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

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Abstract: Lithium diisopropylamide-mediated dehydrobrominations of exo-2-bromonorbornane, 1-bromocloctene, 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 ligand4 capable of promoting deaggregation and ion-pair separation. Of particular importance, their spectroscopic studies in the limit of slow solvent exchange 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—

\[
\text{THF} \quad \text{excess HMPA} \quad \text{HMPA}
\]

\[
i-\text{Pr}^+ \quad \text{N}^+_{\text{Li}} \quad \text{N}^-_{\text{i-Pr}} \quad \text{N}^-_{\text{i-Pr}}
\]

\[
\text{THF} \quad \text{HMPA}
\]

\[
\text{monomer}
\]

dimer mixtures of either lithium hexamethyldisilazide (LiHMDS) or lithium \(N,N',N''\)-tetramethylpiperidide (LiTMP)7b results in ionization of the dimers to form triple ions,7a,b 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,7c,d yet the nearly solvent-insensitive relative rate constants, belies deep-seated mechanistic complexities.11 Whereas the LDA/THF-

\[
\text{O-t-But} \quad \text{LDA} \quad \text{OLi}
\]

solvent

hexane, -53 °C

\[
\text{o-t-But}
\]

solvent: THF 10 equiv HMPA/THF

\[
k_{\text{rel}} \quad 1.0 \quad 2.0
\]

(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 \(+\text{Li(HMPA)}\) counterion.


(13) 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.


mediated enolization proceeds via disolvated monomer 5, the analogous enolization with added HMPA appears to proceed via a combination of monosolvated monomer analogues enolization with added HMPA appears to proceed via a combination of monosolvated monomer 6 and tetrasolvated triple-ion 7.\textsuperscript{71} 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\textsuperscript{12} is at odds with conventional wisdom.\textsuperscript{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.\textsuperscript{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

\begin{align*}
\text{THF} & \quad \text{HMPA} \\
\text{Me}_3\text{Si} & \quad \text{Li}_2\text{N}(\text{THF})_2 \\
\text{Me}_3\text{Si} & \quad \text{Me}_3\text{Si} \\
\text{Li}_2\text{N}(\text{HMPA})_2 & \quad \text{THF}
\end{align*}

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.

Results

Substrate-dependent relative rate constants (\(k_{\text{HMPA}}/k_{\text{THF}}\)) 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.\textsuperscript{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.\textsuperscript{17} The losses of the alkyl bromides were monitored by gas chromatography relative to an internal dodecane standard. All reactions

\begin{align*}
\text{LDA} & \quad \text{THF}, -55 \degree C \\
\text{LDA} & \quad \text{THF}, 0 \degree C \\
\text{LDA} & \quad \text{THF}, -10 \degree C
\end{align*}

\begin{align*}
\text{substrate} & \quad T(\degree C) & \quad k_{\text{HMPA}}/k_{\text{THF}}^a \\
8 & \quad -55 & \quad 3000:1 \\
10 & \quad 0 & \quad 3:1 \\
12 & \quad -10 & \quad 30:1
\end{align*}

\textsuperscript{a} Eliminations using 0.10 M LDA in 10.0 M THF with no added HMPA (\(k_{\text{THF}}\)) or with 0.60 M HMPA (\(k_{\text{HMPA}}\)).
follow clean first-order decays, affording pseudo-first-order rate constants (k_{obs}) that are independent of the initial concentrations of substrate (±10%). Isotope effects (k_f/k_i) determined using deuterated analogues 8-d_1, 8-d_6, 10-d_1, and 12-d_1 (Table 2) are consistent with rate-limiting proton transfers and vicinal dehydrobrominations (rather than carbene-based α-eliminations). 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.

### Anti-Dehydrobromination of cis-4-Bromo-tert-butylocyclohexane (8)

Treatment of a cis/trans mixture of 4-bromo-tert-butylocyclohexane with LDA/HMPA at −55 °C affords 4-tert-butylocyclohexane (9) owing to elimination of exclusively the cis (axial) isomer. 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 deuteration-labeling studies. We compromised precision for ease of synthesis by monitoring the loss of the 4:1 mixture of trideuterated cyclohexylbromides 8a-d_1 and 8b-d_3. The axial proton resonance of 8a-d_1 and the equatorial proton resonance of 8b-d_3 were identified using standard ^1H NMR spectroscopy aided by single-frequency decouplings (Supporting Information). Although, in principle, the loss of 8a-d_1 and 8b-d_3 could be monitored in situ by ^1H NMR spectroscopy, THF resonances at approximately 1.7 ppm proved to be problematic.

![Diagram](Image)

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

```
−d[RBr]/dt = k_1(\gamma \text{Pr}_2\text{N}^+\text{Li}^-)_2(\text{THF})_2^{1/2}[\text{THF}]^2[RBr]
```

(20) The derivations and experimental details are included in the Supporting Information.
The LDA/HMPA-mediated elimination of 8 is very fast compared with HMPA-free conditions (Table 1). A plot of \( k_{\text{obsd}} \) versus HMPA concentration reveals a second-order HMPA dependence and an insignificant nonzero intercept (Figure 3), consistent with a single pathway. A plot of \( k_{\text{obsd}} \) 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, we invoke triple-ion-based transition structure 15. Experimental and theoretical support for triple ions of hindered lithium amides is considerable. Of special note in the context of the rate studies of enolization, no THF concentration dependence was observed at either low or high HMPA concentration despite a perceived similarity with the enolization mechanism.

**Figure 2.** Plot of \( k_{\text{obsd}} \) 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 \( k_{\text{obsd}} = k[\text{LDA}]^n \) (\( k = 2.7 \pm 0.1 \times 10^{-4}, n = 0.50 \pm 0.02 \)).

\[
\frac{1}{2}(i-\text{Pr}_2\text{NLi})_2(\text{THF})_2 + 2\text{THF} + \text{RBr} \xrightarrow{k_i} [(i-\text{Pr}_2\text{NLi})(\text{THF})_3(\text{RBr})]^+ \tag{8}
\]

The LDA/HMPA-mediated elimination of 8 is very fast compared with HMPA-free conditions (Table 1). A plot of \( k_{\text{obsd}} \) versus HMPA concentration reveals a second-order HMPA dependence and an insignificant nonzero intercept (Figure 3), consistent with a single pathway. A plot of \( k_{\text{obsd}} \) 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, we invoke triple-ion-based transition structure 15. Experimental and theoretical support for triple ions of hindered lithium amides is considerable. Of special note in the context of the rate studies of enolization, no THF concentration dependence was observed at either low or high HMPA concentration despite a perceived similarity with the enolization mechanism.

\[
-d[\text{RBr}] / dr = k_i [(i-\text{Pr}_2\text{NLi})_2(\text{HMPA})_2][\text{HMPA}]^2[\text{RBr}] \tag{9}
\]

\[
(i-\text{Pr}_2\text{NLi})_2(\text{HMPA})_2 + 2\text{HMPA} + \text{RBr} \xrightarrow{k_i} [(i-\text{Pr}_2\text{NLi})(\text{HMPA})_3(\text{RBr})]^+ \tag{10}
\]

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). Addition of HMPA elicits moderate accelerations (Table 1) accompanied by significant changes in mechanism. A plot of \( k_{\text{obsd}} \) versus HMPA concentration displays 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 \( k_{\text{obsd}} \) versus LDA concentration reveals half-order dependencies when measured at both low and high HMPA concentrations. Overall, the data are consistent with eliminations.
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.

\[ \frac{-d[RBr]}{dt} = k_{\text{iii}} [(i-Pr_2NLi)_2(HMPA)]^{1/2} [HMPA]^2 [RBr] + k_{\text{iv}} [(i-Pr_2NLi)_2(HMPA)]^{1/2} [HMPA] [RBr] \] (11)

\[ 1/2 (i-Pr_2NLi)_2(HMPA) + RBr \underset{k_{\text{iii}}}{\overset{k_{\text{iv}}}{\rightleftharpoons}} [(i-Pr_2NLi)(HMPA)(RBr)]^\dagger \] (12)

\[ 1/2 (i-Pr_2NLi)_2(HMPA) + 2\text{HMPA} + RBr \underset{k_5}{\overset{k_6}{\rightleftharpoons}} [(i-Pr_2NLi)(HMPA)_2(RBr)]^\dagger \] (13)

Syn-Dehydrobromination of 1-Bromocyclooctene (12). A plot of \( k_{\text{obsd}} \) versus THF concentration for the elimination of 12 to form cyclooctyne (13) 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.

\[ \frac{-d[RBr]}{dt} = k_{\text{vii}} [(i-Pr_2NLi)_2(HMPA)]^{1/2} [HMPA]^2 [RBr] + k_{\text{viii}} [(i-Pr_2NLi)_2(HMPA)]^{1/2} [HMPA] [RBr] \] (16)

\[ 1/2 (i-Pr_2NLi)_2(HMPA) + RBr \underset{k_5}{\overset{k_6}{\rightleftharpoons}} [(i-Pr_2NLi)(HMPA)(RBr)]^\dagger \] (17)

\[ 1/2 (i-Pr_2NLi)_2(HMPA) + \text{HMPA} + RBr \underset{k_{\text{viii}}}{\overset{k_{\text{vii}}}{\rightleftharpoons}} [(i-Pr_2NLi)(HMPA)_2(RBr)]^\dagger \] (18)

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

\[ \frac{-d[RBr]}{dt} = k_{\text{viii}} [(i-Pr_2NLi)_2(HMPA)]^{1/2} [HMPA]^2 [RBr] + k_{\text{vii}} [(i-Pr_2NLi)_2(HMPA)]^{1/2} [HMPA] [RBr] \] (14)

Figure 5. Plot of \( k_{\text{obsd}} \) versus [HMPA] for the dehydrobromination of \((\pm)-2\text{-exo}-\text{bromonorbornane}\) (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 \( k_{\text{obsd}} = k_{\text{HMPA}} [\text{HMPA}]^n + k' \) (\( k = 1.8 \pm 0.2 \times 10^{-5}, k' = 3.6 \pm 0.2 \times 10^{-5}, n = 0.93 \pm 0.05 \)).

Figure 6. Plot of \( k_{\text{obsd}} \) 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 \( k_{\text{obsd}} = k_{\text{THF}} [\text{THF}]^n + k' \) (\( k = 1.4 \pm 0.1 \times 10^{-5}, k' = 2.3 \pm 0.1 \times 10^{-5}, n = 2.0 \pm 0.1 \)).
1/2(i-Pr₂NLi)₂(HMPA)₂ + 2HMPA + RBr $\rightarrow$ [(i-Pr₂NLi)(HMPA)₃(RBr)]⁺ (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 structures 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 intermediate18 (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 interaction22 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 selectivity, inhibiting solvation. It is clear 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.7,8,15 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 unpublished 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.

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