Mixed Aggregates of Organolithium Compounds

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Abstract: Most organic lithium compounds exist as aggregates. Many lithium compounds also form mixed aggregates with other lithium compounds, which have structures and properties that are different from either of the parent lithium compounds. Mixed aggregate formation can alter the product distribution and rate of reactions involving lithium dialkylamides.

Keywords: Organolithium, lithium amide, lithium enolate, mixed aggregates.

INTRODUCTION

Mixed aggregates are complexes between different lithium compounds with chemical properties that are different from those of either component. The changes in chemical properties may be minor, with reactivity of the mixed aggregate differing only slightly from that of the parent organolithium compound, or the mixed aggregate may cause major changes in chemical reactivity. The formation of mixed aggregates is often discovered by empirical observation of how changes in reaction conditions change the course of reactions. For example, the use of highly purified lithium reagents may yield a different product distribution than that obtained from reagents that have been exposed to small amounts of air, or from alkyllithium compounds that contain residual lithium halides. Many organic reactions are performed in the presence of lithium salts because the salts generate higher yields or purer products, although the mode of action remains unknown.

Mixed aggregates may be formed in a number of ways. Lithium salts or other organic lithium compounds may be intentionally added to the reaction mixture based on empirical observations of their effects on reactivity. This had been common practice even before the structure of mixed aggregates were known, and even today, lithium salts are commonly used in synthesis without a detailed understanding of mixed aggregate formation in the specific systems of interest. Mixed aggregates may be formed inadvertently from impurities in the reaction mixture. These include residual lithium halides formed in the preparation of alkyllithiums, lithium oxides and lithium hydroxide from exposure of alkyllithiums to small amounts of air, and the use of an excess of alkyllithium or lithium dialkylamide base in synthetic reactions. Finally, mixed aggregates may be formed during the course of a reaction from the newly formed lithium-containing products, such as a newly formed lithium enolate generated by lithium diisopropylamide (LDA). Several such lithium diaklylamide-lithium enolate mixed aggregates have been characterized, and often result in auto-catalysis, auto-inhibition, or changes in the course of enolization reactions as the reaction progresses. The preparation, structures, and applications of lithium mixed aggregates are described in the following sections. Common applications include polymer preparation, stereoselective synthesis, and changes in reaction rates caused by mixed aggregates.

Several techniques are central to the discovery and structure determination of mixed aggregates. As will be seen in the following sections, lithium NMR plays an important role. Lithium exists as about 93% ^{7}Li, and the remainder as ^{6}Li. Both nuclei are NMR active, but if spin coupling information is important to the study, ^{6}Li enriched material is usually used because of the smaller quadrupole moment. Spin coupling is readily observed between ^{6}Li and ^{13}C, ^{15}N, ^{31}P, and several other nuclei. Solvation is an important factor in determining the aggregation state of lithium compounds, including mixed aggregate formation. Lithium NMR can be used to determine the solvation state either by direct observation of lithium-heteroatom spin coupling, or by observation of additional lithium resonances as solvation breaks the symmetry of organolithium aggregates. Direct observation of solvent spin coupling to lithium requires an NMR active, non-quadrupolar nucleus of the heteroatom, and a slow ligand exchange on the NMR timescale. Hexamethylphosphoramide (HMPA) meets both of these requirements. The ^{31}P nucleus has a spin of 1/2, the coupling constants are large enough to be observed through two bonds (Li-O-P), and HMPA is strongly coordinated to lithium so that spin coupling is not lost through rapid ligand exchange. Thus, in addition to its role in altering the reactivity of organolithium compounds, HMPA has proven to be extremely useful in investigating the solvation of lithium compounds. The major disadvantage of HMPA is that it is highly carcinogenic and must be handled with extreme care.

When mixed aggregates are formed from lithium-containing reaction byproducts, they frequently cause changes in reaction rates. Therefore, kinetic rate law experiments are important tools for determining mixed aggregate formation. Mixed aggregates may either accelerate or retard organolithium reactions, and may sometimes change the reaction product distribution. A change in rate or product ratios during the course of a reaction is a strong indicator of mixed aggregate formation.

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X-ray crystallography allows for the direct observation of the structure of lithium compounds, including coordinating solvent ligands. Numerous x-ray crystal studies of solvated organolithium compounds have been reported. Crystalline solids often exhibit similar solvated structures to the same compounds in solution, but are subject to crystal packing forces in the solid state. Nevertheless, solid state structures are useful for determining the kinds of solvated structures that are possible for lithium compounds. A large number of mixed aggregates have been observed in the solid state, and these are often very similar to the mixed aggregates formed in solution.

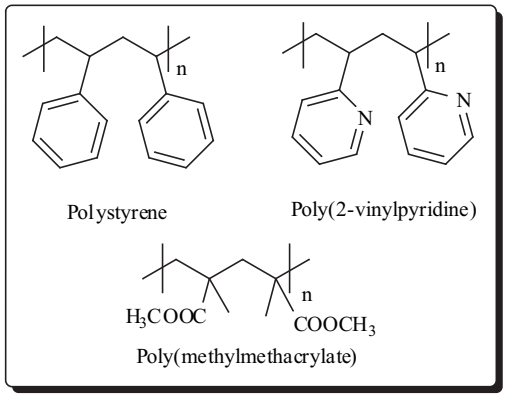
In recent years, computational methods have become increasingly important to the study of organolithium compounds. Major advances took place during the 1990's, with the development of modern semiempirical methods. These have been rendered largely obsolete by the development of faster computers and ab initio and density functional methods that can handle large molecules, including their solvating ligands. Numerous investigations of lithium mixed aggregates now use molecular modeling in conjunction with traditional experiments.

STRUCTURE AND APPLICATIONS OF MIXED AGGREGATES

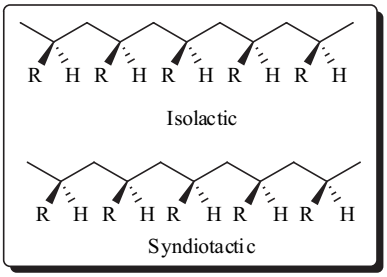
Anionic Polymerization

Polymerization of styrene, vinylpyridines, and related monomers by anionic methods is straightforward. These anionic polymerizations are generally living polymerizations, which have no chain termination steps, and polymerization can therefore be resumed by the addition of more monomer. This allows the formation of block copolymers by sequential addition of two or more monomers. Another important class of polymers is polyacrylates, which are difficult to polymerize by anionic methods because of competing side reactions at the carbonyl group. Nucleophilic addition-elimination reactions of the alkyllithium initiator with the acrylate monomer results in reduced initiator efficiency and consumption of monomer. Similar reactions can occur between the growing chain end and the newly formed polymer. This side reaction, known as back biting, terminates the growing chain and results in a low molecular weight polymer. These side reactions can be largely prevented by use of a sterically hindered initiator, and by performing the polymerizations in the presence of lithium chloride or lithium alkoxides.

Teyssie and coworkers found that lithium halides and lithium tetraphenylborate changed the rate of methyl methacrylate polymerization, and that lithium chloride was most effective in suppressing the side reactions, leading to a living polymer [1]. A large excess of lithium chloride (>10 equivalents) was most effective in controlling side reactions. A lithium-7 and carbon-13 NMR investigation revealed that at least two different mixed aggregates were formed between lithium chloride and methyl-α-lithioisobutyrate (MIB), which served as a model compound for the growing PMMA chain end [2]. At up to one equivalent of lithium chloride, a 1:1 mixed dimer was formed, and 2:1 and possibly 3:1 mixed aggregates were formed at higher lithium chloride concentrations. In contrast, the chain end in the absence of



lithium salts is believed to be largely aggregated, as a mixture of dimers and tetramers were observed with the methyl-α-lithioisobutyrate model compound [3]. Addition of lithium t-butoxide in place of lithium chloride also resulted in a living polymerization, but unlike lithium chloride, lithium t-butoxide formed three different mixed tetramers (MIB_3Li_4Ot-Bu, MIB_2Li_4Ot-Bu_2, and $MIBLi_4Ot$-Bu_3) in equilibrium with each other even at low lithium alkoxide concentrations [4, 5]. When the polymerization was performed in a 9:1 mixture of toluene and THF, the polymerization stereochemistry was also affected by the choice of mixed aggregate, with lithium chloride favoring the syndiotactic (rr) diads, and lithium t-butoxide favoring the isotactic (mm) diads [4].

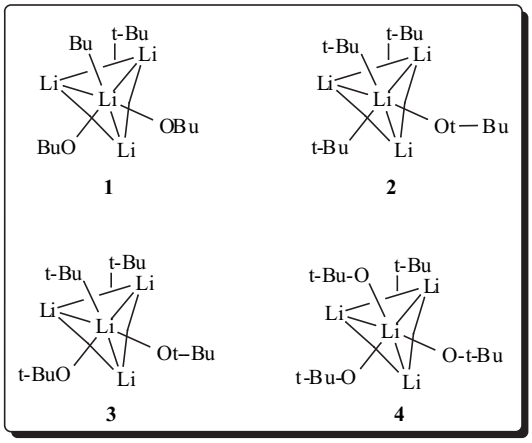


The chelating lithium alkoxide, Lithium 2-(2-methoxyethoxy)ethoxide (LiOEEM) also promotes living polymerization of acrylates and methacrylates, and has been found to be superior to lithium t-butoxide for the preparation of block copolymers [6-9]. Lithium-7 and carbon-13 NMR spectra indicated the formation of a Li-MIB -$(LiOEEM)_2$ mixed trimer, believed to be similar to the LiOEEM mixed aggregate with the chain end [10]. A computational study by Yakimansky and Muller predicted the formation of two different mixed tetramers between methyl-α-lithioisobutyrate and lithium 2-methoxyethoxide (LiMEO), consisting of Li-MIB-$(LiMEO)_5$ and Li-MIB_2-$(LiMEO)_4$ [11]. These calculations neglected the effects of coordinated THF solvent molecules, which frequently result in the formation of lower aggregates.

Mixed aggregates between the anionic chain end of acrylate polymers and lithium halides or alkoxides tend to limit or eliminate side reactions with the carbonyl group. The result is a living polymerization with polydispersities in the range of 1.1 to 1.2. In several cases, block copolymers can be prepared by the addition of a second monomer after the first monomer is consumed. The mechanistic details of the mixed aggregate reactions have not yet been elucidated.

Alkyllithium-Lithium Alkoxide, Alkyllithium-Lithium Amide, and Related Mixed Aggregates

Among the first mixed aggregates to be discovered were those arising from the exposure of alkyllithiums to oxygen. Alkyllithium compounds react with oxygen to form alkyllithium peroxides, which further decompose to lithium alkoxides. Seitz and Brown reported the formation of lithium ethoxide mixed aggregates with methyllithium and ethyllithium, [12]. and several other investigators reported the formation of similar mixed aggregates [13, 14]. The reactivity of the mixed tetramer $Bu_2Li_4(OBu)_2$ (**1**) toward benzaldehyde was similar to the butyllithium dimer, and both species were more reactive than the butyllithium tetramer [15]. Butyllithium mixed aggregates with lithium t-butoxide have been employed for the preparation of isotactic polystyrene, and it is believed that the lithium t-butoxide forms mixed aggregates with the growing chain end [16]. An unusual propyllithium-lithium propoxide mixed aggregate has been reported, $(n\text{-}Pr)_8(n\text{-}OPr)_4Li_{12}$, in which the alkyl groups are bonded to trigonal faces and the alkoxide groups are bonded to square faces of a cuboctahedron [17].

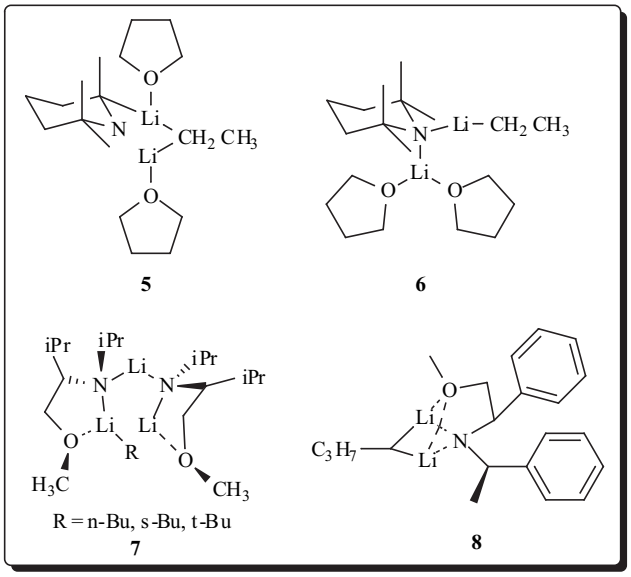


Mass spectrometry experiments have shown the existence of t-butyllithium mixed aggregates with lithium t-butoxide in the gas phase [18]. The mixed species included $Li_4(t\text{-}Bu)_3(O\text{-}t\text{-}Bu)$ (**2**), $Li_4(t\text{-}Bu)_2(O\text{-}t\text{-}Bu)_2$ (**3**), and $Li_4(t\text{-}Bu)(O\text{-}t\text{-}Bu)_3$ (**4**) mixed tetramers. Mixed tetramers of t-butyllithium with lithium t-butoxide and lithium ethoxide of the type $(t\text{-}Bu)_3Li_4(O\text{-}t\text{-}Bu)$ have been observed in hydrocarbon solutions by ^6Li and ^{13}C NMR [19, 20]. In addition, several t-butyllithium-lithium t-butoxide mixed hexamers were observed, including $(t\text{-}Bu)Li_6(t\text{-}OBu)_5$ and two diastereomeric forms of $(t\text{-}Bu)_2Li_6(t\text{-}OBu)_4$ [21]. Decomposition products of these mixed aggregates included lithium hydride-lithium t-butoxide mixed aggregates with the structures $(t\text{-}BuO)_9Li_{10}H$ and $(t\text{-}BuO)_{11}Li_{12}H$. These mixed aggregates were soluble in hydrocarbon solvents and reportedly more reactive than commercially available lithium hydride [22]. A butyllithium-lithium 2-(N,N-dimethylamino)ethoxide has been described as a unimetal "superbase", and has been used for the directed lithiation of pyridines [23]

Mixed aggregates between alkyllithiums and chiral lithium alkoxides have been used in asymmetric additions of alkyllithiums to aldehydes [24, 25]. Addition of butyllithium to benzaldehyde occurred with up to 95% enantiomeric excess in the presence of the lithium salt of (2S,2'S)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine. The enantiomeric excess was strongly dependent on the chiral alkoxide and the solvent, and enantioselectivity was reduced by the addition of lithium chloride or lithium perchlorate, suggesting the competitive formation of achiral mixed aggregates with those salts. Similar asymmetric induction was observed in mixed aggregates resulting from the reaction product of the lithium salt of (R)-1-phenyl-1-propanol-d_1 with benzaldehyde. Thus, the formation of an alkyllithium mixed aggregate with the chiral alkoxide reaction product resulted in a change in the enantioselectivity as the reaction progressed [26]. The use of chiral lithium alkoxides resulted in a modest improvement in the enantioselectivity and diastereoselectivity of Aldol reactions of several lithium enolates [27]. This improved stereoselectivity was attributed to the formation of mixed aggregates.

Alkyllithiums and aryllithiums also form mixed aggregates with lithium dialkylamides. Lithium tetramethylpiperidide (LiTMP) forms a mixed dimer with phenyllithium [28] and with ethyllithium [29, 30]. The ^6Li and ^{15}N NMR spectra are consistent with either a mixed cyclic dimer, (**5**) in which the LiTMP ring flip is slow on the NMR timescale, or a mixed open dimer. (**6**) Ab initio calculations showed that the mixed cyclic dimer is the most stable of the two structures, although the existence of the mixed open dimer as a reactive intermediate cannot be ruled out. The analogous LiTMP mixed aggregate with butyllithium was shown to improve the stereoselectivity of 3-pentanone enolization, producing up to 97% of the E diastereomer. Although the mechanism for this stereoselectivity is not yet known, it appears that the LiTMP-butyllithium mixed aggregate competitively inhibits the formation of LiTMP-enolate mixed aggregates, which are less stereoselective than LiTMP alone. Ethyllithium forms a similar mixed cyclic dimer with lithium diadamantylamide, as determined from ^6Li and ^{15}N NMR experiments [31]. A crystal structure of a more complex mixed aggregate between butyllithium and lithium diphenylamide has also been reported, in which one of the diphenylamine molecules has been lithiated on both the nitrogen and on the benzene ring, producing the structure $2(Ph_2NLi)[Ph(C_4H_4Li)NLi]_2(n\text{-}BuLi)_2(Et_2O)_4$ [32]

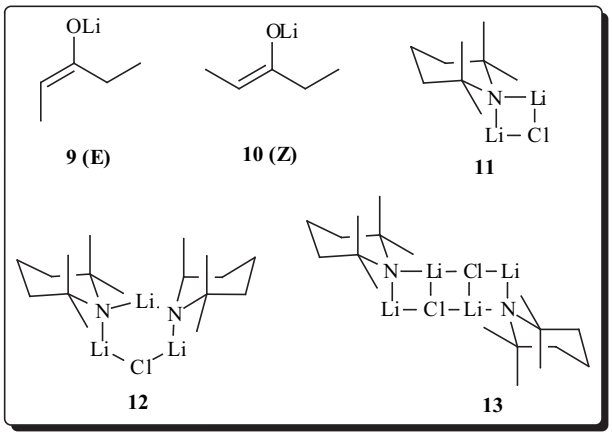
Mixed aggregates between alkyllithiums and chiral lithium amides have been observed in crystal structures. The lithium amide of N-isopropyl-O-methylvalinol formed mixed trimers containing two molecules of the lithium amide and one molecule of n-butyllithium, s-butyllithium, or t-butyllithium [33] (**7**) Butyllithium was found to enantioselectively add to benzaldehyde in the presence of chiral lithium amides [34]. The chiral lithium amide lithium-(2-methoxy-(R)-1-phenylethyl)-((S)-1-phenylethyl)amide (**8**) was shown by ^1H and ^6Li NMR studies to form a mixed dimer, which was in equilibrium with the lithium amide and butyllithium [35]. The position of the equilibrium was solvent and concentration dependent, with hydrocarbon solvents favoring free butyllithium and lithium amide. Free butyllithium reacted with benzaldehyde faster than the mixed aggregate, and the solvent effect on the enantioselectivity was attributed to this equilibrium.



5 **6** **7** **8**

Lithium Dialkylamide Mixed Aggregates With Lithium Enolates and Lithium Halides

The problem of stereoselective and regioselective deprotonation of carbonyl compounds is a major one in organic synthesis, and the dependency of selectivity on reaction conditions has been appreciated since the 1960's [36]. Strong bases such as lithium dialkylamides are often used for this purpose to avoid equilibration between the isomeric enolates. With very hindered lithium dialkylamides, however, deprotonation may be slow enough to allow some enolate equilibration. To prevent this, Corey and Gross performed the enolization of 3-pentanone in the presence of chlorotrimethylsilane (TMSCl) to trap the enolate as it was formed [37]. In several cases this internal quench generated different E (**9**)/Z (**10**) ratios than quenching after completion of the reaction, particularly when HMPA was added to the THF solution as a cosolvent. The change in stereoselectivity was attributed to the prevention of equilibration between stereoisomers that would lead to the more stable Z enolate. Other investigations suggested an alternate explanation, in which the reactive species changed during the course of the reaction. Xie and Saunders found that equilibration between the 2-pentanone enolates is slow at temperatures below -40 ^{o}C, and isotopic labeling experiments suggested the presence of more than one reactive base in the reaction mixture [38]. Suspecting that the LiCl byproduct of the TMSCl internal quench might influence the ratio of stereoisomers, Collum and coworkers performed stereoselectivity [39]. and lithium NMR [40, 41]. studies on mixtures of LiTMP in the presence of lithium halides and lithium enolates. It was found that small amounts of lithium chloride enhanced the stereoselectivity of 3-pentanone enolization, producing mostly the E enolate, and that larger amounts of LiCl reduced the stereoselectivity. The NMR investigation revealed the formation of three different LiTMP-LiCl mixed aggregates, including a mixed dimer (**11**) and a mixed trimer of (LiCl)(LiTMP)$_2$ (**12**) stoichiometry, which roughly matched the LiCl concentration that resulted in the highest stereoselectivity. A ladder structure was also observed containing two LiTMP units and two lithium enolates. (**13**) An analogous ladder structure was observed in the solid state between LDA and 5-(t-butyl-dimethylsiloxy)-3,3-dimethyl-2-pentanone. The crystal structure showed chelation of two of the lithium atoms by the t-butyl-dimethylsiloxy group [42]. Similar mixed aggregates were formed with lithium cyclohexenolate. Similar mixed aggregates are formed as the newly formed lithium enolate reacts with the residual lithium dialkylamide base, thereby reducing the stereoselectivity as the reaction progresses. Thus, the highest E/Z ratios were obtained at low percent conversion e. g., with a large excesses of the lithium dialkylamide.



9 (E) **10 (Z)** **11** **12** **13**

Compared with LiTMP, LDA has a lower tendency to form mixed aggregates with lithium enolates in THF solution. LDA will form mixed dimers with the lithium enolates of pinacolone and Z-pyrrolidine propionamide in equilibrium with free LDA. No LDA mixed aggregate with the lithium enolate of cyclohexanone was observed. LDA formed two mixed aggregates with lithium chloride, (LDA)(LiCl) and (LDA)$_2$(LiCl). Addition of 0.3 equivalents of LiCl to a solution of LDA resulted in higher E/Z stereoselectivity of 3-pentanone enolization, similar to that which was observed with LiTMP [43].

Lithium diphenylamide formed analogous mixed dimers and mixed trimers with LiCl in THF. At low THF concentrations in toluene, lithium diphenylamide formed an unusual trisolvated mixed dimer with LiBr, with one lithium atom bound to a single THF ligand and the other lithium bound to a pair of THF ligands. This mixed dimer was shown to accelerate the rate of N-alkylation by 1-bromobutane as evidenced by long induction periods at the beginning of the reaction at low THF concentrations. Addition of one equivalent of LiBr resulted in a first order reaction in the mixed aggregate and bromobutane. E2 elimination was a competing side reaction at high THF concentrations. At elevated THF concentrations, the lithium amide-lithium bromide dissociated to free lithium diphenylamide monomer, and possibly free ions at very high THF concentrations. The latter two species appeared to favor elimination over N-alkylation. [44, 45].

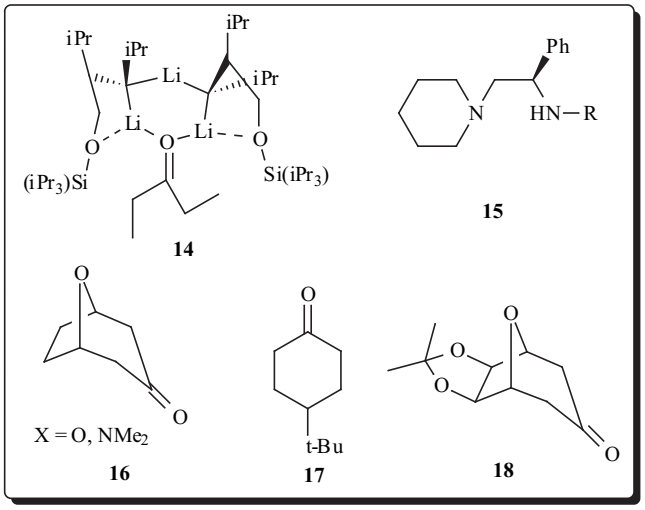
Like LDA, lithium diphenylamide forms limited amounts of a mixed dimer in THF with the lithium enolate of pinacolone but not with the lithium enolate of cyclohexanone [46]. N,N,N',N'-tetramethylethylenediamine (TMEDA) solvated LDA mixed trimers with LiCl, (LDA)$_2$(LiCl), have been observed in the solid state and in toluene-TMEDA solutions [47, 48]. An unusual lithium

diphenylamide-LiCl mixed tetramer, $(Ph_2NLi)_3(LiCl)$ was also observed in the solid state [49]. Mixed aggregate formation between LDA and enolates are solvent dependent. In THF, LDA formed a mixed aggregate with the lithium enolate of t-butyl cyclohexanecarboxylate, in equilibrium with free LDA and free enolate. The poorly coordinating methyl t-butyl ether (MTBE) solvent favored mixed aggregate formation, as did THF-N,N-dimethylpropyleneurea (DMPU) and THF-HMPA solvent systems. In each case, mixed aggregate formation resulted in autoinhibition of the ester enolization [50]. Mixed aggregates with lithium triflate or lithium iodide enhanced the rate of ester enolization by lithium diethylamide. The presence of an alkylating agent appeared to accelerate the ester deprotonation by the lithium amide, which was determined to be catalyzed by the lithium triflate or iodide byproducts [51]

Collum and coworkers reported that LiHMDS forms mixed aggregates with lithium enolates only in poorly coordinating solvents, [50], although LiHMDS mixed aggregates have been observed with the enolates of p-phenylsulfonylisobutyrophenone and 6-phenyl-2-benzyl-α-tetralone in THF solution [52]. Dimethoxyethane solvated mixed aggregates of LiHMDS with the lithium pinacolone enolate have been observed in the solid state as well as several other lithium enolate-lithium amide mixed aggregates [53]. The very sterically hindered lithium diadamantylamide (LiBAA) forms mixed dimers with the lithium enolates of diisopropyl ketone, 3-pentanone, and cyclohexanone. In contrast, LiBAA does not form observable mixed aggregates with LiCl or LiBr [31]. A complex and unusual mixed aggregate between the mono- and dilithio salts of t-butyldimethylsilylallylamine, butyllithium, and lithium oxide was found in the solid state [54]. Ab initio calculations indicate that unhindered lithium amides have a strong tendency to form mixed aggregates with lithium amides and lithium halides in the gas phase, and that solvation by dimethyl ether reduces the tendency toward mixed aggregate formation [55]. Overall, the tendency of lithium amides to form mixed aggregates with alkyllithiums, lithium halides and enolates appears to result from a complex interplay of steric bulk in the lithium amide and alkyllithium, enolate, or halide; the basicity of each mixed aggregate component; and steric, coordinating ability, and dielectric effects of the solvent. Recent computational results show that in the presence of ethyllithium, the LiTMP mixed aggregate with lithium enolates exists in equilibrium with a LiTMP mixed aggregate and an ethyllithium-enolate mixed aggregate [30]. The relative reactivity and stereoselectivity of these mixed aggregates toward ketone is not yet completely understood.

X-ray crystallography has revealed the existence of a chiral lithium amide-lithium enolate mixed aggregate. Two molecules of (S)-O-triisopropylsilyl-N-isopropylvalinol combined with the Z enolate of 3-pentanone to form a mixed cyclic trimer (**14**) [56]. The enolate stereochemistry was determined by dissolving the mixed aggregate crystals, trapping the enolate as the trimethylsilyl ether, and NMR analysis of the trapped enolate. As with achiral lithium amides, the formation of the mixed trimer was dependent on the lithium amide structure and no mixed trimers were found with less sterically hindered valinol derivatives in solution or in the solid state.

Mixed aggregates of chiral lithium dialkylamides have found use in asymmetric aldol reactions. The reaction between the lithium enolate of t-butylpropanoate and several aldehydes proceeded with good diastereoselectivity and enantioselectivity in the presence of polydentate chiral lithium amides. The enantioselectivity and diastereoselectivity were determined on the acylated products, obtained by reaction of the initial aldol product with acetic anhydride in the presence of triethylamine and DMAP. The chiral lithium amides were derived from N-(2-phenyl-2-N-alkylaminoethyl)piperidine (**15**). The best stereoselectivity occurred when the N-alkyl side chain contained chelating oxygen or nitrogen atoms [57]. Another application is the enantioselective deprotonation of several ketones (**16-18**) by chiral lithium amides in the presence of lithium chloride. When the newly formed enolate was trapped in situ suing chlorotrimethylsilane the enantioselectivity was higher than when the enolate was trapped after the deprotonation was complete. The addition of lithium chloride to the chiral lithium amide, followed by ketone deprotonation, and then quenching with chlorotrimethylsilane resulted in enantioselectivity comparable to or better than that using the in situ quench method. This strongly suggests the presence mixed aggregates [58].



Other Lithium Enolate and Lithium Phenolate Mixed Aggregates

Mixed aggregates between lithium enolates and lithium halides are known in solution and in the solid state. Early NMR studies suggested the formation of lithium enolate mixed aggregates with lithium halides [59]. The structures were refined in later investigations. The lithium enolate of isobutyrophenone forms a mixed tetramer containing three lithium enolate molecules and one LiCl unit in dioxolane, as determined by NMR studies. Additional studies showed that the mixed tetramer is also formed in THF and dioxane, and in dimethoxyethane, the lithium enolate forms a mixed dimer as well as a mixed tetramer with LiCl [60, 61]. Similar mixed tetramers are believed to form with $LiClO_4$ and lithium tosylate based on changes in the ratio of carbon/oxygen alkylation of the lithium isobutyrophenone enolate by methyl tosylate in dioxolane. The relative rates of carbon and oxygen alkylation changed over the course of the

reaction, and were shown to be due to the lithium tosylate byproduct. Similar rate changes were observed upon addition of $LiClO_4$ to the reaction mixture [62]. Mixed aggregates of lithium 2,6-dimethyl-, 4-bromo-2,6-dimethyl- and 2,4,6-tribromophenolates and lithium chloride, lithium perchlorate, and lithium tetrafluoroborate have been observed by NMR. Each of the mixed aggregates were believed to be mixed dimers based on the NMR spectra, reagent concentrations, and analogy to known mixed aggregate structures [63]. Mixed dimer formation was favored by more basic phenolate ions, and by weakly coordinating solvents. Lithium p-phenylsulfonylisobutyrophenone forms a mixed dimer with LiBr, as determined by the UV-visible spectra. The mixed dimer inhibited the alkylation of the enolate by p-t-butylbenzyl bromide, resulting in a decrease in reaction rate as the reaction progressed [64]. Crystal structures for the lithium enolate of 2,4-dimethyl-3-pentanone with LiBr and LiI, solvated by TMEDA, have been reported [65]. In both cases the enloate and lithium halide formed a mixed dimer, with one TMEDA ligand chelating each lithium atom.

Lithium enolate mixed aggregates with lithium halides have been used for asymmetric reactions in the presence of chiral amines. While the structure of these mixed aggregate-amine complexes have not yet been determined, they often result in high enantioselectivity. Koga and coworkers noted that the alkylation of cyclohexanone and tetralone by benzyl bromide in the presence of a chiral amine became more enantioselective as the reaction progressed. Suspecting mixed aggregate formation with the lithium bromide byproduct, they performed the reaction in the presence of added lithium salts, including LiBr, LiCl, LiI, LiF, lithium t-butoxide, and lithium triflate. The best results were obtained with LiBr, and resulted in higher enantioselectivity and higher chemical yield as well [66]. The mechanism of stereoselectivity was investigated using the conformationally locked 4-t-butylcyclohexanone. It was determined that in the presence of a chiral amine, one enolate enantiomer favored axial attack by the benzyl bromide electrophile, and the other enantiomer favored equatorial attack. Chiral products were obtained in up to 98% enantiomeric excess [67]. The presence of LiBr was also found to be essential in the enantioselective protonation of alkyl tetralones in the presence of a chiral amine, suggesting the formation of enolate-LiBr mixed aggregates. The enantioselectivity was highest in toluene and decreased in THF and other polar solvents. Acetic acid was most effective as the proton source, generating higher optical yields than 2,2-dimethylpropanoic acid or trifluoroacetic acid [68].

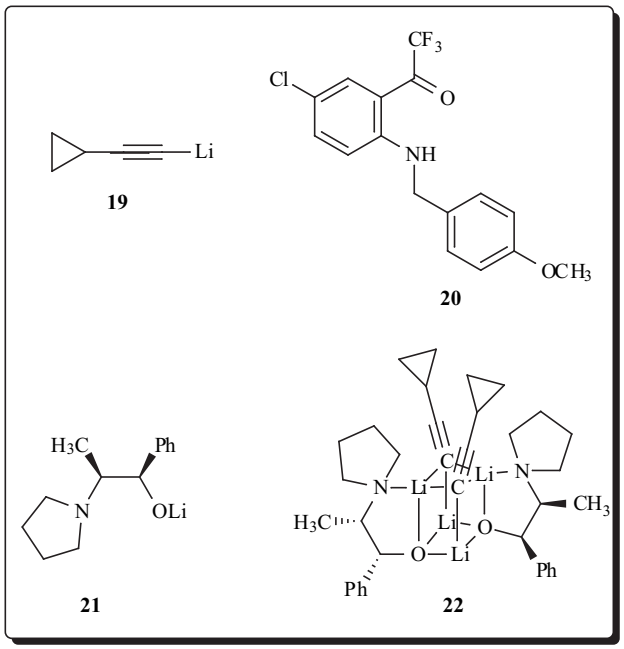
Mixed Aggregates of Alkyllithiums, Aryllithiums, Lithium Acetylides, and Lithionitriles

Several early studies found alkyl- and aryllithium mixed aggregates with lithium halides analogous to those with lithium alkoxides [69-72]. Those mixed aggregates are commonly formed during the synthesis of alkyllithiums from lithium metal and alkyl halides. Several mixed alkyllithium and alkyllithium-aryllithium mixed aggregates have been reported. Diphenyl-(N,N-bis-(2-methoxyethyl) aminomethyl)silyllithium and butyllithium form a ladder structure consisting of two butyllithium and two silyllithium units in the solid state [73]. Similar solid state ladder structures were observed with 1,3-bis(1-(dimethylamino)propyl)benzene and butyllithium, with the mixed aggregate containing two units of each species [74]. 2,4,6-Triisopropylphenyllithium forms an unusual mixed tetramer with butyllithium in which two of the lithium atoms are coordinated to a butyl group and the π-system of the benzene ring. The remaining two lithium atoms bridge the ipso carbon of the ring and the butyl groups [75].

Different aggregates of lithium compounds often undergo rapid exchange even at low temperatures. This is not always the case, as was shown by Collum and coworkers during the synthesis of some key intermediates for the preparation of anti HIV drugs. A key step involved the asymmetric addition of lithium cyclopropylacetylide (**19**) to a ketone (**20**) in the presence of lithium (1R,2S)-N-pyrrolidinylnorephedrate. (**21**) It was found that maximum stereoselectivity occurred only after the solution had been aged above -40 °C prior to ketone addition. An NMR investigation proved that without aging, the reactive and stereoselective mixed aggregate did not completely form, resulting in a loss of stereoselectivity. It was further determined that the reactive species was a mixed tetramer between the lithium ephedrate and the lithium acetylide, and in THF only one of several possible stereoisomers is formed. (**22**) The other stereoisomers were also formed in less polar solvents such as toluene, diethyl ether, and MTBE, and the reaction in those solvents resulted in a loss of stereoselectivity. At different lithium ephedrate: lithium acetylide ratios two other mixed tetramers were formed, $(ROLi)_3(RLi)$ and $(ROLi)(RLi)_3$. The former was much less reactive towards nucleophilic addition to the ketone than the 2:2 mixed tetramer, which provided a clue as to why the reaction proceeded to only 50% conversion at low temperatures unless at least two equivalents of the lithium reagents were used. If one equivalent of the lithium ephedrate and lithium acetylide were used, warming the reaction mixture would result in full conversion, but with a significant loss in stereoselectivity, suggesting that a different mixed aggregate was involved. It was later shown that the product lithium alkoxide formed an unreactive mixed aggregate analogous to the $(\text{lithium ephedrate})_3(\text{lithium acetylide})$, which inhibited the reaction below -50 °C, but which could react with lower stereoselectivity at higher temperatures [76, 77].

The effects of lithium alkoxide-lithium acetylide mixed aggregates were investigated with other lithium alkoxides and substrates. In several cases it was found that a slight excess of LiHMDS as a proton scavenger resulted in improved stereochemistry, raising the possibility of a complex mixture of mixed aggregates involving the two reactants (lithium acetylide and lithium alkoxide), the lithium alkoxide reaction product, and the excess LiHMDS. Of particular interest was the Michael-like addition of lithium cyclopropylacetylide, to a conjugated imine (**23**) in the presence of a chiral lithium alkoxide (**24**), producing a chiral substituted urea (**25**). In THF solution the NMR investigation found that neither the lithium cyclopropylacetylide nor the alkoxide **24** formed mixed aggregates with LiHMDS. In diethyl ether and ethyldimethylamine the lithium acetylide did form a mixed dimer (**26**) and a mixed trimer ladder structure (**27**) with LiHMDS. A possible LiHMDS mixed aggregate with **24**

was formed in diethyl ether, which was not further investigated. [78].

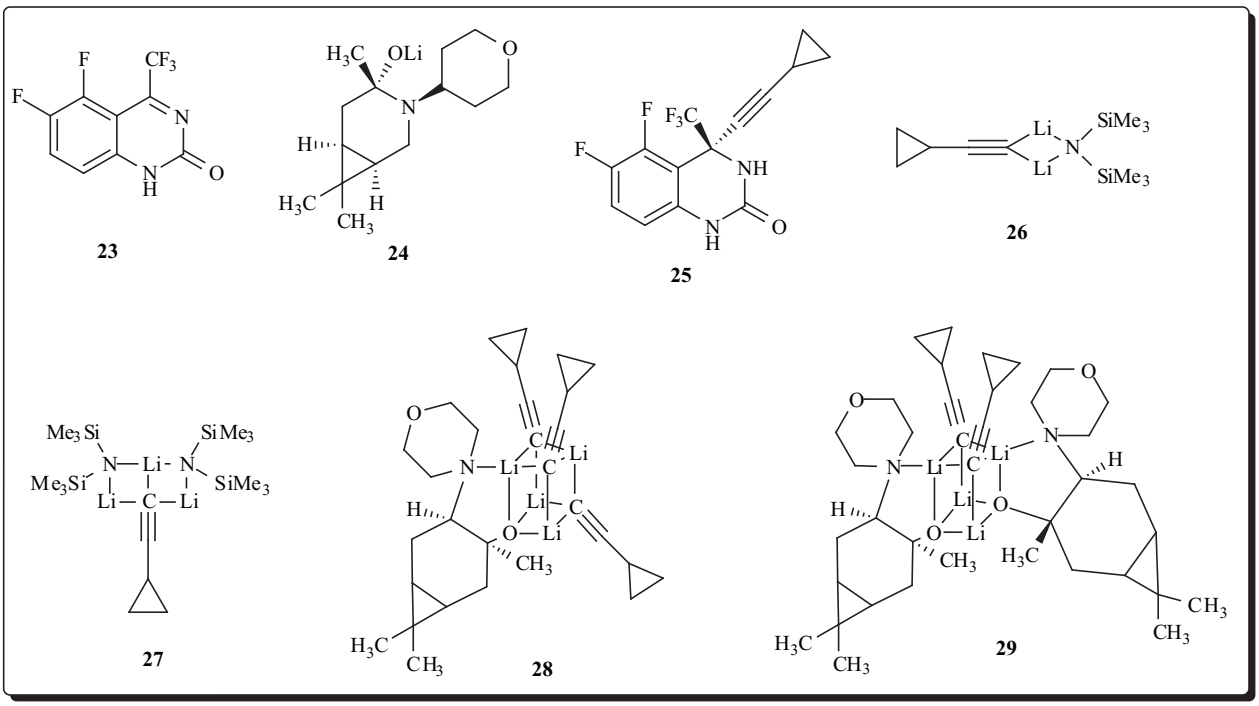


Several NMR experiments revealed the formation of several mixed aggregates bewteen lithium cyclopropylacetylide and **24**, which rapidly interconverted at temperatures above -40 ºC . When the lithium acetylide was mixed with the alkoxide in a 3:1 ratio, a cubic mixed tetramer was observed (**28**). Two stereoisomeric mixed dimers $(LiOR)_2(LiR)_2$ were observed in THF, a symmetrical structure (**29**) and a diastereomer of undetermined geometry. The former mixed tetramer was the only one observed in diethyl ether, while only the latter diastereomer was observed in ethyldimethylamine. At higher alkoxide concentrations a mixed tetramer $(LiOR)_3(LiR)$ was observed, although the exact structure was undetermined. The exact role of these mixed aggregates in the enantioselective Michael addition is not yet known. Similar mixed aggregates with camphor-derived aminoalkoxides have been observed, as was a mixed dimer between the lithium alkoxide and LiHMDS [79]. Analogous mixed tetramers of lithium alkoxides and lithium aminoalkoxides have been reported [80]. A mixed dimer between lithium phenylacetylide and lithium t-butylamide has also been observed, as well as a 2:4 mixed hexamer of undetermined stereochemistry [81]. X-ray structures of analogous butyllithium-lithium phenoxide mixed aggregates have also been reported [82]

Lithiated acetonitriles can form mixed aggregates with lithium dialkylamides, although the formation of these species is highly solvent dependent. Lithiophenylacetonitrile formed a TMEDA chelated mixed dimer in the solid state [83]. An analogous structure was found in toluene-TMEDA solution with LiHMDS and lithiophenylacetonitrile [84]. Similar lithiophenylacetonitrile mixed aggregates have been observed in THF with LDA, LiHMDS, and butyllithium [85].

SUMMARY

Mixed aggregates of lithium compounds are common species in solution and in the solid state. Mixed aggregates may be formed intentionally, inadvertently from impurities, or from reaction products, which may result in autocatalysis or autoinhibition in organolithium reactions. A large number of structures have been determined from NMR spectroscopy and x-ray crystal structures, and computational methods have helped to elucidate structures of mixed aggregates that are difficult to observe directly. The formation of mixed aggregates is often solvent dependent and the solvent dependence does not always correlate in a simple way with solvent polarity.



Mixed aggregates find use in the synthesis of polymers and small molecules, and particularly in stereoselective synthesis. Spectroscopic, kinetic, and computational studies have provided some insight into the mechanisms of stereoselectivity, although much work remains to be done in this area. As was shown by Collum and coworkers, several different homo- and mixed aggregates may coexist in solution, and one or more of those may be responsible for high stereoselectivity. If the aggregate interconversion is slow compared to the rate of reaction, techniques such as rapid injection may help elucidate the reaction mechanisms. Computational methods are becoming increasingly important tools for mechanistic studies, particularly with the development of ab initio and density functional methods that can handle large systems at a reasonable computational cost. Solvation is a difficult problem for computational studies lithium compounds, but the combined use of explicit solvation by coordinating ligands and continuum solvent models has proven useful [30, 55, 86]. Recent advances in quantum and combined quantum-classical molecular dynamics may make these methods practical for computational solvation studies in the near future. A combination of spectroscopic, kinetic, and computational studies is currently being used to elucidate many reaction mechanisms involving mixed aggregates and these methods will continue to be used in the future.

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