Structural and Rate Studies of the 1,2-Additions of Lithium Phenylacetylide to Lithiated Quinazolinones: Influence of Mixed Aggregates on the Reaction Mechanism

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Abstract: The 1,2-addition of lithium phenylacetylide (PhCCLi) to quinazolinones was investigated using a combination of structural and rate studies. 6Li, 13C, and 19F NMR spectroscopies show that deuteration of quinazolinones and phenylacetylene in THF/pentane solutions with lithium hexamethyldisilazide affords a mixture of lithium quinazolinide/PhCCLi mixed dimer and mixed tetramer along with PhCCLi dimer. Although the mixed tetramer dominates at high mixed aggregate concentrations and low temperatures used for the structural studies, the mixed dimer is the dominant form at the low total mixed aggregate concentrations, high THF concentrations, and ambient temperatures used to investigate the 1,2-addition. Monitoring the reaction rates using 19F NMR spectroscopy revealed a first-order dependence on mixed dimer, a zeroth-order dependence on THF, and a half-order dependence on the PhCCLi concentration. The rate law is consistent with the addition of a disolvated PhCCLi monomer to the mixed dimer. Investigation of the 1,2-addition of PhCCLi to an O-protected quinazolinone implicates reaction via trisolvated PhCCLi monomers.

Introduction

Several new classes of potent nonnucleoside reverse transcriptase inhibitors have been developed by DuPont Pharmaceuticals and Merck Research Laboratories.1 Efavirenz (1) is now widely prescribed under the names Sustiva and Stocrin as a second-generation drug candidate.2,3 Efavirenz (1) is currently being prepared by an amino alcohol-mediated addition of alkynyl zinc derivatives.4谭, L.; Chen, C. Y.; Tillyer, R. D.; Grabowski, E. J.; Reamer, R.; Reider, P. J. Org. Chem. 1998, 63, 8536. Thompson, A. S.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. Tetrahedron Lett. 1995, 36, 8937.


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in eq 2. Several simplifications in the protocol have provided sufficient control over aggregate structures to allow detailed rate studies. We preface the mechanistic study by foreshadowing results from the structural studies: Treating THF solutions of quinazolinone 5 and phenylacetylene with LiHMDS under judiciously chosen conditions affords mixed dimer 13 and lithium phenylacetylide (PhCCLi) dimer 14 as the predominant species. The most central and pressing question is what role does mixed dimer 13 play in the 1,2-addition? At the outset, we considered two plausible answers: (1) mixed dimer 13 reacts via an intramolecular mechanism that exploits the reagent proximities afforded by mixed aggregation, or (2) mixed dimer 13 is simply a protected form of quinazolinone 5 that undergoes 1,2-addition by an external nucleophilic PhCCLi fragment.12 A comparison with rate studies of the 1,2-addition to O-protected quinazolinone derivative 11 (eq 2) reveals notable similarities and differences.

Results

Structural Studies. A combination of forethought and serendipity allowed us to control the organolithium solution structures sufficiently to carry out detailed mechanistic studies. The results from NMR spectroscopic studies are summarized in Table 1 and are described below. Selected spectra are illustrated in Figures 1 and 2.

LiHMDS is readily purified through recrystallization,13 serves as an excellent proton scavenger,9 and does not form mixed aggregates except under unusual conditions.9,14,15 Indeed, a mixture of PhCCLi and lithium salt 8 generated in situ with excess [6Li][LiHMDS]13 contains no LiHMDS-derived mixed aggregates.

PhCCLi proves especially important to the success of the solution kinetics. Lithium cyclopropylacetylide (6) and other lithium acetylides typically exist as mixtures of cyclic dimers and cubic tetramers in THF and THF/hydrocarbon solutions.9,16–18 Lithium phenylacetylide in THF/toluene shows a greater tendency to form dimer 14 than do most lithium acetylides, but it affords tetramer 15 at low THF concentrations.18 Such a dimer–tetramer mixture would undermine the rate studies. In contrast, [6Li and 13C NMR spectra recorded on THF/pentane mixtures of [6Li,13C]PhCCLi reveal exclusively dimer 14 (Table 1) in solutions containing as little as 20% THF by volume. The pronounced hydrocarbon effect can be witnessed by incrementally replacing the toluene in 20% THF/toluene solutions of PhCCLi with pentane, causing conversion of a 2:1 15:14 mixture to exclusively dimer 14. The origins of this odd hydrocarbon dependence are being investigated.18 As a practical matter, THF/pentane mixtures offer important structural control for the rate studies.

In situ generation of quinazolinone salt 8 in THF or THF/pentane affords a complex mixture that is characteristic of N-lithiated carboxamides in the absence of added lithium salts.11,19,20 In the presence of excess [6Li,13C]PhCCLi, however, we observe two species displaying spectral data consistent with
mixed dimer 13 and mixed tetramer 16 (Figure 1; Table 1). A 5-fold excess of PhCCLi is required to convert quinazolinone salt 8 completely to the mixed aggregates.

Mixed dimer 13 displays a 6 Li doublet due to coupling to a single 13 C nucleus that is readily discerned from the other

Figure 1. 6 Li spectra were recorded at −115 °C. Spectra A and B were recorded on a 2:1 mixture of [6 Li, 13 C]PhCCLi (0.133 N) and [6 Li]PhCCLi (0.20 N) in 9.5 M THF/pentane; spectrum C was recorded on a 2:1 mixture of [6 Li]PhCCLi (0.20 N) and [6 Li, 1- 15 N] PhCCLi (0.10 N) in 7.6 M THF/pentane. (Residual [6 Li]LiHMDS is marked by *.) Spectrum A is 13 C broad-band decoupled.

multiple in the J(6 Li, 13 C)-resolved and J(6 Li, 13 C)-heteronuclear multiple quantum coherence (HMQC)21,22 spectra (Figure 2).23 A 13 C quintet indicates coupling to two symmetry-equivalent lithium nuclei. The lack of chelation by the quinazoline is confirmed by the absence of coupling when dimer 13 is generated from 15 N-enriched quinazolinones [1- 15 N] and [3- 15 N]. A single 19 F resonance attests to the symmetry of mixed dimer 13 and provides a means to monitor reaction rates (vide infra).

Mixed tetramer 16 manifests two lithium resonances in a 1:1 ratio (Figure 1A). Both 6 Li resonances are coupled to a common

Figure 2. J(6 Li, 13 C)-resolved spectrum (A) and J(6 Li, 13 C)-HMQC spectrum (B) recorded on 0.133 N [6 Li, 13 C]PhCCLi and 0.067 N [6 Li]8 in 7.6 M THF (pentane cosolvent) at −115 °C. [6 Li]LiHMDS is indicated by an asterisk (*)

(20) N-Lithiated carbamoylides form mixed aggregates with lithium acetylates as well as lithium alkoxides (such as 7): Winemiller, M. D.; Collum, D. B., unpublished.
13 C nucleus (Figure 1B and 2B). Tetramer 16 prepared from [1-15 N]5 shows a distinct N–Li coupling in one 6 Li resonance (Figure 1C), whereas 16 prepared from [3-15 N]5 affords no coupling. Several isomers of tetramer 16 are consistent with the spectroscopic data. Cubic tetramers, however, are excluded by the coupling patterns.8,9 We originally suspected the chelated mixed oligomer to be mixed dimer 17 rather than mixed tetramer 16. The spectroscopically opaque O–Li linkages render 16 and 17 difficult to distinguish. However, the chelated form is promoted relative to mixed dimer 13 at elevated total mixed aggregate concentrations (Figure 3) and low THF concentrations (Figure 4), suggesting the chelated form has a lower solvation number and higher aggregation state than those of mixed dimer 13.

Figure 3. 19 F NMR spectra recorded at −100 °C of 7.6 M THF/pentane solutions of 0.10 N PhCCLi and 8 (at the normality indicated).

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Figure 4. 19 F NMR spectra recorded at −80 °C of THF/pentane solutions of 0.04 N PhCCLi and 0.01 N 8 at the THF concentrations indicated.

Figure 5. Plot of [mixed dimer] versus [mixed oligomer] (measured in normality of subunit 8) in 8.0 M THF solutions containing 0.10 N PhCCLi and a range of concentrations of 8 in pentane cosolvent at −100 °C. The curve depicts an unweighted least-squares fit to [mixed oligomer] = K′ [mixed dimer]m ([mixed dimer] = (3 ± 2) × 102, m = 2.0 ± 0.1).

The relationship of the chelated form to mixed dimer 13 is described according to eqs 3 and 4, which can be rearranged to eq 5. Keeping THF at a high fixed concentration, plotting the relative concentrations of the mixed aggregates (Figure 5) enables calculation of a relative aggregation number, m = 2.0 ± 0.1, that is consistent with the mixed tetramer assignment.
In turn, maintaining a fixed concentration of mixed aggregate and varying the THF concentration (eq 6, Figure 6) affords a high relative per-lithium solvation number, 

\[ n = 2.91 (0.07) \]

Although the measured solvation number seems to implicate an unsymmetrically solvated tetramer, a systemic error causing a deviation from an integer value of either 2.0 or 4.0 seems equally plausible.

Although the complexity caused by the pair of mixed aggregates did not bode well for detailed rate studies, we observed a somewhat surprising and fortuitous promotion of dimer \( 13 \) relative to tetramer \( 16 \) (Figure 7) at elevated temperatures. Indeed, monitoring the temperature-dependent \( 13/16 \) ratios in six combinations of THF and mixed aggregate concentrations (Figure 8 is emblematic) affords relatively invariant (concentration-independent) thermodynamic parameters:

\[ \Delta H^\circ = 1.8 \pm 0.1 \text{ kcal/mol and } \Delta S^\circ = -11.6 \pm 0.9 \text{ cal/(mol K)} \]

Figure 9 shows a plot of the calculated mole fraction of dimer \( 13 \) as a function of THF under conditions that are representative of those used in the rate studies. Thus, under carefully controlled conditions, dimer \( 13 \) is dominant, and tetramer \( 16 \) is largely irrelevant to the rate studies (vide infra).

**Figure 6.** Plot of \([\text{mixed dimer}]^2/\text{mixed tetramer}\) (i.e., \([13]^2/[16]\)) versus [THF] of solutions containing 0.04 N PhCCLi and 0.01 N \( m \) over a range of THF concentrations in pentane cosolvent at \(-80^\circ C\). The curve depicts an unweighted least-squares fit to \([13]^2/[16] = K_{eq}[\text{THF}]^n (K_{eq} = (3.0 \pm 0.5) \times 10^{-5}, n = 2.91 \pm 0.07)\).

\[
(\text{PhCCLi})_m (\text{THF})_{m-n} + n\text{THF} \rightleftharpoons \text{“mixed oligomer”}
\]

\[ m(\text{PhCCLi})(\text{THF})_4 \]  

\[ K_{eq} = [\text{mixed dimer}]^{m}/[\text{THF}]^{m}[\text{mixed oligomer}] \]  

\[ [\text{mixed oligomer}] = K'[\text{mixed dimer}]^{m} \]  

\[ K' = 1/K_{eq}[\text{THF}]^n \approx \text{constant} \]

\[ [\text{mixed dimer}]^{m}/[\text{mixed oligomer}] = K_{eq}[\text{THF}]^n \quad (m = 2 \text{ from Figure 5}) \]

Although the complexity caused by the pair of mixed aggregates did not bode well for detailed rate studies, we observed a somewhat surprising and fortuitous promotion of dimer \( 13 \) relative to tetramer \( 16 \) (Figure 7) at elevated temperatures. Indeed, monitoring the temperature-dependent \( 13/16 \) ratios in six combinations of THF and mixed aggregate concentrations (Figure 8 is emblematic) affords relatively invariant (concentration-independent) thermodynamic parameters: \( \Delta H^\circ = 1.8 \pm 0.1 \text{ kcal/mol and } \Delta S^\circ = -11.6 \pm 0.9 \text{ cal/(mol K)} \). Figure 9 shows a plot of the calculated mole fraction of dimer \( 13 \) as a function of THF under conditions that are representative of those used in the rate studies. Thus, under


(26) The \(^{19}\text{F} \) resonances of \( 13 \) and \( 16 \) coalesce at \(-55^\circ C\).
The temperature- and concentration-dependent dimer—tetramer equilibrium requires additional comment. Conventional wisdom suggests that the more highly solvated lower aggregate would be favored at low temperatures due to a net enthalpic stabilization attributed to the stabilizing enthalpy of solvation. In contrast, the more highly solvated dimer 13 is enthalpically and entropically disfavored when compared to tetramer 16. The dominance of dimer 13 under the conditions used to follow the reaction rates stems from the substantial deviation from the unit-molarity standard state due to the high THF concentration and low mixed aggregate concentration.

The product of the 1,2-addition is depicted generically as dianion 10; spectroscopic studies suggest that 10 is a mixture of species as shown by a broad mound of 19 F resonances. The dianion formulation (rather than a monoanion resulting from protonation by residual hexamethyldisilazane) is supported by control experiments showing that deprotonations of 2 with 1.0 and 2.0 equiv of LiHMDS afford spectroscopically distinct product distributions. Most importantly, however, the product of the reaction is of no consequence under pseudo-first-order conditions used to study the kinetics.

It is also noteworthy that the formation of 10 in the presence of excess [6 Li]PhCCLi shows no evidence of PhCCLi-containing mixed aggregates. Thus, the 1,2-addition in eq 2 does not result in the net consumption of free PhCCLi dimer 14. Consequently, conversion-dependent changes in mechanism that can dramatically increase the mechanistic complexity under stoichiometric conditions are unlikely to intervene.

Rate Studies: 1,2-Addition to Mixed Dimer 13. Pseudo-first-order conditions were initially investigated by monitoring the loss of mixed dimer 13. IR-derived rate data are archived in the Supporting Information.

Unfortunately, the absorbance of 13 is obscured by a product-derived absorbance at 1505−1545 cm−1 that becomes prominent at high THF concentrations. 19 F NMR spectroscopy proves to be a superior analytical method for the current case study. Monitoring the 19 F resonance of 13 reveals a clean first-order decay (Figure 10), provided the THF concentrations are elevated (>7.0 M in pentane). It is normal that a visually clean first-order decay in conjunction with concentration-independent values of kobsd is adequate to demonstrate a first-order dependence on the limiting reagent. However, this complex case demanded that we determine the order by a best-fit protocol. We prefer a method based on a nonlinear least-squares fit to the function in eq 7. The adjustable parameter \( \alpha \) corresponds to the reaction order in 13. The data for the 18 runs used to construct Figure 11 (discussed below) were fit to eq 7 and averaged, affording \( \alpha = 1.05 \pm 0.03 \).

\[
13 = ((\alpha - 1)k_{\text{obsd}}t + [13])_{0}^{-1/(1-\alpha)} \]  

The first-order dependence on the concentration of 13 at high THF concentration is unequivocal. At lower THF concentrations, however, tetramer 16 becomes significant (Figure 9), and we observe considerable deviations from clean first-order behavior. Curiously, the deviations are positive (\( R > 1 \)) rather than negative (\( R < 1 \)). (The order for a mixed-dimer based reaction would approach \( \alpha = 0.5 \) in the limit of complete tetramer formation.) It is possible that a new pathway intervenes at low THF concentration, but we are currently unable to provide additional insight.

The question of whether 13 reacts directly as a mixed aggregate or through the intervention of additional PhCCLi is

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27. Deaggregation is normally promoted at low temperatures and is widely believed to be the result of the dominance of the enthalpy affiliated with higher solvation numbers. It is unclear why the less highly solvated tetramer 16 (as shown by THF concentration dependencies) is enthalpically preferred (as shown by the temperature dependencies).
and a zeroth-order dependence on the THF concentration. The concentration of PhCCLi refers to the concentration of the monomer (33).

The predominant pathway displays a zeroth-order THF concentration expected for first-order or inverse-first-order dependencies on $k$. A plot of $k_{\text{obsd}}$ versus [THF] in pentane for the 1,2-addition of PhCCLi to mixed dimer 13 (0.005 N of 8) at 10 °C. The curve depicts an unweighted least-squares fit to $k_{\text{obsd}} = \alpha\text{[PhCCLi]}^b (\alpha = (1.16 \pm 0.01) \times 10^{-3}, b = 0.42 \pm 0.01)$.

addressed by determining the rate dependencies on the PhCCLi concentration. A plot of $k_{\text{obsd}}$ versus [PhCCLi] at 7.75 M THF/pentane affords an order of 0.42 ± 0.01 (Figure 11). Although 0.42 is lower than expected, it is strongly suggestive of the half-order dependence anticipated for a mechanism requiring deaggregation of PhCCLi dimer 14.

A plot of $k_{\text{obsd}}$ versus THF concentration (Figure 12) reveals nearly [THF]-independent rates. (Recall that the values of $k_{\text{obsd}}$ are only approximate because of deviations from a first-order decay that are due to the appearance of tetramer 16). The slight negative drift does not approach the >4-fold changes in $k_{\text{obsd}}$ expected for first-order or inverse-first-order dependencies on the THF concentration. Therefore, we conclude that the predominant pathway displays a zeroth-order THF concentration dependence.

Overall, the evidence supports a first-order dependence on mixed dimer 13, a half-order dependence on PhCCLi dimer 14, and a zeroth-order dependence on the THF concentration. The idealized rate law described by eq 8 is consistent with the mechanism depicted generically in eqs 9 and 10. We do not intend to suggest the requisite intermediacy of a discrete solvated monomer 18 or even a specific sequence of events; rather, we emphasize the incorporation of the PhCCLi(THF)$_2$ fragment in rate-limiting transition structure 19.

The 1,2-additions to 11 were carried out using methods similar to those described for the additions to 13. Monitoring the $^{19}$F resonance of 11 shows a clean first-order decay (Supporting Information). The addition of PhCCLi to 11 is $10^9$ times faster than its addition to 13, consistent with the higher electron density on 13. The rate data for 1,2-addition to 11 reveal notable similarities and differences with 13. A plot of $k_{\text{obsd}}$ versus [THF] for the addition to 11 displays a first-order dependence on the THF concentration (Figure 13). A plot of $k_{\text{obsd}}$ versus PhCCLi concentration in 8.6 M THF reveals a fractional (0.45 ± 0.04) order. The idealized rate law (eq 11) implicates a mechanism based on trisolvated PhCCLi monomers (eqs 12 and 13).

Discussion

The highly enantioselective addition of lithium acetylides to quinazolinones illustrated in eq 1 is the key step in the syntheses of quinazolinones that we have been able to accomplish. A complete understanding of the mechanism will require the development of synthetic methods that will allow the isolation and characterization of the active enolate species. Further investigations into the factors that influence the stereochemistry of these reactions are under way in several laboratories. We hope that the results presented herein will encourage others to explore this area of research.

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(33) The concentration of PhCCLi refers to the concentration of the monomer unit in units of normality (N).

(34) A low basal reactivity of 13 without intervention of additional lithium acetylide could explain the reduced fractional order in PhCCLi. Indeed, if the rate data are fit to $k_{\text{obsd}} = (13)^b + c$, a small nonzero intercept, c, is accompanied by a fractional order of b = 0.54. We hasten to add, however, that such fits in which fractional orders and nonzero intercepts are adjustable parameters are inordinately sensitive to the quality of the data. In our opinion, the closer fit to a one-half order cannot be interpreted beyond simply a demonstration of the general principle.

(35) The values of $k_{\text{obsd}}$ are independent of LiHMDS and free hexamethyl disilazane concentrations (zeroth order).

(36) Simple O-alkylations of quinazolinone 5 were problematic. O-Silylation proceeded without event, but desilylation tended to occur under the conditions of the 1,2-addition.


(38) Trauner and co-workers recently reported a crystal structure of an aryllithium with an ortho methoxymethyl protected phenol in which only the methoxy group coordinates to lithium: Hughes, C. C.; Scharn, D.; Mulzer, J.; Trauner, D. Org. Lett. 2002, 4, 4109.

(39) Quenching the reaction with aqueous NH$_4$Cl followed by an extractive workup affords a crude mixture of two compounds displaying spectroscopic behavior consistent with tautomeric imino ethers. Alternatively, quenching the reaction with 2 N HCl affords the dihydroquinazoline.

(40) The data for the 18 runs used to determine the order in PhCCLi were fit to eq 7 and averaged, affording $\alpha = 1.01 \pm 0.09$. 

Figure 11. Plot of $k_{\text{obsd}}$ versus [PhCCLi] in 7.75 M THF/pentane for the 1,2-addition of PhCCLi to dimer 13 (0.005 N of 8) at 10 °C. The curve depicts an unweighted least-squares fit to $k_{\text{obsd}} = \alpha\text{[PhCCLi]}^b (\alpha = (1.16 \pm 0.01) \times 10^{-3}, b = 0.42 \pm 0.01)$.

Figure 12. Plot of $k_{\text{obsd}}$ versus [THF] in pentane cosolvent for the 1,2-addition of PhCCLi (0.20 N) to 13 (0.005 N of 8) at 10 °C. The curve depicts an unweighted least-squares fit to $k_{\text{obsd}} = \alpha\text{[THF]} + k' \times (k = (-2.29 \pm 0.02) \times 10^{-3}, k' = (8.0 \pm 0.1) \times 10^{-4}$).

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of nonnucleoside reverse transcriptase inhibitors 2-4. Using unprotected quinazolinones with consequent in situ formation of lithium salt 8 markedly simplifies the synthesis by avoiding a formal protection-deprotection sequence. The coexistence of five lithiated species, however, introduces potentially enormous structural and mechanistic complexities.

We have taken a step toward understanding the enantioslective addition by investigating the nonenantioselective variant in eq 2. Omission of the amino alkoxide 7 simplified the problem. Even so, the structural control necessary to carry out detailed rate studies required careful planning and an element of luck. We knew that readily purified LiHMDS13 could be used in excess as a proton scavenger without the intervention of LiHMDS mixed aggregates.9,14,15 The control of the lithium acetylide structure was essential. Although lithium acetylides in THF and THF/hydrocarbon mixtures normally exist as mixtures of cyclic dimers and cubic tetramers, we found that PhCCLi exists as dimer 14 to the exclusion of tetramer 15 in THF and THF/pentane mixtures. The reluctance to form cubic tetramers is unique to this particular lithium acetylide/solvent combination16 for reasons that are unclear.18

Characterizing and controlling the structure of lithium quinazolinide salt 8 in the presence of PhCCLi was particularly challenging. At the very low temperatures used to investigate solution structures, a mixture of excess PhCCLi and 8 in THF/pentane solutions affords primarily ladder-based mixed tetramer 16 (or an isomeric ladder) along with low concentrations of mixed dimer 13. However, the conditions that are optimal for rate studies, low total mixed aggregate concentrations, high THF concentrations, and elevated temperatures, promote the formation of mixed dimer 13. Consequently, the rate studies were carried out with mixed dimer 13 as the dominant mixed aggregate (≥90%; Figure 9), rendering tetramer 16 largely inconsequential.

Monitoring the rate of the 1,2-addition by in situ IR spectroscopy and 19F NMR spectroscopy provided self-consistent results; the high resolution offered by 19F NMR spectroscopy was particularly convenient.29 Given the complexity of this case study, we took special precautions to show that the reaction was first order in dimer 13. (A method based on a nonlinear least-squares best fit to eq 7 is noteworthy.) At low THF concentrations wherein tetramer 16 becomes a significant component, deviations from first order are observed. Control experiments show that LiHMDS and its conjugate acid (HMDS) do not influence the rate. The reaction also appears to be zeroth order in THF, indicating no additional per-lithium solvation of 13 or 14 occurs en route to the rate-limiting transition structure. Finally, an approximate half-order dependence on PhCCLi indicates that PhCCLi dimer 14 dissociates to a dissolved monomer before the 1,2-addition. The collective concentration dependencies are consistent with the idealized rate law and mechanism illustrated in eqs 8-10.

Although, in principle, mixed dimer 13 contains the components necessary for a 1,2-addition, the structural and rate data implicate a transition structure of stoichiometry [(PhCCLi)2-(8)(THF)b]2 (eq 10).41,42 Of course, the rate law does not provide insight into connectivity or the three-dimensional structure. We envision [(PhCCLi)2(8)(THF)b]2 as a composite of mixed dimer 13 and PhCCLi(THF)2 monomer and provide 22 as a working model. The most important implication of this model is that mixed dimer 13 is simply a protected quinazolinone and the PhCCLi component of mixed dimer 13 is of no mechanistic consequence.

![Figure 13](image)

Figure 13. Plot of $k_{obs}$ versus [THF] in pentane cosolvent for the 1,2-addition of PhCCLi (0.05 N) to 11 (0.005 M) at -40 °C. The curve depicts an unweighted least-squares fit to $k_{obs} = a[THF]^b$ ($a = (2.1 ± 0.2) \times 10^{-4}$, $b = 1.09 ± 0.04$).

We investigated the analogous 1,2-addition to O-protected quinazoline 11 to understand the nuances of the 1,2-addition to lithium quinazolinide 8. The methoxymethyl protecting group was chosen due to its ease of preparation;26 mounting evidence argues that the often-cited special (polydentate) ligating properties of acetals are overstated.37,38 Quinazoline 11 is $10^3-10^5$ times more reactive than mixed dimer 13 toward 1,2-addition, qualitatively consistent with the relative electron densities on 11 and 13. The first-order dependence on the THF concentration (Figure 13) and the half-order dependence on the PhCCLi concentration are consistent with a trisolvated PhCCLi-monomer-based addition. Conventional thinking might suggest that the three coordinated THF ligands implicate a transition structure such as 23 lacking an N-Li interaction (and the affiliated Lewis acid assistance43) so as not to exceed four-coordinate lithium. One could further argue that this pathway does not appear in the 1,2-addition to mixed dimer 13 due to the excessive electron density that would develop at the transition structure or the steric demands of the mixed dimer coordination sphere.

![Structured Chemical Image](image)

![Structured Chemical Image](image)

Conversely, we believe that the observed trisolvation does not necessarily exclude a Li−N interaction. There is evidence that lithium can exceed four-coordinate.34−38 Three poignant examples include: (1) octahedral +Li[(η3-DME)]3, commonly observed crystallographically;34 (2) a trigonal bipyramidal +Li-(THF)3 observed crystallographically;35 and (3) (Me3Si)2NLi-(THF)4 (and the oxetane-solvated analogue) observed spectroscopically.36 Therefore, we submit that a contact ion pair such as 24 is reasonable.37,38 In fact, reflecting back on transition structure 22, it is not altogether obvious that the six THF ligands would necessarily be distributed evenly on the three lithiums as drawn.

Conclusion

The proximity of an electrophilic imine moiety and potentially nucleophilic acetylide fragment in mixed dimer 13 is provocative. It might be tempting to invoke an intraggregate condensation. Nonetheless, the rate studies lead us to conclude that mixed dimer 13 is simply an O-protected quinazolinone that reacts with an external (additional) disolvated PhCCLi monomer via transition structure 22. The condensation of PhCCLi is shown to react analogously through a more highly solvated analogue suggested to be 23 or 24.

In principle, such studies move us closer to understanding how the enantioselective addition in eq 1 occurs. In practice, significant speculation would be premature. We ask one rhetorical question: If mixed dimer 13 or its protected quinazolinone, is it possible that chiral lithium amino alkoxide 7 converts lithium quinazolinide 8 to a mixed aggregate that is functionally an O-protected form bearing a chiral auxiliary? We suspect that, despite the complexity of the reaction mixture in eq 1, the high enantioselectivity likely derives from a single, compelling control element.

Experimental Section

Reagents and Solvents. THF and pentane were vacuum-transferred from degassed blue or purple stills containing sodium benzophenone ketyl. The pentane still contained 1% tetraglyme to dissolve the ketyl. Air- and moisture-sensitive materials were manipulated using vacuum line and syringe techniques. Quinazolinone 5 was prepared using a literature procedure.1 Quinazolinones [1−15N]5 and [3−15N]5 were prepared using [15N]chloroaniline (>99%) and [15N]benzyl isocyanate (99%).1 [6Li]PhCCLi and [6Li,13C]PhCCLi were prepared in situ using triply recrystallized [6Li]LiHMDS3 and commercially available phenylacetylene and [13C-2]phenylacetylene. The phenylacetylenes were vacuum-transferred from 4 Å molecular sieves. Lithium salt 8 was generated in situ from quinazolinone 5 and LiHMDS.

NMR Spectroscopic Analyses. All NMR tubes were prepared using stock solutions and sealed under partial vacuum. [6Li]LiHMDS was kept in excess at all times to scavenge the acidic protons of phenylacetylene and quinazolinone. Standard 6Li, 13C, and 19F NMR spectra were recorded on a 400 MHz spectrometer at 58.84, 100.58, and 376.38 MHz (respectively). The 6Li, 13C, and 19F resonances are referenced to 0.3 M [6Li]LiCl/MeOH at −90 °C (0.0 ppm), the CH2O resonance of THF at −110 °C (67.35 ppm), and C6F6 (−162.55 ppm set at the recording temperature), respectively. The spectra were recorded with a three-channel probe designed to accommodate lithium and carbon pulses. 6Li, 13C-HMQC spectroscopy21 and 1J(6Li,13C)-resolved spectroscopy have been reported.9,22−23

Rate Studies by 19F NMR Spectroscopy. All spectroscopic samples for monitoring the rate of the 1,2-additions were prepared using stock solutions, sealed under partial vacuum, and stored at −78 °C (for mixed dimer 13) or at −196 °C (for quinazoline 11) before analysis. Detailed protocols are outlined in the Supporting Information.

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Supporting Information Available: NMR spectra, rate data, and experimental protocols (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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