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Alkali-Metal Amides

Synthetically Important Alkali-Metal Utility Amides: Lithium, Sodium, and Potassium Hexamethyldisilazides, Diisopropylamides, and Tetramethylpiperidides

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Most synthetic chemists will have at some point utilized a sterically demanding secondary amide (R_2N^-). The three most important examples, lithium 1,1,1,3,3,3-hexamethyldisilazide (LiHMDS), lithium diisopropylamide (LiDA), and lithium 2,2,6,6-tetramethylpiperidide (LiTMP)—the "utility amides"—have long been indispensible particularly for lithiation (Li-H exchange) reactions. Like organolithium compounds, they exhibit aggregation phenomena and strong Lewis acidity, and thus appear in distinct forms depending on the solvents employed. The structural chemistry of these compounds as well as their sodium and potassium congeners are described in the absence or in the presence of the most synthetically significant donor solvents tetrahydrofuran (THF) and N,N,N',N'*-tetramethylethylenediamine (TMEDA) or closely related solvents. Examples of hetero-alkali-metal amides, an increasingly important composition because of the recent escalation of interest in mixed-metal synergic effects, are also included.*

From the Contents

1. Introduction

First utilized several decades ago, alkali-metal secondary amides represent one of the most commonly encountered classes of reagents in synthetic chemistry today.[1] This usage can, in general terms, be attributed to their considerable complementary Brønsted basicity and poor nucleophilicity, thus making them rival candidates to the more basic but more nucleophilic alkyllithium reagents for abstracting a proton from a substrate (exchanging a C–H bond for a polar, reactive C–metal bond), a prerequisite for functionalization of a substrate. Furthermore, they are generally more soluble in hydrocarbon media and are safer to handle than their principal rivals, the alkali-metal hydride or alkyl reagents, for this task. The most important secondary amides are 1,1,1,3,3,3-hexamethyldisilazide (HMDS), diisopropylamide (DA), and 2,2,6,6-tetramethylpiperidide (TMP, Figure 1), which we collectively refer to as the "utility amides" because of their immense popularity with the synthetic community. Their collective popularity was evident as early as 1984 when Fraser and Mansour[2] noted: "*LiTMP has become widely used in organic reactions as has lithium bis(trimethylsilyl)amide and perhaps most frequently, lithium diisopropylamide.*"

Indeed, the utility amides each command their own dedicated sections in one of the premier resources of organic chemistry, *Fieser and Fieser's Reagents for Organic Synthesis*.[3] Their popularity is not only attributable to the ease with which they operate and can be handled, but also to economic considerations. The parent amines diisopropylamine and 1,1,1,3,3,3-hexamethyldisilazane are currently commercially available at £12.20 and £12.90 per 100 mL, respectively, which equates to a price of £15.99 and £27.04 per mole. 2,2,6,6-Tetramethylpiperidine is noticeably more expensive at £129.40 for 100 mL, or £220.03 per mole.[4] However, TMP(H) still garnishes a lot of attention as it has the highest pK_a value of the three secondary amines. This considerably greater price can principally be attributed to its more complicated synthesis. Indeed, Collum and co-workers have utilized the slightly modified 2,2,4,6,6-pentamethylpiperidine [PMP(H)] in its place to restrict rapid conforma-

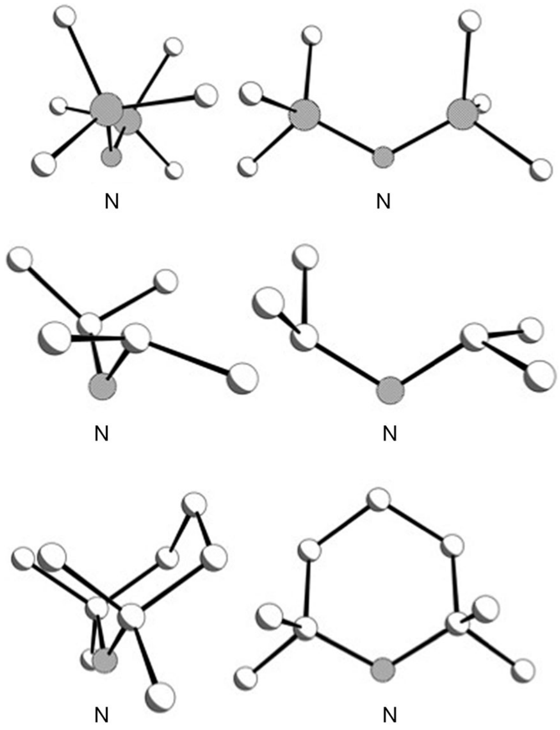

Figure 1. Side-on and face-on views of the molecular structures of the amide anions of HMDS (top), DA (middle), and TMP (bottom).

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tional exchange (chair–chair interconversions) of TMP.[5] The extra methyl group in the 4-position is remote from the site of reactivity and thus has a negligible effect on the reactivity. While not yet commercially available, a cheap procedure for the preparation of PMP(H) may well establish it as a utility amide of the future.

It is a synthetic chemist's dream to design an all-purpose organometallic reagent that can perform any and every proton abstraction task selectively. While the realization of that dream remains some way off, it is noteworthy that, together, these three amides account for a huge proportion of known deprotonation applications. It is of course not only the deprotonation reaction which can be executed with alkali-metal utility amides (see Section 2). For example, lithium–halogen exchange using alkali-metal amides is well documented, while alkali-metal amides are the reagent of choice for the generation of enolates because of their non-nucleophilic nature precluding them from adding across sensitive carbonyl functions.

These reagents can often have their reactivity boosted by deaggregation through either a stoichiometric or bulk amount of a "solvating" Lewis donor ligand. Given the frequent use of the alkali-metal utility amides, it is highly desirable to understand their chemical make-up both in the solid state (through X-ray crystallographic molecular-structure determinations) and in the solution state (predominantly through NMR spectroscopy). Although these structures may differ between the two states for any given compound, it is still desirable to be fully appraised of both, because of the close relationship between structure and reactivity and the fact that the former structures often provide important first clues as to the nature of the more complex latter structures. There is of course a rich diversity of architectures open to a class of aggregating compounds such as this: they can form both cyclic and acyclic motifs and can form extended structures in many instances according to the now well established ring-stacking and ring-laddering principles which are pervasive within alkali-metal chemistry.[6] The latter principle is particularly germane in the context of amide structures.[7]

Unsurprisingly, the lithium derivatives have commanded the most attention for a variety of reasons, which include their superior stability with respect to their heavier sodium and potassium analogues, their increased tolerance of polar solubilizing Lewis donor ligands (many of the more aggressive Na/K utility amides will attack such ligands), their higher solubility, which in turn increases the opportunities for obtaining crystalline materials of sufficient quality to perform a molecular structure determination, and of course the availability of a good NMR handle (in the form of ^{6}Li and ^{7}Li) to make their solution-state characterization considerably more facile. That said, a wealth of research has also been carried out on sodium and potassium utility amides, and to a lesser extent the rubidium and caesium analogues. While some reviews of the solution-state characteristics of the individual utility amides[8] or the molecular structures of alkali-metal-containing species in general[9] have appeared in the literature, we felt that it was timely to have an up-to-date single-source survey of the literature dedicated to both the solution and solid-state structures of this globally important class of compound. This will enable their behavior in various solvents to be easily compared and contrasted and could allow correlation of the data with similarities and differences in their molecular structures. We begin with a brief summary of the preparation and synthetic uses of the title compounds before embarking on a comprehensive treatise of their solution and solid-state structures in the presence of a variety of synthetically important solvents, commencing with the now well-established homometallic derivatives, before finally introducing briefly the relatively new class of hetero-alkali-metal amides.

1.1. Scope

This Review is limited to those homoanionic utility amides which contain only the alkali-metals lithium, sodium, or potassium (either on their own or in combination with one another), as these metals are by far the most synthetically important members of Group 1 for organic transformations. Indicative of the widespread interest in the field, a search of the crystallographic database for alkali-metal NR$_2$ structures records 155, 54, and 135 hits for HMDS, DA, and TMP, respectively.[10] Those complexes within these numbers which contain another (non-alkali) metal are not reviewed here as many of these complexes have been previously discussed extensively elsewhere.[11] Thus, with synthetic chemists in mind, we have restricted the crystallographic discussion to those complexes which contain either no donor, or the common synthetically significant Lewis donors THF and TMEDA[12] as well as their close derivatives. The

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Stuart D. Robertson comes from Falkland, Fife, Scotland. He obtained his MChem (2002) and PhD (2006) at the University of St. Andrews, the latter in the group of Prof Derek Woollins. This was followed by three years of postdoctoral research at the University of Calgary, Canada, under the mentorship of Prof. Tris Chivers. In 2009 he returned to Scotland to join Prof. Robert Mulvey's group at the University of Strathclyde, where he now holds a Royal Society of Edinburgh/BP Trust Fellowship.

numbering system employed is designed simply to collate complexes with the same alkali metal and anionic make-up and in no way is intended to give details of aggregation state, degree of solvation, etc. The solid- and solution-state chemistry of the homometallic species will be discussed in separate sections; however, we have combined the two classes for heterometallic complexes for brevity as there is much less literature pertaining to them, and the two classes have invariably been addressed within the same publication or series of publications.

2. Preparation and Uses in Synthesis

Table 1 lists some key milestones in the development of alkali-metal utility amides. The oldest of the three amines considered here, to the best of our knowledge diisopropylamine, was first prepared in 1868 by Siersch from KCN and 2-iodopropane.[13] Nowadays, it is typically prepared by the hydrogenation and ammoniation of acetone[14] and is the cheapest of the utility amines when bought commercially. Its lithium form (prepared by deprotonating the secondary amine with phenyllithium) was first used by Hamell and Levine in 1950 in their study of the reactions of esters with substituted lithium amides.[15] These authors noted that there was no addition at the double bond ,but only attack of the α-hydrogen atom. Ten years later, Levine was also responsible (this time with Raynolds) for the first preparation of the sodium congener, which was used as the condensing agent for the direct acylation of 3-picoline with aliphatic esters to yield alkyl 3-picolyl ketones.[16] The heavier potassium congener KDA was first used in 1978,[17] essentially as a non-nucleophilic amido rival to the by then well-established Lochmann–Schlosser KO*t*Bu/Li*n*Bu superbase.[18] Prepared in a similar manner by adding DA(H) to a superbasic suspension of the Lochmann–Schlosser reagent in hexane, or by adding *n*BuLi to DA(H)/KO*t*Bu, this was found to be superior than either LDA or KHMDS for the deprotonation of weakly acidic compounds.

Table 1: Important milestones in the development of utility amides.[a]

Year	Comment
1868	The first report of DA(H) appears in the literature by Siersch
1885	Canzoneri and Spica prepare TMP(H) in an impure form
1905	Franchimont and Friedmann synthesize "α,α′-tetramethylpiperidine"
1944	HMDS(H) prepared by Sauer
1950	LiDA used for the α-deprotonation of esters by Hamell and Levine
1955	Wittig observes increased reactivity of mixed Li/Na-phenyl complex
1959	Wannagat and Niederprüm make LiHMDS
1960	Levine and Raynolds use NaDA for the synthesis of picolyl ketones
1961	Na and KHMDS isolated, again by Wannagat and Niederprüm
1967	Lochmann and Schlosser independently witness superior metalating power of a *n*BuLi/KO*t*Bu mixture, thereby resulting in their eponymous superbase
1972	LiTMP used in two independent publications—rearrangement of epoxides and deprotonation α to a boron atom
1978	KDA paired with *n*BuLi to form an amido-centred rival to the Lochmann–Schlosser superbase
1986	Ahlbrecht and Schneider exploit the high pK_a value of KTMP for the acidity measurements of benzyl compounds
1999	NaTMP isolated and characterized by Lappert and Mulvey

[a] Style of year represents amide in question (**bold**, HMDS; *italics*, DA; underlined, TMP).

Sauer first described hexamethyldisilazane in 1944 as a precursor to trimethylsilanol and obtained by ammonolysis of trimethylchlorosilane.[19] The alkali-metal HMDS complexes were subsequently described by Wannagat and Niederprüm, firstly the lithium derivative in 1959[20] and then the heavier sodium and potassium congeners two years later.[21] These heavier salts had previously been alluded to (by Goubeau and Jiménez-Barberá,[22] and Hauser and Hance,[23] respectively), but they had only been prepared as in situ intermediates and apparently not isolated or characterized. The successful preparation of the sodium derivative, prepared by a radical reaction involving sodium metal in styrene, was in sharp contrast to the findings of Sauer and Hasek, who had earlier noted the stability of the NH bond of HMDS(H) when heated at reflux in the presence of sodium for 16 h.[24]

Franchimont and Friedmann are generally credited as preparing TMP(H) for the first time (but they referred to it as α,α′-tetramethylpiperidine),[25] although they themselves noted that Canzoneri and Spica had prepared it (albeit in an impure condition) 20 years earlier.[26] The method of Franchimont and Friedmann involved reduction of 4-bromotetramethylpiperidine with a copper–zinc couple. Currently, the method of choice is Wolff–Kishner–Huang reduction of cheap 2,2,6,6-tetramethyl-4-piperidone (triacetonamine), as recently described by Schlosser and co-workers (Figure 2).[27] The lithium derivative was first considered in 1972 in the base-induced rearrangement of epoxides[28] and as a sterically hindered base for deprotonation at a carbon center adjacent to a boron atom[29] (since base coordination to boron is the typical outcome when an unhindered base is utilized). The strong basicity of KTMP was exploited by Ahlbrecht and Schneider in 1986[30] to determine the p*K* values of some (weakly acidic) benzyl compounds, since the increased basicity of KTMP allowed them to span a wider range of p*K* values than had been accessible previously. Similar to DA, this base was essentially an amido derivative of the Lochmann–Schlosser superbase as it was derived from a LiTMP/KO*t*Bu couple. Sodium TMP was first reported by the joint research groups of Lappert and Mulvey, who had independently synthesized it by deprotonation of the parent amine with *n*BuNa or transmetalation of the lithium salt with NaO*t*Bu, respectively.[31]

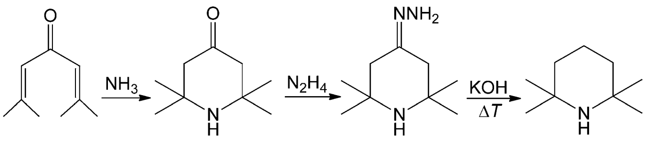


Figure 2. Synthesis of TMP(H).

As mentioned previously, the principal use of the alkali-metal utility amides is as a proton abstractor, with their non-nucleophilicity making them ideal tools for deprotonating ketones or aldehydes, since addition across the double bond is precluded. Indeed, Collum has noted that lithium dialkylamides are the preferred bases for the formation of ketone enolates.[8a] Lithium utility amides have received the most attention in this context because of the previously discussed reasons of increased solubility and ease of handling with respect to their heavier sodium and potassium congeners. These heavier alkali metals can be turned to, however, when a challenging, less acidic site is the target of deprotonation, as exemplified by Brandsma and co-workers in the metalation of isoprene.[32] Furthermore, they of course constitute a component part of the multicomponent alkali-metal-mediated metalating agents and inverse crown family of complexes, which have been comprehensively discussed elsewhere.[11a,b,33] The effectiveness of alkali-metal utility amides for deprotonation stems from their high pK_a values. The pK_a values of utility amides has provoked much discussion, with their acid dissociation constants being heavily dependent on variables such as alkali-metal identity, solvent (and by extension aggregation state), temperature, and reference acid. Consequently, it has proven difficult to obtain a consensus of opinion regarding either experimentally determined or theoretically calculated pK_a values for the utility amides. What appears to be universally accepted is the order of the pK_a values of these three bulky secondary amides, with the value for HMDS considerably lower than that of DA, which in turn has a moderately lower value than that of TMP. The variety of reported values for lithium derivatives are summarized in Table 2.

Table 2: Reported pK_a data for lithium utility amides.

Author	HMDS	DA	TMP	Method
Fraser[2,34]	29.7	35.7	37.3	^{13}C NMR spectroscopy in THF
Ahlbrecht[30]	–	34.4	37.9	^{1}H NMR spectroscopy in THF
Streitwieser[35]	24.37	35.41	35.53	computed at HF-6-31+G* level
Streitwieser[35]	23.1	–	–	single indicator technique in THF

This ordering of the pK_a values can be attributed to a combination of electronic and steric effects. From a steric point of view, the nitrogen atom of TMP clearly has the greatest steric protection, as demonstrated qualitatively in Figure 3. One might consider the $SiMe_3$ group to be bulkier than $CHMe_2$; however, as Figure 3 shows, the longer N–Si and Si–C bonds, with respect to the N–C bonds, diminishes the steric profile of this tertiary group compared to that of the secondary alkyl group.

It would be a mammoth task to report every single literature usage of the title compounds in synthesis;[3] however, in an attempt to highlight the versatility of this powerful class of reagent some of the more important general uses are summarized briefly below. The use of alkali-metal amides (particularly those of the lightest member lithium) as selective agents for directly replacing a hydrogen atom with an alkali metal (that is, usually where the alkali metal occupies the exact position vacated by the hydrogen atom, although sometimes isomerizations through resonance take place) has been individually reviewed elsewhere[3] and consequently we will not go over old ground here. These selective proton abstraction powers also make alkali-metal amides excellent facilitators for the generation of enolates from substrates containing a hydrogen atom on a carbon center which is adjacent to a carbonyl function [Eq. (1)].[36]

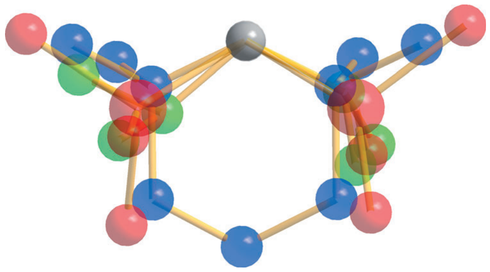
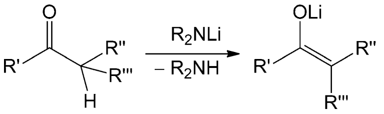


Figure 3. Superimposition of the amides HMDS (red), DA (green), and TMP (blue) to allow comparison of steric bulk, with the nitrogen atoms (gray) occupying a common point.

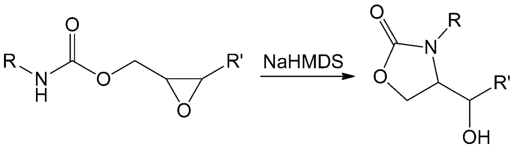


(1)

The straightforward synthesis of alkali-metal secondary amides by deprotonating the parent amine (R_2NH) with an alkyl lithium reagent, for example, makes them ideal reagents for the preparation of softer metal amides through salt metathesis processes with the relevant metal halide [Eq. (2)]. As a pertinent example, the Group 12 bisamides $M(TMP)_2$ ($M = Zn$,[37] Cd[38]) are prepared in a facile manner by exposing MCl_2 to pre-prepared Li(TMP), while Lappert and co-workers have prepared a series of lanthanide TMP complexes by a similar method.[39]

$$x\,R_2NH + x\,R'Li \xrightarrow[-x\,R'H]{} x\,R_2NLi \xrightarrow[-x\,LiCl]{MCl_x} M(NR_2)_x \qquad (2)$$

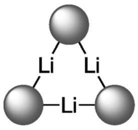
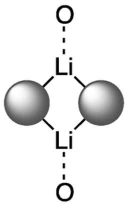
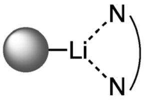
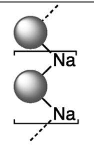
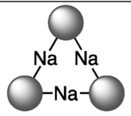
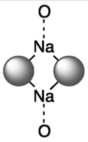
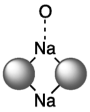
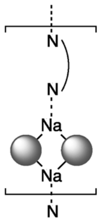
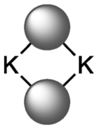
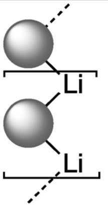
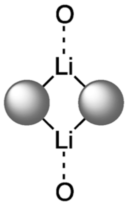
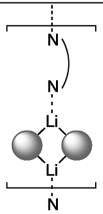
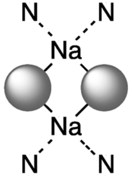
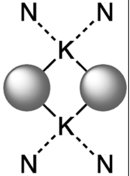
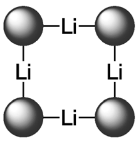
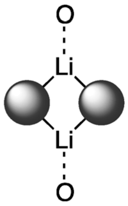
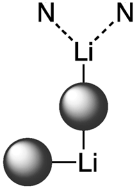
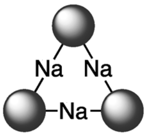
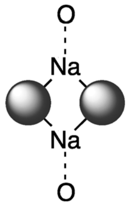
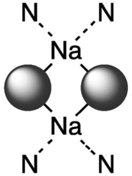
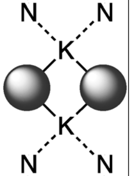
Alkali-metal amides, in particular NaHMDS, have been exploited in natural product synthesis for the cleavage/ring formation reaction of oxiranes to yield five-membered heterocycles [Eq. (3)].[40]



(3)

Other areas of reactivity[41] to be documented in the literature include the use of utility amides to promote Wittig-type reactions[42] and isomerization processes.[43]

Table 3: Graphical representation of crystallographically characterized homometallic alkali-metal utility amides.

	Li			Na			K		
	None	THF	TMEDA	None	THF	TMEDA	None	THF	TMEDA
HMDS				 	 			-	-
DA				-	-		-	-	
TMP							-	-	

3. Structures of 1,1,1,3,3,3-Hexamethyldisilazides

3.1. LiHMDS (1)

In the absence of any solvation support, parent LiHMDS (**1**) exists in the solid state as a cyclic trimer, as initially revealed by Böttcher and co-workers in 1969.[44] Compound **1** is the first crystallographically characterized alkali-metal utility amide (see Table 3 for a summary of molecular structures pertinent to this manuscript; and Table 4 for their most important bond parameters). A more detailed study by Atwood and co-workers almost 10 years later[45] established that the central Li_3N_3 ring is planar to within 0.01 Å [Li–N bond length, 2.00(2) Å] with the endocyclic N-Li-N angles deviating markedly from planarity [147(3)°] and the Li-N-Li angles being close to right angles [92(2)°]. Missed in the original study, the shortest Li⋯H agostic interaction was noted as being 2.56(1) Å.[46] The N-SiMe$_3$ unit is excellent for providing such interactions, as the δ^+ charge on the silicon atom polarizes the group, thereby resulting in a δ^--methyl group and priming it for interaction with the electropositive metal.[47] The addition of THF partially deaggregates LiHMDS into a symmetrical cyclodimer (**1**·THF),[48] with each lithium center solvated by a single THF molecule to give three-coordinate lithium atoms and thus marginally elongating the Li–N bonds to 2.025(9) Å. This extra coordination understandably forces the N-Li-N angle to a less obtuse 106.3(6)°. A third motif is witnessed in the presence of the bifunctional donor TMEDA, with this diamine chelating to a single lithium atom through both nitrogen atoms and providing sufficient steric protection and electronic stabilization to yield a rare example of a mononuclear alkali-metal amide (three-coordinate lithium) with the shortest Li–N bond seen thus far in a utility amide [1.893(3) Å].[49]

3.2. NaHMDS (2)

A molecular structural determination of complex **2** (performed on monoclinic crystals grown from mesitylene) was first divulged in 1977 by Grüning and Atwood, who reported this complex to be a polymer with alternating N and Na atoms along the chain.[50] The Na–N bonds were reported as averaging 2.355 Å in length while the chain angles at the Na (two coordinate) and N (four coordinate) atoms were 150.2 and 102.0°, respectively. A full 20 years later, a near-planar cyclotrimeric polymorph of complex **2** (this time having a triclinic unit cell) was simultaneously reported by the research groups of Nöth[51] and Driess.[52] Analyzing Nöth's data (although that of Driess was virtually identical), the Na–N bonds were marginally longer than those of the polymer [average 2.378 Å], possibly because of the strain of being part of a ring, while the angles at the Na atom were unsurprisingly less obtuse by more than 10° [average 139.7°]. The angles at the nitrogen atom range from 97.7 to 102.2° and are thus comparable with the chain polymer. The presence of short intra- and intermolecular Na⋯H agostic interactions ranging from 2.384 to 2.616 Å in the trimer were also noted, which help stabilize the two-coordinate metal center.

Table 4: Selected bond parameters of crystallographically characterized homometallic alkali-metal utility amides.

		Li				Na						K			
		None	THF	TMEDA		None		THF			TMEDA	None		THF	TMEDA
HMDS	M C.N.	2	3	3		2 (polymer)	2 (trimer)	3 (disolvate)	2 (monosolvate)	3	3	2 (toluene)	2	-	-
	M-N [Å]	2.00	2.025(9)	1.893(3)		2.352 2.358	2.376(8) 2.394(7) 2.358(8) 2.382(8) 2.363(8) 2.394(8)	2.399(2)	2.388(5)	2.400(5)	2.436(1) 2.451(1)	2.745(3) 2.801(3)	2.770(3) 2.803(3)		
	M-D [Å]	-	1.882(14)	2.067(3) 2.095(3)		-	-	2.267(2)	-	2.285(6)	2.566(1)	-	-		
	N-M-N [°]	148	106.3(6)	-		150.2(1)	141.8(3) 137.6(3) 139.8(3)	101.67(7)	99.7(2)	99.0(2)	99.58(3)	94.2(1)	94.47(9)		
	M-N-M [°]	92	73.7(5)	-		102.0(1)	100.0(3) 102.2(3) 97.7(3)	78.33(7)	[c]	[c]	80.42(3)	85.8(1)	85.53(9)		
DA	M C.N.	2	3	3		-		-			4	-		-	4
	M-N [Å]	1.957(5) 1.934(5) 1.956(4) 1.939(4)	1.975[a] 1.983[a] 2.020[a] 2.040[a]	2.017[b]							2.441(2) 2.453(2) 2.448(2) 2.448(2)				2.706(2) 2.837(2)
	M-D [Å]	-	1.956[a] 1.961[a]	2.163[b]							2.594(2) 2.612(2) 2.626(2) 2.646(2)				2.878(2) 2.894(2)
	N-M-N [°]	177.9(3) 174.1(2)	108.36[a] 107.29[a]	107.0[b]							103.44(7) 103.38(7)				100.54(5)
	M-N-M [°]	108.3(2) 109.5(2)	71.94[a] 72.19[a]	72.9[b]							76.47(5) 76.70(6)				79.46(5)
TMP	M C.N.	2	3	2	3	2		3			4	-		-	4
	M-N [Å]	2.00[b]	2.012(3) 2.019(3) 2.093(3) 2.088(3)	2.049(5) 1.885(5)	1.949(5)	2.307(2) 2.362(2)		2.439(2) 2.413(2) 2.364(2) 2.350(2)			2.427(2) 2.542(2) 2.433(2) 2.478(2)				2.744(2) 2.836(2) 2.825(2) 2.764(2)
	M-D [Å]	-	1.964(3) 1.983(3)	-	2.091(6) 2.121(6)	-		2.296(2) 2.279(2)			[d]				2.934(2) 2.948(2) 2.882(2) 3.039(2)
	N-M-N [°]	168.5[b]	109.90(16) 109.85(16)	172.6(3)		143.76(6)		105.82(7) 107.09(8)			101.21(6) 102.92(6)				101.41(4) 101.20(4)
	M-N-M [°]	101.5[b]	70.10(13) 69.86(13)	98.8(2)		96.24(6)		73.28(6) 73.50(6)			77.15(5) 78.48(5)				78.95(4) 78.43(4)

[a] No values were reported in the original publication; values are taken from the crystallographic database with no estimated standard deviations (esds; two independent molecules per unit cell, only parameters of one reported here, parameters of the other are very close). [b] Only the average value was reported in the original publication. [c] Not reported. [d] Value not reliable because of disorder in the donor.

Dehnicke reported the molecular structure of the THF solvate of NaHMDS (**2a**·THF) as a cyclodimer with one molecule of donor per metal, thereby giving a complex similar to its lighter lithium sibling **1**·THF with a nearly centrosymmetric central Na_2N_2 ring [Na–N distances, 2.398(2) and 2.399(2) Å].[53] Emphasizing the coordinative flexibility inherent in this area, a hemisolvated variant (**2b**·THF) was later disclosed by Bochmann and co-workers in 2006,[54] the product being obtained fortuitously from a cooled light-petroleum solution. While this donor-deficient complex still contained a central Na_2N_2 ring, only one of its sodium atoms was solvated with THF, thus resulting in both a two- and a three-coordinate sodium center. Despite the difference in coordination number, the two sodium atoms display virtually identical bond lengths to the HMDS nitrogen atoms as well as similar N-Na-N bond angles. Steric shielding of the two-coordinate "open" sodium atom by methyl groups of the HMDS ligand were noted, with the closest carbon atom being located 3.104(6) Å away and the closest hydrogen atom at 2.61 Å.

Finally, NaHMDS displays an as yet uncharacterized structural motif in the presence of TMEDA. This complex (**2**·TMEDA) can best be described as a "polymer of dimers", that is the NaHMDS unit remains as a cyclodimer, but the potentially bidentate diamine preferentially switches to a monodentate nonchelating role, bridging between cyclodimers to propagate the polymer.[55] The result is a distorted trigonal-planar three-coordinate sodium center. This recently divulged structure is perhaps unsurprising given that the diamine homologue *N*,*N*,*N*′,*N*′-tetramethylpropylenediamine with a propylene backbone gave a similar structural arrangement (**2**·TMPDA),[49] although a shorter ethylene backbone may well have favored bidentate coordination because of its smaller bite angle. The Na–N bonds of the four-membered ring of **2**·TMEDA are marginally longer than in the THF solvate, measuring 2.436(1) and 2.451(1) Å, respectively. Unsurprisingly, the more sterically encumbered, less Lewis basic donor is further from the metal cation [2.566(1) Å], while the Na_2N_2 ring is planar [ΣNa–N bond angles, 360°].

3.3. KHMDS (3)

Surprisingly, no THF or TMEDA complexes of KHMDS (**3**) have thus far been reported in the literature, although in the references of one of their papers[56] Williard and Nichols alluded to three different structures, namely a mono- and di-THF solvated cyclodimer (that is one with a pair of three-coordinate potassium cations and one with a pair of four-coordinate potassium cations) and a di-TMEDA-solvated cyclodimer with four-coordinate K cations (a common structural motif in TMEDA-solvated potassium utility amide chemistry, see Sections 4.3 and 5.3). Presumably the different THF solvates result as a consequence of controlling the stoichiometry of the THF added; it is unlikely that the THF is required to provide "protection" to the potassium centers since they are comfortable in a cyclic two-coordinate environment, as revealed by their unsolvated molecular structures. Currently there are two known "unsolvated" structures of **3**, both exhibiting dimeric $(KN)_2$ rings. The first was reported as a toluene solvate by Williard in 1988[57] (this can be considered as unsolvated since the arene is simply the solvent of crystallization and displays no interactions with the metal amide, despite the well-established affinity of soft potassium centers for π-electron density),[58] and this was followed two years later by the second bona fide unsolvated derivative reported by Hanusa and co-workers.[59] The four-membered planar ring of the former displays a moderate amount of asymmetry, with one K–N bond [2.745(3) Å] being noticeably shorter than the other [2.801(3) Å]. This asymmetry, although less pronounced, is also evident in the latter unsolvated structure [2.770(3)/2.803(3) Å]. No K···H(C) agostic interactions were noted as having a stabilizing influence on the dimeric ring.

4. Structures of Diisopropylamide

4.1. LiDA (4)

The champion utility amide lithium diisopropylamide, arguably the most common of the selective lithiating agents,[60] adopts an appropriately special structure in the solid state, as revealed by Mulvey and co-workers in 1991.[61] Rather than being a "simple" chain polymer, **4** displays a helical arrangement with near-linear N-Li-N units (average 176.0°), with the twists in the helix being propagated at the amido N atoms (average Li-N-Li, 108.9°). Four Li–N_{DA} units make up the repeating unit, and alternate between slightly shorter [1.934(5)/1.939(4) Å] and longer [1.957(5)/1.956(4) Å] Li–N bonds.

As in the case of LiHMDS, the THF solvate of LiDA (**4**·THF)[62] is a discrete Li_2N_2 cyclodimer with a donor molecule solvating each alkali metal atom for an overall coordination number of 3. The ring is virtually planar [Σ of the endocyclic bond angles: 359.78°], with one pair of opposing Li–N bonds being marginally shorter [average 1.979 Å] than the other [average 2.030 Å]. The TMEDA solvate (**4**·TMEDA)[63] also displays three-coordinate lithium cations, in a polymer of dimers motif similar to that seen previously for NaHMDS. As is to be expected, the Li–donor distance (average 2.163 Å) is considerably longer than in the oxygen-donating THF derivative, while the Li–N cation–anion distances are much shorter than these Li–N dative contacts (average 2.017 Å). However, as shown in Table 4, the parameters of the Li_2N_2 ring are essentially the same in the discrete and joined dimers, with an obtuse angle at Li (average 107.0°) balanced by an acute angle at the negatively charged nitrogen atom (average 72.9°).

4.2. NaDA (5)

There are currently no known unsolvated or THF-solvated molecular structures of NaDA reported in the literature. The only structure in the Cambridge Crystallographic Database of direct relevance to this section is the TMEDA solvate (**5**·TMEDA) described by Andrews et al.[64] This structure consists of the now familiar M_2N_2 (noncentrosymmetric) cyclodimeric substructure with the bifunctional TMEDA bidentately capping each sodium atom to give a spirocyclic structure consisting of a five-, four-, and then five-membered ring with sodium atoms at the junctions. The TMEDA molecules lie close to perpendicular to the planar $(NaN)_2$ ring (angle between N_{TMEDA}-Na-N_{TMEDA} plane and N_{DA}-Na-N_{DA} plane, 76.7°), thereby giving the sodium atom a distorted tetrahedral NaN_4 environment. The central rhomboidal ring (average angle at Na: 103.41°; average angle at N: 76.59°) has essentially identical Na–N bond lengths [2.441(2)–2.453(2) Å]. Noticeable also is the staggered arrangement of the methyl fingers of the isopropyl arm so as to minimize steric interactions across the ring.

4.3. KDA (6)

Similar to its lighter sodium sibling, KDA has only been characterized in the solid state as its TMEDA solvate (**6**·TMEDA). This structure contains a central cyclodimer with a bidentate TMEDA capping each end to give a distorted tetrahedral KN_4 environment, as described by Clegg, Mulvey et al.[65] The central K_2N_2 ring is planar and somewhat asymmetric, with a pair of longer [2.837(2) Å] and shorter [2.706(2) Å] K–N bonds. Distortion of this rhomboidal ring is evident, although not as pronounced as in the sodium structure, with the angles at K being considerably larger [100.54(5)°] than those at the diisopropylamido N atom [79.46(5)°]. This is at least in part attributable to the presence of the chelating TMEDA molecules, since a similar K_2N_2 ring in $[KHMDS]_2$ (**3**) is less distorted in the absence of any donor. However, despite this difference, **6**·TMEDA contains several secondary intramolecular K···H(C) contacts in the range of 2.816 to 2.952 Å, which if counted gives a total coordination number of 7 for the potassium center.

5. Structures of 2,2,6,6-Tetramethylpiperidide

5.1. LiTMP (7)

Similar to its congeners LiHMDS and LiDA, LiTMP displays great structural diversity when unsolvated or solvated by simple Lewis donor ligands. The combined research groups of Lappert and Atwood revealed the molecular structure of unsolvated LiTMP (**7**) to be a cyclotetramer.[66] Its central Li_4N_4 ring is essentially planar, with the Li_4 and N_4 planes both coplanar and the nitrogen atoms less than 0.01 Å out of the Li_4 plane. The bond angles at Li (average 168.5°) and N (101.5°) are noticeably larger than those in the other cyclic lithium amide mentioned thus far (LiHMDS, **1**), thus reflecting the greater degree of oligomerization. The greater steric demands of the TMP anion with respect to HMDS were considered to play the key role in this increase in oligomer size. Mulvey, Robertson, and co-workers confirmed that in the presence of THF, LiTMP forms the now familiar cyclodimer (**7**·THF) with each metal atom solvated by a donor molecule for an overall threefold, distorted trigonal planar coordination.[67] While this motif matches those of the THF solvates of LiHMDS and LiDA, there is considerably more skewing of the central rhomboidal ring in **7**·THF (almost 0.08 Å difference between adjacent Li–N bonds) than in **1**·THF (identical Li-N distances) or **4**·THF (approximately 0.05 Å difference). The Li-THF coordination is also the weakest of these three complexes (average 1.974 Å compared to 1.882(14) and 1.963 Å (average) for HMDS and DA, respectively), presumably reflecting the greater steric shielding provided by the cyclic secondary amido ligand. Finally, the TMEDA solvate, **7**·TMEDA, represents one of the most structurally interesting motifs presented here, namely Williard's "open dimer" (Figure 4).[68]

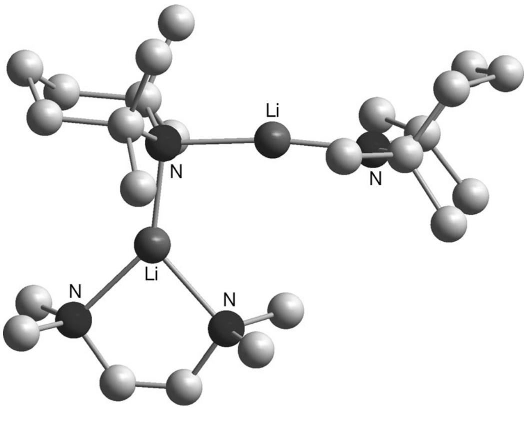


Figure 4. "Open dimer" structure of LiTMP-(TMP)Li(μ-TMP)Li·TMEDA.

Although not strictly an open dimer (a more accurate description would be hemisolvated acyclic dinuclear), this terminology is helpful and has thus found use for describing both this and other similar structural arrangements (an alternative interpretation would be a contacted lithium lithiate). A mimic of a proposed intermediate in the aldol reaction between lithium amides and carbonyl-containing substrates, this open structure represents the sole example of a solvated polynuclear homometallic alkali-metal utility amide presented herein which does not form a central azametallacycle. The result is different coordination numbers for the two lithium atoms (2 and 3) and a rare terminal amido ligand forming only one M–N bond. Free from the constraints of a ring, the bridging amide provides a Li-N-Li angle of 98.8(2)°, with the bond angle at the two-coordinate lithium center being close to linearity at 172.6(3)°. The three lithium–nitrogen bonds are unsurprisingly significantly different in length, with the terminal one being the shortest [1.885(5) Å] because of the lack of a second metal interaction concentrating the negative charge at the nitrogen atom into this bond. The bridging N atom gives longer bonds to lithium, with that to the two-coordinate lithium atom [2.049(5) Å] being longer than that to the three-coordinate lithium atom [1.949(5) Å], thus reflecting the fact that the former lithium bonds to two anions whereas the latter bonds to one. Finally, the TMP rings are both in the chair conformation, which in the case of the bridging TMP enforces two of the methyl arms into proximity with the lithium atom, with closest Li···H(C) contacts of 2.247 and 2.316 Å.

5.2. NaTMP (8)

The molecular structures of NaTMP and its solvated derivatives are all motifs seen previously for other sodium utility amides described herein. Disclosed by Lappert, Mulvey, and co-workers, the parent unsolvated structure (**8**) is a strictly planar Na_3N_3 cyclotrimer.[31] Although structurally similar to one polymorph of NaHMDS (**2**), this trimer has greater symmetry (hexagonal point group $P6_3/m$) and thus displays only two distinct Na–N bond lengths rather than six. The sodium cation is slightly disposed towards one of its amido neighbors [Na–N bond lengths of 2.307(2) and 2.362(2) Å] and, perhaps surprisingly, these values are shorter than the average value in complex **2** (2.378 Å) despite the bulkier amide being present in **8**. However, this is in part offset by more obtuse endocyclic bond angles at Na [143.76(6)° versus an average of 139.73° in **2**]. Several Na···C close contacts in the range 3.031(1)–3.211(1) Å were noticed; it was intimated that these [and their associated Na···H(C) interactions] were partially responsible for the overall stability of the two-coordinate (with respect to N atoms) sodium centers. Despite **8** adopting a lower oligomeric ring structure to LiTMP (**7**), the addition of THF results in a similar deaggregation, namely a cyclodimer with each metal atom stabilized by monosolvation.[67] Unlike the related HMDS structure, there is a pronounced distortion in the lengths of the pairs of parallel Na–N bonds of the ring, with an average value on one side of 2.426 Å and 2.357 Å on the other side. This, coupled with the longer Na-O_{THF} distances (average 2.288 Å) suggests perhaps that even in a larger Na_2N_2 ring the steric bulk of the anion is still playing a major role in the strain of the ring and thus in the overall structure. O'Hara recently revealed that the TMEDA adduct (**8**·TMEDA) also adopts the common doubly solvated cyclodimer motif in the solid state.[69] Its Na–N bonds vary in length across the range 2.427(2)–2.542(2) Å, while the bond angles within the ring are closer to right angles than those in the corresponding THF solvate **8**·THF. These smaller bond angles at Na (and concomitantly larger bond angles at N) are presumably due to the increase in coordination number at the sodium center from a distorted trigonal-planar three in **8**·THF to a distorted tetrahedral four in **8**·TMEDA.

5.3. KTMP (9)

Similarly to the scarcity of KDA examples, to date only a solitary solvated structure of KTMP (**9**·TMEDA) has been reported in the literature.[69] This is isostructural with its lighter congener **8**·TMEDA, even displaying similar M$_2$N$_2$ ring angles despite the increase in the metal–nitrogen bond lengths. The K$_2$N$_2$ bond lengths differ, ranging from 2.744(2) to 2.836(2) Å. Likewise, bidentate TMEDA varies with respect to the proximity of the Lewis-donating nitrogen atoms towards K, with the closest being 2.882(2) Å and the furthest being 3.039(2) Å, a variation of more than 0.15 Å. The central ring bears close similarities to that of the sodium congener **8**·TMEDA, with the average endocyclic bond angles at both N and M being within 1° of each other. The principal difference is understandably the metal–nitrogen bond lengths, which are on average 0.322 Å longer in the potassium complex.

6. Heterometallic Derivatives

As previously mentioned, alkali-metal utility amides represent one of the most widely utilized components of heterometallic co-complexes popularized over the past decade. Collectively, these can be regarded as alkali-metal-mediated metalating agents.[33] Indeed, the majority of the published crystal structures containing an AM-NR$_2$ fragment fall within either this category or the closely related category of heterometallic inverse crown ethers. Far less is known about mixed alkali-metal/alkali-metal complexes, despite the enhanced capability of such bases to execute deprotonation reactions being recognized more than 50 years ago by Wittig, who reported on the increased activity of a 1:1 phenylsodium/phenyllithium mixture compared to homometallic derivatives.[70] Indeed, one of the most well-known and most powerful metalating agents in synthetic chemistry, the Lochmann–Schlosser superbase (LiCKOR),[18] contains both lithium and potassium, albeit in a heteroleptic (*n*Bu–*t*BuO) complex whose exact molecular structure (or structures) remains thus far elusive. Boche and co-workers reported the structure of the related *n*BuLi/*t*BuOLi complex as being tetrameric (Li$_8$*n*Bu$_4$O*t*Bu$_4$).[71] Such heteroleptic hetero-alkali-metal chemistry is currently receiving renewed attention thanks to the work of O'Shea and co-workers, who noticed a change in the selectivity of the deprotonation reactions of substituted benzylic substrates in the presence of the LiTMP/KO*t*Bu combination ("LiNK" chemistry).[72] This selectivity relies on the presence of the utility amide (Figure 5).[73]

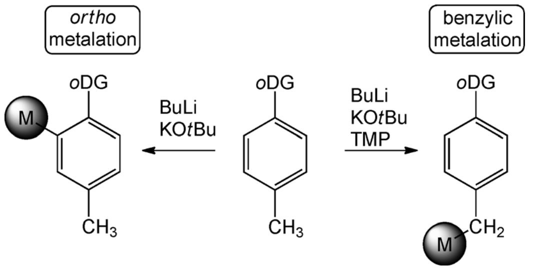


Figure 5. Selectivity of deprotonation using a hetero-alkali-metal base in the presence and absence of TMP (*o*DG = *ortho*-directing group).

However, some light has been shed on hetero-alkali-metallic utility amides and the following section briefly summarizes those that have been characterized crystallographically and in the solution state. These results are summarized in Table 5 while pertinent bond parameters are provided in Table 6.

Table 5: Graphical representation of crystallographically characterized heterometallic alkali-metal utility amides.

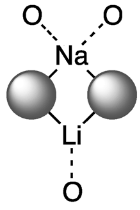
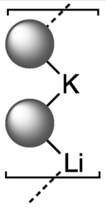
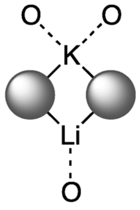
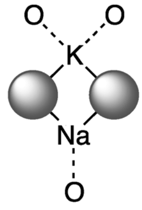
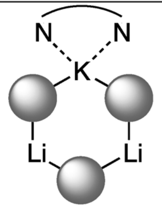
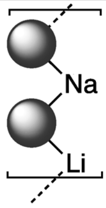
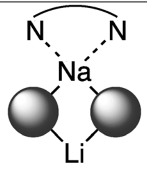
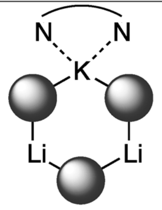
	Li/Na			Li/K			Na/K		
	None	THF	TMEDA	None	THF	TMEDA	None	THF	TMEDA
HMDS	-		-			-	-		-
DA	-	-	-	-	-		-	-	-
TMP	-			-	-		-	-	-

Table 6: Selected bond parameters of crystallographically characterized heterometallic alkali-metal utility amides.

		Li/Na					Li/K						Na/K			
		None	THF		TMEDA		None		THF		TMEDA		None	THF		TMEDA
HMDS	M	-	Li	Na	-		Li	K	Li	K	-		-	Na	K	-
	M C.N.		3	4			2	2	3	4				3	4	
	M-N [Å]		2.024(6)	2.509(4)			1.9348(11)	2.8612(11)	2.053(5)	2.832(3)				2.365(3)	2.810(3)	
	M-D [Å]		1.964(9)	2.433(3)			-	-	1.926(9)	2.689(3)				2.292(3)	2.709(3)	
	N-M-N [°]		116.59[a]	86.69[a]			176.4(3)	180.0	119.55[a]	77.54[a]				109.72[a]	86.68[a]	
	M-N-M [°]		78.36[a]				107.80(9)		81.45[a]					81.80[a]		
DA	M	-	-		-		-		-		Li	K	-	-		-
	M C.N.										2	4				
	M-N [Å]										1.912(3) 1.972(3)	2.869(1)				
	M-D [Å]										-	2.907(1)				
	N-M-N [°]										161.9(2)	107.30(4)				
	M-N-M [°]										98.4(1) 91.7(1)					
TMP	M	[b]	-		Li	Na	-		-		Li	K	-	-		-
	M C.N.				2	4					2	4				
	M-N [Å]				1.917(4)	2.513(3)					1.950(2) 1.987(2)	2.890(1)				
	M-D [Å]				-	2.535(3)					-	3.016(1)				
	N-M-N [°]				132.5(4)	88.57(11)					164.23(14)	107.05(3)				
	M-N-M [°]				69.5(2)						97.87(8) 88.75(10)					

[a] No values were reported in the original publication; values are taken from the crystallographic database with no estimated standard deviations (esds). [b] Values not reported because of disorder.

6.1. HMDS Bases (Li/Na: 10, Li/K: 11, Na/K: 12)

Hetero-alkali-metal utility amides were first reported in the early 1990s by Williard and Nicholls, who published three isostructural complexes of general formula THF·M^1(μ-HMDS)$_2M^2$·2THF, with M^1 being the lighter of the two alkali metals in the combinations Li/Na (**10**·THF), Li/K (**11**·THF), and Na/K (**12**·THF).[56] The structural template on which this series of complexes is founded combines a three- and a four-coordinate metal center within a distorted central $M^1M^2N_2$ ring. The structural consequences of this transformation to a heterometallic complex, as compared to the homometallic structures described earlier, are summarized in Figure 6. Specifically, the ring is heavily distorted, with the M^1—O bond longer than in the homometallic species.

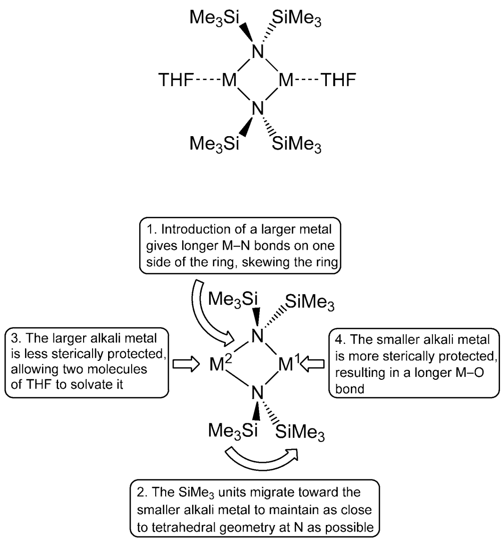


Figure 6. Structural reorganization on transforming from a homometallic (top) to a heterometallic (bottom) HMDS complex.

In the presence of four molar equivalents of THF at −80 °C in a toluene solution, **11** appears to equilibrate in to the heterometallic THF-solvated species plus each of the two homometallic derivatives.[74] However, when TMEDA was added, only homometallic species were witnessed. The addition of THF to these TMEDA-solvated homometallic species saw the re-emergence of resonances consistent with the homo- and heterometallic THF-solvated species, thus showing that in this case the alkali metals prefer THF solvation over TMEDA solvation when offered the choice between the two.

Following this, Henderson and co-workers revealed the structure of unsolvated Li/K HMDS (**11**) as a one-dimensional chain polymer with alternating lithium and potassium atoms,[75] each with a coordination number of two, typical for all nonsolvated alkali-metal utility amides discussed herein. The metal atoms were in similar environments, with that of the potassium being strictly linear as imposed by crystallographic symmetry and that of lithium somewhat distorted from linearity [N-Li-N, 164.4(3)°]. These values are different from the N-M-N angle of the other HMDS chain polymer discussed, NaHMDS, whose corresponding angle at the sodium center is 150.2(1)°. The metal–nitrogen bond lengths were consistent with no disorder of the metals being present [Li—N, 1.9348(11) Å; K—N, 2.8612(11) Å]. No NMR spectroscopic or other solution-state characterization was reported for this mixed-metal polymer.

6.2. DA Bases (Li/K: 13)

Only a single hetero-alkali-metal complex of diisopropylamide has thus far been reported, namely a cyclic species combining lithium and potassium in a 2:1 stoichiometric ratio, with TMEDA solvating the larger potassium center (**13**·TMEDA).[76] This complex thus has a distorted tetrahedral potassium center and near-linear two-coordinate lithium atoms [N-Li-N = 161.9(2)°], with the ring potentially causing this slight deviation from linearity since the corresponding bond angle in the homometallic LiDA polymer (**4**) is 176.0° on average. A study of the solution behavior of **13**·TMEDA in nonpolar cyclohexane by ^{1}H and ^{7}Li NMR spectroscopy suggested that the complex maintained its trinuclear integrity in such a medium (in contrast to its TMP congener **15**·TMEDA, see Section 6.3), although DOSY NMR studies were consistent with a rapid coordination/decoordination of the bidentate donor.

6.3. TMP Bases (Li/Na: 14, Li/K: 15, Na/K: 16)

A remarkable series of seven hetero-alkali-metal TMP complexes were introduced recently by Mulvey, Robertson, and co-workers.[77] The TMEDA-solvated Li/Na complex (**14**·TMEDA) revealed a Li-N-Na-N ring with a solitary molecule of TMEDA solvating the heavier alkali-metal atom in a bidentate fashion and the lithium atom lying in a strained two-coordinate environment [N-Li-N = 132.5(4)°]. The solution behavior of **14**·TMEDA could not be probed adequately, as full decoordination of TMEDA occurs rapidly, thereby causing the resulting solvent-free parent complex (**14**) to precipitate from solution as a chain polymer with alternating lithium and sodium atoms. To the best of our knowledge, this is the only structurally characterized Li/Na chain polymer. Although the alkali-metal atoms were disordered throughout this polymer, the mixed-metal constitution was unequivocal given that the homometallic possibilities are already known to exist as a cyclotetramer (**7**) and cyclotrimer (**8**) for lithium and sodium, respectively (see Section 5). When TMEDA was replaced with the larger tridentate donor *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA), the resulting complex (**14**·PMDETA; Figure 7) mirrored the TMEDA derivative in terms of constitution, namely with a dinuclear Li/Na composition. However, the extra Lewis donor coordination had the effect of opening up the four-membered ring to give an "open" acyclic structure, thus mimicking the aforementioned homometallic lithium complex of Williard (**7**·TMEDA). This structure consequently displayed a distorted tetrahedral four-coordinate sodium atom and a bent two-coordinate lithium atom, with one TMP anion functioning in a "typical" bridging manner, while the other occupies a more unusual terminal position.

The secondary effect of the change in donor solvent was enhanced stability of the solvated species in solution, with **14**·PMDETA needing more than an hour to extrude polymeric, insoluble **14**, thus facilitating an NMR study. The cyclohexane-soluble crystals displayed only one species in solution according to ^{7}Li NMR spectroscopy. Different TMP environments (bridging or terminal) could not be distinguished by ^{1}H NMR spectroscopy.

On substituting sodium with potassium, a cyclic trinuclear complex (**15**·TMEDA) such as that seen for DA (**13**·TMEDA) was observed. The six-membered $\mathrm{Li_2KN_3}$ ring had marginally longer bonds in the TMP congener than the DA one, and the TMEDA molecule could not get as close to the potassium atom, thus suggesting strain in the molecule as a consequence of the greater steric hindrance of the bulky TMP anions. Analogous to **14**, this strain was released by changing to a tridentate donor, thereby producing a lithium-rich "open trimer" (**15a**·PMDETA)—essentially a U-shaped N-Li-N-Li-N-K chain with the potassium terminus capped, or better clamped, by PMDETA. A ^{7}Li NMR spectroscopic analysis of both the closed and open trinuclear variants of **15** showed the presence of two species in the hydrocarbon solution, which were assigned as being a dinuclear Li/K species and LiTMP (**7**) in equilibrium with the trinuclear parent compound [Eq. (4)]; the two heterometallic species were believed to share coincidental resonances in the ^{7}Li NMR spectrum, while LiTMP was identified by comparison with an authentic sample.

$$\mathrm{Li_2K(TMP)_3\cdot donor \rightleftharpoons LiK(TMP)_2\cdot donor + LiTMP} \qquad (4)$$

Support for this redistribution equilibrium came from the identification of a dinuclear derivative (**15b**·PMDETA) during the pursuit of the first trimetallic (Li/Na/K) TMP complex; this complex displayed a central highly strained four-membered LiNKN ring. The PMDETA coordinated to the potassium atom in a tridentate fashion to make it five-coordinate, while lithium, as has frequently been seen before,

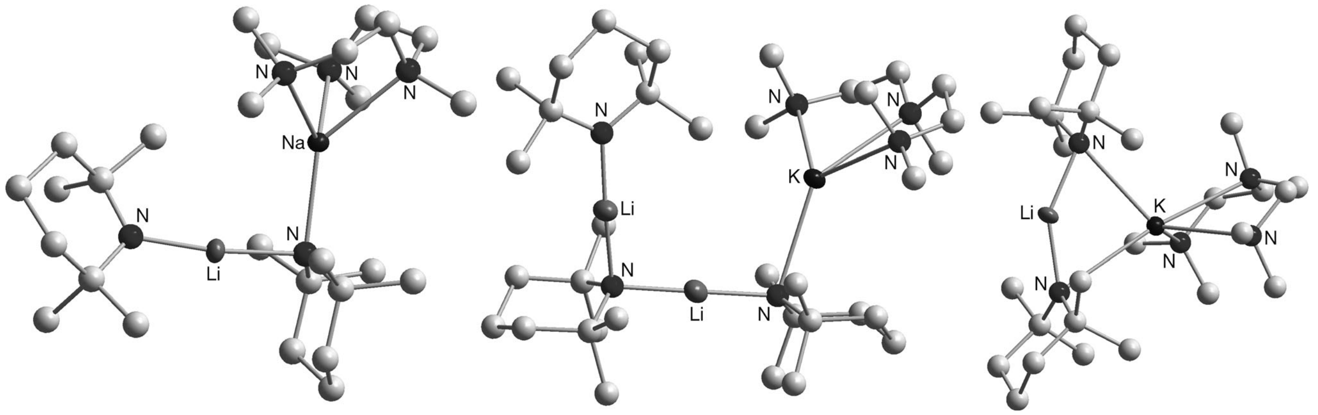


Figure 7. Molecular structures of PMDETA-solvated hetero-alkali-metal TMP species **14**·PMDETA (left), **15a**·PMDETA (middle), and **15b**·PMDETA (right).

was content in a two-coordinate environment. Interestingly, this complex was obtained as a 9:1 mixture with its Na/K congener **16**·PMDETA, which has the same basic motif as **15b**·PMDETA.

The Na/K species could be obtained rationally by mixing the homometallic constituent parts in the appropriate stoichiometry (that is, through a 1:1:1 NaTMP, KTMP, and PMDETA mixture) but the Li/K species could not; the trinuclear species mentioned previously was the sole product regardless of the stoichiometry. ^{7}Li NMR studies suggested that the dinuclear Li/K complex maintained its constitution in solution, with the chemical shift of the resonance lending further support to the coincidental nature of the dinuclear/trinuclear resonances proposed earlier. The open or closed nature of all these heterometallic complexes of TMP was never identified in solution with NMR spectroscopic techniques.

7. Solution Behavior

In this section we will analyze the various aggregation states of the homometallic alkali-metal utility amides in solution as determined by a variety of traditional and modern NMR spectroscopic techniques. As a general rule, we avoid simply reporting NMR spectroscopic analysis when this is presented only to confirm the amide/donor ratio, for example, and concentrate on analysis which either confirms the aggregation state or reveals the breakdown of a complex into multiple individual components.

The solution behavior of the alkali-metal utility amides has focused primarily on lithium salts. Multiple reasons exist for this, with the main ones being the fact that lithium salts are very common, they tend to exhibit greater solubility than their heavier counterparts (particularly in nonpolar solvents), and, perhaps most importantly, the alkali metal itself has NMR-active nuclei (^{6}Li, ^{7}Li), thus providing a greater opportunity to study such compounds. This has been particularly well exploited by Collum and his many co-workers over the past 20 years. They have made a sterling contribution to the area, especially by utilizing isotopically enriched (^{6}Li/^{15}N) samples and studying their coupling in an attempt to glean valuable information on aggregation states and their solution dynamics. Recently, Williard and co-workers introduced diffusion ordered spectroscopy (DOSY) into the study of alkali-metal species.[78] This has proved to be a highly informative tool for the identification of the molecular weight (or volume) of a sample in solution as it allows the practitioner to deduce the approximate molecular weight of samples when inert standards of known molecular weight are used alongside the sample in question. The ease with which this technique can be applied coupled with the use of more economically viable non-enriched samples has also made this the solution characterization method of choice for our research group.

7.1. HMDS Bases

To the best of our knowledge the earliest comprehensive NMR spectroscopic study of an alkali-metal utility amide was that by Kimura and Brown in 1971. By studying various temperatures and concentrations of LiHMDS in either a hydrocarbon or ethereal (THF) medium, they were able to identify a dimer–tetramer equilibrium in the former case and a monomer–dimer equilibrium in the latter.[79] Monomer is the predominant species in THF solution, although the relative proportion of dimer increases with either increased temperature or increased concentration. Only cyclodimer was witnessed in arene (toluene) solution. As THF (0.3 molar equivalents) is added to a solution of isotopically enriched LiHMDS in pentane, a pair of resonances in the ^{6}Li spectrum and a single environment in the ^{15}N spectrum are observed. These findings are consistent with a monosolvated cyclodimer corresponding to the molecular structure revealed by Bochmann (see Section 3.2).[80] At 0.7 molar equivalents of THF, these resonances are supplemented by an additional set, which is consistent with the disolvated dimer also being present. Such a disolvated dimer is the only observable species once more than 1.0 molar equivalents of THF are introduced.[81] At even greater THF concentrations, new resonances are evident which correspond to a heavily solvated monomeric species. Lucht and Collum concluded that this mononuclear species has either three or possibly even four THF molecules solvating the lithium center (Figure 8).

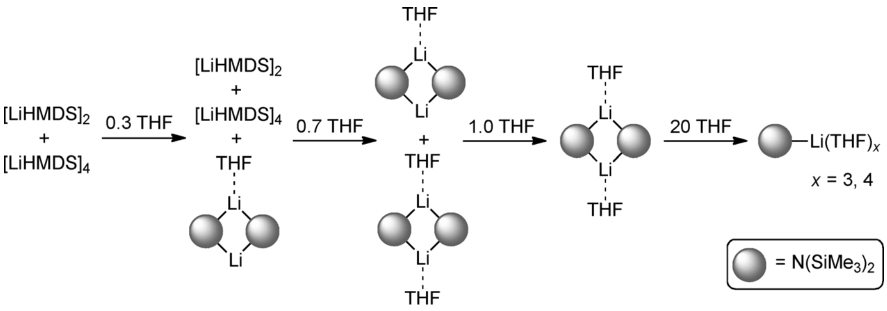


Figure 8. THF-dependant aggregation and solvation of LiHMDS in pentane solution.

It was noticed that the monomer/dimer ratio changed dramatically as the steric bulk adjacent to the Lewis basic oxygen atom of the THF framework was increased (Figure 9). With unsubstituted THF this ratio was 1:3, but on changing to 2,2-dimethyltetrahydrofuran it changed to 35:1. However, the even more substituted and sterically hindered 2,2,5,5-tetramethyltetrahydrofuran resulted in the dominant species reverting to dimer. This pattern was explained by the donor-solvent/amide interactions of the dimer forcing monomerization to compete with the donor-solvent/donor-solvent interactions in the monomer.

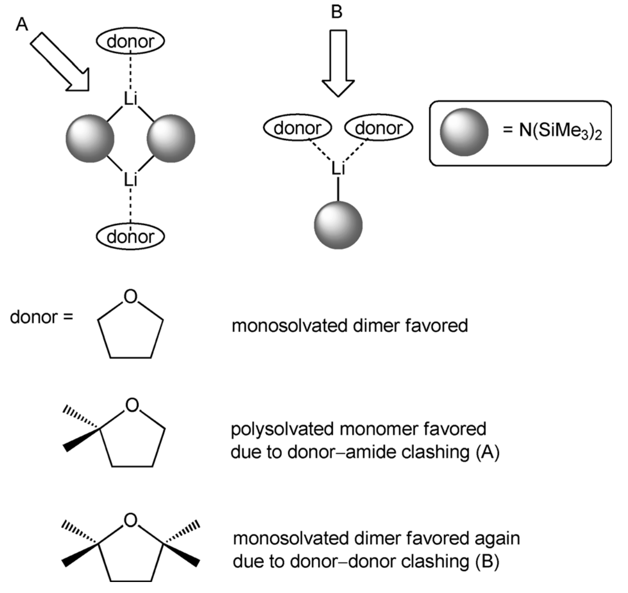


Figure 9. Effect of donor substitution and bulk on the LiHMDS monomer–dimer equilibrium.

Adding 0.5 molar equivalents of bifunctional TMEDA to a solution of LiHMDS in toluene resulted in two distinct species, namely solvated monomer and unsolvated dimer. Only the solvated monomer was seen when the volume of TMEDA was increased to 1.0 molar equivalents.[82]

7.2. DA Bases

Through ^{6}Li-^{15}N double-labeling experiments Collum and co-workers were able to show that LiDA exists in nonpolar noncoordinating hexane solution in multiple oligomeric forms, with anywhere between three and five different such oligomers present. These were assigned as being cyclic dimer, cyclic trimer, and higher cyclic oligomers.[14] On moving to THF solution, inverse-detected ^{15}N homonuclear zero-quantum NMR spectroscopy gave data consistent with a cyclic dimer being the predominant solution species and with no evidence of monomeric species.[83] This finding was in contrast with earlier cryoscopic measurements by Bauer and Seebach which suggested a monomer/dimer equilibrium, with the monomer being favored.[84] Rutherford and Collum were also able to identify a mixture of mono- and disolvated cyclodimers and mono- and disolvated cyclotrimers when studying LiDA in pentane/toluene in the presence of substoichiometric quantities of THF.[85] The trimeric species constitute the minor species in solution with the disolvated dimer only seen once the concentration of THF exceeds 1.0 molar equivalents.[86] ^{13}C INEPT DOSY NMR spectroscopy on commercially available LiDA·THF shows it maintains a disolvated dimeric constitution in toluene solution.[87]

^{6}Li and ^{15}N NMR spectroscopic studies of isotopically enriched LiDA in neat TMEDA suggest the lithium amide exists as a cyclic dimer with an η^1-coordinated TMEDA bound to each metal center for an overall coordination number of 3, as opposed to the more typical η^2 coordination regularly seen for this potentially bidentate donor.[63] Interestingly, with a single molar equivalent of TMEDA (in nonpolar hexane solution), the binding of TMEDA was favored at low temperature (−100 °C), with unsolvated LiDA being the favored product as the temperature is raised to 20 °C. Furthermore, the solvating competition reaction between equimolar amounts of THF and TMEDA for LiDA in hexane showed that the Lewis acidic metal in this case has a clear preference for monodentate THF (see Figure 10 for a summary of solution structures).

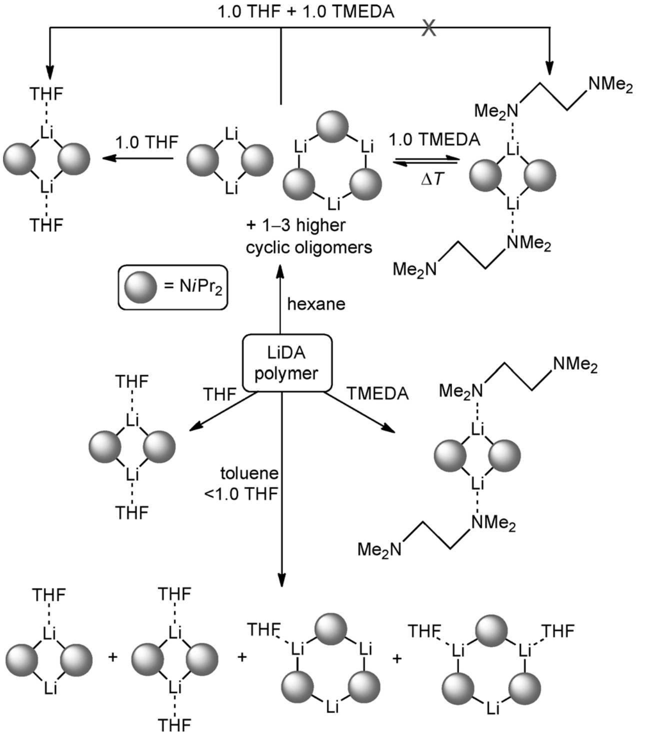


Figure 10. Structures of LiDA in different solvents in the presence or absence of stoichiometric quantities of Lewis donors.

7.3. TMP Bases

Unsolvated LiTMP (studied in pentane solution) displayed ^{6}Li and ^{15}N NMR spectra consistent with a pair of cyclic oligomers, with the predominant species having the higher degree of oligomerization of the two.[5b] A homonuclear zero-quantum NMR spectrum confirmed that both oligomers were larger than simple cyclodimers. Believing these oligomers to be a cyclotrimer and cyclotetramer, Lucht and Collum surmised that there are a total of two and four possible solution structures, respectively, depending on the symmetry of the TMP chairs (see Figure 11 for different potential conformations). Given that chair–chair flipping might hinder their studies, they turned to the closely related but extra-substituted 2,2,4,6,6-pentamethylpiperidide (PMP), which should not be subject to such facile ring adjustments. This successfully allowed them to identify, through ^{6}Li-^{15}N correlation NMR spectroscopy, one of the two cyclotrimers and all four of the cyclic tetramers in the solution, with the

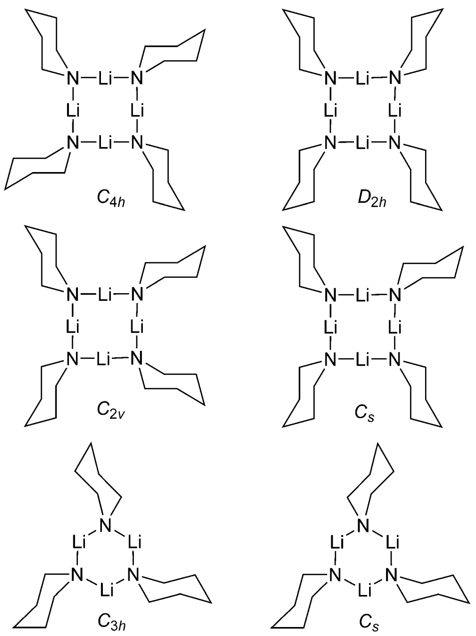


Figure 11. Proposed isomeric forms of cyclotetrameric and cyclotrimeric LiTMP. The methyl groups have been omitted from the piperidine rings for clarity.

tetramers in nearly equal proportions. Zero-quantum NMR spectroscopy on LiTMP in benzene gave a splitting pattern consistent with a cyclic oligomer higher than a dimer, although whether this was a cyclotrimer or a cyclotetramer (matching the solid-state structure) could not be definitively determined.[83a] On moving to THF solution, a monomer–dimer equilibrium was proposed by Renaud and Fox on the basis of ^{7}Li NMR spectroscopy, with the equilibrium favoring the dimer as the concentration is increased.[88] Collum and co-workers confirmed that the cyclic species was indeed a dimer by zero-quantum NMR spectroscopy.

While the majority of solution-state studies of LiTMP have involved either a complete lack of donor (that is, carried out in nonpolar solvents) or a massive excess of donor (that is, carried out in neat donor), much less attention has been paid to solutions with stoichiometric quantities of donor. However, Collum and co-workers studied the effect of adding various amounts of TMEDA to a solution of LiPMP in toluene/pentane (2:1).[5c] They noted a mixture of open dimer and solvated monomer (with no unsolvated cyclo-oligomer) in the presence of 0.75 molar equivalents of the bifunctional donor, with monomer being the sole observable species when greater than 10 molar equivalents of TMEDA were introduced.

Mulvey and co-workers utilized crystals of their THF-solvated LiTMP and NaTMP cyclodimers in cyclohexane to study the aggregation with a precise stoichiometric amount of donor (in this case one molecule of THF per metal center).[67] Through a combination of ^{7}Li and DOSY NMR spectroscopy they observed a concentration-dependent disproportionation of LiTMP into a solvated cyclodimer and unsolvated higher cyclo-oligomer, with a minor amount of solvated monomer also present. This result was in contrast to the solution behavior of NaTMP in the presence of a stoichiometric amount of THF, which appears to maintain its cyclodimeric integrity in such nonpolar media. What is certainly clear from both solid-state and solution-state studies of LiTMP is that the steric bulk and flexible chair conformation of the amide coupled with the relatively short Li–N bond length makes for a rich and diverse chemistry.

8. Outlook

The alkali-metal utility amides have been in the service of synthetic chemists for several decades. However despite their old age they show no sign of retiring and drawing their pension just yet. Researchers attracted by the dual benefits of high basicity and low nucleophilicity will often turn to these utility amides as the first option when tasked with carrying out a challenging selective deprotonation reaction. Page through any current specialist synthetic journal or general journal which covers synthetic developments and you will see lithium amides, in particular, used time and again for that purpose. Limitations of these reagents are well known. Aside from the air and moisture sensitivity, which is the Achilles' heel of every polar organometallic compound, these reagents can attack sensitive functional groups and solvents, can generate metalloaromatic intermediates of low stability, and often require subambient temperatures for their reactions to avoid decomposition pathways. That notwithstanding, none of these limitations would deter chemists from performing small-scale reactions with utility amides, which is why their popularity has never waned but only increased, although they would of course hinder large-scale industrial manufacturing processes. Such limitations are, however, now being overcome by the recent emergence of multicomponent metalating agents (referred to elsewhere as "avant-garde metalators"[11b]). Looking at the formulas of the best known of these younger competitors [for example, (TMP)MgCl·LiCl;[89] Li(TMP)(tBu)Zn(tBu);[90] TMEDA·Na(TMP)(tBu)Zn(tBu);[91] TMEDA·Na(TMP)(nBu)Mg(TMP);[92] LiCd(TMP)$_3$[93]] they all contain an alkali metal and a TMP component, and thus can be regarded as offshoots of utility TMP amides. A key advantage of these multicomponent metalators is that often the presence of a softer metal (especially zinc) in the deprotonated organic substrate can facilitate their direct use in tandem bond-forming processes such as Negishi cross-coupling reactions.[94] It is not usually possible to achieve this with utility amides in single-component systems, as their hard metalated organic substrates invariable require transmetalation with a zinc halide salt prior to being employed in such transition-metal-based methods. The great challenges in metalation processes remain the same today with the multicomponent metalators as they have been all along with the traditional utility amides: innovative ways must be found for transforming stoichiometric reactions into catalytic reactions and for making these processes more resistant to air and moisture.[95] Meanwhile, we look forward to monitoring progress in the other important area of s-block utility amide chemistry—the alkaline-earth derivatives, the chemistry and applications of which are currently being upgraded and increased by a number of leading research groups worldwide including in particular those of Harder,[96] Hill,[97] and Westerhausen.[98]

Many excellent chemists, whose names appear in relevant references, have contributed to the development and elaboration of these priceless reagents. They all have our admiration. Special mention must be made of Ron Snaith, a selfless mentor who inspired R.E.M.s interest in lithium amides. Generous funding from the EPSRC, the Royal Society/Wolfson Foundation, the Royal Society of Edinburgh (RSE/BP Trust Fellowship to SDR), the EU, the Nuffield Foundation, AstraZeneca, and the University of Strathclyde is gratefully acknowledged. Additionally, we specifically thank Dr. Jan Klett for kindly preparing the frontispiece and Jenni Garden for assistance in researching the historical aspects presented.

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