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Structural Consequences of the Addition of Lithium Halides in Enolization and Aldol Reactions

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Abstract: Aggregates consisting of lithium halides with either lithium amides or lithium enolates have been characterized by X-ray crystallography. Two structural types, solvated heterodimers and heterotrimers, have been found for halide/amide combinations. Two compounds containing both lithium halide and lithium enolate have also been identified as heterodimers. Using this information, we propose a reaction sequence for enolization and subsequent aldol addition reaction involving halide-containing aggregates. An *ab initio* and PM3 theoretical study of model systems shows that solvated heterodimers between LiBr and either $LiNH_2$ or $LiOC(H){=}CH_2$ are favored over the respective homodimers. Calculations reveal a stable eight-membered ring transition state for the enolization step between $LiCl{\cdot}LiNH_2$ and acetaldehyde. Two independent transition states, a 4,8 and a 4,4,6 ring system, were calculated for the model reaction between the heterotrimer $[(LiNH_2)_2{\cdot}LiCl]$ and acetaldehyde. Dissociation of donor solvent was computed to require more energy for heterodimers than for homodimers.

Introduction

One of the premier topics of modern organic chemistry is asymmetric synthesis.[1] In large part, this is a consequence of increasing interest in natural product chemistry and the manufacture of biologically active molecules.[2] Great strides have taken place in the development of many aspects of chiral synthesis, but much remains to be done. A general problem is in the specificity of synthetic strategies. For example, it is commonplace to find that the degree of asymmetric induction in a particular system is critically dependent on the physical nature of the reagents.[3] Even relatively small changes in structure have drastic effects on the reaction's outcome. It is therefore usually necessary to conduct time-consuming repeat syntheses in order to find suitable reagents, conditions, *etc*. A relatively recent approach to solving some of the problems pertaining to selectivity questions is to study the structure of the intermediates involved.[4] The aldol addition reaction is a visible example.[5] Structural studies have utilized NMR spectroscopy,[6] X-ray diffraction,[7] and theoretical calculations.[8] One increasingly important aspect in chiral synthesis is in the use of Lewis acid additives to increase regio- and stereoselective control.[9] For instance, the addition of achiral lithium salts in asymmetric alkylation and aldol addition reactions has been shown to affect reactivity, selectivity, and solubility.[10] A striking example was reported by Ashby that the rate of reaction between MeLi and 4-*tert*-butylcyclohexanone was increased 350-fold by addition of $LiClO_4$.[11] The origin of these effects is not fully understood.

It has been proposed that these additives form mixed aggregates.[12] Solution NMR spectroscopic studies by Brown[13] and Collum[14] have revealed that lithium halides form mixed

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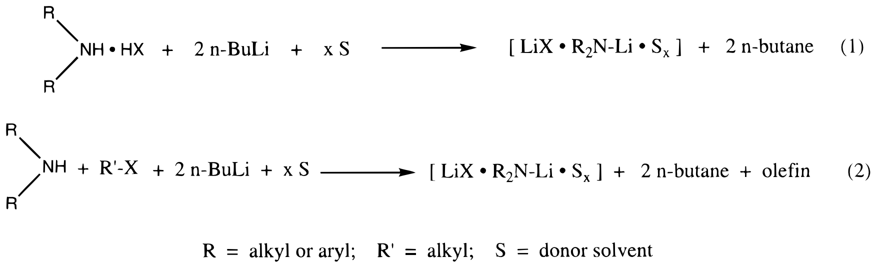
Scheme 1



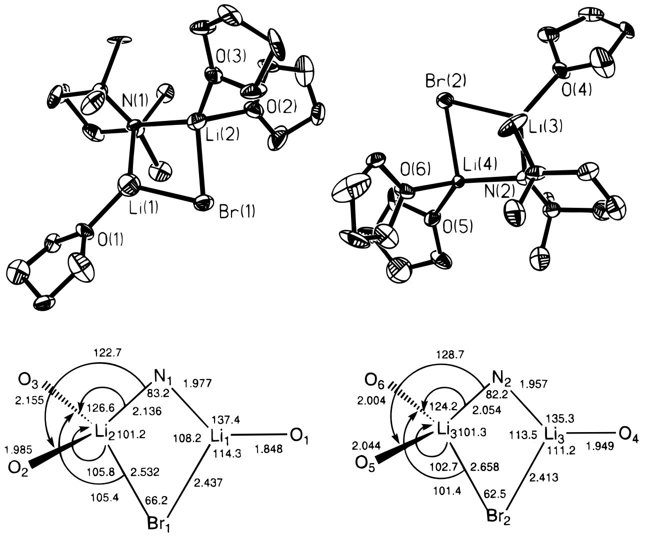
aggregates with alkyllithium and dialkylamidolithium compounds. In light of the poor understanding of the function of lithium halides as additives, we undertook a structural investigation of these species. This report outlines the synthesis and structural characterization of some mixed anion species involved in enolization reactions and describes a theoretical study of the formation and structure of mixed amide/halide and enolate/halide lithium aggregates.

Results and Discussion

Lithium Amide/Halide Aggregates. Soluble mixtures of lithium halide and lithium amide were prepared by two methods. The first used an amine hydrohalide ($R_2NH{\cdot}HX$) as the source of both halide and amine.[15] A slurry of the hydrohalide with either tetrahydrofuran (THF) or *N*,*N*,*N*′,*N*′-tetramethyethylenediamine (TMEDA) in toluene was treated with Bu^nLi (Scheme 1, eq 1). Clear solutions resulted after vigorous stirring. In the second procedure an alkyl halide, an amine, and a donor solvent were mixed in toluene before addition of Bu^nLi (Scheme 1, eq 2). The latter method was preferred due to solubility problems of the amine hydrohalides.

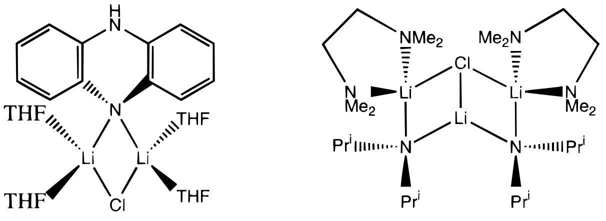
To confirm that mixed anion species were formed, we grew crystals from the reaction between TMP•HBr (where TMP = 2,2,6,6-tetramethylpiperidine) and Bu^nLi in the presence of THF. X-ray analysis gave the structure [LiBr•LiTMP•$(THF)_3$] (**1**) (Figure 1).[16] Compound **1** crystallizes with two independent but almost identical molecules in the asymmetric unit. The heterodimeric structure of **1** has a central four-membered LiNLiBr ring. Only two crystal structures have been previously characterized for an alkali metal complex consisting of an amide and a halide: the 5,10-dihydrophenazine derivative [LiCl•$LiNC_{12}H_8NH{\cdot}(THF)_4$] (**2**)[17] and the diisopropylamide complex [LiCl•$(LiNPr^i_2)_2{\cdot}(TMEDA)_2$] (**3**)[15] (Figure 2).

A few distinctions between compounds **1**, **2**, and **3** are worth pointing out. Since **2** and **3** contain chlorine in place of bromine in **1**, direct comparisons of the bond lengths and angles between the structures are not useful. **3** differs from **1** in that it is a heterotrimer. **2**, being a heterodimer, is more closely related to **1**. However, in **2** each lithium atom is tetracoordinated by bonding to two anions and two dative bonds from THF molecules. Such tetracoordination is commonly found for solvated lithium halides and amidolithiums.[18] A much more unusual structure is found for **1**. One lithium is coordinated by two THF molecules, and the second is coordinated by a single THF molecule. This unusual structural motif may be caused by steric factors associated with the very bulky TMP ligand.[18] It is likely that addition of a fourth THF molecule is unfavorable since the TMP group is already clearly tipped toward the tricoordinated lithium center as is shown in Figure 3. The three-coordinate lithium center also exhibits relatively short contacts with two methyl groups of the TMP ligand (average Li−C distance of 2.81 Å). Although the hydrogen atoms could not be located from the diffraction data, agostic Li−H interactions may be present.[19] Without considering the weak Li−C inter-



a **b**

Figure 1. Two independent molecules in the unit cell of **1**. Pertinent bond lengths (Å) and angles (deg) are shown.



2 **3**

Figure 2. Structures of the other known lithium amide/halide aggregates.

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[15] Mair, F. S.; Clegg, W.; O'Neil, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 3388.

[16] Crystal data for **1**: $C_{42}H_{84}Br_2Li_4N_2O_6$, triclinic, $P1$, $a = 8.491(2)$ Å, $b = 11.766(2)$ Å, $c = 12.736(3)$ Å, $\alpha = 92.58(3)°$, $\beta = 97.31(3)°$, $\gamma = 98.20(3)°$, $V = 1246.6(5)$ Å^3, $Z = 1$, $d_{calc} = 1.200$Mg/m^3, $F(000) = 480$, $2\theta_{max} = 47°$, 4843 measured reflections, 3965 independent reflections, 3965 reflections used in the refinement, $R(1) = 0.0424$, $wR(1) = 0.0766$.

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[18] For reviews on the structural chemistry of lithium see: (a) Weiss E., *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1501. (b) Gregory, K. P.; Schleyer, P. v. R; Snaith, R. *Adv. Inorg. Chem.* **1991**, *37*, 47. (c) Mulvey, R. E. *Chem. Soc. Rev.* **1991**, *20*, 167. (d) Schleyer, P. v. R. *Pure Appl. Chem.* **1984**, *56*, 151. (e) Schleyer, P. v. R. *Pure Appl. Chem.* **1983**, *55*, 355.

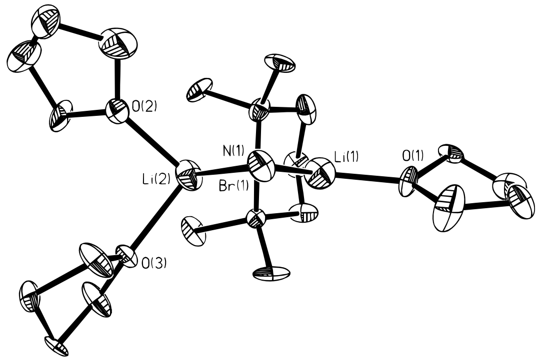
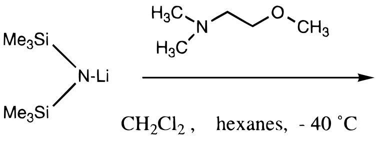


Figure 3. Crystal structure of molecule **a** of compound **1**, viewed down the N−Br axis. The amido ligand is clearly tipped toward Li(1).

Scheme 2



$$[\, LiCl \bullet \{ LiN(SiMe_3)_2\}_2 \bullet (Me_2NCH_2CH_2OMe)_2 \,] \quad (3)$$

actions, there is one pseudotetrahedral and one pseudotrigonal planar lithium atom in **1**. Unsymmetrical solvation is also seen in the complexes of lithium hexamethyldisilazide with both fluorobenzene and 1,2-difluorobenzene and in the THF-solvated mixed cation (Li, Na, K) dimers of hexamethyldisilazide (HMDS).[20]

Also apparent from Figure 3 is that the central LiNLiBr ring is puckered (12.9° and 9.4° for **a** and **b**, respectively, from the N−Br axis). The unsymmetrical nature of **1** is also seen from the bond lengths of the central ring. As expected, bond lengths at the three-coordinate lithium are distinctly shorter than for the tetracoordinated metal (averaged differences are 0.13 Å for Li−N and 0.15 Å for Li−Br).

Using a third route for halide incorporation gave a HMDS-containing mixed aggregate. The sensitivity of HMDS toward acid negates the possibility of preparing its hydrohalide derivative. Attempts at preparing mixed HMDS/halide compounds by the "ammonium salt route" of Snaith *et al.*[21] or by using LiCl as halide source failed. A new method utilizing methylene chloride was developed (Scheme 2, eq 3).

The complex $[LiCl\cdot\{LiN(SiMe_3)_2\}_2\cdot(Me_2NCH_2CH_2OMe)_2]$ (**4**) was determined crystallographically to exist in a three-rung ladder form similar to **3** (Figure 4).[22] This is further evidence for the stability of three-rung ladder structures proposed in solution.[10a,23] Other products were not identified, although the synthesis of **4** proved reproducible.

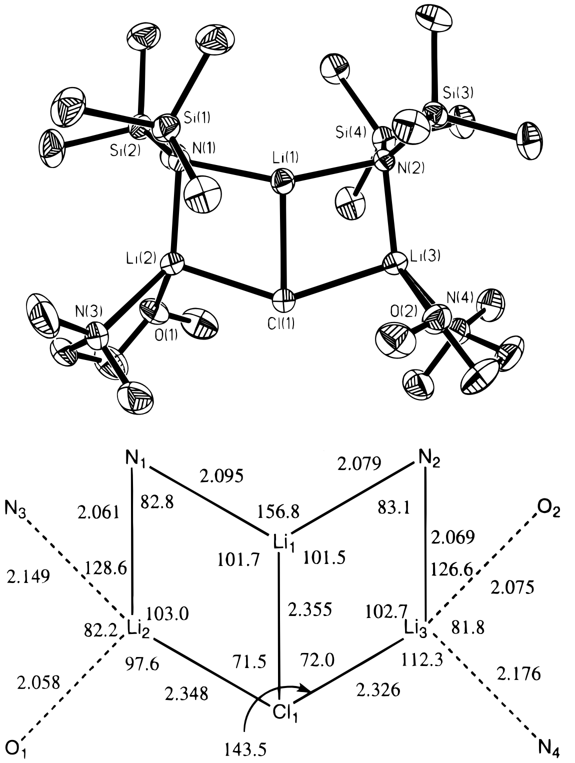


Figure 4. Molecular structure of **4** shows the mean plane through the atoms. Hydrogen atoms are omitted for clarity, and the heteroatoms are labeled. Important bond lengths (Å) and angles (deg) are shown.

The alkyl halide route with TMEDA as donor solvent gave $[LiCl\cdot\{(Me_3Si)_2NLi\}_2\cdot(TMEDA)_2]$ (**5**). Although the starting materials Bu^nCl, HMDS, TMEDA, and Bu^nLi were mixed in a 1:1:2:2 ratio, no heterodimer of the $[LiCl\cdot LiHMDS\cdot(TMEDA)_2]$ type was obtained. The crystal structure of **5** showed another three-rung ladder framework (Figure 5).[24] The gross structural features of **4** and **5** are very similar to **3** and will only be discussed briefly.

In the heterodimers each of the two terminal lithium atoms, Li2 and Li3, lies in a pseudotetrahedral geometry, bonding to one amido anion, chlorine, and one chelating ligand, with either 2-(*N*,*N*-dimethylamino)ethyl methyl ether (DAME) in **4** or TMEDA in **5**. In both structures the trigonal planar bridging lithiums bond to the chlorine and two amido anions. The ladder cores are twisted from planarity, with Li(2) lying 0.29 and 0.37 Å below and Li(3) lying 0.22 and 0.25 Å above the anion plane in **4** and **5**, respectively.

The chelation of the DAME ligand is noteworthy. The complexes of LiHMDS solvated by TMEDA or dimethoxyethyl ether (DME)[25] are not bis-solvated cyclic systems as in **4** and **5**. A chelated monomer of [LiHMDS·TMEDA] and a bis-η^1-solvated dimer of [{LiHMDS·DME}$_2$] have been found in the solid state.[25] Similarly, no bis-solvated TMEDA complex of LiHMDS was detected in solution.[26] The chelation in **4** and **5** may be due to the lower steric strain in the mixed anion rings containing chlorine. Both the oxygen and the nitrogen of the

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[19] Li−H interactions have been noted in other structures including: (a) Chen, H.; Bartlett, R. A.; Dias, H. V. R.; Olmstead, M. M.; Power, P. P. *Organometallics* **1991,** *30,* 2487. (b) Barr, D.; Clegg, W.; Mulvey, R. E.; Snaith, R. *J. Chem. Soc., Chem. Commun.* **1984**, *285*, 287.

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[21] (a) Barr, D.; Snaith, R.; Wright, D. S.; Mulvey, R. E.; Wade, K. *J. Am. Chem. Soc.* **1987**, *25*, 7891. (b) Barr, D.; Doyle, M. J.; Drake, S. R.; Raithby, P. R.; Snaith, R., Wright, D. S. *J. Chem. Soc., Chem. Commun.* **1989**, 318. (c) Banister, A. J.; Barr, D.; Brooker, A. T.; Clegg, W.; Cunnington, M. J.; Doyle, M. J.; Drake, S. R.; Gill, W. R.; Manning, K.; Raithby, P. R.; Snaith, R.; Wade, K.; Wright, D. S. *J. Chem. Soc., Chem. Commun.* **1990**, 105. (d) Barr, D.; Brooker, A. T.; Doyle, M. J.; Drake, S. R.; Raithby, P. R.; Snaith, R.; Wright, D. S. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 285.

[22] Crystal data for **4**: $C_{22}H_{62}Cl_1Li_3N_4O_2Si_4$, monoclinic, $P2(1)/n$, $a = 12.726(4)$ Å, $b = 19.422(5)$ Å, $c = 15.874(3)$ Å, $\beta = 101.93°$, $V = 3824(2)$ Å^3, $Z = 4$, $d_{calc} = 1.013$ Mg/m^3, $F(000) = 1280$, $2\theta_{max} = 47°$, 5839 measured reflections, 5561 independent reflections, 5561 reflections used in the refinement, $R(1) = 0.0414$, $wR(1) = 0.0950$.

[23] (a) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9187. (b) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9198.

[24] Crystal data for **5**: $C_{24}H_{68}Cl_1Li_3N_6Si_4$, monoclinic, $P2(1)/c$, $a = 17.744(5)$ Å, $b = 13.115(2)$ Å, $c = 18.794(4)$ Å, $\beta = 113.49°$, $V = 4011(2)$ Å^3, $Z = 4$, $d_{calc} = 1.009$ Mg/m^3, $F(000) = 1344$, $2\theta_{max} = 45°$, 6454 measured reflections, 5236 independent reflections, 5235 reflections used in the refinement, $R(1) = 0.0857$, $wR(1) = 0.2103$.

[25] Williard, P. G.; Liu, Q.-Y. 204th National Meeting of the American Chemical Society, Washington D.C., Aug 1992.

[26] Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227.

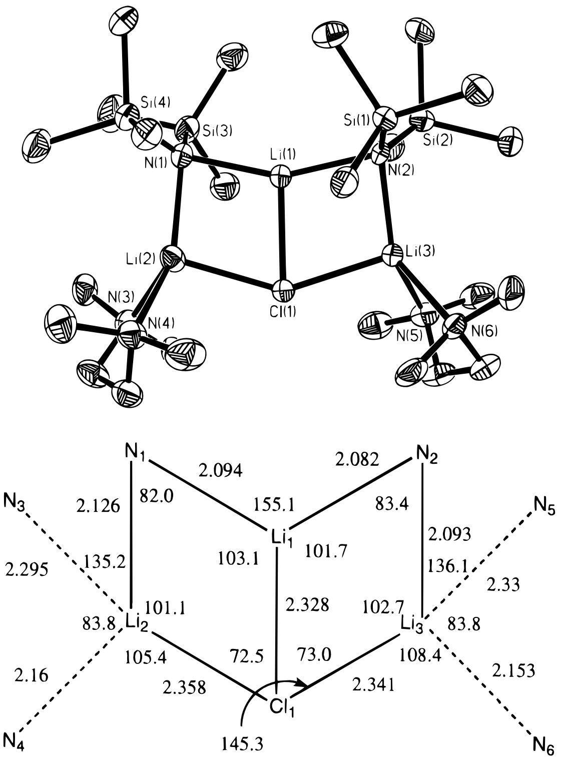
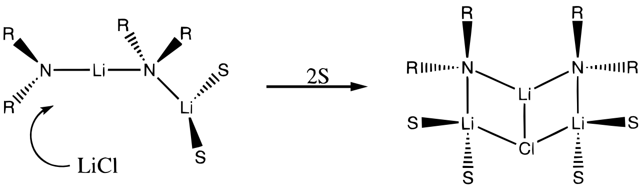
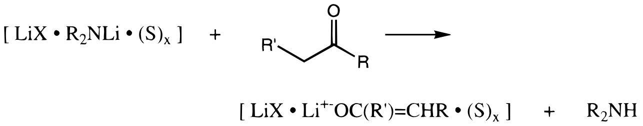


Figure 5. Molecular structure of **5** showing the mean plane through the atoms. Hydrogen atoms are omitted for clarity, and the heteroatoms are labeled. Important bond lengths (Å) and angles (deg) are shown.

Scheme 3



Scheme 4



DAME and TMEDA ligands bind to the metals as a result of the reduced strain.

It was originally proposed that formation of structures such as **3**−**5** could arise from a lithium chloride molecule trapping two $[R_2NLi\cdot S)_x]$ monomers.[15] However, recent NMR spectroscopic studies of LiHMDS aggregates suggests another possibility: the incorporation of a LiCl molecule into an open $[(R_2NLi)_2\cdot(S)_x]$ dimer.[7c,23] The dimer may then close into the three-rung ladder frame, as illustrated in Scheme 3.

Lithium Enolate/Halide Aggregates. We also wished to characterize the complexes formed from reactions of the halide/amide mixtures with ketones. The lithium amide in these solutions should react as a base toward the carbonyl group to give an enolate (Scheme 4, eq 4).

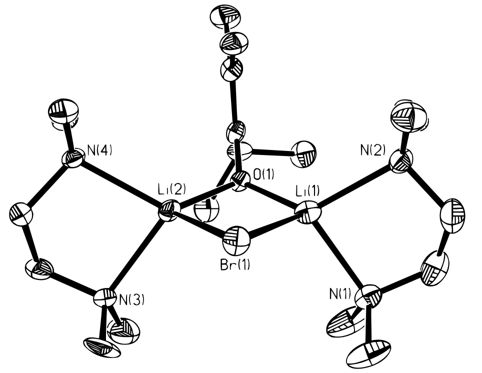


Figure 6. Crystal structure of **6** with hydrogens omitted for clarity and heteroatoms labeled.

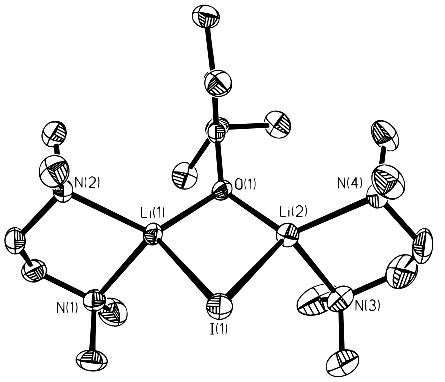


Figure 7. Crystal structure of **7** with hydrogens omitted for clarity and heteroatoms labeled.

Table 1. Bond Lengths (Å) and Angles (Deg) for the Heterodimers and the Homodimers (Averaged Values)

angle/length	Li_2BrO (**6**)	Li_2IO (**7**)	Li_2Br_2 (**8**)	Li_2I_2 (**9**)
Li−X−Li	63.9	59.6	73.7	73.8
X−Li−X	99.2	98.9	106.0	106.3
Li−O−Li	95.3	99.2		
Li(1)−X	2.569	2.874	2.487	2.74
Li(2)−X	2.582	2.842	2.500	2.75
Li(1)−O(1)	1.85	1.883		
Li(2)−O(1)	1.841	1.845		

Two compounds were successfully characterized as a mixed anion species by X-ray crystallography. The enolate complexes $[LiBr\cdot LiOC(Pr^i){=}CMe_2\cdot(TMEDA)_2]$ (**6**)[27] and $[LiI\cdot LiOC(Pr^i){=}CMe_2\cdot(TMEDA)_2]$ (**7**)[28] are isostructural (Figures 6 and 7), except for the difference in halide present. Compounds **6** and **7** can be prepared by either the hydrohalide or the alkyl halide route. Both complexes crystallize in the orthorhombic *Pbca* space group with almost identical unit cell parameters. These two complexes are the first enolate/halide aggregates to be fully characterized.

Bond lengths and angles in **6** and **7** can be compared to those of the dimers of $[(LiBr\cdot TMEDA)_2]$ (**8**) and $[(LiI\cdot TMEDA)_2]$ (**9**).[29] The Li−Br bond lengths of the heterodimer are 0.08 Å (averaged) longer than those of the homodimer. Similarly, the

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[27] Crystal data for **6**: $C_{19}H_{45}Li_2N_4O_1Br_1$, orthorhombic, $a = 14.999(2)$ Å, $b = 12.025(3)$ Å, $c = 29.024(3)$ Å, $V = 5235(2)$ Å^3, $Z = 8$, $d_{calc} = 1.115$ Mg/m^3, $F(000) = 1888$, $2\theta_{max} = 45°$, 4265 measured reflections, 3384 independent reflections, 3383 reflections used in the refinement, $R(1) = 0.0667$, $wR(1) = 0.1062$.

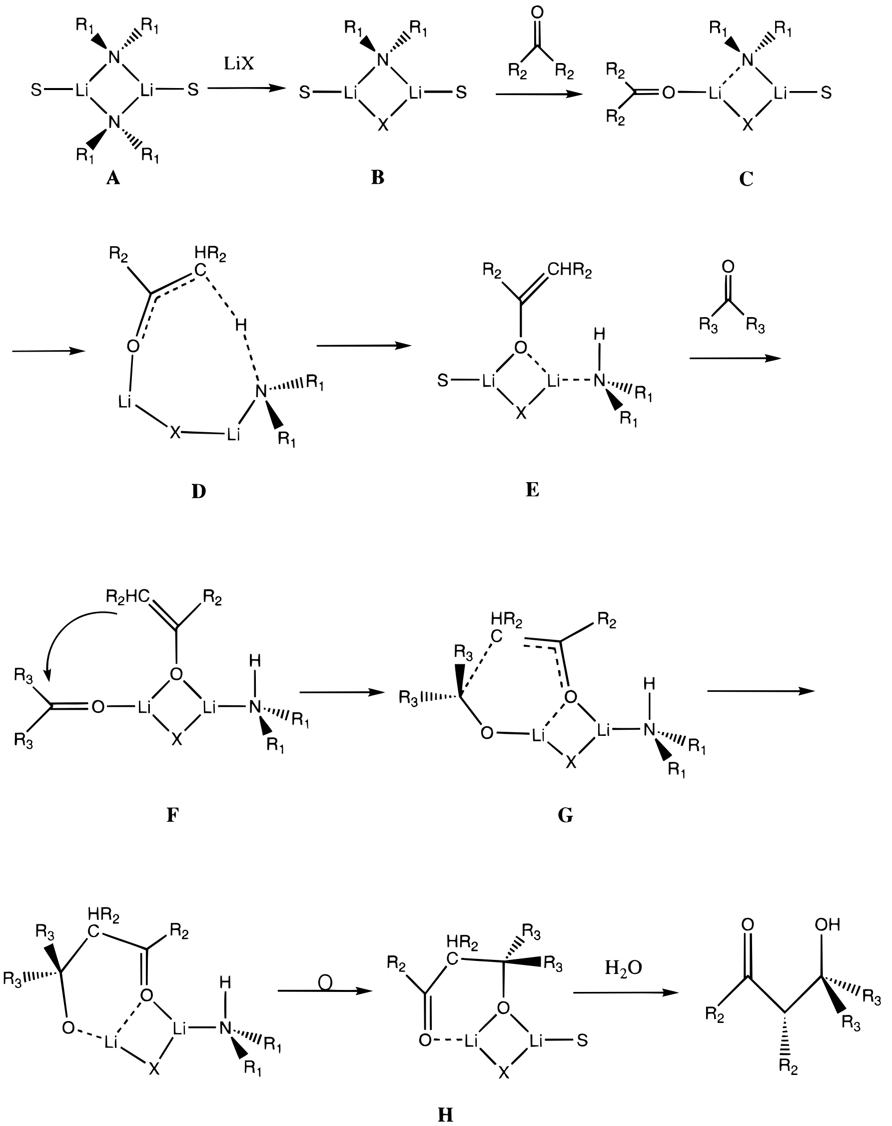
[28] Crystal data for **7**: $C_{19}H_{45}Li_2N_4O_1I_1$, orthorhombic, $a = 14.976(2)$ Å, $b = 12.234(2)$ Å, $c = 29.230(3)$ Å, $V = 5355.4(13)$ Å^3, $Z = 8$, $d_{calc} = 1.206$ Mg/m^3, $F(000) = 2032$, $2\theta_{max} = 50°$, 5829 measured reflections, 4716 independent reflections, 4714 reflections used in the refinement, $R(1) = 0.0515$, $wR(1) = 0.1173$.

[29] Raston, C. L.; Skelton, B. W.; Whitaker, C. R.; White, A. H. *Aust. J. Chem.* **1988**, *41*, 1925. Disorder for compound **8** led to relatively poor refinement of the structure. We crystallized compound **8** under solvent conditions different from those descibed in the above reference and were able to refine the structure to an *R* value of 0.0515% from a triclinic cell. The values quoted in Table 1 refer to our data.

[30] Henderson, K. W.; Williard, P. G. Unpublished results.

[31] (a) Lochmann, L.; Trekoval, J. *J. Organomet. Chem.* **1975**, *99*, 329. (b) Williard, P. G.; Liu, Q.-Y.; Lochmann, L. *J. Am. Chem. Soc.* **1992**, *113*, 348.

Scheme 5



iodine hetero dimer has averaged Li−I bond lengths 0.11 Å longer than the homodimer. No structural data are available for the enolate $[\{LiOC(Pr^i){=}CMe_2\}_n]$, so no direct comparison of the structural features can be made concerning this residue. Nevertheless, the average Li−O bond length found for simple homodimeric lithium enolates in the Cambridge Structural Database is 1.90 Å. Hence, the Li−O distance of 1.84 Å for **6** and 1.86 Å for **7** is slightly shorter than for homodimeric lithium enolates.

Significant differences are found between the hetero- and homodimers for the central four-membered ring angles (Table 1).

Both the homo- and heterodimer are significantly distorted from square, but their angles are very different. The much more acute Li−X−Li angle in the heterodimers can be accounted for by a shortening of the Li−Li distance in the heterodimers. This is a result of the much shorter Li−O bonding pulling the two metals closer together.

In both **6** and **7** the enolate residue lies almost perfectly perpendicular to the plane of the LiOLiX ring, being 94.0° for **6** and 88.0° for **7**. Hence, the C=C double bond of the enolate and the lithium atoms do not interact as has been found in less solvated systems.[32] The four-membered LiXLiO rings in **6** and **7** are puckered in a manner similar to that discussed for **1** (18.3° and 20.9° from the O−X axis for **6** and **7**, respectively). Puckering has the effect of reducing the ring angle at the lithium atoms; *i.e.*, the O−Li−X angles are reduced by 1.1° and 1.4° for **6** and by 2.7° and 0.7° for **7**, compared to the planar conformation. This decrease in the O−Li−X angles leads to a more nearly tetrahedral conformation at lithium.

In our experience, the crystallization of mixed anion species is uncertain. In numerous instances the complexes precipitating from solutions containing both lithium halide and lithium enolate (or amide) often gave only homodimers of either anion. Solution NMR studies of a variety of lithium compounds show more than one distinct species to be present in solution.[6,10,13,14,23,25] Relatively small structural variations can be critical in the determination of the isolable products. When isobutyrophenone was used as the enolizable ketone, under reaction conditions identical to those for **7**, only the dimeric iodine compound **9** precipitated. When similar conditions with either Bu^nBr or Bu^nCl as halide source were used, only homodimeric enolate $[\{LiOC(Ph){=}CMe_2{\cdot}TMEDA\}_2]$[30] was crystallized.

Insights into the Reaction Mechanism. The following reaction sequence (Scheme 5) involving heterodimers is in accordance with previous data for enolization reactions as well

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[32] Henderson, K. W.; Williard, P. G.; Bernstein, P. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1117.

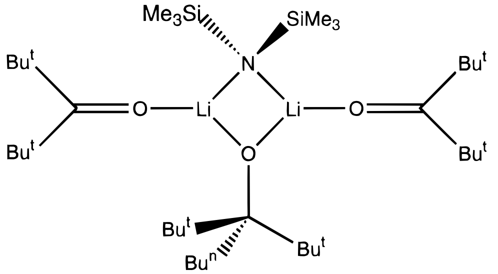


Figure 8. Framework of the dimeric structure of the ketone solvated, mixed alkoxide/amide complex **8**, $[LiN(SiMe_3)_2 \cdot LiOC(Bu^n)Bu^t{}_2 \cdot (Bu^tC{=}O)_2]$.

as the known structural types of mixed halide species. As the coordination number of the metal atoms may change during the course of the reaction, a simplified version involving monosolvated species is outlined in Scheme 5. Dimers such as **A** are now well established as common species both in solution and in the solid state.[18] Compounds **1** and **2** illustrate heterodimers like **B**. Although compound **C** is yet to be identified, homodimers of lithium hexamethyldisilazide solvated by unreacted ketone or ester (preenolization complexes) are analogous to **C**.[31] However, a closer match to **C** is the heterodimeric mixed anion $[LiN(SiMe_3)_2 \cdot LiOC(Bu^n)Bu^t{}_2 \cdot (Bu^tC{=}O)_2]$ (Figure 8).[30] This complex contains an amide and an alkoxide with each of the lithium atoms being tricoordinate by solvation from a di-*tert*-butyl ketone molecule.

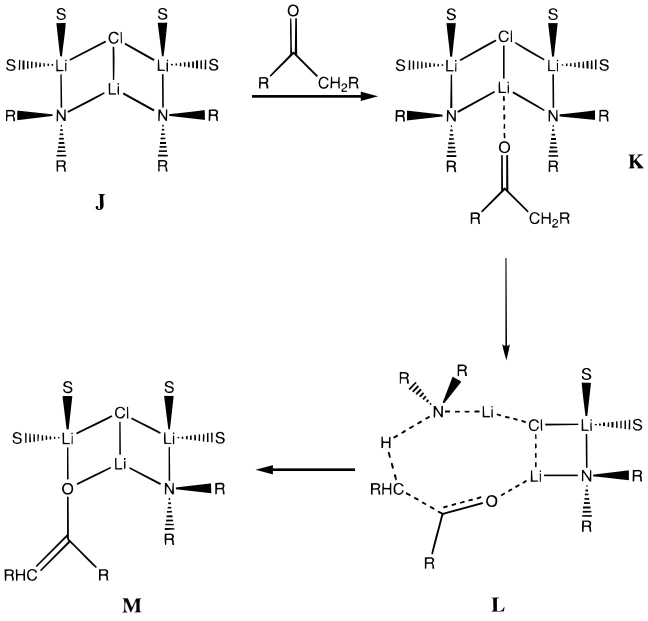
The structures of **6** and **7** with TMEDA as bis solvating donor are analogous to **E** in Scheme 5. Once the enolate has formed, the reconstituted secondary amine may be utilized as donor; note the crystal structure of $[Li_2Na_4\{OC(Bu^t){=}CH_2\}_6 \cdot (Pr^i{}_2NH)_2]$.[32] Hence, a model for complexes in the form of **E** are available.

The carbonyl of a second ketone coordinated to a lithium center is directed toward the π-bond of the enolate as shown by **F**. It is vital that chiral amine remains in the complex if it is to be used for asymmetric induction. It may then direct the facial attack of the reactant. Competition between donor solvent and chiral amine for coordination to lithium will lead to a reduction in stereoselectivity. However, since asymmetric induction has been observed for systems that contain only chiral amine as additive, some degree of amine complexation is likely.[10e] The second enolization and formation of a new carbon−carbon bond completes the sequence in Scheme 5. There are numerous species similar to complexes **F** and **H** that do not contain a halide atom.[33] We are attempting to prepare such halide-containing complexes.

While the sequence suggested in Scheme 5 involves only dimers, higher oligomers such as tetramers might also be involved. The stoichiometry of the halide may also be important. Enolate trapping reactions of lithium 3-pentanolate with trimethylsilyl chloride show an optimum 1:3 LiCl:LiNR$_2$ ratio for selectivity.[10a] Hence, a possible enolization mechanism involving three-rung ladders similar to **3**−**5** is outlined in Scheme 6.

Mair[15] noted that an incoming enolate may be attracted to the relatively open site of the central lithium of the ladder **3**. Directional control would be exerted if enolization took place *via* an intermediate of type **L**. Several key questions pertaining to the mechanism and relative stability of mixed anion formation remain to be answered. A molecular orbital study of these species was undertaken in order to probe these questions and investigate the credibility of the models proposed in Schemes 5 and 6.

Scheme 6



Theoretical Calculations

Methods. Most calculations were carried out using the Gaussian 92 program package.[34] Geometry optimizations were carried out at the HF/LANL1DZ[35,36] level. Single-point energy calculations were carried out at MP2=FC/LANL1DZ(POL) using HF/LANL1DZ geometries. The LANL1DZ(POL) basis set is obtained from the LANL1DZ basis set by adding the following *d*-orbital exponents: C, 0.8; N, 0.8; O, 0.8; Li, 0.2; Br, 0.389. Additional calculations on larger systems were performed using the MOPAC program package.[37]

Structure **6**, the "mixed" dimer of lithium bromide and lithium diisopropylketone enolate, crystallizes in preference to the corresponding homodimers. While several factors can influence the relative ease of crystallization of these species, a simple explanation for the exclusive formation of the mixed dimer might be that the homodimers are thermodynamically less stable. We tested this hypothesis by performing *ab initio* calculations[34] on the model systems $[LiBr \cdot LiOC(H){=}CH_2 \cdot (NH_3)_4]$ (**I**) (analogous to **6**), $[\{LiBr \cdot (NH_3)_2\}_2]$ (**II**), and $[\{LiOC(H){=}CH_2 \cdot (NH_3)_2\}_2]$ (**III**) and calculating the energy of the hypothetical reaction:

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[33] (a) Amstuz, R.; Dunitz, J. D.; Laube, T.; Schweizer, W. B.; Seebach, D. *Chem. Ber.* **1986**, *119*, 434. (b) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462. (c) Williard, P. G.; Salvino, J. M. *Tetrahedron Lett.* **1985**, *26*, 3961. (d) Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 7288. (e) Geol, S. C.; Chiang, M. Y.; Buhro, W. E. *J. Am. Chem. Soc.* **1991**, *113*, 7069.

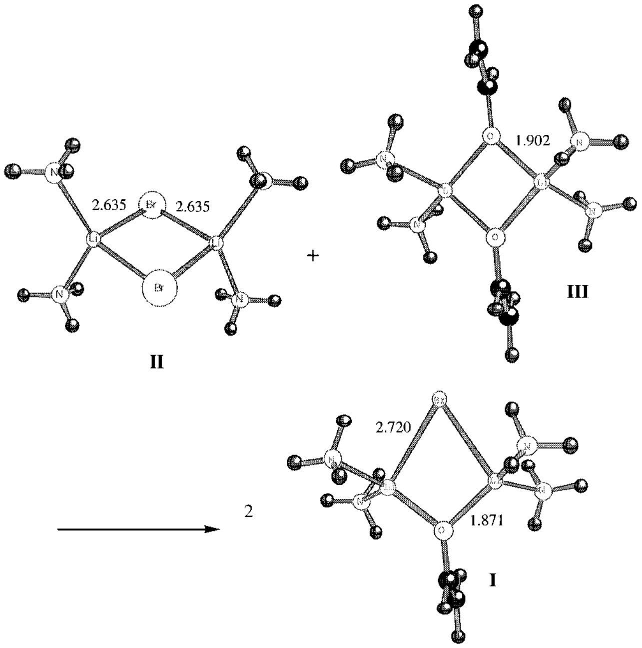
[34] The Gaussian 92 program was used for all calculations described here: Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; DeFrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *Gaussian 92*, Gaussian, Inc.: Pittsburgh, PA, 1992.

[35] (a) Hay, P. J.; Wadt, W. R. *J . Chem. Phys.* **1985**, *82*, 270. (b) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 284.

[36] Although the out-of-plane conformation of the enolate group in **I** and **III** mimics that in **6**, our calculations indicate that the in-plane conformation is slightly preferred at HF/LANL1DZ: **I′** is 0.1 kcal mol^{-1} more stable than **I**, while **III′** is 0.2 kcal mol^{-1} more stable than **III**. At MP2/LANL1DZ(POL)//HF/LANL1DZ, the out-of-plane conformers become more stable, with **I** lying 0.3 kcal mol^{-1} below **I′** and **III** 0.7 kcal mol $^{-1}$ below **III′**.

[37] Stewart, J. J. P. MOPAC, Version 6.0. For the PM3 parameterization of lithium, see: Anders, E.; Koch, R.; Freunscht, P. *J. Comput. Chem.* **1993**, *14*, 1301. The keyword PRECISE was used for the optimizations.

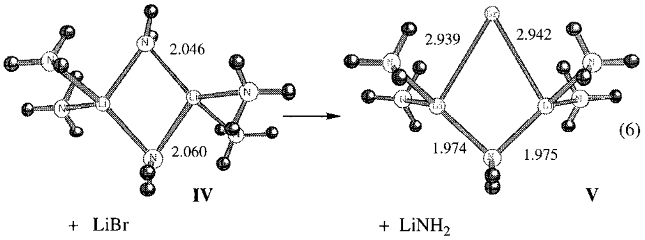
$$\mathbf{II} + \mathbf{III} \rightarrow 2\mathbf{I} \qquad (5)$$



According to HF/LANL1DZ[34−36] geometry optimizations, reaction 5 is exothermic: two molecules of **I** are 3.1 kcal mol^{-1} more stable[38] than [**II** + **III**]. The Li−Br bonds in **I** are longer than in **II**, while the Li−O bonds in **I** are shorter than in **III**. This suggests that the origin of the stability of **I** lies in charge transfer from the enolate oxygen to the bromine center. This is analogous to what is observed at anomeric carbon centers in X−C−Y groups, where the bond between carbon and the donor atom X (bearing a lone pair) is shortened, while the bond between carbon and the center Y is lengthened. In our case, a similar effect is observed for the bonds to lithium. The magnitude of the negative charge on bromine increases from −0.86 in the homodimer **II** to −0.90 in the heterodimer **I**. This effect is absent in the homodimers. However, single point MP2/LANL1DZ(POL) energy calculations using the HF/LANL1DZ optimized structures (hence denoted MP2/LANL1DZ(POL)//HF/LANL1DZ) gave only a 0.1 kcal mol^{-1} preference for the products in eq 5. This small difference in stability indicates that the homodimers may be also present.

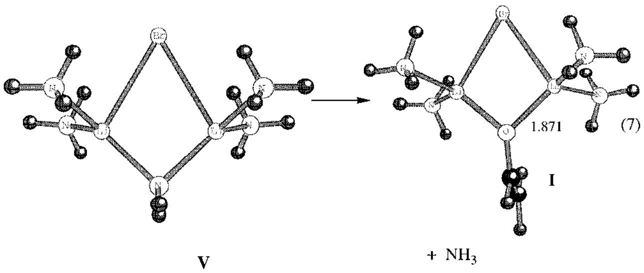
The relative stability of homo- and "mixed" dimers is important in light of the lithium halide's influence on the stereochemical outcome of the enolate's reactions.[10] Scheme 5 proposes a mechanism to account for the effect of the halide anion: the starting lithium amide dimer **A** is first converted to the mixed dimer **B** before being reacted with the carbonyl compound to give the key intermediate **E**, also a mixed dimer, analogous to **I**. To assess the viability of Scheme 5, we have calculated the energy required for the conversion of model amide dimer [{$LiNH_2 \cdot (NH_3)_2$}$_2$] (**IV**) to mixed dimer [$LiBr \cdot LiNH_2 \cdot (NH_3)_4$] (**V**) (eq 6).

$$\mathrm{IV} + \mathrm{LiBr} \rightarrow \mathrm{V} + \mathrm{LiNH_2} \qquad (6)$$



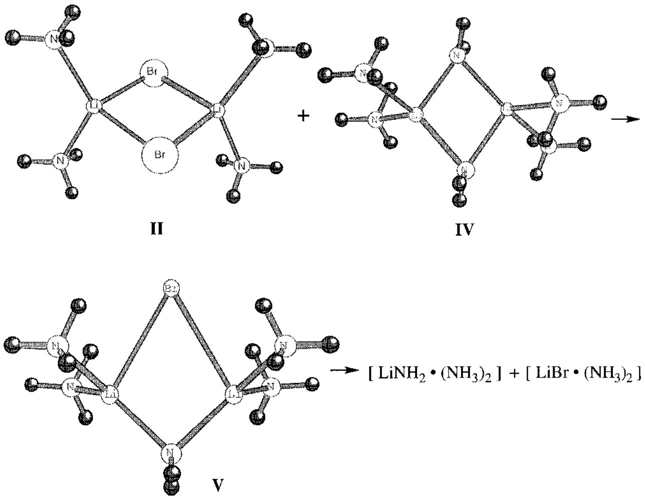
We also calculated the energy for the subsequent deprotonation of acetaldehyde by **V** to give ammonia and **I** (eq 7):

$$\mathrm{V} + \mathrm{CH_3CHO} \rightarrow \mathrm{I} + \mathrm{NH_3} \qquad (7)$$



The 12.4 kcal mol^{-1} exothermicity of eq 6 (at MP2/LANL1DZ(POL)//HF/LANL1DZ) supports the notion that mixed dimer **V** is involved in the reaction sequence. The optimized geometry of **V** is analogous to that of **I**: the N−Li bonds are shorter in **V** than in the homodimer **IV**, and the Li−Br distances are very long (2.93 A, compared to 2.72 A for the Li−Br distance in **II**). Both the long Li−Br distance and the large calculated natural[39] charge (HF/LANL1DZ(POL)) of −0.90 on Br indicate that structure **V** is best described as a "salt" of the bromine anion and the complex cation [$LiNH_2Li \cdot (NH_3)_4$]$^+$. In eq 7, the right-hand side is strongly favored (by 18.6 kcal mol^{-1} at MP2/LANL1DZ(POL)//HF/LANL1DZ), since CH_3CHO is more acidic than NH_3. Equation 8, which is analogous to eq 5, gives another measure of the stability of **V**. Equation 8 is 9.4 kcal mol^{-1} exothermic at MP2/LANL1DZ(POL)//HF/LANL1DZ.

$$\mathrm{V} + \mathrm{LiBr} \rightarrow [\mathrm{LiNH_2 \cdot (NH_3)_2}] + [\mathrm{LiBr \cdot (NH_3)_2}] \qquad (8)$$



Both mixed dimers and homodimers are strongly favored over their constituent monomeric "fragments". In the case of **V**, for

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[38] Absolute energies (Hartrees) at HF/LANL1DZ are as follows: **I**, −405.158 60; **I′**, −405.158 83; **II**, −265.850 84; **III**, −544.461 28; **III′**, −544.461 63; **IV**, −350.978 32; LiBr, −20.462 29; **V**, −308.425 75; $LiNH_2$, −63.044 75; NH_3, −56.180 41; CH_3CHO, −152.869 19; $LiBr \cdot 2NH_3$, −132.901 62; $LiNH_2 \cdot 2NH_3$, −175.463 50. Absolute energies (Hartrees) at MP2/LANL1DZ(POL)//HF/ LANL1DZ are as follows: **I**, −406.512 76; **I′**, −406.512 31; **II**, −266.850 86; **III**, −546.174 60; **III′**, −546.173 44; **IV**, −352.108 35; LiBr, −20.594 75; **V**, −309.487 29; $LiNH_2$, −63.235 56; NH_3, −56.359 29; CH_3CHO, −153.355 18; $LiBr \cdot 2NH_3$, −133.398 91; $LiNH_2 \cdot 2NH_3$, −176.024 00; **VI**, −350.119 79; **VII**, −489.785 53.

example, the energy required for the reaction in equation 9 is 40.4 kcal mol^{-1} at MP2/LANL1DZ(POL)//HF/LANL1DZ.

The corresponding calculated values for the dissociation of **I** and **III** are 37.0 and 40.7 kcal mol^{-1}. Hence, mixed dimers such as **V** and **I** appear to be viable intermediates which are not liable to break apart to give monomeric species.

A crucial question remains to be addressed: why does the aldol addition proceed with enhanced stereoselectivity in the presence of lithium halides? It is not readily obvious why a chiral mixed dimer (analogous to **I**) should react with higher asymmetric induction than a chiral homodimer (analogous to **III**). Since both **I** and **III** are highly stable to dissociation to the monomers—**III** even more so than **I**—the lower enantioselectivity in the reaction of homodimers is probably not due to the involvement of a nonselective monomer. We considered the possibility that any loss in enantioselectivity might be due to the dissociation of the chiral amine coordinated to a lithium center and that this dissociation might be easier for a homodimer such as **III**. Model MP2/LANL1DZ (POL) calculations were carried out on structures [$LiBr{\cdot}LiOC(H){=}CH_2{\cdot}(NH_3)_3$] (**VI**) and [$\{LiOC(H){=}CH_2\}_2{\cdot}(NH_3)_3$] (**VII**), derived from **I** and **III**, respectively, by simply removing a NH_3 group while maintaining the rest of the geometry unchanged. The energy of NH_3 loss from **I** to **VI** (21.1 kcal mol^{-1}) is larger than the corresponding energy dissociation (18.7 kcal mol^{-1}) for **III** into **VII** and NH_3. This lends some support to our hypothesis that the lower enantioselectivity of the homodimer may be due to easier dissociation.

A final comment on the formation of the enolate involves the transition structures **D** and **L** in Schemes 5 and 6, respectively. An analogous eight-membered structure to **D** has been proposed recently by Collum[8f] on the basis of MNDO calculations for the reaction of a lithium amide homodimer. We have calculated structure **VIII** at HF/6-31G* for the reaction of the mixed dimer $LiNH_2{\cdot}LiCl$ with acetaldehyde (Figure 9). PM3 calculations gave a similar eight-membered ring structure **VIII′** (heat of formation −132.3 kcal mol^{-1}). PM3 calculations on the reaction of the heterotrimer [$(LiNH_2)_2{\cdot}LiCl$] with acetaldehyde gave a 4,8 ring system transition structure **IX** (heat of formation −171.4 kcal mol^{-1}), analogous to **L** in Scheme 3. A second stable 4,4,6 ring system transition state **IX′** (heat of formation −173.1 kcal mol^{-1}) was located. The eight-membered structure for deprotonation by a homodimer or mixed dimer and also for a heterotrimer appears to be a plausible route. However, in light of the stability of **IX′**, tricyclic transition structures cannot be discounted.

Conclusions

Mixed lithium amide/halide and enolate/halide anion aggregates exist as distinct species. Theoretical calculations show that heterodimer formation is competitive with and sometimes favored over homodimerization.

The computed geometries are in general accord with the crystal structures. The calculated shortening of the Li−O bonds and a lengthening of the Li−Br going from the homo- to the heterodimers was shown in structures **6** and **7** (for Li−I). This has been explained in terms of charge transfer from the enolate group to the halide. Also of interest is the stability of the eight-membered ring transition states **VIII**, **VIII′**, and **IX**. It appears that the eight-membered ring remains “open” during enolization giving credence to structure **D** in Scheme 5 and also to structure **L** in Scheme 6. A more closed transition state of type **IX′** cannot be ruled out for reactions involving heterotrimers.

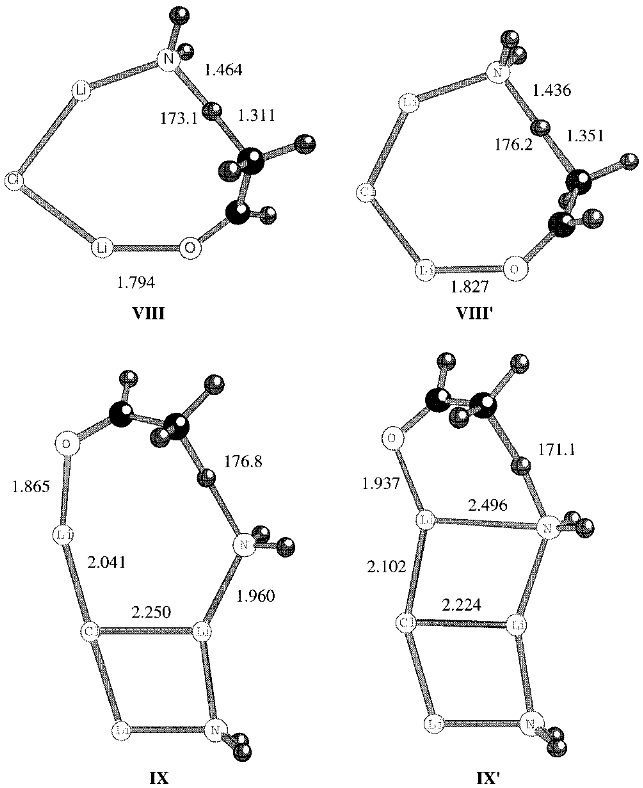

Figure 9. Transition structures **VIII**, **VIII′**, **IX**, and **IX′** for the deprotonation of acataldehyde.

In regard to the question of why the presence the lithium halide affects stereospecificity, several points may be raised. Each aggregate type has a distinct physical form which shows differing preferences for orientational control. Steric hindrance is greater in dimers compared to monomers; therefore, heterodimers will induce more directional control than simple monomers. Theory predicts that donor molecules will bind more strongly to a heterodimer than to a homodimer. Hence, chiral amine will bind to lithium more strongly in enolization reactions when lithium halide is present. This will lead to a greater degree of asymmetric induction.

The models proposed (Schemes 5 and 6) are very much simplified. Several possible aggregated species are likely to be involved in the aldol addition step during the course of the reaction. Some or all of these aggregates may incorporate halide as the reaction proceeds.

In summary, it is concluded that the formation of lithiated mixed anion species between amides or enolates with halides must be regarded as important intermediates in the reaction sequence for enolization. By continuing to isolate and to characterize structurally the species involved in enolization and aldol addition reactions, it should be possible to gain further insights into the reaction mechanism.

Experimental Section

All solvents were distilled over sodium/benzophenone until blue and used directly from the still. Amines and ketones were distilled over CaH_2 prior to use. Standard Schlenk techniques were employed for the preparation and manipulation of the highly air- and moisture-sensitive materials. All reactions were carried out under a pre purified argon blanket. Bu^{n}Li was standardized by titration with 2,5-dimethoxybenzyl alcohol before use. The hydrohalides were prepared as either their diisopropylamine (DPA) or TMP derivatives. All hydrohalides

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(39) For comparison, the charge on Br in the homodimer **II** is −0.86. Natural charges were calculated by means of the NBO program (incorporated in Gaussian 92 as Link 607): (a) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO* Version 3.1. See also: (b) Reed, A. E.; Weinhold, F. *J. Chem. Phys.* **1983**, *78*, 4066.

were prepared in a similar manner and the synthesis of DPA·HI is given as an example.

Diisopropylamine Hydroiodide (DPA·HI). A 57% hydriodic acid (100 mmol) solution was diluted by 200 mL of ether and cooled to 0 °C. TMP (95 mmol) was added slowly, giving an instant white precipitate. The mixture was stirred for 30 min, and the solid was then filtered and washed with ether (3 × 10 mL). After being dried under vacuum for 30 min, the solid was ready for use.

[LiBr·LiTMP·(THF)$_3$] (1). To a slurry of TMP·HBr (0.9 mmol) in THF (0.55 mL, 6.8 mmol) was added Bu^{n}Li (1.8 mmol) at 0 °C with vigorous stirring. After several minutes, the resulting clear, colorless solution was placed in a freezer at −78 °C. After 1 week, X-ray diffraction quality crystals of **1** had formed.

[LiCl·{LiN(SiMe$_3$)$_2$}$_2$·(Me$_2$NCH$_2$CH$_2$OMe)$_2$] (4). Addition of Bu^{n}Li (1.25 mmol) to HMDS (0.28 mL, 1.33 mmol) in 1 mL of hexane at 0 °C gave a cloudy white mixture after 3 min of stirring. A clear solution was achieved after addition of 0.20 mL of DAME. After 5 min, methylene chloride (0.16 mL, 2.50 mmol) was added without any visible change. Opaque white crystals were grown after 12 h at −40 °C, and these became almost clear after 1 week at −40 °C. An edge of one of the needle crystals was cut and used for X-ray analysis.

[LiCl·{LiN(Me$_3$Si)$_2$}$_2$·(TMEDA)$_2$] (5). Bu^{n}Cl (2 mmol), HMDS (2 mmol), and TMEDA (4 mmol) were mixed with 3 mL of pentane and the solution cooled to 0 °C. Bu^{n}Li (4 mmol) added over a period of 2 min yielded a clear pale yellow solution. When the mixture was cooled to −78 °C, a white solid was precipitated which was then redissolved, and the solution was placed at −40 °C. After 1 day, colorless crystals of **5** deposited.

Compounds **6** and **7** were prepared by both the hydrohalide and the alkyl halide routes. For brevity a general preparation using either method is described.

[LiBr·LiOC(Pr^i)=CMe$_2$·(TMEDA)$_2$] (6). A solution containing Bu^{n}Br (2 mmol), diisopropylamine (2 mmol), and TMEDA (4 mmol) in 2 mL of toluene was cooled to 0 °C while Bu^{n}Li (4 mmol) was added dropwise. The pale yellow solution was stirred for 10 min at 0 °C before the slow addition of diisopropylketone (2 mmol). After being stirred for a further 10 min, the solution was placed in a −40 °C freezer. Clear colorless crystals of **5** were formed after 2 days.

[LiI·LiOC(Pr^i)=CMe$_2$·(TMEDA)$_2$] (7). Bu^{n}Li (4 mmol) was added to a suspension of TMP·HI (2 mmol) and TMEDA (4 mmol) in 2 mL of toluene at 0 °C. The mixture was stirred for 5 min and then subjected to ultrasound for 2 min. This gave a clear yellow solution. When the solution was recooled to 0 °C, diisopropyl ketone (2 mmol) was added, yielding a clear, colorless solution. After the solution was cooled at −50 °C for 3 days, crystals of **6** precipitated.

X-ray Crystallography. Suitable crystals from the samples were mounted in an oil drop directly from the crystallization vessels, to the diffractometer, under a stream of nitrogen gas at −60 °C. Data were collected on a Siemens P4 X-ray crystallographic system fitted with a LT-2 low temperature device. The structures were solved by direct methods using SHELXL-90. All atoms are refined isotropically with the exception of the hydrogens (which were fitted in idealized positions). Full-matrix least-squares refinement on F^2 was completed using SHELXL-93. Complete crystallographic data is available in the supporting information.

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Supporting Information Available: A full list of bond lengths and angles, atomic coordinates, and anisotropic thermal parameters for the structures elucidated (33 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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