

Mechanistic Variations Due to the Solvation State in the Reaction of MeLi in Dimer and Trimer Aggregates with Formaldehyde

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Abstract: An ab initio study (MP2/6-31+G**//HF/6-31+G*) has been performed to investigate how solvation affects the mechanism in carbonyl addition of methyllithium (MeLi) in dimeric and trimeric complexes to formaldehyde. The computations were performed on a homo-dimer of MeLi and a hetero-dimer and -trimer of MeLi and amide base. Results show that a polar solvation comprising one formaldehyde and one water molecule around the lithium ions, coordinating the reactive methyl group, causes the addition to occur according to a concerted mechanism involving a four-membered-ring transition state. However, a hydrophobic solvent and a low substrate concentration promote a nonconcerted mechanism involving ring opening of the dimers and the trimer.

Introduction

The discovery of open dimers of TMEDA- and THF-solvated lithium 2,2,6,6-tetramethylpiperidides using crystallography and NMR has suggested these to be crucial intermediates in enolization and aldol reactions.^{1,2} Several theoretical studies support this mechanism.^{3–5} Romesberg and Collum found from experiments and semiempirical studies that the metalation rate of ketones and *N*-alkylimines increases with poorly coordinating solvents.^{6,7} In strongly coordinating solvents, on the other hand, the metalation rate slows down. Recent studies of metalation reactions by Sun and Collum show solvent-dependent mechanisms involving monomeric, dimeric, and trimeric MeLi.^{8,9} Nakamura et al. proposed in a theoretical study that addition of aldehydes to dimeric MeLi involves ring opening of the dimer.^{10,11} They suggested that the methyl group is presented to the carbonyl group by means of opening and formation of an activated intermediate. This is followed by a nucleophilic attack of the methyl group on the carbonyl carbon and subsequent product formation. To account for the solvent they included one water and one dimethyl ether molecule in the computations. The water molecule was coordinated to the lithium ion coordinating the formaldehyde molecule. The other lithium ion in the MeLi dimer was solvated with the dimethyl

ether molecule. With such a solvation, they could not locate an open intermediate, but instead the closed ground state dimer complex was geometry optimized. They reasoned that this lithium ion must be desolvated from the dimethyl ether molecule before the reactive open intermediate can form and the reaction proceed to product. Kaufmann et al. examined the addition of formaldehyde to the dimer of MeLi in a theoretical study.¹² They proposed a concerted mechanism involving a four-center transition state. However, no solvation was considered in their study. In a more recent semiempirical study by Thompson et al., addition of lithium acetylide to a ketone (ArCOCF₃) mediated by lithium ephedrate was studied with THF as the solvent. With full THF-solvation no open dimer intermediates or transition states could be located.¹³

Recently, we discovered an aggregate in the solid state, where three lithium ions coordinate two amide bases and an alkyl group in a six-center complex.¹⁴ We have recently determined the solution structure with NMR.¹⁵ This trimer has only been characterized in hydrocarbon solvents such as toluene and heptane.^{14,15} This contrasts reactions involving dimeric aggregates which form in polar solvents such as diethyl ether and THF.¹⁶

We have in this study investigated how solvation affects the mechanism involved in the carbonyl addition of a methyl anion, complexed in a homo-dimeric (two MeLi), a hetero-dimeric (MeLi and NH₂Li), and a hetero-trimeric aggregate (MeLi and two NH₂Li), to formaldehyde. The aggregates were solvated with one formaldehyde and one water molecule coordinated to the lithium ions anchoring the reactive methyl anion. The systems studied herein are shown in Figure 1 and the mechanisms investigated are presented in Figure 2. We found that carbonyl addition reactions proceed through closed dimeric and

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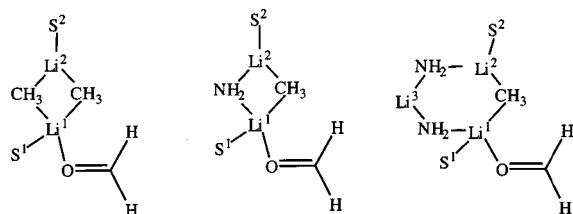


Figure 1. Model systems studied. S^1 and S^2 denote one water molecule coordinated to either Li^1 or Li^2 .

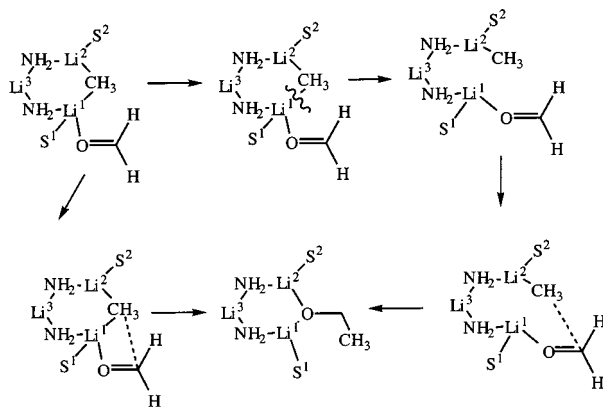


Figure 2. The two mechanisms studied of addition of methyl anion to formaldehyde. The left route shows the concerted mechanism where the six-center complex passes a four-membered-ring transition state to the product. The right route shows a nonconcerted mechanism where an open intermediate is formed, followed by a low barrier transition state to the product. The two lithium ions anchoring the methyl group are solvated with one water molecule denoted S^1 and S^2 .

trimeric aggregates in polar solvents. From the results it was also concluded that metalation reactions proceed through open dimer intermediates and are favored in noncoordinating polar solvents or hydrophobic solvents with a low concentration of the carbonyl compounds.

Computational Details

We investigated one concerted and one nonconcerted mechanism using the Hartree-Fock (HF) and second-order Møller-Plesset (MP2) levels of theory. The 6-31+G* split-valence shell basis set was used in all calculations. Ground states, intermediates, transition states, and product complexes were geometry optimized at the HF/6-31+G* level of theory and checked by means of frequency calculations. Electron correlation was computed using MP2/6-31+G* single-point calculations on the geometry-optimized structures. Intrinsic reaction coordinate (IRC) calculations were performed on the hetero-dimer in the gas phase and with one water molecule coordinated to Li^1 and Li^2 at the HF/6-31+G* level of theory to confirm that the transition states connect with the right ground states, intermediate, and products. These reactions take place in ether solvent. However, the small differences between the computed $Li-OH_2$ and solid-state $Li-O(\text{ether})$ bond lengths demonstrate that water well represents ether.¹⁷ To test the solvation model we added two more water molecules to the homo-dimeric complex, one to Li^1 and one to Li^2 . Geometry optimization of this system caused unrealistic hydrogen bonds in the structures of the ground state and the transition state. Therefore, we replaced all three water molecules with methanol molecules. The ground state, the transition state, and the product were geometry optimized at the HF/6-31+G* level of theory and electron correlation was computed using MP2/6-31+G*. Frequency calculations on these structures showed that the ground state and the product all had real frequencies, while the transition state had one imaginary frequency. All computations were performed using the Gaussian 94 program.¹⁸

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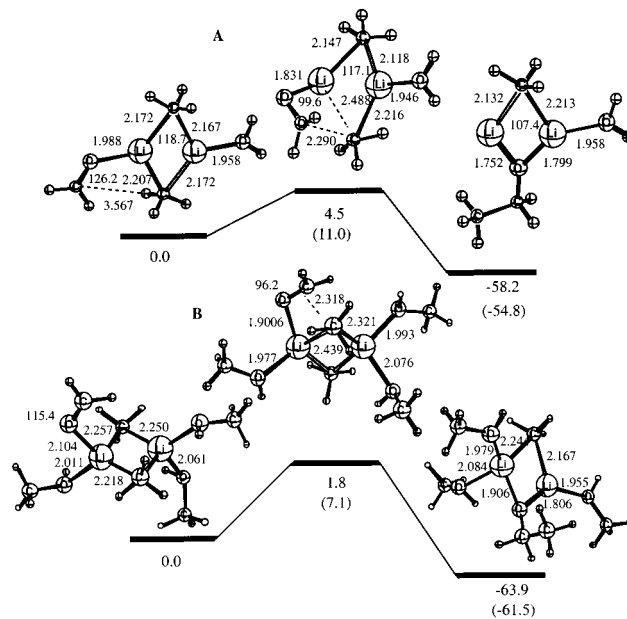


Figure 3. (A and B) Addition of MeLi solvated in a homo-dimer with one water molecule coordinated to Li^2 . In this solvation state the reaction follows a concerted mechanism involving a four-membered-ring transition state (A). Addition of MeLi solvated in a homo-dimer with one methanol molecule coordinated to Li^1 and two methanol molecules coordinated to Li^2 (B). This more realistic solvation model shows the same characteristics as the simpler solvation shown in part A. The MP2 and HF energies (in parentheses) are given (kcal/mol) and selected bond lengths (Å) and bond angles (deg) are shown.

Results

We found that addition of dimeric MeLi to formaldehyde with one water molecule coordinating to Li^2 follows a concerted mechanism (see Figure 3A). The complexed methyl group attacks the carbonyl carbon perpendicular to the carbonyl plane. At the transition state, the $Li^1-C(\text{methyl})$ bond has stretched from 2.207 to 2.488 Å. The $Li^2-C(\text{methyl})$ bond has only stretched from 2.172 to 2.216 Å. The carbon bond between the methyl group and the carbonyl has started to form (2.290 Å). Following the path along the IRC from the transition state to product shows that the forming carbon bond shortens while both the $Li^1-C(\text{methyl})$ and $Li^2-C(\text{methyl})$ bonds stretch out and break. When the carbon bond is almost formed, the formaldehyde oxygen starts to migrate toward Li^2 . Finally, the oxygen is located between the two lithium ions. No open dimer intermediate structure could be located in this solvation state. The activation energy is 4.5 kcal/mol. We suggest that this solvation state impedes the intermediate formation and promotes a concerted mechanism. Further, this demonstrates that the methyl group does not need to be separated from Li^1 to be reactive. A more extensive solvation where the lithium ions were solvated with three methanol molecules showed similar structures of the ground states, transition state, and product (see Figure 3B). The activation barrier was only 1.8 kcal/mol. To study the influence of the solvent on the ground state, geometry optimization (HF/6-31+G*) was done on a dimeric MeLi complex with one formaldehyde and one water molecule coordinated to Li^1 . The MP2 energy of this structures is 3.2 kcal/mol higher in energy than the corresponding ground state where the water molecule is coordinated to Li^2 .

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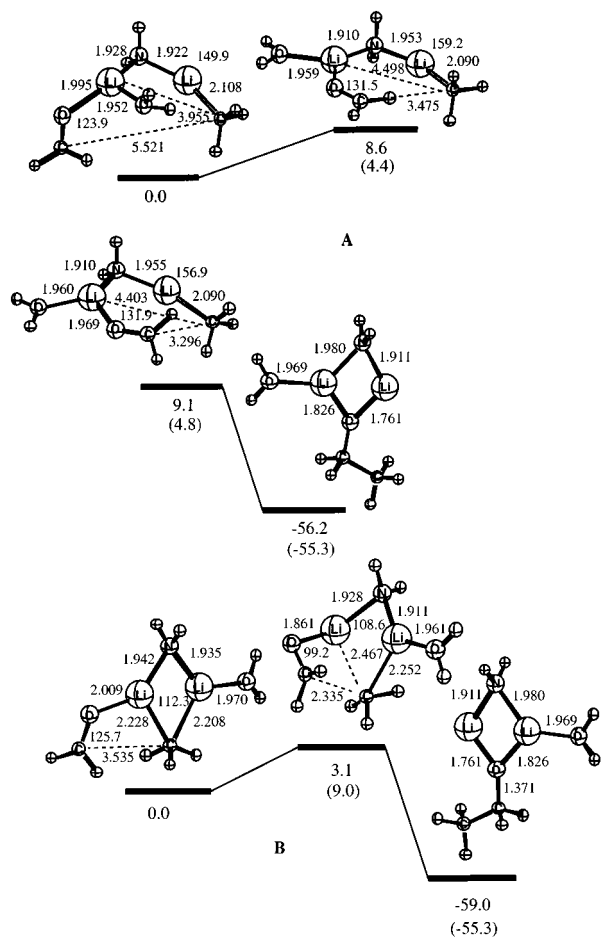


Figure 4. (A and B) Addition of MeLi solvated in a hetero-dimer with one formaldehyde and one water molecule coordinated to Li^1 . This solvation state causes a nonconcerted mechanism to operate and the reaction to pass an open intermediate (A). Addition of MeLi solvated in hetero-dimer with one water molecule coordinated to Li^2 . The reaction proceeds via a four-membered-ring transition state (B). MP2 and HF energies (in parentheses) are given (kcal/mol) and selected bond lengths (\AA) and bond angles (deg) are shown.

The carbonyl addition reaction of the hetero-dimer comprising a MeLi and a NH_2Li molecule with one formaldehyde and one water molecule coordinated to Li^1 is presented in Figure 4A. The $\text{Li}^1\text{-C}(\text{methyl})$ bond is broken, which shows that the water molecule well stabilizes the positive charge of Li^1 and that lithium in this environment prefers to be three-coordinated.¹⁹ No four-membered-ring transition state was found in this solvation state. Instead an intermediate was located using symmetry constraints. It is planar and the methyl group forms almost a linear arrangement with Li^2 and the amide group. The π^* -orbital of the carbonyl group is perpendicular to the plane and, consequently, does not interact with the in-plane methyl group. Rotation of both the methyl group (around the $\text{Li}^2\text{-C}(\text{methyl})$ bond) and the formaldehyde (around the $\text{C}=\text{O}$ bond) brings the intermediate to a transition state where one hydrogen of formaldehyde and one hydrogen of the methyl group are eclipsed to each other. The activation energy of this reaction was computed to be 9.1 kcal/mol. The IRC computation shows that after passage of this transition state, the π^* -orbital and the lone pair of the methyl group begin to overlap, and the carbon bond between the carbonyl and the methyl group starts to form. Simultaneously, the oxygen of formaldehyde starts to migrate toward Li^2 and subsequently the product complex is formed.

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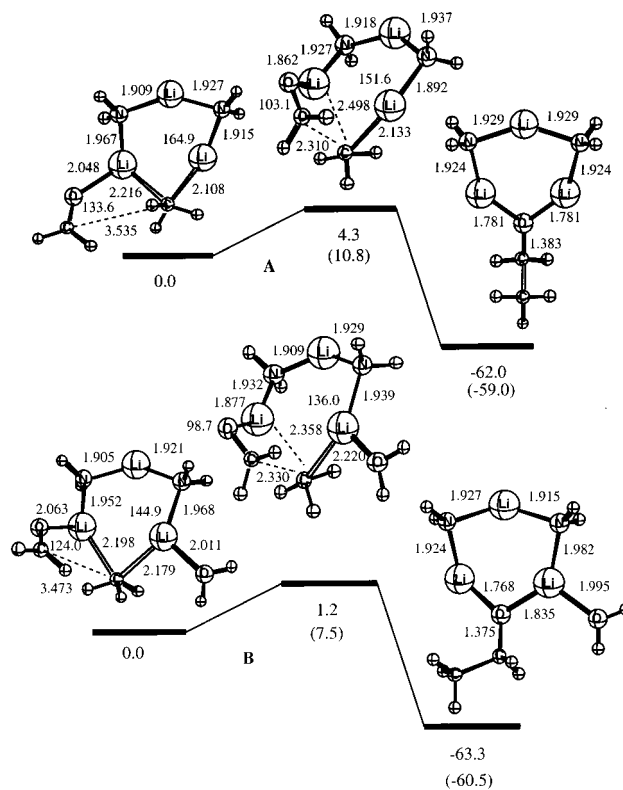


Figure 5. (A and B) Addition of MeLi solvated in hetero-trimer to formaldehyde in the gas phase. The reaction is concerted (A). Addition of MeLi solvated in hetero-trimer with one water molecule coordinated to Li^2 . The reaction follows a concerted mechanism involving a four-membered-ring transition state (B). MP2 and HF energies (in parentheses) are given (kcal/mol) and selected bond lengths (\AA) and bond angles (deg) are shown.

In the gas phase no open intermediate could be located, but a transition state was found, similar to the one found when one water molecule is coordinated to Li^1 . The activation barrier is close to that of the nonconcerted route (8.0 kcal/mol).

The addition reaction performed in an homogeneous solvation state, where formaldehyde coordinates to Li^1 , and a water molecule coordinates to Li^2 , is presented in Figure 4B. The geometry-optimized four-membered-ring transition state is similar to that of the homo-dimer. The $\text{Li}^1\text{-C}(\text{methyl})$ and $\text{Li}^2\text{-C}(\text{methyl})$ bond lengths are almost of the same lengths in the ground state (2.228 and 2.208 \AA). At the transition state, however, the bond between the carbonyl carbon and the methyl carbon has started to form (2.335 \AA) and, consequently, the $\text{Li}^1\text{-C}(\text{methyl})$ bond has weakened and stretched to 2.467 \AA . The activation energy of this reaction is 3.1 kcal/mol, which is about 5 kcal/mol lower than that for the nonconcerted route. Again, no open intermediate was found. Thus, like the homo-dimer case, a concerted mechanism operates in a polar homogeneous solvation state. These results show that the dimer aggregates react faster when they are homogeneously solvated. The reactions of both the homo-dimer and the hetero-dimer are exothermic (see Table 1).

The hetero-trimer comprising one MeLi and two NH_2Li molecules reacts via the concerted mechanism in the gas phase (see Figure 5A). We also located an open intermediate structure. However, this stepwise route is energetically unfavorable (4.3 kcal/mol for the concerted and 14.3 kcal/mol for the nonconcerted mechanism). With one water molecule coordinated to Li^1 no four-membered-ring transition state was located. Instead, an open trimer intermediate was found and the activation energy

Table 1. Computed MP2/6-31+G* and HF/6-31+G* Energies (kcal/mol) Relative to the Ground State^{a,b}

reaction mechanism	homo-dimer		hetero-dimer		hetero-trimer		
	w(Li ²)	g	w(Li ¹)	w(Li ²)	g	w(Li ¹)	w(Li ²)
four-membered TS (concerted)	4.5 (11.0)			3.1 (9.0)	4.3 (10.8)		1.2 (7.5)
intermediate (nonconcerted)			8.6 (4.4)		14.3 (11.4)	10.1 (4.5)	
TS (nonconcerted)		8.0 (6.4)	9.1 (4.8)				
product	-58.2 (-54.8)	-58.6 (-54.5)	-56.2 (-55.3)	-59.0 (-55.3)	-62.0 (-59.0)	-63.8 (-63.2)	-63.3 (-60.5)

^a HF energies are in parentheses. ^b Abbreviations: g = gas phase; w(Li¹) and w(Li²) = one water molecule coordinated to lithium ion 1 and 2, respectively (see Figure 1).

of this stepwise reaction was computed to be 10.1 kcal/mol. A four-membered-ring transition state was located with the water molecule coordinated to Li² (see Figure 5B). The computed activation energy is only 1.2 kcal/mol. Both the hetero-dimer and the hetero-trimer aggregates react slowly via the nonconcerted mechanism. In particular, the hetero-trimer aggregate reacts slowly when following the stepwise pathway. The trimer aggregate reacts exothermically (see Table 1). The MP2 energies give low activation barriers for the concerted mechanism involving four-membered-ring transition states of both the dimeric and trimeric aggregates, whereas the HF energies result in higher barriers. The effect of the electron correlation has an opposite effect in the nonconcerted mechanism, where the MP2 energies give higher and HF energies give lower activation barriers. The concerted mechanism involves tighter transition states than the nonconcerted mechanism. This can explain the opposite effect of the electron correlation in the computation of these activation barriers.

Discussion

Kaufmann et al. suggested from the results of ab initio calculations (HF/3-21G) that the carbonyl addition reactions of the dimeric forms of LiH and MeLi in the gas phase with formaldehyde follow a concerted mechanism.¹² A four-center transition state with formaldehyde complexed to a dimeric aggregate of LiH was located, and a more ladder-like transition state with dimeric MeLi. Nakamura et al. studied formaldehyde complexed to MeLi in dimeric form in the gas phase and with one water and one dimethyl ether molecule solvating the dimer-formaldehyde complex using the (MP2/6-31+G*//HF/6-31+G*) level of theory.¹⁰ They proposed a nonconcerted mechanism, where the formation of an open dimer causes one of the methyl groups to be exposed to the carbonyl. Nakamura et al. reasoned that this is a necessary step before the addition can take place. An open intermediate structure in the gas phase was located, and another open intermediate in which a water molecule coordinates to the lithium (Li¹) that coordinates formaldehyde. However, with a more realistic solvation, solvating the other lithium ion (Li²) with a dimethyl ether molecule, no intermediate could be located. They suggested that Li² is *desolvated* before the ring breaks and the intermediate forms.

In a more recent theoretical work by Mori et al. addition of MeLi dimer to α - and β -alkoxy aldehydes was investigated.²⁰ They found that only one of the lithium ions is engaged in the chelate formation with the aldehyde. This chelation causes an heterogeneous solvation of the dimer and a nonconcerted mechanism to operate.

The proposed model by Nakamura et al. requires a heterogeneous polar solvation of the dimer aggregate. In a solution this is not likely to occur. We found that the energy of the ground state homo-dimer where one water molecule is coordinated to the same lithium ion (Li¹) as the formaldehyde molecule

is higher in energy by 3.2 kcal/mol compared to the ground state homo-dimer where the same water molecule instead is coordinated to Li². This favors the concerted mechanism even further over the nonconcerted mechanism. A situation with a heterogeneous solvation could arise in complex unsymmetric dimer aggregates where the lithium ions are bound to ligands with different size, shape, and electronic properties which shield the lithium ions differently from the solvent.

Thus, in solution it is likely that the dimer and the trimer aggregates found are homogeneously solvated. This suggests that the lithium ions are equally solvated and that the concerted mechanism dominates in polar solvents. The mechanisms of the addition of the dimer aggregates to formaldehyde can be rationalized as follows. When a formaldehyde and a water molecule both coordinate to Li¹, the lithium ion coordinates four ligands, whereas Li² coordinates only two ligands. In this solvation state, the Li¹-C(methyl) distance becomes longer than the Li²-C(methyl) distance. This implies that the Li¹-C(methyl) bond strength decreases, and the bond breaks easier to form the open intermediate. Cleavage of the Li¹-C(methyl) bond causes Li² to attract negative charge from the methyl anion better and in such way stabilizes its positive charge better. With a homogeneous solvation of the lithium ions, both Li¹-C(methyl) and Li²-C(methyl) bonds are equally strong and formation of an open intermediate is less attractive, promoting the concerted route. Our results suggest that the use of hydrophobic or polar noncoordinating solvents together with a low concentration of aldehyde will favor the nonconcerted mechanism, whereas a polar solvent will promote the concerted mechanism.

From experiments it is known that trimers form and react in hydrophobic solvents. Our results show that the trimer react preferably along the concerted route in hydrophobic (approximated with the gas phase state) solvents. The nonconcerted mechanism gives a much higher activation barrier and is therefore not likely to be present in the addition reaction. In a (hypothetical) polar solvation, the reaction rate is much higher than in hydrophobic solvation (see Figure 5A,B).

Romesberg and Collum found from their semiempirical calculations that a bulky noncoordinating solvent, such as NR₃, increases the metalation rate of ketones and *N*-alkylimines, whereas a coordinating solvent such as THF causes a decreased reaction rate.⁷ The metalation proceeds preferably via the open dimer intermediate.⁷ The ground state with its closed dimer is poorly solvated from the sterically hindered NR₃ solvent. With a low substrate concentration the dimer will be monocoordinated, leaving one lithium ion not coordinated by either the substrate or the solvent, and a heterogeneous solvation of the dimer results. The open dimer intermediate is more accessible to NR₃ and can more easily coordinate the solvent. Therefore, a low substrate concentration and the noncoordinating NR₃ stimulate the ring-opening of the dimer and lower the activation barrier.⁷ THF, on the other hand, solvates the closed ground state dimer homogeneously and impedes the ring opening. Recent studies by Sun and Collum show that the reactive species

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in THF is a disolvated monomer and not a dimer.^{8,9} Thus, to circumvent the inhibitory effect the homogeneous polar solvation causes, the reaction re-routes, and follows the monomer complex pathway.

It seems that the addition reactions react preferably via a closed dimer concerted pathway, whereas the metalation reactions proceed via an open dimer aggregate. The solvent has a pronounced effect on these reactions and can nicely be explained by our proposed model.

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Supporting Information Available: Experimental data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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