systems by showing defined stoichiometry, specificity, cooperative effects, heat capacity changes upon binding, and enthalpy–entropy compensation phenomena. Our present study with a congener series of carboxylic acid guests, having variable-size, roughly spherical, alicyclic groups, reveals the importance of both the hydrophobic effect and van der Waals forces in determining the affinity of the CD for the guest.

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# Structure and Reactivity of Lithium Diisopropylamide (LDA). The Consequences of Aggregation and Solvation during the Metalation of an *N,N*-Dimethylhydrazone

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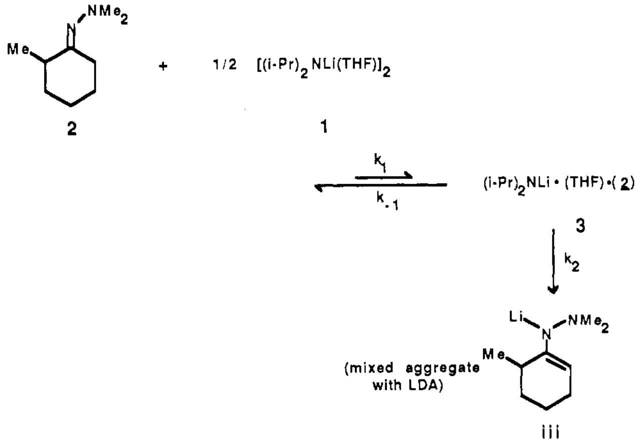
**Abstract:** $^6$Li and $^{15}$N NMR spectroscopic studies of $^6$Li-labeled and $^6$Li,$^{15}$N-doubly-labeled lithium diisopropylamide (LDA) are consistent with a disolvated dimer. Revision of a reported monomer–dimer equilibrium is suggested. Rate studies on the lithiation of 2-methylcyclohexanone *N,N*-dimethylhydrazone (**2**) provide a rate expression of the form $-d[\mathbf{2}]/dt = k[\mathbf{2}][\mathrm{LDA}]^{1/2}[\mathrm{THF}]^0$ and are interpreted in the context of a model involving the following: (1) spectroscopically invisible dissociation of disolvated LDA dimer to an LDA monomer bearing a single ethereal ligand and a complexed hydrazone ligand, followed by (2) rate-determining proton transfer. While the measured lithiation rate is insensitive to the free donor solvent concentration (i.e., [THF]), the nature of the ligands on the solvated LDA dimer in its ground state has a marked effect on the overall reaction rate.

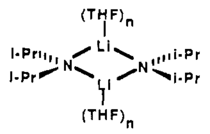
Lithium diisopropylamide (LDA) was first prepared by Hammell and Levine at the University of Pittsburgh in 1950.[1] It remained in relative obscurity[2] until 1967 when a report by Creger highlighted the advantages of LDA as a highly reactive base[3] and sent it on a meteoric rise to become one of the most prominent reagents in organic chemistry.[4] As information on the reactivity and selectivity of LDA accumulated, supportive mechanistic details fell into place far more slowly. Important rate studies of LDA-mediated metalations emanating from the laboratories of Newcomb,[5] Rathke,[6] Saunders,[7] Fraser,[8] Ahlbrecht,[9] and Rickborn[12] have unravelled some of the key parameters affecting LDA reactivity.[10,11] However, in no instance have the roles of solvation and aggregation been elucidated in any detail.[12]

The limitations of our understanding of the chemistry of LDA stem, at least in part, from a shortage of structural information.

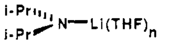
**Scheme I**



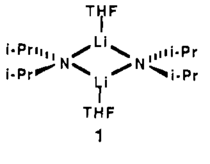
It was only in 1984 that Seebach and Bauer provided the first potentially useable structural data.[13] Through colligative measurements, they concluded that 0.05–0.10 molar solutions of LDA in tetrahydrofuran (THF) at −108 °C contain appreciable concentrations of both dimeric and monomeric forms i and ii, respectively. In 1989, Williard and Salvino revealed by an X-ray crystallographic analysis that LDA crystallizes as disolvated dimer **1** from THF/hydrocarbon mixtures.[14]



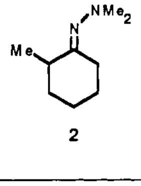
i



ii



1



2

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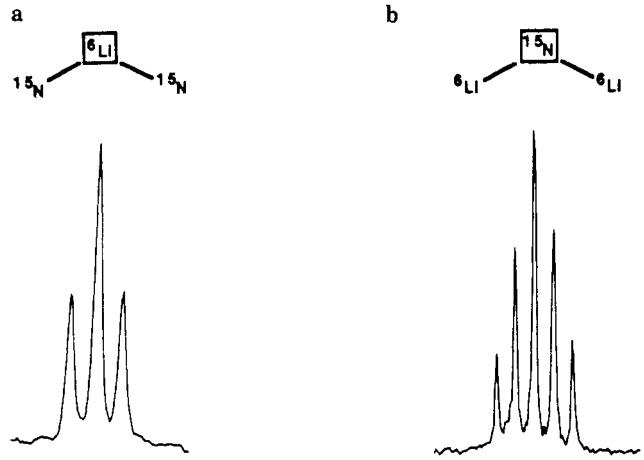


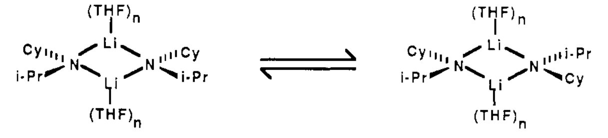
**Figure 1.** $^6$Li and $^{15}$N NMR spectra recorded at −90 °C of toluene-$d_8$ solutions of [$^6$Li$^{15}$N]LDA: (A) $^6$Li NMR spectrum, 0.016 M, 11.0 M THF; (B) $^{15}$N NMR spectrum, 0.098 M, 10.5 M THF. The chemical shifts (see text) are referenced to external standards.

We describe herein $^6$Li and $^{15}$N NMR spectroscopic studies of LDA in solution along with rate studies of the metalation of *N*,*N*-dimethylhydrazone **2**. Our observations and conclusions are placed in the context of the model depicted in Scheme I and include the following: (1) The only spectroscopically observable form of LDA over a wide range of concentrations in THF solution is an aggregate suggested to be disolvated dimer **1**. (2) The lithiation of hydrazone **2** proceeds via dissociation to spectroscopically unobservable monomeric complex **3** without the intervention of additional donor solvent. (3) Despite the independence of the rate on the free donor solvent concentration, the lithiation of **2** is markedly affected by the structures of the ancillary ligands on the LDA dimer in its ground state. Highest metalation rates are observed at very low THF concentrations using hindered 2,5-dimethyltetrahydrofuran (Me$_2$THF) as cosolvent. (4) The mechanistic observations and conclusions described apply to a single case history and should be placed in the context of anecdotal results from other LDA-mediated metalations using extreme caution.

## Results

**Solution Structure of LDA in THF.** We investigated the solution structure of LDA using $^6$Li and $^{15}$N NMR spectroscopy on [$^6$Li,$^{15}$N]LDA. $^6$Li and $^{15}$N NMR spectra (Figure 1) show single resonances ($^6$Li, $\delta$ 1.86 ppm, $^1J_{\text{Li-N}} = 5.1$ Hz; $^{15}$N, $\delta$ 75.2 ppm, $^1J_{\text{Li-N}} = 5.0$ Hz) displaying multiplicities consistent with a cyclic aggregate rather than monomer structure.[15,16] While intermolecular exchange processes cause loss of coupling at elevated temperatures, the triplet is discernible in the $^6$Li NMR spectrum up to 0 °C.

We assign the structure of the aggregated form of LDA as disolvated dimer **1** based on several lines of evidence. Cyclic trimeric and tetrameric lithium amides have been observed on three occasions but only in the absence of donor solvents (viz. [(PhCH$_2$)$_2$NLi]$_3$,[17] [(Me$_3$Si)$_2$NLi]$_3$,[18] and [lithium tetramethylpiperidide]$_4$).[19] In contrast, the corresponding etherates of (PhCH$_2$)$_2$NLi[17] and (Me$_3$Si)$_2$NLi[18,19] crystallize as disolvated dimers. Recently completed studies of the solution structure of lithium isopropylcyclohexylamide (LICA)[15d] showed the only observable structures in solution to be stereoisomeric dimers *cis*-**4** and *trans*-**4**; stereochemistry and symmetry of aggregation played a central role in the dimer assignment. Ab initio calculations have uncovered a strong preference of solvated lithium amides to form cyclic dimers.[20] The almost completely invariant (±0.03 ppm) $^6$Li chemical shift found for LDA in THF/toluene-$d_8$ mixtures of varying compositions argues in favor of the static solvation state of the LDA dimer. The zero-order THF dependence found for the lithiation of **2** further supports such a suggestion (vide infra). Assignment as a disolvate derives from analogy with solid-state structures[21] (including LDA dimer **1**)[14] as well as from solution solvation-state determinations of related N-lithiated species.[15b,e,22]



cis-4 trans-4

In light of the conclusion of Seebach and Bauer that solutions of LDA contain appreciable concentrations (up to 80%) of monomer **ii**, we took special precautions to reproduce the conditions of their freezing-point depression measurements as precisely as possible during the spectroscopic analysis. Hydrocarbon solvents were excluded by preparing a solution of [$^6$Li,$^{15}$N]LDA in THF containing 8% (v/v) toluene-$d_8$, evacuating to dryness, and adding neat THF-$d_8$. Spectra were recorded at −106 °C to avoid the sample freezing that occurs at −108 °C. Since the increased temperature should decrease the monomer concentration (albeit slightly) due to the negative entropy of solvation,[23] spectra were recorded on samples 3-fold more dilute (0.016 M) than the most

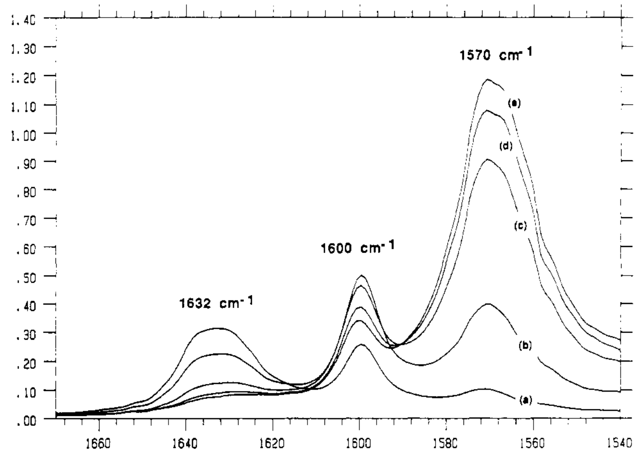


**Figure 2.** FT-IR spectroscopic analysis of the lithiation of hydrazone **2** (0.10 M) by LDA (0.10 M) in neat THF at 20.0 ± 0.3 °C. The curves correspond to (a) 0.75 min, (b) 5.0 min, (c) 20.0 min, (d) 40 min, and (e) 65 min. Base line variation between measurements precluded observation of discrete isosbestic points.

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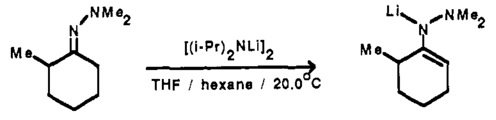
dilute samples monitored in the colligative measurements. In the event, we observed only the resonances and couplings characteristic of the dimeric form of LDA by $^6$Li and $^{15}$N NMR spectroscopies. Thus, we suggest that the measured LDA molalities implicating substantial concentrations of monomer may have arisen from an impurity or other artifact.

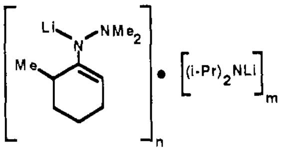
***N*,*N*-Dimethylhydrazone Metalation: Mixed Aggregate Formation.** To initiate investigations of the reactivity of LDA, we sought a substrate that would lithiate at convenient reaction times and temperatures. The slow, yet virtually quantitative metalations of *N*,*N*-dimethylhydrazones seemed to be ideally suited. We ultimately settled upon the lithiation of 2-methylcyclohexanone *N*,*N*-dimethylhydrazone (**2**)[24] illustrated in eq 1.



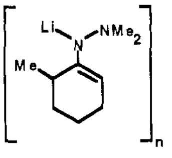
2

(1)

Fourier transform infrared (FT-IR) spectroscopic analysis of the lithiation of **2** under bimolecular conditions (0.10 M **2**; 0.10 M LDA; neat THF) shows that the very weak absorbance corresponding to **2** (1632 cm$^{-1}$) is slowly replaced by absorbances at 1600 and 1570 cm$^{-1}$ at partial conversion (Figure 2). As the reaction approaches full conversion and the LDA is consumed, the absorbance at 1600 cm$^{-1}$ disappears, and the absorbance at 1570 cm$^{-1}$ asymptotically approaches a maximum intensity. The absorbances at 1600 and 1570 cm$^{-1}$ are assigned to an LDA/lithiated hydrazone mixed-aggregate **iii** and lithiated hydrazone homonuclear aggregate **iv**, respectively.[25] Addition of THF solutions of LDA to solutions of **iv** causes the absorbance corresponding to **iii** to reappear. At high LDA/lithiated hydrazone proportions, mixed-aggregate **iii** is the only observable form. By maintaining the LDA and lithiated hydrazone concentrations constant while varying the proportion of THF in THF/hexane mixtures, **iii** was found to be favored at increasing THF concentrations.



iii



iv

The mixed-aggregate **iii** may be similar to that suggested by Denmark and co-workers in the context of some hydrazone alkylation studies.[26] Unfortunately, all efforts to characterize further either **iii** or the homonuclear aggregate **iv** were completely thwarted by the poor spectroscopic properties of lithiated hydrazones at low temperatures.[27,28] Most importantly, $^6$Li NMR spectra of the mixed aggregate comprised of either [$^6$Li]LDA or [$^6$Li,$^{15}$N]LDA display broad, featureless mounds. Carbon-13 spectra are equally uninformative.

***N*,*N*-Dimethylhydrazone Metalation: Kinetics.** The rate expression for the metalation of **2** was investigated under pseudo-first-order conditions while maintaining relatively normal LDA concentrations (0.1–0.2 M) by reducing the concentration of hydrazone **2** to 0.004 M. At these concentrations, the mixed-aggregate **iii** is the major or exclusive product, depending on the THF concentration. The THF was maintained at high yet adjustable concentrations (0.26–12.28 M) using cosolvents hexane and Me$_2$THF. The metalations were run in a thermostatted bath at 20.0 ± 0.3 °C and monitored by FT-IR using a continuous flow system designed to minimize temperature fluctuations (see Experimental Section). Through serial dilution experiments, the absorbance of mixed-aggregate **iii** was shown to be proportional to the concentration in accordance with Beer's law.[29] All rate constants and reaction orders were determined by using nonlinear least-squares analyses as described in the Experimental Section.

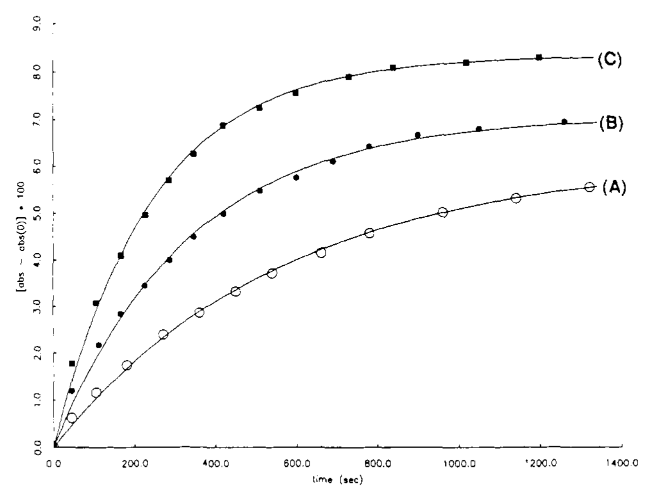


**Figure 3.** Representative raw data sets for the lithiation of hydrazone **2** (0.004 M) by LDA in neat THF at 20.0 ± 0.3 °C. The nonlinear least-squares fits are derived from the general expression $\mathrm{abs} - \mathrm{abs}_0 = (\mathrm{abs}_\infty - \mathrm{abs}_0)(1 - e^{-kt})$. The curves correspond to the following initial LDA concentrations: (A) 0.08 M, (B) 0.13 M, and (C) 0.24 M.

The source of the LDA proved not to be a critical variable. Kinetic runs using (1) LDA generated in situ from commercial *n*-butyllithium (Aldrich), (2) LDA generated in situ from recrystallized, doubly sublimed ethyllithium,[30] or (3) solid LDA precipitated from hexane using commercial *n*-butyllithium,[31] all generated reproducible and indistinguishable data sets in numerous comparisons. The rate studies were carried out using solid LDA precipitated and recrystallized from hexane.

No evidence for a spectroscopically observable LDA–hydrazone complexation prior to metalation could be gleaned from IR and NMR spectroscopic probes.[32] The relatively weak absorbance of **2** at 1632 cm$^{-1}$ is not measurably different in the presence or absence of LDA nor are any new absorbances apparent. Solid solvent-free LDA suspended in hexane is not visibly dissolved (and thus not highly solvated) by hydrazone **2**. The $^{13}$C chemical shifts corresponding to hydrazone **2** and the $^6$Li NMR resonance of LDA are not measurably altered in mixtures of varying proportions of **2** and LDA monitored prior to metalation.

When both the LDA and THF concentrations are high, an absorbance at 1612 cm$^{-1}$ appears in the later (>3) half-lives and continues to increase in intensity linearly as a function of time. Since it appears at approximately the same rate in LDA/THF solutions devoid of hydrazone substrate, we assign it to acet-

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(25) While the lithium salts derived from **2** and from cyclohexanone *N*,*N*-dimethylhydrazone crystallize as polymers, a commercial osmometric molecular weight determination on the latter indicates a trimer or tetramer in THF solution. Collum, D. B.; Kahne, D.; Gut, S. A.; DePue, R. T.; Mohamadi, F.; Wanat, R. A.; Clardy, J. C.; Van Duyne, G. *J. Am. Chem. Soc.* **1985**, *106*, 4865.

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(28) For a review of the NMR spectroscopy of lithiated hydrazones and related metalloimines, see: Fraser, R. R. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1980.

(29) We do note, however, that the absorbance of the mixed aggregate **iii** exhibits a modest dependence on the pseudo-first-order concentrations of LDA as indicated by calculated values of $A_\infty$ (cf. Figure 2). This does *not* appear to derive from cancelling changes in the concentration of homonuclear aggregate **iv**.

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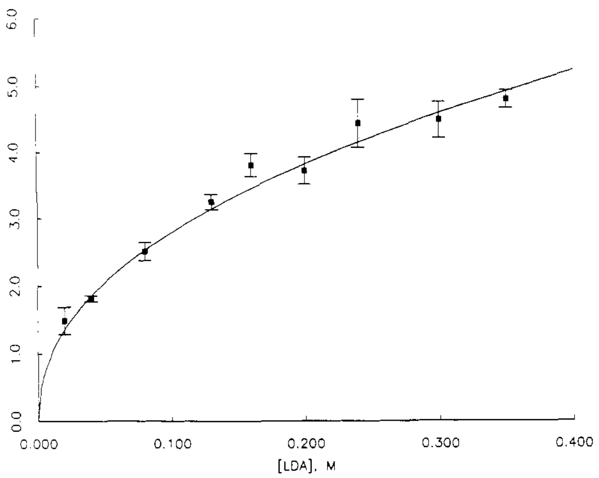
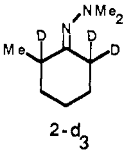


**Figure 4.** Plot of $k_{obsd}$ versus [LDA] for the lithiation of hydrazone **2** (0.004 M) in neat THF at 20.0 ± 0.3 °C. The solid line represents a weighted, nonlinear least-squares fit to the expression in eq 2. The calculated adjustable parameters are as follows: $k' = 7.88 \pm 0.12 \times 10^{-3}$ $s^{-1}$, $n = 0.45 \pm 0.01$. The error bars correspond to ± one standard deviation ($\sigma$) in triplicate runs. The points are weighted to $1/\sigma^2$.

aldehyde enolate derived from THF decomposition.[33] A similar absorbance at 1639 $cm^{-1}$ is observed in LDA/$Me_2$THF solutions at extended reaction times.[34] In neither instance does the solvent-derived absorbance cause serious difficulties.

**Dependence of Rate on Hydrazone Concentration and Kinetic Isotope Effects.** The lithiation of **2** by LDA is first order in hydrazone; several representative raw data sets are depicted in Figure 3. The cleavage of the C–H bond of **2** is found to be rate-determining through a comparison of the rate of metalation of **2** with **2**-$d_3$[35] ($k_H/k_D = 6.4 \pm 0.6$).



**2-$d_3$**

Although the concentration of the mixed-aggregate **iii** is always 10–100 times lower than the LDA concentration even at full conversion, it could still affect the measured rate constants if this complexed form of LDA is inordinately reactive. If so, the rate would accelerate anomalously as the concentration of **iii** increases throughout the course of the reaction.[26,36] Very simple experiments excluded this possibility. On more than a dozen occasions, at the completion of a kinetic run the base line of the FT-IR was zeroed, a second aliquot of hydrazone **2** was injected into the reaction mixture, and rate data were acquired. In all cases, the measured rate constants of the two sequential runs deviated by only a few percent.

**Dependence of Rate on LDA Concentration.** Figure 4 illustrates the dependence of the pseudo-first-order rate constants on the LDA concentration over the range 0.02–0.35 M. From a fit to the general expression in eq 2, the calculated LDA order, *n*, is shown to be 0.45 ± 0.01.[37]

$$k_{obsd} = k'[\mathrm{LDA}]^n \qquad (2)$$

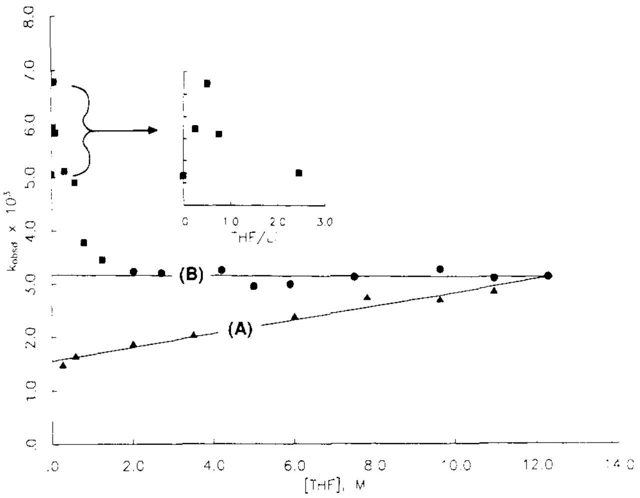


**Figure 5.** Plot of $k_{obsd}$ versus [THF] for the lithiation of hydrazone **2** (0.004 M) at 20.0 ± 0.3 °C in hexane (curve A) and $Me_2$THF (curve B) cosolvents. The solid lines represent linear least-squares fits to the expression in eq 3 (including only the solid circles for curve B). The datum recorded at 0.26 M THF in hexane corresponds to a hydrazone concentration of 0.002 M. Calculated adjustable parameters are listed in ref 38.

**Dependence of Rate on THF Concentration.** A plot of $k_{obsd}$ vs [THF] using hexane as the inert cosolvent (Figure 5, curve A) displays a linearity[38] and nonzero *y*-intercept consistent with the following mathematical form

$$k_{obsd} = k' + k''[\mathrm{THF}] \qquad (3)$$

The substantial nonzero *y*-intercept (corresponding to $k'$) is fully consistent with a THF concentration-independent metalation pathway. However, we were not convinced that the THF-dependent term originated from primary solvation. Since the dielectric constant of THF/hydrocarbon mixtures increases linearly as a function of percent composition of THF,[39] the approximate 2-fold increase in rate in neat THF relative to neat hexane could arise from long range, ill-defined secondary solvation which one might call "dielectric effects".

The influence of the dielectric properties of the medium was investigated using 2,5-dimethyltetrahydrofuran ($Me_2$THF) as the cosolvent. The steric hindrance about the oxygen of $Me_2$THF decreases its donicity toward lithium ion in alkyllithiums by as much as a factor of 200 relative to THF,[40] while reducing its bulk dielectric constant very little relative to THF.[41] The results are shown in curve B of Figure 5. Clearly, when the bulk dielectric properties of the medium are held constant, the metalation rate is independent of the THF concentration (zero-order) between 2.0–12.3 M.[42]

Substantial positive deviations in the rate constants are observed when the THF concentrations are reduced well below the pseu-

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[33] Bates, R. B.; Kroposki, L. M.; Potter, D. E. *J. Org. Chem.* **1970**, *37*, 560.

[34] Maercker, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 972.

[35] Peet, P. N. *J. Label. Compounds* **1973**, *9*, 721.

[36] DePue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5524.

[37] The rate of lithiation of **2** can also be monitored by (1) thermally quenching the reaction at −78 °C, (2) alkylating the lithiated material at −78 °C with methyl iodide (12 equiv; 1.0 h), (3) quenching the reaction at −78 °C, and (4) analyzing the ratio of alkylated to unalkylated hydrazone. Although the method was neither as effective nor as reproducible as monitoring by FT-IR, it provided qualitative confirmation of the metalation rates and an LDA reaction order of 0.49 ± 0.04.

[38] Fit of the data in curve A (Figure 5) to eq 3 affords the following adjustable parameters: $k' = 1.55 \pm 0.03 \times 10^{-3}$ $s^{-1}$, $k'' = 0.124 \pm 0.004 \times 10^{-3}$ $s^{-1}$. Analogous fit to the general expression

$$k_{obsd} = k' + k''[\mathrm{THF}]^n$$

affords $k' = 1.56 \pm 0.02$ $s^{-1}$, $k'' = 0.15 \pm 0.03$ $s^{-1}$, and $n = 0.92 \pm 0.01$.

[39] Harned, H. S.; Owen, B. B. *The Physical Chemistry of Electrolytic Solutions*, 3rd ed.; Reinhold: New York, 1958. *The Chemistry of Nonaqueous Solvents*; Lagowski, J. J., Ed.; Academic Press: New York, 1970; Vol. III.

[40] Gutmann, V. *The Donor-Acceptor Approach to Molecular Interactions*; Plenum: New York, 1978. Chan, L. L.; Smid, J. *J. Am. Chem. Soc.* **1968**, *90*, 4654.

[41] The dielectric constants of substituted tetrahydrofurans are slightly lower than THF. Harada, Y.; Salomon, M.; Petrucci, S. *J. Phys. Chem.* **1985**, *89*, 2006. Carvajal, C.; Tolle, K. J.; Smid, J.; Szwarc, M. *J. Am. Chem. Soc.* **1965**, *87*, 5548.

[42] The measured rate constants for the lithiation of **2** (0.004 M) containing THF (7.5 M) in hexane, $Me_2$THF, and 2,2,5,5-tetramethyltetrahydrofuran ($Me_4$THF) cosolvents are $2.48 \pm 0.08 \times 10^{-3}$, $3.12 \pm 0.05 \times 10^{-3}$, $2.68 \pm 0.08 \times 10^{-3}$ $s^{-1}$, respectively.

do-first-order manifold. The two surprising observations include (1) the rate of lithiation is measurably greater in neat $Me_2THF$ than in neat THF and (2) a maximum rate is observed in $Me_2THF$ containing 0.5 equiv of THF per lithium (1.0 equiv of THF per LDA dimer).[43] $^6Li$ NMR spectroscopic analysis of [$^6Li$,$^{15}N$]LDA shows a triplet (1.85 ppm, $J_{Li-N} = 5.0$ Hz) consistent with a normal dimer structure under these conditions. Possible origins of these curious rate effects will be discussed later.

## Discussion

The solution structural studies of LDA are consistent with the assignment of LDA as disolvated dimer **1**. The rate data on the lithiation of 2-methylcyclohexanone *N*,*N*-dimethylhydrazone (**2**) by LDA are consistent with the rate expression shown in eq 4. Combining these two conclusions, one arrives at the mechanistic scenario shown in Scheme I.

$$-d[\mathbf{2}]/dt = (k_1/k_{-1})k_2[\mathbf{2}][\text{LDA}]^{1/2}[\text{THF}]^0 \qquad (4)$$

The critical features of the mechanistic hypothesis in Scheme I are as follows. Although LDA resides exclusively as an aggregate in its ground state, the rate-determining lithiation proceeds via a spectroscopically invisible, yet kinetically detectable, complex **3** containing an LDA monomer, a molecule of THF, and a molecule of hydrazone **2**. The independence of the reaction rate on the concentration of free THF (in $Me_2THF$) over the concentration range 2.0–12.28 M leads to the interesting conclusion that the deaggregation step does *not* require additional donor solvent. Nevertheless, the reactivity of LDA should depend on the structures of the solvent ligands residing on the lithium ions in its ground state. This is indeed the case as discussed shortly.

However, before further discussion of the ramifications of the mechanism in Scheme I, it is prudent first to highlight the ambiguities underlying the spectroscopic and rate studies. The $^6Li$ and $^{15}N$ NMR spectral data clearly demonstrate LDA to exist in a cyclic aggregate form. Cogent arguments outlined in the Results section supporting the disolvated dimer structure **1** are based on spectroscopic data, analogies with solution and structural studies of closely related lithium amides and N-lithiated derivatives, as well as convincing ab initio calculations carried out by Snaith and co-workers.[20] Regardless of the strength of the arguments, however, species such as trisolvated cyclic trimers or more highly solvated dimers cannot be rigorously excluded.

The zero-order dependence of the lithiation rate on the free THF concentration appears relatively uncontentious and supports a static LDA solvation number. The measured LDA reaction order of 0.45 ± 0.01, on the other hand, is intermediate between the 0.5 order expected for a dimer–monomer preequilibrium and a 0.33 order consistent with a *trimer*–monomer preequilibrium. This intermediate reaction order is not a major concern to the extent that it is readily ascribed to relatively minor random or systematic error. It also does not challenge the conclusion that the metalation requires an LDA deaggregation. However, it is indeed annoying that the measured LDA order does not more rigorously eliminate the ambiguity surrounding the dimer versus trimer structural assignment.

Despite these lingering concerns, a number of interesting observed solvation and aggregation effects are revealing when placed in the context of the mechanism shown in Scheme I. For instance, Fraser[8] demonstrated that the rates of LDA-mediated lithiations of triphenylmethane in a number of the standard donor solvents spanned a 40-fold range. In principle, however, these rate dependencies could stem from any number of factors including (1) long-range solvation phenomena categorically grouped together as "dielectric effects", (2) increases in aggregate solvation without concomitant deaggregation, (3) solvent-dependent deaggregations, and (4) intervention of new reaction pathways via such potentially reactive entities as ion pairs or even ion triplets of general structure $[(R_2N)_2Li]^-//^+Li$.[27]

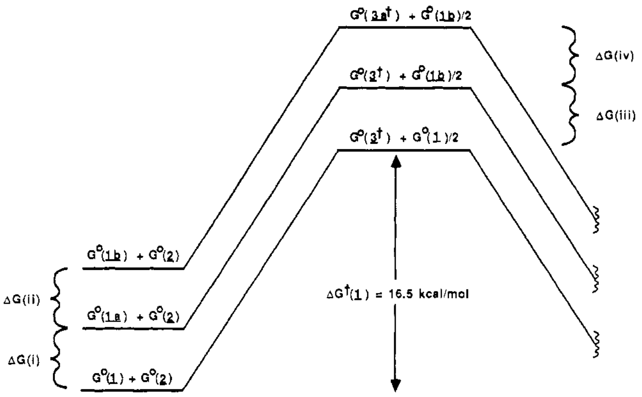
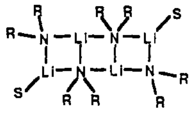


**Figure 6.**

This specific case history begins to shed some light on these issues. The monomeric form of LDA must be substantially more reactive than the dimer toward the metalation of **2**. However, increasing the donicity of the medium, whether through an increasing coordinating ability of the donor solvent or simply an increase in donor solvent concentration, does not *necessarily* increase the reactivity of LDA; *the position of the deaggregation preequilibrium is not directly affected by the free donor solvent concentration.* The lithiation rate displays a very modest (2-fold) linear increase as a function of THF concentration in THF/hexane mixtures. This increase was readily traceable to dielectric effects rather than primary solvation by comparison with the THF concentration-independent rates in THF/$Me_2THF$ mixtures. It is important to note that even the magnitude of such dielectric effects could not have been readily predicted from previous rate studies.



v

An especially interesting and counterintuitive phenomenon is observed when the THF content of the THF/$Me_2THF$ mixtures is reduced below pseudo-first-order concentrations (Figure 5, curve B). The lithiation rate in neat $Me_2THF$—a sterically hindered solvent of low donicity[40]—is measurably greater than in neat THF. Furthermore, the rate is optimized in $Me_2THF$ containing 0.5 equiv of THF per lithium. NMR spectroscopic studies indicate that these conditions do not induce a fundamental change in the LDA aggregate structure, suggesting that partially solvated ladder structures (cf. v) studied by Snaith and co-workers[44] are not likely to be the cause of the rate increases. Although the magnitudes of the rate changes are not very large, we feel that they highlight an often overlooked contribution to organolithium reactivity.

Traditional explanations for solvent-dependent organolithium reaction rates focus to varying degrees upon the stabilization of the rate-determining transition state through a negative free energy of solvation. However, it is instructive to consider the effects of solvation on the free energies of the starting materials (Scheme II, Figure 6).

A detailed analysis of the origins of the rate maximum observed at of 0.5 equiv of THF per lithium in $Me_2THF$ (Figure 2) is rendered impossible by the fact that the problem is seriously underdefined. A simple analysis is as follows. We suggest that LDA exists as a mixture of disolvates **1**, **1a**, and **1b** at THF concentrations between 0 and 1.0 equiv. One would expect that the free energy of dimeric LDA monotonically increases with increasing steric demands of the THF ligands. Similarly, the

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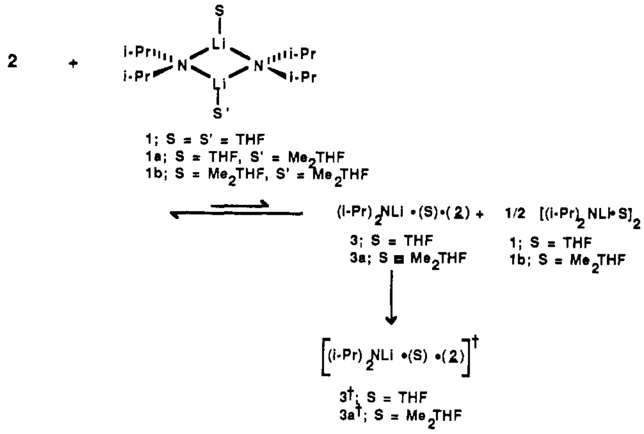
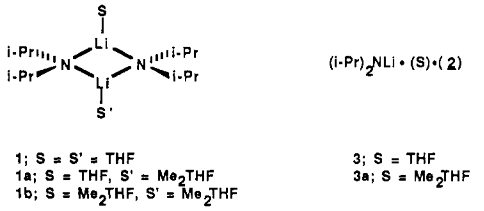
[43] Ethylene polymerization exhibits a similar rate maximum at intermediate THF concentrations. Bartlett, P. D.; Goebel, C. V.; Weber, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 7425.

[44] Armstrong, D. R.; Barr, D.; Clegg, W.; Mulvey, R. E.; Reed, D.; Snaith, R.; Wade, K. *J. Chem. Soc., Chem. Commun.* **1986**, 869. Barr, D.; Clegg, W.; Mulvey, R. E.; Snaith, R.; Wright, D. S. *J. Chem. Soc., Chem. Commun.* **1987**, 716.

**Scheme II**





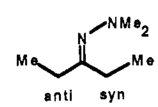
$Me_2THF$ solvated portion of the transition state labeled **3a**$^{\ddagger}$ should be destabilized relative to **3**$^{\ddagger}$. Thus, the 0.28 kcal/mol lower free energy of activation for **1b** relative to **1** (assuming 1.0 M THF in $Me_2THF$ at 20.0 °C as the standard state) derives from a disproportionate *destabilization* of the ground state relative to the transition state. If one further assumes that the THF resides predominantly in the complexed form (as suggested by the shape of the maximum of curve B in Figure 2), then it can be shown that the concentration of **1a** attains a maximum value at 0.5 equiv of THF per lithium. The observed rate would correspond to the sum of the individual pathways (eq 5). The existence and

$$d[\text{product}]/dt = k[\mathbf{1}] + k'[\mathbf{1a}] + k''[\mathbf{1b}] \qquad (5)$$

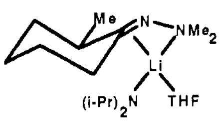
magnitude of the rate maximum, in turn, depends on two general parameters: the relative concentrations of **1**, **1a**, and **1b** (determined by the relative magnitudes of $\Delta G$(i) and $\Delta G$(ii) denoted in Figure 6) and the relative magnitudes of the corresponding rate constants (determined by the relative magnitudes of $\Delta G$(i), $\Delta G$(ii), $\Delta G$(iii), and $\Delta G$(iv)). Indeed, it can be shown through numerical integration procedures that such a model includes, at least qualitatively, provisions for such THF-dependent rate behavior.[45]

Leaving the complexities aside, the important conclusions are as follows. The model depicted in Scheme II and Figure 6 provides one possible explanation for the observed THF-dependent lithiation rates. Most importantly, the increased reaction rates observed in poorly solvating media arise, in one form or another, from disproportionate *destabilization* of the ground state relative to the reaction transition state. This curious phenomenon is most likely to be observed for reactions in which the transition state is *not* more highly solvated than the ground state (zero order in donor solvent). While large rate enhancements arising from ground state destabilization are possible, the 2,2,5,5-tetramethyltetrahydrofuran ($Me_4THF$) solvate of LDA is destabilized to the point of rendering the LDA insoluble in neat $Me_4THF$.

Another interesting concern pertains to the structure and reactivity of the monomeric LDA–hydrazone complex **3**. Bergbreiter and Newcomb reported that 3-pentanone *N*,*N*-dimethylhydrazone (**5**) is lithiated by LDA both syn and anti (75:25) relative to the *N*,*N*-dimethylamino substituent.[46] In this context, we note that transition states for both syn and anti metalation would be accessible from a monomeric LDA–hydrazone complex bound as an $\eta^3$–$\pi$ complex **6**. Such a $\pi$ complex would also satisfy the often-cited preference for lithium ion to achieve tetrahedral coordination in the absence of serious steric interactions.[47] It is still not clear, however, why such hydrazone metalations are many orders of magnitude slower than the corresponding lithiations of ketones and other carbonyl derivatives that occur rapidly at −78 °C.[4] As a final caveat, we note that the results described herein are not necessarily characteristic of the chemistry of LDA in a general sense. Kinetically labile substrates may react readily with LDA aggregates and mixed aggregates.[48]



**5**



**6**

## Experimental Section

**General Procedures.** Tetrahydrofuran (THF), 2,5-dimethyltetrahydrofuran ($Me_2THF$), 2,2,5,5-tetramethyltetrahydrofuran ($Me_4THF$), THF-$d_8$, hexane, and toluene-$d_8$ were distilled under vacuum from blue or purple solutions of sodium benzophenone ketyl. The hydrocarbon stills contained 1% tetraglyme to solubilize the ketyl. The $^6$Li metal (95.5% isotopic enrichment) was obtained from Oak Ridge National Laboratory. Ethyllithium was prepared and purified by a standard literature procedure.[30] The solid LDA was prepared from commercial *n*-butyllithium in hexane (Aldrich) and isolated by a literature procedure.[31] The [$^{15}N_2$]ammonium nitrate used to prepare [$^{15}$N]diisopropylamine was obtained 99% isotopically enriched from Cambridge Isotope Laboratories. Air- and moisture-sensitive materials were manipulated by using standard glovebox and vacuum line techniques with the aid of gas tight syringes.

**NMR Spectroscopic Analyses.** $^6$Li, $^{13}$C, and $^{15}$N NMR spectra were recorded on a Varian XL-400 spectrometer operating at 58.84, 100.56, and 40.53 MHz, respectively. $^6$Li chemical shifts are reported in ppm downfield of an external 0.3 M $^6$LiCl/methanol standard. The $^{15}$N chemical shifts are reported in ppm relative to an external 0.15 M aniline–$^{15}$N/THF standard set at 52 ppm.[49]

The following is a representative procedure for preparing samples for NMR spectroscopic analysis. [$^6$Li]Ethyllithium (3.0 mg, 0.086 mmol) is weighed in a glovebox and carefully transferred to an oven-dried 5-mm NMR tube. After addition of sealed capillaries containing 0.35 M [$^6$Li]LiCl/MeOH and 0.15 M [$^{u5}$N]aniline/THF internal standards, the tube is capped with a septum and septum clamp and removed from the glovebox.. The tube is cooled to −78 °C under positive argon pressure and charged with a 1.39 M solution of [$^{15}$N]diisopropylamine in toluene-$d_8$ (75 $\mu$L, 0.104 mmol) and the appropriate NMR solvent. The tube is then sealed with a flame and maintained at ≤−30 °C until the spectroscopic analysis. For the specific cases in which exclusion of hydrocarbons is important, the tube containing the ethyllithium and diisopropylamine in toluene-$d_8$ is charged with THF, evacuated to dryness, and then charged again with THF-$d_8$ before sealing with a flame.

**Preparation of [$^{15}$N]Diisopropylamine.** To a 50-mL, round-bottomed flask was added 5 mL of commercial Raney nickel slurry (Aldrich), 35 mL of isopropyl alcohol, [$^{15}N_2$]$NH_4NO_3$ (1.0 g, 12.2 mmol),[50] and *n*-decane (GC standard). Formation of diisopropylamine was monitored

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(45) Implicit in Figure 6 and the discussion is the assumption that mixed solvate **1a** reacts exclusively via the transition state comprised of THF solvated monomer complex **3**$^{\ddagger}$ and $^1/_2$ equiv of **1b**. The contrary supposition that the reaction of **1a** proceeds via a transition state comprised of **3a**$^{\ddagger}$ and $^1/_2$ equiv of **1** is equally valid.

(46) Ludwig, J. W.; Newcomb, M.; Bergbreiter, D. E. *J. Org. Chem.* **1980**, *45*, 4666.

(47) Wardell, J. L. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abels, F. W., Eds.; Pergamon: New York, 1982; Vol. 1, Chapter 2.

(48) For examples of mixed aggregation effects, see: Jackman, L. M.; Dunne, T. S. *J. Am. Chem. Soc.* **1985**, *107*, 2805. Jackman, L. M.; Szevernyi, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 4954. McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H.-R. *J. Am. Chem. Soc.* **1985**, *107*, 1810. McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805. Holm, T. *Acta Chem. Scand.* **1969**, *23*, 1829. Smith, S. G.; Charbonneau, L. F.; Novak, D. B.; Brown, T. L. *J. Am. Chem. Soc.* **1972**, *94*, 7059. Eppley, R. L.; Dixon, J. A. *J. Am. Chem. Soc.* **1968**, *90*, 1606. Al-Aseer, M. A.; Allison, B. D.; Smith, S. G. *J. Org. Chem.* **1985**, *50*, 2715. Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373. Seebach, D.; Polt, R. *J. Am. Chem. Soc.* **1989**, *111*, 2622. See also ref 36.

(49) Von Phillipsborn, W.; Muller, R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 383. Levy, G. C.; Lichter, R. *Nitrogen-15 NMR Spectroscopy*; Wiley: New York, 1979. Mason, J. *Chem. Rev.* **1981**, *81*, 205.

(50) The reduction of monolabeled $^{15}NH_4NO_3$ (99%) by Raney nickel provides diisopropylamine precisely 50% labeled. In addition, no other ammonium salts or nitrate salts provided even traces of product. We infer that the reduction proceeds via a symmetric intermediate with an N–N bond.

by gas chromatography. After 13 h, the nickel was filtered off, and 750 $\mu$L of trifluoroacetic acid was added. The solution was evaporated to provide the trifluoroacetate ammonium salt as a white solid. The salt was dissolved in 5.0 mL of $H_2O$, brought to pH 10 with 5% aqueous NaOH, and extracted 3 times with 1.0 mL of toluene-$d_8$. The combined toluene-$d_8$ layers were combined and distilled to provide approximately 2.5 mL of a toluene-$d_8$ solution of [$^{15}$N]diisopropylamine. GC analysis using comparison with standardized solutions indicated a molarity of 1.39. Aliquots of solution were stored in sealed ampoules: $^1$H NMR (200 MHz, toluene-$d_8$) $\delta$ 2.98 (1 H, septuplet, $J$ = 6.2 Hz), 1.16 (6 H, dd, $J_{NH}$ = 2.2 Hz, $J_{HH}$ = 6.2 Hz), 1.14 (1 H, dd, $J_{NH}$ = 3.2 Hz, $J_{HH}$ = 6.2); $^{13}$C NMR (100.58 MHz, toluene-$d_8$) $\delta$ 45.8 ($J_{NC}$ = 3.9 Hz), 24.09.

**Kinetics.** Kinetics were run in a 50-mL, round-bottomed flask fitted with a T-joint providing access to the vacuum line and FT-IR spectrometer. The lithiation rate was monitored by using a flow system involving the following: (1) a 1.05-m length of 0.8-mm i.d. intramedic tubing leading from the reaction vessel to an FMI model RP-SY fluid pump, (2) a 0.76-m length of tubing leading from the pump to a standard solution NaCl IR cell of pathlength of 0.20 mm, and (3) a 1.05-m length of tubing leading from the cell back to the reaction vessel. The total volume of the flow system and cell external to the reaction vessel is 1.8 mL. With the pump set at 1.6 mL/min, the vessel-to-vessel turnover time is 67 s. Since the difference between the bath temperature (20.0 ± 0.3 °C) and room temperature (22–24 °C) was small and the percentage of the reaction contents external to the controlled temperature bath was also minor, the temperature fluctuations did not cause serious problems.

A typical kinetic run was effected as follows. An oven-dried, 50-mL, round-bottomed flask equipped with a T-joint is charged with LDA (321 mg, 3.00 mmol) in a glovebox. The flask is removed from the glovebox, evacuated on a vacuum line, and placed under argon. To the vessel at 0 °C is added freshly dried hexane (5.0 mL) and tetrahydrofuran (18.0 mL) via gas tight syringes. After 1 min, the flask is placed in a thermostatted bath at 20.0 ± 0.3 °C and thermally equilibrated for 5 min. The LDA solution is then pumped through the flow system for an additional 5 min. After recording a background IR spectrum (16 scans, 45-s acquisition), a stock solution of **2** in THF (90 $\mu$L, 0.875 mmol) is added to the reaction flask. The course of the reaction is monitored periodically until the reaction exceeds 95% conversion as shown by the growth in the intensity of mixed-aggregate absorbance at 1600 cm$^{-1}$ (cf. Figure 2).

**Rate Constants and Statistics.** All rate constants were calculated by using first-order treatments and nonweighted, nonlinear least-squares fits on data measured to ≥5 half-lives. The reported errors correspond to one standard deviation. The numerical fits were carried out with the LTPLOT statistical package developed in the Materials Sciences Center at Cornell University.

**Acknowledgment.** We thank the National Science Foundation Instrumentation Program (CHE 7904825 and PCM 8018643) for support of the Cornell Nuclear Magnetic Resonance Facility. We express thanks to Elias Michaelides for the preparation of [$^{15}$N]diisopropylamine. D.B.C. express thanks to the A. P. Sloan Foundation for unrestricted support. We thank Dieter Seebach and Walter Bauer for helpful discussions during the structural studies of LDA.

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# Construction of Quaternary Carbon Centers Using Organomolybdenum Chemistry

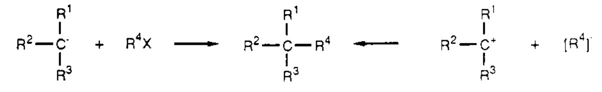
**Anthony J. Pearson* and Vikram D. Khetani**

*Contribution from the Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106.* *Received February 10, 1989*

**Abstract:** Two approaches are described for the construction of quaternary carbon centers using organomolybdenum complexes. The first involves carbon nucleophile addition to the methylated diene terminus of dicarbonyl($\eta^5$-indenyl)(1–4-$\eta$-1,4-dimethylcyclohexa-1,3-diene)molybdenum tetrafluoroborate (**12**). A wide range of nucleophiles add successfully to **12** giving *gem*-disubstituted cyclohexenylmolybdenum complexes. This methodology, coupled with a lactonization/decomplexation reaction, has led to a short synthesis of 2-(2-hydroxy-1,4-dimethylcyclohex-3-enyl)propionic acid lactone (**14**), which has previously been employed as a key intermediate for trichothecene synthesis. The second method involves alkylation of cyano-stabilized carbanions generated from dicarbonyl($\eta^5$-cyclopentadienyl)(1–3-$\eta$-4-cyanocyclohexenyl)molybdenum and dicarbonyl($\eta^5$-cyclopentadienyl)(1–3-$\eta$-4-cyanocycloheptenyl)molybdenum. While a rather limited range of electrophiles could be used in this coupling reaction, it was found that stereochemical control is excellent and allows the construction of quaternary carbon centers with defined stereochemistry relative to other substituents on the cyclohexenyl or cycloheptenyl ligand. During the course of this study it was found that treatment of the exo-cyano-substituted $\pi$-allylmolybdenum complexes with butyllithium led to a novel decyanation reaction. This allowed the generation of nonstabilized carbanion species that could be alkylated regio- and stereospecifically.

A quaternary carbon center, i.e., a molecular substructure consisting of a carbon atom bound to four other carbon atoms, is a feature of a broad range of natural products and therefore constitutes an important target in the context of general synthetic methodology. A review by Martin[1] outlines earlier work in this area and gives an overview of the types of natural products that are of general interest. More recently, Meyers' group reported methodology for the asymmetric construction of quaternary carbon centers.[2]

Using polar reactions there are two basic ways in which such centers can be introduced into an already existing molecule: (1) addition of an electrophilic alkylating agent to a trisubstituted carbanion, e.g., **1** gives **2**; (2) addition of a nucleophilic alkylating agent to a tertiary carbocation or its equivalent (e.g., a tertiary alkyl halide), as in the conversion of **3** to **2**. A combination of (1) and (2) would lead to the formation of two juxtaposed quaternary carbon centers. An example of approach 1 would be the alkylation of a substituted enolate, while the Lewis acid catalyzed alkylation of a silyl enol ether with a tertiary alkyl halide provides an example of (2). Other approaches involve rearrangement



$$R^1R^2R^3C^- + R^4X \longrightarrow R^1R^2R^3C{-}R^4 \longleftarrow R^1R^2R^3C^+ + [R^4]^-$$

**1** **2** **3**

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[1] Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

[2] Meyers, A. I.; Lefker, B. A. *J. Org. Chem.* **1986**, *51*, 1541.

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