Is \(N,N',N'-\text{Tetramethylethlenediamine}\) a Good Ligand for Lithium?

DAVID B. COLLUM
Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301
Received February 5, 1992

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 \(N,N,N',N'\)-tetramethyl-ethlenediamine (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.\(^2+\) 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 metalation.

[Scheme I diagram]

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.

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 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.

(2) Polyamine-Chelated Alkali Metal Compounds; Langer, A. W., Jr., Ed.; American Chemical Society: Washington, DC, 1974.
Is TMEDA a Good Ligand for Lithium?

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). 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 (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. 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. 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, although the relative reactivities of different aggregation states have been directly determined on only a few occasions. In cases where fractional orders evidence reaction via spectroscopically undetectable lower aggregates, 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 a rate retardation according to the principle of detailed balance (compare Figure 1A and 1B). 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. 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. 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. This is true regardless of how conceptually remote they may be from the site of

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.
reactivity. We know very little about the solvent dependencies of mixed aggregation at this time. 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) with the THF for coordination sites on the lithium at some stage along the reaction coordinate. 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 (krel) 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 krel 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.


The Literature

Structural Studies in the Solid State. Many crystallographically characterized organolithium derivatives contain TMEDA coordinated in a bidentate fashion. 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 #-bound TMEDA solvates (5,8) 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.

---

Structural Studies in Solution. The importance of anionic polymerization has provided the impetus for many spectroscopic studies of RLi-TMEDA complexes. While early efforts documented the existence of discrete complexes in hydrocarbon solutions, recent reports have focused more directly upon the impact of TMEDA on both solvation and aggregation states. For example, treatment of phenyllithium and m-, p-tolylolithium with either 2.0 equiv of THF or 1.0 equiv of TMEDA affords dimers. The solution structures of TMEDA-solvated dimers of several heteroarayllithium compounds have been determined.
ions have been described. TMEDA-solvated naphthyllithium–methylthyllithium mixed dimers have been observed in toluene-d₆. TMEDA has been shown to convert hexamers of n-butyllithium to dimers in toluene-d₆. However, the example depicted in Scheme II illustrates that these studies do not constitute evidence of a covalently 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. Partially solvated tetrameric n-BuLi has been suggested to be an observable species at low TMEDA concentrations, consistent with crystallographic and kinetic data. 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. Bransdama and co-workers demonstrated that crystallographically characterized 6 containing two aryllithium tetramers linked by TMEDA retains its basic structure in hydrocarbon solutions. 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. 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. TMEDA drives the phenyllithium monomer–dimer equilibrium in THF completely to dimer. 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. The n-BuLi tetramer–dimer mixture in THF is influenced to a limited extent by added TMEDA. (Recall that n-BuLi/TMEDA forms exclusively dimer in the absence of THF, reinforcing concerns about the often-cited correlation between metal–ligand bond strength and aggregation.) A dithiolated derivative of THF/TMEDA exists as an equilibrium mixture of THF-solvated higher aggregates and TMEDA-solvated lower aggregates. Monomeric lithium(diphenylphosphino)methane–TMEDA complex retains TMEDA ligation in THF solution.

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. 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. Reich finds that substantial concentrations of TMEDA (upward of 10 equiv) are required to compete with bulk THF for coordination of phenyllithium dimer. Several alkyl- and aryllithiums resist coordination by TMEDA in bulk THF. These include t-BuLi, 1-lithio-2,4,6-tri-tert-butylbenzene, neopentyllithium, benzyl lithium, 2-lithio-2-methyl-1,3-dithiane, and several trimethylsilyl-substituted allyllithiums.

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. Arnett and co-workers found that THF, DME, and TMEDA all fail to coordinate to a tetrameric...
lithium aldehyde in hydrocarbon solution. More importantly, the enthalpy of solvation of lithium pina
colate by TMEDA at 5 °C is -2.98 ± 0.39 kcal/mol compared to -6.17 ± 0.46 kcal/mol for THF. Since
cryoscopic and NMR spectroscopic studies at 5 °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 measure-
ments.

Conclusions from solution calorimetry are also haunt-
ed 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.50 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 en-
tropically relative to two Me2N ligands.53 MNDO computational studies of lithium amide-TMEDA sol-
vates suggest that the high steric demands of TMEDA may be highly destabilizing.5,52

Rate Studies. The influence of TMEDA on reaction
rates is documented most thoroughly and quantitatively in the literature of anionic polymerization. Unfortu-
nately, 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-Li ratios (R = living polymer) of 0.56 1.0,5,58,61 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 incoherencies in the polymerization
kinetics may stem from a desolvation of TMED-
A-Li complexes between 0 and 60 °C and conse-
quent formation of partially solvated aggregates.
Temperature-dependent polymerization rate maxima
are consistent with such a temperature-dependent
solvation equilibrium.58 The effect of TMEDA on
polybutadiene vinyl content (k1,3-ddd vs k1,4-ddd) shows a sharper levelling off (saturation) when the polyme-
ization is effected at 30 °C than at 70 °C.65 Polymer-
ization rate maxima observed at less than stoicho-
metric concentrations of TMEDA may stem from
disorderedly 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,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

(54) Dumas, S.; Sledz, J.; Schue, F.; Raynal, S.; Bywater, S.; Worsfold,
D. Organ. Polym. 1983, 24, 1381. Miller, R.; Young, K. N.; Lucton,
Polymer 1978, 17, 613.
1972, 33, 687.
68, 1227.
Lett. 1978, 16, 81.
(59) Smirnov, N.; Zgonnik, V.; Kalinskis, K.; Erusalimskii, B. L.
Trans. 1972, 68, 1.
(63) Vinogradova, L. V.; Nikoicov, N.; Sgonnik, V. N.; Begleni, B.;
(64) Anionic Polymerization: Kinetics, Mechanism, and Synthesis;
McGrath, J. E., Ed.; American Chemical Society: Washington, DC,
1981; Chapters 1, 2, 30.
(65) Catala, J. M.; Clouet, G.; Brosses, J. J. Organomet. Chem. 1968,
128, 139.
(66) Antkowiak, T. A.; Oberster, A. E.; Halasa, A. E.; Tate, D. P.
1969, 91, 7425.
(69) Houk, K. N.; Rondan, N. G.; Schleyer, P. v. R.; Kaufman, E.;
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 metatlations, explanations of the role of the TMEDA have been addressed in the literature of organolithium chemistry. The authors' suggested mechanism involving a transient n-BuLi\(\text{TMEDA}(n^2)\) complex is strongly supported by computational results. The most ambitious study of TMEDA rate effects was that of Beak and co-workers on the formation of dipole-stabilized carbanions.

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.

The most dramatic and well-documented example appears to be the reported 100-fold greater rate for a benzylithium-arylithium equilibration in THF/TMEDA when compared to THF alone. However, the LDA-mediated metatlation in eq 1 described by Fraser and Mansour offers special importance 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, and (2) we have checked and confirmed the result. 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.

\[ \text{Ph}_2\text{C}-\text{Li} + \text{LDA/TMEDA} \rightarrow \text{Ph}_2\text{C}-\text{Li} \]

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

\[ \text{Ph}_2\text{C}-\text{Li} \rightarrow \text{Ph}_2\text{C}-\text{H} \]


(74) Over 10 equiv of TMEDA is needed to asymptotically approach the optimum rate of living polymer carborylation: Quirk, R. P.; Yin, J.; Fetters, L. J. Macromolecules 1989, 22, 85.


cosolvent suggest that coordination of the cosolvent is occurring competitively or cooperatively.\textsuperscript{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.\textsuperscript{87} Both suspect that TMEDA may stabilize resulting aryllithium intermediates toward undesirable inter- and intramolecular condensations rather than increase the kinetic basicity of the alkyl-lithium base.\textsuperscript{88} If so, a high affinity of TMEDA toward aryllithiums (but not alkylolithiums) 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 through deaggregations of the ground-state structures. Relatively nonstabilized \( ^{1} \)-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.

I am deeply indebted to my talented co-workers for their skill, enthusiasm, and dedication. I owe a special thanks to Max P. Bernstein for carrying out the experimental studies of TMEDA-solvated lithium amides that elicited many of the ideas described herein. I am also grateful to a number of individuals for helpful discussions and comments pertaining to this manuscript. These include Charles Wilcox (Cornell), Barry Carpenter (Cornell), Peter Beak (University of Illinois), Victor Snieckus (University of Waterloo), Gideon Fraenkel (Ohio State), Scott Denmark (University of Illinois), Jay Siegel (University of California—San Diego), Lloyd Jackman (Penn State), Dieter Seebach (ETH), Donald Slocum (University of Western Kentucky), Lambert Brandsma (University of Utrecht), Paul Williard (Brown), Edwin Vedejs (Wisconsin), Larry Blasczak (Eli Lilly), Franklin Davis (Drexel), and an especially diligent referee. They do not, of course, bear any culpability for the ideas presented.

**Registry No.** 1, 110-18-9.