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Deprotonative Metalation of Methoxy-Substituted Arenes using Lithium 2,2,6,6-Tetramethylpiperidide: Experimental and Computational Study

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ABSTRACT: The reaction pathways of lithium 2,2,6,6-tetramethylpiperidide (LiTMP)-mediated deprotonative metalation of methoxy-substituted arenes were investigated. Importantly, it was experimentally observed that, whereas TMEDA has no effect on the course of the reactions, the presence of more than stoichiometric amount of LiCl is deleterious, in particular without *in situ* trap. These effects were corroborated by the DFT calculations. The reaction mechanisms, such as the structure of the active species in the deprotonation event, the reaction pathways by each postulated LiTMP complex, the stabilization effects by *in situ* trapping using zinc species, and some kinetic interpretation, are discussed herein.

INTRODUCTION

Deprotonative lithiation using alkyllithiums and hindered lithium dialkylamides is an efficient way to functionalize regioselectively aromatic compounds.[1] The method has been widely used, but its scope is nevertheless restricted by the low compatibility existing between polar organolithiums and electrophilic functional groups that can decorate the aromatic substrates. In addition, when employed alone, the lithium bases can exhibit an insufficient reactivity toward non-activated substrates.

To tackle these issues, lithium bases have been combined with Lewis donor ligands (e.g. TMEDA; TMEDA = *N,N,N',N'*-tetramethylethylenediamine)[2] or alkali metal alkoxides (e.g. potassium *tert*-butoxide,[3] lithium 2-dimethylaminoethoxide[4]). For the same purpose, other metal bases have been activated with salts (Turbo bases)[5] or in the form of lithium -ate complexes (e.g. zincates,[6] cuprates[7]).[8] Owing to less aggregated bases (increased reactivities) or to less polar organometals (higher compatibility with sensitive substrates), the scope of the reaction has been extended to less activated aromatics and to substrates prone to nucleophilic attack, respectively.

In situ trapping of the generated aryllithiums, by either transmetalation or trans-metal-trapping (TMT),[9] is another way to achieve these goals.[10] The aryllithiums formed by reaction with non-nucleophilic lithium amides are rapidly intercepted by compounds that may contain silicon, boron, zinc, aluminum and gallium. As a consequence, they do not attack sensitive functions and are more efficiently formed. In this context, LiTMP[11] (TMP = 2,2,6,6-tetramethylpiperidide) can be employed to ensure room-temperature deprotometalation of a large range of substrates, and studies notably evidenced $Zn(TMP)_2$,[12] $ZnCl_2$,[13] $ZnCl_2$·2LiCl[13] and $ZnCl_2$·TMEDA[14] as efficient *in situ* traps for this purpose. If it is recognized from NMR,[11,15] theoretical calculations,[15] and experimental data[16] that the synergy observed in the reactions using these pairs results from reversible deprotolithiation shifted by *in situ* trapping by zinc species (lithium amide acting in tandem with separated zinc species), little is known about the precise deprotonation pathway.

Thus, if the LiTMP base plays an important role in organic synthesis due to both strong Brønsted basicity and low nucleophilicity towards electrophiles (e.g. carbon centers),[17] being used either to accumulate aryllithiums from activated arenes including heterocycles, or in the presence of *in situ* traps for less activated arenes, there is still much to learn about reaction pathways using LiTMP.

By using diffusion ordered NMR spectroscopy (DOSY), LiTMP·2LiCl (±TMEDA) was pinpointed as the possible active species of the basic combination *in situ* prepared from $ZnCl_2$·TMEDA and LiTMP in a 1:3 ratio, and supposed to be 1:1 LiTMP-$Zn(TMP)_2$.[11] Recently, LiTMP monomers and dimer

(triple ion) were proposed as reaction intermediates to rationalize *ortho*-lithiations of activated arenes.[18]

Herein, we report our experimental and theoretical investigations on the mechanism of LiTMP-mediated deprotometalation of methoxy-substituted arenes, notably concerning the impact of additives such as LiCl and TMEDA, and of the subsequent *in situ* trapping step by $Zn(TMP)_2$.

RESULTS AND DISCUSSION

The solid-state and solution structures of LiTMP depend on Lewis donor solvents or ligands.[19] While LiTMP can exist as a C_{4h} cyclotetramer[20] or a C_{3h} cyclotrimer[21] in the crystal, or a mixture of trimers and tetramers in hydrocarbon solution,[22] deaggregation takes place in the presence of THF (THF = tetrahydrofuran) to give a cyclodimer in which each metal is solvated.[23] More precisely, ^{7}Li NMR spectroscopy shows monomer-dimer equilibrium, with the former favored at higher concentrations.[23-24]

Probably by reason of more important steric hindrance, the Li-O bond of the THF-solvated cyclodimer solid-state structure is larger in the case of LiTMP than observed for LiDA (DA = diisopropylamide).[23] Replacing THF by bidentate TMEDA even causes dimer opening to afford the hemisolvated 'open dimer' TMEDA·$(LiTMP)_2$[25] in addition to monomer species.[17] On dissolution, the 'open dimer' seems to be cleaved into LiTMP and monomeric TMEDA·LiTMP.[26]

In the case of LiDA, solvating competition experiments between THF and TMEDA were performed, and lithium showed a preference for the former.[27] Nevertheless, for LiTMP, THF and TMEDA equally coordinate the amide metal.[17]

In the presence of other lithium species (e.g. lithium halides), lithium amides can form mixed aggregates. In particular, ^{6}Li and ^{15}N NMR studies on 0.1 M THF solutions of LiTMP allowed the mixed dimer LiTMP-LiCl and mixed trimers 2LiTMP-LiCl to be identified in the presence of LiCl (0.3 to 1.2 equiv) at temperatures around −100 °C.[24b] A similar observation was made using LiBr and, with both salts, the mixed dimers LiTMP-LiX are favored by using stoichiometric amounts of salt.[24b,28] Thus, TMEDA and LiCl, both generated by reacting $ZnCl_2$·TMEDA with LiTMP, might possibly be present in deprotonating species and modify reaction pathways.[29]

Collum and co-workers have studied the impact of LiCl on LiDA-mediated aromatic deprotometalation in THF under non-equilibrium conditions (low temperatures).[30] For example, by using 1-chloro-3-(trifluoromethyl)benzene as substrate, the authors observed different transition states depending on if LiCl is present or not.[31] Without lithium salt, LiDA deaggregation (conversion of the cyclodimer to the open dimer, and possibly to the monomer)[32] is the rate-limiting step, and (C2) proton transfer involves dimer-based triple ion transition state. In contrast, LiCl allows LiDA to be deaggregated, making (C6) proton transfer rate-limiting, step rather based on solvated LiDA monomer. Two mechanisms, either through triple-ion-like species with possible bridging THF, or through three- and four-rung ladders, were proposed for such LiCl-mediated LiDA deaggregation.[30] Nevertheless, these conclusions are both substrate- and temperature-dependent (LiCl can catalyze at a temperature and inhibit at another one),[33] and do not reflect what happens when LiTMP is used.

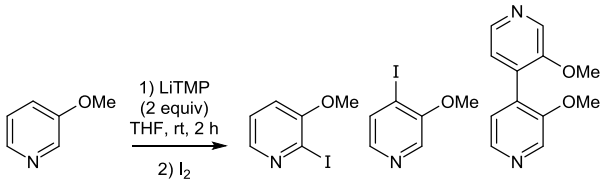
Mack and Collum recently compared LiDA- and LiTMP-mediated deprotometalation of substituted benzenes in THF, and showed reactions with the latter 5-500 times faster than with the former.[18] By using LiTMP, large isotope effects were noticed in agreement with rate-limiting proton transfers. Less favored stabilizing aggregation is expected using LiTMP due to higher steric hindrance. Toward 1,3-bis(trifluoromethyl)benzene, LiDA reversibly deprotonates the more acidic site between the substituents whereas LiTMP irreversibly attacks the less hindered 4 position. The deprotolithiation mechanisms involving LiTMP are substrate-dependent, with transition states based either on triple ions or on solvated monomers.

Thus, even if LiCl can impact LiDA-mediated deprotonation transition states, this salt is absent from their composition. As a consequence, it seems most unlikely that LiTMP·2LiCl could be the active species in deprotonation-trapping sequences. So, we have gone in search of a suitable substrate to investigate the impact of LiCl and TMEDA in the course of reactions with LiTMP. To this purpose, we selected three aromatic substrates, 3-methoxypyridine (**1a**), anisole (**2a**) and 4-bromoanisole (**3a**).

Experimental Study

3-Methoxypyridine (**1a**) can be functionalized at its 2 position upon treatment with n-BuLi·TMEDA,[34] mesityllithium[35] or TMPMgCl·LiCl[36] in THF. Mixtures of 2- and 4-substituted derivatives are formed either by using LiDA in the presence of chlorotrimethylsilane as *in situ* trap,[35] or with the base *in situ* prepared from $ZnCl_2$·TMEDA and LiTMP in a 1:3 ratio (1:1 LiTMP-$Zn(TMP)_2$).[12,37] Regioselective deprotometalation at the 4 position takes place either by using hindered TMP-zincate $Li(TMP)Zn(^tBu)_2$ in THF[38] or $(PMDETA)_2K_2Mg(CH_2SiMe_3)_4$ (PMDETA = *N,N,N',N'',N''*-pentamethyldiethylenetriamine) in hexane.[39]

Scheme 1. Deprotometalation of 3-methoxypyridine (1a) using LiTMP followed by iodolysis

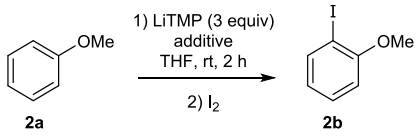


When 3-methoxypyridine (**1a**) was reacted with LiTMP (2 equiv) in THF for 2 h at room temperature (rt) before iodolysis, the results showed that the corresponding lithio product(s) could not be accumulated due to formation of the symmetrical dimer **1d**.[40] Things were not improved in the presence of TMEDA or LiCl (Scheme 1). Note that from isomeric 2-methoxypyridine, only traces of unidentified products were obtained under similar conditions whereas starting material was recovered in the presence of

LiCl (2 equiv). Therefore, methoxypyridines do not appear as suitable substrates for our study.

LiTMP-mediated deprotometallation of anisole is far from being quantitative.[41] It is nevertheless possible to evaluate the effect of TMEDA and LiCl on the course of the reaction (Table 1). The next experiments were thus performed from anisole (**2a**) in THF under thermodynamic conditions using 3 equivalents of LiTMP. Without additive, it resulted in a low 20% conversion, as evidenced by subsequent trapping with iodine to afford **2b** (entry 1). The presence of TMEDA (3 equiv) proved to have no effect on the course of the reaction (entry 2), as well as traces of LiCl (entry 3). In contrast, when 3 equivalents of LiCl were present (in the presence or absence of TMEDA), the conversion dropped to 4-5% (entries 4 and 5).

Table 1. Deprotometalation of anisole (2a) using LiTMP followed by iodolysis



2a **2b**

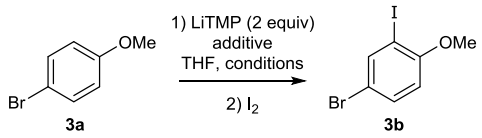
Entry	Additive	**2b**:**2a** ratio[a]
1	-	20:80
2	TMEDA (3 equiv)	20:80
3	LiCl (0.02 equiv)	20:80
4	LiCl (3 equiv)	5:95
5	TMEDA (3 equiv) + LiCl (3 equiv)	4:96

[a]Ratio determined from the ^{1}H NMR spectrum of the crude.

In order to confirm these findings, we decided to select a more reactive substrate, and chose 4-bromoanisole[42] (**3a**) for this purpose (Table 2). By carrying out the reaction using 2 equivalents of LiTMP at −40 °C for 15 min before iodolysis, 4-bromo-2-iodoanisole (**3b**) was obtained in a ~1:1 ratio together with the substrate **3a** (entry 1). In the presence of LiCl (2 equiv), a ~1:4 ratio was noticed instead (entry 2). A similar drop was observed when the reaction was conducted at −50 °C (entries 3 and 4). These results confirm that LiCl has a negative impact on the course of the reactions of methoxy-substituted arenes with the LiTMP base.

In situ zinc species are capable of exerting a strong effect on the efficiency of the LiTMP-mediated deprotolithiation of methoxy-substituted arenes by intercepting the aryllithium generated (e.g. by the equilibrium reaction between anisole and LiTMP).[9d,10] Thus, starting from anisole (**2a**), we studied the effect of additives on the reaction with LiTMP (Table 3).

Table 2. Deprotometalation of 4-bromoanisole (3a) using LiTMP followed by iodolysis



3a **3b**

Entry	Additive	Conditions	**3b**:**3a** ratio[a]
1	-	-40 °C, 15 min	47:53
2	LiCl (2 equiv)	-40 °C, 15 min	18:82
3	-	-50 °C, 15 min	35:65
4	LiCl (2 equiv)	-50 °C, 15 min	8:92

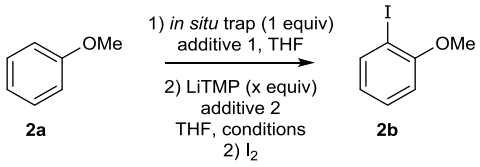
[a]Ratio determined from the ^{1}H NMR spectrum of the crude.

We first tried to use $ZnCl_2$·TMEDA to *in situ* intercept (before iodolysis) the generated aryllithium, but we rapidly realized that it is not a suitable zinc species in the case of this weakly activated arene. Indeed, when 1 equivalent of LiTMP was employed between −20 °C to rt, only starting anisole (**2a**) was recovered, probably because added LiTMP directly reacts with $ZnCl_2$·TMEDA (entry 1). A low 20% conversion was recorded by using 2 equivalents of LiTMP (entry 2) whereas complete reaction was only reached with 3 equivalents (entry 3). Similar results were noticed with $ZnCl_2$ (entry 4), and the presence of LiCl (1 equiv) did not affect this conversion (entries 5 and 6).

We next check the ability of putative $Zn(TMP)_2$,[43] *in situ* generated from $ZnCl_2$·TMEDA and LiTMP in a 1:2 ratio, to work as an *in situ* trap. When 1 equivalent of LiTMP was employed at rt for 2 h, the iodide **2b** was quantitatively formed (entry 7). In contrast, by keeping the reaction mixture at −20 °C, the conversion dropped to 14% (entry 8). We thus chose 0 °C as intermediate contact temperature to evaluate the effect of the additives. Under these conditions, the iodide **2b** was formed with a 55% conversion (entry 9), and TMEDA (1 equiv) has no effect on the reaction (entry 10). When LiTMP was stirred with LiCl before its addition to the reaction mixture containing anisole (**2a**) and preformed $Zn(TMP)_2$, the conversion was slightly reduced to 47% (1 equiv of additive, entry 11) and 40% (2 equiv of additive, entry 12).

Thus, whereas TMEDA seems to have no effect on the course of the reactions, the presence of LiCl is deleterious, in particular without *in situ* trap.

Table 3. Deprotometalation of anisole (2a) using LiTMP followed by iodolysis



2a **2b**

Entry	*In situ* trap	Additive 1	x	Additive 2	Conditions	**2b**:**2a** ratio[a]
1	$ZnCl_2$·TMEDA	-	1		-20 °C then rt, 2 h	0:100
2	$ZnCl_2$·TMEDA	-	2		-20 °C then rt, 2 h	20:80
3	$ZnCl_2$·TMEDA	-	3		-20 °C then rt, 2 h	100:0
4	$ZnCl_2$	-	3		-20 °C then rt, 2 h	100:0
5	$ZnCl_2$·TMEDA	LiCl (1 equiv)	3		-20 °C then rt, 2 h	100:0
6	$ZnCl_2$	LiCl (1 equiv)	3		-20 °C then rt, 2 h	100:0
7	$Zn(TMP)_2$[b]	-	1		-20 °C then rt, 2 h	100:0
8	$Zn(TMP)_2$[b]	-	1		-20 °C, 2 h	14:86
9	$Zn(TMP)_2$[b]	-	1		-20 °C then 0 °C, 2 h	55:45
10	$Zn(TMP)_2$[b]	-	1	TMEDA (1 equiv)[c]	-20 °C then 0 °C, 2 h	54:46
11	$Zn(TMP)_2$[b]	-	1	LiCl (1 equiv)[d]	-20 °C then 0 °C, 2 h	47:53
12	$Zn(TMP)_2$[b]	-	1	LiCl (2 equiv)[d]	-20 °C then 0 °C, 2 h	40:60

[a]Ratio determined from the ^{1}H NMR spectrum of the crude. [b]*In situ* prepared from $ZnCl_2$·TMEDA and LiTMP (2 equiv). Note that all the experiments using $Zn(TMP)_2$ *in situ* prepared from $ZnCl_2$·TMEDA and LiTMP (2 equiv) contain stoichiometric amounts of LiCl, that's why we did not study the effect on the reaction of LiCl as additive 1 (with $Zn(TMP)_2$) but as additive 2 (mixed with LiTMP) in order to favor the presence of mixed dimers or trimers with LiTMP. [c]LiTMP was stirred for 10 min at -20 °C in the presence of TMEDA before transfer. [d]LiTMP was stirred for 20 min at -20 °C in the presence of LiCl before transfer.

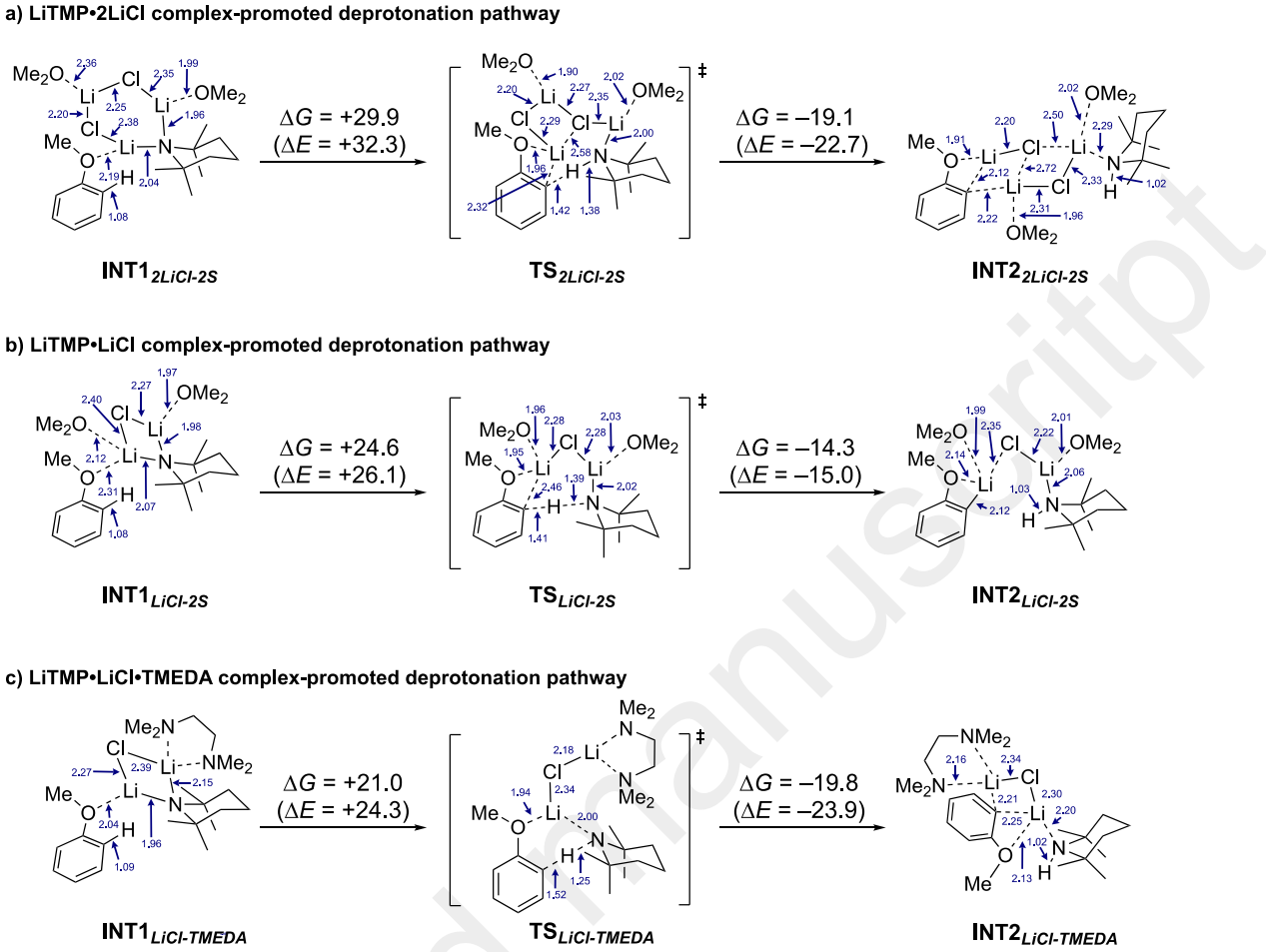
DFT Calculations

The preliminary studies above showed that anisole is a suitable model substrate to study theoretically its LiTMP-mediated deprotometalation and subsequent interception with $Zn(TMP)_2$. Thus, we conducted DFT calculations at the B3LYP/6-31+G** level of theory to find out which species are involved in the deprotonation and investigate the reaction pathways to afford zinc-trapped arenes.

Though LiTMP·2LiCl±TMEDA was proposed as possible active species in the reactions using the basic combination *in situ* prepared from $ZnCl_2$·TMEDA and LiTMP in a 1:3 ratio (suggestion based on the results of DOSY NMR experiments),[11] to the best of our knowledge, complexes having 1:2 constitution between LiTMP and LiCl have never been reported. We thus sought the possible structures of LiTMP·2LiCl involved in the deprotonation event. Among those obtained, the transition state structure $\mathbf{TS}_{2LiCl\text{-}2S}$ described in Scheme 2a was most stable, while it still needs high activation barrier ($\Delta G^{\ddagger}$ +29.9 kcal/mol), making this pathway unlikely. Instead, given that LiTMP can form 1:1 aggregates with lithium salts,[24b,28] we considered the possibility with mixed dimer LiTMP-LiCl as deprotonating species. A slightly lower activation energy ($\Delta G^{\ddagger}$ +24.6 kcal/mol) was observed for the pathway via $\mathbf{TS}_{LiCl\text{-}2S}$ (Scheme 2b). Given the uncertain description as "±TMEDA,"[11] the effects of coordination of TMEDA, instead of the solvent molecules, were examined. The deprotonation of anisole with LiTMP·LiCl·TMEDA complex requires a moderate activation barrier ($\Delta G^{\ddagger}$ +21.0 kcal/mol, Scheme 2c), while we could not identify the reaction pathway using LiTMP·2LiCl·TMEDA as a lithiating reagent.

These results indicated that the composite containing LiCl should be unlikely to be an active species in the deprotonation of anisole. In addition, 1) LiTMP·2LiCl species have never been observed both in solution and solid phase, 2) even if they could be characterized in solution, we should be careful since it should not necessarily be the active species involved in the reaction, and 3) given the numerous mechanistic interpretations for the lithium amide-promoted arene deprotonation by Collum[18,30] and others,[19a,44] none of lithium amide-lithium halide complexes have been proven to be an active deprotonating species. Therefore, the tight combination of experimental and theoretical results led us to conclude that LiTMP-LiCl complexes would not promote the deprotonation of anisole at the *ortho*-position of a methoxy group.

Scheme 2. Reaction pathways of the deprotonation of anisole (2a) with LiTMP-LiCl complexes. Energy changes and bond lengths at the B3LYP/6-31+G level of theory are shown in kcal mol^{-1} and Å, respectively. Me_2O was used as a model of a solvent molecule (THF).**

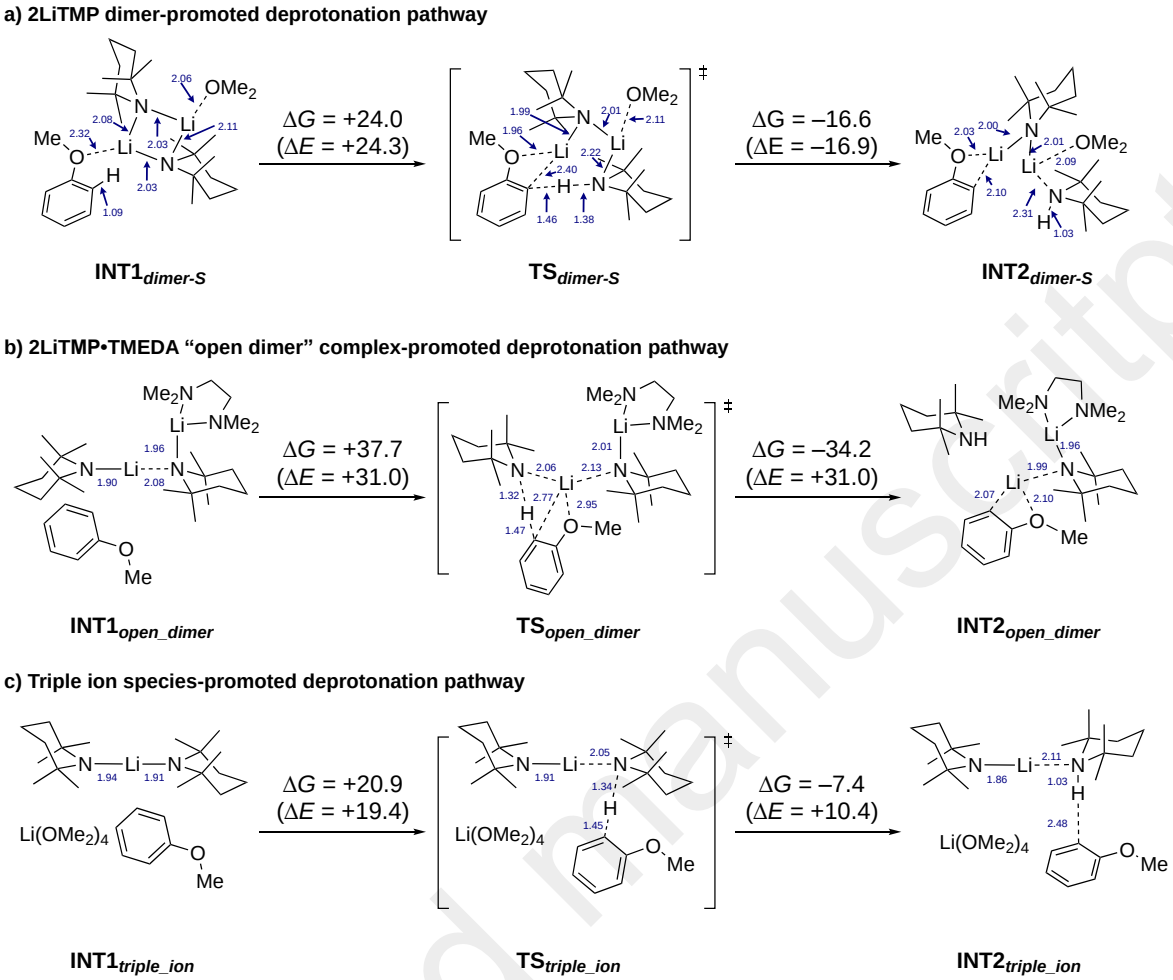


Since LiTMP is a 10:1 mixture of dimeric and monomeric species in THF,[21-22] we next examined the dimeric LiTMP species in the present deprotonation event. The C_{2h} LiTMP cyclodimer could take part in the deprotonation. However, the calculated activation energy for **TS**$_{dimer\text{-}S}$ was still high (+24.0 kcal/mol) and, after the lithiation, insufficient stabilization was observed (**INT2**$_{dimer\text{-}S}$, Scheme 3a).

In addition, the presence of TMEDA facilitated the so-called "open-dimer" formation,[25] but the required high activation energy (+37.7 kcal/mol) made this pathway impracticable (Scheme 3b). A triple ion transition state structure, as reported for the reactive (relatively acidic) arenes,[18] was also identified (Scheme 3c), and the activation barrier was lower than those of above two (+20.9 kcal/mol). The trapping of the resultant deprotonated arene species (**INT2**$_{triple\_ion}$) would make this pathway more feasible even with a weakly activated substrate, anisole (**2a**).

Finally, the reactions of monomeric LiTMP as an active lithiating reagent were investigated. Indeed, the conditions in Table 3 essentially contained LiCl in the reaction mixture, and the presence of LiCl can catalyze the deaggregation of dimer to the monomeric LiTMP. Thus, we examined the monomeric LiTMP having varied coordinating molecules (LiTMP·L; L = 0 to 2 solvent molecules or TMEDA) as summarized in Figure 1a. The activation barriers were reasonably low enough, and, in particular, two-solvent molecule-coordinating species (i.e. L = 2S) should promote the deprotonation most preferentially ($\Delta G^{\ddagger}$ = +14.3 kcal/mol). Collum and co-workers reported that the lithiation of 1,3-dimethoxybenzene with LiTMP proceeds with similar species.[18] Notably, in all cases, the intrinsic reaction coordinate (IRC) calculations revealed the insufficient or small stabilization of lithiated arenes (**INT2**$_{mono\text{-}L}$) compared with the initial complexes (**INT1**$_{mono\text{-}L}$), and the small energy gaps between **TS**$_{mono\text{-}L}$ and **INT2**$_{mono\text{-}L}$. The former resulted in the insufficient deprotonation using the stoichiometric amount of LiTMP (Table 1, entry 1),[18] and was compensated by *in situ* trapping with $Zn(TMP)_2$, which offered the thermodynamic stabilization (Figure 1b). The latter would intrinsically imply the existence of retro-reaction and, thus, the equilibrium of this deprotonation while LiTMP-promoted deprotonations show the kinetic regioselectivity with some arenes.[18] We speculate that such small equilibrium (not between the two different positions) would not affect the regioselectivity, and the deprotonation at the acidic and more sterically-hindered position might be kinetically hampered under the reaction conditions, which should apparently result in the "kinetically" regioselective lithiation.

Scheme 3. Reaction pathways of the deprotonation of anisole (2a) with dimeric LiTMP complexes. Energy changes and bond lengths at the B3LYP/6-31+G level of theory are shown in kcal mol^{-1} and Å, respectively. Me_2O was used as a model of a solvent molecule (THF).**



Thus, the present calculations combined with the experimental results described herein provided not only the information of the active species to facilitate the proton transfer, but also the precise reaction pathway and mechanism of LiTMP-promoted arene deprotonative metalation.

CONCLUSION

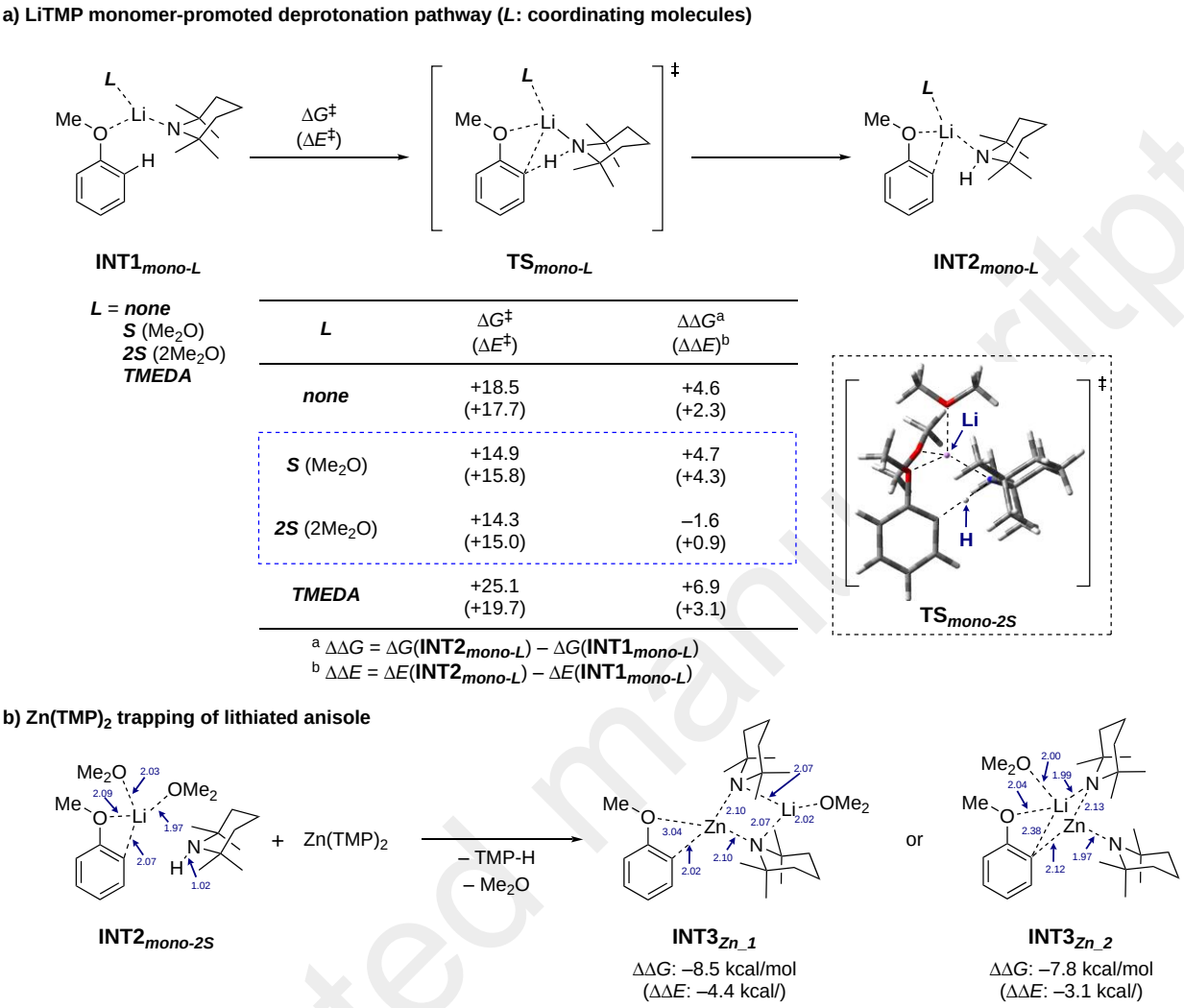
Deprotonative metalation of methoxy-substituted arenes using LiTMP, followed by *in situ* trapping giving zinc species, was investigated both experimentally and theoretically.

The negative impact of more than the stoichiometric amount of LiCl on the deprotolithiation step observed experimentally (Tables 1 and 2) was corroborated by the DFT calculations, which suggest that LiTMP-LiCl complexes, including previously postulated LiTMP·2LiCl,[11] should not be responsible for the *ortho*-deprotonation.

A thorough investigation that consisted in examining (i) the impact of TMEDA and LiCl on the course of the reactions and (ii) the likelihood of structures for the LiTMP complexes in the reaction pathways by DFT calculations led to the conclusion that the solvated LiTMP monomer should be the actual active species in the deprotonation event; subsequent *in situ* trapping with $Zn(TMP)_2$ would facilitate the deprotonative metalation process by stabilizing the resultant metalated species.

Further details, such as the precise number of coordinating solvent molecules by kinetic experiments, as well as variation of reaction pathways with different substrates, are currently ongoing.

Figure 1. a) Reaction pathways of the deprotonation of anisole (2a) with monomeric LiTMP complexes. The inset shows the structure of $TS_{mono\text{-}2S}$. b) The formation of $Zn(TMP)_2$-trapped species ($INT3_{Zn}$). Energy changes at the B3LYP/6-31+G level of theory are shown in kcal mol^{-1}.**



EXPERIMENTAL SECTION

General information. All the reactions were performed in Schlenk tubes under an argon atmosphere. THF was distilled over sodium/benzophenone. Commercial LiCl was used after heating under vacuum until complete water removal. Liquid chromatography separations were achieved on silica gel Merck-Geduran Si 60 (63-200 μm). Melting points were measured on a Kofler apparatus. ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III spectrometer at 300 and 75 MHz, respectively.

Reaction of 3-methoxypyridine (1a) with LiTMP. To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.67 mL, 4.0 mmol) in THF (5-6 mL) was added n-BuLi (about 1.6 M hexanes solution, 4.0 mmol). The mixture was stirred for 15 min at 0 °C before introduction of 3-methoxypyridine (0.20 mL, 2.0 mmol) at 0-10 °C. After 2 h at rt, a solution of I_2 (1.0 g, 4.0 mmol) in THF (7-8 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of $Na_2S_2O_3$ (10 mL) and extraction with AcOEt (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel (eluent: heptane-AcOEt 20:80) led to the following products. **3,3'-Dimethoxy-4,4'-bipyridine (1d)** was isolated in 25% yield (54 mg) as a white powder: mp 178-180 °C (lit.[40] 179 °C); its ^{1}H and ^{13}C NMR data are in accordance with those previously described.[40] **4-Iodo-3-methoxypyridine (1c)** was similarly isolated in 6% yield (28 mg) as a pale yellow powder: mp 88-90 °C (lit. 88-90 °C);[12] its ^{1}H and ^{13}C NMR data are in accordance with those previously described.[12] **2-Iodo-3-methoxypyridine (1b)** was identified by its ^{1}H NMR spectra.[12]

Reaction of anisole (2a) with LiTMP. To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.67 mL, 4.0 mmol)

in THF (5-6 mL) was added n-BuLi (about 1.6 M hexanes solution, 4.0 mmol). The mixture was stirred for 15 min at 0 °C before introduction of anisole (0.14 g, 1.3 mmol) at 0-10 °C. After 2 h at rt, a solution of I_2 (1.0 g, 4.0 mmol) in THF (7-8 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of $Na_2S_2O_3$ (10 mL) and extraction with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated (no reduced pressure to avoid evaporation of anisole). The **2b**:**2a** ratio was determined from the ^{1}H NMR spectra of the crude. The ^{1}H NMR spectrum of 2-iodoanisole (**2b**) was found as reported previously.[45]

Reaction of 4-bromoanisole (3a) with LiTMP. To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.67 mL, 4.0 mmol) in THF (5-6 mL) was added n-BuLi (about 1.6 M hexanes solution, 4.0 mmol). The mixture was stirred for 15 min at 0 °C before introduction of 4-bromoanisole (0.25 mL, 2.0 mmol) at -50 °C. After 15 min at -40 °C, a solution of I_2 (1.0 g, 4.0 mmol) in THF (7-8 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of $Na_2S_2O_3$ (10 mL) and extraction with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated (no reduced pressure to avoid evaporation of 4-bromoanisole). The **3b**:**3a** ratio was determined from the ^{1}H NMR spectra of the crude. The ^{1}H NMR spectrum of 4-bromo-2-iodoanisole (**3b**) was found as reported previously.[46]

Reaction of anisole (2a) with LiTMP in the presence of a zinc species. To a stirred solution of anisole (0.14 g, 1.3 mmol) and $ZnCl_2$·TMEDA[47] (0.34 g, 1.3 mmol) in THF (3-4 mL) cooled at -20 °C, was added a cooled (-20 °C) solution of LiTMP (prepared by adding n-BuLi (about 1.6 M hexanes solution, 4.0 mmol) to a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.67 mL, 4.0 mmol) in THF (5-6 mL) and by stirring for 15 min at 0 °C). The mixture was stirred for 2 h at rt before dropwise addition of a solution of I_2 (1.0 g, 4.0 mmol) in THF (7-8 mL). The mixture was stirred overnight before addition of an aqueous saturated solution of $Na_2S_2O_3$ (10 mL) and extraction with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated (no reduced pressure to avoid evaporation of anisole). The **2b**:**2a** ratio was determined from the ^{1}H NMR spectra of the crude. The ^{1}H NMR spectrum of 2-iodoanisole (**2b**) was found as reported previously.[45]

ASSOCIATED CONTENT

Supporting Information. Computational details - Cartesian coordinates and energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.
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Graphic entry for the Table of Contents (TOC):