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 and developed in the following three decades by major contributions from Ziegler (who first prepared n-BuLi and other alkylithiums from alkyl chlorides) and Gilman and Wittig (who independently discovered aromatic metatation 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 metatation (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), 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), 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, ketosulfides, 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.

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 LiNCMe2) has been very thoroughly explored by the Collum group (far more than any other lithium species) and has been reviewed at intervals. 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 alkylithium reagents formed for the purpose of asymmetric reactions (industrial applications have been reviewed recently).

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”, 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
Occasionally two, five, or six. Some of the sites are occupied by the negatively charged carbon or another basic group in the lithium reagent. Usually the remainder of the sites are filled by basic solvent molecules, by chelating groups, or by secondary interactions with the organic fragment or a neighboring cluster. Tricoordinate lithiums are regularly observed in sterically crowded situations and sometimes result in subtle structural reorganizations to feed electron density to the ligand-deficient lithium.

The balance between lithium sites occupied by carbon and those occupied by basic solvents (and hence the type and nature of aggregation) is governed in a major way by the donor strength and availability of solvents (more basic solvents typically lead to lower aggregates). Steric effects between the various ligands on lithium are important, as illustrated by the substantial reduction in the dimer–monomer equilibrium constant in the series of 2-substituted phenyllithiums 1 in Figure 2.

![Figure 2. Dimer–monomer equilibria of ortho-substituted phenyllithiums. Adapted from ref 12. Copyright 2003 American Chemical Society.](image)

The basicity of the carbanion center is also important, with less basic carbanions typically resulting in lower aggregates, as in the series of (2-lithiophenyl)oxazolines 2 (Figure 3), where the 4-tert-butyl compound has the highest and the 4-chloro compound the lowest concentration of dimer.

![Figure 3. Dimer–monomer equilibria of substituted (oxazolinylphenyl)lithiums.](image)

Chelating groups can replace external solvation, and in the absence of basic solvents the presence of single or multiple chelating groups can lead to lower aggregates. Bidentate solvents or cosolvents (Figure 4) such as TMEDA and its analogues deaggregate tetramers to dimers or more rarely convert them to open tetramers, whereas tridentate cosolvents such as PMDTA and TMTAN, if they interact at all, usually do so to produce monomers or aggregates with open structures.

### 2.1. Types of Solid-State Structures

The following brief survey of solid-state aggregate organolithium structures is not intended to be exhaustive, but does attempt to cover the various structural types known for common organolithium reagents.

#### 2.1.1. Hexamers and Higher Aggregates

In the absence of ether or other coordinating solvents, unhindered alkylolithium reagents form nonamers, octamers, and hexamers. The first crystal structure obtained of a hexamer was that of cyclohexylithium. Subsequently, X-ray structures of n-BuLi, i-PrLi, and Me,SiCH2Li hexamers were reported. In all of them the lithium atoms are arranged in a distorted octahedron, with six of the eight faces capped by a carbanion unit. Unsolvated enolate hexamers such as the enolates of pinacolone and isobutyrophenone form a more nearly hexagonal prism arrangement of Li and O atoms.

Mixed higher aggregates have also been characterized by X-ray, especially those incorporating n-BuLi. This includes mixed hexamers (n-BuLi)2(RO), the mixed octamer (n-BuLi)2(t-BuOLi), and a variety of complicated mixed aggregates with a bis(phenoxide). A mixed heptamer consisting of six molecules of a lithium β-aminoalkoxide and one of benzyllithium was inadvertently formed by deprotonation of toluene solvent by a n-BuLi–alkoxide superbase. An interesting mixed octamer is formed by eight molecules of (2,6-dimethoxyphenyl)lithium and one of Li2O. A truly remarkable mixed decamer, consisting of four dilithiocyclopentadienides, four lithium tetramethylpiperidides, and two n-BuLi units, has been characterized.

#### 2.1.2. Tetramers

In the cubic tetramers found for EtLi and MeLi, each lithium has close contacts with three charged carbons. The fourth site is in proximity to electron-rich CH bonds of another cluster. Such interactions are prevented in hindered reagents such as the t-BuLi tetramer. When basic solvents are present, two to four of the remaining open lithium sites are coordinated to solvent molecules. Tetrameric solid-state structures of this type are found for many organolithium reagents with unhindered carbon atoms and little charge delocalization. These include (MeLi)4(THF)4, (n-BuLi)4(THF)4, (vinylolithium)4(THF)4, (PhLi)4(Et2O)4, and numerous other aryllithiums ((2,6-dimethoxyphenyl)lithium, (2-methoxyphenyl)lithium, thienyllithium) and alkylolithiums.

Unsolvated solvated lithium enolates typically form tetramers, such as cyclopentenolate–THF, pinacolate–THF, and the tri- and tetrapyridine complexes of pinacolate. Chelating groups which can form five- or six-
membered rings will occupy some of the coordination sites, as in 3-lithio-1-methoxybutane, 3-lithio-1-(dimethylamino)propane, or [2-[(dimethylamino)methyl]phenyl]lithium. 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 stereo-isomeric four-center ladder tetramers, the step-ladder 4a and the bowl-ladder 4b, in which one face of the cubic tetramer has been expanded. Phenyllithium forms a similar ladder structure with sparteine and a sparteine surrogate. A more unusual ladder, 5, is formed by \( \text{LiCH}_2\text{NMe}_2 \), which involves both normal four-center \( C\text{-Li-C-Li} \) and less common five-center \( C\text{-Li-C-Li-N} \) rings. The sulfoximine PhS(==O)(==NMe)CH\(_2\)LiTMEDA forms a complex ladder in which all three basic sites (O, N, C) contact the lithium atoms.

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. PMDTA as a ligand usually does not permit more than one \( C\text{-Li-C-Li} \) contact, although chelating groups can lead to formally pentacoordinate lithiums, as for \( [2\text{-fluoro-6-}(\text{phenylsulfonyl})\text{phenyl}]\text{liium} \cdot \text{PMDTA} \). 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.

Monocyclic tetramers are also known. Thus, eight-membered rings with a \( (\text{Li-C})_4 \) framework are formed by benzyl-lithium coordinated to an amino ether (7), metalated 1,2-bis(dimethylamino)cyclohexane, the analogous metalated TMEDA, and the substituted allyllithium. A 12-membered cyclic tetramer with a \( (\text{C-Li-P})_4 \) framework is formed by \( \text{Ar}_2\text{PC}_3\text{H}_4\text{Li} \) (Ar = 2-[(dimethylamino)methyl]phenyl). An alternate mode of tetramerization is shown by unsolvated 2,4,6-trisubstituted phenyllithiums, which crystallize in a macrocyclic \( \pi \)-complex.

Mixed tetramers of two different lithium reagents (such as \( (\text{n-BuLi})_2\cdot(\text{ArLi})_2 \)) or lithium reagents and lithium halides (such as \( (\text{PhLi})_3\cdot(\text{LiBr})_1\cdot(\text{Et}_2\text{O})_3 \) and \( (\text{cyclopropyl-Li})_2\cdot(\text{Et}_2\text{O})_4 \) 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. This can be considered as basically a normal four-center dimer, with an LDA coordinated to each side. A chelated \( 2:2\text{ArLi} \cdot n\)-BuLi mixed tetramer forms a ladder structure, 12. Other similar mixed tetrameric ladders involving \( n\)-BuLi and t-BuLi have been reported. A more extended ladder structure is found for the lithiumphosphazene--lithium phenoxide 2:2 mixed tetramer 13.

Even a mixed tetramer, 14, consisting of three different lithium species, one \( \text{LiBr} \), one \( (\text{Me}_3\text{Si})_2\text{NLi} \), and two lithium enolates of pinacolone, has been crystallized.

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 (\( \alpha\)-phenylvinyl)lithium reagent, 15, crystallizes as an unsolvated cyclic trimer, as do several 2,6-disubstituted phenyllithiums (bis-t-BuO, bis-Me\(_2\)N, and Me\(_2\)N and t-BuO). A very unusual chelation-framework-induced trimer structure is provided by the triamine complex of t-BuLi.

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

Mixed trimers of two different lithium reagents (such as \( (\text{n-BuLi})_2\cdot(\text{ArLi})_2 \)) or lithium reagents and lithium halides (such as \( (\text{PhLi})_3\cdot(\text{LiBr})_1\cdot(\text{Et}_2\text{O})_3 \) and \( (\text{cyclopropyl-Li})_2\cdot(\text{Et}_2\text{O})_4 \))
carbon, as in the nine-membered phosphate-chelated structure \[\text{(Me}_2\text{PhSi)}_2\text{CHLi}\].

Several mixed trimers between chiral lithium amides and RLi species have been characterized, such as compound 20.\textsuperscript{64,65}

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, a \[\text{Li}^\text{−NMR active}\] species such as \(\text{Ph}_2\text{PLi}\) or \(\text{LiPh}_2\) can distinguish a dimer from a trimer (i.e., the remote lithium in the trimer is not coupled (or coupled by a much smaller coupling constant) to the \(\text{X}\) nucleus, whereas the other two lithiums are strongly coupled).\textsuperscript{62a} Since such techniques are not routinely applied, it does seems probable that a small fraction of the aggregates casually identified as dimers may in fact be trimers.

![Dimer: AA’XX’ spin system](image1)

![Trimer: AAA’XX’XX’ spin system](image2)

### 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., \(\text{PhLi}\)) or to other parts of the carbanion fragment (e.g., \(\text{Me}_3\text{SiCH}_2\text{Li}\)). 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 \(\text{Li}^\text{−[1,5-bis(methoxy-3-carbethoxyphenyl)]ammonium}\)) or solvent molecules (e.g., \(\text{Li}^\text{−[(THF)]_2}\)).

Chelated eight-membered ring dimers are formed by several \([\text{pyridylmethyl}]^\text{−[pyridylmethyl]}\) or \([\text{pyridylmethyl}]^\text{−[pyridylmethyl]}\) lithium \(28,88\) and \([\text{pyridylmethyl}]^\text{−[pyridylmethyl]}\) lithium \(29,89\). Eight-membered cyclic structures with no C−Li contacts are formed by several lithium sulfones (e.g., \(30,90\)) and sulfoximines.\textsuperscript{91} A macrocyclic dimer involving both \(\text{CH}_3−\text{Li}\) contacts and cyclopentadienyl \(\pi\)-contacts is formed by a lithiated cyclopentadienylphosphonium ylide.\textsuperscript{92}

Although more rare, several dimers of the triple ion type (R−Li−R′−Li\textsuperscript{−}) have been characterized, including sterically hindered systems such as [tris(trimethylsilyl)methyl] lithium,\textsuperscript{93} \(\beta\)-dicarbonyl enolates such as lithium ethyl acetocetate,\textsuperscript{94} and lithium bis coordinated to anionic \(\pi\)-systems such as cyclohexadiene,\textsuperscript{95} cyclopentadienide,\textsuperscript{96} and boratabenzene.\textsuperscript{97}
Dimethylbenzyl]lithium—TMEDA 31 and bis[(2-pyridylmethyl)lithium]−(12-Cr)32 also form triple ions. Dimers form triple ions as a consequence of a significant energetic advantage of unequal solvation of the two lithiuns. For example, in (Me3Si)2CLi a normal four-center dimer may have room to coordinate only two THF molecules, if that (the phenyl analogues (PhMe3Si)2CLi64b and PhMe2Si−(Me3Si)2CLi44a 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 32100 (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 lithiuns. 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 3754b and 2578 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 benzyl锂ions107), situations of high steric crowding of the carbanion carbon (as in (2,4,6-tri-tert-butylphenyl)lithium108a and other 2,6-disubstituted aryllithiums108b−c), 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−PMATA,109 (2-methoxyphenyl)lithium−PMATA,30d [2-fluoro-6-(phenylsulfonyl)phenyllithium−PMATA,41 BnLi−TMTAN,52 Me2SiCH2Li−PMATA,110 and Me2P(Me3Si)CHLi−PMATA.56c In sterically encumbered situations or when the anion is delocalized, bidentate ligands such as TMCDA (t-BuLi58a and s-BuLi (38)76), sparteine (t-BuLi111 indenyllithium,112 and allyllithium113), and TMEDA (CpLi96b,d,114 BnLi,115 and allyllithium116a) 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−PMTA complexes.80 It also happens when charge is delocalized and the lithium is well-coordinated elsewhere in the molecule, as for compounds such as 3999 40117 41118 and 42119 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 tetramer121a 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 ebullioscopic (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% 13C-enriched MeLi–LiI,[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 13C.[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 T1 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 (13C, 15N, 31P), even though the 6Li–X couplings are smaller by a factor of about 2.6 than the 7Li–X couplings.[126,127] The long T1 values also mean that NOE experiments (HOESY) can be carried out to detect the proximity of lithium to protons.[128] Since both 6Li and 13C 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 JLiC in the 13C NMR spectra. Doubly enriched materials with 13C at the carbanion carbon are sometimes prepared to allow high-sensitivity observation of coupling in both the 6Li and 13C NMR spectra.[122] Natural-abundance 13C satellites have been occasionally detected in the 7Li NMR spectra, bypassing the need for 13C enrichment.[125]

The natural line width of 7Li signals is quite variable as a result of coupling between quadrupolar T1 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. T1 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 (T1 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), JLiC 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 13C 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-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 13C NMR spectra of Ph6Li in Et2O and THF in Figure 5.[103] The 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 (ΔG2 between 7 and 17 kcal/mol). For alkyllithiums 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-BuLi)$_4$ in cyclopentane can be observed even at room temperature ($\Delta G_f > 16$ kcal/mol). For the tetramer–hexamer mixture of i-PrLi$_{125d}$ and s-BuLi$_{132a}$ coupling and distinct aggregate signals can be resolved below 0 °C ($\Delta G_f > 14.5$ kcal/mol), and for EtLi$_{132d}$ and n-PrLi (both mixtures of hexamers and octamers), temperatures below −30 °C are required ($\Delta G_f > 13$ 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$_2$O, separate NMR signals are observable below −80 °C$_{103}$ whereas in THF the monomer and dimer signals$_{129}$ decoalesce at ca. −100 °C ($\Delta G_f = 8$ kcal/mol$_{103}$). 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 tri- and tetraatomic ions135), trimers a 1:3:3:1 ratio, tetramers a 1:4:6:4:1 ratio for the A$_4$, A$_3$B, A$_2$B$_2$, AB$_3$ and B$_4$ species, and so on. Figure 6 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 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$_B$ species.$^{136}$

One of the earliest proofs of the tetrameric nature of methylthiium in ether solution was of this type.$^{137}$ Solutions of defined mixtures of methyl- and ethylthiium gave appropriate $^7$Li 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$_2$Et, MeEt$_2$, or Et$_3$). The most refined version of this method involves isotopically perturbed mixed aggregates, for example, CH$_3$Li and CD$_3$Li, where isotope shifts provide a 1:4:6:4:1 ratio of $^6$Li signals for the various isotomers of the tetramer.$^{125b,138}$

The method has been especially useful in cases where NMR coupling is not available, such as lithium enolates$_{60,134a,b,139}$ and phenoxides,$^{134d}$ or when $^13$C enrichment is difficult, as in aryllithium triple ions.$^{135}$ Of course, E/2 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 acetonaphenone lithium enolate$_{80a}$ provides a series of HMPA complexes readily identified by characteristic $^7$Li chemical shifts and Li–P couplings. Four species are observed in addition to the THF-solvated tetramer, (RLi)$_2$(HMPA)$_2$ (1:3 ratio of $^7$Li NMR signals), (RLi)$_4$(HMPA)$_2$ (2:2 ratio of signals), (RLi)$_4$(HMPA)$_3$ (3:1 ratio of signals), and (RLi)$_4$(HMPA)$_4$ (one signal), which could only form if the species was tetrameric. For a dimer, only two new species are observed, (RLi)$_2$(HMPA)$_2$ (1:1 ratio of $^7$Li NMR signals) and (RLi)$_2$(HMPA)$_3$ (one $^7$Li NMR signal, a doublet). Additional HMPA usually results in dissociation to monomers, which give only two new signals, (RLi)$_2$(HMPA)$_2$ (a doublet in the $^7$Li NMR spectrum) and (RLi)$_2$(HMPA)$_3$ (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

![Figure 6](Chemical Reviews)
monomeric CIP in THF, which undergoes ion pair separation with HMPA,\textsuperscript{146} that the lithiothiophosphonamide \textbf{43} is a CIP, and that the benzyl system \textbf{44} is an SIP.\textsuperscript{147} Lithiated sulfone monomers and dimers in THF are converted to SIPs with HMPA.\textsuperscript{148} This technique and others have been used to show that numerous methylithium species with two anion-stabilizing groups (e.g., SR, SeR, SiR\textsubscript{3}, Ph, vinyl, and alkynyl)\textsuperscript{149} 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)\textsubscript{2}·(TMEDA)\textsubscript{1} and (RLi)\textsubscript{2}·(TMEDA)\textsubscript{2}.\textsuperscript{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 vinylolithium\textsuperscript{29} and for [2-[(dimethylamino)methyl]phenyl]lithium (21)\textsuperscript{67} and has also been seen in the solid state when a third coordination site is not available.\textsuperscript{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.\textsuperscript{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.\textsuperscript{154}

An NMR parameter with the potential of providing information about structures in solution is the \textsuperscript{7}Li quadrupolar coupling constant (QCC), which is sensitive to both aggregation and solvation. Determination of the QCC requires measurement of the \textsuperscript{7}Li T\textsubscript{1}, some estimate of the effective rotational correlation times, which can be obtained from \textsuperscript{13}C relaxation, and some estimate of molecular asymmetry.\textsuperscript{155} The method has been used only occasionally,\textsuperscript{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 sp\textsuperscript{2} and sp carbons are especially sensitive to aggregation.\textsuperscript{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.\textsuperscript{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 \textsuperscript{13}C Δδ values of the enolate carbons are almost linear with the aggregation state (more specifically, with the number of O–Li contacts).\textsuperscript{160}

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

2.3.1. Alkylolithiums. \textit{Methylolithium} 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.\textsuperscript{76} A tetratosolvent cubic tetramer crystallizes from THF.\textsuperscript{27} It is also a tetramer in ether\textsuperscript{124b,161} and THF\textsuperscript{125b} solutions. Even the very polar cosolvent HMPA causes no detectable deaggregation, but sequentially replaces the coordinated ethers by HMPA.\textsuperscript{144b} Only strong chelating diamines can reduce the aggregation state to dimeric in the solid state.\textsuperscript{76}

The mixed aggregates between MeLi, LiI, and LiBr were identified by the earliest researchers in the area soon after NMR spectroscopy became available,\textsuperscript{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.\textsuperscript{163} A detailed NMR study in THF of 1:1 mixtures of MeLi–LiBr and MeLi–LiI using the isotope perturbation method\textsuperscript{125b,138b} showed that for LiBr (monomer in THF\textsuperscript{164}) a 66:17 ratio of (MeLi)\textsubscript{4} to (MeLi)\textsubscript{2}·(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)\textsubscript{4} to (MeLi)\textsubscript{2}·(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 trisolvated from DOSY measurements.\textsuperscript{154}

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

\textit{Ethyllithium} is hexameric by cryoscopy in benzene and cyclohexane.\textsuperscript{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.\textsuperscript{125d}

\textit{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 \textsuperscript{6}Li-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.\textsuperscript{134} A well-defined mixed dodecamer of (n-PrLi)\textsubscript{4}·(n-PrOLi)\textsubscript{4} was characterized in cyclopentane.\textsuperscript{169}

\textit{n-Butyllithium} is by far the best studied of all organolithium reagents. A hexamer crystallizes from pentane,\textsuperscript{169} and it is mainly hexameric in hydrocarbon solvents,\textsuperscript{125d,170} tetramer in diethyl ether,\textsuperscript{170} and a tetramer–dimer mixture in THF (see Figure 7),\textsuperscript{171} with ΔG\textsuperscript{T} for interconversion of around 11 kcal/mol. Chelating diamines such as TMEDA\textsuperscript{28,125b,150a,158,172} or TMCDA\textsuperscript{35} 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 \textsuperscript{7}Li
quadrupolar couplings, that \( n{-}BuLi \) forms a monomeric complex with PMDTA.\textsuperscript{156e} Chelating triamines such as TMTAN and PMDTA, which will often produce monomeric \( n{-}BuLi \), and tert-butyllithium, 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.\textsuperscript{173}

Because of the extensive use of \( n{-}BuLi \) 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 \( RLi \rightleftharpoons n{-}BuLi \)) include the bischelated 2:2 \( n{-}BuLi-\pi\text{-}ArLi \) cubic tetramer 45 (in toluene solution a mixture of 3:1 and 2:2 tetramers as well as the homodimer was characterized)\textsuperscript{50} and a 2:2 \( n{-}BuLi-\pi\text{-}chelated benzyl lithium system.\textsuperscript{125a,174} Mixed ladder tetramer 12 is formed by a bischelated \( \pi\text{-}ArLi \). Similar ladders are formed by \( n{-}BuLi \) and an \( \alpha\text{-}((trimethylsilyl)benzyl) \) system,\textsuperscript{51e} by \( n{-}BuLi \) and two \( \text{R}_2\text{SiCH}_2\text{Li} \) units,\textsuperscript{51b} between \( t{-}BuLi \) and lithiated TMCD,\textsuperscript{10b} and between \( t{-}BuLi \) and metalated TMTAN.\textsuperscript{52} A hindered \( \pi\text{-}ArLi \) forms a 2:2 \( n{-}BuLi \) \( \pi\)-complexed mixed tetramer, 46 (analogous to the homotetramer 10).\textsuperscript{46}

Secondary alkyl lithiums are less aggregated than primary ones. \( s{-}BuLi \) is a mixture of hexamer and tetramer in hydrocarbon solvents,\textsuperscript{135} as is \( i{-}PrLi.\textsuperscript{125d} \) In THF a mixture of dimer and monomer is seen for \( s{-}BuLi \), which is converted entirely to monomers with PMDTA.\textsuperscript{129} Several dimeric solid-state structures of \( i{-}PrLi \) coordinated to diamines have been reported, as well as the interesting and unusual trimeric structure 18, consisting of an \( i{-}PrLi \) unit coordinated to a cyclic dimer.\textsuperscript{59} Other secondary alkyl lithiums have also been characterized in THF solution. 7-Norbornadienyllithium 47 is a mixture of mainly dimer and small amounts of monomer in THF.\textsuperscript{175} The aggregation state of menthyl lithium (48) was not determined, but its unusually high reactivity (compared to \( n{-}BuLi \) or \( s{-}BuLi \)) toward a number of electrophiles was attributed to steric inhibition of aggregation.\textsuperscript{176}

\textit{tert-Butyllithium} crystallizes as a tetramer from pentane\textsuperscript{16} and is tetrameric in hydrocarbon solvents.\textsuperscript{125c,177} A disolvated dimer crystallizes from Et\(_2\)O\textsuperscript{16} and a dimer is seen in solution.\textsuperscript{175} In THF \( t{-}BuLi \) is exclusively monomeric.\textsuperscript{179} A series of mixed tetramers and hexamers of \( t{-}BuLi \) and \( t{-}BuOLi \) have been characterized and their fluxional properties examined by DNMR spectroscopy.\textsuperscript{178}

The structure of an interesting mixed crystal consisting of one (\( t{-}BuLi \))\textsubscript{4} and four [2-(dimethylamino)phenyl]lithium homoaggregated tetramers was determined. On the mixed crystals being dissolved in toluene, the three possible 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 \(^7\text{Li} \) EXSY experiments.\textsuperscript{152e}

\textit{Lithium Amide Mixed Aggregates.} Although out of scope for this paper, a number of mixed aggregates of MeLi, \( n{-}BuLi \), \( s{-}BuLi \), \( t{-}BuLi \), and others with chiral lithium alkoxides,\textsuperscript{143c,179} alkoy-substituted lithium amides,\textsuperscript{180} amino-substituted lithium amides\textsuperscript{70,165b,181} and phosphino-substituted amides\textsuperscript{182} 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 \( \pi \)-delocalized charge are typically less aggregated, with the \( \pi \)-system often occupying more than a single coordination site on lithium. Early colligative property measurements suggested allyllithium was polymeric in Et\(_2\)O (the TMEDA complex was found to be polymeric in the solid state\textsuperscript{183}) and approximately dimeric in THF on the basis of colligative property measurements,\textsuperscript{184} including cryoscopy in THF.\textsuperscript{185a} The crystal structure of a monomeric PMDTA complex was reported.\textsuperscript{185b} Saunders’s isotope perturbation experiments\textsuperscript{186} suggest an asymmetric \( \pi \)-bonded structure.\textsuperscript{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 crotlyllithium favoring the \( Z \) isomer 85:15 in THF.\textsuperscript{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.\textsuperscript{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.

Alkoy-substituted allyllithium reagents (metalated allyl ethers) give only \textit{cis} products when they react at the \( \textit{Z} \)-position.\textsuperscript{189} \textit{[1-(Dimethylamino)allyl]lithium} 49 (mixture of monomer and dimer by NMR and cryoscopy) is all \( Z \) in THF.\textsuperscript{190} \textit{[1-(Phenylthio)allyl]lithium} 50 is monomeric in THF (cryoscopy\textsuperscript{191}), and a 2:1 mixture of the \( Z \) and \( E \) isomers is seen in the \(^1\text{H}\) and \(^13\text{C}\) NMR spectra at \(-120^\circ\text{C}\) in 3:2 THF–Et\(_2\)O. The signals coalesce above \(-70^\circ\text{C}\). When HMPA was added to form the SIP, a similar ratio of isomers was seen. [2-\( (\text{Pyridylthio})\text{allyl} \)lithium is also a 3:2 mixture of \( Z \) and \( E \) isomers.\textsuperscript{192} An X-ray structure of \( \text{SIP} \)–TMEDA showed the \( Z \) isomer.\textsuperscript{116a} Solution NMR studies suggested mainly the \( Z \) isomer for \( \text{SIP} \) and the \( Z \) isomer for \( \text{SIP} \). However, NMR spectra
were taken at 220 K, which may not have been low enough to decoalesce the rotamers.\textsuperscript{195} Trialkylsilyl-substituted allyllithiums are exclusively in the \( E \) geometry,\textsuperscript{196} although chelating substituents can force conversion to \( Z \) isomers to improve internal ion pairing.\textsuperscript{195}

\[
\begin{align*}
\text{Me}_2N^+\text{Li}^- \quad \text{PhS}^- \quad \text{Bu}^- \\
49-Z \quad 50-Z \quad 50-E \\
51-Z \quad 52-Z
\end{align*}
\]

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

Interesting insights into coordination and solvation of allyl systems is provided by the X-ray structures of 54 and 55.\textsuperscript{112} In the former, the Li is trisolvated and the indenyl allyl system is monocoordinated to lithium. In 55, the lithium is biscoordinated by the sparteine ligand and the allyl fragment is \( \pi \)-coordinated to lithium, in spite of the increased hindrance due to the butyl group. The \( \pi \)-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).\textsuperscript{70,197,198,199}

\[
\begin{align*}
\text{Soc}^+\text{Ar}^- \quad \text{Li}^+ \\
53 \\
54 \\
55
\end{align*}
\]

2.3.3. Benzyllithiums. Several crystal structures have been reported for benzyllithium. A polymer crystallizes from ether,\textsuperscript{66c} and an eight-ring tetramer complexed with MeOCH\(_2\)CH\(_2\)NMe\(_2\) crystallizes from toluene.\textsuperscript{43} This complex is dimeric in toluene solution. Monomeric benzyllithiums coordinated to TMEDA–THF,\textsuperscript{107a} quinuclidine,\textsuperscript{107b} and PMDTA have been crystallized.\textsuperscript{43} Benzyllithium is also monomeric in THF solution.\textsuperscript{115} 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) \( ^6\)Li–C coupling of 3.8 Hz in THF for BnLi–TMEDA, compared to 17 Hz\textsuperscript{120} for typical monomers.\textsuperscript{200} A similar small coupling was observe for a crown-belted BnLi.\textsuperscript{201}

\[
\begin{align*}
\text{Ph} \quad \text{Me} \quad \text{N}^- \quad \text{Li}^+ \\
56
\end{align*}
\]

\[
\begin{align*}
\text{PhS}^- \quad \text{Bu}^- \quad \text{Li}^+ \\
57
\end{align*}
\]

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 \( \delta \) 196.4.\textsuperscript{209} Propargyllithiums have this carbon between \( \delta \) 90 and \( \delta \) 100. Allenyllithium is a mixture of dimer and monomer in THF solution.\textsuperscript{210} (1-Methoxyallenyl)lithium 62 is a dimer in THF and a tetramer in Et\(_2\)O.\textsuperscript{211} All other simple alkylated allenyllithiums examined also have allenyl structures and are monomeric in THF.\textsuperscript{210} An exception is the (1-alkynylcyclopropyl)lithium 63, which is propargylic, presumably as a result of angle strain.\textsuperscript{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).\textsuperscript{210,213} An X-ray structure of a thioisobamoyl-substituted sparteine complex 66 showed localized bonding of lithium to the propargyl carbon.\textsuperscript{214}

\[
\begin{align*}
\text{PhMe} \quad \text{Li}^+ \\
58 \\
59 \\
60
\end{align*}
\]

\[
\begin{align*}
\text{Ph} \quad \text{Me} \quad \text{N}^- \quad \text{Li}^+ \\
61
\end{align*}
\]

Saunders’s isotope perturbation experiments\textsuperscript{136} 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 \( \pi \)-type bonding and localized bonding of lithium to either the allenyl or propargyl terminus of the anion.\textsuperscript{215} This is also seen in a pair of X-ray structures. The
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, \(^{69}\) and a mixture of tetramer and dimer is seen in diethyl ether solution. In THF a mixture of dimer and monomer is found \(^{103,129}\). 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. \(^{69}\)

Substituted aryllithium reagents follow a similar pattern. Steric effects are pronounced as illustrated in Figure 2. Mesityllithium is monomeric in dilute solution in THF \(^{135}\) (although it crystallizes as a THF-solvated dimer \(^{198}\)) and dimer is present in THF–toluene solution. \(^{216}\) PMDTA forms a monomeric complex. \(^{129,195}\) (2,4,6-Trifluorophenyl)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 (OEt)_2 complex, as well as the (OEt)_2·THF, (OEt)_3·THF, (OEt)_4·THF, and (THF)_4 solvates. The structures reveal in a direct way the better solvating power of THF over Et_2O 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)\(^{72}\) 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 \(-101^\circ\text{C}\) and \(>12.5 \text{ kcal/mol}\) for (21) at \(-36^\circ\text{C}\)). 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\(^{-}\cdot\text{Li}(\text{HMPA})_n\)\(^{+}\)) in THF–HMPA solutions. \(^{12,67,103,135}\) For several 2,6-disubstituted phenyllithiums (Me_2, i-Pr_2, (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 \(^{6}\text{Li}-\text{HMPA}^\ddagger\) doubly enriched compound, showing that even the presumably very electron rich central lithium of a triple ion retains some electrophilic properties. \(^{97}\)

The chelation–aggregation correlation is seen elsewhere as well. 8-Lithio-1-methoxynaphthalene is dimeric in THF (no monomer seen)\(^{6,8d}\) even though it is more sterically hindered and probably has better charge delocalization than PhLi. (2-Oxazolinylphenyl)lithium 77 crystallizes as a chelated dimer from THF and in solution is slightly more aggregated than is o-tolylithium, in spite of the steric demand and electronic
stabilization of the substituent.13 [2,6-Bis(oxazolino)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. (Triphenyldiethyletherate)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 B13,68,208 but several type A crystal structures have been reported67,219 (especially diamine complexes220 as in (21)2·TMEDA67). In solution, mixtures of two211 or even all three67,142 isomers have been detected. Such isomerism has also been seen for chelated alkyllithium reagents.54,141

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); and its stereoisomer (inversion at one P-center).223 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.125c 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 metatation of tosylhydrazones (Shapiro reaction).225 They have been widely used as synthetic reagents.7

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 osmometry127). 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-Ethoxylvinyl)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 84231 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.76 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-buty lacetylidylenes crystallize as a THF-solvated cubic tetramer31c 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 Cyclopropylacetylidylenes are a tetramer–dimer mixture in THF.233 Lithium acetylidylenes with carbation-stabilizing substituents (biphenyl,234 Ph,122,235–237 Me2Si,238 Ph2Si,238 PhSi238) are dimeric or even monomeric (PhSO2238) in THF solution. A diamine-complexed dimer of phenylacetylidylenyl 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.129,239,240 They concluded that in dioxolane and THF 86a was tetrameric, and they detected two solvation states, probably the tetracarbene and trisolvate.53a 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 isobutyrophene-
none enolates crystallize as hexamers, whereas cubic tetramers crystallize from THF, with one THF coordinated to each lithium. A number of additional X-ray structures of TMEDA- and ether-complexed dimers, and PMDTA-complexed monomers 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. Within the limits of NMR detection, unconjugated unhindered enolates such as cyclopentanone, cyclohexanone, acetonitrile, and amide enolates and lithium amides, have been characterized.

The ketone enolates of cyclopentanone, cyclohexanone, acetonitrile, and acetylene, all tetrameric in THF, form dimers with TMEDA in hydrocarbon solutions, and such dimers have also been seen in the solid state for isobutyrophenone and pinacolone. A metastable dimer can be observed in RINMR experiments if the TMEDA complex is injected into THF at −120 °C, where its dimerization to tetramer in the presence of TMEDA can then be readily followed. Even PMDTA or TMTAN does not convert several of the tetrameric ketone enolates to lower aggregates.

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-ethanol (also X-ray), and 1,3-diphenyl-2-propanone, 2-phenyltetralone, and 6-phenyl-2-benzyltetralone were shown to be tetramer–monomer mixtures in THF.

The ketone enolates of cyclopentanone, cyclohexanone, acetonitrile, and acetylene, all tetrameric in THF, form dimers with TMEDA in hydrocarbon solutions, and such dimers have also been seen in the solid state for isobutyrophenone and pinacolone. Interestingly, addition of TMEDA to the tetramer solution of, for example, lithiated 2,3,9-diisoproplamine as well compared to enolates. Lithiated cyclohexanone, cyclopentanone, and acetonitrile, and amide enolates and lithium amides, have been characterized.

Ester enolates follow a pattern similar to that of the ketone enolates, although far fewer structures are known. Methyl α-tet-butylacetate enolate (90) forms a THF-solvated tetramer in the solid state, and tert-butyl isobutyrate (91) and tert-butyl propionate enolates form dimeric THF complexes. tert-Butyl propionate is dimeric in THF from cryoscopic measurements. Like ketone enolates, several esters and lactone enolates were shown to form dimers in TMEDA–toluene solutions. 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. A later study detected in addition two isomeric trimers. tert-Butyl isobutyrate is tetrameric in THF and forms mixed tetramers with t-BuOLi.

Two chelated ester enolates, ethyl α-(diethylamino)acetate (92), and the β-amino enolate 93 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. The N,N-dimethylacrylamidamide enolates 95a and 95b are mainly dimers in THF, with monomer detectable for the latter (K_{MD} = 450 M^{−1}) PMDTA forms monomeric PMDTA and HMPA complexes with 95a. HMPA in addition forms triple ions and a higher lithiate, (RO)Li^2−(Li^+)^80b. The more hindered and conjugated 96 is less aggregated, with K_{MD} = 40 M^{−1}.

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

Mixed aggregates have been detected between ketone, ester, and amide enolates and lithium amides, or even both halide and amide (compound 14).

2.3.9. Lithiated Imines. The nitrogen analogues of enolates have found important applications in organic synthesis, 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-dimethylhydrazine (97) forms an unsolvated polymeric structure when crystallized from THF in which lithium is π-coordinated to one enamine anion, as well as π-coordinated to the enamine nitrogen of another one. In THF solution the osmometric molecular weight indicated a predominantly tetrameric structure. A bis(disopropylamino) solvate of lithiated N-phenylhydrazine 98 has a normal four-center dimer structure. In THF solution a mixture of dimer (cis and trans stereoisomers) and monomer was detected. The N-cyclohexylamine showed more complicated behavior with monomers, monosolvated and bis-solvated dimers, and stereoisomeric trimers detected in THF or THF solution.

2.3.10. Lithiated Nitriles. Considering their extensive use in synthesis, 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. Cryoscopy in THF suggested a nearly monomeric aggregation state, but some caution is in order about this assignment since LiCH2CN forms both mixed dimers (in THF) and trimers (in Et2O) with chiral chelated lithium amides in which both C−Li and N−Li contacts are detected. Both N−Li and C−Li contacts were also present in the polymeric solid-state structure of (cyanocyclopropyl)lithium.

The X-ray crystal structure of lithiumphenylacetonitrile–TMEDA shows an N−Li four-center dimer structure, as does a mixed dimer with LDA (100). In solution the TMEDA and Et2O 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 LiN(SiMe3)2 was characterized in toluene solution. In THF lithiophenylacetonitrile is nearly monomeric by cryoscopy; no Li−N coupling could be observed, and no mixed aggregates with LiN(SiMe3)2 were detected. HMPA causes ion separation. Several (α-aminocyanobenzyl)lithiums have shown that Me2NCH2Li forms a THF-solvated ladder polymer, a four-center THF-solvated dimer, and a six-center dimeric TMEDA complex, shows how close the balance is between the four- and six-ring dimers.

2.3.11. Lithiated Amines. X-ray structures of simple (aminomethyl)lithiums have shown that Me2NCH2Li forms a THF-tetrasolvated ladder tetramer,59 and (CH2)2NCH2Li a THF-disolvated cubic tetramer.66 PhNCH2Li forms a THF-trisolvated four-center dimer. The lower levels of solvation appear to be a consequence of the routinely observed coordination of just carbon but also the nitrogen to the lithium.

The common polyamine ligands are often used with n-BuLi and other alkyllithiums. 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 mononmeric structure. A later crystal structure of the six-center dimer led these workers to suggest that dimer might also be present in solution, which would explain the coupling and the unexplained signal doubling observed. Lithiated TMTAN forms an analogous six-center dimer, as well as a 2:2 mixed ladder tetramer, 103, with t-BuLi. Metalated TMCDCA forms a six-center trimer, with an eight-center tetramer, and a 2:2 mixed tetramer, with t-BuLi. Metalated TMEDA forms an eight-center tetramer, 104.

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. The pyrrolidine 105 appears to be a four-center dimer in THF from the coupling to two lithi ums observed for the C−Li carbon in the 13C 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. Lithiated piperidine, on the other hand, shows coupling of lithium to only one carbon, as well as to nitrogen (in the 14N-enriched compound), so a mononmeric 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 RSCH2Li in section 2.3.12.

2.3.12. Lithiated Sulphides. 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. The 2-methyl analogue crystallizes as a TMEDA-complexed six-center dimer (27), but in THF solution it is a monomer by cryoscopy and NMR spectroscopy. 2-Phenylldithiane crystallizes as a solvated monomer and is also monomeric in THF. Several lithiodithianes investigated gave SIPs on treatment with HMPA.

Crystal structures of PhSCH2Li have included a monomeric PMDTA complex, a polymeric alternating four-ring, six-ring THF-solvated ladder polymer, a four-center THF-solvated dimer, and a six-center dimeric TMEDA complex. These results, and the observation that MeSCH2Li forms a four-center TMEDA-complexed dimer, shows how close the balance is between the four- and six-ring dimers.

In THF (cryoscopy) and Me2O solutions (JClLi), PhSCH2Li 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.

A characteristic feature of solid-state and solution structures of S-substituted (as well as Se-, Si-, and P-substituted) alkyllithiums is the strong preference for close alignment of the C−Li bond (or carbanion lone pair orbital) with the C−S interactions.
bond. This lone pair $σ^*$-interaction is strong enough that pronounced conformational preferences are seen, and that rotation around the C−S bond rather than pyramidal inversion at carbon is the principal barrier to enantiomerization of such compounds.

### 2.3.13. Lithiated Sulfones

These typically have lithium bonded to oxygen in the solid state, either in monomeric structures or in eight-membered ring dimers (30) leaving a bare or weakly coordinated carbanion carbon. The carbanion is sufficiently stabilized that crypt causes ion separation in the solid state for lithiated isopropyl phenyl sulfone. Solution structures are less well-defined, but sulfones seem to be minimally aggregated in THF (mostly dimers and monomers). Much is known about the stereochemistry of the lithio sulfones, which can even be prepared in optically active form at low temperature. 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 Ph$_2$PCH$_2$Li crystallizes as a monomer, and it is probably monomeric in THF as well. An infinite chain of four- and six-ring ladders crystallizes from THF. Several other lithiated phosphines crystallize as six-center dimers, including Me$_2$PCH$_2$Li−TMEDA, Me$_2$PhPCH$_2$Li−TMEDA, Me$_2$PCH(SiMe$_3$)$_2$Li−TMEDA, Me$_2$PC(SiMe$_3$)$_2$Li, and (Me$_3$P)$_2$CI−THF. A 9-membered ring cyclic trimer (19) and a 12-membered cheletated open tetramer of (2-(Me$_3$NCH$_2$)C$_6$H$_4$)$_2$PCH$_2$Li are also known.

### 2.3.15. Lithio Phosphine Oxides

Like enolates, sulfides, and sulfones, lithiated phosphine oxides, phosphonamides, and phosphonates, 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. Solution structures appear to be similar.

The related phosphine imines (phosphazenes) tend to have both N and C coordinated to Li in monomeric, dimeric (110), or open tetramer (111) structures.

### 2.3.16. Lithiated Silanes

Lithiated silanes follow the structural pattern of hindered alkylithium reagents. Thus, Me$_3$SiCH$_2$Li has crystallized as an unsolvated hexamer, a tetrameric bis-Et$_2$O complex, and a four-center dimer complexed to DME$_2$TMEDA, Me$_2$NCH$_2$CH$_2$OMe, and sparteine. A monomeric PMDTA complex is also known. In cyclohexane solution Me$_3$SiCH$_2$Li is a hexamer and in benzene a tetramer, with higher aggregates appearing at molar concentration. As usual, cheletated, 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.

A variety of lithiosilanes with an additional anion-stabilizing group, such as R$_3$Si (115a, 116a, 116b, 118), PhS (115b, 119a, 117, 116b, 119b, 118), and PhSe (115c, 119b), 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 (Ph$_2$S)$_2$(PhMe$_2$Si)CLi, are SIPs in THF solution and have quite high barriers to enantiomerization as a result of high rotation barriers. Lithium reagents with three silyl groups on the anionic carbon form several unusual structures as a result of extreme steric effects. Most notably, (Me$_2$Si)$_2$CLi is a mixture of the SIP, the CIP, and the triple ion in THF solution (see section 3.5.3). X-ray structures of (PhMe$_2$Si)$_2$CLi show a mono-THF-solvated monomer and (MeOMe$_2$Si)$_2$CLi, a complex eight-ring cyclic dimer in the solid state.

Table 1 summarizes the aggregation states of representative simple lithium reagents in hydrocarbon, Et$_2$O, 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 form and that they might well play crucial roles in the chemistry. Indeed, early workers noticed significant reduction in reactivity of n-BuLi when LiBr or LiCl was present. 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, a mixture of MeLi and Li was observed, left over from formation of Mel from MeLi, later shown to be (MeLi)$_2$ (Li)$_3$. 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 profiles) 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-BuLi solutions will almost invariably contain small amounts of the mixed tetramer (n-BuLi)$_2$ (n-BuOLi)$_2$ from reaction with oxygen. See Figure 7 for $^1$H NMR spectra of n-BuLi and the mixed alkoxides formed when n-BuOH is added to n-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
Review

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

<table>
<thead>
<tr>
<th>RLi</th>
<th>hydrocarbon</th>
<th>Et₂O</th>
<th>THF</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeLi</td>
<td>4ᵢ₀</td>
<td>4ᵢ</td>
<td></td>
</tr>
<tr>
<td>EtLi</td>
<td>9/8/6ᵢ</td>
<td>4ᵢ</td>
<td></td>
</tr>
<tr>
<td>PrLi</td>
<td>9/8/6ᵢ</td>
<td>4ᵢ</td>
<td></td>
</tr>
<tr>
<td>n-BuLi</td>
<td>9/8/6ᵢ</td>
<td>4ᵢ</td>
<td></td>
</tr>
<tr>
<td>i-PrLi</td>
<td>6/4ᵢ</td>
<td>4½ᵢ</td>
<td></td>
</tr>
<tr>
<td>s-BuLi</td>
<td>6/4ᵢ</td>
<td>4½ᵢ</td>
<td></td>
</tr>
<tr>
<td>t-BuLi</td>
<td>4ᵢ⁽²⁾</td>
<td>2ᵢ</td>
<td></td>
</tr>
<tr>
<td>Me₂SiCH₂Li</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PhSiCH₂Li</td>
<td>1ᵢ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₃=C=CHLi</td>
<td>4/2ᵢ⁽²⁾</td>
<td>1½ᵢ</td>
<td></td>
</tr>
<tr>
<td>PhLi</td>
<td>4/2ᵢ⁽²⁾</td>
<td>2½ᵢ</td>
<td></td>
</tr>
<tr>
<td>PhC≡C≡ClLi</td>
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<td></td>
</tr>
<tr>
<td>t-BuC≡C≡ClLi</td>
<td>4/2ᵢ⁽²⁾</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c-PrC≡C≡ClLi</td>
<td>4/2ᵢ⁽²⁾</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me₂SiC≡C≡ClLi</td>
<td>2ᵢ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PhSiO₂C≡C≡ClLi</td>
<td>1½ᵢ</td>
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<td></td>
</tr>
<tr>
<td>AllylLi</td>
<td>&gt;10⁻⁷</td>
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<td></td>
</tr>
<tr>
<td>BuLi</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>H₂C≡C≡CHLi</td>
<td>2½ᵢ⁽²⁾</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

The interconversion of organolithium aggregates in ether solvents is typically not or cannot be distinguished. A dramatic well-characterized example is provided by the LiCl-catalyzed dissociation of LDA which comes into play for reactions at the Curtin–Hammett borderline. 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. 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 LDA 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). Less reliable is the coalescence of C–Li coupling, 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 (MeLi)₄ with Me₂AlLi or with mixed halide complexes. The n-BuLi tetramer—dimer exchange has barriers near 10 kcal/mol, measured by DNMR methods. Although analysis of the concentration dependence suggested that the exchange might proceed by an associative process, the very similar values obtained by an unambiguous method, the rate of reaction of (n-BuLi)₄ by RINMR under conditions where dissociation is the rate-determining step, show that the DNMR experiments were also measuring dissociation.

The PhLi tetramer—dimer exchange in Et₂O has a ΔG° of 10 kcal/mol at −84 °C, and the dimer—monomer exchange in THF is around 8 kcal/mol at −93 °C. Other dimer dissociations in THF have quite variable free energy barriers, ranging from 7.0 kcal/mol for 4-methyl-2-lithiothiophene (74) to 9.4 kcal/mol for [2-[2-(dimethylamino)ethyl]-phenyl]lithium and ≥12.5 kcal/mol for [2-[(dimethylamino)methyl]phenyl]lithium (21). From the reported data, 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.

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. The tetramers of 4-fluorocarboxophenone lithium enolate dissociate to dimers with a barrier of ca. 16 kcal/mol.

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° 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-BuLi with 4-methylthioacetophenone in benzene (see section 3.5.1 for details). Similarly, fast kinetic studies by Holm of n-BuLi reactions with methyl trifluoracetate (see section 3.5.5) and PhCN (see section 3.5.8) were probably under the Curtin—Hammett limit. The RINMR technique, pioneered by McGarrity and Ogle, allows study of some organolithium aggregates below the Curtin—Hammett lines.

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 (ΔG° < 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 dynamics. The first observations involved hindered lithium amides: exchange between free and coordinated ethers in disolvated bis(trimethylsilyl)amide 120 (ΔG° = 8.6 kcal/mol for Et₂O, ΔG° = 10.8 kcal/mol for THF) and in monosolvated 121 (slow at −80 °C, ΔG° = 8.5 kcal/mol for Et₂O, ΔG° = 10.9 kcal/mol for THF).

For organolithium reagents, the first observation in ether solvents was the detection of diastereomeric solvates and a slow exchange between Me₂O and other solvents in 122 (ΔG° = 6.5 kcal/mol). Two different coordinated THF signals were observed in the mixed aggregate 123 below −90 °C. Slow exchange between coordinated and free solvent has been observed for the hindered vinyl lithium reagent 15. 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, PDMTA, 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. In enolate complexes the barrier for PDMTA 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.  

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.\textsuperscript{314} Two such barriers have been measured for lithium species by NMR coalescence, the interconversion between the CIP and SIP of \([\text{bis}[3,5-bis(trifluoromethyl)phenyl][thio]methyl]lithium with \(\Delta G^\ddagger = 5.3\) kcal/mol and that of \((\text{Me}_3\text{Si})_3\text{CLi}\) in THF−Me_3O mixtures with \(\Delta G^\ddagger = 9.6\) kcal/mol.\textsuperscript{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-diphénylëthylene in benzene at 30 °C, dimeric menthyllithium (Q188) is at least 70 times as reactive as tetrameric s-BuLi,\textsuperscript{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.\textsuperscript{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,\textsuperscript{7} 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 benzylithium species. Indeed, the first reported example of a metalation, that of fluorene by ethyllithium in 1928, was of this type.\textsuperscript{821} In 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]\textsuperscript{322a} 0.18-order in [n-BuLi],\textsuperscript{322c} and 0.28-order in [t-BuLi].\textsuperscript{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 aggregate 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.\textsuperscript{323} An alternative explanation, extensively explored by Klumpp and co-workers involves complex formation between RLi and the substrate.\textsuperscript{14,295} Such complexes have been observed in the solid state.\textsuperscript{121b} If the substrate first forms a complex with RLi with a significant association constant\textsuperscript{121b} 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 \(K_{eq}\).

In a very extensive series of studies on the metalation of triphenylmethine 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.\textsuperscript{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 triphenylmethine 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 Ph₂CH in THF with n-BuLi (a very difficult experiment because of the high rates) gave orders of 0.25 and 0.53 in [n-BuLi]. The latter value seems much more consistent with what is now known about n-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. These researchers also measured the activation parameters, which gave $\Delta G^{\ddagger} = 20.6$ 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. $\Delta S^{T}$ for tetramer dissociation to dimer in THF was reported by DNMR methods to be $-31.3$ eu and $-7$ eu and by RINMR to be $-7.6$ eu.

Metalation of Ph₂CH in THF was found to be have an order of 0.28 in [MeLi] (tetramer) and 0.24 in [vinyl lithium] (largely tetramer in THF, with about 10% dimer at 1.6 M). 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 and several enolates, so dissociation of tetrarner to monomers in ether solvents is not unreasonable.

Phenyllithium gave an order of 0.64 in reaction with Ph₂CH, consistent with later findings that PhLi was a mixture of dimer and monomer in THF (Figure 5). The fractional order and other kinetic behavior of PhLi in THF were fitted to a monomer–dimer $K_{MD} = |D|/|M|^2 = 100$ M⁻¹ at 25 °C. This is in modest agreement with values later found of 30 M⁻¹ at −109 °C by cryoscopy and 40 M⁻¹ by NMR spectroscopy at −75 °C. According to their analysis, PhLi dimer is 17 times as reactive as monomer, 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 [BnLi]. Since BnLi is nonmoneric 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-BuLi, both mainly tetrarners. The reaction of allyllithium with Ph₂CH in THF is also first-order in [RLi]. The aggregation state of allyllithium in THF has been examined several times. Vapor pressure osmometry gave values of ca. 1.3. Later cryoscopic measurements indicated that it was dimeric, so possibly the dimer is the reactive species in this metalation. Allicy organometallics generally show very special reactivity because the anionic carbon is not necessarily blocked by the metal.

### 3.3.2. Allylic and Benzyllic Metalations.

Side chain metalations of aromatic compounds and allicy metalations have an extensive history as routes to synthetically valuable RLi species.

A mechanistic study was performed of the metalation of the allylamine 124 to form 125 in toluene using the n-BuLi–sparteine complex, whose structure was not determined, but is likely a biscomplexed dimer, (n-BuLi)$_2$ (sparteine)$_2$, judging from several X-ray structures of related compounds determined subsequently. The metalation reaction shows a large isotope effect ($k_{H}/k_{D} = 86$ at −75 °C) and is first-order in [124] and zeroth-order in [n-BuLi–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 n-BuLi–sparteine complex. An unusual and interesting feature of this deprotonation is that it is strongly inhibited by an excess of n-BuLi over the amount of sparteine. There must be competitive complexation of free nBuLi with 124 to form an unreactive complex with $K_{eq}$ larger than the n-BuLi–sparteine $K_{eq}$ and indeed, it was confirmed that n-BuLi formed such a complex, but did not significantly metalate the substrate under these conditions.

The vinylthium 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.

In t-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-BuOMe-solvated dimer at 30 °C. The data also showed that 85 is ca. 60 times as reactive as vinylthium (mainly tetramer) in this solvent and that n-BuLi (mixture of dimer and tetramer) is only 7 times as reactive as 85. The reactive aggregate in each of these comparisons is unknown.

The kinetic product of the metalation of the aminophosphine 126 is the benzylthium reagent 127, which is a dimer in the solid state and retains the dimer structure in toluene solution. This compound rearranges to the more stable (phosphinomethyl)liothium 128 in toluene above room temperature. The rearrangement is first-order in [127] 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. A very detailed NMR study was carried out of the metalation of the N-benzylphosphinamide 129 with s-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 benzylthium 58, which cyclized reversibly to four diaster-
3.3.3. Dipole-Stabilized Metalations. During metatation 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 metatation 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. Only one rather complicated mechanistic scenario was found that fit all the rate data for this metatation. The s-BuLi tetramer becomes progressively complexed to 1–3 molecules of the amide, with each association constant smaller than the previous one (Kₒ = 50 M⁻¹ for [s-BuLi]₁[133]/[(s-BuLi)₂[133]], Kₒ = 2000 M⁻³ for [s-BuLi]₂[133]/[(s-BuLi)₃[133]], but with each complex having progressively higher reactivity (k = 0.001–15 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. A crystal structure of the monoetherate was later obtained. A kinetic study of the metatation of N-Boc-pyrrolidine showed that the metatation was essentially zeroth-order (<0.20) in the [RLi] complex, consistent with near-quantitative precomplex formation (Kₒ > 300 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. Details of the deprotonation are unknown, but an open dimer transition state was suggested, consistent with other reactions which have been more completely characterized and the results of high-level computations.

3.3.4. Silane Metalation. In an NMR study with some qualitative rate observations, Thomas showed that addition of MeOSiMe₃ to (i-BuLi)₄ in cyclopentane resulted in partial conversion to the alkoxy-complexed dimer (i-BuLi)₂((MeO-SiMe₃)₂). This was fully characterized by ¹H, ⁷Li, and ¹³C NMR (the two species were in slow exchange at −90 °C). Metatation of the SiCH₃ group proceeded at −60 °C over a period of hours to form a mixed tetramer, (i-BuLi)₃((MeOMe₂SiCH₃)Li)₇, also characterized by NMR spectroscopy. As this tetramer builds up and the dimer is depleted, the rate of metatation 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 metatation reactions to "stall out" or at least slow down has been observed repeatedly 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 metatation 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. Although the dimer is too reactive to measure directly (τ₁/₂ < 1 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 k₁/k₀ 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)₂ with (trimethylsilyl)acetylene was zeroth-order in [acetylene] and from the rate of deprotonation of deuterated (trimethylsilyl)acetylene (which had a half-life of several seconds) and from the isotope effect k₁/k₀ 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).
reactive acetylenes were examined, and (phenylthio)acetylene was found to react with \((n\text{-BuLi})_2\) slightly faster than dissociation to dimers. From a series of competition experiments, the (phenylthio)acetylene rate with \((n\text{-BuLi})_2\) could be measured, leading to an estimate that \((n\text{-BuLi})_2\) is \(3 \times 10^6\) times as reactive as \((n\text{-BuLi})_4\) in this deprotonation (Figure 10).258

A more limited study of the deprotonation of several acetylenes with the aryllithium reagent 119 showed similar 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 \(-135\ ^\circ\text{C}\) (\(\Delta G^\circ = 7.2 \text{ kcal/mol}\)) and certainly on any time scale currently achievable by RINMR (the practical lower limit on \(\Delta G^\circ\) on a 5 s time scale at \(-130\ ^\circ\text{C}\) is about 8.6 kcal/mol). However, the interconversion of \((119)_4\) with the lower aggregates is much slower (\(\Delta G^\circ = 11.7 \text{ kcal/mol}\)). It was shown by extrapolations using the relatively acidic (phenylsulfonyl)acetylene that \((119)_4\) was at least \(10^{14}\) times as reactive as \((119)_2\) toward this acetylene, presuming that the monomer is the reactive species.239,258

3.3.6. Aromatic Ortho-Metalations. Among the most important applications of organolithium species in synthetic chemistry is the ortho-metalation reaction.316 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 or other additives, such as potassium alkoxides or lithium amonio-alkoxides.344 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 (\(X = \text{OMe}\)) with \(n\text{-BuLi}\) has been examined repeatedly.156,253,258 Much discussion has centered around the role of precomplexes and the CIPE effects, first suggested by Roberts and Curtin.58a Indeed, addition of anisole to hexameric \(n\text{-BuLi}\) in toluene solutions forms a tetrameric 1:1 complex, but no metalation occurs at room temperature. Addition of TMEDA forms the dimeric \(n\text{-BuLi}–\text{TMEDA}\) 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.146b Primary H/D isotope effects \((k_{\text{H}}/k_{\text{D}} = 2.5–3.5)\) 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 \((n\text{-BuLi})_2\) (TMEDA) 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 alkoxynaphthalenes provided a more detailed picture.334 The metalation in pentane showed first-order kinetics in \([(n\text{-BuLi})_2\text{TMEDA}]_2\) 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 effects, although internal lithiums in triple ions have been shown to be capable of forming chelates (see 72 and 3158).

1-Methoxynaphthalene (143) shows interesting selectivity in metalation at the 2- and 8-positions.339b,342 \(t\text{-BuLi}\) in hexane gave \(>99\%\) 8-metalation (144), whereas \(n\text{-BuLi}–\text{TMEDA}\) gave predominantly metalation at the 2-position (145). As with anisole, addition of 143 to solutions of \(n\text{-BuLi}–\text{TMEDA}\) formed a complex, but metalation did not occur. Addition of TMEDA freed 143, and metalation to give 145 occurred. A large isotope effect \(k_{\text{H}}/k_{\text{D}}\) 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 \((t\text{-BuLi})_4\) 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 \((t\text{-BuLi})_4\) 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, since the rate of interaggregate exchange for (t-BuLi)$_2$ has been estimated (this is presumably the rate of dissociation to dimers). Qualitatively, the metalation rates do seem to be comparable to the rates of t-BuLi dissociation.

In an NMR study of the metalation of the peri-position of naphthol with (n-BuLi)$_2$·(TMEDA)$_2$, in addition to the homodimers (n-BuLi)$_2$ and (1-naphthyl-OLi)$_2$, a 1:1 mixed aggregate was detected by NMR, shown to be (1-naphthoxide)·(n-BuLi)·(TMEDA), characterized by $J_{3Li}$, $J_{-Li}$ HOESY, and QC. 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-BuLi with the chiral lithium amide 146, an ortho-metalation was observed to form 147. The reaction was first-order in [n-BuLi] and showed saturation kinetics (an increase in [n-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-BuLi aggregate on 146.

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)-phenyl ether (148) in diethyl ether with n-BuLi, which cannot be pushed past 50% reaction. This was subsequently traced to the formation of a 2:2 mixed aggregate, 149 (X-ray structure), 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-BuLi, which does not form such mixed aggregates, performed a rapid and complete metalation.

An isotope effect study of the ortho-metalation of N$_2$N-disopropylbenzamide with s-BuLi−TMEDA in THF gave $k_{3H}/k_{3D} > 20$ both for the intramolecular (2-deuterio compound) and for the intermolecular (dideuterio vs dipropotio) competition. Thus, the deprotonation itself is rate limiting. Any precomplexes are formed reversibly.

A kinetic study of the metalation of a series of oxazolines by (n-BuLi)$_2$·(TMEDA)$_2$ in pentane gave first-order kinetics in the metalating agent and zeroth-order kinetics in excess [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.

Lithium diisopropylamide ortho-metalations of phenyl carbamates (e.g., 152) have also been subjected to detailed mechanistic investigation. 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 [THF], or in a reaction that was inhibited by excess LDA and second-order in [THF] and thus involved THF-assisted dissociation to the much more reactive monomer. Interestingly, in t-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.

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.

Related to these ortho-lithiatiations is an interesting observation on the behavior of aryl triflates. When 159 was treated with n-BuLi in THF (Li/Br exchange), the observed products were derived from the chlorobenzene 160. On the other hand, LDA deprotonation of 161 under the same conditions gave the
sulfonyl migrated product 162. Thus, different intermediates must be involved. The authors suggested that the aryllithium reagent gives benzene, 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. Such carbanion formed by deprotonation by an LDA triple ion) undergoes the reagent gives benzyne, but that the free aryl anion (perhaps as well. Such carbanion as well.359

3.3.7. Solvent Metalations. A persistent problem with the use of organolithium reagents is the tendency for the more aggressive alkyllithiums 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 Ph₃CH by n-BuLi in THF discussed above,324 it was observed that the formed Ph₃CLi decayed in a kinetically well behaved way in a reaction with the solvent. The process was strictly first-order in [Ph₃CLi]. 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-BuLi with THF at 25 °C, Corset and co-workers showed that the decomposition was first-order in [n-BuLi].361 They identified the three species formed during the reaction by vibrational signatures (using computed IR spectra) as the mixed dimer (BuLi)₁(CH₂═CHOLi)₃, 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, Kₙ,t = [T]/[D] ≥ 2 × 10⁶ 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 tetratomers were detected. An NMR study of acetaldehyde lithium enolate indicated a tetrameric structure.242b

Another reaction of n-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-BuLi] and showed an isotope effect kH/kD of 3–4, so a simple four-center unimolecular elimination within the aggregate was proposed. Deliberate addition of n-BuOLi caused small rate increases (a factor of 2 with 22% n-BuLi replaced by n-BuO Li).362

3.3.8. Miscellaneous Metalations. A detailed NMR investigation, including DOSY and 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-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-BuLi)₂(TMEDA)₂ was first-order in substrate and 0.5-order in (n-BuLi)₂. Similar results were found for (PhLi)₂(TMEDA)₂. The reaction was zeroth-order in excess TMEDA, so the reactive nucleophile was

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**Figure 11.** Mechanism of ortho-metalation of a fluorobenzenamide. Reprinted from ref 356. Copyright 2008 American Chemical Society.
A somewhat unusual metalation studied in some detail is the intramolecular proton transfer in the ferrocenophane 167. The solid-state structure was monomeric and had an exo-bonded lithium cation. This was also the solution structure in ether, 2,5-dimethyltetrahydrofuran, and THF. DNP studies of the degenerate proton transfer showed a modest isotope effect ($k_{\text{H}}/k_{\text{D}} = 7.4$ at 320 K) and a significant Saunders isotope perturbation in the monodeuterio compound. The solvent dependence (proton transfer was 4000 times as fast in THF as in Me$_2$THF) 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 $\alpha$-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 $\beta$-lithiation. Careful NMR investigation of the natural abundance as well as the doubly $^{13}$C-enriched compound showed that 168 was a mixture of monomer and four stereoisomeric dimers (presumably diastereomers at carbon as well as chelation isomers).

The deuteration of styrene oxide with s-BuLi in THF gave solutions of the $\alpha$-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 $\beta$-lithiation. Careful NMR investigation of the natural abundance as well as the doubly $^{13}$C-enriched compound showed that 168 was a mixture of monomer and four stereoisomeric dimers (presumably diastereomers at carbon as well as chelation isomers).

The metation 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, configurationally isomerization of 169 was rapid.

Metation of related aziridines has also been studied. trans-1,2-Diphenyl-N-propylaziridine is metalted 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.

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 2.05-order in [172]. Thus, the isomerization mechanism involves a pre-equilibrium dissociation of (172)$_2$ to the monomer, followed by proton transfer to form 173.

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 $\pm 50$ °C (alkylation with Mel increases by a factor of 7500). The reaction was first-order in [enolate] and zeroth-order in excess [HMPA]. 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)$_4$.

### 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 polysisoprene. The studies related to polymerization are not in the scope of this review, nor are those whose primary focus is the synthetic aspects of the reaction. 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–Et$_2$O) 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. These effects are illustrated in the tandem cyclization of the lithium reagent 176 to form 177 and then 178.

Alkylolithiums, aryllithiums, and vinylolithiums undergo such cyclizations. The mechanism of these reactions has been minimally investigated. Activation parameters for the cyclization in pentane–Et$_2$O solution of 174 ($\Delta H^\ddagger = 11.8$ kcal/mol, $\Delta S^\ddagger = -30$ eu) and a related acetylene ($\Delta H^\ddagger = 23.0$ kcal/mol, $\Delta S^\ddagger = 4.8$ eu) have been

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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 stereoechemical preferences support the intervention of lithium-alkene complexes as intermediates, and such complexation has been experimentally detected in a noncyclizing system. The substituted hexenyllithium cyclizes to the products (E)-180 and (Z)-180 in an 11.7:1 ratio, suggesting the ordered transition state shown.

\[ \text{MoLi} \rightarrow \text{MeLi} + \text{Li} \rightarrow \text{MeLi} \rightarrow \text{Li} \]

Except for additions to ethylene (section 3.4.4), intramolecular additions to double bonds are usually successful only with alkenes bearing activating substituents such as vinyl, aryl, thio, or silyl, 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. 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.

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

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 °C in pentane- Et₃O before retrocarbolithiation to the homoallyl system occurs. The equilibrium can be moved entirely to the side of the cyclopropyl system with suitable alkyl substitution, as in 184 (X-ray structure). 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.

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 R₃SnBr or MeI gave optically active products which showed that ring-opening had occurred with >90% retention of configuration at the lithiated carbon in 190. Duryllithio compounds were shown to be configurationally stable under these conditions.

3.4.2. Addition to Aromatic Rings. In favorable situations additions of organolithium reagents to suitably activated aromatic rings can be observed, including fullerenes and nanotubes.

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 [t-BuLi] was found. This was interpreted in terms of dissociation of the (t-BuLi), 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 later), 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, typically the benzyl anion then adds to additional styrene molecules to form a polymer. Alkylithium 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 [n-BuLi] and 0.11-order in [EtLi] and 0.25-order in [t-BuLi] all reasonably consistent with a monomer-based mechanism. In 4% Et₃O−benzene somewhat higher orders were found for EtLi (0.28), n-BuLi (0.5), and PhLi (0.4), probably better rationalized by dimer reactions, since both n-BuLi and PhLi are mostly tetrameric in Et₃O. 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. 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 °C, the orders in RLi were measured for benzylithium (1.1), allylithium (1), phenyllithium (0.66), vinyllithium (0.34), and methylolithium (0.27). The rates of the n-BuLi reaction were too fast for accurate measurements, but 0.4-order was estimated. Another study at −40 °C using a stopped-flow technique gave 0.5-order in n-BuLi. Except for allylithium, which is now believed to be dimeric in THF, 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, so the 0.4−0.5-order is appropriate. PhLi is monomer with some dimer (Figure 5), so 0.66-order could be consistent.
Vinylithium is mostly tetrameric, but with a significant fraction of dimer, 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 ethenylation occurred without added ethers, but Et$_2$O, THF, 1,4-dimethoxybutane, and triethylamine were all effective catalysts. In reactions with $>5$ equiv of Et$_2$O, the reaction with $s$-BuLi and $i$-PrLi was first-order in [ethylene], first-order in [RLi], and second-order in [Et$_2$O]. Thus, the principal aggregate (tetramer) was the reactive one, and the transition state has two more molecules of Et$_2$O than the prevailing solvated form. Unfortunately, the degree of solvation with Et$_2$O was not known, but the level could be measured with Me$_2$O using vapor pressure measurements in heptane solution and was found to be a little above 2 (main species ($s$-BuLi)$_4$(Me$_2$O)$_2$). The authors hypothesize that the more hindered Et$_2$O perhaps forms only ($s$-BuLi)$_4$ (Et$_2$O)$_2$, and that the transition state consists of the trisolvated tetramer, coordinated to ethylene at the remaining vacant site: ($s$-BuLi)$_4$(Et$_2$O)$_2$CH$_2$=CH$_2$.

Alternatively, if Et$_2$O also dissolves ($s$-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, thus forming a nonreactive species (chelate, ether chelate, the bischelated dimers), tetrameric chelates, and aggregated lithium reagents, Klumpp et al. used internal coordinates here. Excess THF eventually blocked all four coordination sites vacated (presumably the ethylene coordination here). Excess THF eventually blocked all four lithium sites, requiring decoordination before carbometalation can occur.

However, $t$-Buli is now known to be dimeric in Et$_2$O and monomeric in THF, 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 tetrarners 193.

### 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.

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.

### 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]. 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 $k_{\text{obsd}}$ values between 20 and 100 s$^{-1}$ ($\Delta G^\ddagger$ of ca. 15 kcal/mol). Since the barrier for dissociation of (MeLi)$_4$ in Et$_2$O has been estimated at around 11 kcal/mol, it is probable that these experiments were under Curtin–Hammett conditions. The course of the reaction followed the rate law rate = [MeLi]$_{0.25}$[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)$_n$ which then continues to produce. However, no complex formation could be detected in the rapid-scan UV spectra used for the kinetic studies. Such complexes were detected in similar Grignard additions in Et$_2$O 305 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]. 299 The origin of these rate reductions is not known; a factor of 5 reduction in rate. The rate law was still 0.25-order observed with both LiBr and LiI. One equivalent of LiBr caused responsibility for the rate acceleration was slower than addition of 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 $\Delta G^\ddagger$ 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 cyclohexane, 165 which occurred well above $-25$ °C. Assuming a coalescence temperature of 0 °C, with $\gamma = 2.3$ Hz, we can estimate $\Delta G^\ddagger = 15.0$ 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)$_n$ with ketone (detected by IR), followed by addition, and (2) dissociation to (s-BuLi)$_n$ 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)$_n$ and a larger proportion of the reaction went through monomer pathway. 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 PhSCH$_2$Li 410c with benzophenones in ether at 0 °C. They found no detectable $^{13}$C-$^{12}$C kinetic isotope effect at the carbonyl group. Hammett correlations were also done and gave $\rho$ values from 0.17 to 0.26. This is in contrast to Grignard additions, which gave significant isotope effects and $\rho$ values of 0.5–0.9. The KIE and small $\rho$ values were considered as supporting a SET mechanism, although it is not clear why formation of a negatively charged radical anion should not have a substantial Hammett $\rho$. 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 $\rho$ 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 $\rho$ values. A Hammett study of the reaction of MeLi with benzophenones using carefully controlled continuous slow addition gave a $\rho$ 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 $\rho$ 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)$_3$ 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 stereoechemistry at the lithium center. The reaction of (S)-2-lithio-N-methylpyrrolidine (105, dimer in THF) 274 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. 313

Deuterium isotope effects have also been measured for the addition of alkyl lithium reagents CD$_3$Li and CH$_3$CD$_2$Li to ketones in Et$_2$O. 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 carbon anion 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. 314 However, a steric effect could also be the source of an isotope effect, where the smaller size of the CD$_3$ 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 CD₃Li than for CH₃Li 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 (β-silylmethyl)lithiums.][1]

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-tolyllithium 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 alkoxyde 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, ¹⁵N-, and ¹³C-enriched materials as the C₂-symmetric 2:2 adduct 206. This aggregate gave high levels of asymmetric induction in ketone additions.⁴¹³

### 3.5.2. Enones

Many studies of the addition of organolithium reagents to enones 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.

![Figure 207 and 208. Dimer: 1,4-addition and Monomer: 1,2-addition.][2]

A reinvestigation of this and other lithionitrile reactions 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.  

An interesting observation was made in 1979 by several researchers, \(^{421}\) 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 Et\(_2\)O 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 \(^{444}\) 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 enone 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 \(^{12}\)C/\(^{13}\)C, \(^{13}\)C/\(^{15}\)C, 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 \(\rho\) value of 0.18 and a \(^{12}\)C/\(^{13}\)C 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 Et\(_2\)O solution using competition experiments. \(^{424}\) No special precautions were reported for efficient mixing of the reagents. Taking into consideration the electrochemical properties of the reactants, they concluded that allyl-Li \((k_D/k_H = 1.095)\) reacted by an SET process, whereas MeLi \((k_D/k_H = 0.88)\) reacted by polar addition, as did PhLi \((k_D/k_H = 0.95)\). n-BuLi and t-BuLi showed \(k_D/k_H = 0.99\); 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 Ogle\(^{315}\) 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 \((n-BuLi)_4\) estimated by a factor of 10 (later shown to be a large underestimate \(^{238}\)), 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.

MacGarrity 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 \((n-BuLi)_2\) 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 20000 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, \(^{420}\) long the benchmark of aggregate relative reactivity, was presumably the result of operating too close to the “Curtin–Hammet 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.

Gajewski reported that in the competition experiments at 0 °C in THF, PhLi and t-BuLi showed \(k_D/k_H = 0.99\), and 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.

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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 °C (ΔG°,ν = 14.3 kcal/mol) and for 211C/S below −130 °C (ΔG°,ν = 9.6 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 °C, but that of 211T was quite slow (monomers were at least 107 as reactive as the triple ion at −130 °C) and showed some interesting properties. Solutions of pure 211T were prepared by scavenging the monomers 211S and 211C with Mel (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 (CF3-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-competes 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 1010 times as reactive as 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.505

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 Thermo-chemical 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 methylecyclohexane at −80 °C (half-life of 13 s) with the goal of applying the Eberson 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 pinacolinate 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 pinacolinate aldol reactions, including the interesting and well-supported conclusion that the accelerating effect of α-alkoxy substituents (acetone vs methoxacetone, 379X) 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 °C,238 it became possible to actually study the aldol process kinetically. The lithium enolate of 4-fluorocetophenone is a tetramer in THF, (214), with no other aggregates detectable by NMR spectroscopy.804 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.444 A tetrameric aldolate from pinacolone and pivaldehyde crystallizes from pentane.453

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When 4-fluoroacetophenone is deprotonated at −120 °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 ($214)_2$. 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 °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 $10^9$). 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).

A small Hammett $\sigma$ study was also done of the reaction of ($214)_4$ with benzaldehydes, giving a $\rho$ value of 4.0.

The Yamataka group has applied $^{12}$C/$^{13}$C kinetic isotope effects and a Hammett treatment to the reaction of pinacolone lithium enolate with benzaldehydes in THF at 0 °C. From the Hammett $\rho$ 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 n-BuLi. Unfortunately, both the enolate and lithionitrile aldol reactions were unobservable to react 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 catalyzes the rate of dissociation of LiN(LiOPh), 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 when dissociation is rate limiting.

### 3.5.5. Carboxylic Esters

The first kinetic study of an RLi–ester addition was by Holm, 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 Et$_2$O 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 $-28$ °C and 0.007 s$^{-1}$ at $-80$ °C, which gives a $\Delta G^\ddagger = 12.8$ kcal/mol. Reference to Figure 8 shows that the predicted barrier to (n-BuLi)$_4$ dissociation in 3:1 Me$_2$O–THF (a significantly more polar solvent than Et$_2$O) 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 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 Et$_2$O (reaction with ketone was also inhibited by LiBr and Li$^{299c}$), actually caused a rate increase (3 equiv of LiBr increased the rate 20-fold at $-80$ °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.

An IR stopped-flow kinetic study by the Smith group of the reaction of s-BuLi, n-BuLi, and c-pentylLi with several benzoate esters in cyclohexane at 25 °C showed exceedingly complex behavior, but gave several interesting results. An ester–(RLi)$_4$ complex was detected with modest $K_{eq}$ (27–138 M$^{-1}$ for s-BuLi with various esters). Ketone–(RLi)$_4$ 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.
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 $\text{p-}(\text{phenylsulfonyl})\text{isobutyrophene}$ (86c, a monomer–dimer mixture in THF) and $\text{p-phenylisobutyrophene}$ (86b, a monomer–tetramer mixture in THF) with benzoate esters is first-order in [ester]$^{325a}$. Surprisingly, in contrast to the ca. 10$^4$ higher reactivity of monomers compared to dimer or tetramer in alklylation reactions (section 3.8.1),$^{248,440}$ in the acylation process, (86b)$_t$ and (86b)$_u$ have nearly identical reactivity (for phenyl benzoate $k_{86b}/k_T$ 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; $k_{86b}/k_D$ rate ratios of at least 100 can be estimated for 86c. In contrast, benzoylprazole 222, where coordination analogous to that in 219 is plausible, gave a more modest $k_{86b}/k_D$ ratio of 5.8.$^{325c}$

\[ \begin{align*}
\text{219} & \quad \text{220} & \quad \text{221} & \quad \text{222}
\end{align*} \]

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 $k_{86b}/k_D$ 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 benzimidazoline 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 ($R = n-$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 $K_{d/t}$. The dimer was found to be 13 times as reactive as the tetramer. In dioxolane, where 223 is a mixture of tetramer and hexamer, 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 ($R = n-$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 n-fluorobenzoate with ($\text{p-}$fluorophenyl)lithium (monomer–dimer) shows measurable rates at $-110 \, ^\circ\text{C}$ in 1:3 THF–Me$_2$O. 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 $-90 \, ^\circ\text{C}$ to form ketone and then tertiary alcohol if any ArLi is left.

\[ \begin{align*}
\text{223–d} & \quad \text{224} & \quad \text{224–d} & \quad \text{223}
\end{align*} \]

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 ($t_{1/2} < 2 \, \text{s}$ at $-130 \, ^\circ\text{C}$). With N-methoxy-N-methylbenzamidine, 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 $^6\text{Li}$- and $^{13}$C-enriched lithium reagent, and kinetic study of the addition of lithium phenylacetylide to 227 in hexane–THF mixtures at $-50 \, ^\circ\text{C}$ 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].\textsuperscript{237} The initial phase of the reaction proceeded smoothly at \(-50\) °C to 50% conversion and then slowed down dramatically. This was traced to formation of a 2:2 mixed tetramer, \textsuperscript{228} with very reduced reactivity. At room temperature this species was slowly converted to the 3:1 mixed tetramer \textsuperscript{229}, which was still less reactive.

An interesting observation was made during studies of the reactivity of a series of electrophiles toward (n-BuLi), using RINMR. All common ones except for aldehydes and DMF are unreactive toward (n-BuLi),\textsuperscript{238} The reaction of (n-BuLi), with a benzoate ester in 1:3 THF−Me$_2$O had a \(t_{1/2}\) of 24 s at \(-131\) °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.\textsuperscript{301c,437}

3.5.7. Imines. The addition of nucleophiles to imines constitutes a major synthetic route for the preparation of amines.\textsuperscript{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 BF$_3$ to enhance reaction rates. In a study of the mechanism of the addition of lithium phenylacetylide to imine \textsuperscript{230} using n-Bu$_3$N-BF$_3$ as the catalyst, it was found that the reaction was first-order in [n-BuLi], first-order in \([n\text{-}Bu_3N\text{-}BF_3]\), zeroth-order in [acetylide], and zeroth-order in excess [n-Bu$_3$N]. Thus, the mechanism involves a rate-determining nucleophilic attack of the imine on boron to form the imine complex \textsuperscript{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 BF$_3$.\textsuperscript{446}

The addition of (n-BuLi)$_2$·(TMEDA)$_2$ and (PhLi)$_2$·(TMEDA)$_2$ in pentane to the aldime \textsuperscript{232} was first-order in substrate, 0.5-order in [(n-BuLi)$_2$], and zeroth-order in excess [TMEDA]. n-BuLi gave no detectable \(\alpha\)-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 \textsuperscript{233}. The effect of different dianimes on the rate was complex.\textsuperscript{563a}

Extension of these studies to an aldime, \textsuperscript{234}, with a potentially chelating group gave much more complicated behavior.\textsuperscript{563b} The addition rate of (n-BuLi)$_2$·(TMEDA)$_2$ to \textsuperscript{234} was about 1000 times faster than to the nonchelated model \textsuperscript{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-BuLi)$_2$·(TMEDA)$_2$ as the reactive RLi species. At low [TMEDA] the open dimer transition state \textsuperscript{236} (S = OEt$_2$) was implicated by an additional dependence on the concentration of added diethyl ether, which does not detectably complex to (n-BuLi)$_2$·(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-BuLi)$_2$·(TMEDA)$_2$·Solv.\textsuperscript{234}, suggesting the somewhat unusual octahedrally coordinated transition structure \textsuperscript{237}. Octahedral coordination of lithium is often seen in Li$^+$·(DME)$_2$ species,\textsuperscript{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 TMEDA and THF as the additional donor ligand (S = THP).\textsuperscript{563c}

A more complex imine addition involves reactions of lithium acetylides with quinazolone \textsuperscript{238} to form \textsuperscript{239}, a model study related to the synthesis of some promising antiviral drugs. Mixing lithium phenylacetylide with the lithium salt of the quinazolone produced two mixed aggregates, spectrscopically characterized as the dimer \textsuperscript{240} and a 2:2 ladder tetramer, \textsuperscript{241}. Under conditions where \textsuperscript{240} was the main quinazolone species, the reaction was first-order in \textsuperscript{240}, 0.5-order in excess [LiCCPh] (which is dimeric in THF solutions), and zeroth-order in [THF]. Thus, the conversion of \textsuperscript{240} to product is not an intramolecular transfer of carbanion to the electrophilic imine (a reasonable supposition), but rather involves attack of an external dissolved monomeric acetylide on \textsuperscript{240} (transition state \textsuperscript{242}).\textsuperscript{536}

3.5.8. Nitriles. An early kinetic study by Holm of the reaction of n-BuLi with benzonitrile in Et$_2$O at \(20\) °C gave an order of 0.33 in [n-BuLi],\textsuperscript{536} similar to studies of n-BuLi reactions with Ph$_2$CH\textsuperscript{227,524} and 1,1-diphenylethylene,\textsuperscript{502} even
although 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. 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° 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, making the dimer the active nucleophile in the exchange. 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 ΔG° = 12.8 kcal/mol, very similar to the substrate-independent rate with methyl trifluoracetate (see section 3.5.5). Therefore, here it appears that the rate-limiting step has also become dissociation of the (n-BuLi)₄.

A similar kinetic study of the reaction of PhLi with benzonitrile in Et₂O gave an order of 0.64 in [PhLi]. Since PhLi is now known to be a nearly 1:1 mixture of tetramer and dimer under the conditions of the experiment, 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. It is possible that here the increase in nucleophilicity in ArLi by an electron-donating substituent is smaller for substituted benzonitriles, giving a factor of 9 between 4-chloro- and 4-methylbenzonitrile.

### 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. We mention here an intriguing report of an unusual elimination of an amine. t-BuLi forms a monomeric complex, with trans-1,2-bis(diethylamino)-cyclohexane. On raising the temperature, ethylene is evolved, with an increase in nucleophilicity in ArLi by an electron-donating substituent.

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

The lithium–iodide, lithium–bromide (halophilic reactions), and related lithium–selenium, lithium–tellurium, and lithium–tin exchanges are the premier methods for the preparation of complex lithium reagents, especially vinyl- and aryllithiums, but also primary and even secondary alkylolithiums. 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, and even aldehydes. 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. Weinreb amides, isoanilides, and even anhydrides are 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 efforts have focused on the question of possible SET pathways and on the intermediacy of ate complex intermediates, as first suggested by Wittig. Although radical products are seen, and radicals can sometimes be detected during Li/I exchanges, 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 favorably cases be structurally characterized and spectroscopically characterized. Primary and secondary iodides with olefinic radical traps can be exchanged without any cyclization, and secondary alkyl iodides (as well as tellurides) 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, but aryl, vinyl, and cyclopropyl halides do not, by the stereochemical and/or cyclizable probe criteria.

One of the few 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 [L]. 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, 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 ΔG° = 23.3 kcal/mol and ΔS° = −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 insenstive to small additions of PhLi, LiBr, or n-BuOLi. A Hammett plot for a variety of bromobenzenes gave β = 2, with bromoanilines 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) mixtures with PhLi (Figure 13). At 1 equiv of metalloid, −exchanges are fast on the NMR time scale down to below accessible temperatures. Thus, both the Li/I and Li/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,M exchanges using several DNMR and classical exchange methods gave relative rates as follows (in THF extrapolated to 0 °C): I (10⁸), Te (10⁶), Sn (10³), Sb (1.7), Br (0.25), Se (0.025), Cl (10⁻⁶), S (10⁻⁹).475b

Ate complex intermediates could be spectroscopically characterized for the iodine (248),318,466a,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 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)₂ and Ph₂Li (248) at −105 °C are just past coalescence (κ_exch of ca. 600 s⁻¹), whereas those of (PhLi)₃ and Ph₃TeLi are just below coalescence (κ_exch of ca. 300 s⁻¹). Most interesting, the signals for (PhLi)₄ show no broadening, so the dimer exchanges with PhI much more slowly than the monomer.466b

As part of a detailed DNMR investigation of the degenerate exchange between the thiennyllithium 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 at least 10⁶ times as fast as for the 249/250 exchange at −2 °C (ΔΔG° 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,c,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).

3.8. Substitution (SN₂) Reactions

The utilization of simple alkyl lithium 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 SN2 reactions. Specifically, lithiodithianes and related S-, Si-, and P-substituted lithium reagents (often functioning as acyl anion equivalents),261,487,488 lithium enolates,240,426,486 lithium metal-oenamines,261,487 various substituted allyllithium reagents,488 EtLi.489

−5000 M

significantly a testament to the deep-seated energy transition state, ruling out SET processes as rate determining. It is the existence of a monomer that with enolates the aggregates seemed to be the reactive species, unlike many of the organolithium reactions studied up to that time (t-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 LiClO4 was added. This effect was attributed to the intervention of mixed tetraromers, 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 pKα 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)isobutyrophene (86c),492 he demonstrated the existence of a monomer−dimer equilibrium at 25 °C in THF, substantially favoring the dimer (KMD = [D]/[M]2 = 5000 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 (Kag = ([86c]−LiBr)/([86c]−LiBr) = 3600 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 (86c)−LiBr:(86c)−LiBr:(86c)−LiBr of 2700:7:1 at 25 °C.440 A similar mixed aggregate study of 86c with LiN(SiMe3)2 gave a smaller aggregation constant (Kagg = [86c]−LiN(SiMe3)2)/(86c)−LiN(SiMe3)2 = 760 M−1). Kinetic studies of the alkylation process showed that (86c)−LiN(SiMe3)2 was 100 times as reactive as 86c−LiN(SiMe3)2. Similar results were found for the 2-benzyltetralone 89.493

The enolates of 2-phenylcyclohexanone (255a; KMD = [D]/[M]2 = 2800 M−1),250a 2-phenyltetralone (88a; KMD = 1930 M−1), and 2,6-diphenyltetralone (88b; KMD = 2650 M−1) behaved analogously.248 For 88a, the KMD 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.

![Figure 14. Solvent effects on the reaction of benzyl chloride with EtLi.](image)

### 3.8.1. Ketone Enolates.

Because of their great synthetic importance, enolate alkylation 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 LiClO4 was added. This effect was attributed to the intervention of mixed tetraromers, analogous to the 3:1 enolate−LiCl tetramer which was well characterized.159

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![Figure 14. Solvent effects on the reaction of benzyl chloride with EtLi.](image)

The solution structure and reactivity of 2-biphenylylcyclohexanone (255b; KMD = 4300 M−1) were similar to those of the other dimers. Activation parameters were measured for reaction with m-chlorobenzyl bromide (ΔHf = 9.6 kcal/mol, ΔSf = −25.5 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-phenylisobutyrophene lithium enolate 86b, Streitwieser determined that this enolate was predominantly tetramer in THF, with measurable amounts of monomer at low concentrations.252b The alkylation kinetics gave no detectable contribution from reaction of the tetramer; all reaction occurred through the monomer. From the data presented kM is at least 20 times as large as kT. An interesting observation was that (86c)1 was slightly more reactive (a factor of 2.3) toward p-tert-butylbenzyl bromide than (86b)1, even though the latter is 1.2 pKα 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 isobutyrophene was ascribed to the different C:O selectivities of mixed aggregates formed between the enolate and LiOTs.240 Streitwieser stops short of endorsing this, since LiBP4, 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)$_2$). $^{806}$ This may signal an intervention of a 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 monoalkylated 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 ($K_{MD} = [D]/[M]^2 = 3800 \text{ M}^{-2}$). This translates into an equilibrium concentration of 0.001 M ($87$), whereas the enolate of the reaction is $89$ at 0.1 M enolate concentration. In addition, $89$ is 1.8 times as reactive as $87$, toward benzylic 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 PhSO$_2$CH$_2$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 penty1 phenyl sulfone is 20 times as reactive toward the starting enolate (which probably has the structure $86b$-(HMPA)$_2$). $^{806}$ This may signal an intervention of a 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.

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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 tetracoordinated tetramer, $^{10a}$ 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 norborneone enolate $256$ with allyl bromide. This stereoselective process could be rationalized by an initial alkylation of the tetrmeric 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 $\beta$-aminopropionate (93) (synthesis of the coronary drug omirabubon) 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 alkylation agent. $^{140}$

3.8.3. Lithiated Hydrazones. Lithiated cyclohexanone $N,N$-dimethylhydrazone $258$ is a tetramer in benzene–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. $^{397}$ 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 steric ally 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 \(-78^\circ\text{C}\). Moreover, it was shown that, even in THF, it was the tiny fraction of SIP that performed at least 10\(^8\) times as reactive as the CIP. Reaction via SIP for with primary alkyl halides at 0:100 at 25°C.

\[
\frac{k(\text{THF-HMPA})}{k(\text{THF})} = 140,000,000 \quad 7.900
\]

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(aryltithio)methyl]lithium 264, which was already 70% SIP in THF solution. The rate of alkylation of 264 with n-Bul or allyl-Cl was unaffected by addition of HMPA. Tying up the lithium cation as Li(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 \(-78^\circ\text{C}\) 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 \(-78^\circ\text{C}^\text{[96]}\)). Extensive spectroscopic studies\(^{99}\) and later X-ray structures\(^{126d}\) 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.

![Diagram of the reaction](Image)

### 3.8.6. SET Mechanism

The question of SET mechanisms also arises in S\(_2\)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 \(-100^\circ\text{C}^\text{[338]}\)), this means the monomer is the reactive species in a nucleophilic substitution at boron. Other mechanisms (borabenzene, 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.

![Diagram of the reaction](Image)

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 formed a 15.7:1 ratio of the A₂B₂ heterotetramer compared to the sum of the homodimers (A₄ + B₄), 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 A₂B₂ 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 organoselenium, 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 N,N-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 disopropylamide
M monomer
NOE nuclear Overhauser effect
PGSE pulse-gradient spin-echo NMR spectroscopy
QCC quadrupolar coupling constant \(^{7}\)Li NMR
RDS rate-determining step
RINMR rapid injection NMR
SET single-electron transfer
SIP solvent-separated ion pair
T tetraterm
TI triple ion

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