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Lithium Diisopropylamide Solvated by Hexamethylphosphoramide: Substrate-Dependent Mechanisms for Dehydrobrominations

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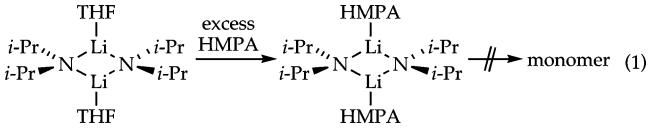
Abstract: Lithium diisopropylamide-mediated dehydrobrominations of *exo*-2-bromonorbornane, 1-bromocyclooctene, and *cis*-4-bromo-*tert*-butylcyclohexane were studied in THF solutions and THF solutions with added hexamethylphosphoramide (HMPA). Rate studies reveal a diverse array of mechanisms based on mono-, di-, and trisolvated monomers as well as triple ions. The results are contrasted with analogous eliminations in THF in the absence of HMPA.

Introduction

Adding hexamethylphosphoramide (HMPA) to ethereal solutions of organolithiums often elicits dramatic improvements in reaction rates, yields, and selectivities.[1,2] Although most discussions of *how* HMPA influences reactivity are highly conjectural, H. J. Reich and co-workers have made great progress toward filling this void.[3] Their investigations of a wide range of organolithium derivatives confirm the consensus that HMPA is a strongly coordinating ligand[4] capable of promoting deaggregation and ion-pair separation. Of particular importance, their spectroscopic studies in the limit of slow solvent exchange of free and coordinated HMPA provide a rare glimpse of lithium-ion solvation at a molecular level of resolution.[5]

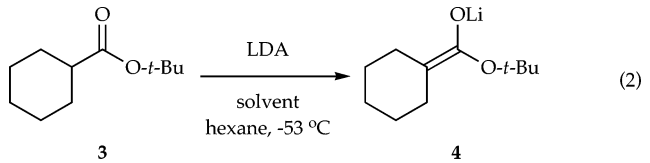
Our interest in HMPA stems from studies of lithium diisopropylamide (LDA) and related N-lithiated species.[6,7] Results from structural and mechanistic studies of LDA/HMPA/THF mixtures deviate significantly from those of other less sterically congested lithium salts. Although HMPA coordinates tenaciously to dimeric LDA compared with standard ethereal solvents such as THF, we detect no measurable deaggregation (eq 1).[7a] Even more surprising, adding HMPA to monomer−



1 **2**

dimer mixtures of either lithium hexamethyldisilazide (LiHMDS) or lithium *N*,*N*,*N*′,*N*′-tetramethylpiperidide (LiTMP)[7b] results in ionization of the dimers to form triple ions,[7a,8] yet further deaggregations are *still* not observed (Scheme 1).[9] In short, HMPA does not fully live up to its reputation as a deaggregating agent in the context of hindered lithium amides.

Rate studies of the LDA/HMPA-mediated ester enolization in eq 2 reveal further anomalies: HMPA fails to match expectations by serving as only a marginal accelerant,[7f,10] yet



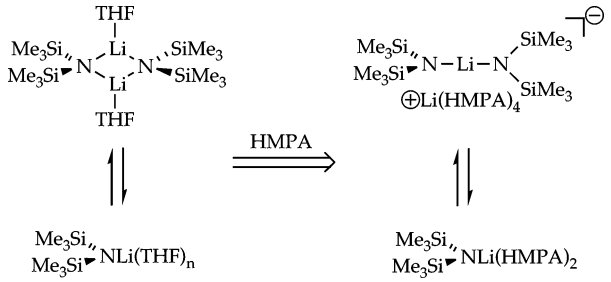
3 **4**

solvent:	THF	10 equiv HMPA/THF
k_{rel}:	1.0	2.0

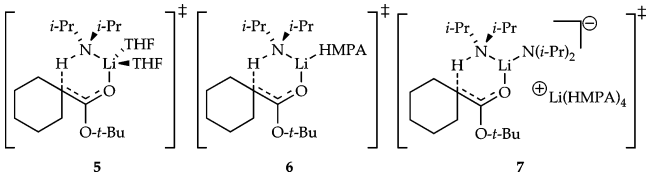
the nearly solvent-insensitive relative rate constants, k_{rel}, belie deep-seated mechanistic complexities.[11] Whereas the LDA/THF-

(1) Dykstra, R. R. Hexamethylphosphoric Triamide. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 4, pp 2668−2675.
(2) For a particularly interesting treatment of stereo- and regioselectivity affiliated with organolithium chemistry, see: Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: New York, 2002.
(3) For additional leading references, see: Reich, H. J.; Sanders, A. W.; Fiedler, A. T.; Bevan, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 13386.
(4) HMPA has been estimated to bind 300 times more strongly than THF in one case. Reich, H. J.; Kulicke, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 273.
(5) (a) Hilmersson, G.; Davidsson, O. *J. Org. Chem.* **1995**, *60*, 7660. (b) Hilmersson, G.; Ahlberg, P.; Davidsson, O. *J. Am. Chem. Soc.* **1996**, *118*, 3539. (c) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 6009. (d) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 9863.
(6) Structural studies of N-lithiated species have been reviewed. Lucht, B. L.; Collum, D. B. *Acc. Chem. Res.* **1999**, *32*, 1035. Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227. Gregory, K.; Schleyer, P. v. R.; Snaith, R. *Adv. Inorg. Chem.* **1991**, *37*, 47. Mulvey, R. E. *Chem. Soc. Rev.* **1991**, *20*, 167.
(7) (a) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5751. (b) Romesberg, F. E.; Bernstein, M. P.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 3475. (c) Romesberg, F. E.; Collum, D. B. *J. Am. Chem.* Soc. **1994**, *116*, 9198. (d) Sakuma, K.; Gilchrist, J. H.; Romesberg, F. E.; Cajthaml, C. E.; Collum, D. B. *Tetrahedron Lett.* **1993**, *34*, 5213. (e) Aubrecht, K. B.; Collum, D. B. *J. Org. Chem.* **1996**, *61*, 8674. (f) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2452. (g) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2459.
(8) An extensive bibliography of triple ions is included in the Supporting Information. Many of the reports cited will *not* be uncovered using current algorithms for electronic database searching. Of particular interest are triple ions derived from N-lithiated species and those based on the +Li(HMPA)$_4$ counterion.
(9) HMPA *promotes* aggregation in one instance. Jackman, L. M.; Chen, X. *J. Am. Chem. Soc.* **1992**, *114*, 403.

Scheme 1



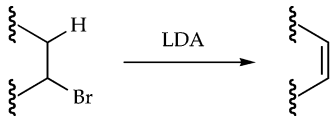
mediated enolization proceeds via disolvated monomer **5**, the analogous enolization with added HMPA appears to proceed via a combination of monosolvated monomer **6** and tetrasolvated triple-ion **7**.[7f] These results are surprising on several levels. We



did not anticipate, for example, that HMPA would divert the monomer-based enolization to a *lower* solvation number (cf., **5** and **6**), although the functional equivalency of two THF ligands and *one* HMPA ligand seems logical in retrospect. Moreover, the second-order dependence on the HMPA concentration and affiliated ionization follows from HMPA's reputation as a strongly coordinating dipolar ligand, yet the affiliation of HMPA with a *dimer*-based mechanism[12] is at odds with conventional wisdom.[13] We also noted a curious influence of the cosolvent: Whereas the rate of enolization via monomer **6** is insensitive to the concentration of THF in HMPA/THF/hexane mixtures, enolization via putative triple-ion **7** is *inhibited* by THF. How does increasing the THF concentration *inhibit* a putative ionization-dependent pathway without influencing the monomer-based pathway? We gingerly suggested that the selective inhibition derived from the net stabilization of free (uncoordinated) HMPA via THF−HMPA interactions.[14] The notion that solvent−solvent interactions remote from the lithium coordination spheres can influence organolithium reactivities piqued our interest.

We describe herein investigations of the LDA/HMPA-mediated dehydrobrominations depicted in eqs 3−5. Even within such a narrowly focused survey, the influence of HMPA on the rates and mechanisms proves to be highly substrate dependent. Moreover, the mechanisms detected in HMPA/THF solutions are markedly different than those in THF solutions without added HMPA.

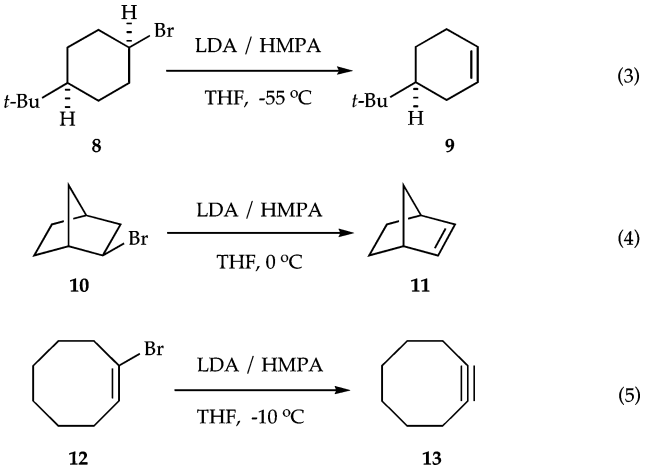
Table 1. Relative Rate Constants for LDA/HMPA-Mediated Eliminations (Eq 6)



(6)

substrate	T (°C)	$k_{HMPA}:k_{THF}$[a]
8	−55	3000:1
10	0	3:1
12	−10	30:1

[a] Eliminations using 0.10 M LDA in 10.0 M THF with no added HMPA (k_{THF}) or with 0.60 M HMPA (k_{HMPA}).



(3)

(4)

(5)

Results

Substrate-dependent relative rate constants (k_{HMPA}/k_{THF}) are summarized in Table 1. Experimentally determined rate laws for LDA/THF- and LDA/HMPA/THF-mediated eliminations are summarized in Table 2. Additional figures and data are archived in the Supporting Information. Putative transition structures depicting spatial details that are salted throughout the text are supported by semiempirical and ab initio studies.[15]

General Methods. Pseudo-first-order conditions were established using low concentrations of the alkyl bromides (0.004 M). LDA, HMPA, and THF were maintained at high, yet adjustable, concentrations with hexane as the cosolvent.[17] The losses of the alkyl bromides were monitored by gas chromatography relative to an internal dodecane standard. All reactions

(10) HMPA can also decelerate organolithium reactions. Reich, H. J.; Green, D. P.; Phillips, N. H. *J. Am. Chem. Soc.* **1989**, *111*, 3444. Reich, H. J.; Phillips, N. H.; Reich, I. L. *J. Am. Chem. Soc.* **1985**, *107*, 4101. Reich, H. J.; Dykstra, R. R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1469. Reich, H. J.; Sikorski, W. H. *J. Org. Chem.* **1999**, *64*, 14.

(11) For a discussion of the limitations of using relative rate constants as mechanistic probes, see: Bernstein, M. P.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 8008.

(12) Behavior of triple ions as one rather than two fragments is a consequence of the extremely low dissociation constants of even the most stabilized ion pairs. Bhattacharyya, D. N.; Lee, C. L.; Smid, J.; Szwarc, M. *J. Phys. Chem.* **1965**, *69*, 608. Wong, M. K.; Popov, A. I. *J. Inorg. Nucl. Chem. Lett.* **1972**, *34*, 3615.

(13) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.

(14) For discussions of solvent−solvent interactions in solutions of HMPA, see: Masaguer, J. R.; Casas, J. S.; Sousa Fernandez, A.; Sordo, *J. An. Quim.* **1973**, *69*, 199. Michou-Saucet, M. A.; Jose, J.; Michou-Saucet, C.; Merlin, J. C. *Thermochim. Acta* **1984**, *75*, 85. Vandyshev, V. N.; Serebryakova, A. L. *Russ. J. Gen. Chem.* **1997**, *67*, 540. Kulikov, M. V. *Russ. Chem. Bull.* **1997**, *46*, 274. Mehta, S. K.; Sharma, A. K.; Bhasin, K. K.; Parkash, R. *Fluid Phase Equilib.* **2002**, *201*, 203. Izutsu, K.; Kobayashi, N. *J. Electroanal. Chem.* **2005**, *574*, 197. Prado-Gotor, R.; Ayala, A.; Tejeda, A. B.; Suarez, M. B.; Mariscal, C.; Sanchez, M. D.; Hierro, G.; Lama, A.; Aldea, A.; Jimenez, R. *Int. J. Chem. Kinet.* **2003**, *35*, 367. Salomon, M. *J. Power Sources* **1989**, *26*, 9.

(15) (a) Armstrong, D. R.; Mulvey, R. E.; Walker, G. T.; Barr, D.; Snaith, R.; Clegg, W.; Reed, D. *J. Chem. Soc., Dalton Trans.* **1988**, 617. (b) Armstrong, D. R.; Barr, D.; Brooker, A. T.; Clegg, W.; Gregory, K.; Hodgson, S. M.; Snaith, R.; Wright, D. S. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 443. (c) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 2112. (d) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9187. (e) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 2166. (f) Liao, S.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 15114. (g) Pratt, L.; Robbins, S. *J. Mol. Struct. (THEOCHEM)* **1999**, *466*, 95. (h) Also, see ref 7.

(16) (a) Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5573. (b) Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 4081.

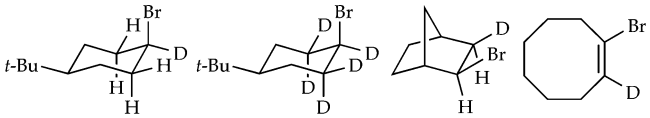
(17) The concentration of the LDA, although expressed in units of molarity, refers to the concentration of the monomer unit (normality). The concentrations of ethereal solvent and HMPA are expressed as total concentration of free (uncoordinated) ligand.

Table 2. Summary of Rate Studies for the LDA-Mediated Dehydrobrominations (Eq 6)

entry	substrate	T (°C)	ligand	ligand order	LDA order	k_H/k_D
1	**8**	20	THF	2.24 ± 0.03[a]	0.50 ± 0.02[b]	4.0 ± 0.1[c,g]
2	**8**	−55	HMPA	1.9 ± 0.2[b,d]	0.96 ± 0.09[e]	9.8 ± 0.1[c]
3	**10**	20	THF	0	0.39 ± 0.02[g]	1.9 ± 0.1[f]
				1.17 ± 0.08[g]	0.48 ± 0.01[g]	
4	**10**	0	HMPA	0	0.54 ± 0.04[h]	1.74 ± 0.04[b,d,f]
				2.0 ± 0.2[b,d]	0.53 ± 0.05[i]	
5	**12**	0	THF	0.93 ± 0.05[d]	0.50 ± 0.03	1.75 ± 0.02
6	**12**	−10	HMPA	0	0.61 ± 0.04[h]	2.6 ± 0.1
				1.4 ± 0.1[b,d]	0.57 ± 0.04[i]	

[a] [LDA] = 0.30 M. [b] [THF] = 10.0 M in hexane cosolvent. [c] Measured using **8** and **8**-d_4. [d] [LDA] = 0.10 M. [e] [HMPA] = 0.30 M in 10.0 M THF/hexane. [f] Measured using **10** and **10**-d_1. [g] See ref 16. [h] [HMPA] = 0.10 M in 10.0 M THF/hexane. [i] [HMPA] = 0.50 M in 10.0 M THF/hexane.

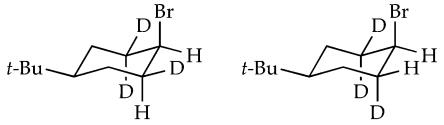
follow clean first-order decays, affording pseudo-first-order rate constants (k_{obsd}) that are independent of the initial concentrations of substrate (±10%). Isotope effects (k_H/k_D) determined using deuterated analogues **8**-d_1, **8**-d_4, **10**-d_1,[16a] and **12**-d_1 (Table 2) are consistent with rate-limiting proton transfers and vicinal dehydrobrominations (rather than carbene-based α-eliminations).[18] For expediency, we note at the outset that *none* of the LDA/HMPA-mediated dehydrobrominations displays a significant dependence on the THF concentration in HMPA/THF/hexane mixtures.



8-d_1 **8**-d_4 **10**-d_1 **12**-d_1

Anti-Dehydrobromination of *cis*-4-Bromo-*tert*-butylcyclohexane (8). Treatment of a cis/trans mixture of 4-bromo-*tert*-butylcyclohexane with LDA/HMPA at −55 °C affords 4-*tert*-butylcyclohexene (**9**) owing to elimination of exclusively the cis (axial) isomer, **8**. Detailed rate studies and mechanistic investigations were carried out using **8** (eq 3) that was purified by selective recrystallization from hexane at −96 °C.

A suspected diaxial elimination of **8** was supported through deuterium-labeling studies.[19] We compromised precision for ease of synthesis by monitoring the loss of the 4:1 mixture of trideuterated cyclohexylbromides **8a**-d_3 and **8b**-d_3. The axial



8a-d_3 **8b**-d_3

proton resonance of **8a**-d_3 and the equatorial proton resonance of **8b**-d_3 were identified using standard ^{1}H NMR spectroscopy aided by single-frequency decouplings (Supporting Information). Although, in principle, the loss of **8a**-d_3 and **8b**-d_3 could be monitored in situ by ^{1}H NMR spectroscopy, THF resonances at approximately 1.7 ppm proved to be problematic. Accordingly, reaction of the **8a**-d_3/**8b**-d_3 mixture was followed by GC analysis of quenched samples to determine the percent conversion. Each sample was then purified using flash chromatography, and the mixtures were analyzed with ^{1}H NMR spectroscopy to determine the **8a**-d_3/**8b**-d_3 ratio. Combination of the two analytical methods afforded rate constants for the loss of **8a**-d_3 and **8b**-d_3. Qualitatively, **8a**-d_3 disappeared substantially faster than **8b**-d_3. By accounting for the relatively slow competing abstraction of the α′-deuterium labels at the doubly labeled six position that cause distortions in the apparent axial−equatorial preference, we measured the preference for axial proton abstraction to be ≥20:1 both with and without added HMPA.[20]

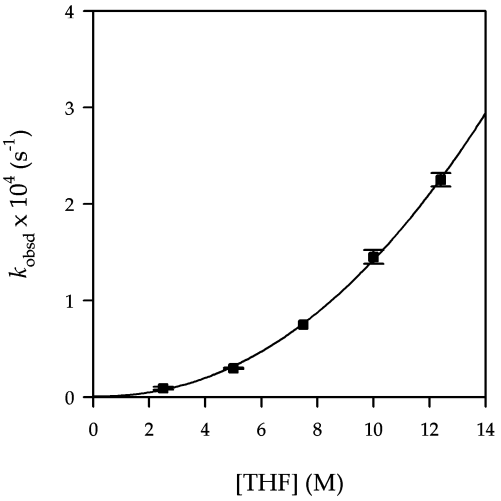


Figure 1. Plot of k_{obsd} versus [THF] for the dehydrobromination of *cis*-1-bromo-4-*tert*-butylcyclohexane (**8**, 0.004 M) by LDA (0.30 M) in hexane at 20 °C. The curve depicts an unweighted least-squares fit to $k_{obsd} = k[\mathrm{THF}]^n + k'$ ($k = 1.0 \pm 0.2 \times 10^{-6}$, $k' = 3.0 \pm 0.3 \times 10^{-7}$, $n = 2.2 \pm 0.1$).

Reaction of cyclohexyl bromide **8** with LDA/THF in the absence of HMPA at 20 °C reveals a second-order THF dependence (Figure 1) and a half-order LDA dependence (Figure 2). The rate law (eq 7) and generic mechanism (eq 8) are consistent with transition structure **14**. This is the first documented example of a trisolvated-monomer-based reaction of LDA. We surmise that the high solvation number derives from the lack of Li−Br interaction demanded by the trans-diaxial alignment (vide infra).

$$-\mathrm{d[RBr]}/\mathrm{d}t = k_i[(i\text{-Pr}_2\mathrm{NLi})_2(\mathrm{THF})_2]^{1/2}[\mathrm{THF}]^2[\mathrm{RBr}] \quad (7)$$

(18) Ashby, E. C.; Park, B. *Acta Chem. Scand.* **1990**, *44*, 291. Ashby, E. C.; Park, B.; Patil, G. S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* **1993**, *58*, 424. Ashby, E. C.; Deshpande, A. K.; Patil, G. S. *J. Org. Chem.* **1995**, *60*, 663. Taber, D. F.; Christos, T. E.; Neubert, T. D.; Batra, D. *J. Org. Chem.* **1999**, *64*, 9673. For a review of lithium carbenoids, see: Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697.

(19) Baciocchi, E. *Acc. Chem. Res.* **1979**, *12*, 430. Bartsch, R. A.; Zavada, J. *Chem. Rev.* **1980**, *80*, 453. Zavada, J.; Pankova, M.; Sicher, J. *J. Chem. Soc., Chem. Commun.* **1968**, 1145. Koning, L. J.; Nibbering, N. M. M. *J. Am. Chem. Soc.* **1987**, *109*, 1715. Schlosser, M.; Lehmann, R.; Jenny, T. *J. Organomet. Chem.* **1990**, *389*, 149.

(20) The derivations and experimental details are included in the Supporting Information.

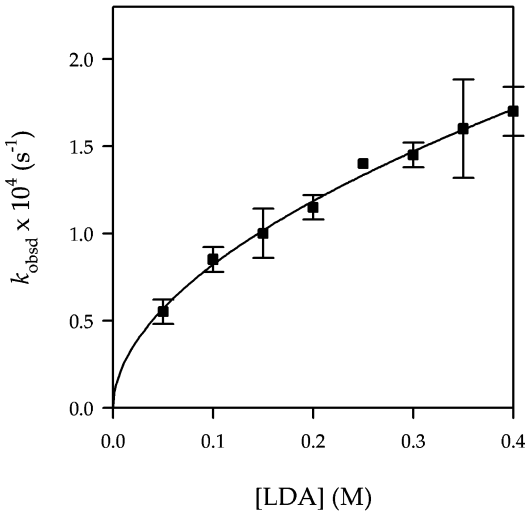
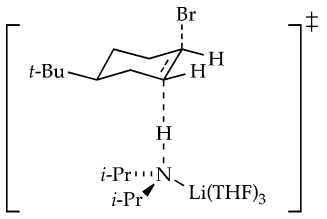


Figure 2. Plot of k_{obsd} versus [LDA] for the dehydrobromination of *cis*-1-bromo-4-*tert*-butylcyclohexane (**8**, 0.004 M) in THF (10.0 M)/hexane at 20 °C. The curve depicts an unweighted least-squares fit to $k_{obsd} = k[\text{LDA}]^n$ ($k = 2.7 \pm 0.1 \times 10^{-4}$, $n = 0.50 \pm 0.02$).

$$1/2(i\text{-Pr}_2\text{NLi})_2(\text{THF})_2 + 2\text{THF} + \text{RBr} \xrightarrow{k_i} [(i\text{-Pr}_2\text{NLi})(\text{THF})_3(\text{RBr})]^{\ddagger} \quad (8)$$

The LDA/HMPA-mediated elimination of **8** is very fast compared with HMPA-free conditions (Table 1). A plot of k_{obsd} versus HMPA concentration reveals a second-order HMPA



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dependence and an insignificant nonzero intercept (Figure 3), consistent with a single pathway. A plot of k_{obsd} versus LDA concentration reveals a first-order dependence (Figure 4). The idealized rate law (eq 9) and generic mechanism (eq 10) are consistent with a reaction via tetrasolvated dimers. Because of the excessive congestion of a tetrasolvated cyclic dimer,[6,15] we invoke triple-ion-based transition structure **15**. Experimental and theoretical support for triple ions of hindered lithium amides is considerable.[8] Of special note in the context of the rate studies of enolization,[7g] no THF concentration dependence was observed at either low or high HMPA concentration despite a perceived similarity with the enolization mechanism.

$$-\text{d}[\text{RBr}]/\text{d}t = k_{ii}[(i\text{-Pr}_2\text{NLi})_2(\text{HMPA})_2][\text{HMPA}]^2[\text{RBr}] \quad (9)$$

$$(i\text{-Pr}_2\text{NLi})_2(\text{HMPA})_2 + 2\text{HMPA} + \text{RBr} \xrightarrow{k_{ii}} [(i\text{-Pr}_2\text{NLi})_2(\text{HMPA})_4(\text{RBr})]^{\ddagger} \quad (10)$$

Syn-Dehydrobromination of *exo*-2-Bromonorbornane (10). Previous studies of LDA/THF-mediated elimination of **10** implicated mono- and disolvated monomers (**16** and **17**, respectively; Table 2).[16a] Addition of HMPA elicits moderate

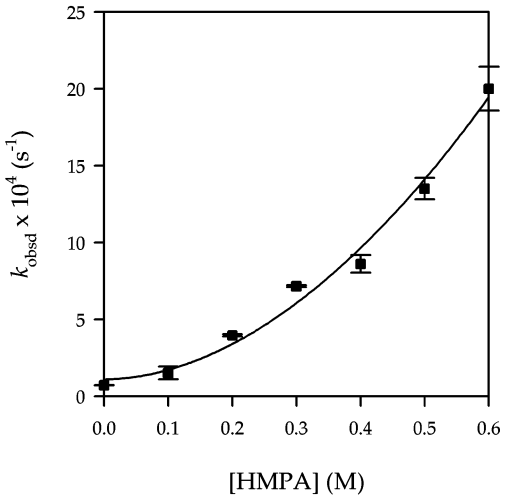


Figure 3. Plot of k_{obsd} versus [HMPA][23] for the dehydrobromination of *cis*-1-bromo-4-*tert*-butylcyclohexane (**8**, 0.004 M) by LDA (0.10 M) in THF (10.0 M)/hexane at −55 °C. The curve depicts an unweighted least-squares fit to $k_{obsd} = k[\text{HMPA}]^n + k'$ ($k = 4.8 \pm 0.7 \times 10^{-3}$, $k' = 1.0 \pm 0.7 \times 10^{-4}$, $n = 1.9 \pm 0.2$).

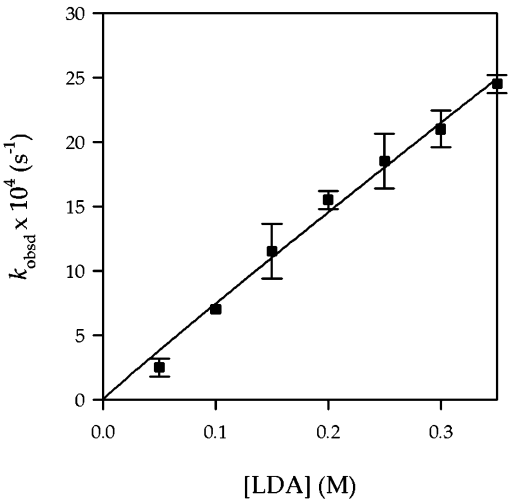
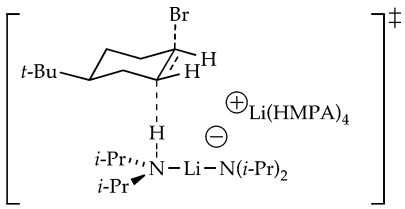


Figure 4. Plot of k_{obsd} versus [LDA] for the dehydrobromination of *cis*-1-bromo-4-*tert*-butylcyclohexane (**8**, 0.004 M) in HMPA (0.40 M)[23]/THF (10.0 M)/hexane at −55 °C. The curve depicts an unweighted least-squares fit to $k_{obsd} = k[\text{LDA}]^n + k'$ ($k = 6.7 \pm 0.8 \times 10^{-3}$, $k' = 4.5 \pm 0.3 \times 10^{-4}$, $n = 0.96 \pm 0.09$).

accelerations (Table 1) accompanied by significant changes in mechanism. A plot of k_{obsd} versus HMPA concentration displays



15

a second-order dependence and a substantial nonzero intercept (Figure 5), consistent with competing HMPA-concentration-independent and HMPA-concentration-dependent pathways. A plot of k_{obsd} versus LDA concentration reveals half-order dependencies when measured at both low and high HMPA concentrations. Overall, the data are consistent with eliminations

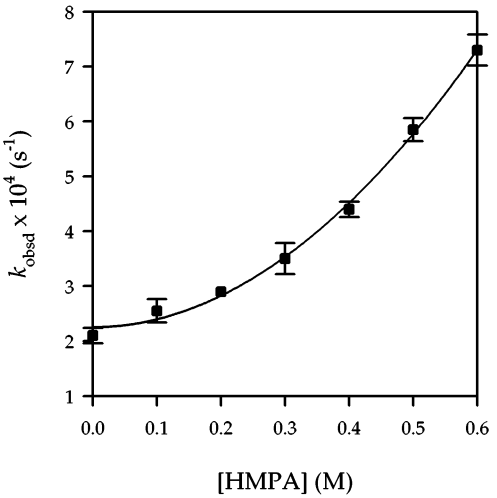


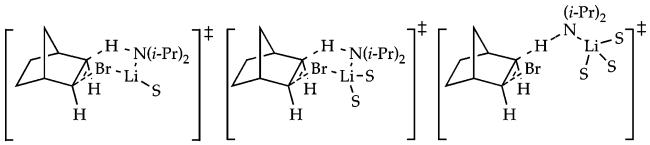
Figure 5. Plot of k_{obsd} versus [HMPA][23] for the dehydrobromination of (±)-2-*exo*-bromonorbornane (**10**, 0.004 M) by LDA (0.10 M) in THF (10.0 M)/hexane at 0 °C. The curve depicts an unweighted least-squares fit to $k_{obsd} = k[\text{HMPA}]^n + k'$ ($k = 1.4 \pm 0.1 \times 10^{-3}$, $k' = 2.3 \pm 0.1 \times 10^{-4}$, $n = 2.0 \pm 0.1$).

via mono- and trisolvated monomer-based pathways (eqs 12 and 13) for which we proffer transition structures **18** and **20**. Evidence of disolvated monomer **19** is absent. Perhaps a Li−Br interaction and the sterically demanding second HMPA ligand are incompatible.

$$-\text{d[RBr]}/\text{d}t = k_{iii}[(i\text{-Pr}_2\text{NLi})_2(\text{HMPA})_2]^{1/2}[\text{HMPA}]^0[\text{RBr}] + k_{iv}[(i\text{-Pr}_2\text{NLi})_2(\text{HMPA})_2]^{1/2}[\text{HMPA}]^2[\text{RBr}] \quad (11)$$

$$1/2(i\text{-Pr}_2\text{NLi})_2(\text{HMPA})_2 + \text{RBr} \xrightarrow{k_{iii}} [(i\text{-Pr}_2\text{NLi})(\text{HMPA})(\text{RBr})]^{\ddagger} \quad (12)$$

$$1/2(i\text{-Pr}_2\text{NLi})_2(\text{HMPA})_2 + 2\text{HMPA} + \text{RBr} \xrightarrow{k_{iv}} [(i\text{-Pr}_2\text{NLi})(\text{HMPA})_3(\text{RBr})]^{\ddagger} \quad (13)$$



16; S = THF
18; S = HMPA

17; S = THF
19; S = HMPA

20; S = HMPA

Syn-Dehydrobromination of 1-Bromocyclooctene (12). A plot of k_{obsd} versus THF concentration for the elimination of **12** to form cyclooctyne (**13**)[21] reveals a linear dependence (Figure 6). A half-order LDA dependence at both low and high THF concentration implicates a mechanism based on disolvated monomer (eqs 14 and 15) via transition structure **22**.[16a] Thus, the LDA/THF-mediated syn eliminations of **10** and **12** in the absence of HMPA show some differences.

$$-\text{d[RBr]}/\text{d}t = k_{v}[(i\text{-Pr}_2\text{NLi})_2(\text{THF})_2]^{1/2}[\text{THF}][\text{RBr}] \quad (14)$$

(21) Cyclooctynes in organic synthesis. Heber, D.; Roesner, P.; Tochtermann, W. *Eur. J. Org. Chem.* **2005**, *20*, 4231.

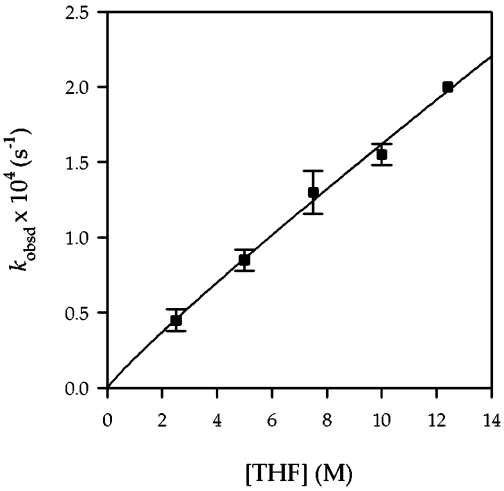
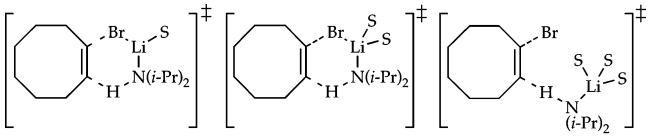


Figure 6. Plot of k_{obsd} versus [THF] for the elimination of 1-bromocyclooctene (**12**, 0.004 M) in hexane at 0 °C. The curve depicts an unweighted least-squares fit to $k_{obsd} = k[\text{THF}]^n + k'$ ($k = 1.8 \pm 0.2 \times 10^{-5}$, $k' = 3.6 \pm 0.2 \times 10^{-5}$, $n = 0.93 \pm 0.05$).

$$1/2(i\text{-Pr}_2\text{NLi})_2(\text{THF})_2 + \text{THF} + \text{RBr} \xrightarrow{k_{v}} [(i\text{-Pr}_2\text{NLi})(\text{THF})_2(\text{RBr})]^{\ddagger} \quad (15)$$

Elimination of **12** by LDA/HMPA/THF appears to be the most mechanistically complex of the three cases studied. A plot of k_{obsd} versus HMPA concentration displays a nonzero intercept and a noninteger dependence ($n = 1.4 \pm 0.1$), suggesting that



21; S = HMPA

22; S = THF
23; S = HMPA

24; S = HMPA

there is an HMPA-concentration-independent pathway and possibly *two* HMPA-concentration-dependent pathways. LDA orders measured at both low and high HMPA concentration show half-order dependencies. Overall, the rate law (eq 16) and generic mechanisms (eqs 17−19) are consistent with monomer-based transition structures such as **21**, **23**, and **24**. Although we have no reason to doubt the veracity of the results, such a complex hypothesis seems unusually vulnerable to minor systematic errors.

$$\text{d[RBr]}/\text{d}t = k_{vi}[(i\text{-Pr}_2\text{NLi})_2(\text{HMPA})_2]^{1/2}[\text{HMPA}]^0[\text{RBr}] + k_{vii}[(i\text{-Pr}_2\text{NLi})_2(\text{HMPA})_2]^{1/2}[\text{HMPA}][\text{RBr}] + k_{viii}[(i\text{-Pr}_2\text{NLi})_2(\text{HMPA})_2]^{1/2}[\text{HMPA}]^2[\text{RBr}] \quad (16)$$

$$1/2(i\text{-Pr}_2\text{NLi})_2(\text{HMPA})_2 + \text{RBr} \xrightarrow{k_{vi}} [(i\text{-Pr}_2\text{NLi})(\text{HMPA})(\text{RBr})]^{\ddagger} \quad (17)$$

$$1/2(i\text{-Pr}_2\text{NLi})_2(\text{HMPA})_2 + \text{HMPA} + \text{RBr} \xrightarrow{k_{vii}} [(i\text{-Pr}_2\text{NLi})(\text{HMPA})_2(\text{RBr})]^{\ddagger} \quad (18)$$

$$1/2(i\text{-Pr}_2\text{NLi})_2(\text{HMPA})_2 + 2\text{HMPA} + \text{RBr} \xrightarrow{k_{viii}} [(i\text{-Pr}_2\text{NLi})(\text{HMPA})_3(\text{RBr})]^{\ddagger} \quad (19)$$

Discussion

Addition of HMPA to LDA/THF-mediated dehydrobrominations causes accelerations by as little as 3-fold or as much as 3000-fold (Table 1.) Using rate studies to peer beneath the surface, a reasonably self-consistent mechanistic picture emerges. The trans-diaxial elimination of **8** (eq 3) offers no provision for a Li−Br interaction. Consequently, the LDA/THF-mediated elimination proceeds slowly via a trisolvated monomer **14** unprecedented for LDA. The marked acceleration imparted by adding the strongly coordinating HMPA is fully in accord with conventional wisdom, yet rate studies implicate triple-ion-based transition structure **15**. Although many might be surprised that the second-order HMPA dependence is affiliated with a *dimer*-based pathway, putative triple-ion **15** is well founded on previous structural, rate, and computational studies.[7,8,15c−e] We have long suspected that reactions requiring ionization may be based on triple ions.

The syn-dehydrobrominations of **10** and **12** by LDA at low HMPA concentrations proceed via monosolvated monomer-based transition structures for which we submit **18** and **21**. The muted advantages offered by HMPA relative to THF may derive from stabilization in the transition state that is largely offset by stabilization in the ground state. Dehydrobrominations of **10** and **12** at higher HMPA concentrations proceed via more highly solvated monomer-based transition structures bearing as many as three coordinated HMPA ligands. We suspect that the most highly solvated monomer-based transition structures (**20** and **24**) has no Li−Br interaction, although this conclusion is based on intuition rather than direct evidence. We were somewhat surprised that **10** did not α-eliminate by a carbenoid intermediate[18] (although limited contributions from additional mechanisms could lurk beneath the error limits of the rate laws.)

One might ask why there is so much variation in the number of coordinated HMPA ligands for monomer-based syn eliminations. We do not, however, find this to be an acutely vexing question. Replacing the putatively weak Li−Br interaction[22] with a strong Li−HMPA interaction could account for some variation. Moreover, given that steric congestion about the lithium coordination sphere appears to be a major determinant of solvation,[15c,23,24] it is not surprising that subtle changes in the substrate influence the solvation numbers in the transition structures. Ongoing investigations of other reactions mediated by LDA/HMPA suggest that such variations can become acute.[25]

We were particularly interested at the outset in determining the role of THF in LDA/HMPA-mediated eliminations. Recall that the ester enolization in eq 2 is *inhibited* by THF, and this inhibition was tentatively attributed to THF−HMPA interactions remote from the lithium coordination sphere.[7g,14] The attenuated Lewis basicity would represent a net stabilization of the ground state relative to a transition state and should influence *all* reactions demanding coordination of additional HMPA ligands. In short, we observed no evidence whatsoever to support this hypothesis. Even elimination of **8** manifesting a second-order dependence on HMPA concentration via putative triple-ion **15** showed no cosolvent effect. We went so far as to reproduce the rate studies of the enolization of ester **3** to confirm the rate-retarding effects of THF. Inhibition of the enolization in eq 1 is for now unsupported by a tenable mechanistic hypothesis.

Conclusion

LDA/HMPA-mediated dehydrobrominations proceed via surprisingly variable reaction mechanisms. We suspect that this derives from two opposing effects: the profound dipolarity, promoting solvation of lithium ion, and the severe steric demands of the HMPA ligand, inhibiting solvation. It is clear that an empirically observed acceleration cannot necessarily be ascribed to a deaggregation-based mechanism as is often the case; triple-ion-based reactions are prevalent. In settings where selectivity is at issue, subtle changes in rate with added HMPA could still be affiliated with marked changes in selectivity. Even small changes in the *concentration* of added HMPA can cause mechanistic reversals, which, in turn, would alter product distributions.

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Supporting Information Available: NMR spectra, rate data, experimental protocols, and a bibliography of triple ions. This material is available free of charge via the Internet at http://pubs.acs.org.

JA060964B

(22) Substitution of one THF ligand on $(i\text{-Pr})_2\text{NLi(THF)}_3$ by MeBr is calculated to be endergonic by 10.6 kcal/mol using B3LYP/6-31G(d).

(23) For early discussions of steric effects on solvation and aggregation, see: Settle, F. A.; Haggerty, M.; Eastham, J. F. *J. Am. Chem. Soc.* **1964**, *86*, 2076. Lewis, H. L.; Brown, T. L. *J. Am. Chem. Soc.* **1970**, *92*, 4664. Brown, T. L.; Gerteis, R. L.; Rafus, D. A.; Ladd, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2135. For more recent discussions and leading references, see: Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 2217.

(24) For discussions of the role of steric effects on lithium-ion solvation by HMPA, see: Ishiguro, S. *Pure Appl. Chem.* **1994**, *66*, 393. Dack, M. R. J.; Bird, K. J.; Parker, A. J. *Aust. J. Chem.* **1975**, *28*, 955. Ishiguro, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1465. Also, see ref 21c.

(25) Yun, M.; Collum, D. B. Unpublished results.