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Lithium Amide Protected against Hydrolysis by Aggregated Lithium Halides: An MS + DFT Investigation

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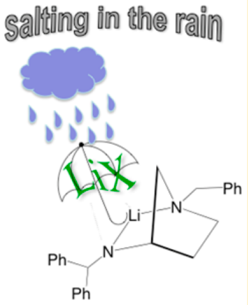
Supporting Information

ABSTRACT: Supported by mass spectrometry experiments, DFT computations indicate that the lithium amide of a 3-aminopyrrolidine (lithium benzhydryl(1-benzylpyrrolidin-3-yl)amide, **1-Li**) is protected, up to a certain limit, against hydrolysis when it is aggregated with a strongly polar partner such as LiCl, LiBr, or MeLi.



INTRODUCTION

Lithium amides, and in particular hindered ones, have been used for decades as strong, non-nucleophilic bases in organic synthesis. They replace advantageously alkylithiums to deprotonate substrates bearing fragile functional groups, likely to react with alkyllithiums. The cation lithium is often preferred to sodium or potassium because it generally entails a higher solubility in organic solvents and higher selectivity in chemical transformations. The popular lithium diisopropylamide (LDA) is certainly the most commonly used lithium amide when it comes to simple deprotonations. Their chiral congeners are also powerful species largely employed in asymmetric synthesis for diastereoselective and enantioselective processes. Actually, these reagents can be used directly as chiral bases,[1] but they can also behave as chiral nucleophiles[2] or be associated with another lithiated reagent and be regarded as chiral ligands.[3]

In most of these matters, the reactivity of the nitrogen of the lithium amides toward acidic protons is a key issue, and these transformations are generally conducted in strictly anhydrous media to avoid a premature protonation of the amide by water. However, Capriati and co-workers[4] have recently challenged this long-standing dogma by suggesting that protic media (and water in particular) can be compatible, to some extent, with highly polarized organometallic compounds.[5] This fascinating finding came after a series of early reports about the (brief) persistence of organolithium entities in the presence of a proton source.[6] These results raise several questions, already underlined by Hevia, Capriati et al.,[7] concerning the water aptitude to behave as a ligand of Li^+, and how, once coordinated, the reactivity of water is modified. More recently, a series of organolithium reagent used in unconventional solvents has been examined, showing that chemical transformations involving these assumed extremely moisture sensitive reagents can be performed in protic media.[8] The problem of the reactivity, at the molecular level, of water toward the nitrogen of lithium amides and their aggregates is thus of interest since better understanding the conditions in which the proton transfer occurs is likely to help to design and, possibly, introduce a water-proof character in such sensitive reagents. An approach similar to ours, combining ion−molecule reactions in a mass spectrometer and theoretical studies, allowed Khairallah et al.[9] to demonstrate enhancement effect of LiCl in the protonation of a lithium acetylide.

In this paper, we present the results obtained by reacting lithiated aggregates with water in the collision cell of a modified triple-quadrupole mass spectrometer.[10] These aggregates are built around the specific amide **1-Li** (lithium benzhydryl(1-benzylpyrrolidin-3-yl)amide) that results from the deprotonation of a 3-aminopyrrolidine (3-AP, see Figure 1). This

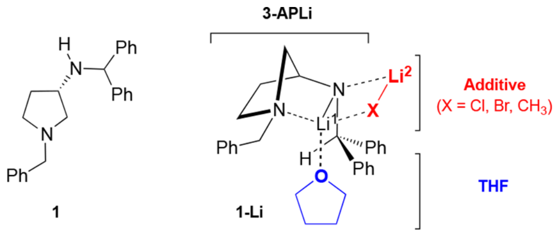


Figure 1. Structure of amine **1** and of the model of the lithium amide mixed aggregates [(**1-Li**−1THF)−LiX] considered in this work (Ph = C_6H_5).

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compound was selected because its behavior and aggregation properties are well-known, in solution, on both experimental and theoretical grounds. In particular, we have observed that these amides adopt a norbornyl-type folded conformation (Figure 1), resulting from the intramolecular chelation of the lithium cation by the two nitrogen atoms of the amide. This puckering applies to both **1**−Li alone and its complexes with LiX. NMR and MS data also led to the conclusion that only one molecule of THF is intimately associated with the **1**−Li aggregates (little or no exchange observed by NMR) and that this THF sits on the lithium atom coordinated to the endocyclic nitrogen (Li^1, Figure 1). On the basis of the mass spectrometry results and motivated by the unexpected behavior of $[(\mathbf{1\text{-}Li}{-}1THF){-}LiCl + H]^+$ in close association with water in the gas phase during collisions, a DFT computational study of a series of complexes involving the chiral lithium amide **1-Li** and three polar partners (LiBr, LiCl, MeLi) has also been undertaken. The three LiX were selected among the most generally employed additives in the literature in papers mentioning a global but unexplained "salt effect" or using mixed aggregates involving a lithium amide and, generally, an alkyllithium. In accord with the MS data and previous studies, only 1:1 complexes between the 3-APLi and lithium halides or MeLi have been considered. Those have been interacted with plain or protonated clusters of water $[(H_2O)_m + (H^+)_n]$ of realistic sizes[11] ($m = 1-5$ and $n = 0-1$).

RESULTS AND DISCUSSION

In a previous study,[12] we have shown that the protonation of the mixed aggregate $[(\mathbf{1\text{-}Li}{-}1THF){-}LiCl]$ in the gas phase resulted in the formation of an HCl adduct preferentially to the protonation of the amide nitrogen (Figure 2).

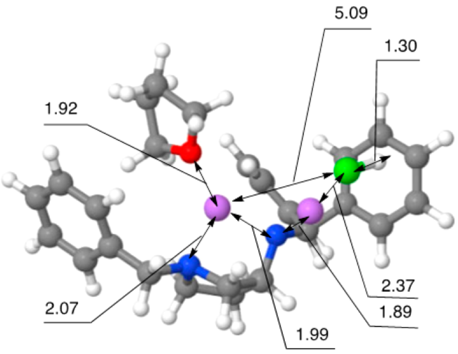

Figure 2. Optimized structure of $[(\mathbf{1\text{-}Li}{-}1THF){-}LiCl + H]^+$ (at the B3P86/6-31+G** level of theory) corresponding to the ion m/z 463 (N in blue, Li in purple, O in red, Cl in green). Selected bond distances are in angstroms.

This preference was unexpected, in particular with respect to what happens in solution: if water is introduced, the basic amide nitrogen immediately captures a proton and provides the amine plus LiCl. We thus decided to evaluate experimentally the ability of such an aggregate to catch, in the gas phase, a proton from water. Following the procedure described in our previous work,[12] we generated the $[(\mathbf{1\text{-}Li}{-}1THF){-}LiCl + H]^+$ species (m/z 463) in the ESI source. Then, H_2O was introduced in the transfer hexapole (H0) or collision cell (H2) (see the SI for details), in the hope that a transfer of a proton of water would occur toward the lithium amide. In our previous work, we have shown that this protonation can be conveniently monitored via the m/z 167 fragment ion which corresponds to the benzhydrylium (Ph_2CH^+) marker of amine **1**.[12] In a first experiment (Figure 3A), water was introduced in the hexapole transfer (H0) and ions m/z 481 were produced, corresponding to the m/z $[463 + H_2O]^+$ adduct.[13] The collision induced dissociation (CID, under argon) spectrum of m/z 481 yielded m/z 463 (low abundance) and a m/z 409 fragment corresponding to m/z $[391 + H_2O]^+$. Our previous study suggested that the structure of this ion should be $[\mathbf{1\text{-}Li}, LiCl + H + 1H_2O]^+$.[12] Interestingly, the ion m/z 167 was not observed. In a second experiment, water was introduced in H2 (Figure 3B), allowing us to adjust the collision energy between the lithiated aggregate and water (this was not possible using H0 as the collision cell). This time, whatever the energy range, mainly water adducts were observed: m/z 367 corresponding to m/z 349 (also observed) + H_2O and m/z 109 corresponding to m/z 91 (also observed) + H_2O. The diagnostic fragment ion of **1** during the collisional process at m/z 167 was detected in very low abundance (∼10%). It thus seems that in our gas-phase conditions collision with water does not initiate reaction but mainly dissociation processes with formation of cationic adducts.

In an effort to understand this intriguing "protecting effect" against water of LiCl on amide **1**−Li, computational studies were next undertaken on aggregates associating **1-Li** and the three lithiated additives mentioned above. To remain in line with our previous theoretical studies on similar structures,[12] all the DFT computations were performed at the B3P86/6-31+G** level of theory with one molecule of solvent (THF) remaining in the starting ion structure m/z 463 after ionization.

We first benchmarked this approach with the simplest possible system that is the solvated, nonaggregated, $\mathbf{1\text{-}Li}{-}1THF{-}1H_2O$ (Figure 4). The water molecule was localized such as to connect its oxygen (via the electrons lone pairs) and the lithium cation. The optimization triggered a direct protonation of the nitrogen amide, affording amine **1**, with concomitant formation of THF-solvated Li−OH, without any energy barrier. This simply corresponds to the expected protonation of the lithium amide, the metallic cation being chelated by the two nitrogen atoms of the regenerated amine.

We repeated the same computational experiment with the mixed aggregate $[(\mathbf{1}{-}Li{-}1THF){-}1LiCl] + H_2O$, approaching the molecule of water on the accessible, less coordinated, Li^2. The optimization led, this time, to a local minimum in which the water remains simply docked on Li^2, leaving the nitrogen amide untouched (Figure 5). The water coordination pulls the cation slightly apart from the amide with respect to the position it occupies in the $[(\mathbf{1}{-}Li{-}1THF){-}LiCl]$ complex alone. The inertia of H_2O in this local minimum is probably due to its location, relatively remote from the nitrogen amide and physically unable to transfer a proton.

To evaluate the order of magnitude of the energy barrier associated with this N-protonation we ran a relaxed potential energy surface (PES) scan on this same system, starting from the above minimum. A barrier of +3.8 kcal/mol was calculated at the B3P86/6-31+G** level of theory, and Figure 6 illustrates the situation at this critical point. Actually, the TS does not correspond to the N-protonation but to the rotation of the molecule of water around the Li atom. This reorganization places one proton of H_2O in close proximity to the N atom of the amide (2.36 Å against 4.26 in the starting point); from there, the H-transfer occurs directly at no extra energy cost. Note that a +3.8 kcal/mol activation barrier is low but remains

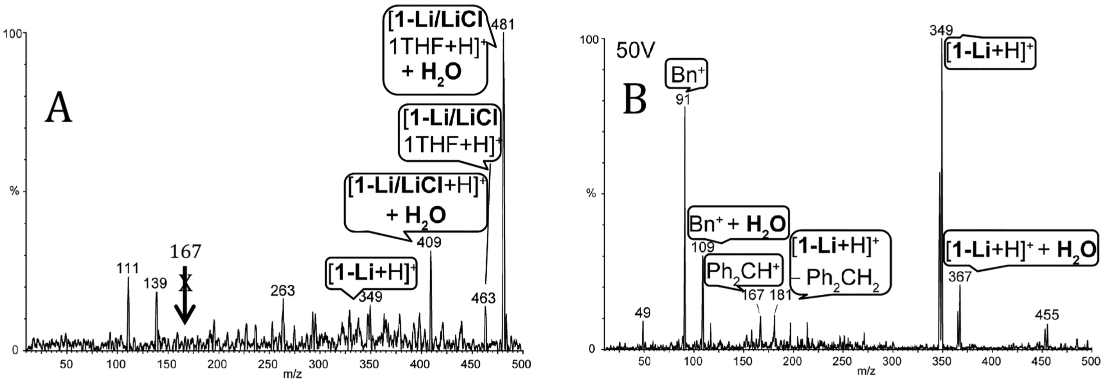

Figure 3. Collision of [(**1**-**Li**-1THF)−LiCl + H]$^+$ with H_2O in H0 (left) or in H2 (right).

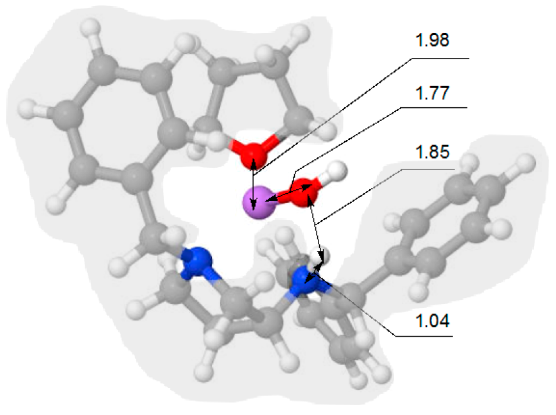

Figure 4. Structure of [**1**−LiOH−THF] resulting from the optimization of [(**1**-**Li**−1THF)] + $1H_2O$ (N in blue, Li in purple, O in red). Selected bond distances are in angstroms.

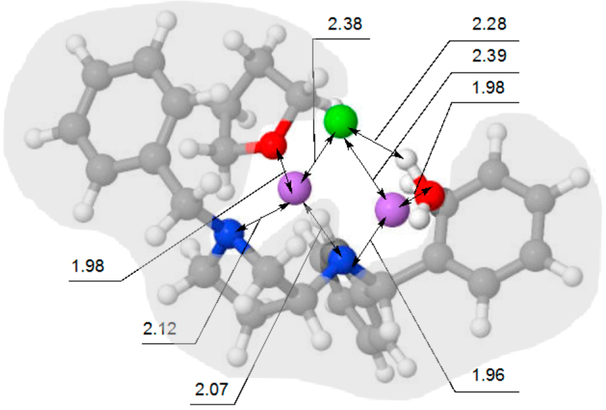

Figure 5. Optimized structure of [(**1**-**Li**−1THF)−LiCl] + H_2O (N in blue, Li in purple, O in red, Cl in green). Selected bond distances are in angstroms.

realistic within the context of such fragile systems and can account for a moderate protecting effect by LiCl. Beyond the TS, the final product is the trimolecular complex between the regenerated amine **1** and LiCl + LiOH, the first lithium cation remaining chelated by the two nitrogen atoms of **1**. Note that its endothermic character, the energy going up all along the scan, impedes the competitive formation of HCl in these conditions.

The presence of water clusters is well established in THF,[14] so we decided to push forward the investigation by self-organizing a few water molecules into little collections associated by hydrogen bonds and triggered their interaction with the same [(**1**-**Li**−1THF)−LiCl] complex. The conformation of such supermolecules is difficult to foretell. Obviously, the water−amide contact relies on the direct O−Li long-distance electrostatic interactions. From there, we tried to design a reasonable starting point, linking the second molecule of water through an hydrogen bond to the O of the first one, while keeping an interaction between the second H and the N atom of the amide. We anticipated that, after a few optimization steps, the water flock would adapt to the "cavity" surrounding the cations. Following this procedure, we introduced progressively 2, 3, 4, and 5 molecules of water and obtained reasonable H-bonded chains fitting the "groove" shape.

In Figure 7, the fully optimized structures of the complexes with 2−4 H_2O are presented. Overall, the topology of the [**1**-**Li**−LiCl] core in the complex remains relatively constant and no proton transfer is computed. However, the data suggest that the N−Li^2 couple undergoes the influence of the increasing number of water molecules: the N−Li^2 bond distance goes from 1.96 to 1.99, 2.03, and 2.07 Å in the complexes including one-four H_2O, respectively. One can assign this significant lengthening to the coordination of the Li cation by water that becomes more and more efficient when the number of water molecules increases. Thus, the self-organization of the water cluster through its network of flexible H-bonds transforms $(H_2O)_n$ into a global, increasingly donor, ligand for the lithium. Note that the optimized complex in the case of 4 H_2O is metastable, with slight displacements of a water molecule triggering an easy proton transfer toward the nitrogen.

Finally, a free proton transfer toward the amide could be computed when a fifth H_2O molecule was included in the model. It is clear from Figure 8 that the addition of this last molecule of water rouses a dramatic reorientation of the fourth molecule of water, locating one of its two protons within reach of the nitrogen amide. Note that the acidity of the proton shuttled between the oxygen and the nitrogen can also be increased by the modification of the surroundings of water 4, now in interaction with molecules 3 and 5. Once the amide nitrogen is protonated, the structure of the complex is attuned: the first Li cation gets fully coordinated by the water molecules, the dihydrated hydroxide (former water 4) and the chloride. It does not interact with the nitrogen anymore and is driven away from Li^2.

In a second experiment, we wondered if the protecting effect of LiCl could resist an increasing acidity of the protonating agent. We thus repeated the set of computations by replacing H_2O with H_3O^+ and $H_3O^+(H_2O)_{n=2-4}$, a model corresponding

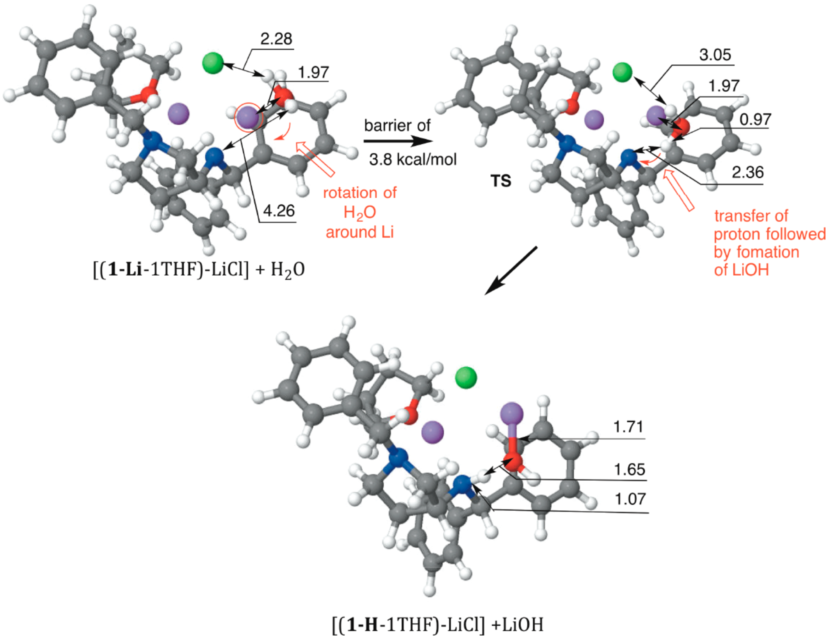

Figure 6. TS associated with the proton transfer between H_2O and the acyclic nitrogen in [(**1-Li**−1THF)−LiCl] + $1H_2O$ (N in blue, Li in purple, O in red, Cl in green).

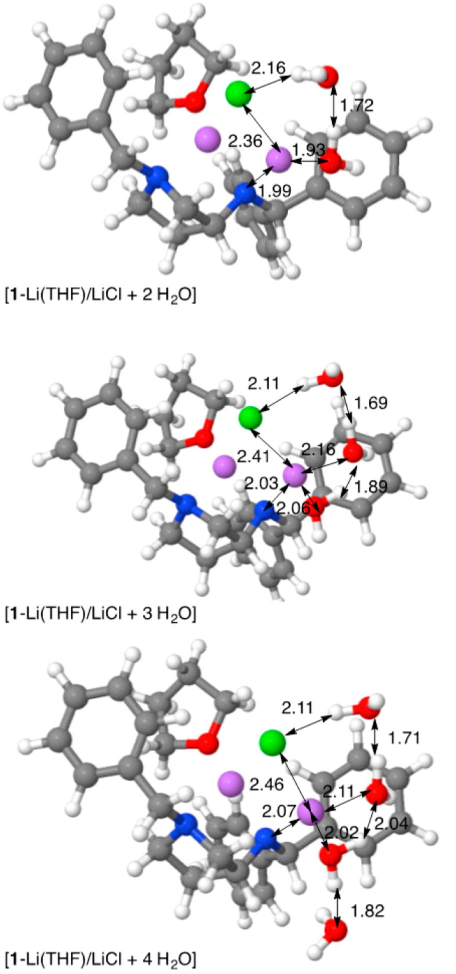

Figure 7. Optimized structure of [(**1-Li**−1THF)−LiCl + 2−$4H_2O$] (N in blue, Li in purple, O in red, Cl in green). Selected bond distances are in angstroms.

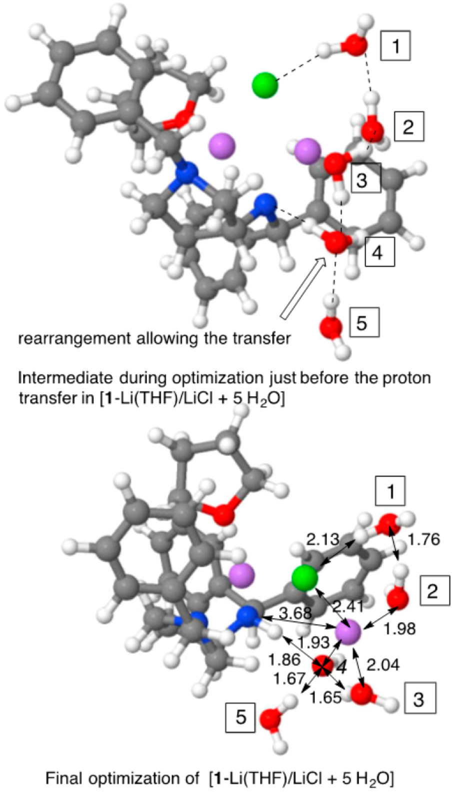

Figure 8. Optimized structure of [(**1**−LiCl−LiOH−1THF) + $4H_2O$] resulting from the optimization of [(**1-Li**−1THF)−LiCl + $5H_2O$]. Selected bond distances are in angstroms (N in blue, Li in purple, O in red, Cl in green).

to a proton associated with small water clusters.[15] Actually, this approach is likely to provide a possibly better description of the gas-phase conditions used in our first mass spectrometry experiments (electrospray in positive mode, observation of MH^+ species).

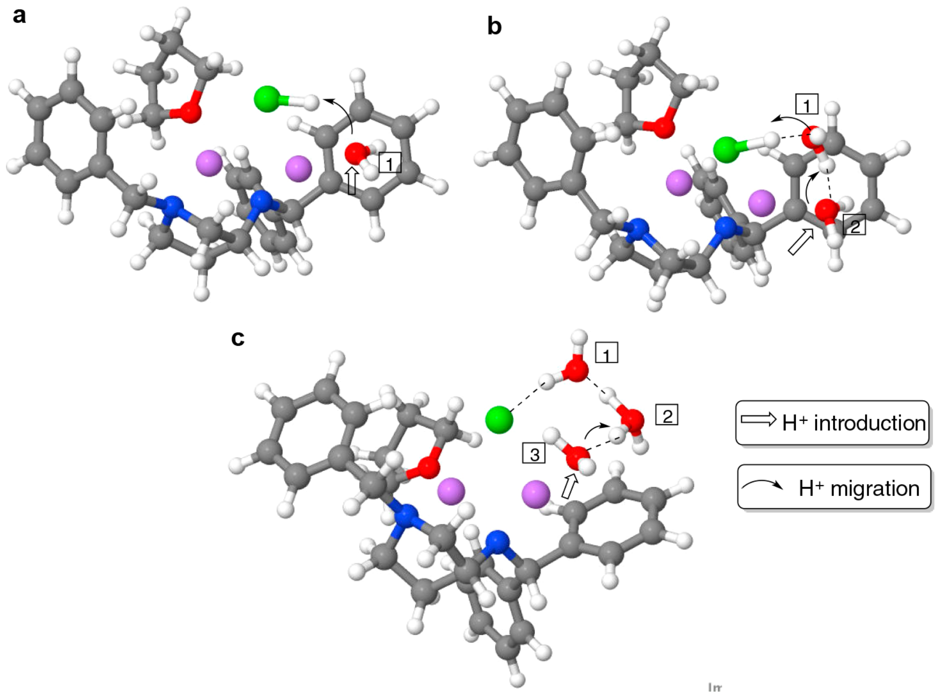

Figure 9. Optimized structure of (a) [(**1-Li**−1THF)−LiCl] + H_3O^+, (b) [(**1-Li**−1THF)−LiCl] + [H_2O,H_3O^+], (c) [(**1-Li**−1THF)−LiCl] + [$2H_2O$,H_3O^+] (N in blue, Li in purple, O in red, Cl in green).

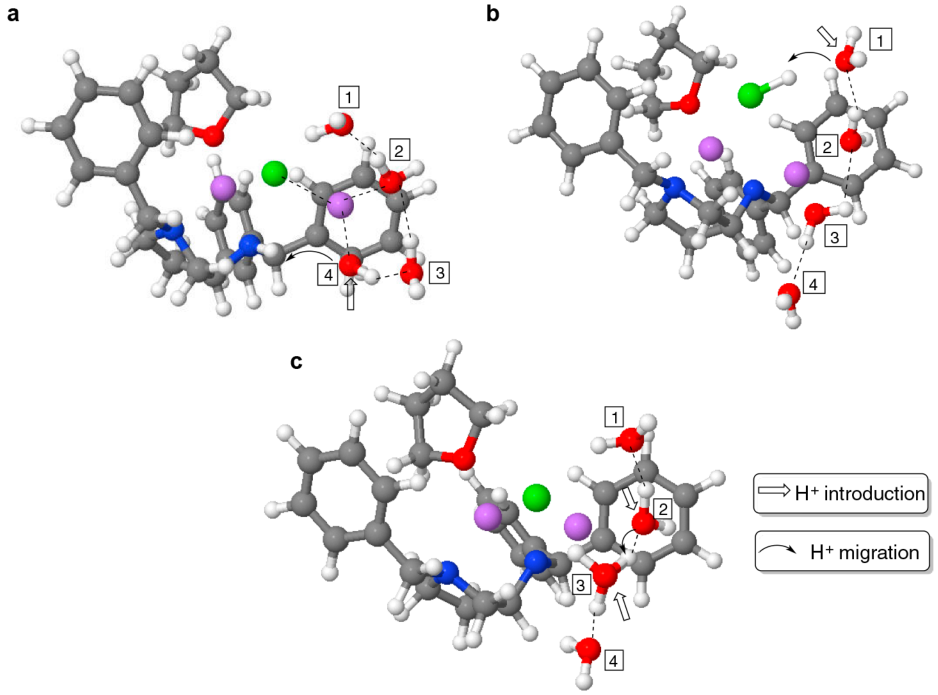

Figure 10. Optimized structure of (a) [(**1-Li**−1THF)−LiCl] + [$3H_2O$,H_3O^+@4], (b) [(**1-Li**−1THF)−LiCl] + [$3H_2O$,H_3O^+@1], (c) [(**1-Li**−1THF)−LiCl] + [$3H_2O$,H_3O^+@2−3] (N in blue, Li in purple, O in red, Cl in green).

Introducing a proton in the modeling changes slightly the results of the computations for the clusters with 1−3 molecules of water. In the case of H_3O^+, the optimization does not trigger the protonation of the amide nitrogen but yields the unexpected formation of HCl (Figure 9a). The result is similar to [H_2O,H_3O^+], except that the proton transferred to the chloride remains somewhat bonded to the water, as indicated by the Cl−H···OH_2 distance of 1.71 Å. Interestingly, the proton initially introduced on the second molecule of water (see Figure 8b) migrates, without any energy barrier, toward the first one (Figure 9b). The situation is identical with [$2H_2O$,H_3O^+]: the proton introduced at the end-chain position, *viz.* on the third water molecule, migrates to the second one and stays there, leading to the metastable cluster depicted on Figure 9c. Hence, in these three cases the nitrogen amide remains untouched despite the protic environment. It appears that the chloride anion, or the water cluster itself, "buffers" the proton before it reaches the nitrogen.

The situation differs with ($3H_2O,H_3O^+$), with the reactivity of the proton depending on its original location. Indeed, if the proton is introduced via the fourth water, the nitrogen amide gets protonated (Figure 10a). In contrast, if H^+ is initially bound to the first molecule of water, which lies near the chloride, the formation of HCl is preferred (Figure 10b). If the optimization is launched with the proton attached to the second or the third molecule of water, it remains within the cluster (Figure 10c) and is shared between waters 2 and 3.

Finally, the computation has been repeated with the ($4H_2O,H_3O^+$) cluster. The results are similar to those obtained with ($3H_2O,H_3O^+$): introducing the proton on the fifth water molecule elicits its migration toward the fourth one, then on the nitrogen amide where its course ends up (Figure 11a). A reorganization of the complex similar to that mentioned above follows the nitrogen protonation (Figure 11b).

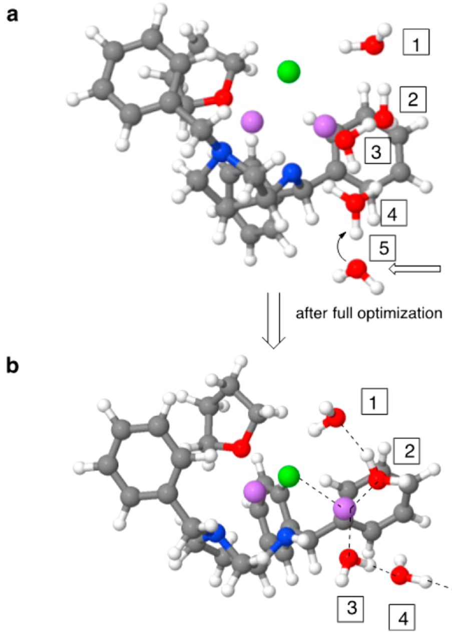

Figure 11. (a) Intermediate during the optimization corresponding to the migration of H^+ from the fifth to the fourth molecule of water. (b) Final optimized [(**1-Li**−1THF)−LiCl] + [$4H_2O,H_3O^+$@5] (N in blue, Li in purple, O in red, Cl in green).

To enlarge the scope of this work and check if other polar partners could exert a comparable protecting effect, we examined the case of the [(**1-Li**−1THF)−LiBr] aggregate. The same $(H_2O)_{1-5}$ water clusters were considered, with and without an additional proton. For the sake of brevity, we do not give details here (see the SI), but the results lead to conclusions very similar to those drawn with LiCl, the only difference being that the $(H_2O)_5$ cluster does not trigger the *N*-protonation of the amide, a (shallow) local minimum being found for this complex. It thus looks like LiBr exerts a protecting effect that is at least as good as that of LiCl. When it comes to the protonated water clusters, the results are exactly similar to those obtained with LiCl: [H_2O,H_3O^+] and [$2H_2O,H_3O^+$] provide HBr, [$3H_2O,H_3O^+$] converges toward a system where the proton remains between the central water molecules while [$4H_2O,H_3O^+$] and [$5H_2O,H_3O^+$] lead to the protonation of the nitrogen.

The last extension of our investigation consisted in replacing the halides by a different, more reactive, anion. We thus considered the [(**1-Li**−1THF)−CH_3Li] mixed aggregate[16] of which methyl anion is much more basic and nucleophile, at least in solution, than the chloride and bromide. This new complex was thus fully optimized and the water molecule(s) was (were) docked following the previous procedure. Actually, the results are more or less the same (see the SI for details): the plain water clusters do not react with the complex and simply behave as an additional ligand to the system, while the protonated clusters afford methane for H_3O^+ and [H_2O,H_3O^+], and the protonation of the amide with larger water complexes. Thus, methyllithium exerts an influence on the lithium amide similar to that of the lithium halides, suggesting that aggregated polar entities repel water through an analogous mode of action.

■ CONCLUSION

Both mass spectrometry and DFT computations suggest that the lithium amide of a 3-aminopyrrolidine (lithium benzhydryl-(1-benzylpyrrolidin-3-yl)amide, **1-Li**) is protected, to some extent, against hydrolysis when it is aggregated with a strongly polar partner such as LiCl, LiBr, or MeLi. This protecting effect is evidenced when small water clusters (less than five molecules) are docked on the aggregate but tend to disappear when protonated systems [nH_2O,H_3O^+] are introduced. In this latter case, a proton shift is computed toward either the nitrogen of the amide or the exogenous anion X^-, depending on the location of the introduced proton. The origin of this phenomenon relies probably on the presence of LiX that repulses the water molecules away form the nitrogen, at least for small clusters, and renders its protonation more difficult. Even though, the optimized complexes we obtain are metastable and the energy barrier, calculated in one case, for the proton transfer is very low, indicating that the mixed aggregate remain fragile toward water. Nevertheless, the stabilization brought by these polar additives could be at the origin of the long and mostly unexplained salt effect observed by many organometallic chemists in different fields.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01419.

> Figure of the device using microreactor for mass spectrometry experiments, figure of the modified mass spectrometer with H0 and H2 collision cells, computational details, and Cartesian coordinates for all molecules reported in this study (PDF)

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Notes

The authors declare no competing financial interest.

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(15) This kind of protonated cluster of water can probably form in the THF spray and interact with the Li aggregate. It would most probably be too fragile to be observed in a mass spectrum after selection.

(16) Aggregates between 3-aminopyrrolidine lithium amides and methyllithium or n-butyllithium have been fully characterized by NMR in THF and their structure described by DFT in previous papers; see: (a) Corruble, A.; Davoust, D.; Desjardins, S.; Fressigné, C.; Giessner-Prettre, C.; Harrison-Marchand, A.; Houte, H.; Lasne, M.-C.; Maddaluno, J.; Oulyadi, H.; Valnot, J.-Y. *J. Am. Chem. Soc.* **2002**, *124*, 15267−15279. (b) Yuan, Y.; Desjardins, S.; Harrison-Marchand, A.; Oulyadi, H.; Fressigné, C.; Giessner-Prettre, C.; Maddaluno, J. *Tetrahedron* **2005**, *61*, 3325−3334. (c) Paté, F.; Gérard, H.; Oulyadi, H.; de la Lande, A.; Harrison-Marchand, A.; Parisel, O.; Maddaluno, J. *Chem. Commun.* **2009**, 319−321.

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