone imine **261** revealed both structural and mechanistic complexity. In THF-containing solvents monomeric, dimeric (stereoisomeric mono- and disolvated forms), and trimeric structures were identified. Most species had low solvation numbers, consistent

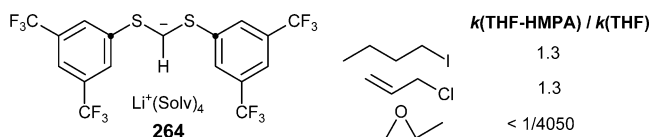
with contributions from π -bonding of the azaenolate to lithium. The alkylation kinetics with *n*-heptyl iodide in *t*-BuOMe solution, which contain mostly the monosolvated dimer (probably the *cis*-isomer **262**), were also complex, showing nonintegral fractional orders (between 0.5 and 1.0) both in the lithio imine and in the solvent, indicating close competition between monomer and dimer pathways.²⁶³



3.8.4. Lithiated Dithiane. In a kinetic study of the alkylation of lithiodithiane **263** in THF and THF–HMPA solutions, it was shown that the reaction was first-order in [**263**] and first-order in [R–X]. Addition of HMPA, which converted the dithiane from a monomeric CIP to an HMPA-solvated SIP, resulted in a rate acceleration of 10^8 in alkylation with primary alkyl halides at -78°C . Moreover, it was shown that, even in THF, it was the tiny fraction of SIP that performed the alkylation reaction; the CIP was inert.^{120c} Thus, the SIP is at least 10^8 times as reactive as the CIP. Reaction via SIP for these lithium reagents explains the difficulty in achieving asymmetric alkylations using chiral solvating agents.⁴⁹⁸

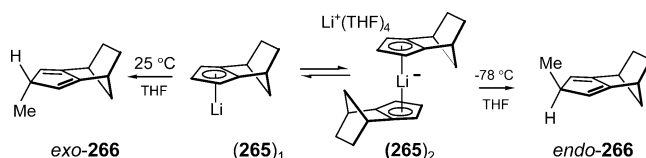


Reaction of **263** with propylene oxide was only accelerated by 10^4 when HMPA was added. The much smaller rate increase was traced to the loss of lithium cation activation of the epoxide leaving group when the Li is sequestered by HMPA. This partially offsets the increase in concentration of the SIP. The two effects could be separated in the alkylation of the [bis(arylthio)methyl]lithium **264**, which was already 70% SIP in THF solution. The rate of alkylation of **264** with *n*-BuI or allyl-Cl was unaffected by addition of HMPA. Tying up the lithium cation as $\text{Li}(\text{HMPA})_4^+$ had no effect, so there was no Lewis acid assistance in departure of iodide or chloride. On the other hand, the reaction of **264** with propylene oxide was dramatically slowed by addition of HMPA. Two equivalents led to 1/270 the rate of alkylation, and at 3 equiv no reaction could be detected; the rate had slowed by at least a factor of 4050.^{120c}



3.8.5. Cyclopentadienides. Substantial changes in the behavior of organolithium solutions with temperature are regularly seen. In one case, an attempt was made to correlate the changes with aggregate structures in solution, although mechanistic studies were not done. At room temperature, the lithio cyclopentadienide **265** reacts with electrophiles such as MeI to give mainly *exo*-**266**, whereas at -78°C the major product is *endo*-**266** (product ratios were unfortunately not given, but with CpTiCl_3 as the electrophile the ratios were 0:100 at 25°C and 95:5 at -78°C ^{96b}). Extensive spectroscopic studies⁴⁹⁹ and later X-ray structures^{96b} established that at low

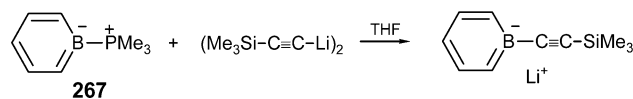
temperature **265** existed as a mixture of monomer and the triple ion dimer, with the facial stereochemistry shown. At room temperature, only the monomer was seen. The change in stereochemistry of alkylation was ascribed to higher reactivity of the triple ion and a different stereopreference for the monomer and triple ion. Although it is unusual for a higher aggregate to be more reactive than a lower one, it seems reasonable in this case since in the triple ion the cyclopentadienide anion is neutralized by half a lithium, whereas in the monomer a full lithium is bonded to the anion. Of necessity, the triple ion must react on the face away from the lithium, leading to *endo*-**266**. At room temperature the monomer is the reactant, which reacts from the less encumbered lithium-bearing face. This also results in more efficient charge neutralization of the leaving group, leading to *exo*-**266**.



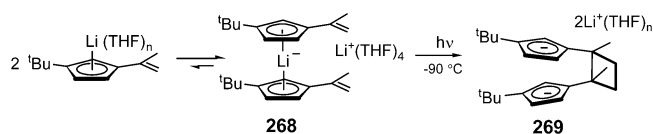
3.8.6. SET Mechanism. The question of SET mechanisms also arises in $\text{S}_{\text{N}}2$ reactions of organolithium reagents. Cyclizable radical probes in the alkylation of 2-lithio-1,3-dithiane failed to show any cyclization.⁵⁰⁰ The stereochemistry of alkylation of nonracemic lithium reagents also provides a sensitive probe. Reaction of *N*-methyl-2-lithiopyrrolidine (**105**) with primary alkyl bromides gave complete inversion of configuration at the C–Li center, and alkylation with a cyclizable probe gave no cyclization products.⁴¹³ On the other hand, benzyl bromide and *tert*-butyl bromoacetate gave completely racemic products, suggesting an SET mechanism for these alkylations. Stereochemistry in the electrophile has also been probed, and substitution with inversion at carbon was seen for alkylation of a secondary alkyl halide with isobutyrophenone enolate.⁵⁰¹

3.9. Miscellaneous Reactions

The reaction of the PMe_3 complex of borabenzene (**267**) with lithium (trimethylsilyl)acetylide in THF shows first-order dependence on [**267**] and half-order dependence on the [acetylide]. Since the acetylide was subsequently shown to be exclusively dimeric in THF (at least at temperatures below -100°C ²³⁸), this means the monomer is the reactive species in a nucleophilic substitution at boron. Other mechanisms (borabenzynes, dissociation of PMe_3) were ruled out.^{97b} Although the solution structure of the product was not determined, a triple ion (sandwich) structure is likely, as found in the solid state for the H analogue.^{97a}

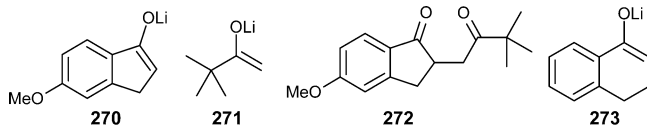


One of the rarely utilized consequences of aggregation in organolithium species is that the lithium binds functional groups in close proximity. This could in principle be used to perform reactions where the C–Li bond is not the dominating chemical feature. A possible example has been reported in the photochemical 2 + 2 cycloaddition of the vinyl-substituted cyclopentadienide triple ion (**257**) to form a cyclobutane, **258**.¹¹⁴



Another reaction of this type might be the photolysis of PhLi in ether, which gives a high yield of biphenyl. It was proposed that this reaction goes through a mechanism in which the excited-state PhLi dimer proceeds directly to the radical anion of biphenyl, followed by loss of lithium metal.⁵⁰²

Another interesting example of a possible aggregate proximity effect was provided by a study of the oxidative heterocoupling of lithium enolates with iodine using the thermodynamics of lithium enolate heteroaggregate formation as a mechanistic probe. The lithium enolates **270** and **271** form a 15.7:1 ratio of the A_2B_2 heterotetramer compared to the sum of the homotetramers ($\text{A}_4 + \text{B}_4$), readily analyzed in low-temperature ^7Li NMR spectra. When this equilibrium ratio of tetramers was oxidized with iodine, a 13.8:1 ratio of heterodimer **272** to the homodimers was formed. On the other hand, enolate **273** formed only a 4.4:1 ratio of A_2B_2 tetramer to the homotetramers, and oxidation gave a 3.0:1 ratio of the analogous mixed diketone. Similar relationships were seen for several other pairs. Thus, the oxidation and coupling apparently occur within tetrameric aggregates.⁵⁰³



4. CONCLUDING REMARKS

Organolithium reagents show an astonishingly wide range of aggregated structures in the solid state, with numerous arrangements of the lithium cations, the basic sites in the carbanion (carbon, oxygen, nitrogen, sulfur, and phosphorus atoms), and the associated solvent and cosolvent molecules. While solution structure determination methods cannot provide the rich detail of the single-crystal X-ray structures, modern spectroscopic methods have detected many in solution as well. Progress in the ways in which these structures react with electrophilic substrates has been slow, but the combination of powerful NMR spectroscopic methods and a variety of kinetic studies, supported by modern computational methods, has made real inroads. A wide variety of behaviors have been detected, and there are now a number of reactions where detailed mechanisms supported by experimental evidence can be proposed.

The generally higher reactivity of lower aggregates has stood up well to close scrutiny, although the reactivity difference between different aggregates varies enormously, from 1 to >8 orders of magnitude. Mixed aggregates are routinely formed during organolithium reactions, and they can be close in reactivity to the reactant aggregates, much less reactive, causing autoinhibition, or more reactive, causing autocatalysis.

The crucial role solvents play in the structure and reactivity of lithium reagents continues to be probed, although gathering experimental evidence has not been easy, since the specific coordination effects and general solvation effect are difficult to separate. Researchers rely heavily on computational methods to provide insights into experimental observations.

For many organolithium reactions precomplexes with substrate are formed and have been spectroscopically detected. Further reaction of these complexes is expected to occur in an intra-aggregate fashion, and that is sometimes the case. However, there are also several counterintuitive examples where the precomplex is attacked by an external RLi species.

Organolithium compounds are rich in diverse structures, often closely balanced energetically, and the transition states for reactions are similarly diverse, often with closely competing pathways. It is a real credit to the researchers who have worked with these highly reactive solutions that a wide range of reactions are now at least partially understood at the molecular level.

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Notes

The author declares no competing financial interest.

Biography



Hans J. Reich was born in 1943 in Danzig, Germany (Gdansk), and emigrated to Canada in 1950. After earning a B.Sc. at the University of Alberta in 1964, he entered graduate school at the University of California, Los Angeles, and received a Ph.D. with D. J. Cram in 1968. He then spent 2 years doing postdoctoral work, the first at Cal Tech with J. D. Roberts and the second at Harvard with R. B. Woodward. In 1970 he joined the faculty at the University of Wisconsin. Professor Reich has held visiting professorships at the University of Marburg in Germany, the Louis Pasteur University in Strasbourg, France, and the University of Alicante, Spain. His research interests include organo-selenium, organosilicon, and organolithium chemistry and the use of NMR spectroscopy to study structures and mechanisms.

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ABBREVIATIONS AND ACRONYMS

CIP	contact ion pair
CIPE	complex-induced proximity effect
D	dimer
DMF	<i>N,N</i> -dimethylformamide
DNMR	dynamic NMR
DOSY	diffusion-ordered NMR spectroscopy
HOESY	heteronuclear Overhauser effect spectroscopy
HSAB	hard and soft acids and bases

KIE	kinetic isotope effect
LDA	lithium diisopropylamide
M	monomer
NOE	nuclear Overhauser effect
PGSE	pulse-gradient spin-echo NMR spectroscopy
QCC	quadrupolar coupling constant (^7Li NMR)
RDS	rate-determining step
RINMR	rapid injection NMR
SET	single-electron transfer
SIP	solvent-separated ion pair
T	tetramer
TI	triple ion

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