

Is *N,N,N',N'*-Tetramethylethylenediamine a Good Ligand for Lithium?

DAVID B. COLLUM

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

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The often-cited relationships between solvation, aggregation, and reactivity in organolithium chemistry are depicted in Scheme I.¹ The remarkable feature of this triad is in its application. Observed rate increases are taken as evidence of highly reactive lower aggregates. Detection of lower aggregates foreshadows high reactivity. Superior ligands are said to afford higher reactivities because they produce lower aggregates. In fact, knowledge of any one of the three components often is taken as evidence of the other two.

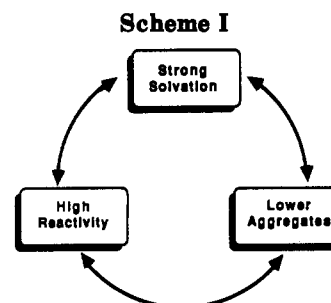
Despite the elements of cyclic logic, the model in Scheme I is pervasive. As to its origins, examination of the literature reveals that *N,N,N',N'*-tetramethylethylenediamine (TMEDA; 1) has played a central role.²⁻⁴ The crystallographic literature is replete with the Li-TMEDA chelate substructure 2, leaving one with the sense that the bidentate metal-ligand interaction must be important.⁵ The kinetic consequences of TMEDA are even more prominent. TMEDA dramatically accelerates organolithium reaction rates, improves product yields, and alters product distributions.²⁻⁴ In short, the triad in Scheme I seems quite logical in the context of a strong, bidentate TMEDA-lithium interaction.



What if the model suggested in Scheme I is seriously flawed? We had occasion to ask this question upon completion of studies of hydrazone metalations mediated by lithium diisopropylamide (LDA) solvated by TMEDA.⁶ A combination of spectroscopic, crystallographic, kinetic, and computational methods led to the following conclusions: (1) TMEDA is inferior to THF as a ligand for LDA and binds reluctantly to LDA at ambient temperatures *even in the absence of competing donor ligands*; (2) chelates of TMEDA are of no structural or mechanistic consequence at any crucial point along the reaction coordinate; and (3) there is little, if any, relationship between the strength of the solvent-LDA interaction and the rate of hydrazone metalation.

We felt that the failure of TMEDA to live up to any of our expectations might be a consequence of the case study chosen since there is little history of TMEDA in

David Collum received a bachelor's degree in biology from the Cornell University College of Agriculture and Life Sciences in 1977. After receiving a Ph.D. in 1980 from Columbia University working with Clark Still, he returned to the Department of Chemistry at Cornell, where he is now Professor of Chemistry. His work at Cornell has addressed topics in natural products synthesis, organotransition metal chemistry, and organolithium structure and mechanism.



lithium amide chemistry.⁶ Yet, close examination of the literature of alkyl- and aryllithiums reveals that the folklore surrounding TMEDA is not well founded. This Account will attempt to trace the origins of the prevailing belief that TMEDA is a good ligand for lithium and to survey the more incisive studies of the last few years that have begun to challenge this notion. The Account concludes with a list of unresolved issues requiring further consideration.

The Issues

Our concerns about the role of TMEDA in organolithium chemistry are most easily understood in the context of questions relating to Scheme I.

When and How Does a Solvent Promote Deaggregation? In cases of solvent-mediated deaggregation in the ground state, the solvent must be providing sufficient stabilization to overcome the aggregation energies.⁷ It seems logical that strong solvent-metal interactions in more highly solvated lower aggregates could provide the stabilization necessary to offset the Li-C (or Li-X) bond stabilization energies enjoyed by

(1) 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. *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; Wiley: New York, 1972; Vols. 1 and 2.

(2) *Polyamine-Chelated Alkali Metal Compounds*; Langer, A. W., Jr., Ed.; American Chemical Society: Washington, DC, 1974.

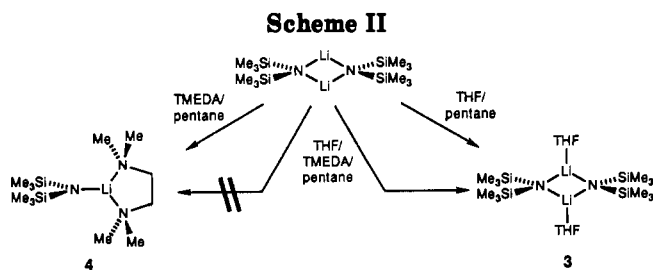
(3) Seebach, D. *Angew. Chem., Int. Ed. Engl.* 1988, 27, 1624.

(4) (a) Beak, P. *Chem. Rev.* 1984, 84, 471. (b) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* 1986, 19, 356. (c) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* 1979, 26, 1. (d) Beak, P.; Snieckus, V. *Acc. Chem. Res.* 1982, 15, 306. (e) Snieckus, V. *Chem. Rev.* 1990, 90, 879.

(5) Schleyer, P. v. R. *Pure Appl. Chem.* 1984, 56, 151. Williard, P. G. In *Comprehensive Organic Synthesis*; Pergamon: New York, in press. Boche, G. *Angew. Chem., Int. Ed. Engl.* 1989, 28, 277.

(6) Bernstein, M. P.; Romesberg, F. E.; Fuller, D. J.; Harrison, A. T.; Collum, D. B.; Liu, Q.-Y.; Williard, P. G. *J. Am. Chem. Soc.* 1992, 114, 5100.

(7) Thermochemical studies on the heats of deprotonation of a wide range of carbon acids revealing a notable insensitivity to the conjugate base aggregation state illustrate the relatively small differences in RLi aggregation state stabilities in THF: Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* 1991, 113, 7122. Aggregation energies without contributions of solvation are substantially larger as determined computationally. Kaufmann, E.; Raghavachari, K.; Reed, A. E.; Schleyer, P. v. R. *Organometallics* 1988, 7, 1597 and references cited therein.



higher aggregates. Yet, if the higher oligomers derive minimal stabilization from solvation, then the lower aggregation states may require only minimal stabilization to be observed. This point is most readily made with an illustration from lithium amide chemistry (Scheme II).⁸ Treatment of lithium hexamethyldisilazide (LiHMDS) with 5.0 equiv of THF exclusively affords dimer 3. In contrast, LiHMDS in the presence of 5.0 equiv of TMEDA exclusively affords monomer 4. It is tempting to infer that TMEDA is a superior ligand; however, a competition with equimolar quantities of THF and TMEDA exclusively affords (THF-solvated) dimer. Thus, TMEDA cannot compete with THF for coordination sites on LiHMDS, and the observable deaggregation in TMEDA/pentane does not necessarily result from a strong metal–ligand interaction.⁹ Recent studies of two ligands with well-documented affinities for lithium ion—hexamethylphosphoramide (HMPA) and C[2.1.1] cryptand—reinforce the notion that generalized solvent donicity–aggregation state correlations are risky.¹⁰

Are Monomers More Reactive Than Aggregates?

While it may be logical that monomers are more reactive than aggregates, the correlation of aggregation state and organolithium reactivity is based more on consensus than on experiment. Evidence of aggregation effects has increased exponentially in the last decade,^{3,11} although the relative reactivities of different aggregation states have been directly determined on only a few occasions.¹² In cases where fractional orders evidence reaction via spectroscopically undetectable lower aggregates,¹ the *transient* lower aggregates are relatively unstable *by definition*. For the sake of discussion, let us assume that adding a strong lithium complexant causes a monomer to become an observable species (monomer-S in Figure 1). Would metalation rates increase? If new reaction pathways are not made accessible, then *formation of the new monomer would represent an unproductive side equilibrium, promoting*

(8) Bernstein, M. P.; Collum, D. B. Unpublished results.

(9) As an additional note, the TMEDA-mediated deaggregation is not necessarily ascribable to the bidentate interaction; dimethylethylamine affords substantially higher concentrations of monomer than does THF despite a demonstrably lower affinity for LiHMDS.⁸

(10) (a) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* 1991, 113, 5751. (b) Jackman, L. M.; Chen, X. *J. Am. Chem. Soc.* 1992, 114, 403. (c) Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* 1988, 110, 3546. (d) Romesberg, F. E.; Bernstein, M. P.; Fuller, D. J.; Harrison, A. T.; Collum, D. B. Unpublished results.

(11) Seebach, D. In *Proceedings of the Robert A. Welch Foundation Conferences on Chemistry and Biochemistry*; Wiley: New York, 1984; p 93. Caubere, P. In *Reviews of Heteroatom Chemistry*; MYU: Tokyo, 1991; Vol. 4, pp 78–139.

(12) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* 1984, 107, 1810. Jackman, L. M.; Dunne, T. S. *J. Am. Chem. Soc.* 1985, 107, 2805. Depue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* 1988, 110, 5524. Jackman, L. M.; Rakiewicz, E. F. *J. Am. Chem. Soc.* 1991, 113, 4101 and references cited therein.

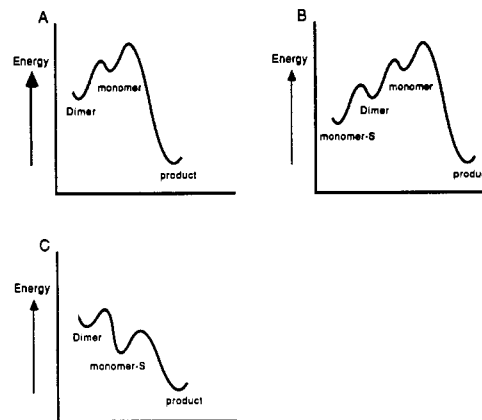


Figure 1.

a rate retardation according to the principle of detailed balance (compare Figure 1A and 1B).¹³ If newly accessible monomeric ground states and monomeric transition states bearing coordinated complexant are both stabilized relative to their more highly aggregated counterparts, then a reaction rate increase is plausible but not mandated (Figure 1C). One should not forget, however, that *any stabilization of the ground state serves to retard the reaction rate*. Even if a reaction must proceed via a lower aggregate, forcing the deaggregation will not necessarily cause a rate acceleration. Moreover, the ideal solvent would be one showing no affinity whatsoever for the ground state and a high affinity for the transition state.

It is difficult yet essential to dissect relative reaction rates into the rate-retarding influence of ground-state stabilization and the rate-accelerating influence of transition-state stabilization. The failure to consider both is logically flawed and can lead to invalid conclusions.

When and How Does Organolithium Reactivity Correlate with Solvent Donicity? Any reduction in the stability of the ground state relative to the transition state—irrespective of the structural form—will increase reactivity. It is not at all clear *why* high reactivity should necessarily correlate with strong metal–ligand interactions. Since substrates are likely to be competing with solvent for coordination sites on the lithium, reported inverse correlations of reaction rate and solvent donicity are consistent with requisite coordinative unsaturation.¹⁴ Thus, whether couched in the terminology of thermochemistry or coordination chemistry, correlations of reactivity with ligand *lability* are intuitively logical, provided the critical relationship of the ground-state and transition-state energies is kept in mind.

One also must consider the complex influence of solvation on mixed aggregation.^{3,11} It is clear that mixed aggregates formed during the course of a reaction can dramatically influence rates, yields, or product distributions. The insidious consequence to any mechanistic hypothesis is that mixed aggregate equilibria and (in turn) reactivity can be influenced by solvation of *any* species in complex equilibria according to the principle of detailed balance.¹³ This is true regardless of how conceptually remote they may be from the site of

(13) Casado, J.; Lopez-Quintela, M. A.; Lorenzo-Barral, F. M. *J. Chem. Educ.* 1986, 63, 450. Hammes, G. G. *Principles of Chemical Kinetics*; Academic Press: New York, 1978; pp 14–15.

reactivity. We know very little about the solvent dependencies of mixed aggregation at this time.^{3,15}

Is TMEDA a Good Ligand for Lithium? It should now be clear how difficult this question will be to answer. It is likely that this question has no single answer. We must differentiate the solid state from the solution state, the ground state from the transition state, and the absence of donor cosolvents from the presence of donor cosolvents. For practical purposes, we will often find it convenient to compare TMEDA to THF and offer the following premise: Addition of TMEDA to THF solutions of organolithium derivatives will have structural and kinetic consequences only if TMEDA can function competitively (or cooperatively^{10a,16-18}) with the THF for coordination sites on the lithium at some stage along the reaction coordinate.¹⁹ We hasten to add that deciphering precisely where along the reaction coordinate consequential solvation events occur remains a formidable task.

The choice of mechanistic probes also must be made judiciously. A 20% improvement in yield, while delightful to a synthetic organic chemist, is viewed differently by a mechanistic organic chemist. An increase from 70% to 90% yield corresponds to a relative rate increase (k_{rel}) of the desired reaction that may be well within experimental error. Contrast this with an improvement from 0% to 20% yield in which the relative rate increase is infinite. While " k_{rel} " values must be interpreted with extreme caution, percent isolated yield rarely provides useful mechanistic insight. The literature includes a surprisingly limited number of tractable comparisons of THF and TMEDA, and the few that exist afford a wide range of mechanistic implications.

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(15) Jackman, L. M.; Rakiewicz, E. F. *J. Am. Chem. Soc.* 1991, 113, 1202 and references cited therein.

(16) Zarges, W.; Marsch, M.; Harms, K.; Boche, G. *Chem. Ber.* 1989, 122, 2303. Karsch, H. H.; Appelt, A.; Mueller, G. *Organometallics* 1985, 4, 1624.

(17) Marsais, F.; Queguiner, G. *Tetrahedron* 1983, 39, 2009. Chadwick, D. J.; Willbe, C. *J. Chem. Soc., Perkin Trans. 1* 1977, 887. Meyers, A. I.; Avila, W. B. *Tetrahedron Lett.* 1980, 21, 3335. Cao, J. *Gaodeng Xueixiao Huazue Xuebao* 1989, 10, 1246. Ludt, R. E.; Hanger, C. R. *J. Org. Chem.* 1971, 36, 1607.

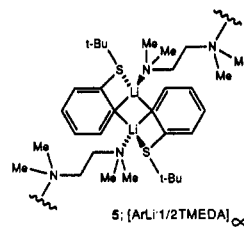
(18) Fraenkel, G.; Chow, A.; Winchester, W. R. *J. Am. Chem. Soc.* 1990, 112, 1382.

(19) The evidence supporting TMEDA as a strong ligand relative to diethyl ether is sparse, yet substantially less contentious. See, for example: Cabiddu, S.; Melis, S.; Piras, P. P.; Sotgiu, F. *J. Organomet. Chem.* 1978, 178, 291. Fusstetter, H.; Nöth, H. *Chem. Ber.* 1978, 111, 3596. Gjøs, N.; Gronowitz, S. *Acta Chem. Scand.* 1971, 25, 2596. Narasimhan, N. S.; Ammanamanchi, R. *J. Org. Chem.* 1983, 48, 39. Neuse, E. W.; Bednarik, L. *Macromolecules* 1979, 12, 187. Shirley, D. A.; Chung, C. F. *J. Organomet. Chem.* 1969, 20, 251. Slocum, D. W.; Koonsvitsky, B. P. *J. Org. Chem.* 1973, 38, 1675. Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* 1976, 41, 3653. Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* 1982, 47, 2101. Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* 1963, 85, 1245. Amstutz, R.; Enz, A.; Marzi, M.; Boelsterli, J.; Walkinshaw, M. *Helv. Chim. Acta* 1990, 73, 739.

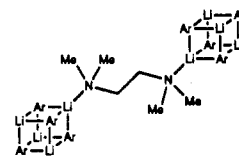
(20) Köster, H.; Thoennes, D.; Weiss, E. *J. Organomet. Chem.* 1978, 160, 1.

The Literature

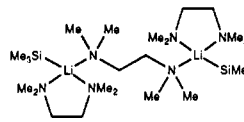
Structural Studies in the Solid State. Many crystallographically characterized organolithium derivatives contain TMEDA coordinated in a bidentate fashion.⁵ The crystalline TMEDA solvates are often in a lower aggregation state than that observed (or expected) without TMEDA. This shows that TMEDA chelates are accessible, insoluble, and nicely crystalline. However, it does not attest to the magnitude of the chelate effect or to the overall strength of the TMEDA-Li interaction. It is tempting to cite the less commonly observed examples of crystallographically characterized η^1 -bound TMEDA solvates (5-8, for example)²¹⁻²⁵ to challenge the stability of TMEDA chelates. However, this is equally invalid; *X-ray crystallography provides little insight into the thermodynamics of aggregation and solvation.*



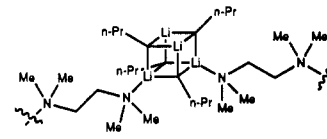
5: $[\text{ArLi}^{1/2}\text{TMEDA}]_{\infty}$



6: Ar = $\eta^2[\text{C}_6\text{O}]o$ -anisole



7



8: $[\text{n-BuLi}^{1/4}\text{TMEDA}]_{\infty}$

Structural Studies in Solution. The importance of anionic polymerization²⁶ has provided the impetus for many spectroscopic studies of RLi-TMEDA complexes.²⁶ While early efforts documented the existence of discrete complexes in hydrocarbon solutions,² recent reports have focused more directly upon the impact of TMEDA on both solvation and aggregation states. For example, treatment of phenyllithium and *o*-, *m*-, and *p*-tolyllithium with either 2.0 equiv of THF or 1.0 equiv of TMEDA affords dimers.²⁷ The solution structures of TMEDA-solvated dimers of several heteroaryllith-

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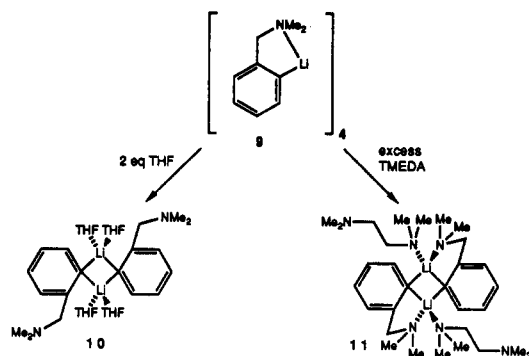
(25) (a) Lithium salts have been reported to crystallize free of TMEDA from solutions containing TMEDA: Maetzke, T.; Hidber, C. P.; Seebach, D. *J. Am. Chem. Soc.* 1990, 112, 8248. Maetzke, T.; Seebach, D. *Organometallics* 1990, 9, 3032. Barnett, N. D. R.; Mulvey, R. E.; Clegg, W.; O'Neil, P. A. *J. Am. Chem. Soc.* 1991, 113, 8187. (b) Solid-state ¹³C NMR spectroscopic studies of lithium fluorene-TMEDA complex reveals a dynamic process involving TMEDA ligand movement: Johnels, D.; Edlund, U. *J. Am. Chem. Soc.* 1990, 112, 1647. (c) A lithium salt containing uncoordinated (η^0) TMEDA has been structurally characterized: Lambert, C.; Schleyer, P. v. R.; Pieper, U.; Stalke, D. *Angew. Chem., Int. Ed. Engl.* 1992, 31, 77.

(26) Szwarc, M. *Carbanions, Living Polymers, and Electron Transfer Processes*; Interscience: New York, 1968. Morton, M. *Anionic Polymerization: Principles and Practice*; Academic Press: New York, 1983. See also ref 64.

(27) (a) Wehman, E.; Jastrzebski, J. T. B. H.; Ernsting, J.-M.; Grove, D. M.; van Koten, G. *J. Organomet. Chem.* 1988, 353, 133. (b) See also: Jackman, L. M.; Scarmoutzos, L. M. *J. Am. Chem. Soc.* 1984, 106, 4627. (c) Reich, H. J. Unpublished results.

iums have been described.²⁸ TMEDA-solvated naphthyllithium-methylithium mixed dimers have been observed in toluene-*d*₈.^{29a,30} TMEDA has been shown to convert hexamers of *n*-butyllithium to dimers in toluene-*d*₈.^{29b}

However, the example depicted in Scheme II illustrates that these studies do not constitute evidence of a highly stabilizing TMEDA-lithium interaction. Furthermore, one can find interesting examples in which TMEDA does not appear to mediate deaggregation. Beak and Smith concluded from detailed colligative studies that *sec*-butyllithium exists as incompletely solvated tetramers in hexane/TMEDA mixtures.³¹ Partially solvated tetrameric *n*-BuLi has been suggested to be an observable species at low TMEDA concentrations,³² consistent with crystallographic²⁴ and kinetic data.³⁰ Vapor-phase osmometry data measured at 37 °C reveal an average aggregation number of 5.2 for lithium pinacolate with added TMEDA compared to the value of 4.1 with added THF.³³ Brandsma and co-workers demonstrated that crystallographically characterized 6 containing two aryllithium tetramers linked by TMEDA retains its basic structure in hydrocarbon solutions.²³ In what is clearly a revealing spectroscopic study, van Koten and co-workers discovered that an excess (4 equiv) of TMEDA or 2 equiv of THF deaggregates tetramer 9 to dimers 10 and 11, respectively.³⁴ The disruption of the internal ligation by THF but not by TMEDA is noteworthy.



It is instructive to focus on experiments in which TMEDA is forced to compete with THF. TMEDA (in THF) appears to influence the structure of the radical anion derived from benzophenone, but not that derived from fluorenone.³⁵ TMEDA drives the phenyllithium monomer-dimer equilibrium in THF completely to dimer.³⁶ While this TMEDA-mediated aggregation

undermines the generality of any dictum proclaiming that TMEDA functions to deaggregate organolithium derivatives, it also constitutes strong evidence that TMEDA can compete with bulk THF for coordination sites on lithium. Seebach found that mixed aggregates of *n*-BuLi/1-bicyclo[1.1.0]butyllithium in THF revert to homonuclear aggregates in THF/TMEDA.³⁷ The *n*-BuLi tetramer-dimer mixture in THF is influenced to a limited extent by added TMEDA.^{37,38} (Recall that *n*-BuLi/TMEDA forms exclusively dimer in the absence of THF,^{29b} reinforcing concerns about the often-cited correlation between metal-ligand bond strength and aggregation.) A dilithiated derivative in THF/TMEDA exists as an equilibrium mixture of THF-solvated higher aggregates and TMEDA-solvated lower aggregates.³⁹ Monomeric lithio(diphenylphosphino)methane-TMEDA complex retains TMEDA ligation in THF solution.⁴²

Thus, one might argue that low concentrations of TMEDA readily compete with excess THF as a ligand for lithium. However, this is not universally true. Hindered dimers of lithium amides resist coordination of TMEDA in the presence of equimolar THF.^{6,8} Fraenkel and co-workers have found that TMEDA pushes the tetramer-dimer equilibrium of a lithium acetylide measurably toward dimer, but only at low temperatures.^{40,41} Reich finds that substantial concentrations of TMEDA (upward of 10 equiv) are required to compete with bulk THF for coordination of phenyllithium dimer.^{27c} Several alkyl- and aryllithiums^{21,43-48} resist coordination by TMEDA in bulk THF. These include *t*-BuLi,⁴³ 1-lithio-2,4,6-tri-*tert*-butylbenzene,⁴³ neopentyllithium,⁴⁴ benzylithium,⁴⁵ 2-lithio-2-methyl-1,3-dithiane,⁴⁶ and several trimethylsilyl-substituted allyllithiums.^{47,48}

One is left with the sense that the relative affinities of TMEDA and THF for lithium may be highly substrate-dependent. Competitions at equivalent activities in the spirit of Scheme II and van Koten's studies of 9 would provide additional insight.

Thermochemical Studies. Solution calorimetry can afford metal-ligand bond strengths in the form of heats of solvation, but only if the contribution of solvent-dependent aggregation state changes can be included in the analysis. The most carefully documented study of TMEDA solvation addressed the aldol condensation.³³ Arnett and co-workers found that THF, DME, and TMEDA all fail to coordinate to a tetrameric

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(30) An equilibrium of *n*-BuLi-TMEDA dimers with the corresponding tetramers bearing η^1 -bound TMEDA has been suggested from kinetic data: Fraenkel, G. In *Lithium: Current Applications in Science, Medicine, and Technology*; Bach, R. O., Ed.; Wiley: New York, 1985.

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(38) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* 1984, 107, 1805.

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(41) Hässig, v. R.; Seebach, D. *Helv. Chim. Acta* 1983, 66, 2269.

(42) Fraenkel, G.; Winchester, W. R. *Organometallics* 1989, 8, 2308.

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lithium aldolate in hydrocarbon solution. More importantly, the enthalpy of solvation of lithium pinacolate by TMEDA at 6 °C is -2.98 ± 0.38 kcal/mol compared to -6.17 ± 0.46 kcal/mol for THF. Since cryoscopic and NMR spectroscopic studies at 6 °C are consistent with the formation of a TMEDA-solvated dimer, the enthalpic cost of deaggregation could explain the low enthalpy for TMEDA solvation. However, Arnett has also found that the relative energies of different aggregation states are generally quite small (<5 kcal/mol).⁷ Furthermore, the cryoscopic studies that led to the dimer assignment argue against, but do not appear to rigorously exclude, partially solvated higher oligomers.

Calorimetric titrations of poly(butadienyl)lithium reveal markedly greater molar enthalpies of solvation with TMEDA than with THF.^{49,50} However, the high enthalpies are observed only when the poly(butadienyl)lithium is in large excess, a situation in which the statistical factor of having two potentially aggregate-bridging termini must be considered. Concentration dependencies appearing at fractions of an equivalent of added ligand make these results difficult to interpret quantitatively. Beak and Siegel found that solvation of both *o*-lithioanisole and *p*-lithioanisole is enthalpically more favorable for TMEDA than for di-*n*-butyl ether.⁵¹ The two aryllithiums are suggested to be dimeric in both donor solvents by colligative measurements.

Conclusions from solution calorimetry are also haunted by their failure to include free energies. In the specific case of TMEDA, the large negative translational entropies associated with ion solvation are likely to be magnified by the restricted degrees of freedom of the TMEDA skeleton upon chelation as well as by the constraints placed upon the organolithium fragment subjected to a sterically demanding solvation.⁵² Indeed, Kminek and co-workers³² suggest that a large negative enthalpy of solvation of *n*-BuLi by TMEDA is largely offset at ambient temperatures by a large negative entropy of solvation. They speculate upon the existence of TMEDA-solvated *n*-BuLi tetramers at ambient temperatures rather than the dimers noted at low temperatures.³⁰ MNDO studies (including frequency calculations) of lithium ion solvation by TMEDA are in full accord with Kminek's results and further suggest that the "chelate effect" of a bidentate TMEDA-lithium complex is destabilizing both enthalpically and entropically relative to two Me₃N ligands.⁵³ MNDO computational studies of lithium amide-TMEDA solvates suggest that the high steric demands of TMEDA may be highly destabilizing.^{6,52}

Rate Studies. The influence of TMEDA on reaction rates is documented most thoroughly and quantitatively in the literature of anionic polymerization. Unfortunately, there has been a controversy that, from the perspective of an outsider peering in, remains unre-

solved.⁵⁴ There are reports of TMEDA-mediated rate accelerations⁵⁵ as well as rate inhibitions.⁵⁶⁻⁵⁹ Maxima in the rates have been reported for TMEDA:RLi ratios (*R* = living polymer) of 0,⁵⁹ 1.0,^{58,61} and ≥ 2.0 .^{62,63} Significant variations in the mathematical forms of the rate equations continue to be debated.^{54,64} In short, polymerization rate studies have not yet delineated the role of the TMEDA additive.

In light of the temperature-dependent desolvation of LDA-TMEDA complexes we had observed,⁶ it occurred to us that the incongruities in the polymerization kinetics may stem from a desolvation of TMEDA-RLi complexes between 0 and 60 °C and consequent formation of partially solvated aggregates. Temperature-dependent polymerization rate maxima are consistent with such a temperature-dependent solvation equilibrium.⁶⁵ The effect of TMEDA on polybutadiene vinyl content ($k_{1,2\text{-addn}}$ vs $k_{1,4\text{-addn}}$) shows a sharper levelling off (saturation) when the polymerization is effected at 30 °C than at 70 °C.⁶⁶ Polymerization rate maxima observed at less than stoichiometric concentrations of TMEDA may stem from partially solvated aggregates akin to the partially solvated *s*-BuLi tetramers observed by Williard²⁴ and invoked by others.^{31,32,58} This supposition is based upon studies of Bartlett showing that initiation of ethylene polymerization occurs optimally from partially (diethyl ether) solvated tetramers bearing free coordination sites.⁶⁷ Greater ethylene pressures are required to attain equivalent polymerization rates in the presence of THF than TMEDA, suggestive of a more restricted access to coordination sites on lithium in THF.^{68,69} Of special note, *N,N,N',N'*-tetraethylethylenediamine (TEEDA) causes a substantial rate acceleration of ethylene polymerization relative to TMEDA.⁷⁰ It seems unlikely that such an acceleration could be the result of a stronger (rather than weaker) metal-ligand interaction.

Turning away from the polymerization literature, we find very few instances in which detailed rate studies have shed light on the role of TMEDA in organolithium chemistry. Schleyer reported that a spectroscopically

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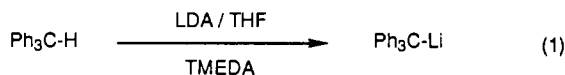
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observable anisole-*n*-BuLi complex in hydrocarbon solution fails to undergo ortho metalation.²⁹ Addition of TMEDA causes the quantitative displacement of the anisole by the TMEDA and commencement of the ortholithiation. While this result provides some insight into the strength of the TMEDA-lithium interaction (anisole is expected to be an inferior ligand³²), it also belies an underlying mechanistic complexity. The authors' suggested mechanism involving a transient *n*-BuLi₂(η^2 -TMEDA)(anisole) complex is strongly supported by computational results. The most ambitious study of TMEDA rate effects was that of Beak, Smith, and co-workers on the formation of dipole-stabilized carbanions.³¹ The mechanistic pathways uncovered in the study were numerous, complex, and incompletely defined. The crux of their conclusion is that partially solvated *s*-BuLi tetramers, not lower oligomers, are the reactive forms. Their results do not support a strong metal-ligand interaction as the source of the TMEDA-mediated rate accelerations. Other semiquantitative studies have revealed interesting rate maxima and minima qualitatively similar to those found for anionic polymerization.⁷¹⁻⁷⁴

It was suggested above that addition of TMEDA to THF solutions of organolithium derivatives will cause rate changes only if TMEDA can function competitively with the THF for coordination sites on the metal at some stage along the reaction coordinate. Surprisingly, it has proven difficult to find well-documented examples of organolithium reactions in which TMEDA/THF mixtures offer rate advantages over THF alone.⁷⁵⁻⁷⁷ The most dramatic and well-documented example appears to be the reported 100-fold greater rate for a benzyl-lithium-aryllithium equilibration in THF/TMEDA when compared to THF alone.⁷⁵ However, the LDA-mediated metalation in eq 1 described by Fraser and Mansour⁷⁷ offers special impact on our thinking for two reasons: (1) We have shown that TMEDA does not bind to LDA at all in the presence of equimolar concentrations of THF,⁶ and (2) we have checked and confirmed the result.⁶ Since TMEDA does not bind to LDA in the ground state, the rate acceleration can be ascribed to transition-state stabilization. In fact, *complexation of the ground state by TMEDA would only serve to inhibit the reaction.* The advantage offered by a bidentate ligand could be a consequence of the poor (or non) precomplexing capacity of the substrate.



Selectivity Studies. The literature of organic synthesis provides countless empirical observations that

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have helped shape the lore of organolithium chemistry. We have attempted to locate examples that shed light on details of solvation by TMEDA.

In cases where THF/TMEDA mixtures are used for metalations, explanations of the role of the TMEDA are extraordinarily elusive.⁷⁸⁻⁸⁴ The vast literature of arene ortholithiation constitutes an excellent case in point. Prior to 1979, virtually all ortho metalations were effected in hexane or diethyl ether both with and without TMEDA.^{4c} Only a handful of authors reported using alkylolithiums in THF or THF/TMEDA, and the results were discouraging.⁸⁵ However, a 1982 report by Beak and Brown⁸⁶ promoting THF/TMEDA mixtures to maximize ortho substitution yields mediated an abrupt turnaround in the technology; THF/TMEDA became the industry standard as shown in recent reviews by Snieckus and Beak.^{4d,e} Nevertheless, among the many papers describing metalations in THF/TMEDA mixtures, there is a notable absence of hard evidence suggesting a role of the TMEDA. TMEDA has been shown to influence reactions effected in THF in some instances,^{78,79} but in other cases its influence is negligible.^{80,81} Cases where metalation selectivities using BuLi-TMEDA show dependencies of the ethereal

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cosolvent suggest that coordination of the cosolvent is occurring competitively or cooperatively.^{16,17} Although it is sometimes implied that the choice of THF/TMEDA emerged from empirical optimizations, tractable comparisons with and without added TMEDA or allusions to the role of TMEDA are usually absent from the discussions altogether. Both Beak and Snieckus—authors of considerable repute in the field—concur that evidence supporting TMEDA as a substantive additive to ortho metalations in THF is less than secure.⁸⁷ Both suspect that TMEDA may stabilize resulting aryllithium intermediates toward undesirable inter- and intramolecular condensations rather than increase the kinetic basicity of the aryllithium base.⁸⁸ If so, a high affinity of TMEDA toward aryllithiums (but not alkyllithiums) is implicated.

Summary. TMEDA has proven to be invaluable to the organic chemistry community as a modifier of organolithium reactivity. The voluminous results have dramatically influenced our notions of solvation, aggregation, and reactivity. Unfortunately, an extensive survey of the literature of TMEDA reveals a highly confused view of the mechanisms by which TMEDA modifies organolithium structure and reactivity. We submit the following guidelines for consideration.

1. TMEDA appears to manifest a highly substrate-dependent affinity for lithium. The TMEDA–lithium interaction may be strongest (although not necessarily strong) in the sterically least demanding lithium derivatives and especially weak in sterically congested environments.

2. TMEDA should have the most pronounced effects on organolithium structure and reactivity in the absence of strong donor solvents such as THF.

3. The affinity of TMEDA for lithium and the resulting influence on reactivity may have an inordinate temperature sensitivity.

4. TMEDA does not necessarily influence reactivity

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through deaggregations of the ground-state structures. Relatively nonstabilized η^1 -solvated and partially solvated oligomers may play more prominent roles than previously suspected. Analogies with transition metal coordination chemistry suggest ligand *lability* could be the source of observed high reactivities.

5. Maximum rate effects may stem from strong solvation (chelation) of relatively unhindered transition structures in conjunction with poor solvation of the sterically congested ground-state structures.

6. Many applications of TMEDA in the presence of strong donor ligands (THF in particular) may be the result of a placebo effect, with perceived improvements falling within the experimental error.

7. The complexity imparted by mixed aggregation and mixed solvation is poorly understood. Attaching mechanistic significance to TMEDA-mediated structure, rate, and selectivity changes requires more caution than is usually exercised.

8. Overall, models based on the logic that bidentate ligands such as TMEDA have high donicities and, through deaggregation, increase organolithium reactivity may have notable limitations.

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