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## COMMUNICATION

# Base or Nucleophile? DFT Finally Elucidates the Origin of the Selectivity Between the Competitive Reactions Triggered by MeLi or LDA on Propanal

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**The competition between basicity and nucleophilicity of two standard organolithium reagents was studied by DFT. Comparing the reactivity of solvated (MeLi)<sub>2</sub> and (LDA)<sub>2</sub> toward propanal finally explains why methyl lithium adds onto the carbonyl while LDA deprotonates the  $\alpha$ -position, in accord with experiment and Ireland's deprotonation TS.**

Sterically demanding secondary amides are extraordinarily useful reagents. They have been recently identified as "essential utilities",<sup>[1]</sup> and lithium diisopropylamide (LDA) has even been suggested to be the "most commonly used reagent in organic synthesis".<sup>[2]</sup> Strong basic properties associated to a negligible nucleophilic character explain this success. Conversely, the alkyl- and aryllithium reagents are surely the most employed building blocks in organic synthesis<sup>[3,4]</sup> because their nucleophilic character is much more pronounced.<sup>[5]</sup> Curiously, the factors justifying the mainly basic properties of one family of reactants and the mainly nucleophilic capacities of the other have never been, to our knowledge, the object of an in-depth scrutiny, the generic "steric bulkiness" qualifier being generally sufficient to account for most experimental observations. We present here a DFT analysis aimed to revisit, in parallel, the energetic and conformational parameters shaping the competition between these two reactions for prototypic examples of the two families, viz. (MeLi)<sub>2</sub> on the one hand and (LDA)<sub>2</sub> on the other, toward a model enolisable aldehyde (Figure 1).

Literature reveals that the mechanisms of both the deprotonation and addition reaction have been, unconnectedly, the object of an intense interest and a large corpus of experimental (spectroscopic and kinetic) and theoretical data has amassed over the years.<sup>[6]</sup> In particular, the influence of the deprotonation mode on the *E/Z* selectivity of the resulting enolates has been discussed widely during the 80's and 90's.<sup>[7]</sup> Similarly, the 1,2-addition of RLi's on model aldehydes has been detailed in seminal articles by Schleyer, Houk, Nakamura or Hæffner.<sup>[8]</sup> These original theoretical results, obtained at the Hartree-Fock level, relied on small systems in which water or methanol mimicked the solvents. DFT can also account for the nucleophilic addition of RLi's onto aldehydes.<sup>[9]</sup> A preliminary study

on the functional and the basis set led us to select the B3P86 functional and the 6-31+G\*\* basis set, as implemented in JAGUAR 7.0.<sup>[10]</sup> This approach describes well the interactions between lithium dimethylamide or methyl lithium and formaldehyde, the data obtained fitting those from computations with the 6-311++G\*\* basis, using the B3P86 DFT on the one hand and MP2 on the other.<sup>[9a]</sup> The Relaxed Potential Energy Surface Scan have been performed prior to the optimization of the TS. The length of the forming bond (C-H or N-H for the deprotonation, C-C or N-C for the addition) was taken as the reaction coordinate. Full geometry optimizations were run without symmetry restraints. The TS were characterized by frequency calculations. The Zero-Point Energy corrections have been included but the Basis Set Superposition Errors (BSSE) has been ignored. This factor does not modify the order of the complex stabilities nor that of the energy barriers.<sup>[9a,11]</sup>

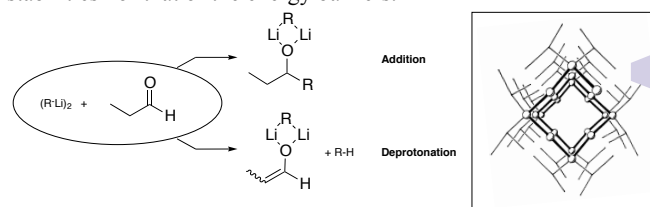


Figure 1. Reaction of organolithiums toward propanal: addition vs. deprotonation (left). Right box: axial view of the helix structure of crystalline LDA (taken from Ref. 18).

The choice of a proper model is essential to tackle this problem. Recent papers have shown that the dimeric form of these species are the aggregates most likely involved in the two reactions.<sup>[12]</sup> A series of RINMR experiments disclosed recently have shown that *n*-BuLi tetramer converts into its dimer before deprotonating (trimethylsilylacetylene).<sup>[13]</sup> Similarly, Garcia-Rio *et al.* have identified, by kinetic and NMR measurements, a dimer of *n*-BuLi solvated by 3 THF and on which the substrate of a deprotonation docks before the reaction starts.<sup>[14]</sup> The situation is also very clear for LDA of which disolvated dimer (LDA)<sub>2</sub>-2THF has been depicted in solution.<sup>[15]</sup>

The electrophile we have retained is propanal, *viz.* the shortest enolisable aldehyde exhibiting a *E/Z* selectivity problem (Fig. 1).

Solvation governs the efficacy and selectivity of these reactions and its accurate theoretical description is a key issue.<sup>[16]</sup> For instance, the right box in Figure 1 shows that LDA adopts a polymeric helical structure in the absence of THF.<sup>[17]</sup> Previous works have shown that including explicit THF is critical to mimic the solvation shells.<sup>[18]</sup> Here, we followed a protocol<sup>[18b]</sup> that consists in saturating the first shell with discrete THF until one is ejected upon optimization. Next, the docking complex was obtained by replacing one THF with the aldehyde. This procedure led to consider (MeLi)<sub>2</sub>-3THF-EtCHO on the one hand,<sup>[19]</sup> and (LDA)<sub>2</sub>-2THF-EtCHO on the other.<sup>[15]</sup>

**MeLi-complexes.** The optimization of (MeLi)<sub>2</sub>-3THF-EtCHO leads to 2 isoenergetic conformers ( $\delta E < 0.1$  kcal.mol<sup>-1</sup>) which differ mainly by the orientation of the carbonyl group with respect to the almost planar C-Li-C-Li organometallic core. In both conformers, one lone pair of the oxygen of the carbonyl interacts with a lithium cation (Li<sup>A</sup> on Fig. 2)<sup>[8]</sup> with a Li<sup>A</sup>-O distance  $\approx 2.08$  Å and a Li<sup>A</sup>-O=C<sup>1</sup> angle of  $\sim 120^\circ$ . The disparity between conformers comes from the angle  $\gamma = \text{H}^1\text{C}^1\text{O}Li^A$  that is worth  $\approx 0$  or  $180^\circ$ .<sup>[20]</sup> The C<sup>1</sup>-C<sup>A</sup> distance is 3.40 Å in the first case ( $\gamma = -6$ ) and 4.00 Å in the second case ( $\gamma = 176$ ), whereas the H<sup>2</sup>-C<sup>A</sup> distance is only 2.58 Å. These two complexes can thus be considered as reasonable starting points for the addition and deprotonation reactions, respectively (Fig. 2).

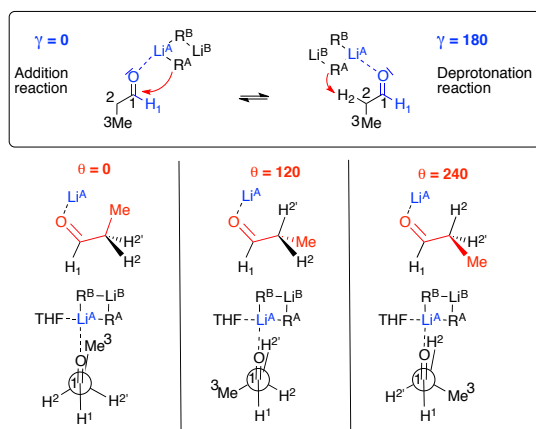


Figure 2. Definition of the  $\gamma$  and  $\theta$  angles necessary to describe the two reactions

The propanal conformation, as defined by the dihedral angle  $\theta = \text{OC}^1\text{C}^2\text{C}^3$  (Fig. 2) is central since it controls the *E/Z* configuration of the enolate resulting from the deprotonation. If two local minima are known for isolated propanal ( $\theta = 0$  and  $120$ ),<sup>[21]</sup> three minima are localized in the complex because of the desymmetrization imposed by the Li-O coordination (Fig. 2). The pro-addition and pro-deprotonation complexes exhibit similar  $\theta$  ( $131$  and  $130$ , respectively).

**MeLi-TS.** Let us now focus on the TS of the two reactions in competition. Upon decrease of the C<sup>A</sup>-C<sup>1</sup> or C<sup>A</sup>-H<sup>2</sup> distances, all the relevant conformers go through a TS and lead to the expected product (lithium alkoxide or enolate, respectively). On Figure 3 are displayed the lowest energy route for each reaction.<sup>[22]</sup> For the addition, the conformer considered ( $\theta = 120$ ) is not the most stable

one ( $\delta E = +0.6$  kcal.mol<sup>-1</sup> with respect to  $\theta = 0$ ) but its TS is  $>4$  times lower ( $+1.3$  vs.  $+5.6$  kcal.mol<sup>-1</sup>). This TS involves a “closed” dimer as the (MeLi)<sub>2</sub> core, conserved along the reaction pathway [ $d(\text{Li}^A-\text{C}^A) \approx 2.20$  Å]. Its geometrical features fit the expectations of an early TS as the C<sup>A</sup>-C<sup>1</sup>-O angle is  $\approx 107^\circ$  (Bürgi-Dunitz), the aldehyde pyramidalizes ( $\text{OC}^1\text{C}^2\text{H}^1 = 167^\circ$ ) and  $d(\text{C}^1-\text{C}^A) \approx 2.65$  Å is rather long (2.72 and 2.32 Å, respectively, in Nakamura’s<sup>[8b]</sup> and Häffner’s<sup>[8c]</sup> papers on a mono-hydrated model). Simultaneously the  $d(\text{Li}^A-\text{O})$  shortens to 1.95 Å. For the deprotonation, the most stable conformer ( $\theta = 120$ )<sup>[22]</sup> passes by the lowest TS (Fig. 3) that is depicted by: (i) an unaltered  $d(\text{Li}^A-\text{O}) = 2.08$  Å; (ii) the alignment of C<sup>2</sup>-H<sup>2</sup>-C<sup>A</sup>; (iii) the C<sup>2</sup>-H<sup>2</sup> and H<sup>2</sup>-C<sup>A</sup> distances ( $\approx 1.3$  and  $\approx 1.6$  Å respectively, in line with literature data<sup>[23]</sup>); (iv) the position of H<sup>2</sup>  $\approx 60^\circ$  above the carbonyl H<sup>2</sup>-C<sup>2</sup>-C<sup>1</sup>-O plane (in fine agreement with Heathcock’s conformational hypotheses).<sup>[24]</sup> Fig. 3 shows that the addition, which passes through a very low TS, will be largely preferred over the deprotonation.

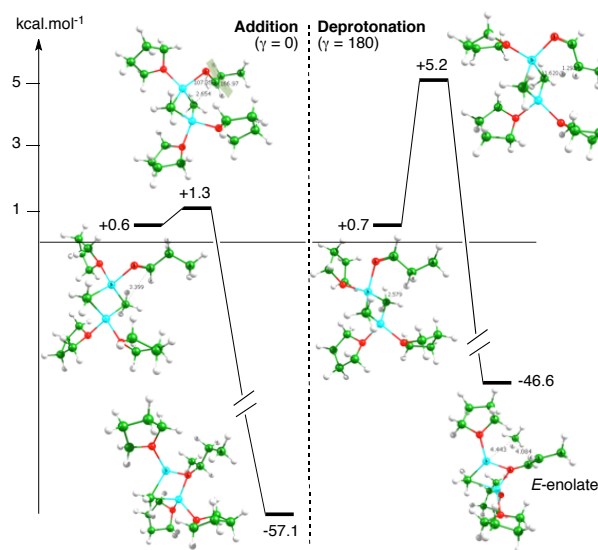


Figure 3. Energy profiles for the addition/deprotonation of propanal by (MeLi)<sub>2</sub>-3THF

**MeLi-products.** The two reactions lead to two mixed aggregates between one unreacted MeLi and the new lithium alkoxide, on the addition side, or lithium enolate, on the deprotonation one. Both routes are highly exothermic, the addition product being the most stable one. Because it involves a  $\theta = 130^\circ$  conformer, the deprotonation should lead selectively to the (*E*)-enolate. Finally, the interaction between this latter and the CH<sub>4</sub> produced is expected to be weak:  $d(\text{C}^A-\text{Li}^A) > 4.4$  Å.

**LDA-complexes.** We now focus on (LDA)<sub>2</sub>-2THF-EtCHO. The driving forces of the two reactions, and therefore the organization of the original complexes, are the same as above. The major difference with respect to (MeLi)<sub>2</sub>-3THF-EtCHO is the orientation of the aldehyde. The *i*-Pr groups on the nitrogen now pointed toward the outskirts of the complex such as to avoid the steric repulsion triggered by the alkyl chain. The two complexes ( $\theta = 120 / 240$ ) involved in the deprotonation had to be considered here since they are isoenergetic ( $\delta E = 0.1$  kcal.mol<sup>-1</sup>).<sup>[21]</sup>

**LDA-TS.** Reaching the TS of the two reactions requires a significant reshuffling of the three complexes:  $d(N^A-C^1)$  goes from 4.23 to 2.13 Å for the addition, while for the deprotonation  $d(N^A-H^2)$  goes from 4.36 to 1.63 ( $\theta = 120$ ) or from 4.14 to 1.61 Å ( $\theta = 240$ ). Both TS now proceed through an “open” dimer: the  $d(N^A-Li^A)$  varies from 2.10 to 2.67 Å for the addition, and from 2.06 to  $\approx 2.40$  Å during the deprotonation, whatever  $\theta$ . The open and closed dimer threshold situations have been described before by Nakamura<sup>[8b]</sup> and Hæffner<sup>[8c]</sup>. The latter has shown that the solvation influences the closed *vs.* open nature of the TS. Our results generalize these computations and indicate that the nature of the nucleophile also effects this geometrical pattern. The two reactions TS have their own characteristics: the addition proceeds through a late TS (compared to that for MeLi), the  $N^A-C^1-O$  angle is worth  $\approx 107^\circ$  and the aldehyde pyramidalizes ( $OC^1C^2H^1 = 145^\circ$ ). At the TS of the deprotonation, and in accord with literature data<sup>[23]</sup>: i)  $C^2-H^2-N^A$  align ( $\approx 170^\circ$ ); ii)  $C^2-H^2 \approx 1.3$  Å and  $N^A-H^2 \approx 1.6$  Å; iii)  $H^2$  lies  $\approx 60^\circ$  above the carbonyl plane, in line, again, with Heathcock’s considerations.<sup>[24]</sup>

Energywise, the 3 activation barriers are low (9.8, 9.0 and 8.3 kcal.mol<sup>-1</sup>, respectively), but significantly higher than those computed for (MeLi)<sub>2</sub>, in particular for the addition reaction ( $\times 14$ ). The limited differences between the deprotonation and addition TSs suggest that both routes are competitive. However, the pro-addition complex can convert, passing through a low-lying TS,<sup>[25]</sup> into the lowest pro-deprotonation one ( $\theta = 240$ , Fig. 4). Therefore, despite the little differences between energy barriers ( $< 2$  kcal.mol<sup>-1</sup>), the deprotonation route is expected to be preferred with (LDA)<sub>2</sub>.

**LDA-products.** Three different products are obtained, *viz.* the lithium  $\alpha$ -aminoalkoxide derived from the addition, and the (*E*) + (*Z*) lithium enolates due to the deprotonation. All consist in mixed

aggregates including one unreacted LDA and are notably less stable than those derived from MeLi (Fig. 3), especially the addition product. Also significant is the enolate-LDA complexes in which diisopropylamine coordinates the lithium of the enolate ( $Li^2-N = 2.14$  Å), in accord with experimental data,<sup>[26]</sup> forming a 5-membered cycle. Expectedly, the enolate configuration is ruled by the aldehyde conformation at the TS, the  $\theta = 240$  conformer providing the *Z* isomer, and the  $\theta = 120$  the *E* one. Since the reactivity of these two conformers seems similar ( $\delta\Delta E^\ddagger \approx 0.7$  kcal.mol<sup>-1</sup>), a low selectivity is expected, and thus a mixture of the (isoenergetic) *E* and *Z* isomers should be recovered. Experimental data on the deprotonation of pentanone<sup>[27a]</sup> or 4-heptanone,<sup>[27b]</sup> *i.e.* substrates analogous to propanal, by LDA in THF show that it is indeed the case (*E/Z*  $\approx 77:23$  and  $60:40$ , respectively).<sup>[28]</sup>

## Conclusions

These computations compare the reactivity of MeLi or (LDA)<sub>2</sub> dimers, explicitly solvated by THF, toward propanal. The results account for the experimental chemoselectivity (MeLi adds to the carbonyl while LDA deprotonates) and the stereoselectivity (low *E/Z* ratio after deprotonation by LDA). The data show that MeLi addition is quick since its barrier is 4 times lower than the deprotonation one. For LDA not only the deprotonation TS is about 15% lower than the addition one, but the pro-addition complex can easily convert into a pro-deprotonation one. The results also fully support Ireland’s six-membered ring model for the TS, even if its conformation is far from an ideal chair, as spotted before by McKee.<sup>[6]</sup> Finally, the good agreement between this model and the experimental data suggests that such procedure could be extended to complex reactants and substrates. Works are in progress and the results will be reported in due course.

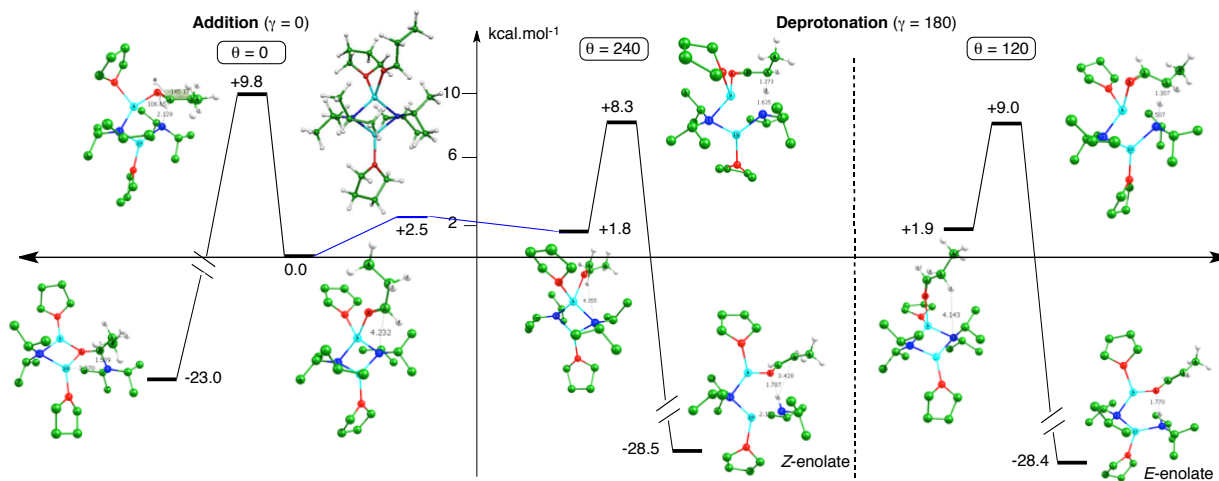


Figure 4. Energy profiles for the addition and deprotonation of propanal by (LDA)<sub>2</sub>-2THF. Some protons have been removed from the sketches for clarity.

## Notes and references

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