The Directed Lithiation of Benzenoid Aromatic Systems

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Dedicated to the memory of Ron Snaith. An inspirational teacher and a great friend

Keywords: Aromaticity / Directing group / Lithium / Solid-state structure / Solution structure

Directed metallation using organolithium bases is one of the best ways of regiospecifically elaborating aromatic systems and their substituents. For benzenoid arenes, deprotonation occurs at the ortho, lateral or peri positions. The reasons for each type of reaction will be considered in the context of the propensities of different directing groups for complex formation with the incoming organolithium base, acidification of the reactive site(s) and post-reaction stabilisation of the metal ion(s). Discussion will concentrate on structural investigations, for the most part by single-crystal X-ray diffraction and/or by multinuclear NMR spectroscopy. Theoretical studies will also be incorporated.

Introduction

Directed metallation using Group 1 organometallic bases in general, and organolithium substrates in particular, represents one of the most selective ways of regiospecifically elaborating benzenoid aromatic rings and substituents thereon, with deprotonation generally taking one of three forms: ortho, lateral or peri (Figure 1). The synthetic applications of the first of these have formed the basis for several review articles.[1] Orthometallation occurs both because the directing group can raise the acidity of the ortho hydrogen and also because the incoming organometallic substrate closely approaches this position. It is in the context of this reactivity that, for example, the recent total syntheses of phomactin, narciclasine, and analogues of meridine and atpenin B have been achieved.[2] The elaboration of aromatic substituents by means of directed lateral lithiation, that is metallation of, for example, alkyl groups located ortho to a directing group,[3] has facilitated the preparation of many polycyclic products, including corydalic acid methyl ester and fredericamycin.[4] Selectivity for ortho- vs. lateral lithiation is poorly understood, though kinetic, thermodynamic and steric effects all seem to play a role. Stereochemical aspects of the formation and reaction of laterally lithiated amides have been investigated,[5] with enantio-[6] and atroposelective lateral lithiations[7] having been published. Less

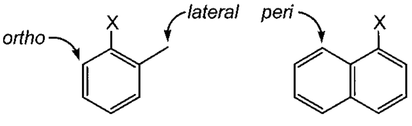

Figure 1. Schematic showing ortho-, lateral, and perilithiation sites

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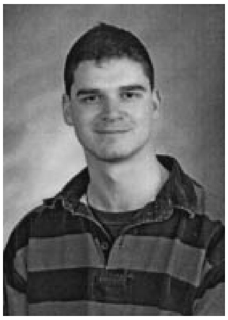

Dr. Andrew Wheatley graduated from the University of Kent and did his Ph.D. (University of Cambridge, 1995−1998) for the late Dr. Ron Snaith after which he became a Research Fellow at Gonville & Caius College (1998−2002). In 1999 he was awarded the Harrison Memorial Medal by the Royal Society of Chemistry and in 2000 he was made a University Assistant Lecturer at Cambridge. In 2002 he became a Fellow of Fitzwilliam College and he was made University Lecturer in 2003. He has published extensively in the field of Main Group organometallic chemistry. He specialises in the elucidation of organolithium reaction intermediates and the development of alkali metal 'ate complexes and Main Group metal interstitial hydrides.

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commonly employed as a synthetic tool, the perimetallation of arenes occurs not because of directing group acidification of this position (*cf.* orthometallation) but because the incoming organometallic substrate closely approaches it.

The manifold synthetic applications that have been developed in light of the reactivities discussed above have recently been the subject of comprehensive review.[8] Nevertheless, it is remarkable that little is known of the organometallic products of metallation reactions involving demonstrably useful directing groups. The success of such synthetic protocols, involving metallation in general and lithiation specifically, have been interpreted in terms of promotion of the "complex-induced proximity effect",[9] with kinetic isotope effect evidence suggesting that rate-determining deprotonation of the arene proceeds in the wake of the formation of an equilibrating substrate-organometallic complex.[10]

The aim of the present article is to amalgamate the reported structural data for the products of the directed deprotonation of benzenoid aromatic systems by organolithium substrates. "Complex bases" have been used to occasion the derivatization of aromatic substrates as heterometallic Li-Group 1,[11] Li-Cu,[12] Li-Zn[13] and other Li-(d-block)[14] salts. However, only homometallic lithium derivatives will be considered by the present article since it is with these compounds that the synthetic utility of alkali metallated arenes lays.[8] The three main parts of the text will each deal with a different deprotonation position and, thereafter, the article is sub-divided firstly into solution studies and, secondly, into solid-state structural studies. Each of these two sub-sections will be ordered, with homoaromatics preceding heteroaromatics and with further categorisation occurring by directing group. Discussion of both solution and solid-state studies will be augmented by that of theoretical investigations where appropriate.

Orthometallation

Since the seminal studies that established the ability of substituted aromatic systems to undergo regioselective reaction[15] many synthetic procedures have been developed that utilise ortholithiation,[1a] and extensive studies have been undertaken into the relative directing abilities of a wide variety of substituents, many of which contain heteroatoms.[16] It is acknowledged that the best directors of orthometallation−and also the most versatile−are the so-called "N+O class" amide-type functional groups such as secondary and tertiary amides, carbamates and oxazolines.[1a] Other powerful (though less synthetically useful) orthodirecting groups include "S+O class" sulfones, sulfonamines[17] and *tert*-butyl sulfoxides.[18] Less potent are "O class" (e.g. ether) and "N class" (e.g. amine) substituents.[8] Halogens ("X class") are of importance, though prone to undergo halogen-metal exchange.[19]

The orthometallation of electron-deficient benzenoid heterocycles has been utilised synthetically,[8] though competition between deprotonation of and addition to the ring has been noted.[20] In the context of heterocyclic arenes, by far the most commonly employed systems are those of pyridyl derivatives. In spite of this, there are no reported structural characterisations of pyridines that have undergone alkali metallation at the ortho position.

Solution Studies

The ^{13}C NMR spectrum of 2,4,6-tri-*tert*-butylphenyllithium (**1**) in THF has been studied in some detail, with electric quadrupole relaxation of ^{7}Li incurring the partial averaging of $^{1}J(^{13}C,^{7}Li)$ while metal-carbon bond exchange has been reported between ^{6}Li enriched isotopomeric monomers.[21] In a similar vein, mesityllithium has been probed as a PMDETA complex (**2**), with data suggesting an asymmetric structure in which the metal is chiral at low temperature.[21]

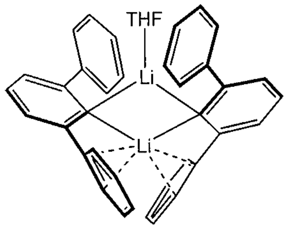
The ortholithiation of anisole by *n*BuLi has been extensively studied by NMR spectroscopy.[22] Low temperature ^{1}H and ^{13}C NMR spectroscopy suggests that upon the addition of organolithium substrate a tetramer of the complex *n*BuLi·MeOPh (**3**) forms with the introduction of TMEDA causing its replacement by dimers of *n*BuLi·TMEDA (**4**). The spectroscopic benefits of ^{6}Li enrichment having been previously demonstrated,[23] the conversion of **3** to **4** has been corroborated by ^{6}Li,^{1}H HOESY and it has been suggested that orthometallation only proceeds in the presence of (more reactive) **4**.[22] This interpretation of the metallation of anisole, depending on the conversion of **4** to $(n\text{BuLi})_2$·TMEDA·MeOPh (**5**), has also been scrutinised theoretically with MNDO calculations suggesting that the orthodirecting functionality stabilises the transition state during deprotonation.[24] More recently, the reactivity of 1-methoxynaphthalene towards various organolithium substrates has been probed.[25] Whereas it has been previously noted that 1-methoxynaphthalene reacts with a 1:1 mixture of *n*BuLi and TMEDA to give an almost uniquely orthometallated product **6**, regioselectivity has proved less easy to control if an excess of Lewis base is present.[26] Accordingly, ^{1}H, ^{13}C and ^{6}Li,^{1}H HOESY spectra suggest that in the absence of a donor a 1-methoxynaphthalene-(*n*BuLi) complex **7** forms initially, whereas in the presence of TMEDA such complexation is precluded. The observation that ortholithiation nevertheless results from the employment of *n*BuLi/TMEDA, when taken in conjunction with the detection of an isotope effect (in [D$_8$]THF) whereby the exchange of hydrogen at the ortho position by deuterium incurs a slower lithiation process, suggests kinetic control. This view is reinforced by the observation that at elevated temperatures, the ortholithiated complex slowly converts into the corresponding perimetallate **8**.[25]

The ability of a [2-(dimethylamino)]-containing substituent to exhibit chelation control[27] during an orthometallation reaction has been demonstrated by the structural elucidation of $[\text{Me}_2\text{NN(Me)}]\text{C}_6\text{H}_4\text{Li}\cdot{}^{1}/_{2}\text{TMEDA}$ (**9**)[28] and 2-(dimethylaminomethyl)phenyllithium (**10**)[29] in various media. The asymmetric solid-state structure of **9** (see below) is based on a $(\text{CLi})_2$ metallacyclic core, the integrity of which in [D$_6$]benzene is suggested by the observation of a septet [$^1J(^{13}C,^7Li) = 20$ Hz] for the metallated carbon centre by ^{13}C NMR spectroscopy at room temperature.[28] While it is known that **10** takes the form of a chelated tetramer in hydrocarbon solution[30] it had been formerly suggested that the introduction of etherate solvent not only incurred separation into dimers[31] but also disrupted internal coordination.[32] However, more recent work using the doubly labelled (^{6}Li,^{15}N) compound, indicates that three interconverting isomeric and fully chelated dimers are retained in the presence of THF, and that internal coordination is not depleted even upon treatment with HMPA.[29]

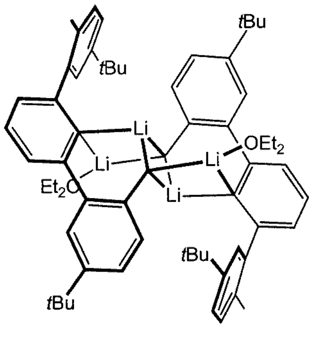
The ability of lithium itself to direct subsequent metallation has applications in the lateral deprotonation of aromatics (see below) but is also revealed in the context of ortholithiation by the reaction of 2-lithio-1-phenylpyrrole (**11**), a solid-state dimer,[32] with *n*BuLi.[33] ^{6}Li,^{1}H HOESY suggests that in [D$_8$]THF/TMEDA a co-complex forms in which the ortho position of the benzenoid ring may be agostically activated.[32] In a like vein, *trans*-1-lithio-1,2-diphenylhex-1-ene (**12**) undergoes orthometallation of the 2-phenyl substituent upon treatment with *n*BuLi. In the same way as for **11**, ^{6}Li,^{1}H HOESY points to activation of the position of ultimate dilithiation.[34] Low temperature ^{1}H and ^{13}C NMR spectroscopy suggests that the dissolution of (nBu)[C_6H_4(Li·TMEDA)-2]C=C(Li·TMEDA)Ph (**13**) in [D$_8$]THF yields a mixture of essentially unaltered **13** and a pseudo-cubic dimer of (nBu)[C_6H_4(Li·[D$_8$]THF)-2]C=C(Li·[D$_8$]THF)Ph (**14**).[34] ^{6}Li,^{6}Li COSY with fixed delays reveals scalar coupling between the two chemically inequivalent metal locations in this last species[35] and interchange of the metal centres between **13** and **14** has been demonstrated by ^{6}Li,^{6}Li EXSY.[36]

Solid-State Studies

Several straightforward examples of substituted phenyllithium compounds have been fully characterised, both in their pure forms and as complexes with Lewis bases. Dilithiated biphenyl has been characterised as the TMEDA solvate μ_2-biphenyl-C2,C2, C2′,C2′-bis(lithium-TMEDA) (**15**).[37] Concerning polysubstituted arenes, various dimers of unsolvated 2,6-$R_2C_6H_3Li$ are known. Whereas for R = mesityl (**16**)[38] the structure is based on a normal (CLi)$_2$ core, for the more sterically congested ligand in which R = 2,6-(iPr)$_2C_6H_4$ (**17**) dimerisation occurs by the η^6-interaction of one R group on each ligand with the metal component of an adjacent monomer.[39] Solvated analogues exhibit even more diverse behaviour; 2,6-($C_{10}H_7$)$_2C_6H_3$Li·2THF (**18**),[40] 2,6-$Ph_2C_6H_3$Li·2OEt$_2$ (**19**),[41] 2,6-[4-(tBu)C_6H_4]$_2C_6H_3$Li·2OEt$_2$ (**20**),[42] 2,6-(4-MeOC_6H_4)$_2C_6H_3$Li·2OEt$_2$ (**21**) (wherein the methoxy groups are passive with respect to the metal),[43] 2,6-[2,4,6-(iPr)$_3C_6H_2$]C_6H_3Li·L (L = OEt$_2$ **22**,[44] η^6-C_6H_6 **23**[39]) and 2,4,6-$Ph_3C_6H_2$Li·2OEt$_2$ (**24**)[45] are monomers in the solid state while 2,4,6-(iPr)$_3C_6H_2$Li·OEt$_2$ (**25**)[46] and 2,4,6-$Me_3C_6H_2$Li·2THF (**26**)[47] form differently solvated dimers. The complex 2,4,6-$Ph_3C_6H_2$Li·$^1/_2$THF (**27**) is unusual by virtue of its asymmetry. While both metal ions in its dimeric structure straddle the formal charge centres, one is mono-THF solvated and the other is bis(η^2-Ph) supported.[40] In a like vein, the dimer of 2,6-$Ph_2C_6H_3$Li·$^1/_2$THF, **28**, reveals Lewis base stabilisation of one metal centre and the η^2-interaction of two phenyl rings with the other.[40] Whereas the simple monolithiate **21** is formed by lithium-halogen exchange with the corresponding iodide,[19] application of *excess* *n*BuLi to the related substrate 2,6-[2-Me-4-(tBu)C_6H_3]$_2$-C_6H_3I has yielded the dilithium complex 2-[2-CH$_2$Li-4-(tBu)C_6H_3]-6-[2-Me-4-(tBu)C_6H_3]C_6H_3Li·OEt$_2$ (**29**).[42] As part of the same study, a 1:1 co-complex (**30**) between *t*BuLi and 2,6-[2,4,6-(iPr)$_3C_6H_2$]$_2C_6H_3$Li (*cf.* **22**, **23**) has been reported to incorporate a (CLi)$_2$ core.[42] As already mentioned, **21** reveals coordinatively inactive methoxy substituents.[43] However, in the THF-solvated co-complex (**31**) between lithium iodide and 2,6-bis(2-methoxyphenyl)phenyllithium each metal centre is singly MeO-bonded.[48] Just as the tetramer of 2,4,6-tris(isopropyl)phenyllithium, **32**, reveals η^6-support of the metal centres[39] so the butyllithium-phenyllithium complex *n*BuLi·[2,4,6-(tBu)$_3C_6H_2$Li] (**33**) exhibits a dimeric solid-state structure by virtue of there being η^6-links between the component monomers.[38] Lastly, as previously pointed out the extensively conjugated system *trans*-1-lithio-1,2-diphenylhex-1-ene (**12**) has been reported to react with one equivalent of *n*BuLi at the 2-phenyl substituent to give **13**.[34] This last complex reveals a solid-state structure similar to that of μ_2-biphenyl-C2,C2, C2′,C2′-bis(lithium-TMEDA) **15**.[37]



(28)$_2$



(29)$_2$

The potential for passivity on the part of MeO groups towards lithium has already been alluded to in the context of the diethyl ether solvate **21**.[43] However, the lithiation of anisoles is more commonly known to proceed at the position ortho to this weak "O class" director, with internal Li−O stabilisation of the metal occurring. While solution studies into such processes have already been discussed (see above), several examples of chelated lithioalkoxyarenes have been characterised in the solid state. The metallation of anisole itself using *n*BuLi has long been known to yield a tetramer of the simple orthometallate 2-$MeOC_6H_4Li$ (**34**),[49] with the methylcyclopropane solvate 2-$MeOC_6H_4Li{\cdot}OCH_2CHMe$ (**35**) having a similar structure[50] and 2-$MeOC_6H_4Li{\cdot}{}^1/_8$TMEDA (**36**) revealing pairs of tetramers that are TMEDA bridged.[51] While the simplest poly(methoxy) example of such species is a dimer of 2,6-(dimethoxy)phenyllithium (**37**), in which each metal is supported by interaction with both charge centres and one oxygen atom on each ligand,[52] more extensive (tetrameric) aggregation of **37** has also been reported.[53] Meanwhile, increasing the steric demands of alkoxy groups [in 2,6-di-(*tert*-butoxy)phenyllithium (**38**)] has been noted to incur the formation of a rare cyclic trimer based on a $(CLi)_3$ core.[54]

Remaining with chalcogen-based directing groups, polymeric chains based on $(CLi)_2$-centred dimers of 2-(tBu)$SC_6H_4Li{\cdot}{}^1/_2$TMEDA (**39**) have been noted to form by virtue of the ability of TMEDA to adopt a dimer-bridging motif.[55] Biphenyl sulfide has been shown to undergo dimetallation in TMEDA (in a manner analogous to that revealed by biphenyl, *cf.* **15**)[37] to yield μ_2-biphenyl sulfide-C2,C2, C2′,C2′-bis(lithium-TMEDA) (**40**).[56] In the context of "S+O class" directing agents, 3-fluorophenyl(phenyl)sulfone has been shown to undergo lithiation on the fluorinated ring between the two substituents to afford 3-FC_6H_3(Li·PMDETA-2)SO_2Ph (**41**).[57] Of the two possible coordinating substituents, it is the SO_2 moiety that dominates, with one of its two oxygen centres interacting with the metal [Li−O = 2.170(8) Å; Li···F = 3.672(7) Å]. Nevertheless, in spite of the lack of Li−F coordination, the arene-fluorine distance is, at 1.389(5) Å, longer than normal. This has been interpreted in terms of the observation that **41** eliminates LiF at +60 °C.[57] The dilithiated sulfone 2-[$(Me_3Si)_2C(Li{\cdot}OEt_2)SO_2$]$C_6H_4Li{\cdot}OEt_2$ (**42**) has been reported, wherein both O-directed ortholithiation (the solid-state structure reveals Li−C_{ortho} and Li−O coordination) and deprotonation of the sulfone α-carbon are seen.[58] Reaction of racemic EtS(=O)(Ph)=NMe with *n*BuLi/TMEDA in the presence of a trace oxide source[59] yields the heterochiral mixed α-mono- and α,orthodilithiated sulfoximine $[MeCHLiS(=O)(Ph)=NMe]_2{\cdot}[MeCHLiS(=O)(C_6H_4Li\text{-}2)=NMe]_2{\cdot}Li_2O{\cdot}3$TMEDA (**43**),[60] the solid-state structure of which reveals chiral resolution. Consequently, the aggregate is composed of two (*S*)-configured α-metallated sulfoximine monoanions and two (*R*)-configured α,orthometallated dianions. At the structure core, and interacting with six of the eight metal centres present, is a rogue oxide dianion (thought to arise from LiOH contamination of the organolithium reagent). The α-Li centre in the monolithiated moiety interacts with neither the oxygen nor the nitrogen centres in the same unit but sits *gauche* with respect to these atoms and bonds, instead, to TMEDA and the O-centre of a dianionic sulfoximine unit (Figure 2a). Each of these dianions interact with both metal counterions *via* their deprotonated ortho positions — the corresponding two metals being stabilised by intramolecular N,O-coordination. The α-C lone pair in the dianion adopts a *gauche* conformation with respect to both nitrogen and deprotonated arene (Figure 2b).[61]

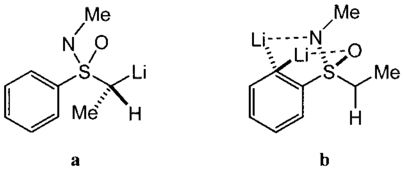
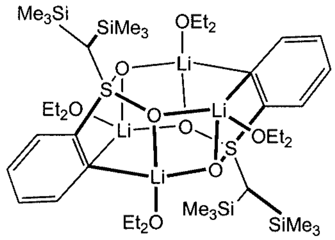
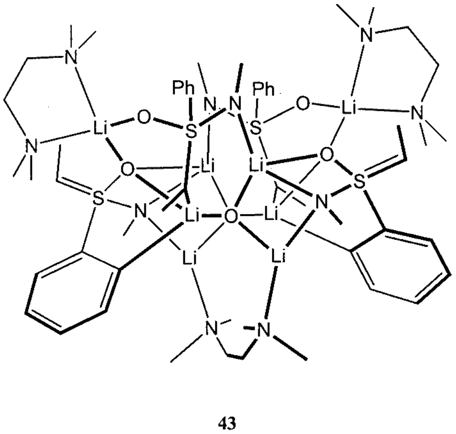


Figure 2. a) Li^+ in the monolithiated component of **40** bonds to TMEDA and the O-centre of a dianionic sulfoximine unit and, b) the α-C lone pair in the dianion adopts a *gauche* conformation with respect to nitrogen and arene[60]



$(\mathbf{42})_2$



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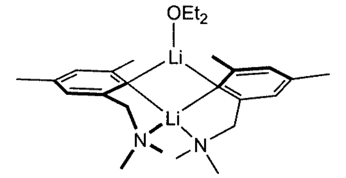
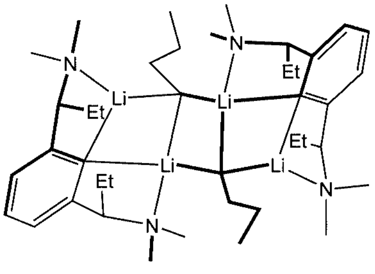
The solution structures incurred by the action of the purely "N class" directing group in 2-(dimethylaminomethyl)-phenyllithium (**10**) have already been discussed[29] in the context of retention of the pseudo-cubic tetramer noted in the solid state.[30a] The substrate 3,5-dimethyl(dimethylaminomethyl)benzene has been shown to undergo orthodirected metallation upon treatment with *n*BuLi/OEt_2. The result is a dimer of 2-Me_2NCH_2−4,6-$Me_2C_6H_2Li{\cdot}{}^1/_2OEt_2$ (**44**), an asymmetric species in which one metal centre in a $(CLi)_2$ core is supported by two amine N-donors while the other metal is mono(diethyl ether) solvated (*cf.* **28**). This species is thermally unstable with respect to the formation of (2-Me_2NCH_2−4,6-$Me_2C_6H_2Li$)·(Me_2NCH_2−3,5-Me_2-C_6H_3) (**45**).[28] As part of the same study, the TMEDA-solvated structural analogue of **44** has been obtained using trimethylhydrazine directors. Whereas *n*BuLi/OEt_2 fails to effect lithiation of $Me_2NN(Me)Ph$, the use of *n*BuLi/TMEDA affords the asymmetric complex **9**, which is known to retain its solid-state structure in hydrocarbon solution (see above).[28] Extensive crystallographic work has been done on bis(amine) compounds of the type 2,6-$(R_2NCHR')_2C_6H_nR''_{3-n}Li$. For $n = 3$, the pure ortholithiates 2,6-bis(*N*,*N*-diethylaminomethyl)phenyllithium (**46**)[61] and 2,6-bis[1′-(dimethylaminoethyl)]phenyllithium (**47**)[62] have both been shown to adopt dimeric structures in the solid state. The 1:1 co-complex of 2,6-bis[1′-(dimethylaminopropyl)]phenyllithium with *n*BuLi **48** is based on a more complicated $(CLi)_4$ ladder, in which the *n*-butyl ions reside in the ladder middle while the ortho deprotonated aromatic systems both intercept laddering and straddle ladder edges.[62] The compound 2,3,5,6-$(Me_2NCH_2)_4C_6HLi$ (i.e., $n = 1$) (**49**) exists as a dimer in which each metal in the core $(CLi)_2$ ring is supported by the 2- and 6-aminomethyl groups in either ligand, the remaining substituents being coordinatively inactive.[63] In a related vein, 2-Me_2N-6-$Me_2NCH_2C_6H_3Li$ (**50**) reveals a dimer incorporating both four- and five-membered chelate rings,[64] whereas 2,6-$(Me_2N)_2C_6H_3Li$ (**51**) is a $(CLi)_3$-based trimer incorporating only four-membered C_2NLi chelate rings.[65] Just as (O-directed) 2,6-di-(*tert*-butoxy)phenyllithium (**38**)[54] and (N-directed) **51** are unusual by virtue of the fact that they exist as cyclic trimers in the solid state, in 2-(*t*Bu)O-6-$Me_2NC_6H_3Li$ (**52**) trimerisation is noted to result from the employment of both N- and O-directing groups.[66] In contrast to the intramolecular N-stabilisation revealed by **50** and **51**, 2-[(4-methylpiperazinyl)phenyl-C,N]lithium-THF (**53**) exhibits a dimeric structure based on an eight-membered $(C_2NLi)_2$ core by virtue of intermolecular stabilisation of the metal ions by piperazinyl α-nitrogen atoms.[67] The investigation of orthometallated compounds incorporating polyfunctional substituents has been extended to cover the solid-state structure of 2-(dimethylaminoethoxy)phenyllithium (**54**)[68]and also that of 2-[*N*-alkyl(*N*′,*N*′-diethylaminoethyl)aminomethyl]phenyllithium (alkyl = methyl **55**,[69] ethyl **56**[70]). The use of α-aminolithium alkoxides[71] has allowed the regiospecific metallation of arylaldehydes. Hence, in situ protection of variously substituted benzaldehydes and heterocyclic arylaldehydes[72] has been reported[71,73] by reaction with lithium dialkylamides, and has been followed by ring lithiation, affording a convenient one-pot route to orthosubstituted arylaldehydes. In a comparable area, **54** exhibits a tetrameric structure in the solid state. Unusually, for such an aggregation state, a straightforward pseudo-cubane does not result. Instead, two boat-shaped eight-membered $(C_2OLi)_2$ rings are found to be stacked with one being inverted and twisted by approximately 90° to the other. In a manner analogous to *N*,*N*,*N*′-trialkylethylenediamine-substituted aromatics,[70] the 2-(dimethylaminoethoxy)phenyl anion acts as an N,O-chelating ligand in **54** such that each metal is rendered four-coordinate by the action of nitrogen.[68] Compounds **55** and **56** have revealed a $(CLi)_2$-based dimer with both donor centres on each side-chain chelating a given metal centre.[69,70] A related co-complex has been reported; that of 2,6-bis[*N*-methyl(*N*′,*N*′-dimethylaminoethyl-)aminomethyl]phenyllithium with BrLi (**57**) is centred on a four-membered $CBrLi_2$-ring.[74] The polyfunctional ligand *N*-(2-phenoxyphenyl)-*N*-(trimethylsilyl)amine has been used to afford a variety of structural motifs upon dilithiation.[75] As such, simple deprotonation in DME to give, for example, N,O-chelated 2-$PhOC_6H_4N(Li{\cdot}DME)SiMe_3$ (**58**), can be followed by reaction with further *n*BuLi in the presence of different Lewis bases to give the dimer of diglyme-bridged 2-$(C_6H_4Li\text{-}2')OC_6H_4N(Li{\cdot}OEt_2)SiMe_3{\cdot}{}^1/_2$-$O(CH_2CH_2OMe)_2$ (**59**), the dimer of 2-$(C_6H_4Li\text{-}2')OC_6H_4N(Li{\cdot}DME)SiMe_3$ (**60**) or *n*BuLi-containing co-complex *n*BuLi·2-$(C_6H_4Li\text{-}2')OC_6H_4N(Li{\cdot}OEt_2)SiMe_3$ (**61**).[76] Attempts to react dilithiates such as **59** or **60** with $LaCl_3$ in Et_2O have serendipitously afforded a decalithium cluster that comprises two units of formulation EtOLi·[2-$(C_6H_4Li\text{-}2')OC_6H_4N(Li{\cdot}OEt_2)SiMe_3]_2$ (**62**).[76] The dilithiation of *N*-phenylcarbazole in TMEDA gives μ$_2$-*N*-phenylcarbazole-C1,C1, C2′,C2′-bis(lithium-TMEDA) (**63**)[56] (*cf.* **15**[37] and **40**[56]). Whereas previous studies into the propagation of reactions between organolithium substrates and amines have typically utilised an excess of amine and so generated species of the type $R_2NLi{\cdot}HNR_2$,[77] a recent probe has investigated the reaction of *n*BuLi with Ph_2NH using as much as a sixfold excess of organolithium substrate. Such work has afforded the remarkable (*n*BuLi)-containing (mixed anion)-dianion co-complex $(nBuLi)_2{\cdot}[Ph(C_6H_4Li\text{-}2)NLi{\cdot}OEt_2]_2{\cdot}Ph_2NLi$ (**64**).[78] The structure of **64** incorporates three connected units. The first two are $(CLi)_2$-based $(nBuLi{\cdot}OEt_2)_2$ and a dimer of dilithiated $Ph(C_6H_4Li\text{-}2)NLi{\cdot}OEt_2$. The four negative charge centres of the latter fragment interact with the third component of the structure; a single Ph_2NLi molecule.[78]



(44)$_2$



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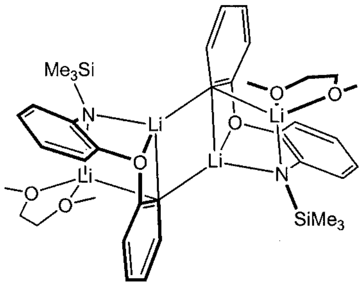
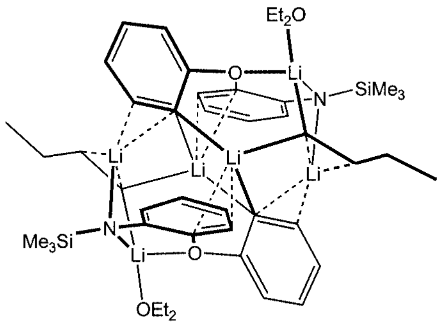


(60)$_2$



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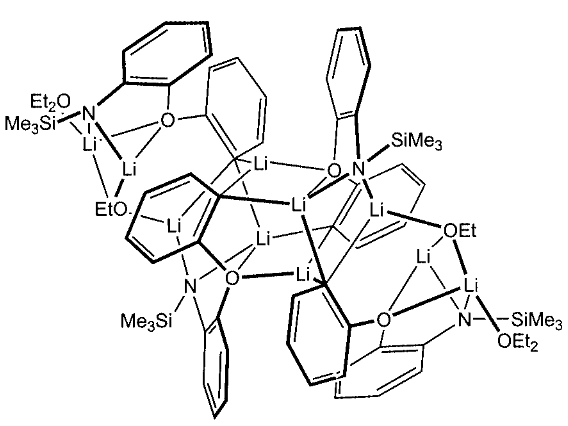
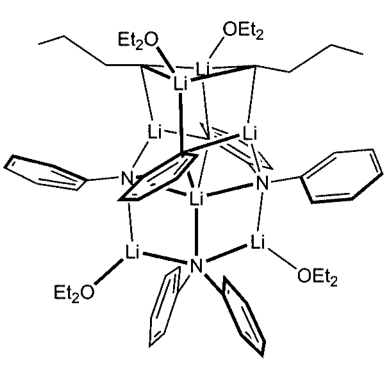
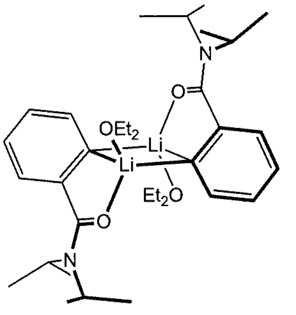


(62)$_2$



64

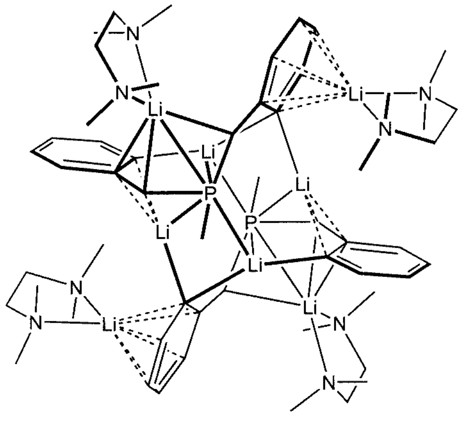
Remaining with the nitrogen-based chelation of metal centres, two common ligand types have been found to exhibit a predilection for stabilising lithium cations; those that contain separate “N class” and “O class” directing groups and those that feature “N+O class” directors. In the context of the first of these, compounds **52** and **59−62** have already been discussed.[66−76] Concerning the latter, mixed “N+O class”, it has already been mentioned that about the best and most versatile orthodirecting substituents of all are those incorporating amide-type groups in general[1a] and tertiary amides specifically.[16a] In spite of this utility it is only recently that the propensity of even the simple amides $(i\mathrm{Pr})_2\mathrm{NC(O)Ar}$ (Ar = Ph, $\mathrm{C_{10}H_7}$) for directing lithiation has been adequately explained with reference to the known sterically induced amide-arene twist-angle.[79] While it is well documented that this angle has a bearing on the rate of lithiation,[79a] even these two relatively rigid and nearly perpendicular amides undergo efficient orthometallation.[79b][80] Accordingly, treatment of $(i\mathrm{Pr})_2\mathrm{NC(O)Ph/OEt_2}$ with *t*BuLi yields crystalline $(i\mathrm{Pr})_2\mathrm{NC(O)C_6H_4(Li{\cdot}OEt_2)}$-2 (**65**) with X-ray diffraction revealing a $(\mathrm{CLi})_2$-centred dimer in which the core is stabilised by the O-centres of $\mathrm{OEt_2}$ and of the amide carbonyl functionalities (amide-arene twist-angle of 47°). A similar structural motif is noted for $(i\mathrm{Pr})_2\mathrm{NC(O)C_{10}H_6(Li{\cdot}THF)}$-2 (**66**; twist-angle 65°), which is obtained from the 1:1 reaction of $(i\mathrm{Pr})_2\mathrm{NC(O)C_{10}H_7}$ with *t*BuLi in THF.[81] More complicated is the behaviour of 2-ethyl-*N*,*N*-diisopropylbenzamide with respect to *t*BuLi. Recent crystallographic results suggest that ortho- and lateral lithiation are in strongly solvent-dependent competition, with the formation of $(i\mathrm{Pr})_2\mathrm{NC(O)}$-2-Et-$\mathrm{C_6H_3Li{\cdot}THF}$ (**67**) − a dimer in the solid state − and $(i\mathrm{Pr})_2\mathrm{NC(O)C_6H_4CH(Li{\cdot}PMDETA)Me}$-2 (**68**; see below) being made possible by the employment of different reaction media.[82]



(65)$_2$

Unsurprisingly, 2-(*P*,*P*-dimethylphosphanylmethyl)phenyllithium-$\mathrm{OEt_2}$ (**69**)[83] and 2,6-bis(*P*,*P*-dimethylphosphanylmethyl)phenyllithium (**70**)[84] reveal solid-state dimers related to that of internally coordinated “N class”-controlled **46**.[61] Triphenylphosphane also undergoes efficient “P class” orthodirected metallation in the presence of *n*BuLi/$\mathrm{OEt_2}$. However, while 2-$\mathrm{Ph_2PC_6H_4(Li{\cdot}OEt_2)}$-2 (**71**) is a dimer in the solid state, its structure contrasts with that of **69** insofar as it fails to demonstrate Li−P bonding.[85] Bis(2-bromobenzyl)methylphosphane undergoes lithiation of both aromatic benzylic positions in the presence of TMEDA. This is of note in the context of the recently reported ring-activating properties of lithium substituents themselves.[86] Hence, bis(orthometallation) of the phosphane proceeds, upon treatment with *n*BuLi and via a lithium-halogen exchange mechanism,[19] to give $MeP[CH_2(C_6H_4Li\text{-}2)]_2{\cdot}2TMEDA$ (**72**). However, the monolithiation of each benzyl α-carbon centre in **72** occurs readily upon the subsequent introduction of *n*BuLi/TMEDA. The product (**73**) is a dimer in the solid state with four metal ions adopting a near planar equilateral rhombus, the edges of which are bridged both by as many deprotonated ortho carbon centres and two phosphane Group 15 donors. Peripheral to this core, four TMEDA-chelated metal ions are positioned: two are η^4-bonded to ligand phosphorus and benzyl centres and one ipso carbon centre while two more are each η^6-stabilised by the two remaining aromatic rings.[87]

A single crystallographic example of "P+N class" ortho-directed lithiation has been reported. Whereas reaction of the iminophosphorane $(2\text{-}C_5H_4N)_3P{=}NSiMe_3$ with MeLi proceeds via nucleophilic attack on the phosphorus, the same is not true of $Ph_3P{=}NSiMe_3$. In this latter case, the direction of ortholithiation affords an asymmetric dimer of $Me_3SiN{=}PPh_2C_6H_4Li{\cdot}{}^1/_2OEt_2$ (**74**) (*cf.* **44**).[28] The solid-state structure of **74** reveals that the orthometallated iminophosphorane anions N,C_{ortho}-chelate one of the two metal centres.[88]



(73)$_2$

Whereas an example in which "S+O class" direction supersedes "X class" direction of an ortholithiation process has already been discussed (*cf.* **41**)[57] it is, nonetheless, the case that the fluorine-based direction of orthometallation has been reported in synthetic contexts[26b] and, in rare instances, in the solid state. As part of an investigation into the magnitude of carbon-fluorine bond extension upon ortholithiation both 1,2,3,4-tetrafluorobenzene and (from it) the benzyne precursor (2,3,4,5-tetrafluoro)phenyllithium-tris(THF) (**75**) have been prepared. Complex **75** is a monomer in the solid state wherein external solvation of the metal obviates the need for lithium-fluorine interaction. However, at 3.448(4) Å $Li{\cdots}F_{ortho}$ is less than in **41**,[57] and this is consistent with the observation that **75** undergoes LiF elimination at temperatures as low as −40 °C.[89] Conversely, in spite of the inclusion of coordinating diethyl ether, metal-fluorine interactions are noted in the dimer of (2,4,6-trifluoromethyl)phenyllithium-OEt_2 (**76**).[90] In this case each metal centre is in part stabilised by two fluorine atoms on ortho-CF_3 groups.

Lateral Metallation

Lateral or benzylic metallation results from the ability of a directing group situated ortho to a given lateral group to both coordinate an organometallic substrate and withdraw electrons from the lateral group in question. The result is that ortho- and lateral metallation are competitive processes that result from the presence of the same classes of directing group.[3] The promotion of lateral metallation by a directing group is emphasised by the observation that whereas toluene can be laterally metallated by *n*BuLi/TMEDA,[91] 2-(dimethylaminomethyl)toluene affects the same reaction much more rapidly on treatment with *n*BuLi/OEt_2.[27][92]

Solution Studies

Fluorenyllithium (FlLi; **77**) has been studied with a view to understanding whether it exists as a contact ion pair (CIP) or a solvent-separated ion pair (SSIP). SSIP and CIP solid-state structures have been reported for fluorenyl derivative $Fl^-(Li^+{\cdot}4THF)$ (**78**)[93] and the related complex $FlLi{\cdot}2N(CH_2CH_2)_3CH$ (**79**),[94] respectively (see below). It has been noted that **77** affords SSIPs in THF solution at low temperature.[93] This view has been reinforced by $^6Li,^1H$ HOESY. Data suggest that **78** dissolves in [D$_8$]THF to give mostly SSIPs at low temperature but a higher proportion of CIPs in which the metal η^5-interacts with the central Cp ring at elevated temperatures.[95] In contrast, analysis of a [D$_{10}$]diethyl ether solution of **78** reveals that in this inferior solvent a CIP structure in which the metal is η^1-bonded to fluorenyl-C9 is preferred.[95]

The lateral direction of metallation by a lithium aryloxide moiety has been noted in $2,6\text{-}(CH_2Li)_2C_6H_3OLi{\cdot}TMEDA$ (**80**).[96] The solid-state structure (see below) reveals a tetramer, the solution integrity of which is implied (in hydrocarbon media at room temperature) by the ^1H NMR spectroscopic discrimination of aromatic 3- and 5-positions and the observation of three different metal environments in the ^7Li NMR spectrum. At elevated temperatures and in [D$_8$]THF symmetry about the Ar−O axis is implied spectroscopically.[96]

Whereas the ortho-directing capacities of 2-(dimethylaminomethyl) fragments have already been discussed,[29] their ability to incur lateral deprotonation has been probed by NMR spectroscopic study of the co-complex *n*BuLi·[2,6-$(Me_2NCH_2)_2{-}3,5\text{-}Me_2C_6HCHLiR$]. (R = H **81**,[97] $SiMe_3$ **82**, *t*Bu **83**, 4-toloyl **84**[98]). At low temperature, a ^6Li-enriched sample of **81** reveals two signals, with $^6Li,^6Li$ INADEQUATE spectroscopy[99] affording a homonuclear scalar coupling and suggesting retention of the tetranuclear co-complex noted in the solid state (see below).[100] Unambiguous assignment of the two ^{6}Li resonances is enabled by ^{6}Li,^{13}C HMQC spectroscopy[35c] on the basis that the metal ions bonded to *two* butyl anions show the higher intensity ^{6}Li,^{13}C$_\alpha$ correlation; assignment of these ^{6}Li resonances also allows interpretation of the ^{15}N and ^{6}Li,^{15}N HMQC[101] NMR spectra (natural abundance with respect to ^{15}N). Accordingly, 1:1:1 triplets observed in the first of these experiments are attributable to ^{6}Li,^{15}N interactions.[29] For **81**−**84**, reaction of 1,3-bis(dimethylaminomethyl)-2,4,6-trimethylarene with *n*BuLi has yielded a 2:2 mixed butyllithium-aryllithium cluster. However, whereas that noted for **81** is pseudo-cubic, the use of **82** gives a ladder structure (see below). NMR spectroscopy and cryoscopic relative molecular mass measurements combine to suggest that **81** retains its pseudo-cubane structure in hydrocarbon solution. Hence, at low temperatures (< -10 °C) the ^{1}H NMR spectrum of **81** reveals four signals for the two NMe$_2$ functions, two signals for the two ArMe groups, two AB multiplets for the two CH$_2$N units and an ArH singlet. Such diastereotopicity of the dimethylaminomethyl moieties suggests the absence of a symmetry plane through ipso and para positions perpendicular to the arene. Such a symmetry element is, however, manifest above room temperature, where a single AB pattern, two NMe signals and one ArMe singlet are seen. If the sample is heated to above +100 °C then the AB pattern and NMe peaks coalesce into single lines. In conjunction with the ^{6}Li NMR spectrum, which reveals a single peak, these data suggest rapid scrambling of the four organic anions.[97] For **82**, ^{1}H NMR spectroscopy points — through the observation of two AB patterns for the NCH$_2$ groups — to asymmetric interaction of the benzylic anion with two Li$^+$ ions (see below) and to the static nature of Li−N interactions at and below room temperature. However, a rapid fluxional process involving the dissociation/association of these bonds is evidently manifest at higher temperatures, with one singlet and one AB pattern observed for the two NMe$_2$ and NCH$_2$ groups, respectively.[98] In solution, both **83** and **84** appear to be close structural analogues of **82**.[98]

The establishment that lateral metallation occurs under the influence of a tertiary amide directing group has recently been probed both theoretically and in the solid state (see below).[102] This follows on from formative studies, which established that enantiomerically pure α-stanyllated anilides undergo tin-lithium exchange and electrophilic workup with retention and inversion of configuration, respectively.[103] Thus, 2-ethyl-*N*,*N*-diisopropyl-1-naphthamide has been metallated using *s*-BuLi to give a pair of configurationally stable diastereomeric *syn* atropisomers of (iPr)$_2$NC(O)C$_{10}$H$_6$CHLiMe-2 (**85a**). Reaction of **85a** with Bu$_3$SnCl yields the corresponding *syn* and *anti* stannylated atropisomers in the kinetic ratio 89:11, with subsequent heating establishing a 4:96 equilibrium.[104] While lithiation of the thermodynamic *anti* stannylated atropisomer yields *syn*-**85a**, the *syn* stannylated atropisomer itself lithiates to give a 60:40 *syn*:*anti* (**85a**:**85b**) mixture. ^{1}H NMR studies have corroborated the non-stereospecific nature of each of these two reaction steps, revealing the existence of non-interconverting *syn* and *anti* stannylated diastereoisomers in THF at −40 °C.[104] In contrast, the dissolution of preformed (iPr)$_2$NC(O)C$_{10}$H$_6$CH(Li·3THF)Me-2 (**86**; see below) in [D$_8$]THF appears to yield (by ^{1}H NMR spectroscopy) one dominant solution species, with the observation of two diastereotopic *i*Pr groups at −25 °C pointing to slow rotation about the amide C−N bond below room temperature. Two diastereotopic *i*Pr moieties are also noted at −25 °C in [D$_8$]-toluene, as are signals attributable to the deprotonated α-CH group. However, at −48 °C in [D$_8$]-toluene all ^{1}H NMR resonances split into two in a 60:40 ratio, suggesting that diastereoisomers interconvert very much faster, with NMR spectroscopy showing rapid exchange in solution above this temperature.[102]

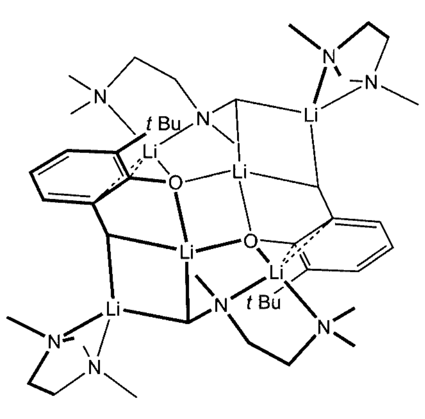
Metallation of the tertiary phosphane MeP(C$_6$H$_4$CH$_2$NMe$_2$−2)$_2$ using *t*BuLi yields a dimer of the benzyllithium product MeP(C$_6$H$_4$CH$_2$NMe$_2$−2)-(C$_6$H$_4$CHLiNMe$_2$−2)$_2$ (**87**) that exhibits novel dynamics in [D$_8$]toluene solution.[105] In spite of this it is apparent that the main features of the solid-state structure are retained at 203 K. However, ^{31}P and ^{7}Li NMR spectroscopy reveal that at elevated temperatures each metal can be associated with either phosphorus atom in the dimeric structure, but not with both simultaneously.

Solid-State Studies

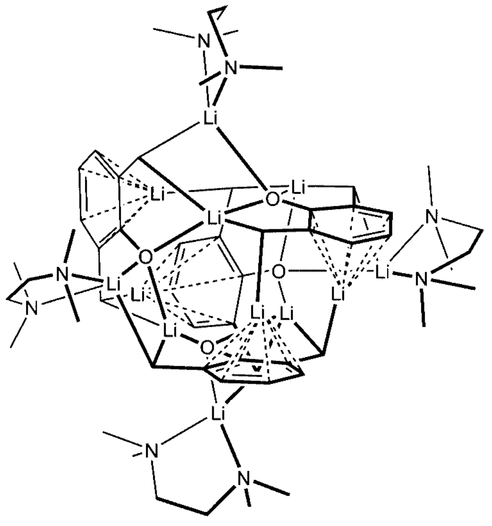
Several solid-state structures have been published in which metallation has been laterally directed by the acidifying (delocalising) action of a 1-aryl substituent. In this context, the biphenyl derivatives 2-(CH$_2$Li·PMDETA)-6-MeC$_6$H$_3$(C$_6$H$_3$Me$_2$−2,6) (**88**)[106] and (the dimer of) 2-(CHRLi·TMEDA)C$_6$H$_4$ (R = H **89**, SiMe$_3$ **90**)[107] have been characterised. Moreover, the structure of 2,2′-bis(TMEDA)lithiomethyl-1,1′-binaphthyl (**91**) has also been reported.[106] Just as ortholithiation has been noted in aromatic alkenes (*cf.* **13**),[34] so the 1,3-dialkyl lateral direction of metallation has been noted in the α-deprotonation of styrene. Hence, simple dimers of 2,6-Me$_2$C$_6$H$_3$C(Li·L)=CH$_2$ [L = OEt$_2$ **92**, MeO(tBu) **93**] have been reported.[108] Whereas both SSIP and CIP structures have been noted for fluorenyllithium complex **78** upon dissolution in Lewis base media,[95] X-ray crystallography has established an ion-separated structure in the solid state.[93] Meanwhile, the related species **79** has been found to be a CIP with η^3-stabilisation of the metal via the 1-, 9- and 10-fluorenyl positions.[94] More recently, two lithium complexes have been generated from the substituted fluorenyl ligand 9-(dimethylaminoethyl)fluorenyl (Fl$^{\mathrm{N}}$). In either case deprotonation at the 9-position is accompanied by internal amine-coordination, the presence of etherate solvent also supporting the metal. In Fl$^{\mathrm{N}}$Li·OEt$_2$ (**94**) the metal exhibits η^5-interaction with the anion, while this is reduced to η^2-bonding in Fl$^{\mathrm{N}}$Li·2THF (**95**).[109]

In contrast to **92** and **93**, where external solvation combined with the lack of directing group donor sites to obviate the possibility of clear metal-directing group interaction, a single example of a (2-methoxy)-stabilised aromatic allene has been reported. In 2-MeOC$_6$H$_4$C(Li·OEt$_2$)=C=CPh$_2$

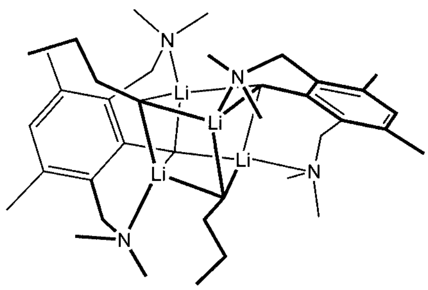
(**96**) the metal forms part of a five-membered ring incorporating both the methoxy oxygen atom and the site of formal deprotonation.[110] Whereas a methoxy directing-group is itself passive to direct metallation, the other common "O class" director hydroxyl is, of course, itself susceptible to deprotonation. As such, this latter group will only act as a director of subsequent reaction in its phenoxide form and in the presence of excess metal. Sterically congested 2-methyl-6-(*tert*-butyl)phenol undergoes just such a reaction to give a hexalithium aggregate of 2-CH_2Li-6-(tBu)$C_6H_3OLi{\cdot}Me_2N(CH_2)_2N(Me)CH_2Li{\cdot}$TMEDA (**97**). This complex contains a laterally lithiated aromatic system and both deprotonated and unchanged TMEDA.[111] Dimerisation of **97** occurs *via* the formation of an $(OLi)_2$ ring, each metal component of which is also supported by interaction with $ArCH_2^-$ (that is, chelated by the aryl dianion) and NCH_2^-. An investigation of "superbase" structural chemistry[112] has led to the deprotonation of 2,6-dimethylphenol in the presence of TMEDA and the unexpected formation of a dodecalithium tetramer of 2,6-$(CH_2Li)_2C_6H_3OLi{\cdot}$TMEDA (**80**) wherein the lack of steric congestion [relative to that noted for 2-methyl-6-(*tert*-butyl)phenol] combines with the introduction of a second acidic methyl substituent on each aromatic ring to allow the generation of organic trianions.[96] The tetramer core is defined by an elongated eight-membered $(OLi)_4$ boat-shaped ring, at either end of which reside $Li^+{\cdot}$TMEDA units. Such a structure contains three unique metal environments; an observation consistent with solution studies (see above).[96]



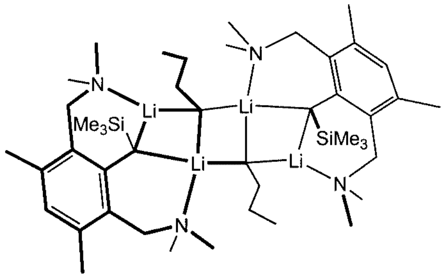
(97)$_2$



(80)$_4$



(81)$_2$



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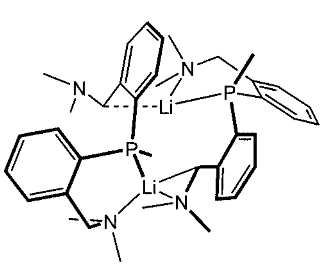


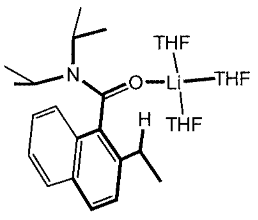
(87)$_2$

The lateral directing capacity of "N class" substituents such as R_2N- and $R_2N(CH_2)_n$- have been the subject of investigation. As already discussed, extensive solution studies have been carried out on the various lateral lithiates obtained utilising the directing abilities of 2,6-bis(dimethylaminomethyl) substituents. As part of these studies, the (n-butyllithium)-containing co-complexes nBuLi·[2,6-$(Me_2NCH_2)_2$−3,5-$Me_2C_6HCHLiR$] (R = H **81**,[97] $SiMe_3$ **82**, tBu **83**, 4-toloyl **84**[98]) have been prepared and fully characterised. The solid-state structure of **81** reveals a $(CLi)_4$ pseudo-cubic dimer of dimers with each metal centre being supported by a single dimethylaminomethyl donor centre.[97] Attempts to overcome pseudo-cubane formation have revolved around the introduction of a non-hydrogen α-substituent, with R = trimethylsilyl affording **82**. The solid-state structure of **82** reveals a $(CLi)_4$ ladder, at either end of which resides an asymmetrically bonded benzylic anion.[98] The straightforward lithium salt 2-Me_2N-

$Me_3Si(TMEDA{\cdot}Li)CHC_6H_4$ (**98**) is a solid state monomer incorporating N-centre chelation of the metal, with transmetallation yielding the potassium congener as a precursor to the bis(benzyl)strontium species.[113] Moreover, the higher Group 15 analogue 2-Ph_2P-Me_3Si-$(TMEDA{\cdot}Li)CHC_6H_4$ (**99**) has been reported.[114] Nitrogen and phosphorus donor centres can, of course, act in tandem and, as such, the previously discussed benzyllithium dimer of $MeP(C_6H_4CH_2NMe_2{-}2))C_6H_4CHLiNMe_2{-}2)_2$ (**87**) reveals both intra- and intermolecular direction of lithiation in the solid state. Whereas one metal centre is η^2-bonded by both the benzylic carbon with which it is formally associated and the adjacent α-nitrogen, the second metal ion shows no intramolecular N-stabilisation. It instead exhibits a weak intermolecular interaction with a benzylic carbon centre. Both alkali metal ions are intermolecularly chelated by P- and N-donors.[105]

Concerning "N+O class" directing agents, the competitive formation of $(i\mathrm{Pr})_2NC(O)$-2-Et-$C_6H_3Li{\cdot}THF$ (**67**) and $(i\mathrm{Pr})_2NC(O)C_6H_4CH(Li{\cdot}PMDETA)Me$-2 (**68**) has already been alluded to.[82] This latter compound is structurally analogous to the product of reaction between 2-ethyl-*N*,*N*-diisopropyl-1-naphthamide and *t*BuLi in toluene/THF. Crystallography reveals that $(i\mathrm{Pr})_2NC(O)C_{10}H_6CH(Li{\cdot}3THF)Me$-2 (**86**) is monomeric in the solid state, there being no Li−C interaction and the metal instead being entirely oxygen-supported.[102] Calculations (at the 6-311G**/B3LYP level) on $(i\mathrm{Pr})_2NC(O)C_{10}H_6CH(Li{\cdot}3OMe_2)Me$-2 corroborate the stability of the crystallographically characterised tris(solvate) and suggest that cleavage of the $Li{-}C_\alpha$ interaction occurs in order to allow coordination of the third solvent molecule. In consequence, the calculated enthalpy of complexation for the introduction of this donor molecule is largely negated.[102]

Whereas the absence of structural data on ortholithiated pyridines has already been mentioned, 2-[bis(trimethylsilyl)methyl]pyridine is known to undergo lateral deprotonation. It is now several years since the solid-state structure of the dimeric product was first revealed.[115] Recently, however, this species has been revisited, with a topological analysis of single crystal neutron diffraction data being combined with DFT calculations to reveal that in the dimer of $2\text{-}(Me_3Si)_2CLiC_5H_4N$ (**100**) delocalisation of the C−Li bonding electrons over the agostic alkyl group controls the geometry of the Si−C−Li bond angle.[116] Just as ortho- and lateral deprotonation represent competing reactions in the case of 2-[bis(trimethylsilyl)methyl]pyridine, the lithiation of 2,6-disubstituted analogues has led to the elucidation of both the monolithiate $[2\text{-}Me\text{-}6\text{-}CH_2LiC_5H_4N]_2$ (**101**)[117] and the monomeric dilithiate $2,6\text{-}[Me_3SiCH(Li{\cdot}TMEDA)]_2C_5H_4N$ (**102**).[118] In this last complex the aromatic dianion acts as a η^2-donor to each of the two metal ions, utilising its formal charge centres and pyridyl nitrogen to do this. More complicated is the mixed anion-dianion product of reaction between 2-hydroxy-6-methylpyridine and *n*BuLi. Deprotonation is effected not only at the hydroxy position in all ligands within the cluster, but also at the orthomethyl group in four of these ligands, making the product $(2\text{-}OLi\text{-}6\text{-}CH_2LiC_5H_3N)_4{\cdot}(2\text{-}OLi\text{-}6\text{-}MeC_5H_3N)_6{\cdot}9THF$ (**103**).[119]



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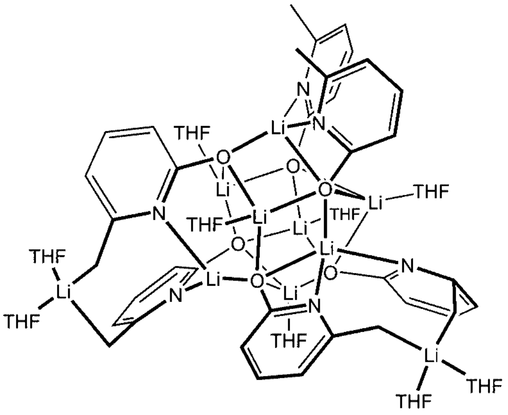

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Perimetallation

Contrary to ortho- and lateral metallation, perimetallation occurs in the absence of electron-withdrawing properties in the directing group. Instead, whereas evidence exists (see above) for the kinetic nature of deprotonation at the ortho position, a perimetallated salt represents the thermodynamic product of reaction between organolithium and substituted arene.

Solution Studies

The THF-solvated and perilithiated derivative of 1-(dimethylamino)naphthalene has been probed by low-temperature ^{13}C NMR spectroscopy, with both the observed $^1J(^{13}C,^7Li)$ coupling constant of 20.5 Hz and the sevenfold multiplicity of the peri carbon resonance suggesting that 1-(dimethylamino)-8-naphthyllithium·THF (**104**) is dimeric in $[D_8]$THF at −90 °C.[120]

In light of formative MNDO studies,[121] the perimetallation of 1-naphthol in THF to give $LiOC_{10}H_6Li\text{-}8{\cdot}THF$ (**105**) has been studied both as a function of the *n*BuLi:1-naphthol ratio and (for reaction in a 4:1 ratio) as a function of temperature. Moreover, $^6Li,^1H$ HOESY[122] has revealed the presence of a strong correlation for the peri hydrogen and has thus established the intermediacy of a mixed aggregate in the deprotonation of 1-naphthol.[123] Whereas the ortholithiation of 1-methoxynaphthalene by *n*BuLi/TMEDA (to give **6**) has already been alluded to effect perimetallation. Moreover, the isotope effect suggestive of kinetic control in the former reaction is not observed in the latter case, pointing to perimetallated product **8** representing the thermodynamic one.[25]

The ability of lithium itself to direct perimetallation has been investigated in the context of the dilithiation of naphthalene. ^{6}Li,^{1}H HOESY[122] and one-dimensional ^{6}Li{^{1}H} spectroscopy[36b] have been employed to probe the 1:1 complex between 1-naphthyllithium and TMEDA (**106**) with data suggesting chelation of the metals in a dimeric aggregate. Treatment of **106** with *n*BuLi has long been known to effect the formation of $1,8\text{-}Li_2C_{10}H_6$ (**107**),[124] with ^{6}Li,^{1}H HOESY more recently revealing a cross-peak involving the peri hydrogen atom prior to reaction and suggesting activation of this position.[122]

Solid-State Studies

Little structural work has been done on perimetallated systems in the solid state. The simple dimers of 1-(dimethylamino)-8-naphthyllithium·THF (**105**) and 1-methoxy-8-naphthyllithium·THF (**108**) obtained from the reaction of *n*BuLi with “N class” and “O class” directors 1-(dimethylamino)naphthalene[120] and 1-methoxynaphthalene,[120,125] respectively, have been crystallographically characterised. In each case the metal components of a core $(C_{peri}Li)_2$ ring are supported by reaction-directing amine or methoxy heteroatoms and, for **105**, this renders the structure analogous to that noted in Lewis base solution (see above). The core-naphthyl twist-angle of 63° in the crystal structure of **105** is decreased to 38° in that of **108**. If the inferior Lewis base OEt_2 is used in place of THF then the twist-angle is reduced further, such that dimeric 1-(dimethylamino)-8-naphthyllithium·OEt_2 (**109**) reveals an 11° twist.[69,126] This trend is backed up by semi-empirical (PM3) calculations.[120]

Conclusions

Directed metallation using Group 1 organometallic bases in general and organolithium substrates in particular has been shown to be of great efficacy in regiospecifically elaborating benzenoid rings (ortho-, perimetallation) and their substituents (lateral metallation). While the manifold synthetic applications of this chemistry have been extensively reviewed[1,3,8] the structural parameters surrounding lithiated species of types salient to such processes have been discussed here.

Of interest in interpreting the ability of directing groups to interact with incoming organolithium substrates are the structural elucidation of several species that incorporate either *tert*- (*cf.* **30**)[42] or *n*BuLi. The latter have taken the form of both organolithium-organic complexes (*cf.* **3**, **4**, **7**)[22,23,25] that represent precursors to directed reaction and mixed-anion organolithium co-complexes (*cf.* **33**, **48**, **61**, **64**, **81−84**).[38,62,75,78,97,98] This latter class of aggregates pose interesting questions about the nature of multilithiation processes.[78]

In the context of straightforward monolithiates many of the compounds discussed reveal structural characteristics normal to the field of organolithium chemistry. However, the inclusion of various mono- (e.g. “O class” or “N class”) or polyheteroatom (e.g. “N+O class”) directing groups has had significant effects in several cases. The ability of various electron-rich directors to interact with metals at ortho, lateral and peri sites is richly demonstrated and has been shown to effect observed chemistries in synthetically important transformations such as tertiary amide directed metallation.[81−82] Less predictable are polymetallated species. Nevertheless, fundamentally similar chelation-control processes to those noted in monolithiates dictate their structures. Overall, the synthetic utility of directed metallation is well established and promises to facilitate the development of new methodologies and total syntheses in the future. Central to the understanding of these processes is the understanding of organolithium complexes of the types discussed here.

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