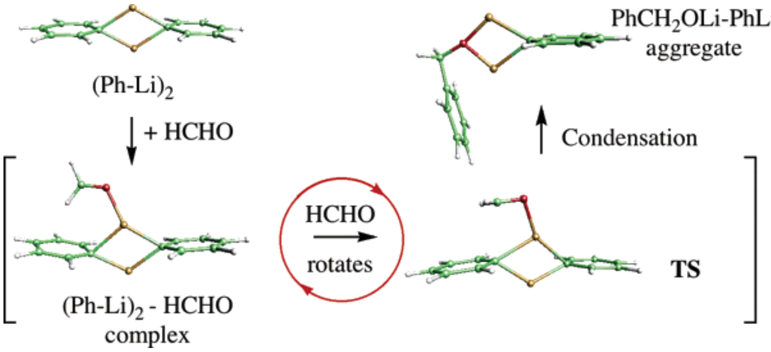
A DFT Theoretical Study of the Condensation of Aggregates of sp^2 Organolithium Compounds on Formaldehyde

Catherine Fressigné,[†] Anne Lautrette, and Jacques Maddaluno*

Institut de Recherche en Chimie Organique Fine, UMR 6014 CNRS, Université de Rouen,
76821 - Mont St Aignan Cedex (France)

jmaddalu@crihan.fr

Received March 15, 2005



The interaction between three different sp^2 organolithium compounds (vinyllithium, 2-methoxyvinyllithium and phenyllithium) and formaldehyde has been investigated using DFT theoretical methods. The unsolvated monomers and dimers have been considered and compared to the 1:1 mixed aggregates formed with lithium dimethylamide. In all cases, the separate entities, their docking complexes, the transition states, and the condensation products have been characterized and compared to the corresponding situations involving methyllithium, taken as a prototypic sp^3 nucleophile. Regarding the monomers, this study shows that, in the three cases considered, formaldehyde forms a pretransition state complex in which the oxygen of the carbonyl interacts with the lithium cation along one of its lone pair. A small energy barrier ($\leq$2.1 kcal·mol^{-1}) brings to the transition state, then to the lithium alcoholate resulting from the largely exothermic condensation ($\sim$40 kcal·mol^{-1}). The structure of the homogeneous dimers considered in a second step has been optimized and lead to arrangements in which a planar quadrilateral C−Li−C−Li is always obtained. In the presence of formaldehyde, these entities provide complexes exhibiting lithium−oxygen interaction similar to those occurring with the monomers. For the dimers, the geometry at the TS evokes a π-complex between the C═O and the lithium cation, particularly pronounced in the case of phenyllithium. The resulting alcoholates are obtained following a larger exothermic reaction ($\sim$55 kcal·mol^{-1}). The heterogeneous dimers with lithium dimethylamide have been finally examined. In these cases, the aldehyde can orientate toward either the carbon or the nitrogen, leading to the expected lithium alcoholate or α-amino alcoholate, respectively. Whatever the orientation, the complexes present characteristics close to those calculated for the homogeneous dimer complexes. These similarities are conserved at the transition state.

Introduction

Organolithium compounds are probably the most widely used organometallic reagents, employed in a large variety of organic reactions, going from deprotonations to nucleophilic additions.[1] Actually, their high reactivity turns out to be an advantage in terms of chemical yields but an inconvenient in terms of enantioselective catalysis and knowledge of the mechanisms, on both chemical and stereochemical points of view. In general, these very rapid reactions can hardly be followed by spectroscopic methods.[2] This explains that a relatively large set of (static) semiempirical and ab initio results dealing with

---

* Corresponding author: Tel: 33 235 522 446/Fax: 33 235 522 971.

[†] Present address: Laboratoire de Chimie Théorique, UMR 7616 CNRS, Université P. & M. Curie, 4 place Jussieu, 75252 Paris Cedex 05 (France).

(1) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Amsterdam, 2002.

10.1021/jo050524n CCC: $30.25

the structure and the behavior of small species (such as methyllithium) in model reactions (such as the condensation on aldehydes) is available.[3] However, two major difficulties are associated to the theoretical treatment of these systems: (i) the tendency of organolithium compounds to form multiple aggregates in equilibrium; (ii) the strong but poorly directional interactions between RLi and their usual solvents such as diethyl ether or THF. Experimentally, the former property can be turned into an advantage since mixed aggregates of a chiral lithium amide and an alkyllithium have been shown to be chemically and stereochemically efficient in the asymmetric condensation on aldehydes.[4] To date, the applications of mixed aggregates in organic synthesis are almost exclusively restricted to sp^3 alkyllithium derivatives.[5] But even in these cases, spectroscopy is seldom able to produce convincing data to describe the structure of intermediates and mechanistic pathways, for which most information comes from calculations. We have previously reported the results of a DFT study dealing with the interactions of monomeric MeLi and Me$_2$NLi, as well as their homogeneous and heterogeneous aggregates, with aldehydes[6] (Figure 1). This study led to the conclusion that the aldehyde docks on a lithium along the direction of one of the carbonyl oxygen lone pair, as expected from previous data based on crystallographic bases.[7] A stable complex **A** is thus obtained in which the aldehyde and the organometallic core are coplanar, in line with previous theoretical[3] and experimental[8] results on similar problems. The reaction could then proceed through a transition state such as **B**, reached upon rotation of the aldehyde out of this plane. Note that the sense of this rotation constitutes the enantio-determining step. The mixed aggregate **C**, which includes the product and the remaining half of the starting dimer, would finally be recovered. A comparable mechanism, in which both the aldehyde and the alkyllithium are activated through the O−Li interaction, has been considered for a mixed aggregate of butyllithium and a lithium alcoholate.[9]

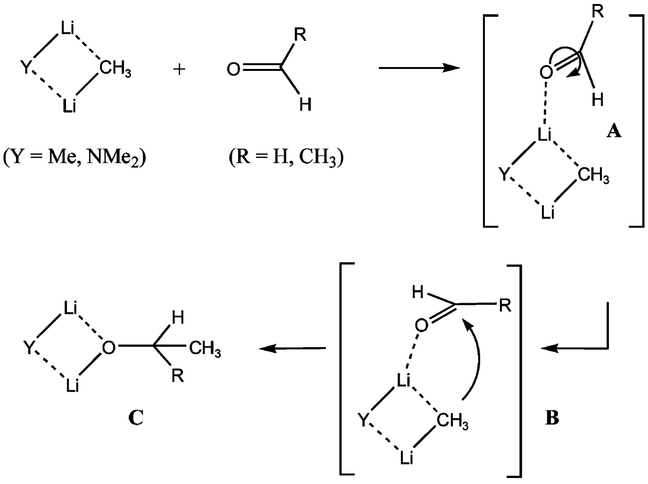


FIGURE 1. Elementary steps in the reaction between model aldehydes and dimeric organolithium aggregates.

We wish to report here the results we have obtained about the interaction between unsaturated organolithium compounds (such as vinyl- and phenyllithium) and formaldehyde, taken as a simple model for alkyl aldehydes.[6] Both monomeric and dimeric complexes have been considered. In relation with an experimental study currently in progress in our laboratories, computations have been performed on the homogeneous (RLi)$_2$ and heterogeneous (RLi-Me$_2$NLi) dimers. The synthetically useful (*Z*)-2-methoxyvinyllithium has also been taken into account.[10]

The reactivity of these sp^2 compounds, of which electronic structure is obviously different from that of sp^3 alkyllithium reagents, toward electrophiles has never been the object of a detailed investigation to our knowledge. The NMR characteristics of vinyllithium have been examined from a theoretical point of view,[11] but only a few papers describe the reactivity of these species.[12] The more recent articles deal with the allyl zincation of vinyllithium (examined at the HF 6-31G* level)[12b] or with the structure of the conjugate base of this latter reagent (optimized at the MP2 level with an extended basis set).[12c] The paper by Houk, Overman, and colleagues[12a] is closer to our interest since it deals with the stereochemical course of the addition of vinyllithium on cycloheptanones. However, lithium hydride was the only nucleophile considered in this study, run at the MP2 level.

---

(2) a) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805−1810. (b) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H.-R. *J. Am. Chem. Soc.* **1985**, *107*, 1810−1815.

(3) a) Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y. D. *J. Am. Chem. Soc.* **1985**, *107*, 5560−5562. (b) Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc*. **1993**, *115*, 11016−11017. (c) Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Chem. Soc. Faraday Trans*. **1994**, *90*, 1789−1798. (d) Mori, S.; Kim, B. H.; Nakamura, M.; Nakamura, E. *Chem. Lett.* **1997**, 1079−1080. (e) Haeffner, F.; Sun, C.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 12542−12546. (f) Uchiyama, M.; Nakamura, S.; Ohwada, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 10897−10903.

(4) a) Eleveld, M. B.; Hogeveen, H. *Tetrahedron Lett.* **1984**, *25*, 5187−5190. (b) Hilmersson, G.; Davidsson, O. *J. Organomet. Chem.* **1995**, *489*, 175−179. (c) Corruble, A.; Valnot, J. Y.; Maddaluno, J.; Duhamel, P. *J. Org. Chem.* **1998**, *63*, 8266−8275. (d) Corruble, A.; Valnot, J. Y.; Maddaluno, J.; Prigent, Y.; Davoust, D.; Duhamel, P. *J. Am. Chem. Soc.* **1997**, *119*, 10042−10048. (e) Arvidsson, P. I.; Davidsson, Ö.; Hilmersson, G. *Tetrahedron: Asymmetry* **1999**, *10*, 527−534. (f) Williard, P. G.; Sun, C. *J. Am. Chem. Soc.* **1997**, *119*, 11693−11694. (g) Arvidsson, P. I.; Ahlberg, P.; Hilmersson, G. *Chem. Eur. J.* **1999**, *5*, 1348−1354.

(5) For mixed aggregates involving lithium enolates see for instance a) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271−1289. (b) Flinois, K.; Yuan, Y.; Bastide, C.; Harrison-Marchand, A.; Maddaluno, J. *Tetrahedron* **2002**, *58*, 4707−4716.

(6) Fressigné, C.; Maddaluno, J.; Marquez, A.; Giessner-Prettre, C. *J. Org. Chem.* **2000**, *65*, 8899−8907.

(7) Amstutz, R.; Dunitz, J. D.; Laube, T.; Schweizer, W. B.; Seebach D. *Chem. Ber.* **1986**, *119*, 434−443.

(8) See for instance the remarkable X-ray characterization of the preliminary ester−lithium amide interaction by Williard, P. G.; Lin, Q. Y.; Lochman, L. *J. Am. Chem. Soc.* **1992**, *114*, 348−350.

(9) Sun, X.; Winemiller, M. D.; Xiang, B.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 8039−8046.

(10) a) Ficini, J.; Falou, S.; Touzin, A.-M.; d'Angelo, J. *Tetrahedron Lett.* **1977**, 3589−3592. (b) Wollenberg, R. H.; Albizati, K. F.; Peries, R. *J. Am. Chem. Soc.* **1977**, *99*, 7365−7367. (c) Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595−1598. (d) Godebout, V.; Leconte, S.; Levasseur, F.; Duhamel, L. *Tetrahedron Lett.* **1996**, *37*, 7255−7258.

(11) See inter alia: (a) Knorr, R. *Tetrahedron* **1981**, *37*, 929−937. (b) Bühl, M.; van Eikema Hommes, N. J. R.; Schleyer, P. v. R.; Fleischer, U.; Kutzelnigg, W. *J. Am. Chem. Soc.* **1991**, *113*, 2459−2465. (c) Ruud, K.; Helgaker, T.; Jorgensen, P.; Bak, K. L. *Chem. Phys. Lett.* **1994**, *226*, 1−10.

(12) a) Ando, K.; Condroski, K. R.; Houk, K. N.; Wu, Y.-D.; Kim, Ly, S.; Overmann, L. E. *J. Org. Chem.* **1998**, *63*, 3196−3203. (b) Marek, I.; Schreiner, P. R.; Normant, J.-F. *Org. Lett.* **1999**, *1*, 929−931. (c) Pratt, L. M.; Kass, S. R. *J. Org. Chem.* **2004**, *69*, 2123−2127.

Computational Details

All computations have been carried out using the 6-31G** basis set.[13] For consistency with our previous papers, the full optimizations have been performed using the B3P86 hybrid functional.[14] The low activation energies constantly found in this work prompted us to perform relaxed potential energy surface scans prior to the optimization of the transition states, the C−C or C−N distance in the forming bond being taken as the reaction coordinate. The transition states were characterized by frequency calculations. Neither the basis set superposition errors (BSSE) nor the zero-point energy corrections have been included in our results. These factors are indeed of relatively minor importance[6] with respect to the neglected solvation effect on the systems considered in this work (see discussion below) since they are not expected to modify the relative order of the complex stabilities nor that of the activation barriers. These series of computations have been carried out using GAUSSIAN98.[15] The complexation energy values given below have been taken as the difference between the energy of the optimized conformation of the complex and that of the isolated entities. The TS barriers have been defined as the difference between the energy at the TS and that of the starting optimized complex. The condensation energies have been calculated as the difference between the energy of the final product and that of the TS.

The electron localization function (ELF) used in this paper relies on a topological approach of the chemical bond described in original articles by Savin and Silvi et al.[16] We[17] and others[18] have shown in previous works that this tool can help to determine the bonding scheme in systems presenting ill-defined valences such as noncovalent organolithium aggregates. Therefore, we thought that such an electron distribution, which implicitly takes into account the superposition of the resonance forms, could provide useful information on the electron reorganization induced by the interaction between these complexes and formaldehyde. This information is particularly interesting around the transition state. In all the ELF figures presented hereafter, the colors code characterizes the cores (magenta), the monosynaptic (orange) and disynaptic (green) valence basins, and the hydrogens (blue). Note that a comparable approach of the problem of the bonding in the methyllithium − acetamide complex resorting to Bader's topological electron density analysis has been proposed before.[19]

The Boys localization performed for the homogeneous dimers was run using GAMESS[20] and the B3LYP functional (B3P86 is not implemented in this software), the basis set remaining 6-31G**.

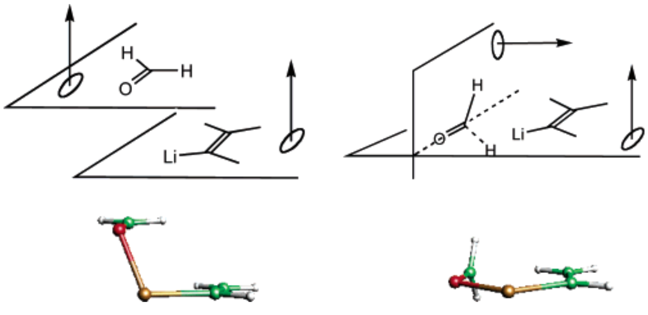


FIGURE 2. π (left, $\alpha = 0$) and σ (right, $\alpha = 90$) attack of vinyllithium on formaldehyde.

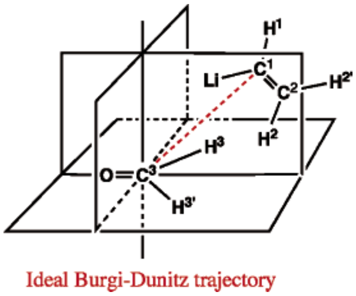


FIGURE 3. Ideal Bürgi-Dunitz trajectory for the addition of a nucleophile on formaldehyde.

Describing the approach of the two planar entities required a reference system in which the orientation of the plane of the aldehyde with respect to that of the vinyllithium can be defined. If it is generally admitted that nucleophilic additions on carbonyl compounds occur within the π-plane of the carbonyl and along a privileged direction (the Bürgi-Dunitz trajectory).[21] The orientation of the vinyl plane during this reaction does not seem to be known. The angle α between the two directions perpendicular to the molecular planes (i.e., the scalar product of their normal vectors) measures the interplanes angle. It can thus be employed to characterize the nucleophilic attack (Figure 2): α will vary between 0, if the aldehyde approaches along a direction perpendicular to the vinyl plane (π attack), and 90 if this approach takes place parallel to the vinyl plane (σ attack).

Actually, the 3-dimensional character of the attack requires several geometrical descriptors along the reaction pathway such as the C^1C^3O angle and the $C^1C^3OH^3$ diedral. In an ideal Burgi-Dunitz trajectory, which concerns neutral nucleophiles or isolated anions, these parameters should be worth 109 and 90°, respectively (Figure 3). Note that we found previously for MeLi that an approach in which the plane of formaldehyde remains parallel to the C−Li direction (corresponding here to $\alpha = 0$), takes place without any activation barrier.[6]

If the rotation step is, for vinyllithium like for methyllithium, associated to the passage of the reaction activation barrier, the H^3C^3OLi dihedral at the TS can be regarded as a probe to evaluate the relative "timing" of the reaction (H^3 being taken syn to the lithium atom). The transition states involving organolithium compounds and electrophiles are generally

---

[13] Frisch, J. M.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265−3269.

[14] a) Perdew, J. P. *Phys. Rev.* **1986**, *B33*, 8822−8824. (b) Becke, A. D. *J. Chem. Phys.* **1989**, *90*, 5622−5629.

[15] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewfki, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, F.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *GAUSSIAN 98*, Revision A5; Gaussian Inc., Pittsburgh, PA, 1998.

[16] a) Silvi, B.; Savin, A. *Nature* **1994**, *371*, 683−686. (b) Savin, A.; Silvi, B.; Colonna, F. *Can. J. Chem.* **1996**, *74*, 1088−1096. For a review, see: c) Savin, A.; Nesper, R.; Wengert, S.; Fässler, T. F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1808−1832.

[17] Fressigné, C.; Maddaluno, J.; Giessner-Prettre, C.; Silvi, B. *J. Org. Chem.* **2001**, *66*, 6476−6479.

[18] a) Chesnut, D. B. *J. Phys. Chem. A* **2000**, *104*, 11644−11650. (b) Chesnut, D. B. *J. Phys. Chem. A* **2003**, *107*, 4307−4313.

[19] Bachrach, S. M.; Ritchie, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 3134−3140.

[20] Schmidt, M. W.; Balridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347−1363.

[21] a) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065−5067. (b) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563−1572. (c) Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153−161.

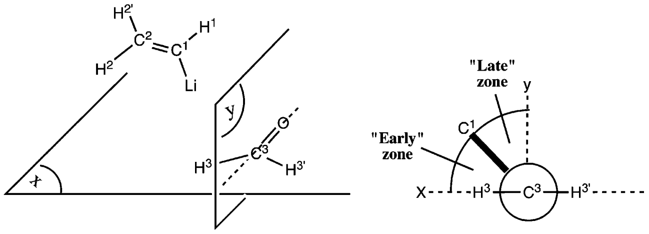


FIGURE 4. Planes *x* and *y* to describe the nucleophilic attack of vinyllithium on formaldehyde.

considered as early.[22] A finer measurement of this earliness could possibly be obtained from H^3C^3OLi, an extremely early transition state (reached within plane x before any rotation of the aldehyde, Figure 4) corresponding to $H^3C^3OLi = 0$, while 90° would be observed in a "later" transition state (aldehyde within plane y, the full rotation being completed at the TS).

Results and Discussion

Study of the monomers.

With these tools in hand, we first considered the case of monomeric vinyllithium. The full optimization of the complex formed between formaldehyde and vinyllithium (Figure 5) leads to a compact (A "syn", non coplanar) and a loose (B "anti", coplanar) situation. The first of these arrangements, which keeps the nucleophilic and electrophilic centers within a reasonable distance and is thus likely to yield the expected condensation product, was found to be favored by 1.8 kcal·mol^{-1}. A H-π stabilizing interaction between H^3 and the vinyl double bond probably contributes to this slight preference (Figure 5A, $d(H^3{-}C^1) = 2.65$ Å). Note that at the HF level conformer B is not a local minimum and optimizes into A.

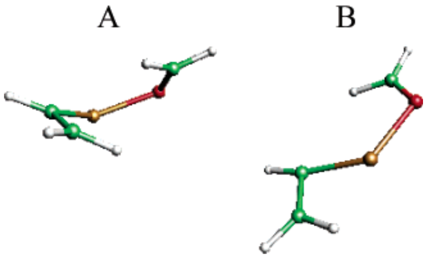


FIGURE 5. The syn (A) and anti (B) arrangements of formaldehyde docked on monomeric vinyllithium.

The interaction energy between formaldehyde and vinyllithium in the optimized syn arrangement was found to be −20.9 kcal·mol^{-1}. The O−Li complexation takes place in the plane of the aldehyde ($H^3C^3OLi = 1°$, Figure 6A and Table 1), along the oxygen lone pair direction ($C^3OLi = 111°$, O−Li = 1.95 Å). Note that the directionality of this interaction is not obtained at a lower level of calculations.[3a,23] The lithium remains in the plane of the vinyl ($LiC^1C^2H^3 = 0$) and the interplanar angle α is 53° while $C^3OLiC^1 = 7°$. Similar observations can be made for the two other monomers (2-methoxyvinyllithium, phenyllithium) considered here (see below).

As for sp^3 nucleophiles, proceeding to the transition state ($d_{Li-O} = 1.92$ Å, Figure 6B) requires a rotation of the aldehyde, which increases the H^3C^3OLi dihedral to more than 42°, and is associated to a very low activation barrier (<2 kcal·mol^{-1}). The mixed π and σ character of the arrangement at the TS is associated to α = 34°. The final strongly exothermic condensation (−43.4 kcal·mol^{-1}) leads to the expected lithium alcoholate in which a π-cation interaction between the double bond and the lithium can be noticed (d [Li− middle of C═C] = 2.30 Å, Figure 6C).

A comparable set of calculations was then repeated with monomeric (Z)-2methoxyvinyllithium. The optimized structures of the resulting complex, TS and final product are displayed in Figure 7. Significant differences with the previous case can be noticed at the level of the complex: while the lithium remains within the plane of the aldehyde ($H^3C^3OLi = C^3OLiC^1 = 1$ and $C^3OLi = 108°$), an anti arrangement between the aldehyde and the vinyl appendage is found more stable than the previous syn one (Figure 5) with the two planes more or less parallel (α = 4). Also, the complexation energy is slightly smaller (18.2 vs 20.9 kcal·mol^{-1}), probably because of the supplementary intramolecular coordination undergone by the lithium. At the TS, the aldehyde has significantly rotated (α = 65°). In the final lithium alcoholate, the O−Li intramolecular coordination is preferred over the π-cation interaction mentioned above. Note that the overall exothermicity of the reaction (as well as the complexation energy) is smaller than that for vinyllithium by 2.7 kcal·mol^{-1}, while the energy barriers are similar.

When considering the case of monomeric phenyllithium, the original PhLi−HCHO complex is relatively similar to that obtained with the vinyllithiums ($C^3OLiC^1 = 5$, $H^3C^3OLi = 1$, $C^3OLi = 111$, α = 60, Figure 8A and Table 1). Note that the distance between H^3 and the center of the phenyl ring is relatively short (3.38 Å).

As for methoxyvinyllithium, the TS is reached upon a small rotation of the aldehyde (α = 70° with a barrier of 2.1 kcal·mol^{-1}, Figure 8B). The final lithium alcoholate exhibits a π-cation interaction (d[Li-middle of C_6H_5 ring] = 2.77 Å, Figure 8C), probably contributing to the slightly larger calculated condensation energy (−45.1 kcal·mol^{-1}).

Comparing the relative behavior of the three monomeric entities shows that, in the complexes formed by vinyllithium and phenyllithium, the planes of the formaldehyde and of the nucleophile are twisted (α = 53° and 60°, respectively) while in the case of (Z)-2-methoxyvinyllithium, in which the lithium atom is tricoordinated, these two reactants are almost coplanar (α = 4). This is probably related to the anti and syn (in which the coplanarity is sterically forbidden) characters of these arrangements, respectively. Note also that the TS of all these sp^2 nucleophiles lies slightly higher in energy than those involving MeLi (sp^3): the TS are here in the 2 kcal·mol^{-1} range while for the reaction between formaldehyde and monomeric methyllithium, the barrier was calculated to be 0.9 kcal·mol^{-1} at the same computational level.[6]

It is worth underlining that the reaction trajectories followed by the three nucleophiles considered are relatively similar since at the TS: (i) the C^1C^3O angles are found in the 90° range (a "small" value with respect to

---

[22] Beutelman, H. P.; Xie, L.; Saunders, W. H., Jr. *J. Org. Chem.* **1989**, *54*, 1703−1709.

[23] Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 4635−4643.

TABLE 1. Value of Dihedral Angles α and Other Geometrical Parameters in Docking Complexes and Transition States Involving Monomeric Nucleophiles

	complex[a]				transition state[a]			
nucleophile	C_3OLi	C_3OLiC^1	α	H^3C^3OLi	C^1C^3O	$C^1C^3OH^3$	α	H^3C^3OLi
$CH_2{=}CHLi$	111	7	53	1	85	55	34	42
(*Z*)-$MeOCH{=}CHLi$	108	1	4	1	89	48	65	44
C_6H_5Li	111	5	60	1	89	45	70	45
MeLi[b]	108	0	-	0	89	40	-	41

[a] See Figure 1 for definition of α and Figure 2 for the other angles. [b] Values taken from computations described in ref 6.

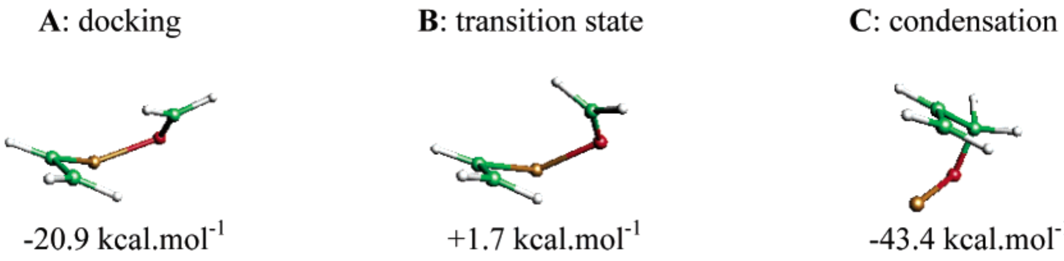


FIGURE 6. The successive steps of the reaction between monomeric vinyllithium and formaldehyde.

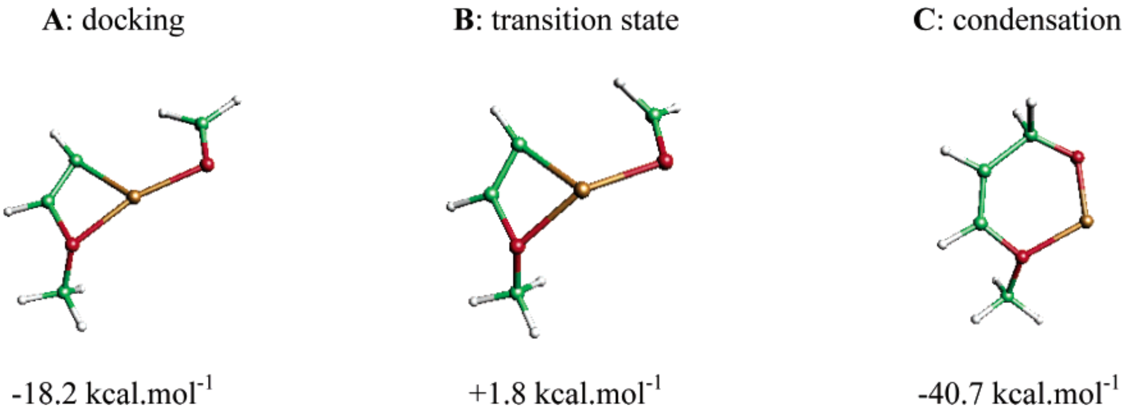


FIGURE 7. The successive steps of the reaction between monomeric (*Z*)-2-methoxyvinyllithium and formaldehyde.

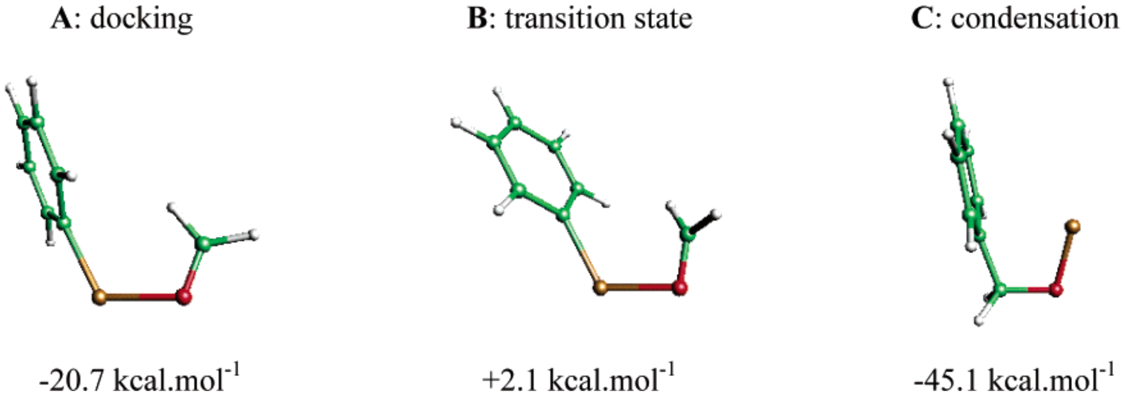


FIGURE 8. The successive steps of the reaction between monomeric phenyllithium and formaldehyde.

the 109° in the Bürgi-Dunitz trajectory, Figure 3), as expected for hard nucleophiles (vide infra); (ii) the $C^1C^3OH^3$ angles are very close (~50°), suggesting that the approach takes place almost within the xy bisector plane (Figure 4); (iii) the H^3C^3OLi angles are ~45°, that is midway between an "early" and "late" TS. Let us add that these figures are extremely similar to those calculated at the transition state of the reaction between MeLi and HCHO ($C^1C^3O = 89$, $C^1C^3OH^3 = 40$, $H^3C^3OLi = 41°$).[6] By contrast, the α values at the TS differ significantly when going from vinyllithium to phenyllithium, translating quite different arrangements of the formaldhyde. Note also that α at the TS does not correlate with α in the complex. The conclusions to be drawn from these values are discussed below.

Study of the homogeneous dimers.

If the monomeric entities considered above can be the key intermediates in the reaction,[24] the corresponding

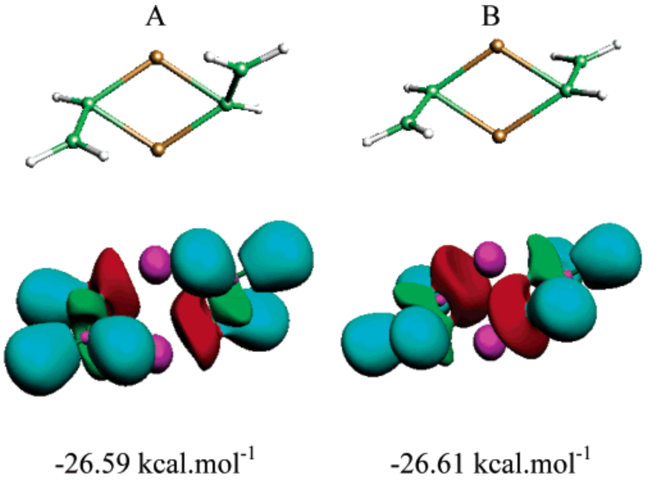


FIGURE 9. Optimized cis (A) and trans (B) arrangements of vinyllithium dimer (top), their ELF representations (middle) and dimerization energies (per monomer, bottom).

dimers are also likely to play an important part if an open-dimer type mechanism is involved.[25] In particular, phenyllithium has been shown to undergo a monomer−dimer equilibrium in THF.[26] We thus decided to examine the homogeneous dimers, as well as some heterogeneous aggregates involving our model compounds and lithium dimethylamide. Mixed dimers have been shown to play a key role in many reactions involving organolithiums species.[27]

The case of the vinyllithium dimer has been considered first. Its full optimization leads to two minima in which the vinyl C^1 are more or less tetrahedral despite their sp^2 hybridization. These two isomers exhibit a similar planar C^1LiC^1Li core around which the bent vinyl appendages can be either cis (Figure 9A) or trans (9B) with $C^2C^1Li^2Li^1 = 49°$ and 52°, respectively. In both cases the dimerization energy [taken as E(dimer) − ΣE(monomer)] is 26.6 kcal·mol^{-1}. The two conformers are almost isoenergetic ($\Delta E = 0.1$ kcal·mol^{-1} in favor of the trans), as noted previously in the relatively similar case of acetaldehyde lithium enolate.[28] Despite the quasi-perfect symmetry of the core, the dissymmetrical arrangements of the vinyl leads to an unbalanced localization of the electrons of the C−Li bond, as shown on the ELF representations (Figure 9). The numerical data suggest that the valence basins are monosynaptic (orange-colored) and centered on carbon C^1. The contribution of the Li atomic basin to the V(C) population is very small (0.04 out of 2.43 electrons in both the cis and trans arrangements), characteristic of a largely ionic C−Li bond.[29]

Next, a molecule of formaldehyde was docked on one of the lithium of the more stable trans dimer (Figure 10). As before, in the optimized complex the aldehyde lies slightly out of the $C^1Li^1C^{1'}Li^2$ core plane ($C^3OLi^1C^1 = 14°$ and $H^3C^3OLi^1 = 0°$), with $C^3OLi^1 = 122°$. By contrast, α is worth 90° (calculated between the plane of the aldehyde and that of its closest vinyl appendage), indicating that the planes of the vinyl and of the aldehyde are now fully perpendicular. This orientation puts the proton of the aldehyde in direct interaction with the π-plane of the vinyl as indicated by d(H^3−C^1) = 2.70 Å, close to that observed for the "syn" arrangement of the monomer (vide supra). Note that docking the aldehyde in a "bridging" position such that the each free doublet of the CO interacts with one lithium does not correspond to an energy minimum, the system returning to the previous arrangement.

At the TS, α = 32°, similar to that calculated for the monomer, while all other geometrical parameters are increased. The ELF analysis indicates that the electron repartition undergoes little change upon docking of the aldehyde (compare Figures 9B and 10A). The same remark applies at the transition state (Figure 10A,B): the bonding scheme is hardly modified despite the relatively "late" character of this TS ($H^3C^3OLi = 60°$). This result suggests that, for this type of reaction, the total energy of the system and the distribution of its electrons do not evolve synchronously. It also indicates that, as before, at the TS the coordination of the lithium by the carbonyl does not take place through the oxygen doublet anymore. This latter rotates with the aldehyde as the carbon of the C═O remains sp^2 (31.13% s + 68.69% p and 99.70% p on both C and O for the π_{CO} according to the NBO population analysis). A short-lived interaction between the carbonyl π-system and the lithium, affording an η^2-metallooxirane complex,[30] probably takes over at the TS (see the Boys representation, Figure 10B). As expected, the C═O polarity remains almost unchanged (≈33% on C and 67% on O)[31] between the docking complex and the TS. Comparable values were calculated for the dimers of 2-methoxyvinyllithium and phenyllithium. We checked the validity of the ELF treatment comparing its results to those of the Boys localization on the complex and the TS. The resulting centroids arrange alike the ELF basins (Figure 10, middle).

The docking of the aldehyde on Li^1 is associated to a lengthening of the C^1−Li^1 distance (from 2.17 Å in the complex to 2.21 Å at the TS), while the $C^{1'}$−Li^1 distance shrinks in the same proportions (from 2.18 Å in the complex to 2.14 Å at the TS). A similar phenomenon was described previously by Morokuma and colleagues[3b] who coined the term "open-dimer" to describe the pre-transi-

---

[24] For instance, monomeric LDA has been shown to be the key-reactant in the deprotonation of *tert*-butyl cyclohexane carboxylate in THF: Sun, X.; Kenkre, S. L.; Remenar, J. F.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 4765−4766.

[25] For crystallographic evidences in favor of open-dimers during the deprotonation of carbonyl compounds, see: (a) Sate, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761−763. (b) Williard, P. G.; Liu, Q.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 3380−3381.

[26] Reich, H. J.; Green, D. P.; Medina, M. A.; Goldenberg, W. S.; Gudmundsson, B. O.; Dykstra, R. R.; Phillips, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 7201−7210.

[27] a) Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 7288−7293. (b) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2459−2463. (c) Pratt, L. M. *Mini-Rev. Org. Chem.* **2004**, *1*, 209−217.

[28] Abbotto, A.; Streitwieser, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1997**, *119*, 11255−11268.

[29] Kaufmann, E.; Raghavachari, K.; Reed, A. E.; Schleyer, P v. R. *Organometallics* **1988**, *7*, 1597.

[30] Review on the Lewis acid carbonyl complexation: Shambayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 1, pp 283−324.

[31] For details on the computation of polarization from NBO analysis, see: Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO 3.0 Program Manual*. This document is available on-line (on July 30, 2005) at http://www.ccl.net/cca/software/MS-WIN95-NT/mopac6/nbo/NBO.HTM.

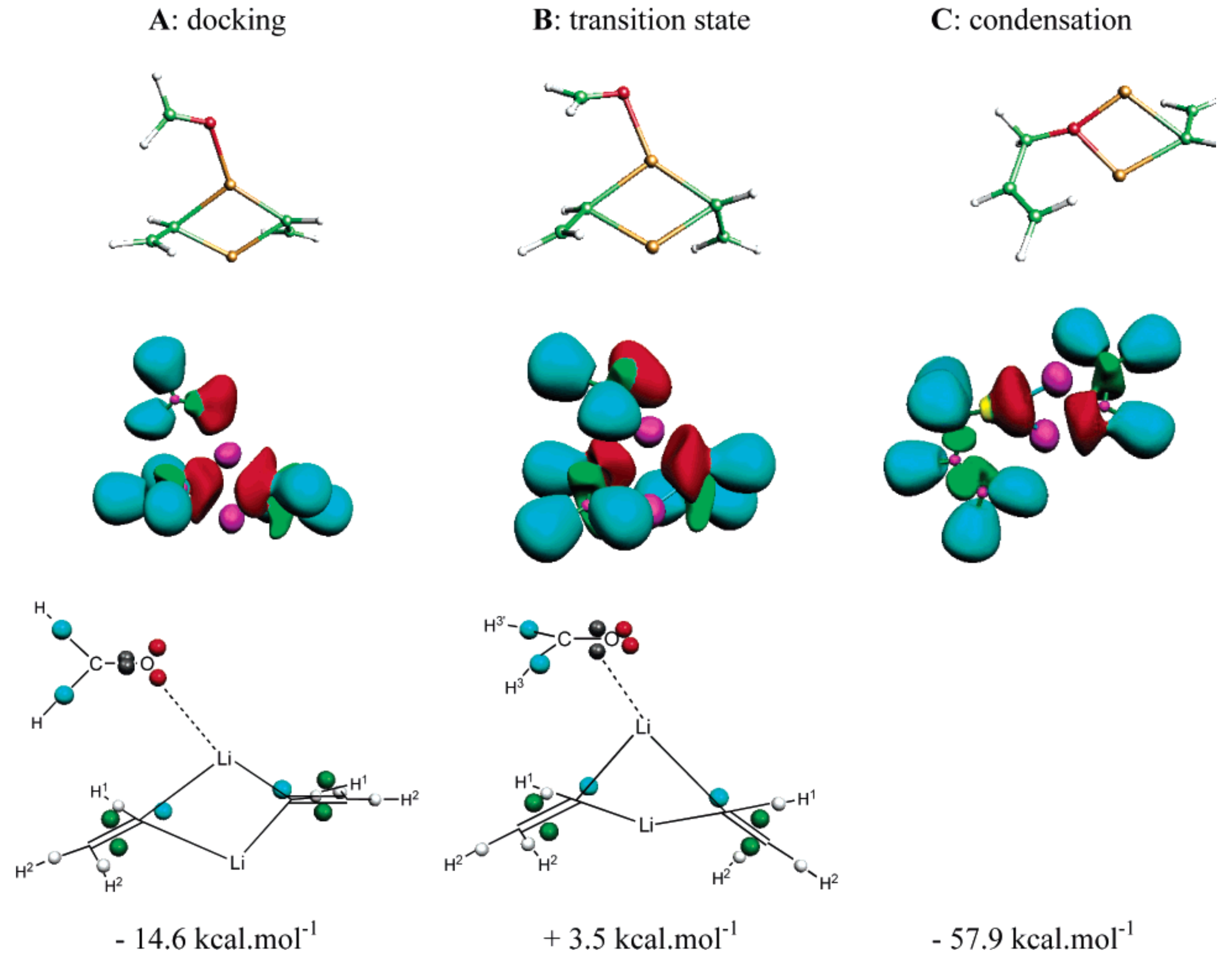


FIGURE 10. The successive steps of the reaction between the trans conformer of vinyllithium dimer and formaldehyde (top), their ELF and Boys localizations (middle) and associated energy values (bottom).

tion state arrangement obtained after docking of one formaldehyde on a dimer of methyllithium solvated by one H_2O.

After the condensation, the resulting alcoholate forms a mixed aggregate with the remaining vinyllithium. Its mainly ionic character appears in Figure 10C, the lithium atomic contributions to the valence basins of $C^{1'}$ and O remaining very small (0.02 for Li^1 plus 0.04 for Li^2 out of 2.43 electrons for the $C^{1'}$ single basin, 0.03 for Li^1 out of 3.58 electrons and 0.03 for Li^2 out of 2.72 electrons for the two O basins). Note also that the trans and cis conformers of the dimer of vinyllithium yield a "trans" and "cis" mixed aggregate respectively (Figures 10C and 11C). However, these two arrangements are isoenergetic and no rotation barrier was found around the C^3–O bond.

The dimer of 2-methoxyvinyllithium was considered next. The more stable conformer was found as a slightly concave eight-membered ring involving two intermolecular O–Li coordinations, isoenergetic to a "convex" isomer ($\delta E = 0.04$ kcal·mol^{-1}, Figure 12). The following calculations have been restricted to the concave isomer.

In these dimers, the C^1 of each vinyl entity lies in a more or less planar surrounding ($H^1C^1C^2Li^1 = 172°$ and $H^1C^1C^2Li^2 = 163°$) and represents a case of nontetrahedral tetracoordinate carbon studied by Schleyer et al.[32] and observed in a few cases by X-ray crystallography.[33] Upon docking of the formaldehyde, a "monomer-type" chelation scheme appears (red circle in Figure 13B). In the case of the complex, the coordination C^3OLi and dihedral C^3OLiC^1 and H^3C^3OLi angles are relatively similar to those calculated in the monomer. By contrast, α goes from a quasi-coplanar situation in the monomer to a perpendicular arrangement in the dimer ($\alpha = 4°$ vs 88°, Figure 13B). At the transition state, the C^1C^3O angle is similar to that in the monomer (91° vs 89°), while (i) $H^3C^3OLi = 39°$, characteristic of a particularly "early" TS, (ii) the $C^1C^3OH^3$ increases from 48 (in the monomer) to 70°, closer to the Burgi-Dunitz trajectory, and (iii) α decreases from 65° to 45°, characterizing a perfect mixed $\sigma + \pi$ orientation of the aldehyde. The condensation yields the final product as a mixed aggregate organized around a [4.4.0] "bicyclic" core (Figure 13D). Energywise, the complexation is less exothermic than for the monomer (−12.5 vs −18.2 kcal·mol^{-1}), while the activation barrier

---

[32] See, for instance: (a) Collins, J. B.; Dill, J. D.; Jemmis, E. D.; Apeloig, Y.; Schleyer, P. v. R.; Seeger, R.; Pople, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 5419–5425. (b) Sorger, K.; Schleyer, P. v. R. *J. Mol. Struct. THEOCHEM* **1995**, *338*, 317–346.

[33] a) Rietveld, M. H. P.; Wehmann-Ooyevaar, I. C. M.; Kapteijn, G. M.; Grove, D. M.; Smeets, W. J. J.; Kooijman, H.; Spek, A. L.; van Koten, G. *Organometallics* **1994**, *13*, 3782–3787. (b) Sorger, K.; Schleyer, P. v. R.; Fleischer, R.; Stalke, D. *J. Am. Chem. Soc.* **1996**, *118*, 6924–6933. (c) Betz, J.; Hampel, F.; Bauer, W. *J. Chem. Soc., Dalton Trans.* **2001**, 1876–1879.

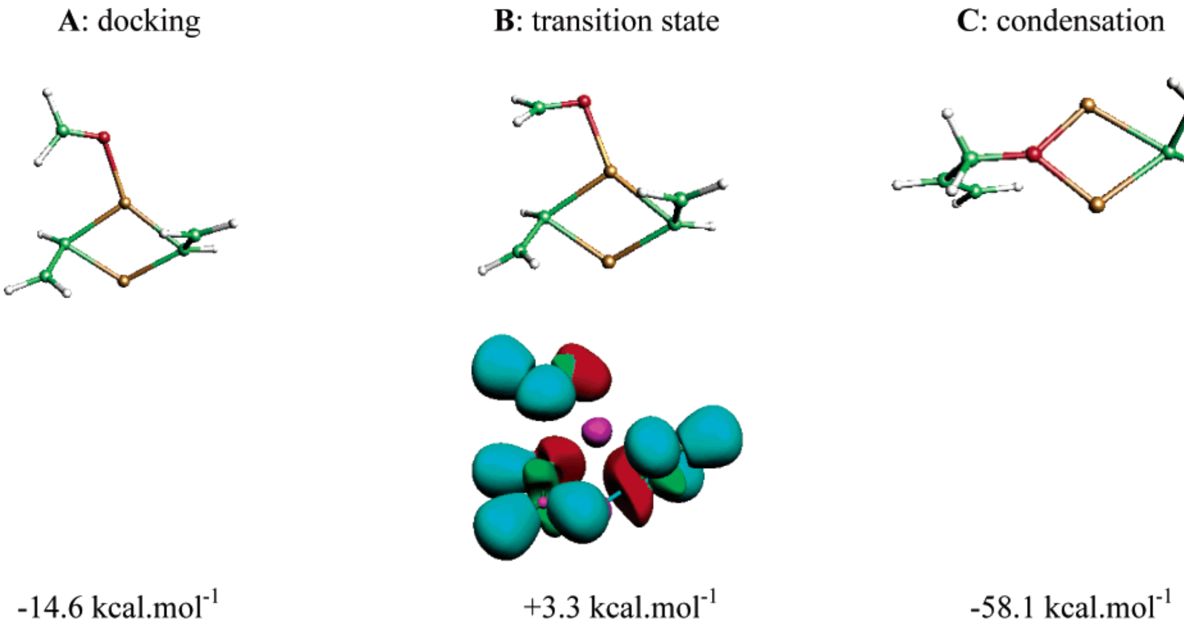


FIGURE 11. The successive steps of the reaction between the cis conformer of vinyllithium dimer and formaldehyde (top), the ELF representation of its TS (middle) and associated energy values (bottom).

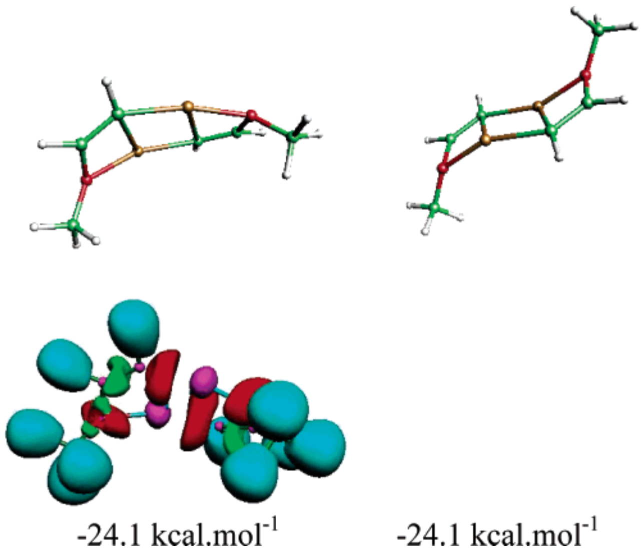


FIGURE 12. The two conformers of the dimer of 2-methoxyvinyllithium, the ELF representation of the most stable one (middle) and associated dimerization energies (bottom).

remains the same (≈+1.9 kcal·mol^{-1}). Finally, the exothermicity of the condensation is larger than that of the vinyllithium dimer.

Regarding the ELF analysis of this reaction, the bonding schemes in the docking complex as well as in the TS are very similar to those described above for vinyllithium dimer, except for a supplementary monosynaptic basin corresponding to the coordination of the lithium by the methoxy appendage. As above, going from the original complex to the transition state does not alter the electron distribution.

The dimer of phenyllithium was the last homogeneous entity considered. This aggregate, which has been first characterized, at the semiempirical MNDO level, as a planar D_{2h} dimer,[34] was found, at the DFT level, to adopt a conformation in which the CLiCLi lozenge core is roughly perpendicular to both phenyl rings (Figure 14A), even in the absence of solvent.[35] Both the X-ray crystallography[36] and solution NMR[26,37] data support this latter arrangement. Actually, the planar D_{2h} conformation is a transition state at the DFT level, characterized by a negative frequency.

The incoming of the aldehyde is of little consequence for the $(PhLi)_2$ unit geometry. The quasi-ideal O−Li coordination translates into small H^3C^3OLi and C^3OLiC^1 angles (2° and 4°, respectively) and a C^3OLi angle close to 120° (Figure 14B). Furthermore, the plane of the formaldehyde is quasi perpendicular to that of the phenyl ($\alpha = 84°$), to be compared to $\alpha = 60°$ in the monomer. This orientation could be favored by the interaction between one proton of the aldehyde and the phenyl ring (characterized by a short $d_{H3-Ar} = 2.32$ Å). The formaldehyde then rotates of almost 90° to access the transition state (Figure 14C) which is associated to C^1C^3O and C^1C^3-OH angles similar to that for the dimeric vinyllithium. By contrast, the value of α plummets to 1 degree, characteristic of a pure π-complex (Figure 14C) and H^3C^3-OLi = 76° (a relatively "late" TS). As underlined above in the case of vinyllithium, the dimer opens slightly at the TS (C^1-Li^1 goes from 2.24 Å in the complex to 2.27 Å while $C^{1'}-Li^1$ remains at 2.16 Å). Note that in the aldehyde, the carbon of the C=O is sp² in the complex (30.44% s + 69.36% p and 99.71% p on both C and O for the π_{CO}) and in the TS, characterized by similar values.

---

[34] Chandrasekhar, J.; Schleyer, P. v. R. *J. Chem. Soc., Chem Commun*. **1981**, 260−261.

[35] Only phenyllithium tetramers seem to have been previously studied by DFT: Kwon, O.; Sevin, F.; McKee, M. L. *J. Phys. Chem. A* **2001**, *105*, 913−922.

[36] (a) Thoennes, D.; Weiss, E. *Chem. Ber.* **1978**, *111*, 3157−3161. (b) Vestergren, M.; Eriksson, J.; Hilmersson, G.; Håkansson, M. *J. Organomet. Chem*. **2003**, *682*, 172−179. (c) Strohmann, C.; Strohfeldt, K.; Schildbach, D.; McGrath, M. J.; O'Brien, P. *Organometallics* **2004**, *23*, 5389−5391.

[37] Reich, H. J.; Goldenberg, W. S.; Sanders, A. W.; Tzschucke, C. C. *Org. Lett*. **2001**, *3*, 33−36.

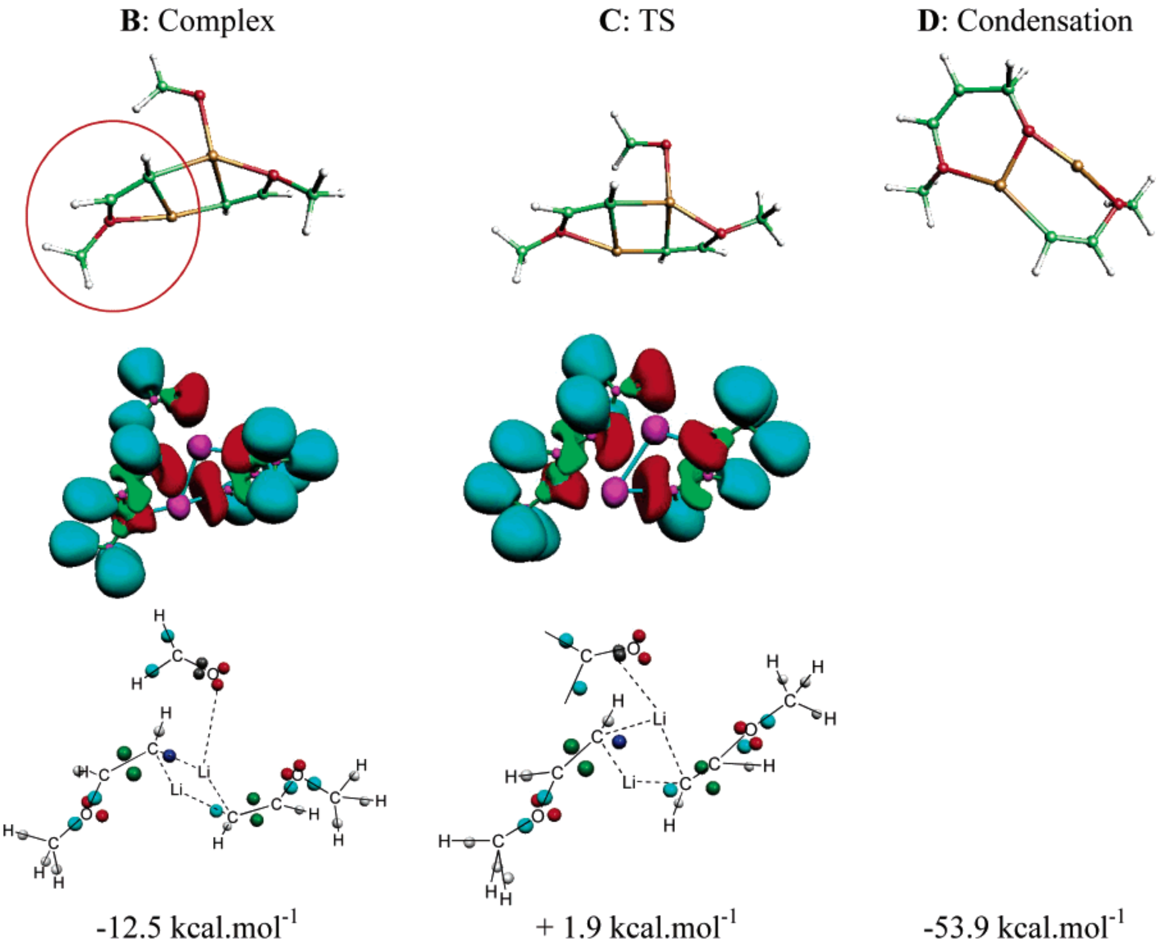


FIGURE 13. The successive steps of the reaction between the 2-methoxyvinyllithium dimer and formaldehyde (top), their ELF representations and Boys localizations (middle) and associated energy values (bottom).

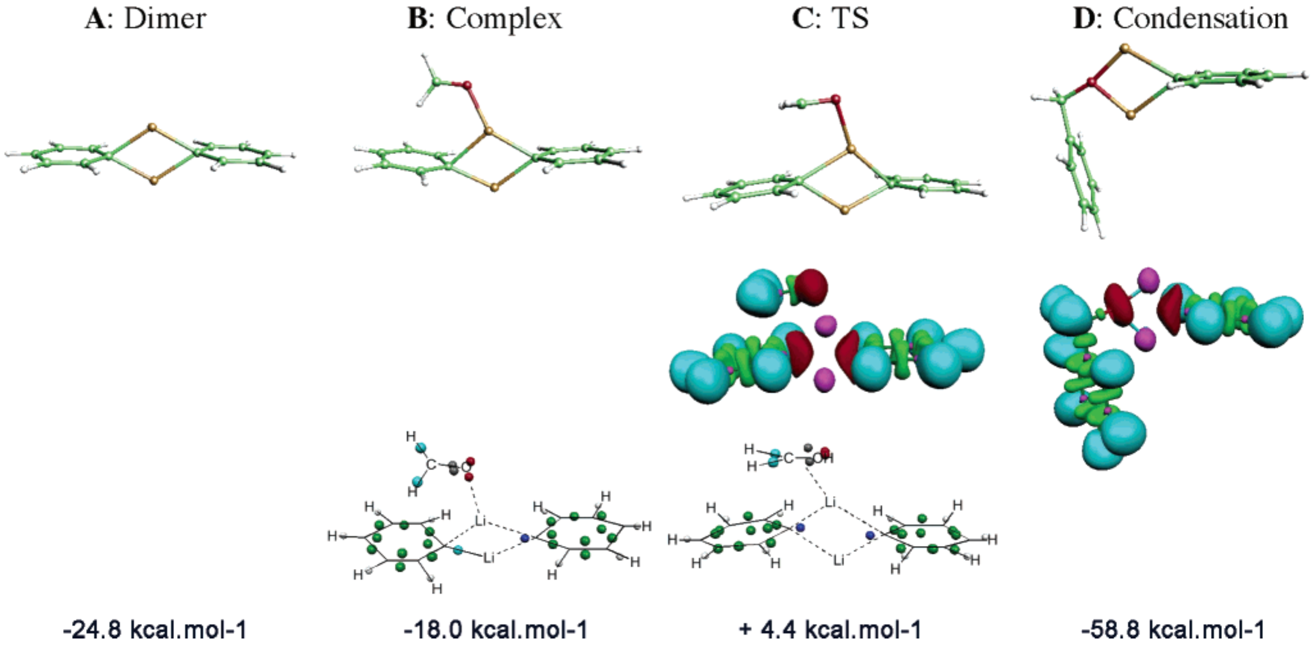


FIGURE 14. The successive steps of the reaction between the dimer of phenyllithium and formaldehyde (top), the ELF representation and Boys localization (middle), and associated energy values (bottom).

Finally, a $PhCH_2OLi-PhLi$ aggregate is obtained, in which a π-cation interaction (dLi − middle of the C_6H_5 ring = 3.10 Å), noted above for the monomer, is conserved. Note that the phenyl ring of the alcoholate stays perpendicular to both the CLiOLi core and to the remaining phenyllithium plane (Figure 14D). If we con-

TABLE 2. Value of Dihedral Angle α and Geometrical Parameters in Docking Complexes and Transition States Involving Dimeric Nucleophiles

	nucleophile	complex[a]				transition state[a]			
		C^3OLi	C^3OLiC^1	α	H^3C^3OLi	C^1C^3O	$C^1C^3OH^3$	α	H^3C^3OLi
1	$(\mathrm{CH_2{=}CHLi})_2$ *cis*	117	19	61	1	95	72	23	61
2	$(\mathrm{CH_2{=}CHLi})_2$ *trans*	122	14	90	0	93	73	32	60
3	$(\mathrm{MeOCH{=}CHLi})_2$	116	23	88	6	91	70	45	39
4	$(\mathrm{C_6H_5Li})_2$	122	4	84	2	99	83	1	76
5	$(\mathrm{CH_3Li})_2$[b]	121	1	-	0	96	83	-	83
6	$\mathrm{CH_2{=}}C\mathrm{HLi/LiNMe_2}$[c]	118	17	82	1	94	70	47	59
7	$\mathrm{MeOCH{=}}C\mathrm{HLi/\ LiNMe_2}$[c]	115	22	69	4	92	70	33	47
8	$C_6\mathrm{H_5Li/LiNMe_2}$[c]	122	1	89	0	100	83	2	81
9	$C\mathrm{H_3Li/LiNMe_2}$[b,c]	122	1	-	0	93	74	-	59
10	$\mathrm{CH_2{=}CHLi/Li}N\mathrm{Me_2}$[d]	112	4[e]	87[f]	0	93[e]	55[e]	30	51
11	$\mathrm{MeOCH{=}CHLi}$ $\mathrm{Li}N\mathrm{Me_2}$[d]	111	2[e]	88[f]	0	93[e]	53[e]	31[f]	47
12	$\mathrm{C_6H_5Li/Li}N\mathrm{Me_2}$[d]	113	2[e]	91[f]	0	92[e]	56[e]	30[e]	52
13	$\mathrm{CH_3Li/Li}N\mathrm{Me_2}$[b,d]	112	0[e]	90[f]	0	70[e]	38[e]	40[f]	22
14	$(\mathrm{LiNMe_2})_2$[b]	111	0[e]	90	0	93[e]	54[e]	32	51

[a] See Figure 1 for a definition of α and Figure 2 for the other angles. [b] Values taken from computations described in ref 6. [c] Docking on the carbon side (see text). [d] Docking on the nitrogen side (see text). [e] The amide nitrogen is considered instead of C^1. [f] α calculated between the plane of the amide and that of the aldehyde.

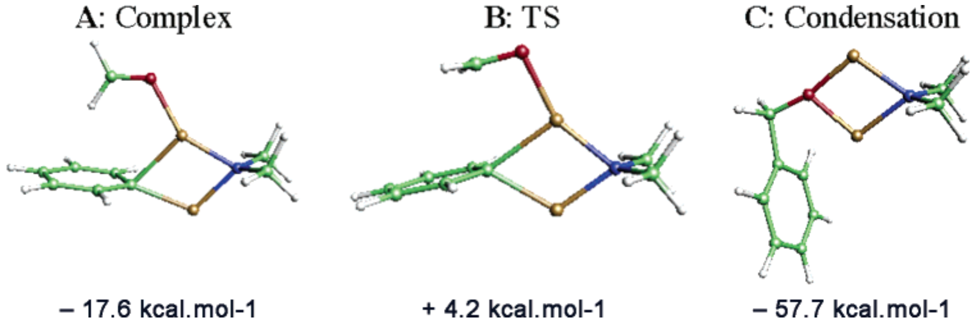


FIGURE 15. The successive steps of the reaction between the heterogeneous dimer phenyllithium/lithium dimethylamide and formaldehyde (top) and associated energy values (bottom).

sider the energy profile of this reaction, the dimerization is exothermic by ~24 kcal·mol^{-1} while both the complexation energy (−18.0 kcal·mol^{-1}) and activation barrier (+4.4 kcal·mol^{-1}) are increased with respect to previous cases. The reaction ends up with a condensation energy slightly larger than the previous ones (−58.8 kcal·mol^{-1}).

Comparing entries 4 and 5 in Table 2 shows that, apart of the π character of its arrangement at the TS, the addition of dimeric phenyllithium follows a trajectory comparable to that calculated for the dimer of methyllithium. The ELF representation in Figure 14C suggests that, as above, the electronic distribution at the ("late") transition state seems unaffected.

Study of mixed aggregates.

In the final part of this study, the mixed aggregates between the same three sp^2 entities and lithium dimethyl amide were considered, in an attempt to evaluate the possible influence of this phenomenon on the course of the nucleophilic additions. Two types of additions have to be envisaged for a mixed dimer since the carbon of the carbonyl can be oriented toward either the carbon or the nitrogen. The resulting product is, in the former case, the usual allylic alcohol while the latter reaction provides a lithium α-amino alcoholate.[38] The entry 9 of Table 2, corresponding to data obtained with the MeLi−NMe_2Li mixed aggregate studied previously,[6] have been added for the sake of comparison.

When one considers the carbon sp^2 or methyl as the nucleophile, the data in entries 6−9 of Table 2 show that going from an homogeneous to an heterogeneous aggregate hardly affects the characteristics of the attack. Note that the value of α at the TS of the vinyllithium and methoxyvinyllithium mixed aggregates (compare entries 1 and 6 and entries 3 and 7) shows an increase and decrease of the σ character of the aldehyde arrangement, respectively. By contrast, the geometry of the phenyllithium addition is unaltered (entries 4 and 8 and Figure 15).

Let us now consider the cases where the nitrogen is the nucleophile (Figure 16). The results have been gathered in entries 10−12 together with the data concerning the dimer of lithium dimethylamide (entry 14), added for the sake of comparison with the sp^2 mixed aggregate. As for the carbon side, the heterogeneous/homogeneous character of the aggregate has almost no influence on the nucleophilic behavior of the nitrogen. The geometrical data in Table 2 indicate that the nucleophilic attack by the amide of the heterogeneous aggregates of sp^2 entities (entries 10−12) takes place in a quite similar way (α ~ 30°, C^1C^3O ~ 92°, and H^3C^3OLi ~ 50°). In addition, for the TS on the *N*-sides: (i) the $C^1C^3OH^3$ angle is always smaller; (ii) the values charac-

---

[38] Zhao, P.; Condo, A.; Keresztes, I.; Collum, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 3113−3118. For applications of α-amino-alcoholates in synthesis, see ref 5a and Comins, D. L. *Synlett*. **1992**, 615−625.

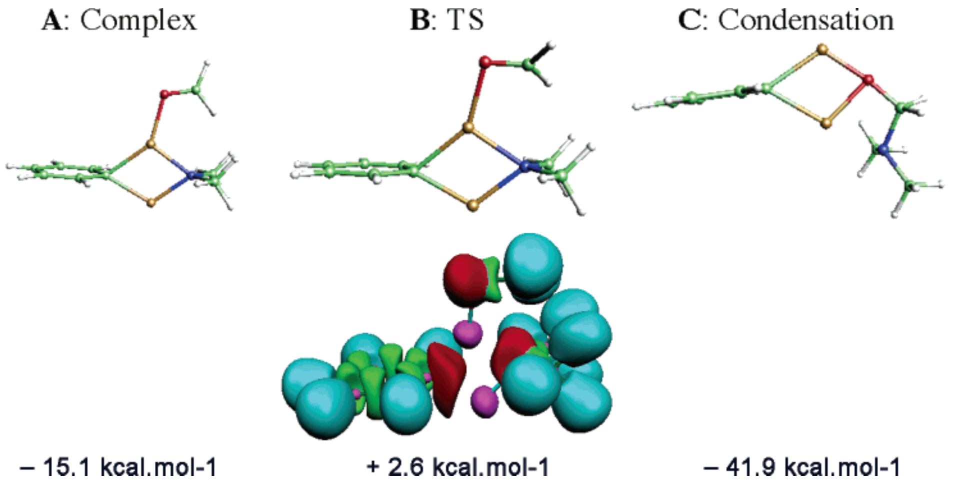


FIGURE 16. The successive steps of the reaction between the heterogeneous dimer phenyllithium/lithium dimethylamide and formaldehyde (top), the ELF representation of the TS (middle), and associated energy values (bottom). The reaction takes place with lithium dimethylamide.

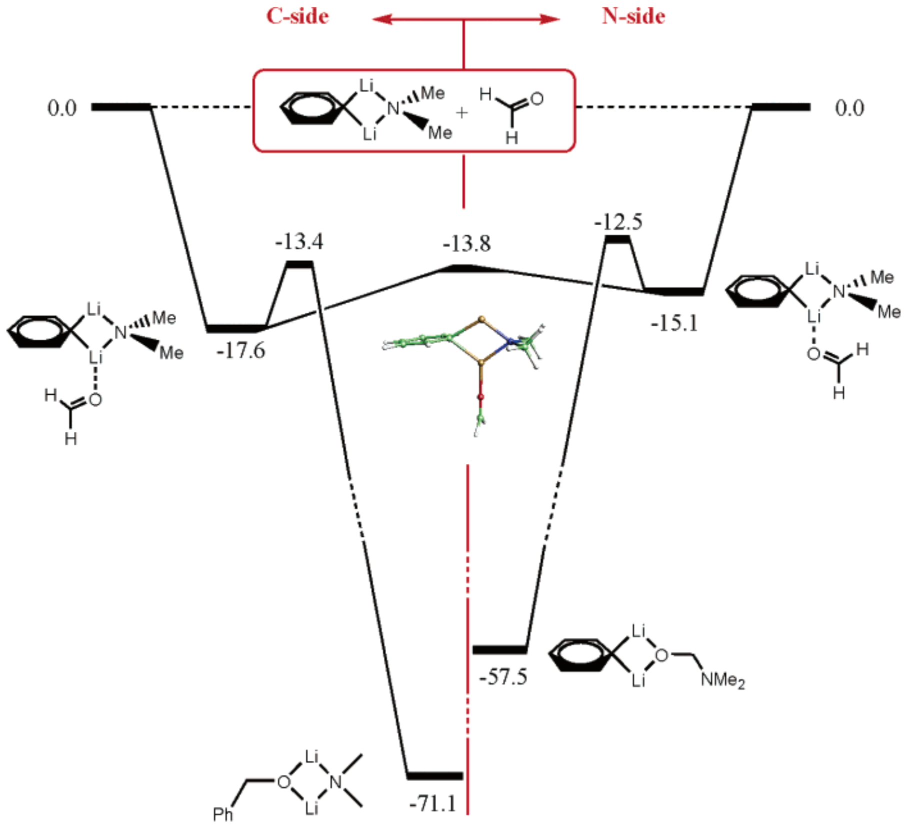


FIGURE 17. Two possible routes for the reaction between the heterogeneous dimer phenyllithium/lithium dimethylamide and formaldehyde. The transition state for the C-to-N side swap of the aldehyde is depicted halfway.

terizing the MeLi$-$NMe$_2$Li mixed aggregate (entry 13) are significantly smaller than those in entries 10$-$12, in violation of the Bürgi-Dunitz trajectory.

The ELF electronic distribution is represented here only for the PhLi$-$NMe$_2$Li aggregate at the TS of the addition. The basins corresponding to the carbonyl oxygen as well as those between the phenyl on one side and the nitrogen on the other, and the two lithiums appear clearly. They show that the mainly ionic characters of these bonds and their electronic distribution at the TS does not seem to be affected with respect to the ground states (see for instance the ELF representation of MeLi$-$Me$_2$NLi aggregate in ref 15).

We have also considered the possibility of a swap of the aldehyde from the carbon to the nitrogen side, a point of importance since it can condition the reactivity of the mixed aggregate. The aldehyde can indeed rotate from one side to the other before the condensation occurs (Figure 17). In this case, the transition state and the activation barrier associated to this rearrangement have to be determined to get a full picture of the reaction pathways.

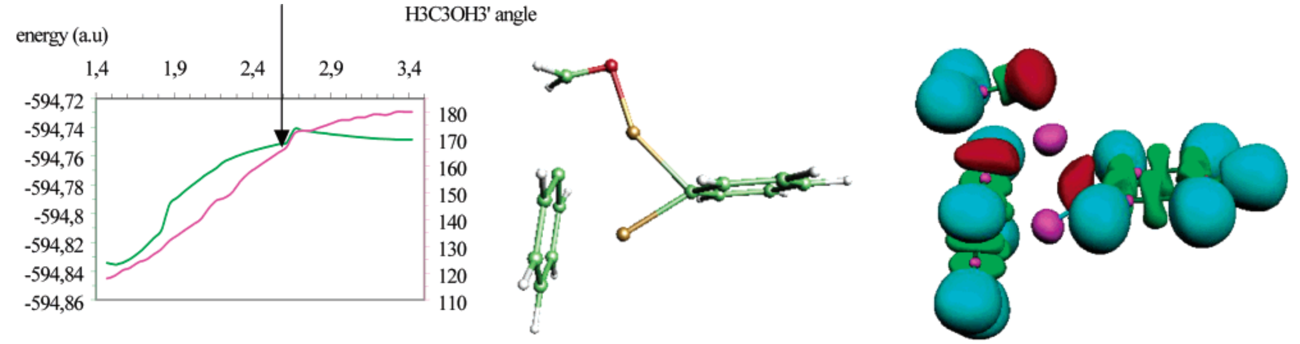


FIGURE 18. Arrangement of the $(PhLi)_2$−HCHO complex soon after the transition state: jobplot of the total energy and the $H^{3'}C^3OH^3$ dihedral vs C^1−C^3 distance (left, the black arrow shows the point considered after the TS), its geometrical arrangement (middle), and ELF representation (right).

The results show that for the sp^2 organolithium reagent considered here, (i) the *C*-side complex is thermodynamically more stable than the *N*-side one, (ii) the activation barrier is smaller on the *N*-side (2.6 vs. 4.2 kcal·mol^{-1}), and (iii) the N-to-C swap energy barrier is lower than the reaction barrier (1.3 kcal·mol^{-1} vs 2.6 kcal·mol^{-1} to form the α-amino alcoholate). Therefore, while our previous mixed aggregate model MeLi−Me_2NLi favored the reaction on the *N*-side on both thermodynamic and kinetic grounds, the PhLi − Me_2NLi system rather tends to support the *C*-side docking, i.e., the formation of a new C−C bond. Finally, the condensation energies are of the same order of magnitude with the MeLi and PhLi aggregates.

These observations are of interest for the applications of mixed aggregates in asymmetric synthesis. They suggest that the competition between the aryllithium and the amide condensations should not be as severe as it was expected[6] (and observed[39]) in the case of alkyllithium−chiral lithium amides aggregates. Therefore, testing simpler and less bulky chiral auxiliaries could remain meaningful in the asymmetric nucleophilic arylation of aldehydes.

Conclusion

This work focuses on the interaction of unsolvated monomers, homogeneous and heterogeneous (with $LiNMe_2$) dimers of three sp^2 organolithium compounds with formaldehyde. In all cases, the separate entities, as well as their Li−O docking complexes, their transition state and the condensation products have been characterized and compared to the corresponding situtations involving methyllithium. Regarding the monomeric form of the nucleophiles, this study shows that the HCHO−RLi complex formed adopts a relatively uniform arrangement probably driven by a H-π favorable interaction, except if an intramolecular chelation takes place (as in 2-methoxyvinyllithium). A small energy barrier (≤2.1 kcal·mol^{-1}), corresponding to the rotation of the aldehyde around the C−O axis, leads to the transition state. At the TS, the interaction between HCHO and the monomeric vinyllithium is mainly σ, while that of 2-methoxyvinyllithium and of phenyllithium are rather of the π type.

The homogeneous dimers lead to complexes with HCHO relatively similar to those formed with the corresponding monomers, except for the α angle values which tend to increase in the dimers. Noteworthy is the case of 2-methoxyvinyllithium, which is coplanar to formaldehyde when monomeric, while its dimer stands perpendicular to the HCHO plane. At the transition state, the dimers behave somewhat similarly and tend to exhibit a π character, particularly pronounced in the case of phenyllithium.

In the case of the heterogeneous dimers, the aldehyde can orientate either toward the carbon or toward the nitrogen. In both cases, the complexes resulting from the HCHO docking present characteristics close to that calculated in the homogeneous dimer complexes. These similitudes are conserved at the transition state.

We think interesting to discuss the characteristics of the reaction course right after the TS with respect to the ideal Burgï-Dunitz trajectory. First, in all the computed TS we obtain, the C^1C^3O angle is always <109° (85−89° in the monomers, 91−100° in the dimers). Orbital and structural reasons can explain this result. First, it is known that for hard nucleophiles (nucleophiles with low lying HOMO's), this angle approaches 90°.[40] Second, while neutral nucleophiles such as water[41] or isolated anions[42] tend to follow nicely the Burgï-Dunitz rule, polar organometallic compounds introduce a Lewis acid cation in interaction with the oxygen of the carbonyl. The trajectories thus probably result from a compromise between the two tendencies.[43]

Comparing the ELF analysis of the docking complexes to that of the corresponding TS shows that the electronic distributions are almost similar in these two situations. This observation, which may seem paradoxical at first sight, can be understood in light of the nature of the transition states considered here which are all reactant like. The TS are all reached by a synchronized rotation of the formaldehyde around its C−O axis associated to a slight shortening of the C^1−C^3 bond. These movements, which concern the aldehyde only, put the two reacting

---

[39] Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *Tetrahedron: Asymm.* **1997**, *8*, 1519−1523.

[40] Liotta, C. L.; Burgess, E. M.; Eberhardt, H. *J. Am. Chem. Soc.* **1984**, *106*, 4849−4852.

[41] Williams, I. H.; Spangler, D.; Femec, D. A.; Maggiora, G. M.; Schowen, R. L. *J. Am. Chem. Soc.* **1983**, *105*, 31−40.

[42] Eisenstein, O.; Schlegel, H. B.; Kayser, M. M. *J. Org. Chem.* **1982**, *47*, 2886−2891.

[43] Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 4635−4643.

entities in a favorable conformation before the reaction starts. It is only beyond the TS that the electron reorganization, and thus the actual bond creation, takes place. We examined, in the case of the phenyllithium dimer, the arrangement of the reaction partners by checking a PES point soon after the TS. Figure 18 provides a snapshot of the C^1-C^3 bond formation on its way (≈0.2 Å beyond the C^1-C^3 distance at the TS, shown by the arrow on the reaction profile curve): the incoming phenyl has left its original position and the nucleophilic carbon now points toward the carbon of the carbonyl, following a pure σ attack. At this point, the pyramidalization of the formaldehyde central carbon is perceptible ($H^{3'}C^3OH^3 = 167°$). The ELF analysis shows that 2.12 electrons are located in the C=O disynaptic basin (vs 2.23e at the TS), while the population of the monosynaptic (orange) basins on the oxygen increase from 2.65 and 2.70 e at the TS to 2.76 and 2.77 e. Note also that in the resulting L-shaped arrangement of the two phenyl, the Li^2 lies just above the Ph^1 nucleus.

Note that the H^3C^3OLi values, a geometrical parameter looking at first intimately related to the reaction timing, varies a lot despite the general earliness of these condensations (hinted by the absence of pyramidalization of the formaldehyde, as well as by the hybridization and polarity of its CO bond). This discrepancy is probably related to the contradictory tendancies of the lithium cation to act as a Lewis acid on one hand and to the nucleophilic attack to take place at right angles to the π-system, as underlined above. Finally, the effect of solvents such as diethyl ether or THF, which has been neglected in this work, will be detailed in a forthcoming publication.

Acknowledgment. Computations have been carried out at the Centre de Ressources Informatiques de Haute-Normandie (CRIHAN, St Etienne-du-Rouvray) and at the Centre de Calcul pour la Recherche (CCR, University Paris 6). We warmly thank Dr Claude Giessner-Prettre for stimulating discussions all along this work and Dr Hilaire Chevreau (LCT, University Paris 6) for calculating the α angles.

JO050524N