J. Am. Chem. Soc. 1994, 116, 9187–9197

Lithium Dialkylamide Mixed Aggregation: MNDO Computational Study of Salt and Solvent Dependencies

Floyd E. Romesberg and David B. Collum*

Contribution from the Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301

Received February 22, 1994[•]

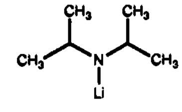
Abstract: Mixed aggregation of lithium dialkylamides with various LiX salts is studied by semiempirical (MNDO) computational methods. The relative stabilities of mixed aggregates of lithium diisopropylamide and lithium 2,2,6,6-tetramethylpiperidide with LiCl as well as the enolates derived from acetone, cyclohexanone, and 2,4-dimethylpentanone are described. The unsolvated forms are compared with the analogous structures solvated by tetrahydrofuran and hexamethylphosphoramide. The structural types studied include mixed cyclic dimers (R_2NLi–LiX), trimers [$(R_2NLi)_2(LiX)_2$], and tetramers [$(R_2NLi)_2(LiX)_2$]; 3-rung ladders [$(R_2NLi)_2(LiX)$] and 4-rung ladders [$(R_2NLi)_2(LiX)_2$]; two isomeric open dimer topologies corresponding to cyclic dimers fragmented at N–Li and X–Li bonds; triple ions ($R_2NLiX^-//^+Li$). A complex interplay of steric effects appears to be the dominant influence on the mixed aggregate structures and relative stabilities.

Introduction

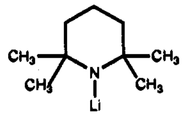
Over the past few years, we have been applying a number of experimental methods to establish structural and mechanistic foundations for understanding the chemistry of lithium amides and related *N*-lithiated species. ^{6}Li and ^{15}N NMR spectroscopic studies provide basic structural details for a single species as well as for species involved in complex solution equilibria.[1] Given the proper structural insights, reaction kinetics restrict discussions of organolithium reactivity to transition structures with explicitly defined stoichiometries.[2,3] Nevertheless, one finds a number of details that are extremely difficult to address with the available experimental methods. It is in this context that computational studies appear to be most helpful.[4–6]

We began our computational studies of lithium dialkylamides with a general belief that direct theory–experiment comparisons would be merited only if the theory could address issues of aggregation and solvation using realistic ligands and *N*-alkyl substituents.[7] While the ab initio quantum mechanical methods would be too unwieldy, the semiempirical (MNDO) methods championed within organolithium chemistry most prominently by Schleyer and co-workers[8] looked very promising. The detailed spectroscopic and kinetic data would allow us to focus on specific questions and minimize the number of arbitrary (unsubstantiable) assumptions. Indeed, MNDO computational studies of homonuclear lithium dialkylamides using the lithium parameters of Clark and Thiel[9] have provided excellent qualitative correlations with some very complex spectroscopically determined solution equilibria.[6]

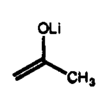
Indirect evidence suggests that mixed aggregates derived from lithium dialkylamides and either lithium halides or lithium enolates can substantially alter the mechanistic and stereochemical course of ketone enolizations and related proton transfer reactions.[10–13] We now present a two-part study of the impact that the LiX salt and the solvent have on the structures and stabilities of lithium dialkylamide mixed aggregates. This manuscript describes MNDO computational studies of mixed aggregates formed from lithium diisopropylamide (LDA; **1**) and lithium 2,2,6,6-tetramethylpiperidide (LiTMP; **2**) with LiCl, lithium acetonate (**3**), lithium cyclohexenolate (**4**), and lithium 2,4-dimethylpentenolate (**5**). General structural types studied include a variety of unsolvated and solvated oligomers of the general forms depicted in Chart 1. Comparisons with previously reported NMR spectroscopic studies of LDA[10] and LiTMP[14] mixed aggregation in tetrahydrofuran (THF) solution reveal excellent qualitative theory–experiment correlations and provide insight into several unresolved issues. We will also explore the influence of hexamethylphosphoramide (HMPA) on mixed



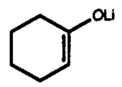
1



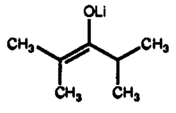
2



3



4



5

[•] Abstract published in *Advance ACS Abstracts*, August 15, 1994.

(1) Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227.

(2) Wanat, R. A.; Collum, D. B. *J. Am. Chem. Soc.* **1985**, *107*, 2078. Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* **1989**, *111*, 6772. Bernstein, M. P.; Romesberg, F. E.; Fuller, D. J.; Harrison, A. T.; Collum, D. B.; Liu, Q.-Y.; Williard, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 5100. Bernstein, M. P.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 8008.

(3) Depue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5524.

(4) Kaufmann, E.; Gose, J.; Schleyer, P. v. R. *Organometallics* **1989**, *8*, 2577 and references cited therein.

(5) Reviews describing structures of lithium dialkylamides and related *N*-lithiated species: Gregory, K.; Schleyer, P. v. R.; Snaith, R. *Adv. Inorg. Chem.* **1991**, *37*, 47. Mulvey, R. E. *Chem. Soc. Rev.* **1991**, *20*, 167. See also ref 1.

(6) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 2112.

(7) Dewar, M. J. S.; Jie, C. *Acc. Chem. Res.* **1992**, *25*, 537.

(8) Kaufmann, E.; Raghavachari, K.; Reed, A.; Schleyer, P. v. R. *Organometallics* **1988**, *7*, 1597. Kaufmann, E.; Tidor, B.; Schleyer, P. v. R. *J. Comput. Chem.* **1986**, *7*, 334.

(9) Thiel, W.; Clark, T. Unpublished results.

(10) Galiano-Roth, A. S.; Kim, Y.-J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5053.

(11) Hall, P.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571.

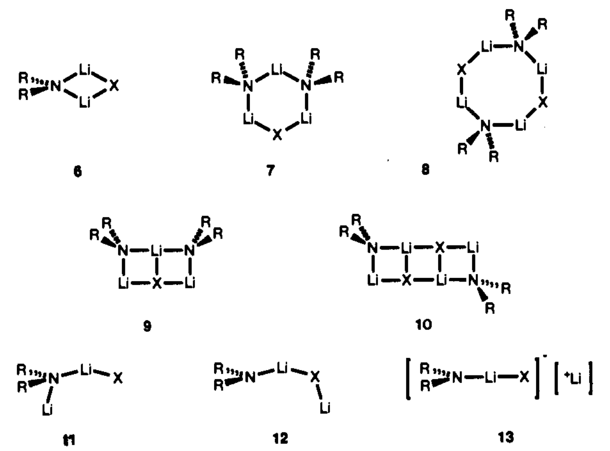
(12) Sakuma, K.; Gilchrist, J. H.; Romesberg, F. E.; Cajthaml, C. E.; Collum, D. B. *Tetrahedron Lett.* **1993**, *34*, 5213.

(13) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. Seebach, D. *Proceedings of the Robert A. Welch Foundation Conferences on Chemistry and Biochemistry*; Wiley: New York, 1984. See also: Caubere, P. *Reviews of Heteroatom Chemistry*; MYU: Tokyo, 1991; Vol. 4, pp 78–139.

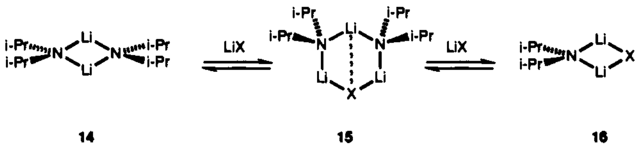
(14) Hall, P.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575.

0002-7863/94/1516-9187$04.50/0

Chart 1

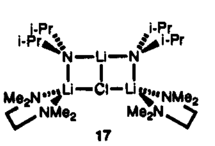


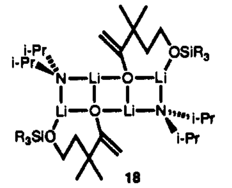
Scheme 1



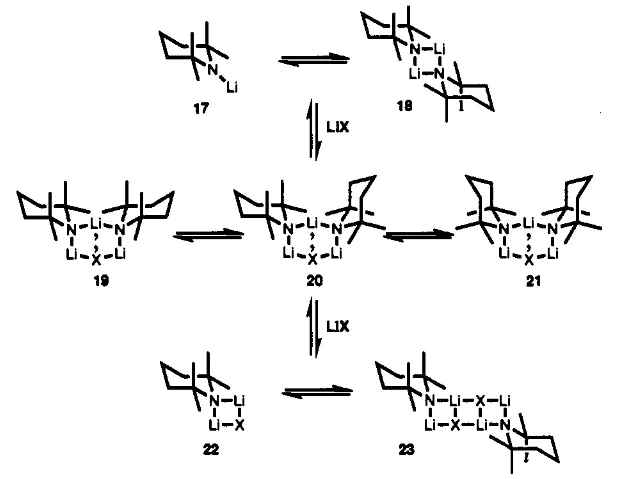
aggregate structures and stabilities. During the course of these latter studies, we were especially careful to complete the computations *prior* to carrying out NMR spectroscopic studies so as to accurately assess the *predictive* power of MNDO. The companion paper describes the spectroscopic determinations of the influence of HMPA on mixed aggregation as well as consequent theory–experiment correlations.[15] While the influence of HMPA on the mixed aggregate equilibria predicted by the calculations follows rational trends, we certainly did not anticipate many of these trends at the onset.

Literature Background. Recent spectroscopic studies have provided a detailed view of lithium dialkylamide mixed aggregation, yet they have left a number of fundamental structural questions unresolved.[1] For example, ^{6}Li and ^{15}N NMR spectroscopic studies revealed that LDA does not readily form mixed aggregates with unhindered lithium enolates such as **4** and forms mixed aggregates with hindered enolates reluctantly.[10] Promotion of mixed aggregation by increasing steric demand of the LiX salt has been ascribed to destabilization of the LiX homonuclear oligomers. In contrast, LDA readily forms both 2:1 and 1:1 mixed aggregates with LiCl and LiBr (Scheme 1). A transannular Li---X interaction in the 2:1 mixed aggregate **15** is depicted with a dotted line since ladders and cyclic trimers seem equally plausible. Ladders receive support from crystallographic analogy (most notably **17** and **18**).[16,17]


17


18

Scheme 2



19a–23a; X = cyclohexenolate
19b–23b; X = Br
19c–23b; X = Cl

Spectroscopic studies of LiTMP in the presence of lithium halides and lithium enolates revealed mixed aggregates of varying stoichiometry and conformational preference (Scheme 2).[14] Lithium enolates and lithium halides (LiBr and LiCl) afford 2:1 and 1:1 mixed aggregates (e.g., **19–21** and **22**, respectively). Lithium cyclohexenolate displays a unique tendency to form low concentrations of a 2:2 mixed aggregate (e.g., **23**) as well. Mixtures of LiTMP and enolate **5** afford only the 1:1 mixed cyclic dimer (**22**) to the exclusion of mixed trimers, supporting suggestions based upon computational studies of homonuclear amides that cyclic trimers and higher cyclic oligomers suffer from steric problems.[5,6,18] Observable 2:1 LiTMP–LiX cyclic trimers present a number of unresolvable structural issues. Firstly, although demonstrably reduced solvation numbers for the trimers relative to the dimers were construed as strong support for the ladder topology, the cyclic oligomer and ladder topologies are not distinguishable spectroscopically. Secondly, only two 2:1 mixed trimer conformational isomers could be detected. The minor isomer was readily shown to be unsymmetrical C_s conformer **20**; however, we could not distinguish which of the C_{2v} conformers **19** or **21** is the major species and which is absent.

A detailed understanding of these inordinately complex phenomena will require an understanding of the potentially more complex and little studied role that solvent plays as a determinant of mixed aggregation.[19,20] Spectroscopic studies of the effects of HMPA on the homonuclear species provides important foundations. Reich has shown that addition of HMPA to a variety of lithium salts (including lithium halides) facilitates deaggregation, often affording solvent separated ion pairs (e.g., $X^-//^+LiS_4$).[21] In contrast, Jackman finds that addition of HMPA to lithium phenolates causes a net *increase in the aggregation state.*[22] Similarly, addition of HMPA to lithium amides such as LDA, LiTMP, and lithium hexamethyldisilazide (LiHMDS), causes profound structural readjustments with *no net change in overall aggregation state.*[23,24] An understanding of the influence of HMPA on mixed aggregate ground state structures would begin

---

[15] Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.*, following paper in this issue.

[16] Mair, R. S.; Clegg, W.; O'Neil, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 3388. See also: Engelhardt, L. M.; Jacobsen, G. E.; White, A. H.; Raston, C. L. *Inorg. Chem.* **1991**, *30*, 3978.

[17] Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539.

[18] Armstrong, D. R.; Barr, D.; Snaith, R.; Clegg, W.; Mulvey, R. E.; Wade, K.; Reed, D. *J. Chem. Soc., Dalton Trans.* **1987**, 1071. Barr, D.; Snaith, R.; Clegg, W.; Mulvey, R. E.; Wade, K. *J. Chem. Soc., Dalton Trans.* **1987**, 2141. Armstrong, D. R.; Mulvey, R. E.; Walker, G. T.; Barr, D.; Snaith, R.; Clegg, W.; Reed, D. *J. Chem. Soc., Dalton Trans.* **1987**, 617.

[19] Reich, H. J.; Borst, J. P.; Dykstra, R. R.; Green, D. P. *J. Am. Chem. Soc.* **1993**, *115*, 8728.

[20] Jackman, L. M.; Rakiewicz, E. F.; Benesi, A. *J. Am. Chem. Soc.* **1991**, *113*, 4101. Jackman, L. M.; Rakiewicz, E. F. *J. Am. Chem. Soc.* **1991**, *113*, 1202 and references cited therein.

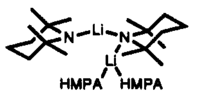
[21] Reich, H. J.; Green, D. P. *J. Am. Chem. Soc.* **1989**, *111*, 8729. Reich, H. J.; Green, D. P.; Phillips, N. H. *J. Am. Chem. Soc.* **1989**, *111*, 3444. Reich, H. J.; Borst, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1835. Reich, H. J.; Gudmundsson, B. O.; Dykstra, R. R. *J. Am. Chem. Soc.* **1992**, *114*, 7937. Reich, H. J.; Dykstra, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 7041.

[22] Jackman, L. M.; Chen, X. *J. Am. Chem. Soc.* **1992**, *114*, 403.

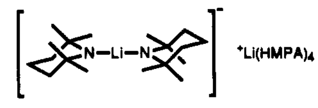
[23] Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5751.

[24] Romesberg, F. E.; Bernstein, M. P.; Fuller, D. J.; Harrison, A. T.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 3475.

to provide requisite foundations for understanding its influence on reactivity.



24



25

Among the many HMPA-solvated lithium amide structural forms observed, open dimer **24** and triple ion **25** may be the most provocative.[23] Lithium dialkylamide open dimers appear to have first been described by Schlosser and co-workers in 1988 in the context of alkyl halide *syn* eliminations.[25] We subsequently rediscovered[26] them during the course of MNDO computational studies.[6] Detailed calculations revealed a recurring stability. This conclusion was confirmed quite decisively by subsequent NMR spectroscopic,[23] crystallographic,[27] and kinetic[28] studies. Although homonuclear[6,27,29] and mixed open dimers[27] have played central roles in several mechanistic hypotheses, the importance or even the existence of mixed open dimers (such as **11** or **12**) has yet to be documented. A similar lack of experimental evidence of mixed triple ions **13** persists as well.[30]

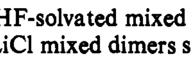
Results

Methods and Protocols. MNDO[31] calculations were performed on an IBM 3090 supercomputer using the MOPAC[32] program with lithium parameters generated by Clark and Thiel.[9] All structures were fully optimized under the more rigorous criteria of the keyword PRECISE with no constraints. Each reported heat of formation is the result of a search for the global minimum starting from several different initial geometries. Symmetrical structures were reoptimized from distorted geometries to insure that the symmetry is not a calculational artifact. For more sterically crowded systems, the keyword GEO-OK was used with caution to overrride the small interatomic distance check.

It has been shown through comparisons with experimental results[33] and ab initio calculations that the current MNDO lithium parameters accurately reproduce lithium interactions with nitrogen and oxygen.[34] However, several concerns should be mentioned. First, the parametrization based on small molecules can lead to anomalous destabilizations in larger systems, as observed in other semiempirical methods.[35] This appeared to be the case in previous studies of highly congested lithium amide homonuclear aggregates.[6] Second, MNDO calculations provide gas phase enthalpies at 25 °C. Quantitative theory–experiment comparisons are impossible without explicit heats of vaporization. Third, it is rarely constructive to compare free energies for reactions of different molecularities (whether calculated or measured) due to the standard state dependence of the entropy component. In some cases, we can minimize the problems associated with concentration dependencies by comparing stabilities of isomeric structures (ΔH) and enthalpies for reactions of equal molecularities ($\Delta\Delta H$). In doing so, entropy contributions tend to cancel (including the concentration dependencies associated with mass action effects), and the $\Delta\Delta H$ values become reasonable approximations of relative free energies. Fourth, we chose not to rely upon calculated enthalpies of homonuclear $(\mathrm{LiX})_n$ aggregates,[36] foregoing studies of the absolute propensities to form mixed aggregates. Instead, we have investigated the relative stabilities of various mixed aggregates through comparisons of balanced equilibria that bypass consideration of the $(\mathrm{LiX})_n$ homonuclear aggregates altogether.

The results are compiled into tabular format as follows: tables containing absolute heats of formation and selected geometric attributes are included as supplementary material; Tables 1–9 describe solvent- and salt-dependent relative enthalpies. Textural descriptions of the results are presented separately for LDA and LiTMP mixed aggregates. Each section includes descriptions of mixed aggregate formation with LiCl and with the enolates of acetone, cyclohexanone, and diisopropyl ketone (**3**–**5**) in unsolvated and solvated forms. These three enolates will often be referred to categorically as following "increasing steric demand" to simplify the presentation. We will also refer to mixed aggregates containing two and three subunits as dimers and trimers (respectively), although this does not adhere to strict definitions. Of special note, the energies are quoted on a *per lithium* (rather than per molecule) basis so as to homogenize numerical comparisons. Consequently, the enthalpies for especially large systems will appear smaller on first inspection.

(A) LDA. Mixed Cyclic Dimers. The calculated geometries of LDA–LiX mixed dimers seem reasonable based upon ab initio[5] and MNDO[6] calculations of homonuclear lithium amide dimers as well as crystal structure data.[5] The planes defined by the C–N–C atoms of the amide fragment are essentially perpendicular to the plane defined by the N–Li–X–Li four-membered ring. Presumably this maximizes overlap of the nitrogen lone pairs with the Li atoms. Unsolvated mixed dimers and higher oligomers tend to form η^2 complexes for the less hindered enolates (e.g., **25a**). Although η^2 Li π complexes are well documented,[37] they render quantitative comparisons with η^1(Li–O) structures potentially problematic due to MNDO's tendency to overestimate C–Li bond strengths.[34] Fortunately, reasonable η^1(Li–O)-coordinated structures were found, and, somewhat surprisingly, they are only marginally less stable than their η^2 counterparts, even in the unsolvated mixed dimers. The N–Li bond lengths in the unsolvated and THF-solvated mixed dimers are sensitive to the LiX salt. LDA–LiCl mixed dimers show the shortest N–Li bonds. LDA–ROLi cyclic dimers show longer N–Li bonds that increase with increasing bulk of the enolate. HMPA solvates, on



25a

---

(25) Matsuda, H.; Hamatani, T.; Matsubara, S.; Schlosser, M. *Tetrahedron* **1988**, *4*, 2865. See also: Schlosser, M.; An, T. D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1039. Schlosser, M.; Tarchini, C.; An, T. D.; Ruzziconi, R.; Bauer, P. J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1041.

(26) We[2,6,28] and others[27a] were unaware of Schlosser's hypothesis during the preparation of several manuscripts.

(27) (a) Williard, P. G.; Liu, Q.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 3380. (b) For related structures, see: Stalke, D.; Klingebiel, U.; Sheldrick, G. M. *J. Organomet. Chem.* **1988**, *344*, 37. Dipple, K.; Klingebiel, U.; Kottke, T.; Pauer, F.; Sheldrick, G. M.; Stalke, D. *Chem. Ber.* **1990**, *123*, 237.

(28) Bernstein, M. P.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 789.

(29) Petasis, N. A.; Teets, K. A. *J. Am. Chem. Soc.* **1992**, *114*, 10328.

(30) The checkered history of triple ions within organolithium chemistry has been discussed previously.[24] For additional references, see: Eiermann, M.; Hafner, K. *J. Am. Chem. Soc.* **1992**, *114*, 135. Tsvetanov, Ch. B. *Eur. Polym. J.* **1979**, *15*, 503. Gill, J. B. *Pure Appl. Chem.* **1987**, *59*, 1127. Khan, I. M.; Hogen-Esch, T. E. *J. Polym. Sci., Polym. Chem. Ed.* **1988**, *26*, 2553. Dotcheva, D.; Tsvetanov, Ch.; Lochmann, L. *J. Polym. Sci., Polym. Chem. Ed.* **1987**, *25*, 3005. Kocienski, P.; Barber, C. *Pure Appl. Chem.* **1990**, *62*, 1933. Pauer, F.; Rocha, J.; Stalke, D. *J. Chem. Soc., Chem. Commun.* **1991**, 1477. Corset, J. *Pure Appl. Chem.* **1986**, *58*, 1133. Hojo, M.; Miyauchi, Y.; Nakatani, I.; Mizobuchi, T.; Imai, Y. *Chem. Lett.* **1990**, 1035. Arnold, J.; Dawson, D. Y.; Hoffman, C. G. *J. Am. Chem. Soc.* **1993**, *115*, 2707. Bazan, G. C.; Schaefer, W. P.; Bercaw, J. E. *Organometallics* **1993**, *12*, 2126. Adler, H. J.; Lochmann, D. *Makromolecules* **1986**, *187*, 1253. Hojo, M.; Fujime, C.; Yoneda, H. *Chem. Lett.* **1993**, 37. Miyauchi, Y.; Hojo, M.; Moriyama, H.; Imai, Y. *J. Chem. Soc., Faraday Trans.* **1992**, 3175. Gornitzka, H.; Stalke, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 693.

(31) Dewar, M. J. S.; Thiel, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 4899; 4907.

(32) Stewart, J. J. P. *QCPE* 581.

(33) Kaufmann, E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1984**, *106*, 1856. Sapse, A.-M.; Kaufmann, E.; Schleyer, P. v. R.; Gleiter, R. *Inorg. Chem.* **1984**, *23*, 1569.

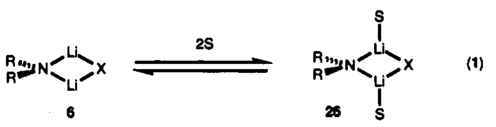
(34) Glaser, R.; Streitwieser, A., Jr. *J. Mol. Struct.* (*THEOCHEM*) **1988**, *163*, 19.

(35) Scano, P.; Thomson, C. *J. Comput. Chem.* **1991**, *12*, 172.

(36) Considerable progress has been made in recent years to elucidate the structures of inorganic lithium salts. For leading references see, ref 21 and the following: Chabanel, H. *Pure Appl. Chem.* **1990**, *62*, 35.

(37) Williard, P. G. *Comprehensive Organic Synthesis*; Pergamon: New York, 1991; Vol. 1, p 1. Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277. Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 354.

Table 1. Heats of Solvation of Mixed Cyclic Dimers (Eq 1)

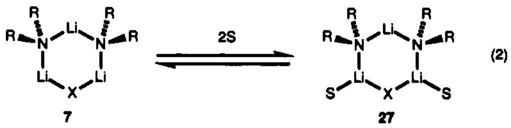


6 26

R_2NLi	solvent, S	LiX			
		LiCl	**3**	**4**	**5**
LDA	THF	-9.0	-6.9	-5.1	0.0
	HMPA	-14.4	-10.8	-9.2	-7.1
	$\Delta\Delta H^a$	-5.4	-3.9	-4.1	-7.1
LiTMP	THF	-8.4	-3.8	-4.6	0.3
	HMPA	-13.7	-7.8	-8.6	-2.6
	$\Delta\Delta H^a$	-5.3	-4.0	-4.0	-2.9

[a] $\Delta\Delta H$ values (in kcal/mol) correspond to the per-Li heats of substitution of THF by HMPA in mixed dimer **26**. Calculated heats of formation of THF and HMPA have been reported previously.[6]

Table 2. Heats of Solvation of Mixed Cyclic Trimers (Eq 2)

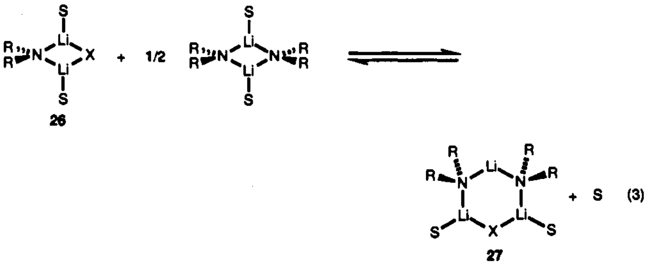


7 27

R_2NLi	solvent, S	LiX			
		LiCl	**3**	**4**	**5**
LDA	THF	-2.3	1.6	4.7	9.9
	HMPA	-6.9	2.3	5.6	9.2
	$\Delta\Delta H^a$	-4.6	0.7	0.9	-0.7
LiTMP	THF	-3.1	4.4	3.2	10.6
	HMPA	-7.3	4.5	6.6	11.6
	$\Delta\Delta H^a$	-4.2	-0.1	3.4	1.1

[a] $\Delta\Delta H$ values (in kcal/mol) correspond to the per-Li heats of substitution of THF by HMPA in mixed dimer **27**.

Table 3. Relative Enthalpies ($\Delta\Delta H$) of Mixed Cyclic Dimers and Trimers (Eq 3)[a,b]



26 27

R_2NLi	solvent, S	LiX			
		LiCl	**3**	**4**	**5**
LDA	unsolvated	-5.5	-7.7	-6.0	-4.9
	THF	-2.1	-3.2	-0.6	0.5
	HMPA	-1.0	0.5	1.1	2.7
LiTMP[b]	unsolvated	-5.0	-5.8	-5.7	-5.0
	THF	-1.4	-0.3	-0.2	1.8
	HMPA	-0.5	2.6	2.7	4.6

[a] Calculated heats of formation of the LDA and LiTMP homonuclear dimers have been reported previously.[6] Enthalpies are reported as kcal/mol per Li. [b] The enthalpies for LiTMP are relative to C_{2v} conformer **51**.

the other hand, all show nearly equivalent N-Li bond lengths, while the Li-X distances uniformly increase with enolate bulk.

Inclusion of THF and HMPA ligands affords LDA-LiX disolvates (one ligand per lithium) as the most stable structures. THF trisolvates of LDA-LiCl and LDA-lithium acetonate mixed dimers are destabilized by 8.1 and 10.4 kcal/mol *per Li*, while minima could not be found corresponding to LDA-**4** and LDA-**5** trisolvated mixed dimers or any HMPA trisolvated mixed dimers. Accordingly, the remaining descriptions will address only the disolvated mixed dimers unless explicitly noted otherwise.

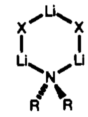
The heats of solvation reveal a strong salt dependence (eq 1, Table 1), with the LDA-LiCl mixed dimer displaying the largest per-THF stabilization. Solvation of the LDA-**3** and LDA-**4** mixed dimers shows moderate exothermicity for both. Solvation of the LDA-**5** mixed dimer by THF is a thermoneutral process, suggesting substantial steric demands about lithium. Disolvation of all LDA-LiX mixed dimers by HMPA is exothermic. The LDA-LiCl mixed dimer is afforded the greatest per-HMPA stabilization and that of LDA-**5** the least. Heats of substitution of THF by HMPA (Table 1) reveal only a modest sensitivity to the nature of the X group.

Mixed Cyclic Trimers. Lowest energy mixed cyclic trimers of LDA of general structure **7** display an approximately planar and hexagonal Li_3N_2X ring in all cases with no unusual distortions. Minima corresponding to significantly nonplanar conformers were not located despite extensive efforts. Lithiums flanked by two nitrogen nuclei (N-*Li*-N) show no tendency toward transannular solvation by the X group to form 3-rung ladders (see below). The XLi-N bond lengths are nearly independent of the solvent and neighboring X-group. The X-LiN bonds are relatively constant within the enolate series yet are shorter when X = Cl. We also see a general lengthening of the X-LiN bonds in the HMPA series.

Mixed trimer solvations show some remarkable trends that would not necessarily be anticipated from simple inspection. Lithiums flanked by two nitrogens (N-*Li*-N) completely resist solvation irrespective of the X group and solvent. Heats of solvation of N-*Li*-X lithiums are substantially reduced in the trimers relative to the dimers (eq 2 and Table 2). Only the LDA-LiCl trimer shows stabilization from solvation. Solvation of the LDA-ROLi mixed trimers is endothermic and becomes markedly so with increasing enolate bulk. Replacement of THF with HMPA from the X-bound lithiums of the trimers is essentially isoenthalpic for all LDA-ROLi mixed trimers.

Reduced enthalpies of mixed trimer solvation appear to be a consequence of the increased steric hinderance accompanying the large internal bond angles of the hexagonal ring. A greater effect on the HMPA solvates is consistent with previous studies supporting a greater overall steric demand by HMPA than by THF.[6]

An alternative 1:2 stoichiometry for LDA-LiCl mixed cyclic trimers (e.g., **28**) was briefly examined for both unsolvated and THF-solvated forms. The geometries proved unremarkable, displaying a planar ring and showing no tendency toward transannular X-Li bond formation. Despite a greater tendency to attain elevated solvation numbers, the 1:2 trimers were found to be significantly less stable than the 2:1 trimers. Since 1:2 R_2NLi-LiX mixed trimers are unprecedented experimentally, these studies were not extended.

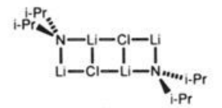


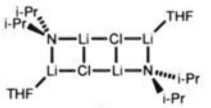
28

Cyclic Dimers vs Cyclic Trimers. Relative heats of formation for the mixed cyclic dimers and trimers (eq 3) are listed in Table 3. The LDA-LiCl and LDA-**3** combinations possess the greatest tendency toward mixed trimer formation. Increasing steric bulk on the enolate causes a relative destabilization of the trimers. Once again, the correlation of decreasing aggregation state with increasing enolate bulk is consistent with the greater congestion (buttressing) imparted by the larger internal angles of the hexagonal ring.

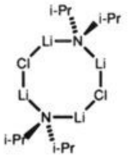
Inclusion of solvation reveals a distinct shift toward dimers, as previously noted in the studies of homonuclear lithium amides.[6,18] One sees a residual modest preference for LDA-LiCl and LDA-**3** trimers solvated by THF. However, increasing enolate bulk causes mixed dimers to be preferred. Moreover, solvation by HMPA drives the dimer–trimer equilibria further toward the dimers, consistent with the notion that HMPA is more sterically demanding than THF. Only LDA–LiCl trimers are found to retain a slight stability relative to the dimers with HMPA solvation.

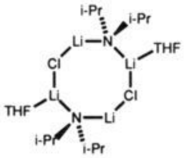
Ladders and Higher Cyclic Oligomers. Investigations of the relative stabilities of mixed cyclic oligomers and ladders confronted problems associated with the ladders. No minima corresponding to the 3-rung ladders were found. All starting geometries converged to the simple hexagonal cyclic trimers. Unsolvated 2:2 LDA–LiCl ladder **29** and the corresponding bis(THF) solvate **30** are the only mixed 4-rung LDA ladders found to be minima on the MNDO energy surface. Ladder **29** displays Li–N bond lengths comparable to those found in the LDA–LiCl cyclic trimers. The Cl–LiN bonds are slightly elongated relative to the 2:1 unsolvated cyclic trimers, while the transannular Li–Cl bonds are considerably longer. Interestingly, solvation by THF affords considerable stabilization ($\Delta H = -7.4$ kcal/mol per Li) with no appreciable lengthening of the bonds to the X-bound (N–Li–X) lithiums. The external lithium atoms of 4-rung ladders appear to be capable of accepting a solvent ligand with minimal structural adjustment.

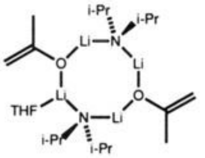

29


30

Unsolvated 2:2 LDA–LiX cyclic tetramers (such as **31**) display bond lengths that are comparable to those of the other cyclic oligomer mixed aggregates. Serial solvation of the 2:2 LDA–LiX tetramers is endothermic in all cases, with a tris-solvate being the maximum attainable solvation state. Lithium acetonate mono-THF solvate (**33**) is the only solvated LDA–ROLi cyclic tetramer found to be a minimum and is 1.4 kcal/mol per Li less stable than the unsolvated form.


31


32


33

With limited comparisons available—the 2:2 LDA–LiCl cyclic tetramers (**31** and **32**) and the corresponding 4-rung ladder (**29** and **30**)—we find a pronounced (7.4 kcal/mol per Li) preference for the cyclic tetramer topology for unsolvated structures. Disolvation by THF dramatically reverses the relative stability of the cyclic tetramer and ladder. However, both the ladder and the cyclic topologies for 2:2 mixed tetramers are congruent, with reduced solvation numbers observed for such higher mixed oligomers.[14]

Mixed Open Dimers. In this section we will refer to the mixed open dimers as either *X*-open (e.g., **11**) or *N*-open (e.g., **12**). Care was taken to find minima free of Li–C interactions in the *N*-open dimers so as to avoid an overestimation of their stabilities. Such minima free of Li–C contacts were located in all cases except the LDA–**3** *N*-open dimer.

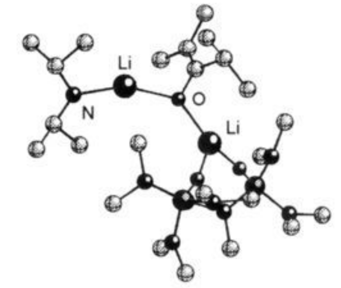


Figure 1. Optimized structure of bis(HMPA)-solvated LDA–**5** *N*-open dimer as calculated by MNDO. Hydrogens are omitted for clarity.

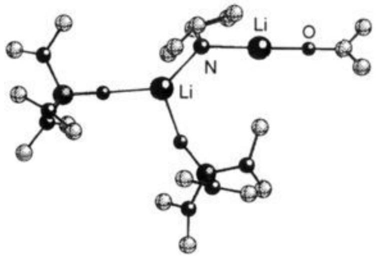
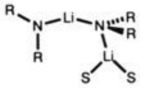
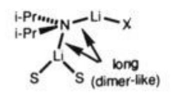


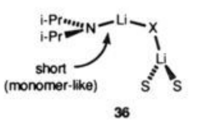
Figure 2. Optimized structure of bis(HMPA)-solvated LDA–**5** *X*-open dimer as calculated by MNDO. Hydrogens are omitted for clarity.

Homonuclear lithium amide open dimers calculated previously[6] display a characteristic 90° rotation of the two planes defined by the C–N–C linkages of the amide fragments. Presumably, this minimizes steric interactions as well as maximizes allene-like orbital overlap of the nitrogen lone pairs with the low lying p-orbitals of lithium.[38] In the mixed open dimers, the atoms corresponding to the NLiXLi and XLiNLi fragments also approximate planes. The *N*-alkyl group as well as the solvent ligands are oriented perpendicular to the N–Li–X–Li plane of the *N*-open dimers, while the enolate alkyl groups lie approximately in this plane (Figure 1). In the *X*-open dimers, the *N*-alkyl groups are perpendicular to the Li–N–Li–X plane, while the solvent ligands and the enolate alkyl groups reside approximately in this plane (Figure 2). The Li–N–Li bond angles in *X*-open dimers are more nearly linear (170–180°) than the Li–X–Li bond angles (160–170°) of their *N*-open dimer counterparts. The Li–N–Li angles also tend to be relatively insensitive to the appended X group. Comparison of the bond lengths in the *N*-open dimers, *X*-open dimers, and homonuclear amide open dimers reveals some interesting trends summarized qualitatively in structures **35** and **36**. Internal LiN–LiX bonds of **35** tend to be longer, suggestive of those found in lithium amide cyclic dimers. In contrast, the terminal N–LiXLi bonds of **36** tend to be characteristically short, akin to those found in lithium amide monomers rather than dimers. Terminal Li–NLiX and Li–XLiN bond lengths of **35** and **36**, respectively, are commensurate with those calculated for lithium amide mixed dimers. These general trends in bond lengths were noted previously in the calculations of homonuclear lithium amide open dimers,[6] are congruent with the bond lengths found in the solid state structure of open dimer **37**,[27] and may correlate with differential $^1J_{\text{Li-N}}$ values found for open dimer **24**.[23]

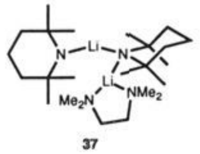

34



35



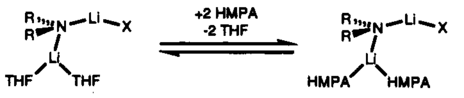
36


37

---

(38) Both Mulliken and Lowdin population analyses on the ab initio (6-31G*) minimized $[H_2N-Li-NH_2]^-$ triple ion show substantial electron donation from the nitrogen lone pairs into mutually perpendicular p-orbitals centered at lithium.

Table 4. Enthalpies of Ligand Substitution of *X*-Open Dimers (Eq 4)[a]



(4)

R$_2$NLi	LiX			
	LiCl	**3**	**4**	**5**
LDA	–8.6	–4.7	–5.6	–5.0
LiTMP	–4.8	–5.2	–4.4	–3.4

[a] Enthalpies are reported as kcal/mol per Li.

Table 5. Enthalpies of Ligand Substitution of *N*-Open Dimers (Eq 5)[a]

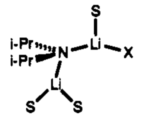
(5)

R$_2$NLi	LiX			
	LiCl	**3**	**4**	**5**
LDA	–8.0	*b*	–6.1	–4.0
LiTMP	–5.2	*b*	–5.6	–4.0

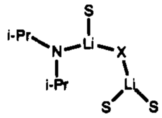
[a] Enthalpies are reported as kcal/mol per Li. [b] Minima void of C–Li contacts could not be located.

One can derive interesting information pertaining to the role solvation plays in the stabilization of LDA–LiX open dimers by comparing the enthalpies of substitution of THF by HMPA. The enthalpies of solvent substitution in the *X*-open dimers (eq 4, Table 4) are weakly sensitive to the nature of the X group. Relative stabilizations by solvent substitution on the *N*-open dimers (eq 5, Table 5) are generally greater, but decreasingly so with increasing steric demands of the enolat e. This is apparently due to the increasing steric demands of both the enolate and solvent ligands. One consequence of the differential solvation enthalpies is that the relative proportions of *N*- and *X*-open dimers (**41** and **39**, respectively) are predicted to be sensitive to THF substitution by HMPA (Scheme 3, Table 6). For THF, increasing enolate bulk stabilizes the *N*-open dimer **41**. This trend is somewhat attenuated with HMPA. *N*-Open dimers generally are favored over the *X*-open dimers (more so for lithium enolates than for LiCl). *N*-Open dimers receive additional relative stabilization by increasing the bulk within the LDA–ROLi series that is compounded by HMPA substitution.

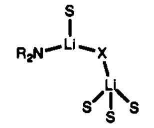
Mounting computational,[6] spectroscopic,[23] kinetic,[28] and crystallographic[27] evidence suggests that solvation of the internal lithium nuclei of lithium dialkylamide open dimers (and triple ions) is not favorable. Minima corresponding to highly solvated LDA mixed open dimers **42** and **43** could be located but proved to be very high in energy and were not studied systematically.



42



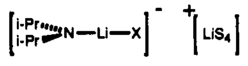
43



44

Nonetheless, selected calculations revealed an interesting cooperativity: solvation of the internal lithium causes an elongation of the terminal N–Li distance with a consequent stabilization of higher solvation numbers on the terminal lithium (e.g., **44**). Despite a relative instability, these higher solvation states could have important kinetic and mechanistic consequences.

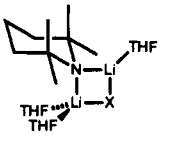
Mixed Triple Ions. Calculated structures of LDA–LiX mixed triple ions show shorter N–Li bonds than those found in the mixed dimers, often approximating the values calculated for monomeric lithium amides.[6] Similarly, the Li–X bonds are shorter than those of corresonding mixed dimers or trimers. The planes defined by the R–N–R fragments are nearly perpendicular to those defined by the C=C(O)—C fragments. Ion paired $^+$Li(HMPA)$_4$ gegenions generally are further removed from the anionic fragment than are the $^+$Li(THF)$_4$ gegenions.



45

Mixed triple ions are less stable than the corresponding mixed dimers and open dimers (Table 6). The enthalpies associated with full ion pair separation (ionization) are reminiscent of the homonuclear lithium amides. Ionization is promoted by HMPA and increasing enolate bulk. LDA–LiCl mixed triple ions ionize more readily than LDA–ROLi triple ions. Nevertheless, the high stabilization imparted by HMPA solvation is not predicted to be sufficient to render the mixed triple ions observable.

(B) LiTMP. Cyclic Dimers. LiTMP–LiX mixed cyclic dimers are structurally similar to those found for LDA, although the bonds are typically longer than those in the LDA mixed cyclic dimers and lengthen upon solvation. Chair conformers of LiTMP are strongly preferred relative to the next most stable (boatlike) conformers. The enthalpies of solvation by THF are also similar to those for the LDA mixed dimers (Table 1). The LiTMP–LiCl mixed cyclic dimer shows the greatest stabilization by solvation. LiTMP–ROLi enolate mixed dimers show decreasing stabilization by solvation with increasing enolate bulk, with the solvation of the sterically congested LiTMP—**5** dimer by THF showing a slight endothermicity. In contrast to the LDA–LiX cyclic dimers showing little tendency to attain trisolvation, a minimum corresponding to trisolvated LiTMP–LiX cyclic dimers could be found, but only for the LiTMP–LiCl (**46**). The third THF ligand in **46** is accommodated exothermically on the lithium disposed axial to the LiTMP chair; no minimum corresponding to disolvation of the equatorial lithium could be found. This



46; X = Cl
47; X = Br

correlates quite well with the structure of the tris(THF)-solvated LiTMP–LiBr dimer **47** determined by Williard and Liu.[42] We previously obtained computational and experimental evidence that LiTMP homonuclear dimers can attain higher solvation numbers than the corresponding LDA homonuclear dimers.[6] We surmised that the observable ring elongations resulting from transannular interactions in the LiTMP homonuclear dimers cause decreased steric demands on solvation at lithium. It seems unlikely that such an explanation can account for the high solvent affinity of the LiTMP mixed cyclic dimer systems. In the subsequent sections, we will restrict our discussion to species bearing only one solvent per lithium.

---

(39) While both the di- and tetra-HMPA-solvated LiTMP dimers are observable spectroscopically, we chose to scale all calculations to the disolvate to homogenize comparisons with other disolvated dimers and minimize the consequences of MNDO's tendency to overestimate steric effects.

(40) Armstrong, D. R.; Barr, D.; Clegg, W.; Hodgson, S. M.; Mulvey, R. E.; Reed, D.; Snaith, R.; Wright, D. S. *J. Am. Chem. Soc.* **1989**, *111*, 4719. Dipple, K.; Klingebiel, U.; Noltemeyer, M.; Pauer, F.; Sheldrick, G. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1074. Engelhardt, L. M.; Jacobsen, G. E.; Junk, P. C.; Raston, C. L.; Skeleton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1988**, 1011. Armstrong, D. R.; Barr, D.; Clegg, W.; Mulvey, R. E.; Reed, D.; Snaith, R.; Wade, K. *J. Chem. Soc., Chem. Commun.* **1986**, 869. Raston, C. L.; Skeleton, B. W.; Whitaker, C. R.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1988**, 987. Hoffmann, D.; Dorigo, A.; Schleyer, P. v. R.; Reif, H.; Stalke, D.; Sheldrick, G. M.; Weiss, E.; Geissler, M. In press.

(41) See ref 8. For early suggestions that steric effects are major determinants of solvation, see: Settle, F. A.; Heggerty, M.; Eastham, J. F. *J. Am. Chem. Soc.* **1964**, *86*, 2076.

(42) Williard, P. G.; Liu, Q.-Y. Unpublished results.

Table 6. Relative Enthalpies of Dimer Fragmentation (Scheme 3)[a,b]

R_2NLi	solvent, S	LiX	ΔH_1	ΔH_2	ΔH_3	ΔH_4
LDA	THF	LiCl	3.3	9.1	−1.6	14.0
		3	3.6	*c*	*c*	18.0
		4	2.9	2.5	−11.3	16.4
		5	1.2	0.2	−11.6	13.0
	HMPA	LiCl	3.5	6.2	−4.3	14.0
		3	2.9	*c*	*c*	14.2
		4	2.2	1.2	−10.1	13.5
		5	0.5	−0.1	−8.2	8.6
LiTMP	THF	LiCl	4.4	6.6	−3.9	14.9
		3	5.8	*c*	*c*	15.5
		4	4.2	−1.8	−13.8	16.2
		5	2.7	−1.8	−10.5	11.4
	HMPA	LiCl	4.8	3.0	−3.3	11.1
		3	2.6	*c*	*c*	11.7
		4	3.8	−3.0	−12.4	13.2
		5	2.3	−3.3	−10.7	9.6

[a] Heats of formation of the solvents have been reported previously.[6] Enthalpies are reported as kcal/mol per Li. [b] The LiTMP *X*-open dimers are axially disolvated. [c] Minima void of C–Li contacts could not be located.

Scheme 3

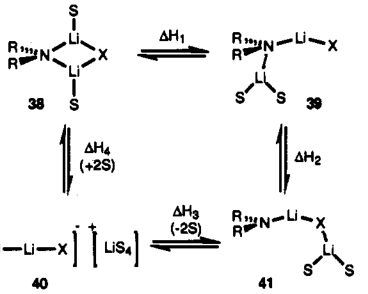
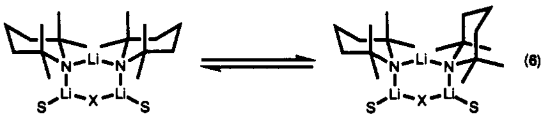


Table 7. Relative Enthalpies of Formation: C_{2v} vs C_s Conformers of LiTMP Mixed Cyclic Trimers (Eq 6)[a]



(6)

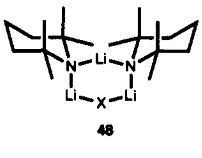
51, C_{2v} **52**, C_s

	LiX			
solvent, S	LiCl	**3**	**4**	**5**
unsolvated	−0.2	−0.1	−0.3	0.1
THF	0.2	0.6	1.3	0.9
HMPA	0.2	−0.7	0.5	1.4

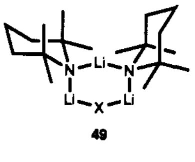
[a] Enthalpies are reported as kcal/mol per Li.

Enthalpies of solvation of LiTMP–LiX cyclic dimers by HMPA are reported in Table 1.[39] The LiTMP–ROLi mixed dimers show markedly attenuated heats of solvation by HMPA relative to the LDA–ROLi cyclic dimers. However, the heats of substitution of HMPA for THF are similar for the LiTMP–LiCl and LDA–LiCl cyclic dimers. As with THF, a tris(HMPA)-solvated LiTMP–LiCl dimer bearing two solvents on the axial lithium was the only higher HMPA solvate found to be a minimum (although the third HMPA ligand is strongly destabilizing).

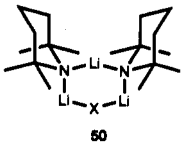
Mixed Cyclic Trimers. LiTMP–LiX mixed trimers show trends in both structure and stability that parallel those from LDA (Table 2). The six-membered Li_3N_2X rings of the LiTMP–LiX (2:1) cyclic trimers are nearly planar and hexagonal. Three conformational isomers resulting from chair–chair flips show relative stabilities in the order **48** > **49** > **50** (Table 7). (Only **48** and **49** converged to minima.) In the LiTMP–**5** trimer, minimization affords an unstable structure exhibiting a partial piperidide ring flip.



48



49



50

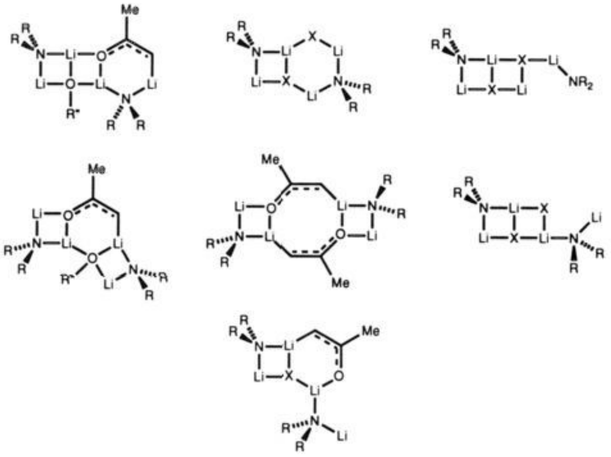
Solvents are accommodated only at the two *X*-bound (X–*Li*–N) lithiums of all mixed trimer conformational isomers (e.g., **51** and **52**, eq 6). Attempts to locate minima where the doubly *N*-bound (N–*Li*–N) lithiums are solvated result in solvent extrusion in all cases. Bond lengthening within the trimers is more pronounced in the disolvated mixed trimers with HMPA than with THF. Overall, the predicted lower solvation state of the mixed trimers relative to that of the mixed dimers correlates well with qualitative spectroscopic observations.[14]

Solvated LiTMP–LiX trimers prefer the C_{2v} conformer **51** in all but the acetone enolate/HMPA case (eq 6 and Table 7). This preference becomes more pronounced with increasing steric demands. Solvation enthalpies of the LiTMP–LiX mixed trimers are attenuated relative to both the LiTMP–LiX mixed dimers and the LDA–LiX mixed trimers (Table 2, eq 2). The 2:1 LiTMP–LiCl trimer is the only mixed trimer stabilized by solvation (as found for the LDA series). Solvation of the LiTMP–**5** mixed trimer is strongly endothermic for both THF and HMPA.

Mixed Cyclic Dimers vs Mixed Cyclic Trimers. The relative stabilities of the LiTMP mixed dimers and trimers (eq 3) are listed in Table 3 (relative to the C_{2v} conformer **51**). All unsolvated cases prefer the higher oligomer, although with an attenuated sensitivity to the X group in comparison with the LDA–LiX cases. Within the enolate series, increased enolate bulk promotes formation of the cyclic dimers. All dimer–trimer equilibria are shifted significantly toward the mixed dimers upon inclusion of THF solvation, more strongly for the LiTMP–**5** cases. LiTMP–LiCl shows the greatest tendency toward mixed trimer formation. This preference seems to arise from a relative insensitivity of the LiTMP–LiCl dimer–trimer equilibrium to the steric demands of solvation. Solvation by HMPA further favors the mixed dimers relative to the more congested trimers. Trimers remain preferred only in the least sterically demanding LiTMP–LiCl case. Dimers within the HMPA-solvated LiTMP–ROLi series are stabilized by enolate bulk, with the most hindered enolate showing a considerable (4.6 kcal/mol per Li) mixed dimer stabilization.

Ladders and Higher Cyclic Oligomers. An LiTMP–LiX mixed ladder minimum is found only for the LiTMP–LiCl 4-rung ladder **53**, displaying a 0.4 kcal/mol per Li greater stability than the unsolvated mixed LiCl dimer. It is interesting that the unsolvated LiTMP–LiCl and LDA–LiCl cyclic dimers show nearly equal propensities to solvate, but the LiTMP–LiCl case shows an attenuated stabilization upon oligomerization to form the 4-rung ladder. All attempts to find other solvated or unsolvated LiTMP mixed ladders resulted in Li–N or Li–X bond cleavage, yielding a variety of plausible structural forms (Chart

Chart 2



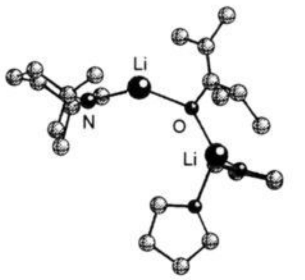
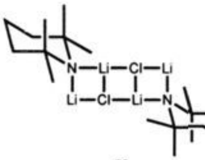
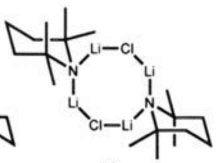


Figure 3. Optimized structure of bis(THF)-solvated LiTMP-**5** *N*-open dimer as calculated by MNDO. Hydrogens are omitted for clarity.

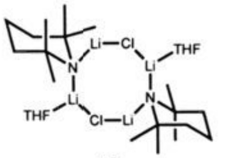
2) that bear some relationship to partially fragmented homonuclear oligomers.[40]



53



54

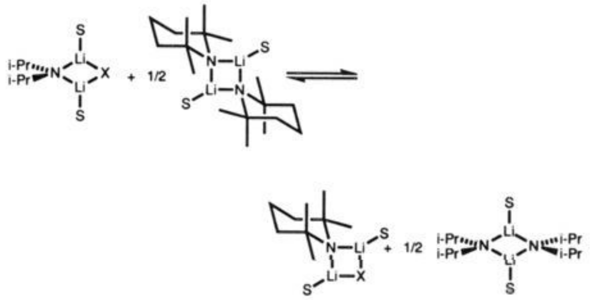


55

Unsolvated LiTMP–LiCl cyclic tetramer **54** is found to be 8.0 kcal/mol per Li more stable than the mixed dimer and 7.6 kcal/mol per Li more stable than the 4-rung ladder. As in the case for the 2:2 LDA–LiX cyclic tetramers discussed above, solvation by THF strongly destabilizes cyclic tetramers relative to mixed dimers. Tetramer **55** is the only stable THF solvate of the LiTMP–LiCl cyclic tetramer and is destabilized by 0.2 kcal/mol per Li relative to the bis(THF)-solvated mixed dimer. In the case of LiTMP, enolates completely fail to afford minima corresponding to either four-rung ladders or cyclic tetramers.

Mixed Open Dimers. Calculated structures of LiTMP–LiX mixed open dimers are unremarkable when compared to the LDA counterparts. The monomer-like N–LiXLi bonds of *N*-open dimers and X–LiNLi bonds of *X*-open dimers are quite similar for LiTMP and LDA (Figure 3). However, we do observe a consistent lengthening of the dimer-like NLi–XLi bonds of *N*-open dimers and XLi–NLi bonds of *X*-open dimers for LiTMP mixed open dimers compared to the LDA cases.

Table 8. Relative Enthalpies of Mixed Cyclic Dimers (Eq 7)[a]



(7)

solvent, S	LiX LiCl	 **3**	 **4**	 **5**
unsolvated	−2.5	−4.1	−2.4	−2.1
THF	−0.9	−1.0	−1.0	−0.8
HMPA	−1.3	−1.4	−1.3	−1.2

[a] Heats of formation of the solvated homonuclear amides have been reported previously.[6] Enthalpies are reported as kcal/mol per Li.

Substitution of THF by HMPA (Tables 4 and 5) is most exothermic for the least hindered LiTMP–**3** mixed *X*-open dimer. Increasing enolate bulk decreases the stabilization by HMPA of *X*-open dimers to a limited extent. Substitution of THF by HMPA in the LiCl *X*-open dimer is of intermediate exothermicity. Substitution by HMPA in the *N*-open dimers (Table 5, eq 5) is consistently more exothermic and more *X*-dependent than that in the *X*-open dimers due to the proximity of the solvent and enolate. Stabilization by HMPA substitution is most pronounced in the LiCl mixed open dimer. Within the enolate series, the heats of substitution by HMPA decrease with enolate steric demand.

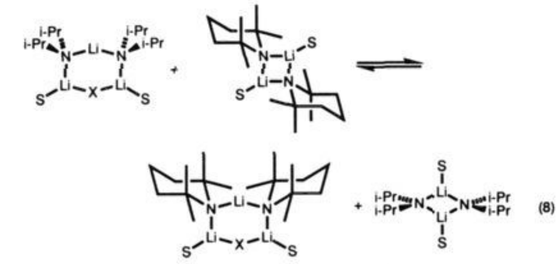
It is instructive to formally consider the influence of LiX salt and solvent on the *N*-open and *X*-open dimer isomer distribution depicted in Scheme 3 (Table 6). THF-solvated LiTMP–LiCl shows a preference for the *X*-open form (but less so than in the LDA–LiCl case). The increased stabilization afforded the *N*-open dimers by HMPA results in a strong shift in the equilibria toward *N*-open dimers for all LiX salts. Only the LiTMP–LiCl cases maintain a preference (albeit small) for the *X*-open form with HMPA ligands.

The relative stabilities of the open and cyclic dimers of LiTMP are displayed in Table 6. If we compare the stabilities of the cyclic dimers with the more stable of the two open dimers (changing on a case-by-case basis), we find that increasing enolate bulk favors open dimers. The least sterically demanding LiTMP–LiCl case shows the largest preference for the cyclic dimer topology. HMPA solvation favors the *N*-open form, but only in sterically demanding cases. Otherwise, HMPA is calculated to have little effect. Interactions between HMPA and the bulk of the enolate and amide are apparently less severe in the open dimer than in the cyclic dimer. This, in conjunction with the preferential stabilization of the *N*-open species, leads to the following generalization: stabilization of the *N*-open form with sterically demanding LiX salt and sterically demanding HMPA ligands leads to the greatest overall stabilization of the open dimer structural form.

Mixed Triple Ions. All LiTMP mixed triple ions show N–Li bonds that are shorter than those found in the mixed dimers, often approximating the values calculated for monomeric lithium amides.[6] Similarly, the Li–X bonds are shorter than those for most other structural forms. The planes defined by the R–N–R linkage in the LiTMP–ROLi mixed triple ions are nearly perpendicular to those defined by the C=C(O)—C linkages. The +Li(HMPA)$_4$ counterions generally are further removed from the anionic fragment than are the +Li(THF)$_4$ counterions.

Overall, the mixed triple ions are less stable than the corresponding mixed dimers and open dimers. Ionizations to

Table 9. Relative Enthalpies of Mixed Cyclic Trimers (Eq 8)[a]

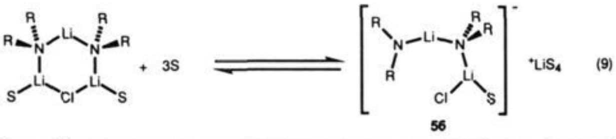


solvent, S	LiCL	3	4	5
unsolvated	−1.8	−1.6	−1.7	−1.6
THF	−2.1	−3.4	−1.9	−2.5
HMPA	−2.1	−2.9	−2.7	−3.0

(LiX spans columns LiCL, 3, 4, 5.)

[a] Heats of formation of the solvated homonuclear amides have been reported previously.[6] Enthalpies are reported as kcal/mol per Li.

Table 10. Relative Enthalpies of Ionic Open Dimers (Eq 9)[a]



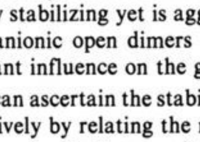
	THF	HMPA
LDA	10.1	7.3
LiTMP	6.3	3.7

[a] Enthalpies correspond to the ion paired forms and are reported as kcal/mol per Li.

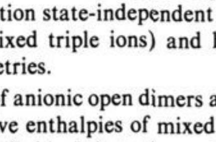
give paired mixed triple ions are promoted by HMPA as well as by increasing the enolate bulk, but these are predicted to be significantly destabilized relative to the nonionized structural forms.

Anionic Open Dimers: An Addendum. During the course of subsequent NMR spectroscopic studies[15] of LiTMP–LiCl–HMPA mixtures, we uncovered a new structural form (**56**) that displays architectural features common to mixed trimers, open dimers, and triple ions. We assigned them the name "anionic open dimers" and briefly probed their structures and stabilities with the aid of MNDO calculations (Table 10, eq 9).

The anionic fragments of the lithium amide–LiCl ionic open dimers all reveal striking structural similarities to the open dimers despite a substantial difference in the net charge. All structures display a greater stability in orientation **56** rather than **57**. Pairing with a +LiS_4 cation affords structures with the cation in the N–Li–N–Li–Cl plane and aligned collinear to the Li–Cl bond (Figure 4). Presumably, this maximizes electrostatic stabilization while avoiding serious steric interactions. Overall, the ion pairing is highly stabilizing yet is aggregation state-independent (comparing anionic open dimers to mixed triple ions) and has no significant influence on the geometries.



56



57

One can ascertain the stability of anionic open dimers at least qualitatively by relating the relative enthalpies of mixed cyclic trimers and anionic open dimers (Table 10) to the analogous relative enthalpies of the mixed cyclic dimers and mixed triple ions (Table 6). In comparison with the formation of paired triple ions from mixed open dimers, formation of paired anionic open dimers from mixed cyclic trimers is measurably less endothermic in the LiTMP–LiCl–HMPA case. This trend proves to be in qualitative agreement with experiment.[15]

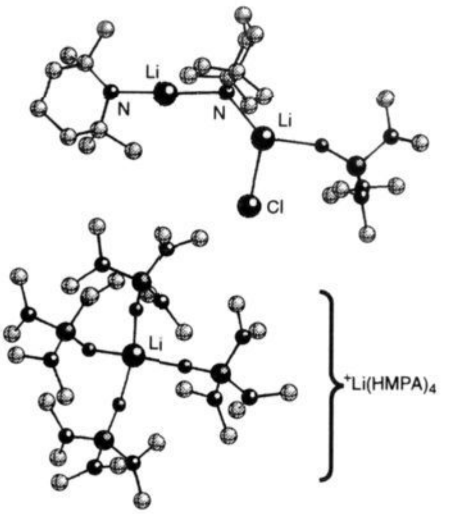


Figure 4. Optimized structure of HMPA-solvated LiTMP–LiCl ionic open trimer (**56**), *N*-open, as calculated by MNDO. Hydrogens are omitted for clarity.

Discussion

Mixed Cyclic Dimers and Trimers. Many of the important relationships of mixed aggregate stability and solvation are embodied in the results found for the mixed cyclic dimers (**6**). As anticipated, solvation of LDA–LiX mixed cyclic dimers is highly stabilizing. Previous studies suggesting that steric demands of both the ligands and the substrate are the prominent determinants of stability also receive considerable support.[6,41] For instance, disolvation (one solvent per lithium) is strongly indicated, with relatively unstable trisolvated mixed dimers observable only under limited circumstances. The LDA–ROLi series reveals a decreasing per-lithium enthalpy of solvation with increasing enolate bulk. In this context, LiCl shows properties anticipated for a minimally hindered enolate. Probably most notable are the high steric demands of HMPA relative to THF. Although HMPA is generally a better ligand for lithium, the stability of the HMPA–lithium interaction is severely attenuated in the most congested systems.

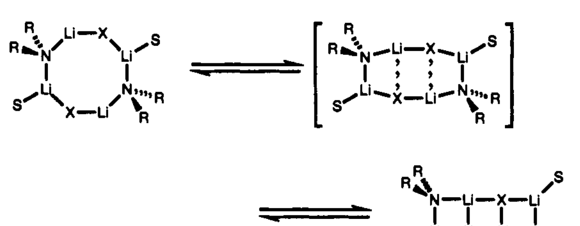
The increased steric demands of LiTMP are manifested by decreasing mixed cyclic dimer solvation enthalpies. The effect becomes most pronounced in the severely hindered environments involving bulky enolates (such as **5**) and the sterically demanding HMPA ligands. One of the more interesting features of the LiTMP mixed aggregates is the increased complexity resulting from conformational isomerism. We find, for instance, a greater propensity of the axial versus the equatorial lithiums of LiTMP–LiX cyclic dimers to accept donor solvents as manifested by (1) more negative enthalpies of solvation of the axial site and (2) an apparent restriction of trisolvates to those such as **46** bearing two ligands on the axial site. The predicted stability of **46** correlates well with trisolvate **47** characterized crystallographically by Williard and Liu.[42] Trisolvation may also be the source of differential axial and equatorial Li–N coupling constants in LiTMP–LiX mixed cyclic dimers.[14]

Difficulties encountered in determining the structures of the LiX species caused us to refrain from calculations of the structures and stabilities of the unsolvated and solvated $(LiX)_n$ species required to determine the absolute propensities of any given R_2NLi–LiX combination to afford mixed aggregates. However, balanced equilibria void of free LiX oligomers can afford *relative* tendencies of two lithium dialkylamides to form mixed aggregates (Tables 8 and 9). We find support for the experimentally observed greater tendency of LiTMP to form both mixed dimer and mixed trimer when compared to LDA. However, this does not appear to stem from high LiTMP–LiX mixed aggregate stabilities *per se*, but rather from the relative destabilization of the highly congested LiTMP homonuclear dimers. It is not surprising, therefore, that HMPA is predicted to enhance the consequences of the R_2NLi bulk and, in turn, promote (albeit modestly) mixed aggregate formation for LiTMP more so than for LDA. Interestingly, while increasing steric demands of the enolates have been shown experimentally to promote mixed aggregation, the calculations suggest that the relative propensities of LiTMP and LDA to form mixed aggregates are not sensitive to the structure of the LiX salt. Presumably, this reflects an absence of direct interaction of the *N*-alkyl substituents and the X groups.

As we turn our attention from the 1:1 mixed dimers to the 2:1 lithium amide–LiX mixed cyclic trimers (**7**), we find some striking differences. Increased internal Li-N-Li and Li-X-Li angles appear to impart restricted access to the lithium sites by solvent ligands, as evidenced by (1) low enthalpies of solvation of the *X*-bound (X-*Li*-N) lithiums, (2) little advantage offered by HMPA relative to THF (i.e., isoenthalpic ligand substitution), and (3) a complete absence of stable minima for structures containing solvated, *N*-bound (N-*Li*-N) lithiums. Consequently, the most stable mixed cyclic trimers—disolvated trimers **27**—tend to be unstable relative to mixed cyclic dimers **26** (eq 3, Table 3). Since the trimers are inordinately sensitive to steric effects, they are further destabilized relative to dimers by increasing steric demands in the X group and solvent. Indeed, trimers are observable spectroscopically in THF solutions of LDA–LiCl (and LDA–LiBr) but not for LDA–lithium enolates.[10] We should add, however, that the calculations suggest trimer formation to be even less favorable in the LiTMP–LiX series. On the contrary, spectroscopic studies reveal observable dimer–trimer equilibria for both the LiTMP–ROLi and LiTMP–LiCl series in THF solution (although increasing enolate bulk does indeed inhibit trimer formation).[14]

MNDO affords relatively clear predictions on the experimentally unresolved issue of conformational isomerism within the 2:1 LiTMP–LiX mixed cyclic trimer series. The relative stabilities of the three conformational isomers of LiTMP–LiX dimers are suggested to be **48** > **49** > **50**. (The instability of isomers of type **50** are only tacitly suggested by unsuccessful attempts to locate stable minima.) Curiously, the relative stabilities of structures of type **48** and **49** are insensitive to the presence of (and type of) solvent despite the apparent proximity to the piperidine ring (Table 7).

Ladders and Higher Cyclic Oligomers. Our efforts to distinguish the ladders (e.g., **9** and **10**) and cyclic oligomers (e.g., **7** and **8**) for observable 2:1 and 2:2 mixed aggregates proved less than satisfying due to difficulties in finding stable minima for the corresponding ladders. We hasten to add that we are reluctant to construe our failure to locate minima for the ladders as evidence of their instability; lithium amide–LiX mixed ladders (such as **17** and **18**) are documented in the crystallographic literature.[5,16,17] The limited viable comparisons—ladders **29** and **30** with cyclic tetramers **31** and **32**—reveal a strong preference for cyclic oligomer in the unsolvated form that is completely reversed upon disolvation. This is a direct consequence of the high solvation enthalpy of the sterically accessible external lithium sites of the ladder. The most important observation is that all higher cyclic oligomers also prefer reduced solvation states (less than one solvent per Li). Consequently, experimentally observed low per-lithium solvation numbers[14] for these higher oligomers cannot be construed as evidence in support of the ladder form. In fact, the partially solvated cyclic oligomers and ladders may prove to be minima separated by potentially facile breathing motions (eq 10) or may even represent limiting distortions of a single structural type. Additionally, ladder forms observed in the solid state[5,16,17] may be stabilized by packing effects.



(10)

Open Dimers, Triple Ions, and Anionic Open Dimers. Homonuclear lithium amide open dimers emerged in the literature only recently. Schlosser may have been the first to invoke lithium dialkylamide open dimers in the context of alkyl halide *syn* eliminations.[25,26] Their existence and importance was subsequently documented during computational,[6] spectroscopic,[23] crystallographic,[27] and kinetic[28] studies. Both homonuclear open dimers (e.g., **34**)[6,25–29] and heteronuclear (mixed) open dimers (**36**)[27] have been invoked in mechanistic hypotheses. Mixed open dimers offer an interesting structural complexity relative to their homonuclear open dimer counterparts due to the possibility of both *X*-open and *N*-open forms (e.g., **35** and **36**, respectively). Furthermore, the calculations reveal additional structural diversity arising from a tendency of the mixed open dimers to attain higher solvation numbers than their homonuclear amide dimer counterparts through solvation of the internal lithium nuclei (e.g., **42** or **43**) as well as through trisolvation (albeit endothermic) of the terminal lithium (e.g., **44**). While mixed triple ions and open dimers certainly could display very different reactivities, in a sense they are simply contact and solvent separated ion pairs of the same general structure.[30]

Calculated stabilities of isomeric mixed open dimers (Scheme 3, Table 6) reveal a complex interplay of solvent and substituent effects. In general, the *N*-open dimers are favored relative to *X*-open dimers by increasing the steric demands of the solvent and dialkylamide consistent with relief of substantial van der Waals strain upon cleaving the N–Li bond. The structural features stabilizing the *N*-open dimers relative to the *X*-open forms are precisely those that stabilize open dimers relative to mixed cyclic dimers. Consequently, *N*-open dimers are more likely to be observed than *X*-open dimers and are most likely to be detected in systems that are maximally congested. However, the origins of the preference for the *N*-open form with increasing bulk of the X-group are not at all clear at this time.

We find the mixed open dimers especially provocative in light of issues of reactivity and selectivity. Imagine, for example, the problem of self-condensation that can accompany deprotonations of ketones, aldehydes, and esters.[43] Conventional wisdom suggests that the competing self-condensations arise solely from the lack of steric congestion. However, the open dimers offer additional considerations. *N*-Open dimers are suitably poised to undergo either intramolecular proton transfer by favorable[44] 8-membered cyclic transition structures (**58**) or aldol condensations via 6-membered ring (Zimmerman–Traxler)[45] transition structures (**59**). In contrast, *X*-open dimers are not well suited for deprotonation due to cloistering of the nitrogen lone pair, leaving only the aldol condensation paths (**60**) available. The *X*-open form is stabilized by minimizing the steric demands of the X group (the resultant enolate in this case), the solvent (including the ancillary solvent ligands and the substrate), and the lithium dialkylamide. Consequently, one could certainly begin to construct a scenario to explain why unhindered carbonyl substrates are more prone to self-condense[43] and why addition of HMPA

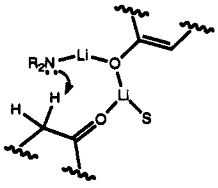
---

[43] Horner, J. H.; Vera, M.; Grutzner, J. B. *J. Org. Chem.* **1986**, *51*, 4212.

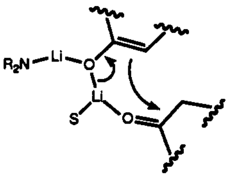
[44] McManus, S. P.; Capon, B. *Neighboring Group Participation*; Plenum Press: New York, 1976; p 58. See also: Bernardi, A.; Capelli, A. M.; Cassinari, A.; Comotti, A.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1992**, *57*, 7029. Bernardi, F.; Bongini, A.; Cainelli, G.; Robb, M.; Valli, G. S. *J. Org. Chem.* **1993**, *58*, 750.

[45] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

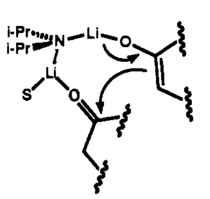
is often necessary to achieve clean deprotonations.[46] Other well-documented reactions of lithium amides such as conjugate additions,[47] reductions,[48] carbonylations,[49] and *N*-alkylations[50,51] are equally intriguing when placed in this context.



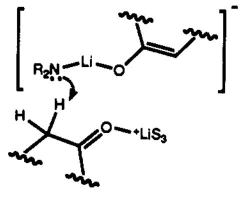
58



59



60



61

Additional extrapolation reveals analogy between mixed dimers and triple ions. One could envision, for example, mechanisms based upon mixed triple ions (e.g., **61**). While triple ion reactivity has been postulated,[30] to the best of our knowledge it has not been documented rigorously. Nonetheless, the mixed triple ions are predicted to be accessible (although not observable[15]), and the advantages offered by electrophilic catalysis[52] by the lithium cation should not be overlooked.

This last notion applies to the anionic open dimers (e.g., **57**) as well. Their documentation as observable ground state structures for the first time in the accompanying paper[15] certainly attests to their current obscurity and precludes any extensive discussions. However, on a final whimsical note, one could envision them as active participants in processes involving lithium alkoxide-directed and other anion-directed metalations.[53]

Influence of HMPA on Mixed Aggregate Equilibria: Predictions. One of the primary goals of this study was to predict the influence of HMPA on the structures of lithium dialkylamide mixed aggregate structures and equilibria. Due to our deliberate exclusion of LiX oligomers from consideration, we cannot predict the effect of HMPA on the *absolute* propensities of lithium amides to form mixed aggregates. However, within this one limitation, we summarize the most prominent predictions (relative to the corresponding THF solvates) as follows.

(1) HMPA will promote mixed dimer formation relative to higher oligomers.

(2) HMPA may promote mixed aggregate formation more efficiently for LiTMP than for LDA.

(3) While HMPA promotes mixed triple ion formation, mixed triple ions are not likely to be observable.

(4) HMPA should promote mixed open dimer formation relative to cyclic dimers, more so for the *N*-open form than for the *X*-open form; however, even the *N*-open dimers are predicted to be observable only for the more hindered LiTMP with the more hindered enolates (**5**).

Spectroscopic studies of the influence of HMPA on R_2NLi–LiX mixed aggregate equilibria described in the companion paper will underscore the predictive power of MNDO.

Acknowledgment. We thank the National Institutes of Health for direct support of this work. The computational studies were conducted using the Cornell National Supercomputer Facility, a resource of the Center for Theory and Simulations in Science and Engineering (Cornell Theory Center), which receives major funding from the National Science Foundation and IBM Corporation, with additional support from New York state and members of the Corporate Research Institute.

Supplementary Material Available: Absolute heats of formation and selected geometric attributes (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

---

(46) Effects of HMPA on the chemistry of lithium amides: Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959. Fraser, R. R.; Mansour, T. S. *Tetrahedron Lett.* **1986**, *27*, 331. Kodomari, M.; Sawa, S.; Morozumi, K.; Ohkita, T. *Nippon Kagaku Kaishi* **1976**, 301. Cuvigny, T.; Larcheveque, M.; Normant, H. *Justus Liebigs Ann. Chem.* **1975**, 719. Reisdorf, D.; Normant, H. *Organomet. Chem. Synth.* **1972**, *1*, 375. Hosomi, A.; Araki, Y.; Sakurai, H. *J. Am. Chem. Soc.* **1982**, *104*, 2081. Cregge, R. J.; Hermann, J. L.; Lee, C. S.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2425. Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543. Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett.* **1989**, 1313. Tanaka, Y.; Tsujimoto, K.; Ohashi, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 788. Kopka, I. E.; Fataftah, Z. A.; Rathke, M. W. *J. Org. Chem.* **1987**, *52*, 448.

(47) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1375. Rudolf, K.; Hawkins, J. M.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1988**, *53*, 3879. Hawkins, J. M.; Fu, G. C. *J. Org. Chem.* **1986**, *51*, 2820. Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 3139. Hawkins, J. M.; Lewis, T. A. *J. Org. Chem.* **1992**, *57*, 2114. Uyehara, T.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1410. Asao, N.; Uyehara, T.; Yamamoto, Y. *Tetrahedron* **1988**, *44*, 4173. Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 113. Liebeskind, L. S.; Welker, M. E.; Fengl, R. W. *J. Am. Chem. Soc.* **1986**, *108*, 6328. Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183. Suzuki, I.; Kin, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10139. Asao, N.; Uyehara, T.; Yamamoto, Y. *Tetrahedron* **1990**, *46*, 4563. Bellassoued, M.; Ennigrou, R.; Gandemar, M. *J. Organomet. Chem.* **1988**, *338*, 149. Uyehara, T.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 753. Davies, S. G.; Ichihara, O. *J. Chem. Soc., Chem. Commun.* **1990**, 1554. Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433.

(48) Leading references: Ashby, E. C.; Park, B.; Patil, G. S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* **1993**, *58*, 424.

(49) Nudelman, N. S. In *The Chemistry of Double-Bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, 1989; Chapter 13, p 799.

(50) Li, X.; Pan, H.; Jiang, X. *Tetrahedron Lett.* **1987**, *28*, 3699. Corriu, R. J. P.; Moreau, J. J. E.; Vernhet, C. *Tetrahedron Lett.* **1987**, *28*, 2963. Uyehara, T.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1410. Rathke, M. W.; Sullivan, D. *Tetrahedron Lett.* **1986**, *27*, 4249. Huisgen, R.; Mack, W. *Chem. Ber.* **1960**, *93*, 412. Kowalski, C.; Creary, X.; Rollin, A. J.; Burke, M. C. *J. Org. Chem.* **1978**, *43*, 2601. Meyers, A. I. *J. Org. Chem.* **1977**, *42*, 2653. Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979. Pez, G. P.; Galle, J. E. *Pure Appl. Chem.* **1985**, *57*, 1917. Petrov, A. A.; Kromer, V. A. *Zh. Obshch. Khim.* **1960**, *30*, 3890. Sanger, A. R. *Inorg. Nucl. Chem. Lett.* **1973**, *9*, 351. Tzschach, A.; Reiss, E. *J. Organomet.* **1967**, *8*, 255. Liebeskind, L. S.; Welker, M. E.; Fengl, R. W. *J. Am. Chem. Soc.* **1986**, *108*, 6328.

(51) For kinetic evidence that lithium amide–lithium halide mixed dimers can undergo *N*-alkylation without prior deaggregation, see ref 3.

(52) Jackman, L. M.; Dunne, T. S. *J. Am. Chem. Soc.* **1985**, *107*, 2805. Pierre, J.-L.; Handel, H. *Tetrahedron Lett.* **1974**, 2317. Loupy, A.; Seyden-Penne, J.; Tchoubar, B. *Tetrahedron Lett.* **1976**, 1677. Buncel, E.; Dunn, E. J.; Bannard, R. A. B.; Purdon, J. G. *J. Chem. Soc., Chem. Commun.* **1984**, 162. Chang, C. J.; Kiesel, R. F.; Hogen-Esch, T. L. *J. Am. Chem. Soc.* **1973**, *95*, 8446. Loupy, A.; Seyden-Penne, J. *Tetrahedron* **1980**, *36*, 1937.

(53) Martin, V. A.; Perron, F.; Albizati, K. F. *Tetrahedron Lett.* **1990**, *31*, 301. Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y.-b.; Albizati, K. F. *J. Am. Chem. Soc.* **1990**, *112*, 6965. Carpenter, A. J.; Chadwick, D. J. *J. Org. Chem.* **1985**, *50*, 4362. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. Estermann, H.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1824. Ohta, H.; Matsumoto, S.; Sugai, T. *Tetrahedron Lett.* **1990**, *31*, 2895. Esswein, A.; Betz, R.; Schmidt, R. *Helv. Chim. Acta* **1989**, *72*, 213. Block, E.; Gernon, M.; Kang, H.; Ofori-Okai, G.; Zubieta, J. *Inorg. Chem.* **1991**, *30*, 1736. Bollinger, P.; Copper, P.; Gubler, H. U.; Leutwiler, A.; Payne, T. *Helv. Chim. Acta* **1990**, *73*, 1197.