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Lithium Bis(2-adamantyl)amide: Structure and Reactivity of an Extremely Hindered Lithium Dialkylamide

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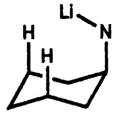
KEY WORDS: lithium amides; enolates; *E/Z* selectivity; mixed aggregation effects; enol silyl ethers.

***Abstract*:** The readily prepared title lithium amide is shown to be monomeric under all conditions, readily forms mixed aggregates with ketone enolates but not with lithium halides, and enolizes ketones with a very high *E/Z* selectivity.

As a result of spectroscopic studies of some of the standard lithium dialkylamide bases, it became clear that increasing the steric demands of the *N*-alkyl substituents on the amide fragment facilitates both deaggregation to monomers *and* formation of mixed aggregates.[1,2] Although counter-intuitive on first inspection, both effects can be understood in terms of destabilization of the homonuclear lithium amide dimer. We wished to test this hypothesis by studying the mixed aggregation of a lithium dialkylamide that exists exclusively as a monomer in THF solution; however, even the severely hindered lithium di-t-alkylamides exist as monomer-dimer mixtures.[3] Furthermore, the introduction of inordinately hindered alkyl substituents is problematic due to the difficulty encountered in the preparation of the di-t-alkyl amines.[4] We reasoned that an axial cyclohexyl substituent (i) should be more sterically demanding than a t-butyl substituent (ii) and that the 2-adamantyl moiety (iii) offers a simple test of this hypothesis. We describe below a brief survey of the solution structure and reactivity of lithium bis(2-adamantylamide) (LBAA, **1**).



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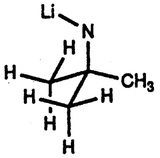

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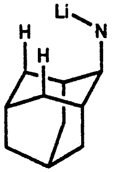

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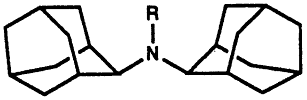
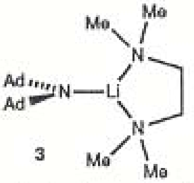


1; R = Li
2; R = H

Preparation and Structure of LBAA Solvates. Bis(2-adamantyl)amine (**2**) was prepared as a colorless solid from adamantanone and NH_4Cl (or $[^{15}N]NH_4Cl$) in 70% yield by reductive amination.[5,6] Treatment of amine **2** with n-BuLi or (crystalline) EtLi in THF at 0 °C affords solutions of LBAA-THF that can be used as is or cooled to -78 to afford an air sensitive white solid (contaminated by ≈10% unreacted amine). ^{6}Li and ^{15}N NMR spectroscopic analyses on [^{6}Li,^{15}N]LBAA-THF reveal a ^{6}Li doublet and ^{15}N triplet consistent with exclusively monomer (Table I). Alternatively, metallation of 2 with [^{6}Li]EtLi in hexane containing 1.0 equiv of TMEDA for 30 min at RT affords a bright yellow homogeneous solution of LBAA-TMEDA. Cooling to -78 °C affords analytically pure LBAA·TMEDA as a white crystalline solid in 64% yield.[6] Assignment of the 1:1 LBAA:TMEDA stoichiometry is based upon titration, ^{1}H NMR integration, and elemental analysis. ^{6}Li and ^{15}N NMR spectroscopic analysis on [^{6}Li,^{15}N]LBAA·TMEDA (in toluene-d_8) again reveals exclusively monomer (presumably chelate 3).[6] Addition of 1.0 or 2.0 equiv of HMPA to LBAA (or LBAA-TMEDA) in THF affords monomers 4 and 5, respectively. The solvation state assignments derive from the observable ^{31}P-^{6}Li (two-bond) coupling.[3,7]



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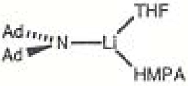

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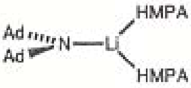

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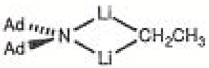
The exclusive formation of monomers under all conditions is consistent with the extreme steric bias of the 2-adamantyl moieties. Indeed, extensive MNDO calculations revealed no discernible tendency to form aggregates. Attempts to enforce dimerization by restricting bond lengths and angles within the Li_2N_2 ring afford optimized structures bearing fragmented C-C and C-N bonds. We also noted that a chelated monomer corresponding to 3 is a minimum, but that ligand substitution is exothermic for both HMPA and THF.



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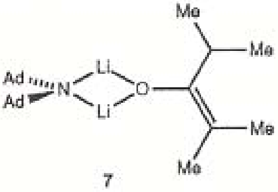

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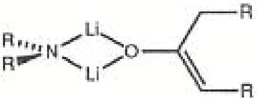


8; R,R = Me,Me
9; R,R = $(CH_2)_3$

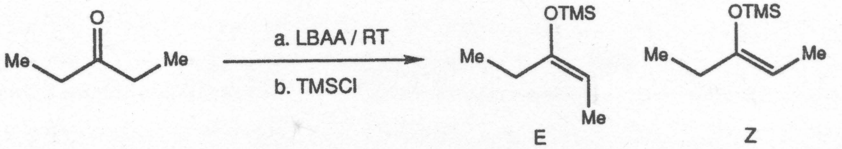
Mixed Aggregates of LBAA. During efforts to prepare analytically pure LBAA we discovered a high propensity of LBAA to form mixed aggregates with ethyllithium. NMR spectroscopic analysis of 0.05 M [^{6}Li,^{15}N]LBAA with 0.5 eq of [^{6}Li]ethyllithium reveals essentially quantitative formation of mixed dimer 6. We were especially interested in monitoring the tendency of LBAA to form mixed aggregates with lithium enolates and lithium halides in light of the suspicion that deaggregation and mixed aggregation are both promoted by the steric demands of the R_2NLi fragment. Addition of diisopropylketone enolate[8] to LBAA in THF affords mixed aggregate 7 quantitatively. Mixed aggregate 8 also forms nearly quantitatively despite a notable lack of high steric bias in the enolate to drive mixed aggregation. Even formation of limited concentrations of mixed aggregate 9 is provocative in light of the resistance of LDA to form appreciable concentrations of mixed aggregate with lithium cyclohexenolate.[9] Given this strong tendency of LBAA to form mixed aggregates with lithium enolates, we were surprised to find that LBAA shows no tendency whatsoever to form mixed aggregates with LiBr or LiCl. In contrast, LDA shows a markedly greater tendency to form mixed aggregates with lithium halides than with lithium enolates.[9]

Table I. ^{6}Li and ^{15}N NMR spectroscopic data of [^{6}Li,^{15}N]LBAA and the corresponding mixed aggregates.[a]

Compound	Temp (°C)	^{6}Li δ (mult., $^1J_{Li\text{-}N}$)	^{15}N{^{1}H} δ (mult., $^1J_{Li\text{-}N}$)
1	-115		51.7 (s)
2	-115	1.60 (d, 9.7)	65.3 (t, 9.6)
3	-80	1.83 (d, 9.9)[c]	72.6 (t, 10.0)[c]
4	-125	1.14 (dd, $J_{Li\text{-}P}$ = 4.5 Hz, $J_{Li\text{-}N}$ = 9.5 Hz)	64.0 (t, $J_{Li\text{-}N}$ = 9.4 Hz)
5[d]	-125	0.96 (dd, $J_{Li\text{-}P}$ = 3.6 Hz, $J_{Li\text{-}N}$ = 8.6 Hz)	64.4 (t, $J_{Li\text{-}N}$ = 8.5 Hz)
6	-120	2.93 (d, 5.0)	49.9 (quint, 5.1)
7	-115	1.36 (d, 5.5)	49.1 (quint, 5.6)
8	-115	1.36 (d, 5.5)	49.7 (quint, 5.5)
9	-115	1.34 (d, 5.3)	---[b]

[a]Spectra were recorded on 2:1 mixtures of [^{6}Li,^{15}N]LBAA (0.05 M) in 3:1 THF/pentane unless noted otherwise. [b]Resonance could not be located. [c]Recorded in neat toluene-d_8. [d]The ^{31}P NMR spectroscopic data recorded at -125 °C are as follows: **4**, 27.4 (t, $J_{Li\text{-}P}$ = 4.5 Hz); **5**, 26.3 (br s).

Stereochemistry of Enolization. The stereochemistry of enolization of 3-pentanone has provided benchmark selectivities for monitoring structure- and condition-dependent changes in lithium amide reactivity (Equation 1), although recent studies have highlighted the extraordinary mechanistic complexity often belied by a simple *E*/*Z* ratio.[3]



(1)

The *E*-*Z* selectivities of 3-pentanone enolization are dramatically higher when LBAA in THF is employed as a base than the 3:1 ratios observed for other amides bearing 2° alkyl substituents,[9] even exceeding those observed for lithium di-t-alkylamide bases (Table II).[3] We observe several curious trends including: (1) a marginal dependence on the THF concentration, absolute LBAA concentration, and reaction temperature; (2) little dependence on the percent conversion or on the presence of added ketone enolate despite the demonstrable formation of LBAA-enolate mixed aggregates, (3) little effect of addition of 1.0 eq HMPA despite the formation of HMPA solvates, and a precipitous decline in selectivity at 4.0 eq; (4) a measurable effect of LiCl despite the absence of detectable LBAA-LiCl mixed aggregates, (5) an erosion of selectivity with added TMEDA that approaches the low selectivities characteristic of LBAA-TMEDA in benzene.

Table II. *E/Z* Enolization Selectivities in THF at 25 °C (Equation 1).[a]

solvent	Additive,	E/Z	solvent	Additive,	E/Z
THF	-----	50:1	THF	0.5 eq HMPA	45:1
THF	(-20°C)	50:1	THF	1.0 eq HMPA	50:1
THF	PhH (80%)	35:1	THF	4.0 eq HMPA	6:1
THF	1.0 eq TMEDA	40:1	THF	0.2 eq LiCl	80:1
THF	5 eq TMEDA	15:1	THF	1.0 eq LiCl	25:1
THF	13 eq TMEDA	12:1	THF	0.2 eq enolate[b]	55:1
PhH	5 eq TMEDA	5:1	THF	0.9 eq enolate[b]	50:1

[a] The metallations were carried out using 1.1 equiv LBAA (0.1 M) at ambient temperature and determined by gas chromatography using standard protocols.[3] [b] Diisopropylketone enolate.[8]

Overall, we find ourselves with a perplexing view of solvation, aggregation, and mixed aggregation. There is no immutable argument for a correlation between the observed ground state structures and reactivities. The trends that do emerge are consistent with substantial mechanistic complexity and a requisite consideration of both ground state and transition state effects.[10,11]

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