Aggregation and Solvation of Sodium Hexamethyldisilazide: Across the Solvent Spectrum

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ABSTRACT: We report solution structures of sodium hexamethyldisilazide (NaHMDS) solvated by >30 standard solvents (ligands). These include: toluene, benzene, and styrene; triethylamine and related trialkylamines; pyrrolidine as a representative dialkylamine; dialkylethers including THF, tert-butylmethyl ether, and diethyl ether; dipolar ligands such as DMF, HMPA, DMSO, and DMPU; a bifunctional dipolar ligand nonamethylimidodiphosphoramide (NIPA); polyamines \(N,N,N',N''\)-tetramethylenediamine (TMEDA), \(N,N,N',N''\)-pentamethyldiethylenetriamine (PMDTA), \(N,N,N',N''\)-tetramethylocyclohexanediamine (TMCDCA), and 2,2'-bipyridine; polyethers 12-crown-4, 15-crown-5, 18-crown-6, and diglyme; 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane ([2.2.2] cryptand); and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1). Combinations of \(^1\)H, \(^{13}\)C, \(^{15}\)N, and \(^{29}\)Si NMR spectroscopies, the method of continuous variations, X-ray crystallography, and density functional theory (DFT) computations reveal ligand-modulated aggregation to give mixtures of dimers, monomers, triple ions, and ion pairs. \(^{15}\)N−\(^{29}\)Si coupling constants distinguish dimers and monomers. Solvation numbers are determined by a combination of solvent titrations, observed free and bound solvent in the slow exchange limit, and DFT computations. The relative abilities of solvents to compete in binary mixtures often match that predicted by conventional wisdom but with some exceptions and evidence of both competitive and cooperative (mixed) solvation. Crystal structures of a NaHMDS cryptate ion pair and a 15-crown-5-solvated monomer are included. Results are compared with those for lithium hexamethyldisilazide, lithium diisopropylamide, and sodium diisopropylamide.

INTRODUCTION

As part of ongoing efforts to pique the community’s interest in organosodium chemistry by probing structure-reactivity-selectivity relationships, we have put considerable effort into removing multiple stigmas associated with sodium diisopropylamide (NaDA).\(^2,3\) By contrast, there are no such constraints placed on sodium hexamethyldisilazide (NaHMDS). It is arguably the pre-eminent organosodium reagent in both academic and industrial laboratories,\(^4\) finding applications requiring nuanced control of regio-, stereo-, and chemoselectivity.\(^5\) Its solubility, stability, and commercial availability appeal to synthetic chemists and render NaHMDS an attractive target for studying aggregation and solvation. Aside from NaHMDS crystal structures of potential interest to synthetic chemists (Chart 1\(^6\)), there are remarkably few physicochemical studies of NaHMDS in solution.\(^6,7−10\) Even the computational community has shown little interest.\(^11\)

We describe herein NMR spectroscopic and computational studies of NaHMDS coordinated by several dozen mono-, bi-, and polyfunctional solvents. We use the terms “ligand” and “solvent” interchangeably. Our intention is to establish structural foundations for subsequent studies of solvent-dependent reactivities and selectivities. A secondary but still important goal is to provide a compendium of NaHMDS-solvent combinations to prompt potential consumers to think beyond the standard solvents. Highly solvent-dependent structures offer a potential opportunity for practitioners to
optimize selectivities and reactivities by targeting the underlying structures.12

RESULTS AND DISCUSSION

Results from spectroscopic and computational studies are summarized in Table 1 and Chart 2. The lettered entries in Table 1 also designate the coordinated solvent on numbered structures throughout. Dimer 12 and monomer 13 are dominant. Occasionally, dipolar and polydentate solvents at elevated concentrations cause phase separations, the appearance of upfield $^{29}$Si resonances as broad mounds, or the complete disappearance of $^{29}$Si signals. A chromatographically characterized cryptate ion pair allows us to attribute aberrant spectroscopic behavior to simple ion pairs (14). Triple ion 16 is observed in several instances. We observed mixed solvates 15 on many occasions owing to the titration protocols routinely employed, as documented in the Supporting Information; only those observed to the exclusion of homosolvated dimers are included in Table 1. The Supporting Information also includes significant data and pertinent undiscussed observations.

This paper begins with general discussions of tactics and protocols for studying aggregation and solvation using a few results emblematically. Data are presented only to illustrate the Supporting Information.

Table 1. Spectroscopic and Computational Data for NaHMDS Dimers and Monomers (12–16, Chart 2) in Different Solvents
d

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>structure (A$_n$S$_m$ (#))</th>
<th>$^{29}$Si shifts (ppm ($^{29}$Si$_{Na}$))</th>
<th>solvation energy per S–Na (kcal/mol)</th>
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<tr>
<td>a</td>
<td>toluene</td>
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<td>-11.7</td>
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<td>AS$_3$ (13z)</td>
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<td>AS$_3$ (14cc)</td>
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$^a$Details of the cosolvent and temperatures are found in the Supporting Information.
silazide (LiHMDS),\textsuperscript{13−15} lithium diisopropylamide (LDA),\textsuperscript{13,16} and sodium diisopropylamide (NaDA).\textsuperscript{3} We conclude by considering binary mixtures of solvents with studies of relative binding affinities that inadvertently revealed cooperative solvation effects. Computed structures of sodium cations may prove useful in understanding ionizations.

**General Methods.** NaHMDS, [\textsuperscript{15N}]NaHMDS, sodium tetramethyldisilazide (NaTMDS,\textsuperscript{17})\textsuperscript{17} sodium bis(dimethyl-(phenyl)silyl)amide (NaDPTMDS,\textsuperscript{18})\textsuperscript{18} and sodium disilazide\textsuperscript{19} were prepared as white crystalline solids from the disilazanes and sodium metal. The synthesis of (Me\textsubscript{3}Si)\textsubscript{2}\textsuperscript{15}NH has also been reduced from 8 days\textsuperscript{20} to 4 h with improved yields. Toluene is used routinely as a cosolvent, but it is not an innocent spectator as discussed below. Substitutionally labile N,N-dimethylethylamine (DMEA), 2:1 pentane/toluene-\textsubscript{d}8,\textsuperscript{21} and tert-butylmethyl ether (MTBE) were used as cosolvents to record spectra at −120 °C or −110 °C and to optimize solubilities and spectral resolution. No attempt is made to justify or clarify the choice of cosolvent on a case-by-case basis, deferring details to the Supporting Information. \textsuperscript{1}H, \textsuperscript{13}C, \textsuperscript{15}N, and \textsuperscript{29}Si NMR spectroscopies offered complementary perspectives; \textsuperscript{13}C and \textsuperscript{29}Si NMR spectroscopy proved most important.

Density functional theory (DFT) computations probe spectroscopically derived structural assignments and experimentally elusive details of solvation. They were carried out at the M06-2X level of theory.\textsuperscript{20−22} The standard Def2-SVP basis set was used for geometric optimizations and the expanded Def2-TZVP basis set for single point calculations.\textsuperscript{23,24} Prompted by a recent publication revealing consequential free energy changes with larger integration grid sizes,\textsuperscript{25} geometric optimizations and single-point calculations employ a refined (99,590) grid. Based on a number of comparisons, the expansion of the grid size has some influence.\textsuperscript{26} The molecular solvation events commonplace in alkali amide chemistry require computational procedures that invoke explicit solvation models instead of using an implicit solvation model. Employing both explicit and implicit solvation models can lead to large statistical errors as shown by Houk.\textsuperscript{27}

**Method of Continuous Variations.** The preferences for NaHMDS to form dimers at low solvent loadings and monomers at high solvent loadings (12 and 13, Chart 2) are shown using a combination of strategies. The method of continuous variations (MCVs) relies on pairing structurally similar species to a family of homo- and hetero-aggregates that are characteristic of the homoaggregates as illustrated for dimers in eq 1. Heteroaggregates displaying 2:1 and 1:2 stoichiometries characteristic of trimers are not observed under any conditions. Monomers observed at elevated ligand concentrations do not heteroassociate.

Pairing partners in MCV are chosen to maximize the NMR spectroscopic resolution while maintaining structural similarity. \textsuperscript{13}C and \textsuperscript{29}Si NMR spectroscopies were used to monitor the ensemble in eq 1. \textsuperscript{1}H NMR spectroscopy was viable but the least effective. \textsuperscript{15}N NMR spectroscopy using [\textsuperscript{15N}]NaHMDS was supportive but would require both partners be labeled for optimization and was not needed.

NaHMDS and its pairing partners 18 and 19 exist as homodimers in weakly coordinating solvents or at low concentrations of strongly coordinating mono- and difunctional solvents. Results from toluene (Table 1, entry a) illustrate the characterization of dimer ensembles. NaHMDS is insoluble in saturated hydrocarbons but readily dissolves as a 0.10 M solution in 2:1 pentane/toluene at −120 °C. Mixtures of [\textsuperscript{15N}]NaHMDS and NaTMDS contain homodimers 12 and

![Figure 1. NMR spectra of 1:1 mixtures (0.30 M total titer) of [\textsuperscript{15N}]NaHMDS and NaTMDS (18) in 2:1 MTBE/toluene recorded at −80 °C show homo- and heterodimers 12, 20, and 21 (eq 1): (a) \textsuperscript{13}C{\textsuperscript{1}H} NMR (toluene-\textsubscript{d}3, 125.79 MHz) spectrum; (b) \textsuperscript{15}N NMR (toluene-\textsubscript{d}3, 60.66 MHz) spectrum; and (c) \textsuperscript{29}Si NMR (toluene-\textsubscript{d}3, 99.36 MHz) spectrum.](https://dx.doi.org/10.1021/acs.joc.0c02546)

20 and heterodimer 21 (Figure 1). Heterodimer 21 displays \textsuperscript{13}C resonances corresponding to the methyl resonances of the TMS and DMS groups in 3:2 proportions, reflecting the number of methyl groups (Figure 1a), a single \textsuperscript{15}N resonance
measured 29 mole fraction of NaHMDS (Figure 1c). 15N the [15N]HMDS and unlabeled TMDS fragments and, more importantly, provides critical structural insights (discussed below).

Plotting the relative concentrations of the homo- and heterodimers versus measured mole fraction31 of NaHMDS (XNaHMDS) affords a Job plot30 showing near quantitative heterodimerization (Figure 2). The nonstatistical preference for heterodimer observed in a number of solvents is supported computationally and presumably derives from relief of congestion in the NaHMDS homodimer. On the other hand, using MTBE/toluene affords a statistical Job plot as shown in Figure 3. The lower preference for heterodimerization can be attributed to a greater solvation energy of the NaHMDS and NaTMDS homodimers, which is supported computationally.

Pairing NaHMDS with the phenyl-containing sodium disilazide 18 unexpectedly favors homodimerization as illustrated in the Job plot in Figure 4. DFT computations of the corresponding homodimer drawn generically as 22 reveal a marked canting of the four phenyl moieties toward the sodium nuclei. We attribute this preference for homodimerization to a stabilizing cation−π interaction unique to mixing partner 18, although this is not confirmed computationally.32

Solvent-Dependent Deaggregation. Elevated concentrations of all but the most poorly coordinating solvents cause NaHMDS to deaggregate. Dimer−monomer exchanges are rapid at −80 °C and slow at −120 °C. The clearest view of solvent-concentration-dependent structural changes is derived from HMPA as illustrated in Scheme 1 and Figure 5. The NaHMDS monomers show no associated forms when NaHMDS is mixed with disilazides 18 and 19, whereas the triple ions 16 form heteroaggregated triple ions.

13C−29Si Scalar Coupling. Figure 5 illustrates coupling that played an unexpectedly important role in the study. In the 1980s, Lukevics and co-workers reported 15N−29Si coupling constants for various disilazanes and several salts.33 Without the benefits of additional data, they attributed the 7.8 Hz 15N−29Si coupling for NaHMDS in benzene to a ligand-free tetramer, which we are now confident is the benzene-solvated dimer. We find that the 15N−29Si coupling constants correlate with the aggregation state: [15N]NaHMDS-containing homodimers 19 display 1JπN−Si = 7−9 Hz, whereas monomers display 1JπN−Si = 12−14 Hz (Table 1). The HMPA-solvated ion pair (Table 1, entry m) showed 1JπN−Si = 16.4 Hz, placing it outside the range of monomers.

The 13C−28Si coupling has the desirable feature that it can be monitored at any temperature, provided that the resonances are not in the midst of coalescing. Figure 6, for example, shows THF-concentration-dependent averaged couplings and 29Si chemical shifts affiliated with NaHMDS deaggregation. The fits attest to the relative solvation numbers of the dimer and monomer. Figure 7 compares the solvent-concentration-dependent coupling for THF and dioxane. The muted tendency of dioxane to deaggregate NaHMDS is evident by the intermediate coupling in neat dioxane, indicating ≈50% of the titer corresponds to the dimer.

We habitually use [15N]NaHMDS for all spectroscopic studies as a cross check. The per-sample cost of the label deriving from [15N]NH4Cl is approximately 7% the price of the NMR tube in which the spectra are recorded.

Titrations. Solvation was studied by titration methods that were recently used for NaDA3 but have roots in the 1960s alkali metal literature.34 Serial additions of a coordinating

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solvent to NaHMDS in toluene elicit solvent-concentration-dependent $^1$H and $^{29}$Si chemical shifts of NaHMDS owing to ligand substitution. Figure 8 shows the binding of $N,N,N',N''$-pentamethyldiethylenetriamine (PMDTA). The linearity and sharp end point at 1.0 equiv of PMDTA per sodium attest to the quantitative binding of a single PMDTA per sodium ion. (The structure was subsequently shown to be a monomer as discussed below.) By contrast, weakly coordinating solvents such as Et$_3$N do not quantitatively displace toluene from the NaHMDS dimer, as evidenced by curvature in the titration (Figure 9). In principle, the details of the curvature attest to the per-sodium solvation number, but such a distinction was not possible. Because of this and the slow exchanges observed at $-120^\circ$C, titrations played minor roles. They did, however, serve as an expedient method to monitor the solvent-concentration-dependent structural changes with serial additions through septa (Figure 5).

**Solvation in the Slow Exchange Limit.** In many cases, homosolvated and mixed-solvated dimers as well as chelated monomers were observed in the limit of slow exchange of free and bound solvent, offering unique probes of solvation numbers and correlated solvation (vide infra). Previous studies of LiHMDS show that slow exchange of monodentate solvents

![Scheme 1. Serial Solvation by HMPA](https://example.com/scheme1.png)

**Figure 5.** $^{29}$Si NMR (various solvents, 99.36 MHz) spectra as follows: (a)–(d) 0.19 M NaHMDS in 2:1 pentane/toluene with 0.0 equiv, 0.25 equiv, 0.75 equiv, and 1.0 equiv of HMPA, respectively; (e) 0.10 M NaHMDS in DMEA at $-120^\circ$C with 5.0 equiv of HMPA; and (g) 0.10 M NaHMDS in 2:1 HMPA/MTBE recorded at $+40^\circ$C (to resolve the coupling).

**Figure 6.** $^{29}$Si chemical shift (green) and $^{15}$N–$^{29}$Si coupling constants (black) plotted versus [THF] in 2:1 pentane/toluene as cosolvent measured at $-20^\circ$C. The functions are fit to a model based on an $A_2S_2$–$AS_4$ equilibrium (Supporting Information). Reprinted from Woltornist, R. A.; Collum, D. B. Using $^{15}$N–$^{29}$Si Scalar Coupling to Determine Aggregation and Solvation States. J. Am. Chem. Soc. 2020, 142, 6852. Copyright 2020 American Chemical Society.

**Figure 7.** $^{15}$N–$^{29}$Si coupling constants plotted versus [THF] (black) and [1,4-dioxane] (green) in 2:1 pentane/toluene as cosolvent at 20$^\circ$C. The functions stem from a model based on an $A_2S_2$–$AS_4$ equilibrium (Supporting Information). Reprinted from Woltornist, R. A.; Collum, D. B. Using $^{15}$N–$^{29}$Si Scalar Coupling to Determine Aggregation and Solvation States. J. Am. Chem. Soc. 2020, 142, 6852. Copyright 2020 American Chemical Society.
requires the rare combination of high barriers to both associative and dissociative ligand substitutions. This slow exchange manifests magnetically distinct \(^{29}\text{Si}\) signals for each form as illustrated in the serial titration of NaHMDS with HMPA (Scheme 1 and Figure 5). In some instances, separate \(^{13}\text{C}\) signals for free and NaHMDS-bound solvents are observable.

**Computed Solvation Numbers.** The solvation numbers in Table 1 are derived from both experimental and computational data. The free energies are reported on a solvent-per-sodium basis and benchmarked to their respective unsolvated dimers and monomers (eqs 2 and 3). However, there are deviations from nonstatistical behavior—so-called “correlated solvation”\(^{38-41}\)—in which \(\Delta G_1 \neq \Delta G_2\) and \(\Delta G_3 \neq \Delta G_4\) are prevalent and highly solvent dependent. The hindered bidentate ligand TMEDA, for example, shows \(\Delta G_1\) is markedly more negative (favorable) than \(\Delta G_2\) (eq 2),\(^{39}\) and \(\Delta G_4\) is more negative than \(\Delta G_3\) (eq 3). Similarly, where two or more solvents share a common sodium ion such as AS\(_2\) (eq 3), serial solvation is often correlated: \(\Delta G_3\) is more negative than \(\Delta G_4\), of dimers and monomers (eq 4) are less compelling and mentioned sparingly. Nonetheless, the solvation energies in Table 1, in conjunction with the energy of aggregation of the unsolvated dimer—monomer (eq 5), enable the reader to calculate the solvent-dependent free energies of deaggregations for any solvent directly from the data in Table 1.

**Toluene and Other Hydrocarbons.** We now consider observations organized by solvent class with only limited comments about specific protocols. The solubility of NaHMDS in toluene and insolubility in saturated hydrocarbons foreshadowed the formation of an explicitly solvated dimer. Potassium hexamethyldisilazide and sodium triisopropylidisilazide crystallize as dimers bearing \(\eta^6\) toluene.\(^{44}\) Many \(\eta^6\) toluene—sodium complexes\(^{32-34}\) and alkali metal—arene \(\pi\) complexes have been characterized crystallographically.\(^{32-34}\) Spectroscopic evidence suggests toluene binds, albeit weakly, to the LiHMDS dimer\(^{35}\) and ether- and amine-solvated monomers.\(^{14,15}\)

Figure 8. Plot of percent monomer versus equivalents of PMDTA in toluene at \(-80\) °C.

Figure 9. Plot of \(^1\text{H}\) chemical shifts of NaHMDS versus concentration of \(\text{Et}_3\text{N}\) in neat toluene at \(-80\) °C.\(^{36}\) Despite such high correlations, Table 1 lists average free energies for the multiple solvent—sodium interactions. The separate values for each solvation event are presented in the Supporting Information. Note that the reported free energies in Table 1 do not account for denticities. Chelated TMEDA has two sodium—solvent contacts but is considered a single solvent. Thus, \(\Delta G_{\text{TMDA}}\) is probably most appropriately compared to \(2\Delta G_{\text{THF}}\).\(^{42}\) Acutely nonisodesmic\(^{43}\) comparisons of dimers and monomers (eq 4) are less compelling and mentioned sparingly. Nonetheless, the solvation energies in Table 1, in conjunction with the energy of aggregation of the unsolvated dimer—monomer (eq 5), enable the reader to calculate the solvent-dependent free energies of deaggregations for any solvent directly from the data in Table 1.

![Diagram](https://dx.doi.org/10.1021/acs.joc.0c02546)
tions, DFT computations, and inference from experience with LiHMDS and other lithium salts.\textsuperscript{14,16} Weak donors such as Et\textsubscript{2}O, MTBE, and trialkylamines (Table 1, entries d–f, i, j) afford disolvated NaHMDS dimers to the exclusion of monomers even in neat solvent (eq 6). LiHMDS dimers solvated by sterically demanding and weakly coordinating\textsuperscript{14,48} trialkylamines in toluene are beginning to find synthetic applications\textsuperscript{15} as may NaHMDS–R\textsubscript{3}N.\textsuperscript{49} The titration of NaHMDS/toluene solutions (Figure 9) shows nonquantitative displacement of toluene by Et\textsubscript{3}N (despite computations suggesting it should be quantitative). Although exchange of Et\textsubscript{3}N or DMEA was rapid at 20 °C, THF-solvated NaHMDS is isostructural to the disolvated NaTMDS heterodimer \(12m\) (Figure 11). THF-solvated dimer \(12m\) is isosctructural to the disolvated NaTMDS monomer.\textsuperscript{14} LiHMDS and LDA dimers.\textsuperscript{14,16} The THF-solvated NaDA dimer, by contrast, is tetrasolvated.\textsuperscript{3} THF-solvated monomer \(13m\) is the sole observable form at >5 equiv of THF per sodium at −120 °C. Tetrasolvation is supported both experimentally (Figure 6) and computationally. A mixture of tri- and tetrasolvated monomers were implicated for the LiHMDS monomer.\textsuperscript{14}

Although dioxane is technically a difunctional ligand, weak binding and the reluctance to form monomers even in neat dioxane (Figure 7) indicate it is serving as a monofunctional ligand with a lower penchant than THF to deaggregate NaHMDS. We hasten to add that the approximately 6 kcal/mol of torsional strain in the boat form of dioxane\textsuperscript{50} accounts for why the chelated form appears to be without precedent. We witnessed gelling at low dioxane concentration even in MTBE, presumably due to linking NaHMDS dimer subunits into networks as found in monomer 9 (Chart 1).\textsuperscript{6h}

Pyridine is shown both spectroscopically and computationally to be moderately superior to THF as a ligand for LiHMDS and other lithium salts.\textsuperscript{14} It may find niche applications in the chemistry of NaHMDS, but a potentially greater motivation would be to understand pyridine–sodium interactions in putative\textsuperscript{6c} \(\text{S}_{\text{Ar}}\text{Ar}\) reactions and other organosodium reactions of pyridine-based heterocycles.\textsuperscript{52} Both titrations and computations suggest the dimer is disolvated. Disaggregation by pyridine is detectably more pronounced than when using THF and is computationally suggested to be a tetrasolvated monomer. Lastly, although pyridine serves as a useful chemical
shift reagent for $^6$Li NMR spectroscopy, we observe no notable $^{13}$C, $^{15}$N, or $^{29}$Si shifts in [15$^N$]NaHMDS.

Pyrrolidine is representative of protic dialkylamines and is isostructural to THF. It is generally considered to be much more strongly Lewis basic than THF$^{53}$ and tetrahedral at nitrogen akin to the oxygen of THF bound to sodium. Oddly, THF and pyrrolidine were indistinguishable as ligands for LiHMDS dimer, although pyrrolidine promoted deaggregation. Titration of NaHMDS with pyrrolidine (Table 1, entry h) shows a measurably more pronounced deaggregation for pyrrolidine when compared with THF, favoring a tetradsolvated monomer.

Monoalkylamines have the trappings of unhindered, highly Lewis basic solvents playing important roles in Birch reductions, $^3$Si$^-$Ar reactions of halogenated arenes and heteroarenes, ester aminolyses, and trans-amidotations. The monoalkylamines unencumbered by additional alkyl groups are exemplified by n-Bu$^+$NH$_2$. Unfortunately, even at low concentrations of amine (<2.0 equiv per Na) in MTBE a coalescence is observed using $^{29}$Si NMR spectroscopy, most likely due to rapid exchange of multiple species.

The attenuated basicity of NaHMDS allows us to investigate strongly coordinating dipolar solvents that would otherwise be ravaged by NaDA and other organosodiuim. Hexamethylphosphoramide (HMPA) offered the best view. Titration of NaHMDS in MTBE with HMPA shows serial formation of monomer (Figure 5). At ≥1.0 equiv of HMPA monomer, 13n displays an HMPA-concentration-dependent chemical shift up to 3.0 equiv, at which point no further changes are noted. The stoichiometry and computations suggest that trisolvated monomer 13n (n = 3) is the limiting structure. A high amount (>15 equiv) of HMPA and elevated temperature (40 °C) afford a new species, manifesting an unusually large 16.4 Hz $^{15}$N–$^{29}$Si coupling that we attribute to ion pair 14n. This is the only well-resolved $^{29}$Si doublet for such an ion pair.

$^{31}$P NMR spectroscopy showed a single time-averaged resonance for the mono- and disolvated dimers and various solvated monomers. Broadening occurs at 1.0–2.0 equiv/Na, which decoalesces at 5.0 equiv of HMPA to show free HMPA and two mounds in an approximate >10:1 ratio. Monomer 13n and ion pair 14n are logical candidates.

Analogous titrations of NaHMDS in MTBE with DMPU serially solvate through 15o and 12o. Higher DMPU concentrations cause the $^{29}$Si resonance to disappear; we suspect the formation of ion pair 14o.

Looking for dipolar solvents without the stigma of HMPA, we turned toward DMSO and DMF. Titration of NaHMDS in DMEA with DMSO at –80 °C resulted in a single $^{29}$Si resonance with a DMSO-concentration-dependent chemical shift and coupling constant signifying a change from dimer to monomer. Even at low DMSO concentration, the monomer was the dominant species. However, at >3.0 equiv, a coalescence was observed. DMF performed poorly, resulting in only dimer and low concentrations of monomer at >2.0 equiv with evidence of decomposition.

**Difunctional Solvents.** Difunctional ligands were not as predictable as expected. The low steric demands of DME (compared with TMEDA)$^{14}$ for example, seemed likely to support doubly chelated dimer, and indeed, computations show strong binding and only limited correlated solvation. Titration of NaHMDS in DMEA with DME (Table 1, entry u) at –120 °C, however, showed a DME-solvated monomer and DMEA-solvated dimer 12d concurrently at <2.0 equiv of DME, evident from an unchanged dimer coupling constant consistent with 12d. We suspect cooperative solvation is at play here, giving rise to a DMEA–DME heterosolvated monomer at these low DME concentrations. Monomer 13v is the sole observable form at ≥3.0 equiv. TMEDA is the quintessential bifunctional ligand that has been instrumental in shaping the thinking of researchers for generations about structure-reactivity relationships for alkali metal chemistry (eq 8)$^{55}$.
persists at >3.0 equiv of TMCDA. Analogous spectroscopic data showing two distinct silyl moieties prompted O’Hara and co-workers to suggest crystallographically characterized 4 retains its structure in solution. Given the two distinct 29Si resonances and the excess of DMEA, mixed-solvated analogue 15 seems logical; however, a highly functional mixed-solvated open dimer of general structure 24 cannot be excluded. To ascertain whether TMCDA fails to bind owing to unforeseen steric effects such as rigidity or poor bite angle on the larger sodium ion, we compared TMEDA versus TMCDA for LiHMDS and NaHMDS monomer fragments (eq 9). Though both LiHMDS and NaHMDS prefer TMCDA-solvated monomer over TMEDA-solvated monomer, the relative binding energy comparing lithium and sodium qualitatively suggests an elevated monomer preference for lithium.

Sparteine (25) has been a workhorse chiral ligand in organolithium chemistry and has shown demonstrably strong binding to the LiHMDS monomer. By contrast, >3.0 equiv of sparteine shows no evidence of binding to NaHMDS in DMEA (Table 1, entry s). We suspect sparteine is too sterically demanding to chelate to dimers or doubly chelate monomers despite crystallographic evidence that less congested sodium salts can support two bound sparteines.

The relatively low reactivity of NaHMDS has allowed us to probe the common transition metal ligand, 2,2′-bipyridine (bipy). At 0.50 equiv of bipy in DMEA, mono- and dichelated dimers are observed. We also detect what appears to be low concentrations of open dimer (26). At 1.0 to >3.0 equiv of bipy, a disolvated dimer persists to the exclusion of monomers. No spectroscopic evidence of destruction is observed after days at room temperature even though the solution color turns hot pink.

Protic amines often presented problems in studies of LiHMDS owing to facile exchanges, causing loss of 15N−29Si coupling. We wondered if we would have anticipated the merits of 15N−29Si coupling if the story had been different. Titrations of NaHMDS with ethylene diamine led to chronic solubility problems even using THF as the cosolvent, possibly due to intervening formation of ion pair or extended hydrogen-bonded networks.

N,N,N′,N″-Nonamethylimidodiphosphoramide (NIPA, 27) is highly dipolar, potentially chelating, and possibly an HMPA surrogate, albeit with unknown toxicity. Unpublished work showed that NIPA affords exclusively monomeric LiHMDS. NIPA has been evaluated as a ligand for a number of inorganic metal salts but has been almost totally overlooked by the alkali metal community. Although the preference of five- versus six-membered ring chelates for lithium is fully established, the preference for sodium is less obvious, largely from a lack of detailed, systematic studies. Unfortunately, titrations of NaHMDS with NIPA resulted in a mixture of species at ≤1.0 equiv and precipitation above 1.0 equiv: NIPA may find niches in time.

**Trifunctional Solvents.** We have ongoing studies of PMDTA on other sodium salts and believe it will be a ligand of central importance to the further development of organo-sodium chemistry; crystallographers have already discovered its merits. Titrations show exclusively NaHMDS monomer (eq 10) with free and bound PMDTA in slow exchange in pentane/toluene at −100 °C. NaHMDS-bound PMDTA displays seven resonances of equal intensity and two resonances corresponding to the two sets of time-averaged terminal methyl groups. Although κ2-PMDTA-solvated dimer could afford eight carbons, MCV and large 15N−29Si coupling confirm the monomer assignment. The magnetic inequivalency of the PMDTA methylenes at low temperature and coalescence to give seven resonances of the bound form at
elevated temperature is consistent with half-chair conformers observed for lithium complexes of PMDTA. DFT computations support the high preference for monomer relative to doubly chelated dimer and showed three distinct monomer conformers, of which the conformer in Figure 14 is preferred.

Figure 14. DFT-computed lowest-energy conformer of PMDTA-complexed monomer 13w.

Diglyme is labile to strong bases but not to NaHMDS, and it is extremely cost-effective for applications in synthesis. NaHMDS with ≥1.0 equiv of diglyme shows exclusively monomer (eq 10) with free and bound diglyme time averaged at −120 °C. Phase separation or peak broadening emblematic of ion pair formation was not observed. Diethylenetriamine, an unhindered analogue of PMDTA and an isostructural analogue of diglyme, by contrast afforded intractable amorphous solid even in THF solution, possibly owing to ion pair formation (see above) or hydrogen-bonded networks.

Polyfunctional Solvents. In 1996, we reported that LiHMDS monomer solvated by the three parent crowns—12-crown-4 (28), 15-crown-5 (29), and 18-crown-6 (30)—showed two odd features that conflicted with consensus: (1) the three crowns display nearly the same binding constant (±0.5 kcal/mol) and (2) all three proved comparable to THF or TMEDA. It was in this context that we investigated the binding of 28–30 to NaHMDS (Scheme 2).

Adding the crown ethers to NaHMDS in DMEA caused phase separation of amorphous solids or liquids. On the positive side, 15-crown-5 afforded diffractable crystals of 13z, the first crystallographically characterized NaHMDS–crown complex (Figure 15). However, due to poor crystal quality, only atom connectivity was ascertained.

Monomer 13z shows four Na–O close contacts (2.44–2.59 Å) that mimic two DME ligands and an elongated (2.60 Å) fifth Na–O interaction. DFT computations show similar structural features. Titrating NaHMDS with crown ethers 28–30 in THF at −105 °C afforded homogeneous solutions with strong evidence of crowns remaining complexed. Titrations using NaHMDS in MTBE with 12-crown-4 converts MTBE-solvated dimer 12j to crown-complexed monomer 13y (1:1 stoichiometry) with no detectable intermediates. At approximately 1.5 equiv of 12-crown-4, a solid precipitates, consistent with ion pair 14y. By contrast, 0.50 equiv of 18-crown-6 consumes >95% of MTBE-solvated dimer 12j, affording a new species to the exclusion of other forms suggested by stoichiometry to be triple ion 16aa. At 1.0 equiv, 16aa is converted to exclusively monomer 13z. Excess crown affords broad upfield 29Si resonances ascribed to ion pair 14aa. Titration with 15-crown-5 affords intermediate behavior. Triple ion 16z and monomer 13z are formed concurrently, with monomer 13z becoming the sole species at 1.0 equiv. At ≥1.0 equiv of 15-crown-5, monomer 13z crystallizes from solution. Crystallization is accelerated by warming also. Ion pair 14z might be viable but is precluded by the crystallization.

Free and NaHMDS-monomer-bound crowns are observed in slow exchange, revealing 1:1 NaHMDS:crown stoichiometries for 29 and 30 and magnetically equivalent carbons despite computations showing significant distortions (Figure 16). High functionality is likely the source of the apparent high symmetry. The evidence of triple ions 16z and 16aa initially was based on the substoichiometric quantities of crown required to
consume MTBE-solvated dimer 12j. To confirm the assignments, a 1:1 mixture of [15N]NaHMDS/NaTMDS in MTBE showing statistical mixtures of homo- and heterodimers (eq 1) was titrated with 18-crown-6, affording an ensemble of homo- and heteroaggregated triple ions (16aa and 30aa). Monomers 13z and 13aa were also confirmed by the absence of heteroassociation. The uniquely high preference for a triple ion with 18-crown-6 may be because only 18-crown-6 can fully encapsulate the sodium within the crown (Figure 17),70 which also impacts the binding of the MTBE cosolvent.

The final step was to compete the crowns against each other to ascertain relative affinities for NaHMDS. Titrations of NaHMDS in MTBE with stock solutions containing 1:1 mixtures of two crowns by monitoring the resolved29Si resonances revealed nearly indistinguishable binding of the three crowns to monomer 13 (Scheme 3).71 Polyether 31, referred to as TDA-1, has its roots in phase transfer catalysis.72 It displays cryptand-like behavior with LiHMDS.14 Serial titrations of NaHMDS afford a triple ion at 0.50 equiv that was confirmed to show a heteroassociated form when mixed with NaTMDS. Monomer 13bb forms to the exclusion of ion pair 14bb at ≥1.0 equiv.

NaHMDS and cryptand [2.2.2] (32) in DMEA afford a white crystalline solid. An X-ray crystal structure shows the anticipated cryptate shown in Figure 18. An analogous structure has been reported by Stephan et al. for the KHMDS-cryptand complex.73 Addition of 0.50 equiv of 32 to NaHMDS in THF causes the disappearance of monomer 13m and the appearance of triple-ion-based cryptate 16cc, along with low concentrations of ion pair 14cc as a broad mound.

Relative Solvation Capacities and Cooperative Solvation. We have described much of what we learned about the capacity of various solvents to compete with each other. We are careful not to call it solvation energy per se because we are comparing different structural forms. With that said, the overall capacities of solvents to compete are summarized in Scheme 4.

Scheme 3. Competition of Crowns Showing Nearly Equal Binding to Form Monomers 13y, 13z, and 13aa

Scheme 4. Scale of Relative Competitive Binding to NaHMDS

using the most important solvents within their respective classes. The weakly bound ethers and trialkylamines reluctantly substitute toluene on the NaHMDS dimer but are easily displaced by ligands designated as having intermediate donicity such as THF. All but the weakest ligands also readily afford monomers at elevated ligand concentrations. A study of diamines showed TMEDA to be far superior to TMCDA. Binding of the crown ethers to the NaHMDS monomer is shockingly independent of crown structure; this result was foreshadowed by studies of LiHMDS.14 There remained, however, a few questions central to our understanding that required explicit competitions not described above. In this context, PMDTA is a pivotal divide between moderately and strongly binding ligands and a useful benchmark.
Competition shows that TMEDA cannot compete with THF, which was also documented for LiHMDS, and THF cannot compete with PMDTA for monomer solvation. THF and other monodentate donor solvents do, however, catalyze the exchange of free and bound PMDTA as evidenced by coalescence of the PMDTA resonances in the $^{13}$C NMR spectra.

Di-, tri-, and polyfunctional ethereal ligands versus PMDTA allow for the assignment of their relative binding affinities. Competing PMDTA and diglyme afford a time-averaged $^{29}$Si signal, but the intermediate chemical shift suggests that $\kappa^1$-polydentate ether-based monomers are favored over the $\kappa^2$-PMDTA-based monomer. Furthermore, competing PMDTA and DME showed a strong preference for DME-solvated monomer. However, using the same titration method with DME and crown resulted in only crown complex at 1.0 equiv of each ligand. Continued addition of both ligands resulted in an increase of the $^{15}$N−$^{29}$Si coupling constant and a decrease in signal intensity, indicating cooperative solvation of an ion pair.

One might surmise that the dipolar ligands bind more strongly than PMDTA and THF. Competitions of PMDTA and HMPA show HMPA solvate to be the sole observable species. Curiously, equimolar PMDTA and HMPA at 1.0 equiv of total ligand concentration showed a new $^{29}$Si signal corresponding to low concentrations of triple ion, suggesting cooperative solvation is at play. It reminds us that combinations of two ligands may cooperatively provide access to atypical aggregation states.

**Sodium Cation Solvation.** The solvation energies of sodium cations were calculated (Table 2), filling what appears to be a gap in the computational literature. These computed energies could guide synthetic chemists hoping to markedly enhance reactivity via ionization and to the sodium battery community. The relative energies corroborate the experimentally determined solvent hierarchy. For example, confirmed ion-pair-forming ligands such as cryptand and HMPA show greater solvation energies than THF, which does not ionize NaHMDS. Furthermore, the solvation energy of the PMDTA-mixed solvates 37−40 demonstrates plausibility for cooperative solvation.

**Table 2. Solvation Energies of Sodium Cations**

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**CONCLUSION**

Exploration of NaHMDS dissolved in >30 solvents showed a dominance of disolvated dimers in neat, weakly coordinating solvents and at low concentrations of strongly coordinating monodentate solvents. Intermediate and strongly coordinating solvents as well as a bevy of di-, tri-, and polyfunctional solvents (usually called ligands) elicited deaggregation without exception. Experimental evidence in conjunction with extensive DFT computations implicated monomers with four- and five-coordinate sodium to be the norm. Ionizations in dipolar and polydentate ligands in the form of both triple ion and ion pairs offer interesting views of sodium cation solvation. On several occasions open dimers were detected, although the evidence was not unassailable.

Most solvents behaved as one might expect when placed in the context of LDA, LiHMDS, and NaDA, but not always. TMCD and sparteine are relatively good ligands for LiHMDS and other organolithiums but show low affinities for NaHMDS. We are reminded of the ultimate truism: sodium and lithium are different metals. Three crown ethers—12-crown-4, 15-crown-5, and 18-crown-6—showed high affinities for NaHMDS but defy consensus by displaying nearly identical binding constants. We suspect few would have predicted this. Probes of relative affinities using binary mixtures uncovered several examples of cooperative solvation, offering creative opportunities to control structure while reminding us that solvent mixtures bring complexities that must be respected. Moreover, substrate complexation during a reaction is merely a variant of cooperative solvation.

Often new tactical advances emerge from a study that expand our toolkit. The standout example in this study was showing that $^{18}$N−$^{29}$Si coupling first studied by Lukevics and co-workers correlates strongly with the NaHMDS aggregation state. $^{29}$Si NMR spectroscopy offered a stupendously convenient window into structure in a variety of solvents over a range of temperatures. We must confess that during studies of $[^6\text{Li},^{13}\text{N}]$LiHMDS we never recorded $^{29}$Si NMR spectra. We did not need them.) Belatedly, we find that correlations of $^{15}$N−$^{29}$Si hold up, albeit with some quantitative
differences when compared to NaHMDS (see 41 and 42). We imagine broader applications to M−N(SiR3)2. Moreover, the ease of recording high-quality 29Si NMR spectra suggests tremendous promise akin to tagging a reagent with 19F.77 Casual survey of the literature suggests that, despite the prevalence of silyl groups and silyl-based protecting groups, 29Si NMR spectroscopy is being underutilized.78 It would be a superb tool to monitor reactions and products by the organic synthesis community. We also optimized the basis set, functionals, and grid size for DFT computations of sodium salts to improve our previous protocols. The computations proved invaluable, but the correlations of theory and experiment are qualitative.

What is gained by knowing detailed structures of NaHMDS beyond merely plugging a glaring hole in the organosodium literature? The empirically minded consumers now have a large choice of solvents and can, at least in principle, pursue changes in reactivity and selectivity by targeting observable changes in the underlying aggregation and solvation states. Of course, the mechanism is more complex than that, but it is a start. We hasten to add that it would be difficult to predict something as simple as the solvent-dependent relative reactivities of NaHMDS. Do they span an order of magnitude or 6 orders of magnitude? We also have a particular fondness for a NaHMDS. Do they span an order of magnitude or 6 orders of magnitude? We also have a particular fondness for a NaTMDS.

**Experimental Section**

**Reagents and Solvents.** Hydrocarbons, monofunctional trialkylamines, monofunctional ethers, HMPA, TMEDA, (R,R)-TMCDCA, (−)-sparteine, PMDTA, and diglyme were distilled from blue or purple solutions containing sodium benzenophenone ketyl. Styrene, DMFU, DMF, DMSO, 12-crown-4, 15-crown-5, and TDA-I were dried over 4 Å molecular sieves prior to use. Bipyridine and [2.2.2]-cryptand were purchased and used without purification. 18-crown-6 was distilled.

**NMR Spectroscopic Analyses.** An NMR tube under vacuum was flame-dried on a Schlenk line, allowed to cool to room temperature, backfilled with argon, placed in a −78 °C dry ice/acetone bath, and charged with NaHMDS and solvents using stock solutions. The sample was mixed with a vortex mixer. Standard 1H, 13C, 15N, and 29Si spectra were recorded on a 500 MHz spectrometer at 500, 125.79, 50.66, and 99.36 MHz, respectively. The chemical shifts are referenced at −120 °C as follows: 1H (Me2Si, 0.0 ppm), 13C (MeSi, 0.0 ppm), 15N (neat Me2N, 25.7 ppm), and 29Si (Me2Si, 0.0 ppm).

[15N]Hexamethyldisilazane. [15N]NH4 was generated by a known procedure2 by mixing [15N]ammonium chloride (3.0 g, 55.0 mmol, >99% 15N isotopic purity) with 6.00 g (150 mmol) of granular NaOH in a 25 mL one-neck round-bottom flask equipped with an NaOH-filled tube through which the ammonia gas is transferred to an empty 100 mL round-bottom flask cooled to −78 °C (see Supporting Information). The mixture was warmed with a heat gun for approximately 20 min. After the transfer of ammonia was complete, 1-(trimethylsilyl)imidazole (14.7 g, 15.3 mL, 105 mmol, 98% purity) was added at −78 °C with stirring. Imidazole precipitated immediately, after which anhydrous diethyl ether (20 mL) was added to the flask, and the mixture was held at 0 °C for 40 min. Cholesterol (3.0 g) was added to the [15N]hexamethyldisilazane with stirring for 45 min to remove excess 1-(trimethylsilyl)imidazole. Short path distillation at atmospheric pressure removed the diethyl ether. Vacuum distillation (40 mmHg, 20 °C) afforded 4.75 mL (47% yield) of (Me2Si)NH4.

[15N]-Sodium Hexamethyldisilazide (1). [15N]NaHMDS was prepared following a known procedure.12 To a flame-dried fine-mesh swivel-frit setup was added sliced sodium metal (1.20 g, 52.4 mmol) in a glovebox. The apparatus was moved to a Schlenk line for the remainder of the procedure. Under argon, [15N]HMDS (7.31 g, 9.45 mL, 45.0 mmol) and 40 mL of DMEA were added to the reaction flask at room temperature. Isopropene (2.62 mL, 26.2 mmol) dissolved in 8 mL of dry DMEA was then added over 1 h via syringe pump to the mixture. After addition of isopropene, the reaction was stirred at RT for an additional 2 h. The solution was subsequently filtered through a frit, transferred with a canula to a second swivel coarse-frit setup, and vacuum evaporated to dryness for at least 10 h to yield a white powder. The powder was suspended in dry pentane (~20 mL), stirred for 1 h, and filtered. Finally, the product was washed with 20 mL of pentane and yielded 6.70 g (91% yield) of [15N]NaHMDS as a white solid,12 which was transferred to a glovebox and stored at room temperature. NaHMDS can be recrystallized as previously described12 but with no detectable improvement. 1H NMR (toluene-d8, 500 MHz): δ 0.2 (s, 18 H). 13C(1H) NMR (toluene-d8, 125.72 MHz): δ 6.8 (d, J15N −C = 2.7 Hz). 29Si NMR (toluene-d8, 99.36 MHz): δ −14.4 (d, J15N −Si = 7.9 Hz).

**Sodium Tetramethyldisilazide (NaTMDs, 17).** NaTMDs was synthesized from 1,1,3,3-tetramethyldisilazane using the prep described for NaHMDS, affording NaTMDs (17) as a white solid (3.0 g, 50% yield).17 1H NMR (toluene-d8, 125.72 MHz): δ 8.9. 29Si NMR (toluene-d8, 99.36 MHz): δ −28.0.

**Sodium Bis(dimethylphenyl)silylamide (NaDPTMDS, 18).** NaDPTMDS was synthesized from bis(dimethylphenyl)silylamide using the same prep described for NaHMDS, affording NaDPTMDS (18) as a white solid (5.3 g, 45% yield).18 1H NMR (toluene-d8, 125.72 MHz, DMEA): δ 13.2, 6.3.

**Sodium 1-Aza-2,2,5,5-tetramethyl-2,5-disilacyclopentane (19).** Sodiated 1-aza-2,2,5,5-tetramethyl-2,5-disilacyclopentane was prepared using the same dissolving-metal-based prep described previously for NaHMDS, affording 19 as a white solid (3.4 g, 70% yield).19 1H NMR (toluene-d8, 125.72 MHz, DMEA): δ 13.2, 6.3.
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ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02546.

Spectroscopic data, rate, and computational data (PDF)

Accession Codes
CCDC 2042630 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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(10) For an extensive review on the chemistry of the alkali metal amides, see: Mulvey, R. E.; Robertson, S. D. Synthetically Important Alkali-Metal Utility Amides: Lithium, Sodium, and Potassium Hexamethyldisilazides, Disopropylamides, and Tetramethylpiperidines. Angew. Chem., Int. Ed. 2013, 52, 11470.


(13) Many of the results for LiHMDS and LDA can be accessed through two review articles. More recent studies not cited therein are provided below.14,16


(22) Several seemingly simple computations at the MP2 level of theory failed for reasons that were unclear. This is not a problem using DFT with M06 functionals.


(24) Legault, C. Y. CYLview, 1.0h; Université de Sherbrooke, 2009 (http://www.cylview.org).


(26) For example, the solution energies of toluene on NaHMDS dimer decreased by 2.0 kcal/mol by switching from a grid size of 75 302 to 99 590.


(29) The intended mole fraction refers to the mole fraction based on what was added to the samples. The measured mole fraction—the mole fraction within only the ensemble of interest—eliminates the distortive effects of impurities. This problem has been highlighted: Bryce, Hubbert, D.; Thorarison, P. The Death of the Job Plot, Transparency, Open Science and Online Tools, Uncertainty Estimation Methods and Other Developments in Supramolecular Chemistry Data Analysis. Chem. Commun. 2016, 52, 12792.


(31) The concentration of NaHMDS, although expressed in units of molarity, refers to the concentration of the monomer subunit (normality).


(36) Double solvation of dimer follows a first- rather than second-order saturation function because of a single solvent per sodium.


(38) We use the term “cooperative” for advantageous (proagonistic) influences of two coordinated solvents. The term “correlated” is intended as a neutral term in which two or more coordinated solvents influence their relative binding irrespective of whether protagonistically or antagonistically. Correlated ligation is an issue across all metals. There is also a statistical factor in a serial substitution that is easily overlooked.
(c) Rubini, P. R.; Rodhueser, L.; Delpuech, J. J. A Nuclear Magnetic Resonance Study of Metal Complexes of Nonamethylimidodiphosphoramide. Inorg. Chem. 1979, 18, 2962.
(h) Titrating a solution of NaHMDS in toluene or MTBE with two ligands (two crowns, for example) will necessarily produce solvates of both at up to 0.5 equiv of each. Only when an excess has been added can the preference be established. The protocol is expedient, and the low concentrations serve as control experiments.