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# Lithium Pinacolone Enolate Solvated by Hexamethylphosphoramide

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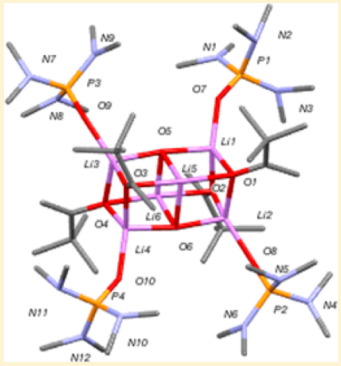
Supporting Information

**ABSTRACT:** We report the crystal structure of a substoichiometric, HMPA-trisolvated lithium pinacolone enolate tetramer $(LiOPin)_4 \cdot HMPA_3$ abbreviated as $\mathbf{T_3}$. In this tetramer one HMPA binds to lithium more strongly than the other two causing a reduction in spatial symmetry with corresponding loss of $C_3$ symmetry. A variety of NMR experiments, including HMPA titration, diffusion coefficient-formula weight (D-FW) analysis, and other multinuclear one- and two-dimensional NMR techniques reveal that $\mathbf{T_3}$ is the major species in hydrocarbon solution when more than 0.6 equiv of HMPA is present. Due to a small amount of moisture from HMPA or air leaking into the solution, a minor complex was identified and confirmed by X-ray diffraction analysis as a mixed aggregate containing enolate, lithium hydroxide, and HMPA in a 4:2:4 ratio, $[(LiOPin)_4 \cdot (LiOH)_2 \cdot HMPA_4]$, that we refer to as pseudo-$\mathbf{T_4}$. A tetra-HMPA-solvated lithium cyclopentanone enolate tetramer was also prepared and characterized by X-ray diffraction, leading to the conclusion that steric effects dominate the formation and solvation of the pinacolone aggregates. An unusual mixed aggregate consisting of pinacolone enolate, lithium diisopropyl amide, lithium oxide, and HMPA in the ratio 5:1:1:2 is also described.




## INTRODUCTION

Hexamethylphosphoramide (HMPA) as an additive or cosolvent plays an intriguing role in reactions of organolithium reagents by altering rates and yields.[1] Its influence on selectivity is most striking and has been intensively studied. For example, HMPA influences the regioselectivity of enolate addition to $\alpha,\beta$-unsaturated compounds.[2] It also influences the stereoselectivity of asymmetric addition and the enolization of carbonyl compounds.[3] In many cases, addition of HMPA results in reaction rate acceleration and higher yields of thermodynamic products.[4] An explanation for the differing reaction selectivity attributed to the presence or absence of HMPA involves deaggregation or formation of ion pairs.[5] Steric effects are also invoked because HMPA is rather large compared to the typical ethereal solvents used with many organolithium reagents. HMPA is also believed to bind more strongly to lithium than THF or diethyl ether.[6] However, recent studies serve to highlight the very complicated nature of HMPA's interaction with organolithium complexes. Thus, the aggregation state of organolithium compounds was shown to increase,[7] decrease,[8] remain unchanged,[9] or form separated ion pairs[10] (SIP) due to the introduction of HMPA. Aggregate behavior in the presence of HMPA is clearly sensitive to the amount added and to the temperature as well as being substrate specific. HMPA–Li interactions are convenient to study by NMR because the direct $J$-coupling between $^{31}P$ and $^{6}Li/^{7}Li$ is observable.[11]

The mechanism of ketone enolization is clearly dependent upon solvation and aggregation state of the base.[12] Ultimately the observation that enolization leads to various enolate aggregates and mixed aggregates, both of which are also solvated, prompted this study. In this paper, we utilize pinacolone enolate as a model to demonstrate the influence of HMPA upon the enolate aggregation state. Reich has gained deep and comprehensive insight into aggregation state, solvation, and ion pair status for over 120 lithium species from HMPA titration experiments below −90 °C.[13] Reich's elegant spectroscopy study concluded that HMPA has only a minor effect on structure at substoichiometric amounts.[14] Thus, for lithium enolates of simple ketones which form cubic tetramers in THF, HMPA replaces THF during titration but does not necessarily disaggregate, i.e., dissociation from tetramer to trimer, dimer, or monomer, or generate SIP's. Nonetheless, with high concentration of HMPA, Reich noted dissociation and formation of ions for the lithium enolates of bisphenyl-2-propanone derivatives, reported as forming dimers and monomers in THF by Streitwieser.[15] Thus, spectroscopic studies led to different observations about aggregate structure.[16]

Single crystal structures of HMPA-solvated lithium enolates do not exist. The only closely related structure is that of HMPA-solvated lithium phenoxide complex $[(PhOLi)_3 \cdot LiNCS \cdot HMPA_4]$ reported by Snaith.[17] This mixed-anion complex forms a structurally similar tetrameric array with three phenoxides and four Li atoms, three of which bear terminal HMPA ligands, and the fourth HMPA forms a $\mu_3$ bridge. A similar bridged HMPA has been observed in the structures of $(KNCS)_3 \cdot HMPA_5$ $(\mu_3)$[17] and $(LiBr)_2 \cdot HMPA_3$ $(\mu_2)$.[18] Snaith also reported an unresolved disorder among HMPA ligands in a tetramer characterized as $(PhOLi \cdot HMPA)_4$ by molecular mass measurement.[17] This tetra-HMPA-solvated tetrameric structure was assigned on the basis of $^{7}Li$ and $^{31}P$ NMR spectroscopy.

**Received:** February 20, 2015
**Published:** May 1, 2015





DOI: 10.1021/jacs.5b01906
J. Am. Chem. Soc. 2015, 137, 7347–7356

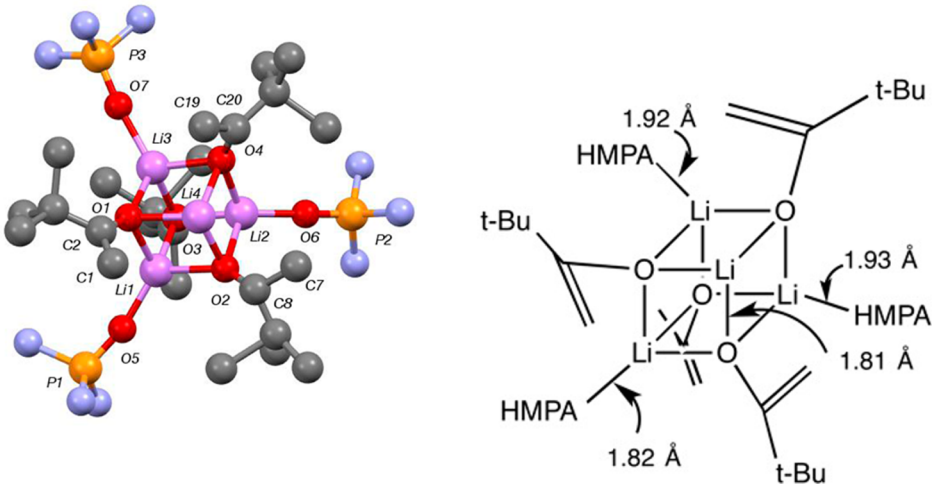



**Figure 1.** Crystal structure of $(PinOLi)_4 \cdot HMPA_3$. Hydrogen atoms omitted for clarity.

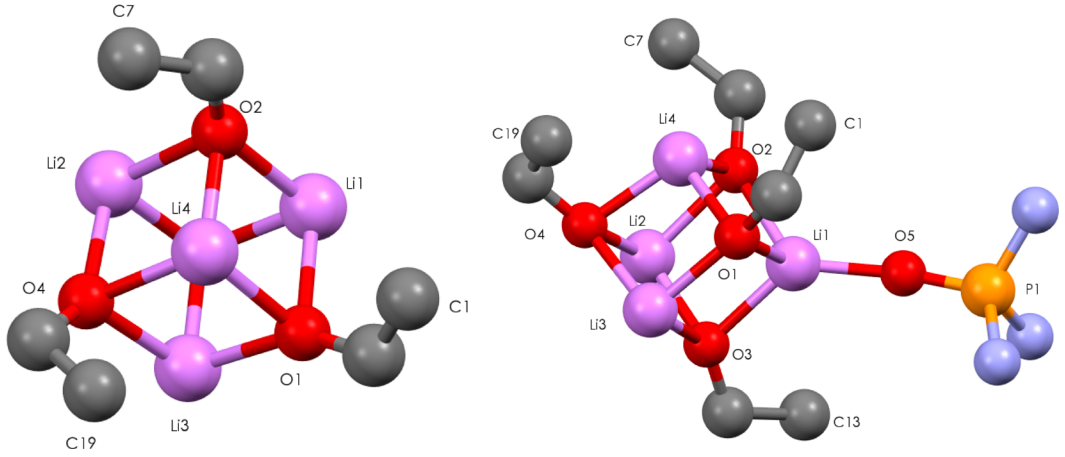



**Figure 2.** Left: Simplified skeleton of $(PinOLi)_4 \cdot HMPA_3$ tetrameric structure from the perspective of an approximately $C_3$ symmetry axis. Right: Distorted $Li_4O_4$ cubic core with all four C═C double bonds and the "tight" HMPA molecule. All the hydrogen atoms and methyl groups have been omitted.

This study targets HMPA-solvated lithium enolate crystal structures and correlates these with their solution structures using diffusion NMR methods. Previous spectroscopic studies utilized HMPA in ethereal solvents; however, in this paper the solution-state study is limited to hydrocarbon solvent.

## RESULTS AND DISCUSSION

**Characterization of HMPA-Solvated Lithium Pinacolone Enolate in the Solid State.** *Crystal Structure of Tri-HMPA-Solvated Lithium Pinacolone Enolate Tetramer.* Lithium pinacolone enolate (LiOPin) was generated in situ by slowly adding the ketone to a lithium amide base (1.05 equiv) in hydrocarbon solvent at 0 °C. After adding HMPA, the solution was stored at low temperature to initiate crystallization. Two bases were utilized, lithium diisopropylamide (LDA) and lithium bis(trimethylsilyl)amide (LiHMDS). Pentane, heptane, and toluene were used as solvents. Crystallization temperature ranged from −20 °C to −80 °C. The amount of HMPA was adjusted from 0.5 to 3.0 equiv. After systemically monitoring all these combinations, we found that the amount of HMPA used was crucial for crystallization with 0.7−0.9 equiv of HMPA providing the optimum result. Hence, adding 0.75 equiv of HMPA to 1.0 M LiOPin in pentane yielded nicely shaped, colorless crystals suitable for X-ray diffraction analysis that grew overnight at −20 °C. No crystallization was observed if more than 1.5 equiv of HMPA was added even at −80 °C. In all cases, recrystallization from pentane provides very pure crystals suitable for X-ray diffraction and further NMR analysis.

As shown in Figure 1, the X-ray structure determination reveals a coordinatively unsaturated trisolvated cubic tetramer ($\mathbf{T}_3$) formed bearing one tricoordinate lithium site, i.e., Li4. One HMPA molecule binds more strongly (Li1−$O_{HMPA}$ bond 1.82 Å) than the other two (Li2−$O_{HMPA}$ bond 1.93 Å and Li3−$O_{HMPA}$ bond 1.92 Å). The cubic framework is slightly distorted. The distance between the bare lithium, i.e., Li4, and one of the adjacent enolate oxygen atoms is only 1.81 Å, much shorter than all the other 11 Li−$O_{enolate}$ bonds (1.95 Å to 2.06 Å) in this structure. We also note that a substoichiometric tetramer of trimethylsilyl methyl lithium solvated by only two *tert*-butyl methyl ether molecules was reported by Stalke et al.[19] The only similar substoichiometric solvated tetrameric lithium enolate structure is tris-pyridine-solvated lithium pinacolone enolate tetramer $(PinOLi)_4 \cdot Pyr_3$ reported by Jacobsen and co-workers in 1992 by combining pinacolone, LiHMDS, and pyridine in the ratio 1:1:0.65 in methylcyclohexane.[20] However, in Jacobsen's structure the three Li−$N_{Pyr}$ bonds are approximately same (2.04, 2.05, and 2.07 Å) with a triad symmetry axis through the bare lithium. It is noteworthy that in the Jacobsen structure the


DOI: 10.1021/jacs.5b01906
J. Am. Chem. Soc. 2015, 137, 7347−7356

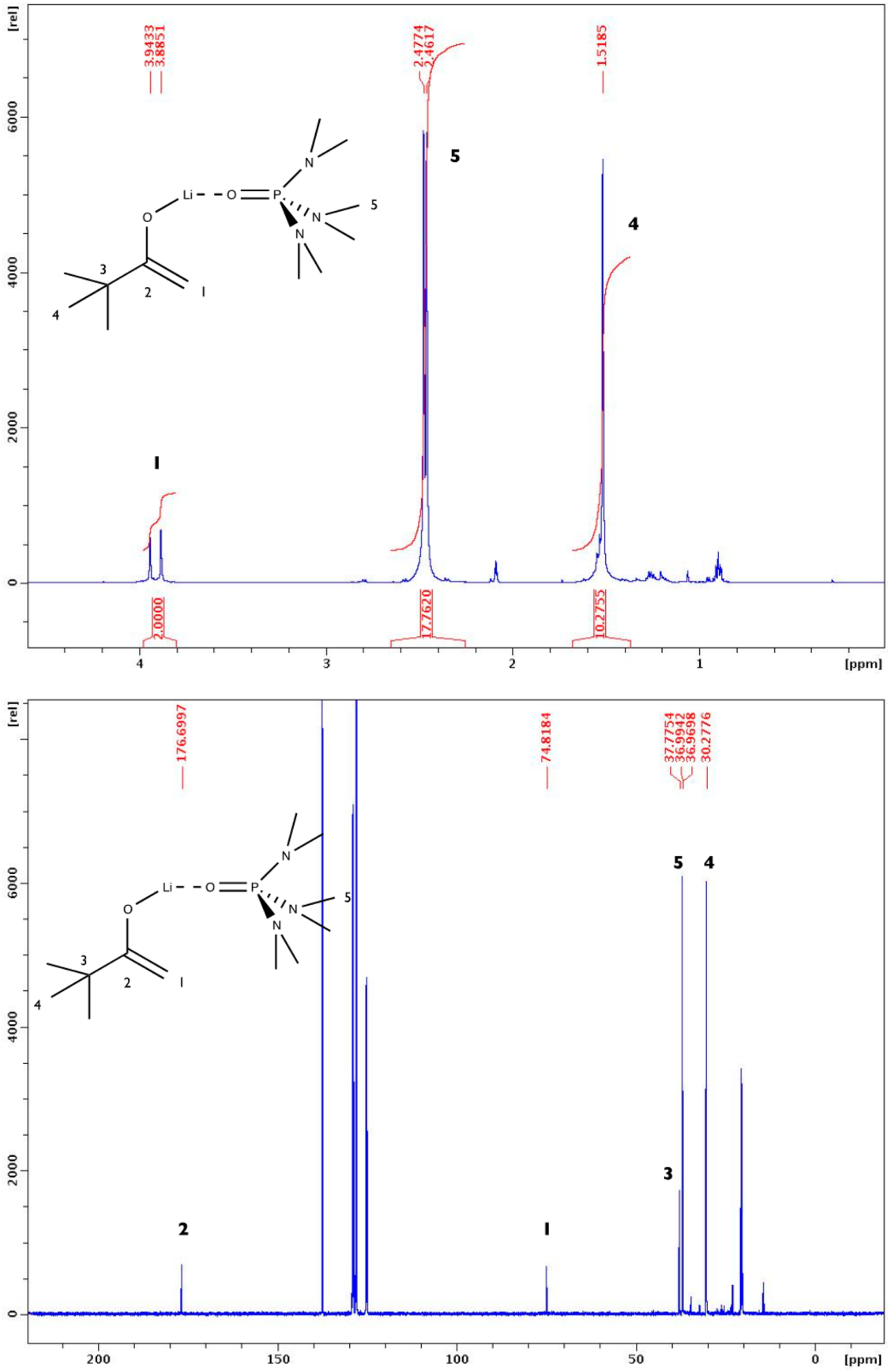



**Figure 3.** $^{1}$H NMR (delay time 60 s) and $^{13}$C NMR of LiOPin/HMPA $\mathbf{T}_3$ complex in toluene-$d_8$ at −20 °C.



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*J. Am. Chem. Soc.* 2015, 137, 7347−7356

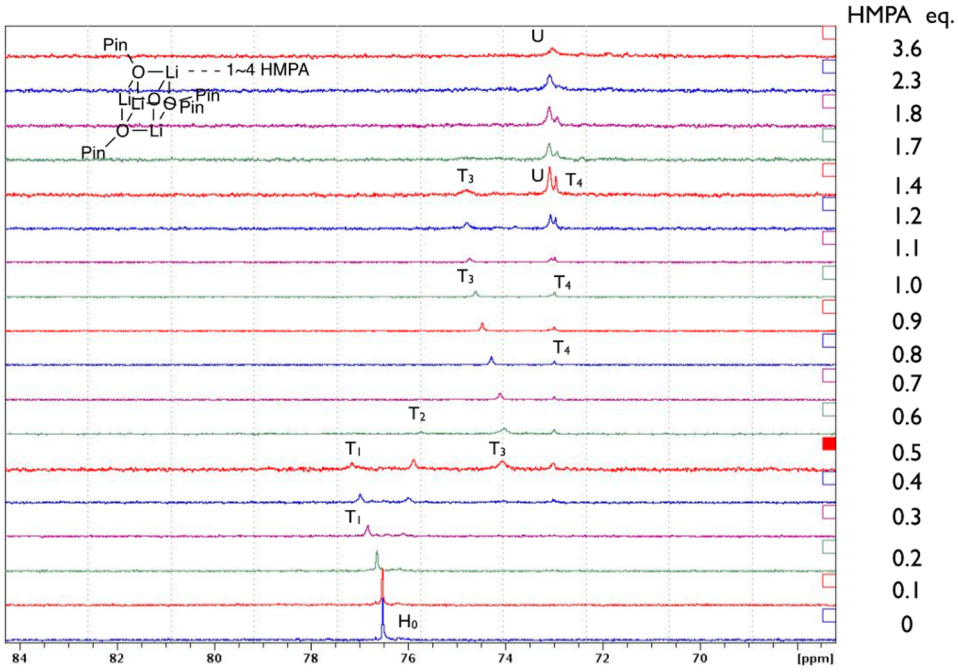


**Figure 4.** HMPA titration experiment of lithium pinacolone enolate in cyclohexane-$d_{12}$ at room temperature showing the 70−80 ppm region (=$CH_2$ carbon of enolate) of the $^{13}C$ NMR spectrum.

tricoordinate lithium is also more closely associated with all adjacent enolate oxygens (avg Li−$O_{enoalte}$ bonds 1.86 Å) than the other nine Li−$O_{enoalte}$ bonds (avg 1.97 Å) by approximately 0.1 Å. The observation that the unsolvated lithium exhibits shorter Li−$O_{enoalte}$ bonds is related to its smaller coordination number.

The orientation of the terminal C=C double bond farthest from the bare lithium in Figure 1 leads to unequal HMPA ligands as determined by the different Li−$O_{HMPA}$ bond distances. It is important to note that in this $\mathbf{T_3}$ aggregate, all the *tert*-butyl (*t*-Bu) groups and HMPA ligands are oriented as far away from the cubic core as possible to lower the steric interactions. Therefore, each terminal C=C bond is directed toward a specific $Li_2O_2$ face of the tetramer. Thus, in Figure 1 it can be clearly seen that the C=C enolate bonds cover the top, front, right, and bottom faces of the cube. More specifically as depicted in Figure 2, the coordinatively unsaturated lithium (Li4) is surrounded by three counterclockwise-rotating C=C bonds, each associated with one of the three faces of the cube adjacent to Li4. All three terminal methylene carbons are more closely associated with Li4 (2.97, 2.92, 2.59 Å) than they are to Li1, Li2, or Li3 (3.54, 3.38, 3.35 Å) respectively. The terminal C=C bond farthest from Li4 covers the Li1−O2−Li2−O3 face, consequently the distance C13−Li1 (3.24 Å) is significantly shorter than C13−Li2 (3.73 Å). The average length of three C=C bonds in this structure is 1.35 Å and one is somewhat longer and is attributed to some disorder. The equivalent average value is 1.33 Å in tripyridine-solvated lithium pinacolone enolate tetramer in which the lengths of four C=C bonds are identical; the average length is 1.33 Å in tetra-tetrahydrofuran-solvated lithium pinacolone enolate tetramer[21] and 1.34 Å in unsolvated lithium pinacolone enolate hexamer.[22] It appears that the Li1 atom interacts with the C=C(13) double bond. Although we still do not understand the nature of these Li−oxallyl anion $\pi$ interactions, this crystal structure strongly supports the presence of such an interaction between the Li atom and oxallyl O−C=C system within this lithium enolate structure. We first noticed these identical $\pi$-oxallyl−Li interactions in the crystal structure of hexameric, unsolvated $(LiOPin)_6$. Clearly the tricoordinated lithium cations in these structures seek to interact with electron density in the $\pi$ orbitals of the enolate as is also seen in the crystal structures of some allyllithium compounds.[23] Moreover, in the hindered crystal structure of tetrapyridine-solvated lithium pinacolone enolate tetramer $(LiOPin{\cdot}Pyr)_4$, two Li−N bonds (avg 2.17 Å) are just slightly longer than the other two (avg 2.13 Å), and these correlate directly to two unusually long C=C bonds (1.45 Å) possibly due to disorder in this structure.[19] Comparing the HMPA aggregate in Figure 1 to Jacobsen's $(LiOPin)_4{\cdot}Pyr_3$ crystal structural, in which all C=C bonds (avg 1.33 Å) and Li−N bonds (avg 2.05 Å) are equal, we propose that an incremental steric effect is the major reason for the interaction between lithium cations and C=C double bonds.

**Characterization of HMPA-Solvated Lithium Pinacolone Enolate Complexes in Solution.** A series of NMR experiments were conducted to characterize these LiOPin−HMPA aggregates in hydrocarbon solution as described. Upon dissolving crystalline samples of the $(PinOLi)_4{\cdot}HMPA_3$ in toluene-$d_8$, one-dimensional NMR spectra indicate that there is only one dominant lithium enolate complex. It was not possible for us to distinguish free and bound HMPA from these one-dimensional spectra. Even at −80 °C, only one set of HMPA peaks is observed as a $^1H$ (doublet, $^3J_{H-P} = 9.6$ Hz), $^{13}C$ (doublet, $^2J_{C-P} = 4.0$ Hz, decoupled by $^1H$), $^{31}P$ (singlet), and $^6Li$ (singlet) in the respective NMR spectra,[24] see Figures S1 and S2, Supporting Information. HSQC and HMBC spectra were also obtained to confirm the assignments noted above, Figures S3 and S4, Supporting Information. A few impurities coexist in these $\mathbf{T_3}$ spectra and were identified as pentane and diisopropylamine (DIPA) from the mother liquor in which the crystals were prepared. By integration of the proton spectrum, HMPA is always present at more than 0.75 equiv, see Figure 3, no matter how carefully the crystals were washed with pentane, i.e., typically around 0.85−1.1 equiv was observed. Possibly the highly polar


DOI: 10.1021/jacs.5b01906
J. Am. Chem. Soc. 2015, 137, 7347−7356

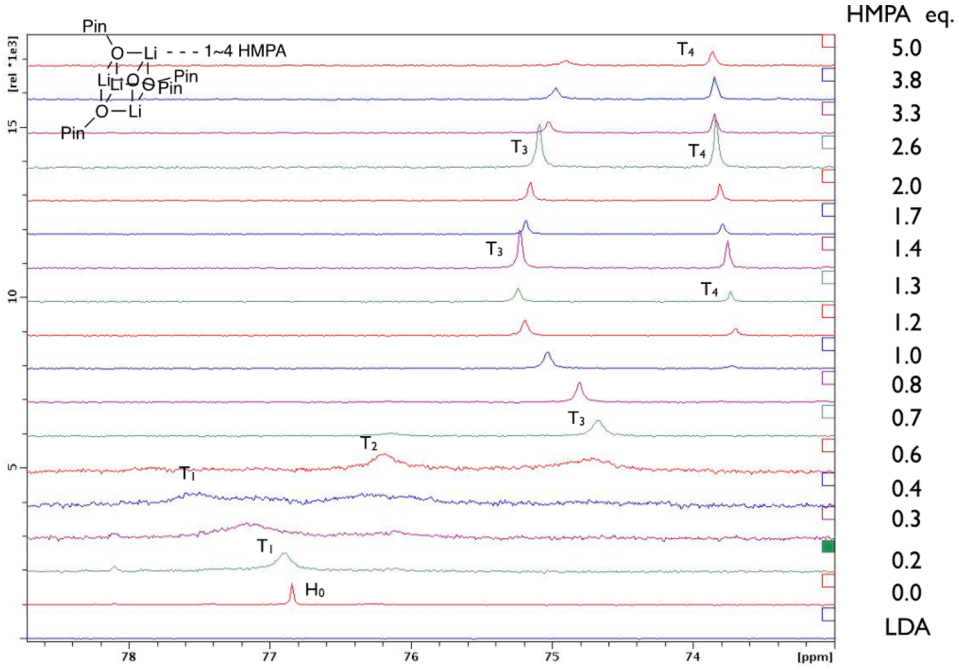


**Figure 5.** HMPA titration experiment of lithium pinacolone enolate in toluene-$d_8$ at −20 °C showing the 70−80 ppm region (=$CH_2$ carbon of enolate) of the $^{13}C$ NMR spectrum.

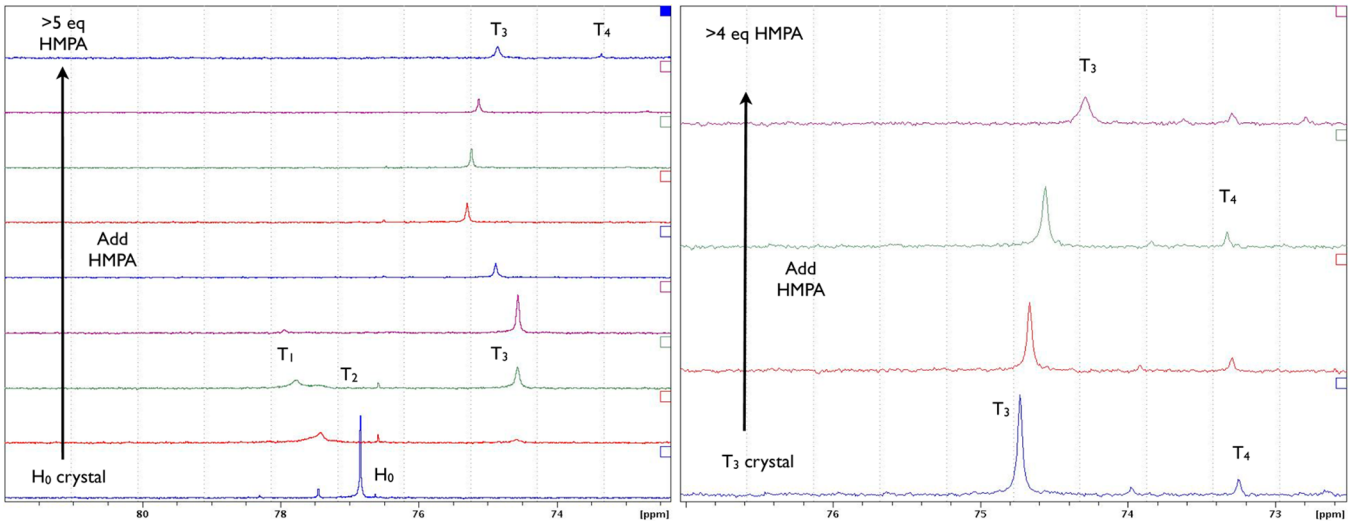


**Figure 6.** HMPA titration experiment of lithium pinacolone enolate in toluene-$d_8$ at −20 °C. The 70−80 ppm region (=$CH_2$ carbon of enolate) of the $^{13}C$ NMR spectrum. (a) Left: beginning with $H_0$ crystal; (b) right: beginning with $\mathbf{T_3}$ crystal.

HMPA prefers to adhere to the crystal surface than to dissolve in nonpolar pentane or alternatively some of the enolate is protonated during the washing and releases free HMPA that is not completely removed along with the free pinacolone. We also observed a significant resonance shift of the enolate terminal methylene peaks in both the $^1H$ and $^{13}C$ spectra, depending on the amount of HMPA present that we characterized by titration experiments (vide infra).

*Characterization of Species in LiOPin/HMPA Solution.* A HMPA titration experiment was performed to determine how HMPA influences the solution structure of lithium pinacolone enolate. Previously published crystal structures and HMPA titration studies suggest that lithium enolates of simple ketones preserve their cubic tetramer core aggregation state with many solvents in both solid and solution structures.[25] Hence, our first titration experiment was to add HMPA into a solution of LiOPin in cyclohexane-$d_{12}$, a nonaromatic hydrocarbon solvent, at room temperature. The results are depicted in Figure 4. LiOPin solution was generated in situ by mixing pinacolone with a slight excess, 1.05 equiv, of LDA to suppress self-aldol reaction. Upon titration of 0−1.0 equiv of HMPA into the enolate solution, four different LiOPin/HMPA complexes appear in sequence. The third to appear in this sequence is identified as $\mathbf{T_3}$ by direct comparison of its spectrum with that of the spectrum of $\mathbf{T_3}$ obtained from dissolution of a crystalline sample that was characterized by diffraction analysis. Notably, $\mathbf{T_3}$ is the major component in solution once 0.6−1.0 equiv of HMPA is added to the solution. Curiously this titration result matches our empirically optimized conditions for preparing $\mathbf{T_3}$ crystals with 0.7−0.9 equiv of HMPA. When more than 1 equiv of HMPA was



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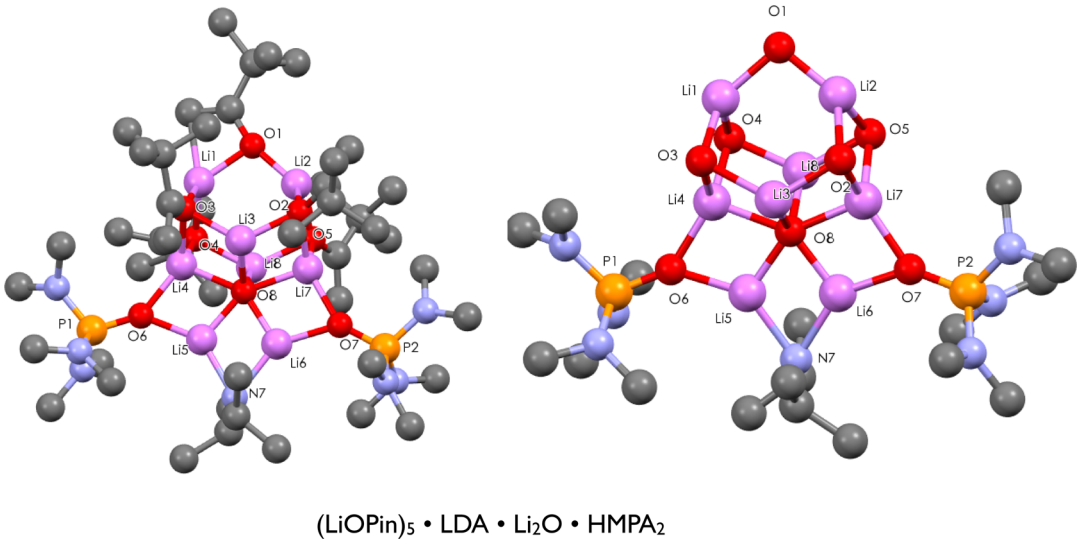



**Figure 7.** Crystal structure of $[(LiOPin)_5 \cdot LDA \cdot Li_2O \cdot HMPA_2]$ (hydrogen atoms omitted). A simplified skeleton with five Pin residues attached to O1–O5 are omitted for clarity in the structure on the right.

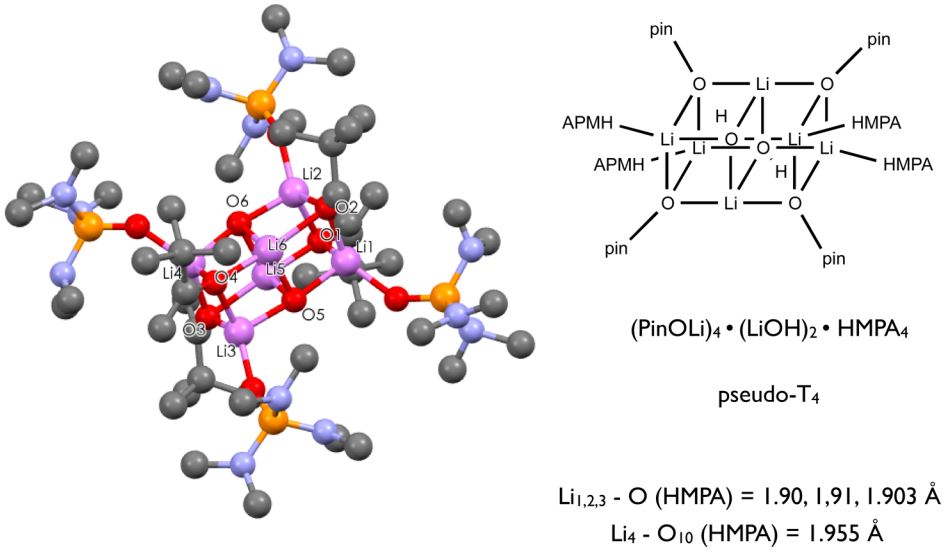



**Figure 8.** Crystal structure of $[(LiOPin)_4 \cdot (LiOH)_2 \cdot HMPA_4]$ (pseudo-$\mathbf{T_4}$), each enolate is solvated by one HMPA (hydrogen atoms omitted).

added, a fifth unknown complex appeared. This titration experiment was repeated in toluene, but much broader peaks were observed so the sample was cooled to −20 °C to achieve a reasonable resolution, Figure 5. Analogously in toluene solution, we also observed that a set of four different methylene carbon peaks emerged in sequence during titration and that these moved upfield with increasing HMPA. In light of Reich's titration experiments, this trend strongly suggests that all four complexes detected are tetrameric aggregates with a different solvation environment. Therefore, we label them $T_1$ to $T_4$, with T indicating a tetrmeric aggregation state and the subscript representing the number of HMPA molecules binding to the tetramer. Owing to NMR peak line broadening in toluene solution, the fifth unknown peak shown in Figure 4, and labeled as U, overlaps with $T_4$ even at −60 °C as shown in in Figure 5.

The following additional observations are noteworthy. When a toluene solution of LiOPin unsolvated hexamer ($H_0$) prepared by dissolution of a crystalline sample was titrated by HMPA, Figure 6a, only $\mathbf{T_1}$–$\mathbf{T_4}$ complexes were observed with $\mathbf{T_3}$ being the dominant component. When we titrated the toluene solution prepared directly from isolated $\mathbf{T_3}$ crystals, Figure 6b, only $\mathbf{T_3}$ and a tiny amount of $\mathbf{T_4}$ were observed. The methylene carbon peak of unknown complex (U) did not appear when we used samples prepared directly from crystals but did appear when the sample of LiOPin was prepared in situ with a slight excess of LDA. This result can be rationalized by assigning the unknown compound (U) as a HMPA-solvated mixed aggregate of LiOPin and LDA, e.g., $[(LiOPin)_n \cdot (LDA)_m \cdot HMPA_x]$. We assume that $n$ is larger than $m$ and also that $x$ would not be smaller than $n$, due to the fact that only a slight excess of LDA remains in solution and also that there is no detectable U unless more than 1.0 equiv of HMPA is added.

Our group has previously reported crystal structures of mixed aggregates consisting of enolates and amide bases such as $(LiOPin \cdot LDA \cdot DME_2)$[26] as well as a lithium enolate/LiHMDS complex with internal chelation of an electron-donating heteroatom atom in the side chain.[27] Collum's spectroscopic studies also confirm that LDA forms mixed aggregates with lithium enolate quantitativly in HMPA/THF solution.[28] Unfortunately, our attempt to obtain a single crystal of the



DOI: 10.1021/jacs.5b01906
J. Am. Chem. Soc. 2015, 137, 7347–7356

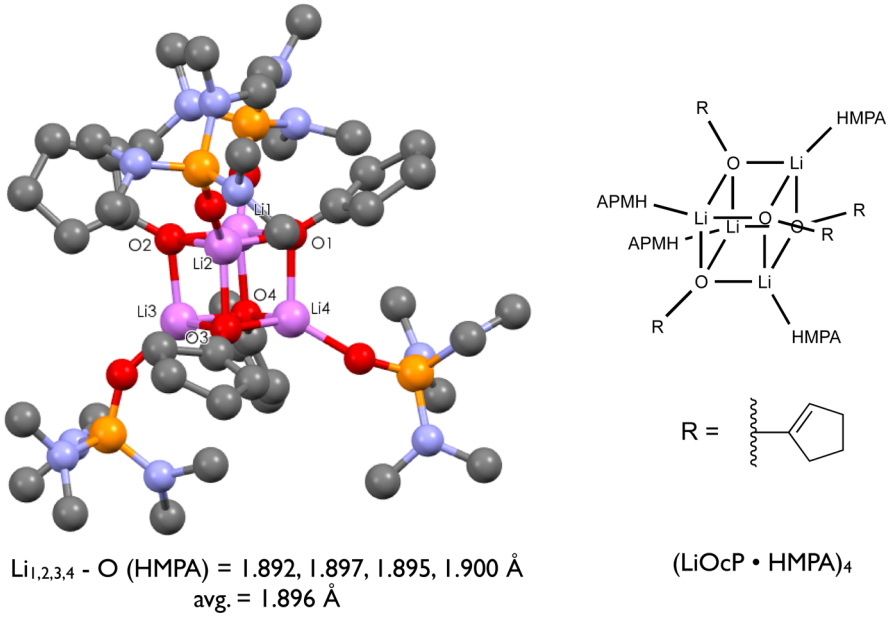



**Figure 9.** Crystal structure of $(LiOcP{\cdot}HMPA)_4$. Hydrogen atoms are omitted.

compound we have identified as U in the NMR spectra shown in Figures 4 and 5 was unsucessful. However, we characterized a very unique mixed aggregate crystal obtained from solutions when only 0.2−0.3 equiv of HMPA was added. This unique complex is depicted in Figure 7. The composition of this aggregate is five pinacolone enolates, one LDA, two solvating HMPA, and a dilithium oxide: $[(LiOPin)_5{\cdot}LDA{\cdot}Li_2O{\cdot}HMPA_2]$.[29] This result supports our assumption that compound U is most likely a mixed aggregate containing lithium enolate, LDA, and HMPA, but we hesitate to directly assign the structure of the species depicted in Figure 7 to this complex identified as U in these NMR spectra.

An intriguing observation encouraged us to pursue the crystal structure of $\mathbf{T_4}$. When $\mathbf{T_3}$ crystals were grown to obtain samples for NMR studies, we occasionally noticed the presence of a minor component when the crystals were allowed to stay in the mother liquor for several days. These particular samples contained both the major component identified as $\mathbf{T_3}$ and a minor component that we labeled $\mathbf{T_4}$ as seen in Figure 6. In contrast, the NMR samples of freshly prepared or recrystallized $\mathbf{T_3}$ crystals exhibited only $\mathbf{T_3}$ peaks. Thus, we concluded that some small amount of $\mathbf{T_4}$ is generated and may coexist with $\mathbf{T_3}$ in some samples after 1 day. Because $\mathbf{T_3}$ is the dominant component in the mixture, we never obtained $\mathbf{T_4}$ in our crystallization experiments. Therefore, if the crystallization of $\mathbf{T_3}$ could be inhibited by adding more than 1.5 equiv of HMPA, we felt that it might be possible to collect $\mathbf{T_4}$ crystals. Following this assumption, a delicate and tiny colorless crystal grew from 1.0 M LiOPin pentane solution with 3.0 equiv of HMPA at −20 °C after 3 days. X-ray diffraction analysis revealed an odd but not altogether surprising structure shown in Figure 8. We refer to this compound as pseudo-$\mathbf{T_4}$, because two lithium hydroxide molecules insert into one normal cubic structure. Thus, adding more HMPA and storing the sample for a longer time increases the possibility of absorbing moisture that we believe accounts for the presence of LiOH in this complex. This face-shared, double-cubic structure is unique for lithium enolates.[30] This structure is also the first mixed aggregate characterized that incorporates both lithium enolate and lithium hydroxide, although we have previously characterized a mixed aggregate consisting of pinacolone enolate, *tert*-butoxide, and KOH.[31] It is noteworthy that the four bulky *t*-Bu groups and the dimethylamino residues of HMPA build up a hydrophobic shell surrounding this aggregate. Considering our tris-solvated $\mathbf{T_3}$ structure and Jacobsen's slightly distorted tetrapyridine-solvated tetrameric structure, it is reasonable that a tetrasolvated $(LiOPin{\cdot}HMPA)_4$ cubic tetramer infrastructure is very unstable. Thus, due to steric constraints based upon the fact that HMPA is larger than both THF and pyridine, we could not crystallize a tetra-HMPA-solvated tetramer of pinacolone enolate whereas Jacobsen was able to characterize a $\mathbf{T_4}$ aggregate solvated by pyridine. By inserting two unsolvated lithium hydroxides that serve to expand the cubic core, it is possible to achieve the more stable pseudo-$\mathbf{T_4}$ structure with stoichiometry $[(LiOPin)_4{\cdot}(LiOH)_2{\cdot}HMPA_4]$ depicted in Figure 8.

To probe the steric effect influencing pseudo-$\mathbf{T_4}$ formation, we prepared a HMPA-solvated lithium cyclopentanone enolate (LiOcP) crystal by adding 0.75 equiv of HMPA to a 1.0 M pentane solution of lithium cyclopentanone enolate. We found that a tetra-HMPA-solvated tetramer $(LiOcP{\cdot}HMPA)_4$ easily crystallized at −20 °C and was characterized by X-ray diffraction as shown in Figure 9. The $Li{-}O_{HMPA}$ bonds in this complex average 1.90 Å, which is still slightly shorter than the shortest $Li{-}O_{HMPA}$ bond found in pseudo-$\mathbf{T_4}$. Hence, we suggest that this crystal structure provides additional evidence that the driving force for the formation of the coordinatively unsaturated $\mathbf{T_3}$ and pseudo-$\mathbf{T_4}$ structures of LiOPin/HMPA is indeed steric hindrance. When the bulky pinacolate is replaced by the smaller cyclopentanone enolate residue and solvated by HMPA or alternatively when HMPA is replaced by a sterically less demanding ligand such as THF or pyridine, a tetra-solvated cubic tetramer forms easily. Alternatively, we also prepared a LiOPin solution with 0.75 equiv of HMPA and 0.25−0.5 equiv of THF to determine the solvation of the pinacolone enolate tetrameric aggregate with mixed solvents, for example possibilities include $[(LiOPin)_4{\cdot}HMPA_2{\cdot}THF_2]$ or $[(LiOPin)_4{\cdot}HMPA_3{\cdot}THF]$. The tri-HMPA-solvated tetramer ($\mathbf{T_3}$) is the only crystal we observed, and this clearly did not incorporate


DOI: 10.1021/jacs.5b01906
J. Am. Chem. Soc. 2015, 137, 7347−7356

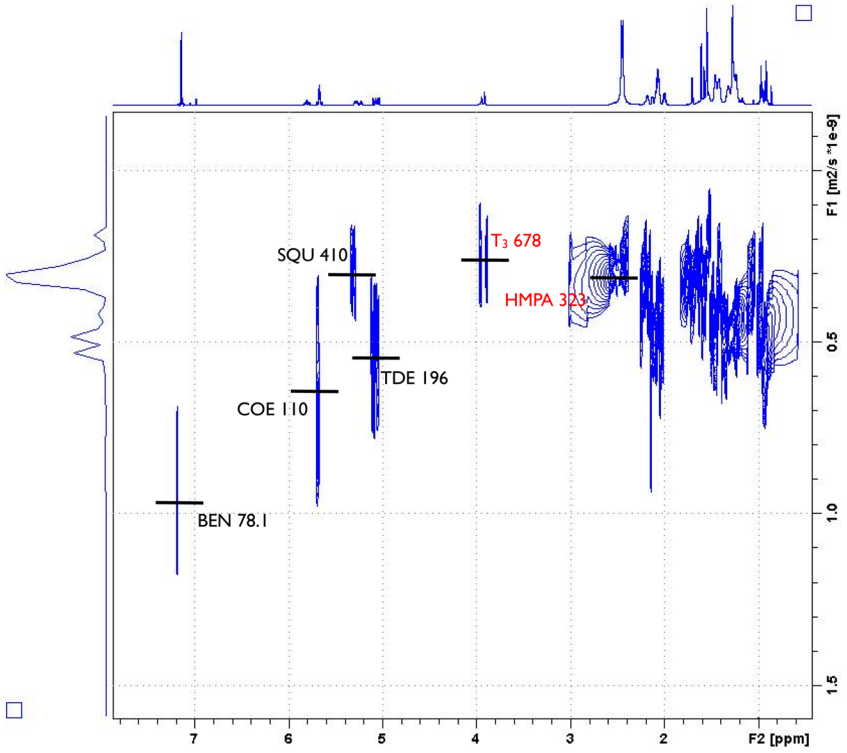
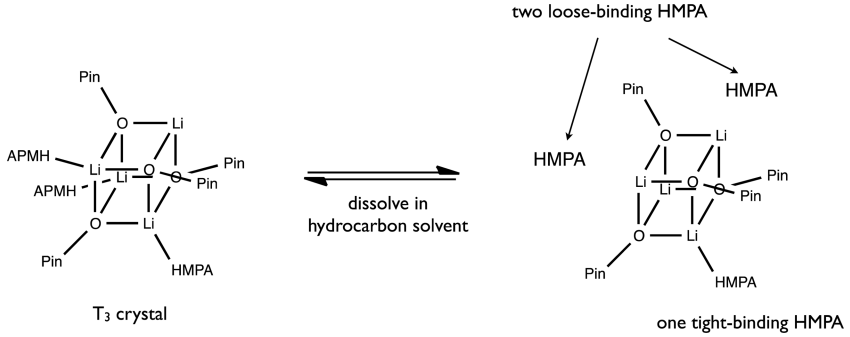



**Figure 10.** $^1$H DOSY of LiOPin/HMPA $\mathbf{T_3}$ complex in toluene-$d_8$ at −20 °C.

**Scheme 1. Dissolving LiOPin/HMPA $T_3$ Crystal in Hydrocarbon Solvents**




THF. It is noteworthy that as Collum has repeatedly pointed out in his elegant studies utilizing the bidentate ligand TMEDA that although deaggregation seems reasonable when bulky Lewis bases or bidentate ligands solvate organolithium aggregates, this is not a foregone conclusion given that we also have not observed the formation of HMPA-solvated LiOPin aggregates smaller than the tetramer or separated ion pairs in this study in hydrocarbon solvents. Thus, $\mathbf{T_3}$ is always the major component of the LiOPin/HMPA complex in hydrocarbon solution when more than 0.6 equiv of HMPA is present.

*Solvation State of $T_3$ by Using DOSY.* Diffusion-ordered $^1$H NMR spectroscopy (DOSY) and diffusion coefficient-formula weight (D-FW) correlation analysis[32] were carried out to study the solvation state of $\mathbf{T_3}$ complex in toluene solution. The FW of an unknown complex is determined by its diffusion coefficient (measured by DOSY) through the linear regression plot of the logarithms of diffusion coefficients against the known FWs of the references. Benzene (BEN, 78.11 g/mol), cyclooctene (COE, 110.2 g/mol), 1-tetradecene (TDE, 196.4 g/mol), and squalene (SQU, 410.7 g/mol) are added to $\mathbf{T_3}$ solution as internal references. The resonances of the enolate terminal methylene protons (3.8−4.0 ppm) and also the HMPA methyl protons (2.45 ppm) were monitored for our D-FW analysis, Figure 10.

We prepared the solution for D-FW analysis by dissolving $\mathbf{T_3}$ in toluene. D-FW analysis of this solution reveals that the formula weight of the complex in solution is approximately 678 g/mol. We note that the formula weight of $[(LiOPin)_4{\cdot}HMPA_3]$ $\mathbf{T_3}$ complex is 961 g/mol, while the formula weight of $[(LiOPin)_4{\cdot}HMPA_2]$ $\mathbf{T_2}$ complex is 782 g/mol and is 603 g/mol for the corresponding monosolvated $\mathbf{T_1}$ complex. We also note that the D-FW analysis for the resonance of HMPA in this solution yields an experimentally determined formula weight of 323 g/mol that is clearly significantly greater than the actual molecular weight of HMPA, 179 g/mol. We have previously observed such a disparity between the main component of a organolithium aggregate and the solvating Lewis acid coordinated to the Li. Presently we interpret this experimental result to suggest that each cubic tetramer has on the time scale of this diffusion experiment approximately one HMPA tightly bound to it and that around 70% of the HMPA exchanges with free HMPA in the solution.


DOI: 10.1021/jacs.5b01906
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After repeating this experiment several times starting with $\mathbf{T_3}$ crystalline samples with a total of 0.85−1.1 equiv of HMPA in solution, we observe that the experimental FW determined by monitoring the enolate terminal methylene peak falls within the range of 580−750 g/mol and varies with the amount of HMPA present. Hence, this experimental observation suggests an aggregate determined by diffusion analysis that is equal to or bigger than $\mathbf{T_1}$ but always somewhat smaller than $\mathbf{T_2}$. Thus, we suggest that when the pure, crystalline $[(\mathrm{LiOPin})_4{\cdot}\mathrm{HMPA}_3]$ $\mathbf{T_3}$ complex dissolves in solution, one of the three HMPA remains tightly bound to the LiOPin cubic core, while the remaining two HMPA are labile, Scheme 1. It is also noteworthy that in the crystal structure of the tris-solvated complex $\mathbf{T_3}$ one $\mathrm{Li{-}O_{HMPA}}$ bond is much shorter than the other two $\mathrm{Li{-}O_{HMPA}}$ bonds by approximately 0.1 Å, supporting the interpretation of the diffusion NMR experiment that one HMPA ligand in this complex is more tightly bound than the others.

## CONCLUSION

Crystal structures of HMPA-solvated lithium simple ketone enolates are reported for the first time. These include a substoichiometric solvated tetramer, an unusual, face-shared double-cube consisting of a mixed aggregate containing LiOPin and LiOH, a unique mix-aggregate consisting of LiOPin and LDA in the stoichiometric ration 5:1, and a tetrasolvated tetramer of cyclopentanone enolate. Intensive NMR studies reveal that with the bulky lithium pinacolone enolate, trisolvated tetramer $\mathbf{T_3}$ is the only major species in solution when more than 0.6 equiv of HMPA is present. This tris-HPMA-solvated tetramer, $\mathbf{T_3}$, consists of one tight-binding HMPA and two loose-binding HMPA ligands in both solid and solution structures. A fourth ligand such as HMPA, THF, or pyridine is sterically challenged in its approach to the bare lithium in the $\mathbf{T_3}$ aggregate because of the bulk of the pinacolone residue. For the less hindered cyclopentanone enolate, tetra-HMPA-solvated tetramer forms easily in pentane and is more favorable than trisolvated aggregate. Hence, we conclude that a major factor controlling solavtion of enolate aggregates is steric interaction within the aggregate.

## EXPERIMENTAL SECTION

**Procedures for NMR Experiments.** NMR samples were prepared in tubes sealed with rubber septa cap and parafilm. NMR tubes were evacuated in vacuo, flame-dried, and filled with argon before use. $^1$H chemical shifts were referenced to toluene-$d_8$ at 7.00 ppm, and $^{13}$C chemical shifts were referenced to toluene-$d_8$ at 137.86 ppm. All NMR experiments were acquired on a 600 MHz spectrometer equipped with a $z$-axis gradient probe. For DOSY experiments, a GRASP II 10A $z$-axis gradient amplifier was employed, with maximum gradient strength of 0.5 T/m. $^1$H DOSY was performed using the standard Bruker pulse programs, employing a double stimulated echo sequence, bipolar gradient pulses for diffusion, and three spoil gradients. Diffusion time was 100 ms, and the rectangular gradient pulse duration was 1300 $\mu$s. Gradient recovery delays were 200 $\mu$s. Individual rows of the quasi-2-D diffusion databases were phased and baseline corrected. Actual diffusion coefficients used for D-FW analysis were obtained using the T1/T2 analysis module in commercially available software.

**Materials and Methods.** Pentane, hexamethylphosphoramide (HMPA), and diisopropylamine (DIPA) were dried by stirring with calcium hydride ($CaH_2$) under Ar atmosphere overnight and then distilled. Unless otherwise stated, purchased chemicals were used as received. All reactions under anhydrous conditions were conducted using flame- or oven-dried glassware and standard syringe techniques under an atmosphere of argon.

**General Procedures for the Crystallization of $(\mathrm{LiOPin})_4{\cdot}\mathrm{HMPA}_3$ ($\mathbf{T_3}$) and Tetra-HMPA-Solvated Lithium Cyclopentanone Enolate Tetramer $(\mathrm{LiOcP{\cdot}HMPA})_4$.** To a 1.1 M DIPA (5.5 mmol) solution in 5.0 mL of pentane at 0 °C under Ar atmosphere was slowly added 2.1 mL of 2.5 M $n$-BuLi (5.25 mmol). The reaction mixture was stirred at 0 °C for 10 min. Ketone (5 mmol) was then added dropwise, and the mixture was stirred at 0 °C for 15 min. Finally, 0.68 g (3.75 mmol, 0.75 equiv) of HMPA was added, and the solution was stirred for another 15 min at room temperature. The clear solution was then stored at −20 °C freezer, and XRD quality crystals were grown after overnight.

**General Procedures for the Crystallization of $[(\mathrm{LiOPin})_5{\cdot}\mathrm{LDA}{\cdot}\mathrm{Li_2O}{\cdot}\mathrm{HMPA_2}]$.** To a 1.1 M DIPA (5.5 mmol) solution in 5.0 mL of pentane at 0 °C under Ar atmosphere was slowly added 2.0 mL of 2.5 M $n$-BuLi (5.0 mmol). The reaction mixture was stirred at 0 °C for 10 min. Pinacolone 0.5 g (5.0 mmol) was then added slowly, and the mixture was stirred at 0 °C for 15 min. Finally, 0.18−0.26 g (1.0−1.5 mmol, 0.2−0.3 equiv) of HMPA was added, and the solution was stirred for another 15 min at room temperature. The clear solution was then stored at −20 °C freezer, and XRD quality crystals were grown after several days.

**General Procedures for the Crystallization of $(\mathrm{LiOPin})_4{\cdot}(\mathrm{LiOH})_2{\cdot}\mathrm{HMPA_4}$ (pseudo-$\mathbf{T_4}$).** To a 1.1 M DIPA (5.5 mmol) solution in 5.0 mL of pentane at 0 °C under Ar atmosphere was slowly added 2.1 mL of 2.5 M $n$-BuLi (5.25 mmol). The reaction mixture was stirred at 0 °C for 10 min. Pinacolone 0.5 g (5.0 mmol) was then added slowly, and the mixture was stirred at 0 °C for 15 min. Finally, 0.54 g (15 mmol, 3.0 equiv) of HMPA was added, and the solution was stirred for another 15 min at room temperature. The clear solution was then stored at −20 °C freezer, and XRD quality crystals were grown after 3 days.

## ASSOCIATED CONTENT

### Supporting Information

NMR and crystallographic data. CCDC 1050617−1050620 contain supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b01906.

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### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

This work was supported by NSF grant 1058051 to P.G.W.

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DOI: 10.1021/jacs.5b01906
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DOI: 10.1021/jacs.5b01906
*J. Am. Chem. Soc.* 2015, 137, 7347−7356