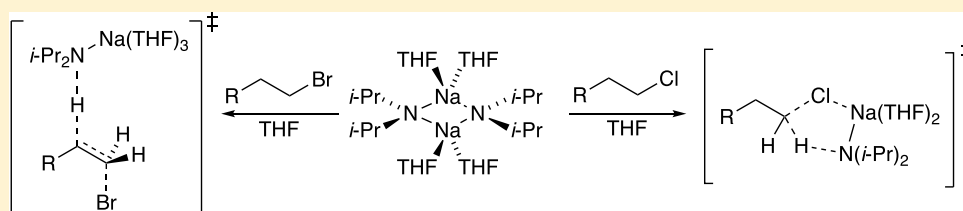


Sodium Diisopropylamide-Mediated Dehydrohalogenations: Influence of Primary- and Secondary-Shell Solvation

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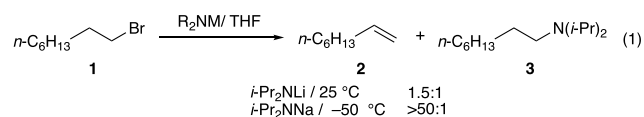
Supporting Information



ABSTRACT: Eliminations of alkyl halides by sodium diisopropylamide (NaDA) in tetrahydrofuran (THF)/hexane or THF/*N,N*-dimethylethylamine (DMEA) solutions are facile and complementary to analogous reactions of lithium diisopropylamide in THF. Rate studies show a dominance of monomer-based metalations and prevalent secondary-shell solvation effects overlaid on primary-shell effects. 1-Halo-octanes exclusively undergo elimination rather than substitution. Rate and isotopic labeling studies on 1-bromooctane reveal an E2-like elimination pathway via trisolvated NaDA monomer. By contrast, 1-chlorooctane is eliminated via disolvated monomer through a carbenoid mechanism. *exo*-2-Norbornyl chloride and bromide are also eliminated via disolvated monomer; a syn E2 mechanism is inferred for these substrates. The *cis*- and *trans*-4-*tert*-butylcyclohexyl bromides show a preference for the elimination of the *cis* isomer ($k_{cis/ax}/k_{trans/eq} = 10$). Rate and isotopic labeling studies are consistent with a *trans*-diaxial E2 elimination via trisolvated monomer for the *cis* isomer and a carbenoid mechanism via disolvated monomer for the *trans* isomer. Vicinal haloethers show substrate-dependent reactivities, affording alkynes and enol ethers. *trans*-1-Bromo-2-methoxycyclohexane provides enol ether 1-methoxycyclohexene, while *trans*-1-bromo-2-methoxycyclooctane provides dimeric products consistent with fleeting cycloocta-1,2-diene (cyclic allene), which was fully characterized as two conformers.

INTRODUCTION

The seemingly subtle factors that dictate whether an anion functions as a base or as a carbon-centered nucleophile can be confounding. Notions of steric effects, nucleophile polarizability, ion pairing, solvent polarity, and counterion effects crucially fail to account for aggregation and primary-shell solvation and are thus too restrictive to fully explain the S_N2 –E2 dichotomy.^{1–3} We find it intriguing, for example, that with lithium diisopropylamide (LDA), 1-bromooctane undergoes both elimination (2) and substitution (3), but with sodium diisopropylamide (NaDA), the elimination product (2) is obtained exclusively (eq 1).⁴ This paper examines NaDA-

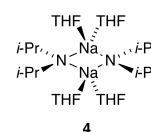
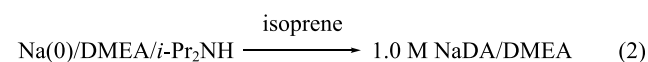


mediated dehydrohalogenations as part of an effort to establish the foundational structure–reactivity principles in organosodium chemistry as well as to pique the interest of consumers of strong bases.^{5–8} What stands out to us is the number of observations that do not follow the script found in standard organic chemistry textbooks.⁹ Moreover, deconvolution of solvation into primary- and secondary-shell effects brings a

noteworthy perspective to the iconic issues of reactivity and selectivity.

RESULTS AND DISCUSSION

Methods. NaDA is prepared from sodium dispersion as a 1.0 M stock solution in *N,N*-dimethylethylamine (DMEA) as illustrated in eq 2.⁴ Owing to our emphasis on mechanism, we



take the added precaution of recrystallizing NaDA. Although we document secondary shell solvation effects, THF/DMEA and THF/hexane solutions of NaDA would be nearly indistinguishable to the average practitioner owing to the highly favorable substitution of THF for DMEA to form tetrasolvated dimer 4 as

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the sole observable form¹⁰ and relatively minor differences in polarity of hexane and DMEA. Thus, while we use THF/hexane mixtures, others are likely to find the stock solutions of NaDA/DMEA with added THF to be more convenient. Because of the volatility of many of the products, yields are often determined using NMR spectroscopy relative to an internal standard (benzene). These calibrated yields are listed in parentheses. Overall, the eliminations are free of significant byproducts unless otherwise noted.

Reaction rates were monitored using ¹H NMR spectroscopy, as previously described.¹¹ The often-preferred strategy of monitoring via in situ infrared spectroscopy is not possible in these reactions, as deposition of sodium halides on the detection window (silicon chip) causes spectral distortion. Precipitation is, however, a useful diagnostic for detecting the onset of reaction.

Rate studies of NaDA-mediated dehydrohalogenations show, without exception, half-order NaDA dependencies that implicate monomer-based metalations. Figure 1 is emblematic;^{12,13} all other measured half orders in NaDA are archived in the Supporting Information.

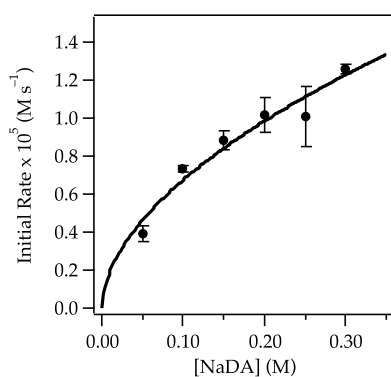
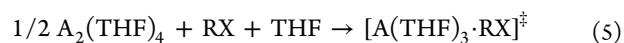
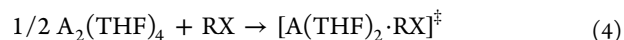


Figure 1. Plot of the initial rate^{19b} versus [NaDA] for the dehydrobromination of 1-bromooctane **1** (0.050 M) in 5.1 M THF/hexane at -78°C . The curve depicts an unweighted least-squares fit to $y = k[\text{NaDA}]^n$; $k = (24 \pm 3) \times 10^{-5}$; $n = 0.55 \pm 0.07$.

The reaction orders in THF are sensitive to the choice of substrate, eliciting THF concentration dependencies denoted in the generalized and idealized rate law (eq 3; $A = i\text{-Pr}_2\text{NNA}$).³ Zeroth, first, and second orders in THF appeared to implicate metalations via di-, tri-, and tetrasolvated monomers, respectively (eqs 4–6). However, control experiments, originally developed for the study of lithium amide chemistry, revealed that most THF-concentration-dependent rates stem from a combination of sterically sensitive primary-shell solvation effects overlaid on sterically insensitive secondary-shell solvation effects.^{12a} In these control experiments, the primary and secondary effects may be disentangled through the use of hindered polyalkylated THF ligands (2,2-dimethyltetrahydrofuran, 2,5-dimethyltetrahydrofuran, or 2,2,5,5-tetramethyltetrahydrofuran) as poorly coordinating but still polar cosolvents.¹⁴ Secondary-shell (medium) effects on the chemistry of LDA typically account for very low (0–20%) rate changes, spanning <1.0 M THF/hexane to neat THF. Having established that NaDA is stable in 2,5-dimethyltetrahydrofuran (2,5-Me₂THF) at $\leq -20^{\circ}\text{C}$,^{10,15} we found secondary-shell effects to be measurable and consequential to the mechanistic interpretation. Most noticeably, apparent evidence of tetrasolvates (eq 6) proved to be illusory, stemming instead from the influence of the secondary-shell solvation on trisolvated monomer-based path-

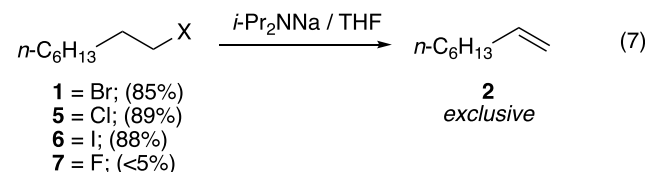
ways (eq 5). Similarly, a number of apparent first-order dependencies are traced to the secondary-shell effects overlaid on zeroth-order dependencies.

$$-d[\text{RX}]/dt = \{k_0[\text{THF}]^0 + k_1[\text{THF}]^1 + k_2[\text{THF}]^2\} [\text{RX}][\text{A}_2\text{S}_4]^{1/2} \quad (3)$$



We attribute the most highly solvated monomers—the trisolvates—to fully open the transition structures and the disolvates to mechanisms accommodating the halogen–sodium contacts in the rate-limiting transition structures.^{1b} Density functional theory (DFT) calculations were carried out at the B3LYP/6-31G(d) level with single-point calculations at the MP2 level of theory.¹⁶ All allusions to transition structures are supported by computed transition structures manifesting a single negative frequency archived in the Supporting Information. The computations are used semiquantitatively to show that the proposed mechanism is plausible rather than to rigorously resolve nuanced mechanistic details. Energies are mentioned sparingly, especially when deviations from isodesmicity¹⁷ or charge separation would create severe energetic distortions owing to electron correlation problems.¹⁸

1-Bromooctane (1). Reaction of 1-bromooctane (0.010 M) with 1.2 equiv of NaDA in THF/hexane at -78°C affords 1-octene to the exclusion of *N*-(1-octyl)diisopropylamine in 85% yield by ¹H NMR spectroscopy relative to benzene as the internal standard (eq 7). Eliminations under pseudo-first-order



conditions, in which NaDA is maintained at synthetically standard concentrations (0.10–0.30 M) in THF/hexane, show clean exponential decays with no evidence of the curvature emblematic of autocatalysis.^{12b} The first-order dependence on 1-bromooctane is confirmed by the concentration-independent pseudo-first-order rate constants (k_{obsd}) versus [1] and by initial rates that linearly correlate with the initial concentrations of 1.^{12d} A plot of initial rates for the elimination of 1 versus NaDA concentration shows a half-order dependence (Figure 1), implicating a monomer-based metalation. A plot of the initial rates¹⁹ versus THF concentration using hexane as an inert cosolvent reveals an approximate second-order THF dependence (Figure 2, curve A). The data seemed to implicate tetrasolvated monomers (eq 6). However, plotting initial rates versus THF concentration using 2,5-Me₂THF as the inert cosolvent reveals an approximate first-order THF dependence (Figure 2, curve B). The rate data are thus consistent with the trisolvated monomer-based mechanism in eq 5.

The eliminations of isotopomers 1,1-*d*₂ (eq 8)²⁰ and 2,2-1-*d*₂ (eq 9)²⁰ implicate an E2 elimination without an intervening carbenoid. DFT computations show both anti- and syn-periplanar transition structures **8** and **9** to be viable, with **8** being >3 kcal/mol higher than **9**. (We routinely found the

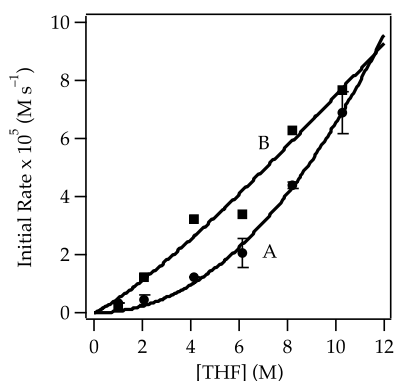
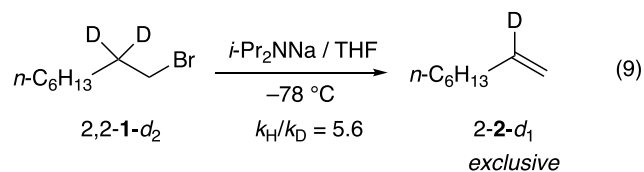
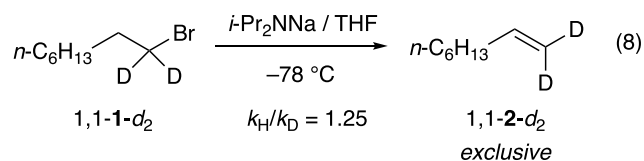
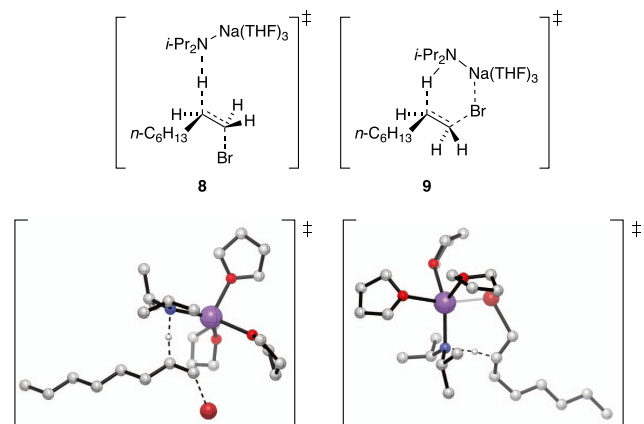


Figure 2. Plot of the initial rate^{19b} versus [THF] for the dehydrobromination of alkyl bromide **1** (0.050 M) with NaDA (0.10 M) at -78 °C in hexane (curve A) or 2,5-Me₂THF (curve B). The curves depict unweighted least-squares fits. Curve A: $y = k[\text{THF}]^n$; $k = (5.25 \pm 0.02) \times 10^{-5}$; $n = 2.09 \pm 0.16$. Curve B: $y = k'[\text{THF}]^n$; $k = (0.93 \pm 0.03) \times 10^{-4}$; $n = 1.18 \pm 0.17$.



computed carbene structures to be unusually stable.) The solvent order, when placed in the context of results from other eliminations described below, makes a strong case for **8**. Literature precedent supports such a hypothesis.¹



1-Chlorooctane (5). NaDA-mediated elimination of **5** proceeds smoothly at -20 °C in 89% NMR yield (eq 7). In contrast with 1-bromooctane, monitoring the reaction by ¹H NMR spectroscopy reveals a linear dependence of the initial rates on THF concentration with a substantial nonzero intercept (Figure 3, curve A). In conjunction with a half-order NaDA dependence (0.6 ± 0.1), the THF dependence would seem to suggest contributions of both di- and trisolvated monomers (eqs 4 and 5) to the exclusion of tetrasolvated monomer. Yet again, however, the solvent dependence is shown to be illusory: use of a

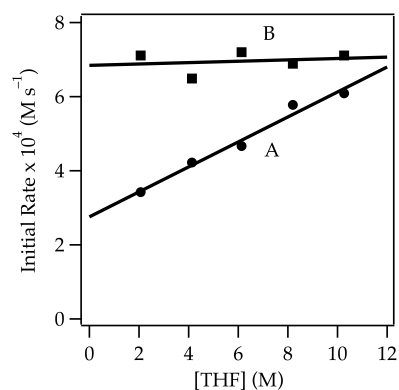
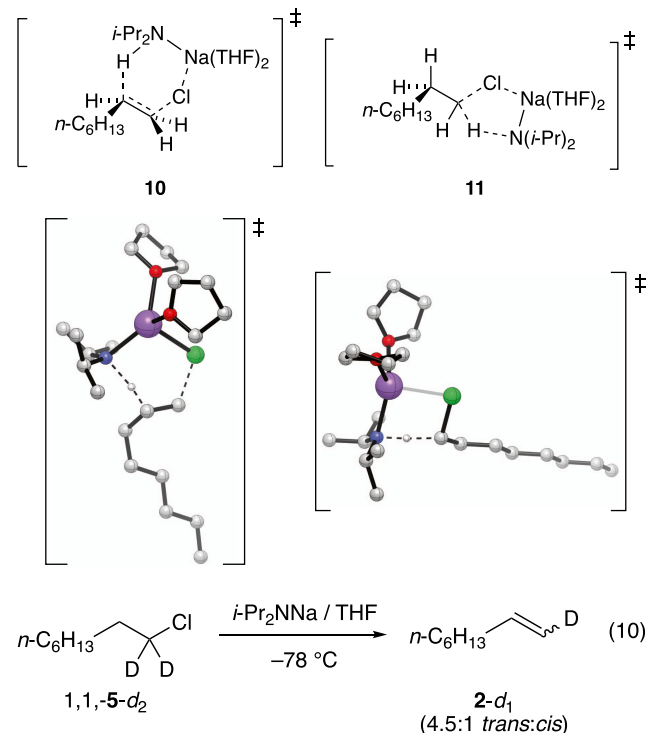


Figure 3. Plot of the initial rate^{19b} versus [THF] for the dehydrochlorination of 1-chlorooctane **5** (0.050 M) with NaDA (0.10 M) at -20 °C in hexane (curve A) or 2,5-THF (curve B). The curves depict unweighted least-squares fits to $y = k[\text{THF}] + k'$. Curve A: $k = (0.37 \pm 0.15) \times 10^{-4}$; $k' = (2.25 \pm 0.29) \times 10^{-5}$. Curve B: $k = (0.02 \pm 0.05) \times 10^{-4}$; $k' = (6.84 \pm 0.33) \times 10^{-5}$.

polar, noncoordinating cosolvent 2,5-Me₂THF in place of hexane reveals a zeroth-order dependence (Figure 3, curve B).

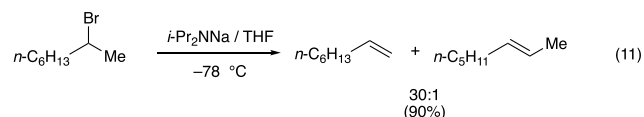
At first glance, the low solvation number appeared to implicate a syn-transition structure **10**, displaying distinct Na–Cl contacts as both plausible and computationally viable. Alkoxide-mediated eliminations in nonpolar (nonhydroxylic) solvents led other investigators to invoke M–X ion pairing.^{1b} However, elimination of 1,1-5-*d*₂ afforded a small but most likely primary isotope effect ($k_{\text{H}}/k_{\text{D}} = 2.5$) and an isotopic distribution (eq 10) consistent with a carbene-based mechanism via the transition structure **11**. Transition structure **11** is calculated to be >5 kcal/mol more stable than **10**.



1-Iodoctane. Reaction of **6** with NaDA in THF/hexane reveals only elimination (eq 7) but is too fast to be monitored conveniently at -78 °C.

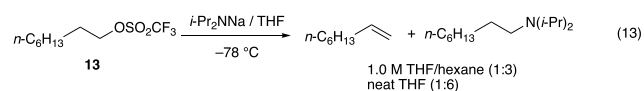
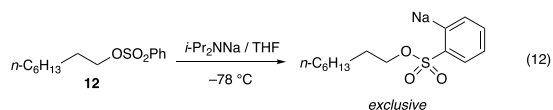
1-Fluorooctane. At 25 °C, the elimination of **7** (eq 7) is too slow to compete with THF decomposition.¹⁰ We will offer a solution to the problems posed by recalcitrant metalations and competing solvent decomposition in due course.

2-Bromooctane. Zaitsev's rule states that "the alkene formed in greatest amount is the one that corresponds to removal of the hydrogen from the β -carbon having the fewest hydrogen substituents."²¹ As a quick check of the veracity of this oft-taught rule, we examined the NaDA-mediated elimination of 2-bromooctane. As shown in eq 11, we observed 30:1 selectivity



for the terminal alkene; this is the highest reported regioselectivity.²² Removal of Zaitsev's rule as a centerpiece of our undergraduate curriculum seems overdue.

***n*-Octylsulfonate Esters.** A brief excursion to investigate *n*-octyl sulfonate esters revealed that NaDA/THF-mediated elimination or substitution of benzenesulfonate **12** is precluded by a dominant orthosodiation (eq 12), as confirmed by



quenching with D₂O. Although this pathway has not been reported for LDA, metalations of benzenesulfonate esters by *n*-BuLi are well documented.^{23,24} Treatment of triflate **13** with NaDA/THF at -78 °C provided a mixture of substitution and elimination products (eq 13).^{25,26} Although the absolute rates are too high to conveniently monitor, the relative proportions of substitution and elimination show THF dependence with a distinct nonzero intercept (Figure 4). The observed independence on the NaDA concentration, in conjunction with the dominance of monomer-based reactions for all NaDA/THF-mediated transformations, leaves little doubt that monomers are

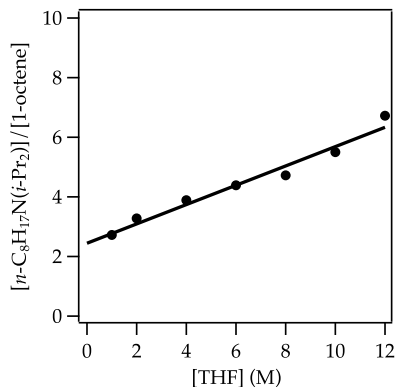
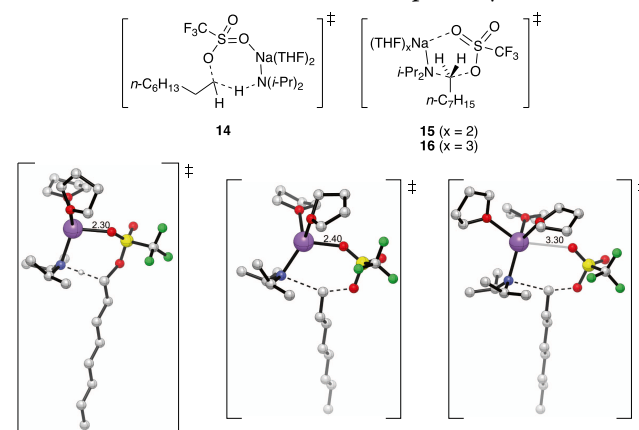
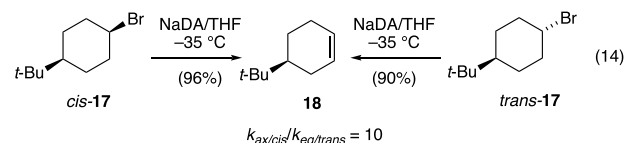


Figure 4. Plot of $[n\text{-C}_8\text{H}_{17}\text{N}(i\text{-Pr})_2]/[1\text{-octene}]$ versus $[\text{THF}]$ in hexane for the reaction of triflate **13** with 0.10 M NaDA at -78 °C (eq 13). The curve depicts an unweighted least-squares fit to the function $f(x) = k[\text{THF}] + k'$ ($k = 0.33 \pm 0.03$; $k' = 2.4 \pm 0.2$).

involved. Noting that sulfonates offer potential Na–X contacts in an S_N2 reaction²⁷ less easily attained with alkyl halides,²⁸ we offer computationally viable transition structures **14–16** as compatible with the THF-dependent selectivities. Computations predict the relative stabilities of 0, 2, and 4 kcal/mol for the transition structures **14**, **15**, and **16**, respectively.

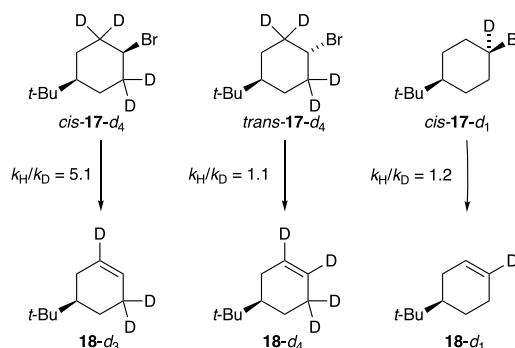


4-*tert*-Butylcyclohexyl bromides. Conformationally constrained cyclohexyl halides offer a pedagogically convenient means to underscore the importance of antiperiplanar (trans-diaxial) alignments in dehydrohalogenations.²⁹ Ironically, we know of only one example of the elimination of a 4-*tert*-butylcyclohexane derivative with adequate isotopic labeling to demonstrate trans-diaxial elimination,³⁰ and it was not a trivial analysis.³¹ Unexpectedly, NaDA/THF-mediated eliminations of both *cis*-**17** and *trans*-**17** afford 4-*tert*-butylcyclohexene (**18**, eq 14) in excellent yields with similar facilities ($k_{ax/cis}/k_{eq/trans} = 10$



in neat THF at -35 °C).³² Mono- and tetra-deuterated cyclohexyl bromides *cis*-**17**-*d*₄, *trans*-**17**-*d*₄, and *cis*-**17**-*d*₁ were used to interrogate the kinetic isotope effects and isotopic distributions (Scheme 1).³¹ Elimination of the *trans*-**17** isotopomers reveals geminal metalations to generate carbenoid intermediates,^{33,34} which are inserted into the proximate C–H(D) bonds. The *cis*-**17** substrates follow a more traditional script for E2 elimination.

Scheme 1. Isotope Effects and Isotope Distributions for NaDA/THF-Mediated Elimination of the Isomers of **17** at -50 °C



Axial isomer *cis*-17 follows a half-order NaDA dependence (0.58 ± 0.08) and a second-order THF dependence in hexane (Figure 5, curve A), which becomes a first-order dependence

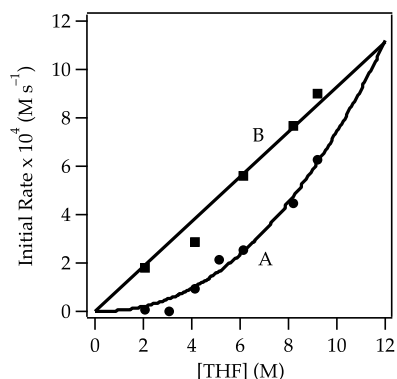
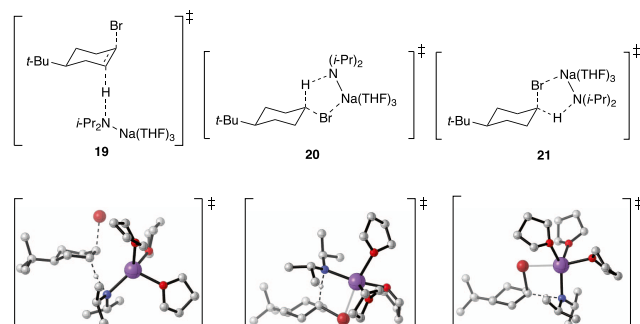


Figure 5. Plot of the initial rate^{19b} versus [THF] for the dehydrobromination of *cis*-17 (0.050 M) with NaDA (0.10 M) at $-50\text{ }^{\circ}\text{C}$ in hexane (curve A) or 2,5-Me₂THF (curve B). The curves depict unweighted least-squares fits. Curve A: $y = k[\text{THF}]^n$; $k = (3.23 \pm 0.01) \times 10^{-6}$; $n = 2.39 \pm 0.24$. Curve B: $y = k[\text{THF}]$; $k = (0.93 \pm 0.03) \times 10^{-4}$.

when 2,5-Me₂THF is used as the cosolvent (curve B).³⁵ Thus, the preferred path is via a trisolvated monomer-based transition structure 19.



trans-17, bearing an equatorially disposed bromide, shows a first-order THF dependence (Figure 6), which, in conjunction with a half-order NaDA dependence, is consistent with the

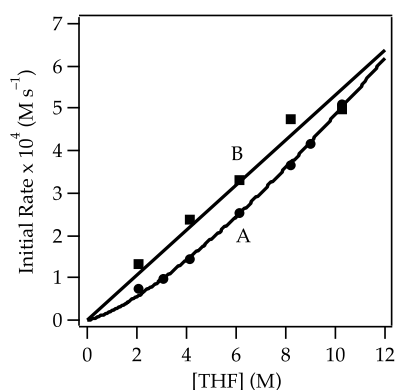
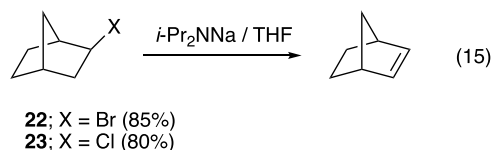


Figure 6. Plot of the initial rate^{19b} versus [THF] for the dehydrobromination of *trans*-17 (0.050 M) with NaDA (0.13 M) at $-25\text{ }^{\circ}\text{C}$ in hexane (curve A) or 2,5-dimethyltetrahydrofuran (curve B). The curves depict unweighted least-squares fits. Curve A: $y = k[\text{THF}]^n$; $k = (2.22 \pm 0.2) \times 10^{-5}$; $n = 1.34 \pm 0.04$. Curve B: $y = k[\text{THF}]$; $k = (0.53 \pm 0.02) \times 10^{-4}$.

trisolvated monomer-based elimination (eq 5). Transition structure 20 is computationally viable and consistent with the rate data and isotopic studies. One might wonder why the axial isomer *cis*-17 does not also show a carbenoid behavior, especially because the calculated activation barriers for 19 and 20 are 7 and 4 kcal/mol higher (respectively) than that of 21.

exo-2-Halonorbornanes. Elimination of 2-bromo- and 2-chloronorbornanes (22 and 23, eq 15) at -40 and $-20\text{ }^{\circ}\text{C}$



(respectively) shows nearly zeroth-order dependencies on THF even in hexane (Figure 7). This is consistent with syn

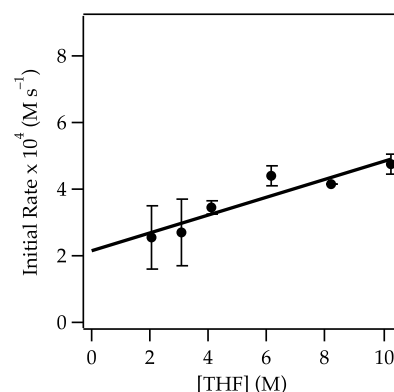
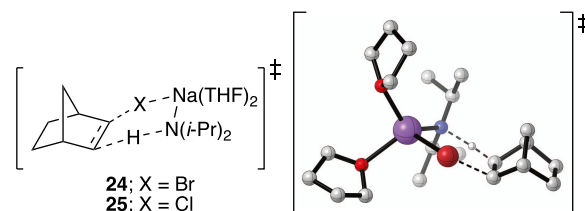


Figure 7. Plot of the initial rate^{19b} versus [THF] in hexane for the dehydrobromination of *exo*-2-bromonorbornane 22 (0.040 M) with NaDA (0.10 M) at $-40\text{ }^{\circ}\text{C}$. The curve depicts an unweighted least-squares fit to $y = k[\text{THF}] + k'$; $k = (2.6 \pm 0.5) \times 10^{-4}$; $k' = (2.2 \pm 0.3) \times 10^{-4}$.

elimination via the computationally viable transition structures 24 and 25.^{31,36,37}



1-Bromocyclooctene. Elimination of 26 to give cyclooctyne (27) necessarily proceeds syn (Scheme 2). Cyclooctyne is not stable under the reaction conditions, clearly isomerizing to cycloocta-1,2-diene (allene) 28 as a 2:1 mixture of symmetric and unsymmetric conformers, 28a and 28b, respectively (Figure 8). These conformers were decoalesced at $-110\text{ }^{\circ}\text{C}$ and characterized by a bevy of two-dimensional (2D-NMR spectroscopic methods (Supporting Information).³⁸ As noted previously,^{39–41} 28 self-condenses when warmed to ambient temperatures to give a complex mixture that includes dimer 29 and a trimer (likely the Diels–Alder adduct of 29 and cyclooctyne). An independently prepared sample of 27³¹ reacts with NaDA analogously.

Rate studies showed a rate-limiting dehydrohalogenation that necessarily proceeds via **27** rather than directly to allene **28**.

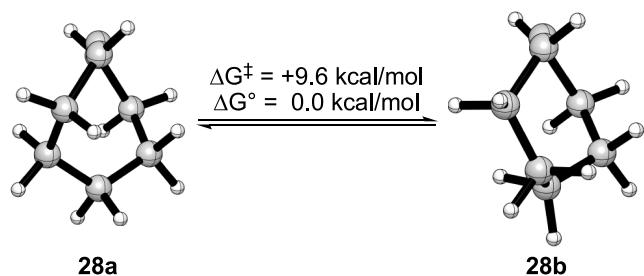


Figure 8. Symmetric and unsymmetric conformers of cycloocta-1,2-diene (**28a** and **28b**, respectively).

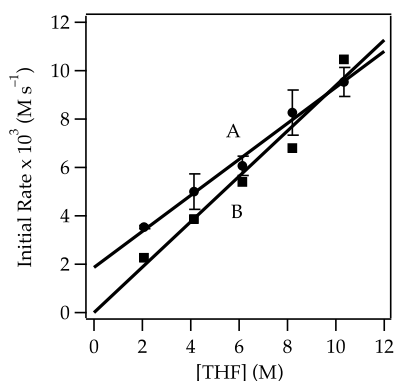
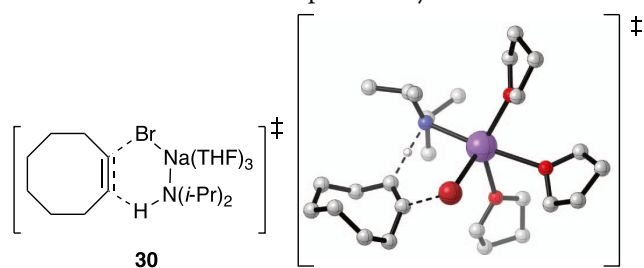


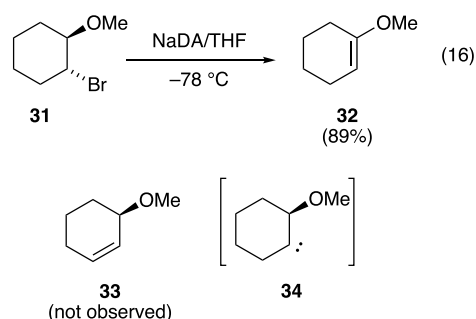
Figure 9. Plot of the initial rate versus [THF] for the dehydrobromination of 1-bromocyclooctene **26** (0.050 M) with NaDA (0.10 M) at -50 °C in (A) hexane and (B) 2,5-Me₂THF. The curve depicts an unweighted least-squares fits. Curve A: $y = k[\text{THF}] + k'$; $k = (0.74 \pm 0.05) \times 10^{-3}$; $k' = (1.90 \pm 0.05) \times 10^{-3}$. Curve B: $y = k[\text{THF}]$; $k = (0.89 \pm 0.12) \times 10^{-3}$; $k' = (2.61 \pm 0.003) \times 10^{-5}$.

Specifically, comparing **26** with **26-d₁**³¹ affords $k_{\text{H}}/k_{\text{D}} = 10$. A linear THF dependence (Figure 9) in conjunction with a half-order dependence on NaDA (0.50 ± 0.07) are consistent with the generic mechanisms depicted in eqs 4 and 5. (The nonzero intercept is relatively minor.) The trisolvated-monomer-based transition structure **30** is computationally viable.

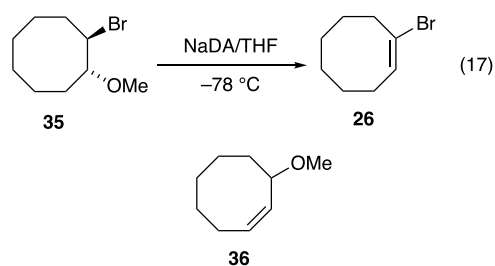


trans-1-Bromo-2-methoxycyclohexane (**31**).^{42,43} Reaction of **31** (eq 16) cleanly affords the enol ether **32** to the exclusion of allylic ether **33** (>20:1).⁴⁴ This result contrasts with a reported *t*-BuOK-mediated elimination to give **33**.⁴⁵ Although it may be tempting to invoke a syn elimination, carbene **34** seems more plausible and has been shown to insert into the C–H bond geminal to the alkoxy moiety with high fidelity.⁴⁶

trans-1-Bromo-2-methoxycyclooctane (**35**). Dehydrohalogenation of **35** by *t*-BuOK/18-crown-6 is reported to give allylic ether **36**,⁴³ while NaNH₂-mediated dehydrohalogenation yields **29** via the transiently stable cycloocta-1,2-diene (allene **28**).⁴¹ These reports prompted us to examine the reactivity of NaDA/



THF with **35**. Treatment of **35** with excess NaDA/THF at -78 °C afforded, upon workup, dimer **29** along with other forms (see Scheme 2). Using only 0.80 equiv of NaDA to minimize allene **28** formation, we obtained 1-bromocyclooctene (**26**) in 62% isolated yield (eq 17). This unusual preferential elimination of the methoxy moiety has meager literature support.^{47–49}



2-Phenyl-2-methoxy-1-bromoethane (37). Reaction of **37** with NaDA/THF was anticipated to provide enol ether **40** given the considerable acidity of the benzylic proton; however, phenylacetylene was formed instead (Scheme 3).⁵⁰ Observation of vinyl bromide **39** at partial conversion, along with the failure of an independently prepared sample of enol ether **40** to give phenylacetylene under the reaction conditions, supports the mechanism as drawn.

CONCLUSIONS

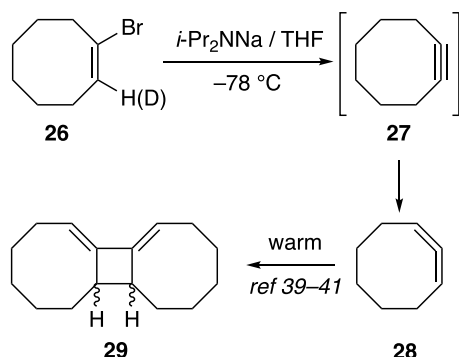
Eliminations of a range of alkyl halides by NaDA in THF/hexane are facile and efficient. The dominance of monomer-based eliminations is a theme that continues from previous studies of NaDA-mediated metalations.^{8,11} The absence of competing S_N2 substitution contrasts with the analogous reaction of 1-bromooctane with LDA/THF in which substitution and elimination pathways compete. The facile elimination of an equatorially disposed cyclohexyl bromide via a carbenoid-based pathway is also notable.^{33,34}

Previous discussions of solvent effects on base-mediated eliminations are couched using the language of ion pairing.^{1b} There is only limited attention to the role of aggregation,³ and solvation is described as bulk properties rather than as molecular phenomena. We trace rate changes to differential solvation numbers that affiliate with the absence or presence of Na–X contacts in the rate-limiting transition structures. The computed disolvated transition structures show Na–X contacts, whereas the trisolvates are more variable. Overlaid on the primary-shell solvation reside sterically insensitive, secondary-shell effects that can be teased out using 2,5-Me₂THF as a polar surrogate for hexane. Although the influences of these secondary-shell polarity effects on reaction rates seem small, the influence on the interpretation of the rate laws and mechanisms is far more consequential. Two important points are that (1) macroscopic

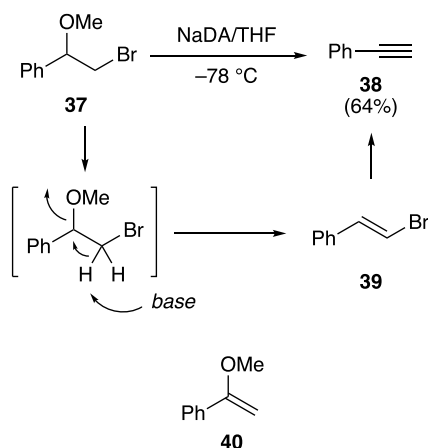
solvation effects can be described in terms of separate contributions of primary and secondary shells, and (2) secondary-shell effects seem moderately more pronounced for NaDA than for LDA.

The ease of synthesis, physical properties, and reactivities of NaDA continue to support our assertion that NaDA is a long-

Scheme 2. Formation of Cycloocta-1,2-diene



Scheme 3. Elimination of Vicinal Haloether 37 to Form Acetylene 38



overlooked base of considerable potential utility. We hope that our studies of structure–reactivity relationships will prompt practitioners to consider NaDA as more than just hyperreactive LDA. The one notable limitation described herein—the failure to eliminate *n*-alkyl fluorides on the timescales of THF decomposition—reminds us that efforts to exploit the high reactivity of NaDA will be capped by the lability of ethereal solvents. An altogether different class of ligand will be needed to maximize reactivity without eliciting decomposition. Stated more broadly, organosodium chemistry may require more than just the ligands that have served organolithium chemistry well.

EXPERIMENTAL SECTION

Reagents and Solvents. THF and hexane were distilled from blue or purple solutions containing sodium benzophenone ketyl. NaDA was prepared from sodium dispersion in *N,N*-dimethylethylamine (DMEA) using a modified⁴ procedure first reported by Wakefield and recrystallized from DMEA/hexane.⁵¹ Solutions of NaDA can be titrated using a literature method.⁵²

NMR Spectroscopic Analyses. An NMR tube under vacuum was flame-dried on a Schlenk line, allowed to cool to room temperature, backfilled with argon, placed in a $-78\text{ }^{\circ}\text{C}$ dry ice/acetone bath, and charged with NaDA and solvents using stock solutions. Substrates were

added in THF-*d*₈ or THF-*d*₈/cosolvent mixtures via a syringe. The tube was vortexed two times on a vortex mixer for 5 s with cooling between vortexing. Standard ¹H NMR spectra were recorded on a 500 MHz spectrometer. The resonances are referenced to residual THF resonances at 1.73 and 3.58 ppm for ¹H and 67.57 and 25.37 ppm for ¹³C. The concentrations of the starting material were referenced to an internal benzene standard (7.27 ppm). Spectra were recorded with a scan rate that varies depending on the rate of reaction.

Elimination of *cis*-17. To a stirred solution of NaDA (80.0 mg, 0.65 mmol) in dry THF (10 mL) under argon atmosphere at $-78\text{ }^{\circ}\text{C}$ was added *cis*-1-bromo-4-(*tert*-butyl)cyclohexane (*cis*-17, 110 mg, 0.50 mmol) in THF (1.0 mL). The reaction mixture was stirred for 1.5 h, quenched by the addition of saturated NH₄Cl solution (1.0 mL), and extracted with Et₂O (2 × 10 mL). The organic layer was washed with brine (10 mL) and dried over Na₂SO₄. Evaporation of the solvent, followed by flash chromatography of the resulting crude residue using neat hexane as an eluent, afforded 18 (66.4 mg, 96% yield).

Cycloocta-1,2-diene (28a). Allene 28a, contaminated by 20% of a minor conformer 28b, was prepared most cleanly from cyclooctyne using the general procedure for NMR spectroscopic analysis using 0.25 equiv of NaDA in neat THF-*d*₈. The NMR spectroscopic data recorded at $-110\text{ }^{\circ}\text{C}$ for the major isomer, 28a, is as follows: ¹H NMR (500 MHz, THF-*d*₈): δ 5.3 (m, 1H), 5.11 (t, *J* = 6.1 Hz, 1H), 2.29 (dd, *J* = 20.2 Hz, 14.4 Hz, 1H); 2.01 (dd, *J* = 10.0, 8.0 Hz, 1H), 1.91–1.95 (m, 2H), 1.78–1.84 (m, 3H), 1.33 (q, *J* = 14.5 Hz, 1H), 1.29 (t, *J* = 16.2 Hz, 1H), 0.84 (t, *J* = 16.2 Hz, 1H). ¹³C NMR (73.57 MHz, THF-*d*₈): δ: 208.6, 95.1, 90.5, 33.4, 31.6, 30.1, 29.1, and 27.4. Note: the multiplicities were derived from 2D ¹H/¹³C HSQC experiments and represent approximate multiplet structure. *J* values smaller than 6 Hz could not be resolved.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b01428.

NMR spectroscopic studies; ¹H NMR spectrum of 1-bromooctane; partial ¹H NMR spectrum of 1-octene (2) in THF-*d*; spectroscopic rate; and computational data (PDF)

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Notes

The authors declare no competing financial interest.

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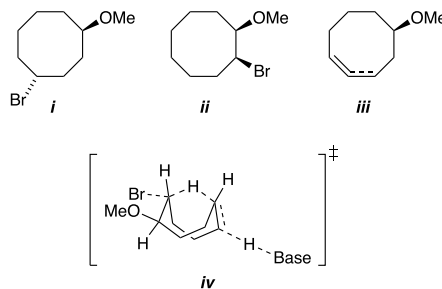
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(45) For a *t*-BuOK-mediated elimination of vicinal alkoxy halides analogous to **29** to give allylic ethers, see: Dulcère, J.-P.; Rodriguez, J. Cohalogenation of Alkenes in Ethylene Oxide: Efficient Methodology for the Preparation of Allyl Vinyl Ether Precursors of γ,δ -Unsaturated Aldehydes. *Synthesis* **1993**, 1993, 399.

(46) (a) Mohamadi, F.; Collum, D. B. Conversion of Ketones to Trisubstituted Olefins Under Neutral Conditions. *Tetrahedron Lett.* **1984**, 25, 271. (b) Xiao, F.; Zhang, Z.; Zhang, J.; Wang, J. Reaction of β -Trimethylsilyloxy α -Diazocarbonyl Compounds with Trimethylsilyl Halides: A Novel Diazo Decomposition Process. *Tetrahedron Lett.* **2005**, 46, 8873. (c) Aggarwal, V. K.; Sheldon, C. G.; Macdonald, G. J.; Martin, W. P. A New Method for the Preparation of Silyl Enol Ethers from Carbonyl Compounds and (Trimethylsilyl)diazomethane in a Regiospecific and Highly Stereoselective Manner. *J. Am. Chem. Soc.* **2002**, 124, 10300. (d) Yoon, C. H.; Zaworotko, M. J.; Moulton, B.; Jung, K. W. Regio- and Stereocontrol Elements in Rh(II)-Catalyzed Intramolecular C–H Insertion of α -Diazo- α -(phenylsulfonyl)-acetamides. *Org. Lett.* **2001**, 3, 3539.

(47) Examples of base-mediated elimination of enol ethers to form allenes: (a) Lyapkalo, I. M.; Webel, M.; Reißig, H. U. Synthesis and Heck Reactions of Ethenyl- and (*Z*)-Butadien-1-yl Nonaflate Obtained by the Fragmentation of Furan Derivatives. *Eur. J. Org. Chem.* **2001**, 4189. (b) Harmata, M.; Gamlath, C. B. Intramolecular 4 + 3 Cycloadditions of 2-Alkoxyallylic Cations Derived from 2-Alkoxyallylic Sulfones. *J. Org. Chem.* **1988**, 53, 6154.

(48) As a humorous aside, **35** was contaminated with significant concentrations of *trans*-4-bromo-1-methoxycyclooctane (*i*); see ref **38**. Thinking we had isolated the *cis*-1-bromo-2-methoxycyclooctane (*ii*)—these things happen—we proceeded to dehydrohalogenate it to give cyclooctenes *iii*. Inspired by numerous transannular effects of cyclooctanes (see ref **49**), with help from a colleague we concocted a homodehydrobromination via transition structure *iv*. Although fictional, *iv* is also computationally viable.



(49) Cope, A. C.; Lee, H. H.; Petree, H. E. Proximity Effects. XII. Reaction of *cis*- and *trans*-Cyclooctene Oxide with Bases. *J. Am. Chem. Soc.* **1958**, *80*, 2849.

(50) Elimination of halo ethers to acetylenes is facile with NaNH_2 :
(a) Matovic, N.; Matthias, A.; Gertsch, J.; Raduner, S.; Bone, K. M.; Lehmann, R. P.; DeVoss, J. J. Stereoselective Synthesis, Natural Occurrence and CB2 Receptor Binding Affinities of Alkylamides from Herbal Medicines Such as Echinacea sp. *Org. Biomol. Chem.* **2007**, *5*, 169. (b) Kikuchi, K.; Tatewaki, Y.; Okada, S. Synthesis and Solid-State Polymerization of a Macrocyclic Compound with Two Butadiyne Units. *Bull. Chem. Soc. Jpn.* **2017**, *90*, 387.

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