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Are sp Lithiated Carbons More Nucleophilic than sp^2 or sp^3 Ones? A Comparative DFT Study of the Condensation of Propynyllithium Aggregates on Formaldehyde

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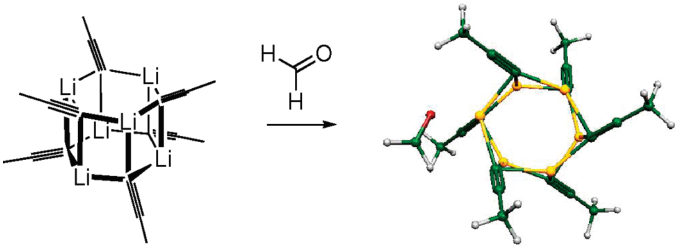
Received October 29, 2009



The interaction between 1-propynyllithium, taken as a model of sp organolithium compound, and formaldehyde has been investigated with DFT theoretical methods. The unsolvated monomer, homogeneous dimer, trimer, tetramer, and hexamer have been considered, as well as the mixed aggregates with lithium dimethylamide in various oligomeric forms. In most cases, the separate entities, their docking complexes, the transition states, and the condensation products have been characterized. Overall, the general reaction scheme remains the same whatever the hybridization and the aggregation. However, the dimeric sp nucleophiles are expected to be more reactive (at least in kinetic conditions), while monomeric sp^3 entities would be the best nucleophiles in kinetic and thermodynamic conditions, even if its docking is the least exothermic. This work also suggests that the aggregation plays a relatively limited role on the model reaction.

Introduction

Alkynyllithiums are useful reagents generally obtained by deprotonation of terminal acetylenes by alkyllithiums or lithium amides.[1] These nucleophilic entities have been known for a long time to react with electrophiles and give the corresponding substituted alkynes. In particular, ketones and aldehydes are good substrates that provide propargylic alcohols in a simple manner.[2] Interestingly, if the mechanism of reactions involving acetylide derivatives of transition metals such as nickel,[3] palladium,[4] indium,[5] or silver[6] has been the object of attention, the condensation of lithium acetylides has been investigated only in one case to our knowledge, but in great detail. Collum and co-workers have indeed published a series of papers about the structure and mechanism of a condensation reaction of a lithium acetylide

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(1) See for instance: Talalaeva, T. V.; Timofeynk, G. V.; Rodionov, A. N.; Ya., K. L. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1965**, 1607–1613.

(2) Among interesting exemples, see: (a) Serrat, X.; Cabarrocas, G.; Rafel, S.; Ventura, M.; Linden, A.; Villalgordo, J. M. *Tetrahedron: Asymmetry* **1999**, *10*, 3417–3430. (b) Wu, G. G.; Huang, M. *Top. Organomet. Chem.* **2004**, *6*, 1–35. (c) Murai, T.; Toshio, R.; Mutoh, Y. *Tetrahedron* **2006**, *62*, 6312–6320. (d) Bo, Q.; Collum, D. B. *J. Org. Chem.* **2006**, *71*, 7117–7119.

(3) Smith, E. H.; Whittall, J. *Organometallics* **1994**, *13*, 5169–5172.

(4) For a recent review, see: (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922. See also: (b) Hongmei, S.; Xinan, P.; Mansheng, C.; Qi, S. *Catal. Lett.* **2003**, *90*, 85–89. (c) Zhan, X.; Yang, M. *J. Mol. Catal. A: Chem.* **2001**, *169*, 57–62. (d) Li, Y.; Yang, M. *J. Mol. Catal. A: Chem.* **2002**, *184*, 161–165.

(5) For a recent review, see: (a) Augé, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739–1764. See also: (b) Harada, S.; Takita, R.; Ohshima, T.; Matsunaga, S.; Shibasaki, M. *Chem. Commun.* **2007**, 948–950.

(6) For recent reviews see: (a) Halbes-Letinois, U.; Weibel, J.-M.; Pale, P. *Chem. Soc. Rev.* **2007**, *36*, 759–769. (b) Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3199–3222.

DOI: 10.1021/jo902315t

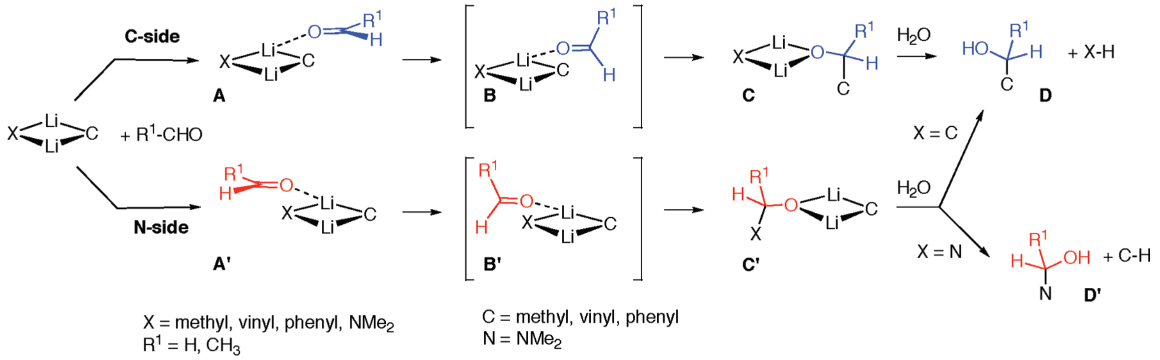

FIGURE 1. Elementary steps in the model reaction between aldehydes and homogeneous or heterogeneous dimeric sp^3 (methyl) and sp^2 (vinyl, phenyl) organolithium aggregates.

in a chiral environment. The accurate NMR data obtained allowed these authors to propose a convincing structure for the intermediates and to deduce a mechanism of induction.[7]

The work described in this paper aims at evaluating the effect of the hybridization of the lithiated carbon on the geometrical and energetic characteristics of the condensation reaction involving monomeric or dimeric RLi's. If the relative acidity of the protons borne on sp, sp^2, and sp^3 hydrocarbons is well-known (sp $>$ sp^2 $>$ sp^3), the nucleophilicity of the corresponding carbanions is not so obvious. We have previously examined by DFT theoretical means the details of the reaction between sp^3 (methyllithium)[8] and sp^2 (vinyllithium and phenyllithium)[9] organolithium derivatives and simple aldehydes such as formaldehyde or acetaldehyde. We now wish to disclose a comparable gas phase study conducted on propynyllithium, taken as a simple prototype of lithium acetylides, and formaldehyde. Because the aggregation is known to play a critical role in organolithium chemistry,[10] we also took this parameter into account and extended the computations to the propynyllithium aggregates, from trimers to hexamers.

The data obtained before with sp^3 and sp^2 derivatives led us to conclude that, in both cases, the aldehyde docks on a lithium along the direction of one of the carbonyl oxygen lone pairs, as expected from previous theoretical works[11] or crystallographic data[12] (Figure 1). A stable complex **A** was thus obtained in which the aldehyde and the organometallic core are coplanar, in line with X-ray data obtained in a similar situation.[13] The reaction could then proceed through a transition state **B**, reached upon a simple rotation of the aldehyde along its C=O axis and out of this plane. The mixed aggregate **C**, which includes the product and the remaining half of the starting dimer, was obtained after passing through an open-dimer transition state,[14] which affords the expected alcohol **D** upon hydrolysis. In our previous works, we also examined the heterogeneous dimers made of one alkyl- or alkenyllithium and one lithium dimethylamide, taken as the simplest prototype of lithium amides. Chiral lithium amide can indeed be involved in mixed aggregates that become useful auxiliaries in asymmetric synthesis.[15] In these cases, two types of additions had to be envisaged since the carbonyl can be oriented toward either the nucleophilic carbon or nitrogen. The latter reaction goes through comparable intermediate complexes **A′**, **B′**, and **C′** and provides a (generally unstable) lithium α-amino alcohol **D′**.[16]

The aggregation of lithium acetylides has been characterized experimentally, both in the solid state[17] and in solution.[18] Since the aggregation level is known to depend on the conditions, and in particular on the solvent and the temperature,[19] we have considered in the following the monomer, dimer, trimer, tetramer, and hexamer of propynyllithium (Scheme 1). The sole electrophile taken into acount here was

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(7) (a) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028–2038. (b) Xu, F.; Reamer, R. A.; Tillyer, R.; Cummins, J. M.; Grabowski, E. J. J.; Reider, P. J.; Collum, D. B.; Huffman, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 11212–11218. (c) Sun, X.; Winemiller, M. D.; Xiang, B.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 8039–8046. (d) Briggs, T. F.; Winemiller, M. D.; Xiang, B.; Collum, D. B. *J. Org. Chem.* **2001**, *66*, 6291–6298. (e) Parsons, R. L. Jr.; Fortunak, J. M.; Dorow, R. L.; Harris, G. D.; Kauffman, G. S.; Nugent, W. A.; Winemiller, M. D.; Briggs, T. F.; Xiang, B.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 9135–9143. (f) Briggs, T. F.; Winemiller, M. D.; Collum, D. B.; Parsons, R. L. Jr.; Davulcu, A. H.; Harris, G. D.; Fortunak, J. M.; Confalone, P. N. *J. Am. Chem. Soc.* **2004**, *126*, 5427–5435.

(8) (a) Fressigné, C.; Maddaluno, J.; Marquez, A.; Giessner-Prettre, C. *J. Org. Chem.* **2000**, *65*, 8899–8907. (b) Corruble, A.; Davoust, D.; Desjardins, S.; Fressigné, C.; Giessner-Prettre, C.; Harrison-Marchand, A.; Houte, H.; Lasne, M.-C.; Maddaluno, J.; Oulyadi, H.; Valnot, J.-Y. *J. Am. Chem. Soc.* **2002**, *124*, 15267–15279.

(9) Fressigné, C.; Lautrette, A.; Maddaluno, J. *J. Org. Chem.* **2005**, *70*, 7816–7828.

(10) See for instance: Clayden, J. *Organolithium: selectivity for synthesis*; Pergamon: Amsterdam, The Netherlands, 2002.

(11) Leading references: (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**, *26*, 1079–1080.

(12) Amstutz, R.; Dunitz, J. D.; Laube, T.; Schweizer, W. B.; Seebach, D. *Chem. Ber* **1986**, *119*, 434–443. For a general reference see: Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353–451.

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

(14) See for instance ref 11d.

(15) (a) Goldfuss, B. *Synthesis* **2005**, 2271. (b) Luderer, M. R.; Bailey, W. F.; Luderer, M. R.; Fair, J. D.; Dancer, R. J.; Bech Sommer, M. *Tetrahedron: Asymmetry* **2009**, *20*, 981–998.

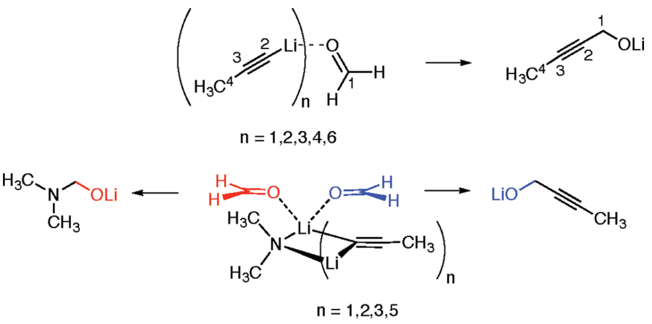
(16) (a) Zhao, P.; Condo, A.; Keresztes, I.; Collum, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 3113–3118. For applications of α-amino-alcoholates in synthesis, see: (b) Comins, D. L. *Synlett* **1992**, 615–625. (c) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271–1289.

(17) For a recent exemple on lithiated dimers, see: Clegg, W.; Garcia-Alvarez, J.; Gracia-Alvarez, P.; Graham, D. V.; Harrington, R. W.; Hevia, E.; Kennedy, A. R.; Mulvey, R. E.; Russo, L. *Organometallics* **2008**, *27*, 2654–2663.

(18) A remarkably accurate observation on the parallel evolution of mixed and homogeneous acetylide aggregates in THF/Me$_2$O has been reported lately: Jones, A. C.; Sanders, A. W.; Bevan, M. J.; Reich, H. J. *J. Am. Chem. Soc.* **2007**, *129*, 3492–3493.

(19) Gregory, K.; Schleyer, P. v. R.; Snaith, R. *Adv. Inorg. Chem.* **1991**, *37*, 47–142.

SCHEME 1



formaldehyde. Despite the known effect played by coordinating solvents such as diethyl ether or THF on the reactivity of organolithium species,[20] we have worked with unsolvated models for at least two reasons: (i) our previous studies were focused on unsolvated species and comparing the hybridization effect on the general mechanism of condensation required comparable species to be taken into account; (ii) the solvation of high oligomers such as hexamers would require excessive computational efforts.

Computational Details

For consistency with our previous papers, we performed all optimizations with the 6-31G** basis set[21] and the B3P86 hybrid functional.[22] The validity of this methodology has been checked in one case (the monomeric propynillithium−formaldehyde system) by rerunning the optimization first at the MP2 then at the CCSD(T)[23] levels, using the same basis set. The results, presented in Table S1 of the Supporting Information (entries 4 and 5), suggest that the activation barriers remain low but are underestimated by the DFT (going from +2.3 kcal·mol^{-1} at the DFT level to +4.2 kcal·mol^{-1} at the MP2 and +4.6 kcal·mol^{-1} at the CCSD(T) ones), as generally reported in literature.[24] Note that this TS energy shift is expected to be systematic and therefore supposed to have little influence on the qualitative ranking of the nucleophiles. In addition, the time-consuming character of the post-Hartree−Fock methods prevents their application to large systems such as those considered in this work. Finally, we kept the DFT approach, previously selected for the sp^3 and sp^2 nucleophiles, to carry out this study on the sp ones.

The low activation energies expected in this type of 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. This assumption was made on the basis of previous results on the sp^3 nucleophile which showed that these corrections are of little importance, with respect to the neglected solvation effect, since they are, once again, not expected to modify the relative order of the complex stabilities nor that of the activation barriers. Nevertheless, the ZPE contribution has been calculated for the monomeric propynillithium−formaldehyde system. It was found to affect mainly the exothermicity of the reaction (see Table S1, Supporting Information, entry 2), but in proportions that do not alter the conclusions of this study. The thermal corrections were also evaluated on this example and led to similar conclusions (entry 3).

All computations have been carried out with use of Jaguar 4.1.[25] The complexation energy values given below have been calculated by finding 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. Similarly, the condensation energies have been taken as the difference between the energy of the final product and that of the TS.

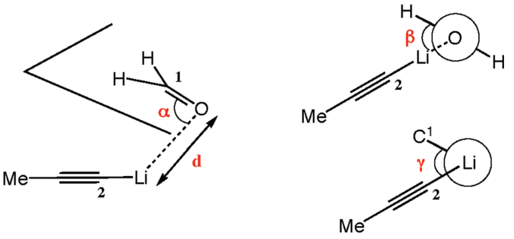
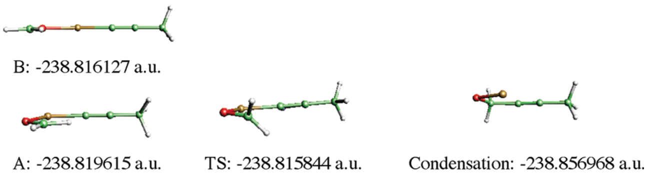


FIGURE 2. Representation of angles α (C^{1}OLi), *β* (HC^{1}OLi), and *γ* (C^{1}OLiC^2), and distance *d*(O−Li).


B: -238.816127 a.u.

A: -238.819615 a.u.

TS: -238.815844 a.u. (+2.3 kcal.mol^{-1})

Condensation: -238.856968 a.u. (-25.8 kcal.mol^{-1})

FIGURE 3. The *syn* (A) and *anti* (B) arrangements of formaldehyde docked on 1-propynyllithium (left), transition state (middle), and condensation product (right).

Results and Discussion

In view of the large number of different aggregates considered in this work, we have chosen to detail the cases of the monomer and homogeneous and heterogeneous dimers. For the sake of space saving, the case of the higher aggregates (homogeneous and mixed trimers, tetramers, hexamers), which can be described in a somewhat similar fashion, will be disclosed more rapidly. To characterize the interactions between the aldehyde and the aggregate, we use in the following three angles α (C^{1}OLi), *β* (HC^{1}OLi), *γ* (C^{1}OLiC^2), and distance *d*(O−Li) displayed in Figure 2.

Study of Monomeric Propynyllithium. The full optimization of the complex formed between 1-propynyllithium and formaldehyde leads to two planar arrangements (A and B, Figure 3). In both situations, the oxygen of the carbonyl interacts with the lithium along one of its lone pairs, the aldehyde being oriented either "syn" (*γ* = 0°) or

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[20] See for instance: (a) Reich, H. J.; Kulicke, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 273–274. (b) Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567–5572. (c) Qu, B.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 9355–9360.

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

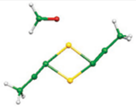
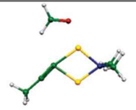
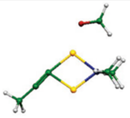
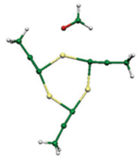
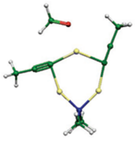
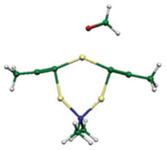
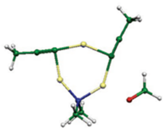
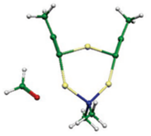
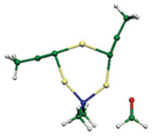
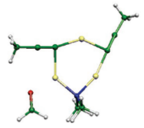
[22] (a) Perdew, J. P. *Phys. Rev.* **1986**, *B33*, 8822–8824. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.

[23] A full optimization was run at the MP2 level, while single point energies on the MP2 geometries were computed at the CCSD(T) level.

[24] See for instance: (a) Fan, L.; Ziegler, T. *J. Am. Chem. Soc.* **1992**, *114*, 10890–10897. (b) Stanton, R. V.; Merz, K. M. Jr. *J. Chem. Phys.* **1994**, *100*, 434–443. (c) Lynch, B. J.; Truhlar, D. G. *J. Phys. Chem. A* **2001**, *105*, 2936–2941. (d) Kang, J. K.; Musgrave, C. B. *J. Chem. Phys.* **2001**, *115*, 11040–11051.

[25] Schrödinger Inc. Portland, OR, 2000.

TABLE 1. **Main Geometrical Parameters Describing the Monomeric, Dimeric, and Trimeric Complexes [(Me—C≡C—Li)$_n$(Me$_2$NLi)$_m$]−HCHO at the Steady and the Transition States**[b]

Entry			Steady state					Transition state			
	n	m		α	β	γ	d	α	β	γ	d
1	1	0		109.5	0.2	0.1	1.95	103.0	47.5	8.8	1.92
2	2	0		115.3	0.7	1.1	2.00	104.2	58.1	13.9	1.99
3	1	1		115.1	0.1	0.6	2.00	104.6	59.1	11.9	1.99
4	1	1		112.8	0.3	1.8[a]	1.99	101.5	52.8	5.6[a]	1.97
5	3	0		120.6	0.1	0.2	2.02	99.1	94.4	1.3	1.99
6	2	1		119.4	2.1	9.4	2.03	99.2	96.1	2.9	1.99
7	2	1		119.6	0.5	2.8	2.01	106.3	66.9	9.9	2.02
8	2	1		119.6	0.4	2.0	2.02	100.1	94.8	1.7	2.00
9	2	1		119.7	0.0	1.3	2.02	100.6	99.1	5.3	2.00
10	2	1		119.5	0.1	16.2[a]	2.01	99.9	55.4	11.6[a]	2.01
11	2	1		115.7	1.4	12.4[a]	2.03	101.0	57.8	8.1[a]	2.03

[a] For the docking on the *N*-side, the angle γ is the dihedral C^{1}OLiN instead of C^{1}OLiC^2. [b] The angles α, β, and γ (deg) and the distance d (Å) are defined on Figure 2.

"anti" (γ = 180°) to the triple bond. Conformer A, which keeps the nucleophilic and electrophilic carbons within a reasonable distance (and is thus likely to yield the expected condensation product), is favored by 2.2 kcal·mol^{-1}. A H−π stabilizing interaction between H^1 and the triple bond probably contributes to this slight preference (Figure 3A, d(H^1−C^2) = 2.41 Å). Note that the OLiC^2 angle increases continuously when going from the sp to the sp^2 and the sp^3

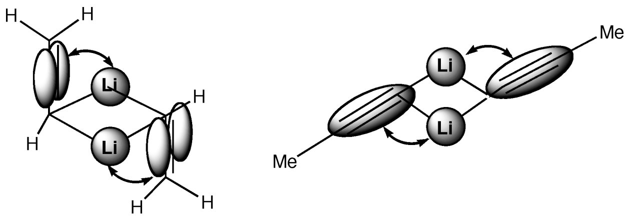


FIGURE 4. Schematic interaction between electron clouds and lithium cations in vinyllithium (left) and in the C_2 conformer of 1-propynyllithium (right) dimers.

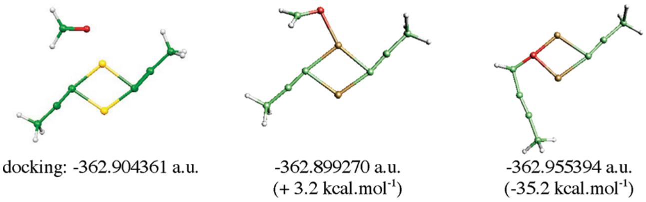


FIGURE 5. Interaction between propynyllithium dimer and formaldehyde: docking (left), transition state (middle), and condensation (right).

cases (113.2°, 118.5°, and 121.7°, respectively), probably following an enhancement of the steric repulsions.

The interaction energy between formaldehyde and propynyllithium in A was found to be -21.5 kcal$\cdot$mol^{-1} (to be compared to -20.9 kcal$\cdot$mol^{-1} for the vinyllithium−formaldehyde couple and -18.4 kcal$\cdot$mol^{-1} for the methyllithium−formaldehyde one). The O−Li complexation takes place as in the sp^3 and sp^2 cases, within the plane of the aldehyde (β = 0.2°, Figure 3) and more or less along the oxygen lone pair direction (α = 109.5°, d = 1.95 Å). Other geometrical characteristics of this complex are given in Table 1 and discussed in relation with higher aggregates.

Going from this metastable arrangement to the transition state (TS) corresponds, as for the otherwise hybridized nucleophiles, to a rotation of the aldehyde around its C=O axis (β = 47.5°, Figure 3, middle). The associated activation barrier is low at our computational level (2.3 kcal$\cdot$mol^{-1}) but slightly higher than that for the sp^2 and sp^3 situations (1.7 and 0.9 kcal$\cdot$mol^{-1}, respectively). The little steric impairment associated to the linear acetylide probably explains that the γ angle at the TS is small (8.8°). Also at the transition state, the OLiC^2 angle varies from 108.7° to 107.9° and 122.5° when going from the sp to the sp^2 and the sp^3 cases, probably resulting from a compromise between the angle change and the steric interactions arising at the early stage of the C−C bond formation. The limited rotation undergone by the aldehyde (β = 47.5° with respect to 0.3 in the initial complex) and the long C^1−C^2 distance (2.9 vs. 3.2 Å) suggest that this TS is early, as in the sp^2 and sp^3 cases.

The exothermic passage from the TS to the condensation product (-25.8 kcal$\cdot$mol^{-1}) corresponds to the creation of the C(sp)−C(sp^3) bond. This energy is significantly lower than the corresponding ones for the C(sp^2)−C(sp^3) and C(sp^3)−C(sp^3) bonding (-43.4 and -46.1 kcal$\cdot$mol^{-1} respectively). The geometry of the product exhibits the expected Li−CC triple bond interaction (Figure 3, right).

The consistency of these energy figures at all the stages of the reaction path has been checked at a higher computational level (see the Computational Details, as well as Table S2 in the Supporting Information).

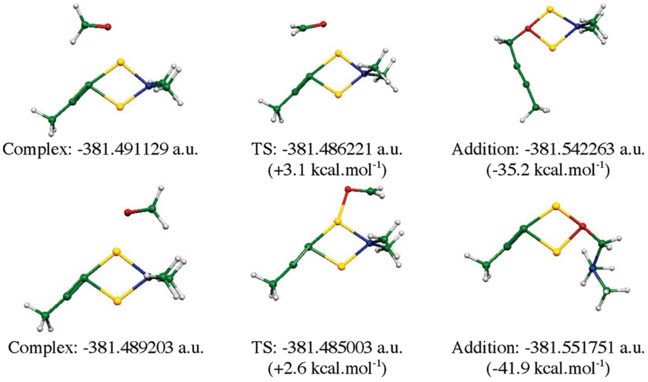


FIGURE 6. Interaction between the propynylithium/dimethyllithium amide heterogeneous dimer and formaldehyde: docking (left), transition state (middle), and condensation (right). Top: On the carbon side. Bottom: On the nitrogen side.

Study of the Homogeneous and Heterogeneous Dimers of Propynyllithium. We next moved to the study of the homogeneous propynyllithium dimer. Starting from different geometries, only two local minima C_2 and C_{2v} were found for this species, and in both the C^{4}C^{3}C^{2}Li atoms tend to remain aligned (C^{3}C^{2}Li = 169.2°). They are almost isoenergetic ($\delta E \leq 0.6$ kcal$\cdot$mol^{-1}, see the Supporting Information, Figure S1), but only the C_2 has been considered in the following since the interaction of these dimers with formaldehyde triggers important conformational changes.

Note that this topology is dramatically different from the one computed for the vinyllithium dimer since, in this latter, the vinyl planes stand perpendicular to the C−Li−C−Li lozenge. However, both theory[26] and X-ray data[17] support the C^{4}C^{3}C^{2}Li quasialignment. We checked this point by repeating the same calculation using the Gaussian98 program[27] and obtained a result very comparable to the Jaguar one. The difference between alkynyl- and vinyllithium is thus probably due to the cylindrical symmetry of the electronic distribution in the CC triple bonds that allows an efficient interaction with the lithium cations, even in a globally planar arrangement (Figure 4).

The comparison between the methyllithium, vinyllithium, and propynyllithium homogeneous dimers shows that if the C−Li−C−Li quadrilateral core remains planar in the three cases (the dihedral angle CLiCLi varying between 0.01° and 0.2°), the C−C distance diminishes when going from the sp^3 (3.6 Å) to the sp^2 (3.5 Å) or the sp (3.3 Å) case, while the Li−Li distance increases (2.17 Å for sp^3, 2.35 Å for sp^2, and 2.47 Å for sp). Thus, the lozenge arrangement tends toward a square when going from sp^3 to sp components.

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(26) Goldfuss, B.; Schleyer, P. v. R.; Hampel, F. *J. Am. Chem. Soc.* **1997**, *119*, 1072–1080.

(27) 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.

TABLE 2. **Selected Energy and Geometry Parameters of Monomers and Homogeneous Dimers of Propynyllithium (sp), Vinyllithium (sp^2), Methyllithium (sp^3), Plus Heterogeneous Dimers (1:1) with Lithium Dimethylamide, in Interaction with Formaldehyde**

parameter	monomer	homo dimer	hetero dimer C[a]	hetero dimer N[b]
interaction energy	$sp > sp^2 > sp^3$	$sp > sp^2 > sp^3$	$sp > sp^2 > sp^3$	$sp > sp^2 > sp^3$
activation barrier	$sp > sp^2 > sp^3$	$sp^3 > sp^2 \approx sp$	$sp^3 > sp^2 \approx sp$	$sp \approx sp^2 > sp^3$
condensation energy	$sp < sp^2 < sp^3$	$sp < sp^2 < sp^3$	$sp < sp^2 < sp^3$	$sp \approx sp^2 \approx sp^3$
$C^2{-}X$ ($X = C^{2'}$ or N)[c]		$sp < sp^2 < sp^3$	$sp < sp^2 < sp^3$	$sp < sp^2 < sp^3$
Li−Li		$sp > sp^2 > sp^3$	$sp > sp^2 > sp^3$	$sp > sp^2 > sp^3$
O−Li−X ($X = C^{2'}$ or N)[c]	$sp < sp^2 < sp^3$	$sp \approx sp^2 \approx sp^3$	$sp \approx sp^2 \approx sp^3$	$sp \approx sp^2 \approx sp^3$

[a] Docking of formaldehyde on the carbon side of the heterogeneous dimer. [b] Docking of formaldehyde on the nitrogen side of the heterogeneous dimer. [c] X = N or C of the homogeneous or heterogeneous dimer, respectively, in the docking complex.

The approach and docking of formaldehyde on the sp dimer occurs exactly like on the monomer, the in-plane docking/out-of-the-plane rotation/condensation sequence being very similar (Figure 5 and Table 1). These events are also similar to those computed for the sp^2 and sp^3 dimers, but the quadrilateral arrangement of the methyllithium dimer undergoes a relatively important deformation at the TS (related to the Walden inversion of the sp^3 carbon during the condensation process)[28] while the sp and sp^2 ones are almost unaltered.

Energywise, the barrier associated to this early TS is +3.2 kcal·mol^{-1}, a value similar to that computed for the vinyllithium dimer (+3.3 kcal·mol^{-1}) and slightly inferior to that of the methyllithium dimer (+5.1 kcal·mol^{-1}). The C−C bond formation is exothermic but by only −35.2 kcal·mol^{-1}. As for the monomer, this figure is noticeably lower than the −62.0 and −58.1 kcal·mol^{-1} associated to the sp^3 and sp^2 dimers, respectively.

The next part of this study was focused on the mixed dimer of propynyllithium and lithium dimethylamide. The structure of the dimer alone was fully optimized and led to the expected arrangement. The docking of H_2CO was then performed on the propynyl and on the amide side. The results are in line with those described above: the geometry of the complexes at various stages of the reaction is very similar to that obtained for the homogeneous dimer (Figure 6). The main geometrical characteristics of the homogeneous and heterogeneous dimer-based complexes are presented in Table 1, where they are also compared to those of the monomer and trimers.

Energywise, overcoming the TS barrier costs +3.1 kcal·mol^{-1} on the carbon side (+4.6 and +3.2 kcal·mol^{-1} for the sp^3 and sp^2 heterodimers, respectively) and +2.6 kcal·mol^{-1} on the nitrogen one (+1.9 and +2.5 kcal·mol^{-1} for the sp^3 and sp^2 dimers, respectively). The exothermicity of the condensation on the carbon side (−35.2 kcal·mol^{-1}) is unchanged (with respect to the homogeneous dimer: compare Figures 5 and 6) and remains inferior to that of the sp^3 (−62.1 kcal·mol^{-1}) and sp^2 (−57.8 kcal·mol^{-1}) dimers. Expectedly, the condensation energies on the nitrogen side are comparable for the three types of carbon hybridization (sp^3: −39.2 kcal·mol^{-1}; sp^2: −41.8 kcal·mol^{-1}; sp: −41.9 kcal·mol^{-1}). These figures indicate that the condensation of the nucleophilic nitrogen, which provides an α-aminoalkoxide, is favored both kinetically and thermodynamically over the condensation of the sp carbon (which furnishes a propargylic alkoxide), in contrast with the kinetically disfavored but thermodynamically favored C−C bond formation computed for the methyllithium and vinyllithium heterogeneous dimers. This finding is of practical interest since it suggests that mixed dimers of propynyllithium and small lithium amide would probably afford mediocre chemical results[29] if they were to be employed as catalysts in the propynylation of formaldehyde.[30]

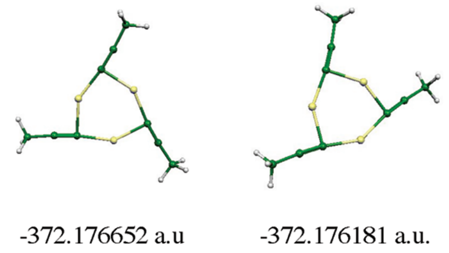

FIGURE 7. Two optimized conformers of propynyllithium homogeneous trimer: C_3 (left) and C_1 (right).

Since our previous studies on sp^3 and sp^2 nucleophiles were limited to monomers and dimers, the description of the influence of the hybridization on the reactivity cannot be extended to the trimers and higher levels of aggregation. We can thus conclude, at this stage, on the hybridization effects. First, comparing the data in Table 1 to those of Table 1S in the Supporting Information suggests that there is no regular variation of the geometry of the condensation process with the hybridization of the nucleophile. However, the data point the finger at the relative flexibility of the C−Li−C−Li core that, in some cases (entries 3 and 7 of Table 1S, Supporting Information), bows to get the nucleophile and the electrophile close enough to reach the TS. Thus, the electrophile is not necessarily the more mobile partner during this reaction sequence.

To extend the comparison, we have gathered some important characteristics concerning the energy and geometry of the three families (sp, sp^2, sp^3) of complexes in Table 2 below. These data lead to the following supplementary conclusions: If the monomer is the reacting entity, the sp nucleophile gives a docking complex more stable than the sp^2 or sp^3 reagents but its reaction is disfavored both kinetically (highest activation barrier) and thermodynamically (lowest condensation energy). If the homogeneous or the heterogeneous (*C*-side) dimers are the reacting species,

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[28] Fressigné, C.; Lecachey, B.; Maddaluno, J., in preparation. The spontaneous inversion of isolated alkyllithiums has been known for a long time: Clark, T.; Schleyer, P. v. R.; Pople, J. A. *J. Chem. Soc., Chem. Commun.* **1978**, 137−138.

[29] Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1519–1523.

[30] Harrison-Marchand, A.; Valnot, J.-Y.; Corruble, A.; Duguet, N.; Oulyadi, H.; Desjardins, S.; Fressigné, C.; Maddaluno, J. *Pure Appl. Chem.* **2006**, *78*, 321–331.

TABLE 3. Energy of Interaction between Complexes [(Me—C≡C—Li)$_n$(Me$_2$NLi)$_m$] and HCHO before, during, and after the Condensation Reaction (kcal·mol^{-1})[a]

entry	system	docking	activation	condensation
1	monomer	−21.5	+2.3	−25.8
2	homo dimer	−16.2	+3.2	−35.2
3	hetero dimer C	−16.0	+3.1	−35.2
4	hetero dimer N	−14.8	+2.6	−41.9
5	homo trimer	−13.1	+2.8	−38.9
6	hetero trimer C	−13.3	+3.0	−38.5
7	hetero trimer C	−13.0	+3.4	−39.2
8	hetero trimer C	−12.8	+3.0	−39.2
9	hetero trimer C	−12.2	+2.9	−39.2
10	hetero trimer N	−10.5	+3.1	−47.5
11	hetero trimer N	−10.8	+2.7	−47.0

[a] The absolute energies for the isolated and loaded oligomers (au) are given in the Supporting Information (Figure S1 for dimers and Figures S2 + S3 for trimers). Graphical representations of the typical C−C and C−N bond formations sequence from the homogeneous and mixed trimers are given on Figure S3 of the Supporting Information.

the sp nucleophile, which also gives a docking complex more stable than the sp^2 or sp^3 reagents, becomes favored kinetically (lowest activation barrier) but remains disfavored thermodynamically (lowest condensation energy). If the heterogeneous (*N*-side) dimer is reacting, the sp nucleophile, which also gives a docking complex more stable than the sp^2 or sp^3 reagents, is disfavored kinetically (highest activation barrier) while the hybridization has, expectedly, no consequence on the condensation energy. The lozenge shape of the C−Li−X−Li core of the homogeneous (X = C$^{2'}$) or heterogeneous (X = N) dimers tends to flatten out when going from sp to sp^2 and sp^3 entities (increasing C−X's and decreasing Li−Li's). The O−Li−X (X = C$^{2'}$ or N) angle in the docking complex increases when going from sp to sp^2 and sp^3 monomeric nucleophiles (probably following increasing steric constraints which keep apart the reagents at first), but is insensitive to the hybridization for dimers.

We next pursued this investigation with higher aggregates (of propynyllithium only), in an attempt to evaluate the impact of the aggregation itself on the course of the model reaction.

Study of the Homogeneous and Heterogeneous Propynyllithium Trimers. The starting arrangements for the trimers of propynyllithium were inspired by previous descriptions of ladder-type and cyclic arrangements.[31] The only local minima we could identify correspond to cyclic complexes that feature the Li—C≡C "alignment" underlined above for the dimers of propynyllithium.

Let us first consider the homogeneous trimer. Two conformations are obtained (of C_3 and C_1 symmetry, Figure 7), depending on the relative orientation of the propynyl chains around the "hexagonal" (LiC)$_3$ core. The C_3 symmetry is favored by only 0.3 kcal·mol^{-1}.

The study of the interaction with formaldehyde has been restricted to the C_3 conformer of which symmetry limits the docking to only one possibility. The usual reaction is then triggered with geometrical and energetic characteristics similar to the previous ones (Tables 1 and 3). A new cyclic heterogeneous trimer is obtained that includes the lithium alkoxide resulting from the condensation, comparable to what was obtained for the cyclic homogeneous dimer in Figure 5, right.

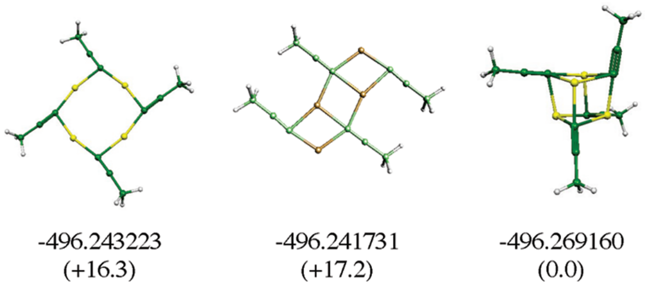

FIGURE 8. Optimized tetramers of propynyllithium (absolute energies are in au and relative ones in kcal·mol^{-1}).

Next, we considered the heterogeneous trimer made out of two propynyllithium units and one lithium dimethylamide. Three cyclic arrangements have been identified for this aggregate and they are, once again, quasi-isoenergetic ($\delta E \leq 0.4$ kcal·mol^{-1}, Figure S2 of the Supporting Information). The docking of formaldehyde on these floppy trimers have been considered in the following and the main geometrical data concerning the complexes and TS's are displayed in Table 1. For one given trimer (homogeneous or heterogeneous), the passage from the steady to the transition state is accompanied by the expected decrease of α (by 15−20°) and increase of β (by 55−100°), d and γ remaining more or less constant.

The data in Table 1 give an overview on the general effect of aggregation. Overall, the α values (Figure 2) of the preliminary complexes seem to increase with the aggregation (an "ideal" value of almost 120° being generally reached for the trimer, entries 5 to 11), while d (≈2.00 Å), β (≈0°), and γ (< 20°) are little sensitive to this factor. At the TS, β is the parameter most affected by the aggregation: its increasing value suggests that for the trimers the reaction tends to be not as early as for the monomer and dimers, at least when a C−C bond is forming. This movement, which puts the nucleophile on a Burgi−Dunitz[32] type trajectory for the rest of the reaction, is amplified with the degree of aggregation. In contrast, d (≈2.00 Å), α (≈100°), and γ (< 20°) are not significantly altered at the TS.

The docking, activation barrier, and condensation energies are compared in Table 3. The docking energies, little sensitive to the surrounding of the lithium, decrease when the aggregation level of the acetylide increases, and they are always lower on the *N*-side of the mixed aggregates. The activation energy is small (≈3 kcal·mol^{-1}) and marginally influenced by the nature of the complex. Note that the *N*-side and the *C*-side of the mixed trimer are associated to comparable barriers (entries 6−11), in contrast to the case of the methyllithium−lithium dimethylamide sp^3 aggregate.[8] Regarding the condensation energies, the N−C bond formation (< −40 kcal·mol^{-1}) seems systematically more exothermic than the C−C one (> −40 kcal·mol^{-1}), as noted

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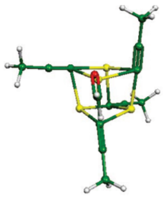
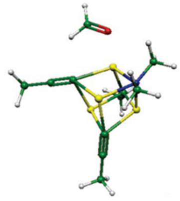
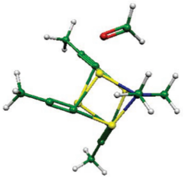
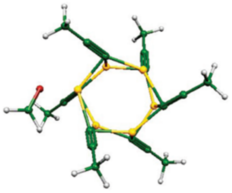
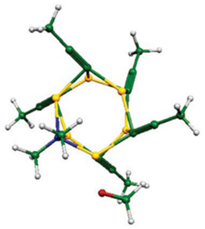
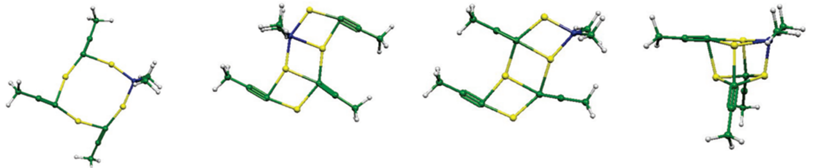
(31) See for instance for trimers: (a) Harder, S.; Boersma, J.; Brandsma, L.; Kanters, J. A.; Bauer, W.; Schleyer, P. v. R. *Organometallics* **1989**, *8*, 1696–1700. (b) Lickiss, P. D. *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.* **1989**, *86*, 261–284. (c) Pratt, L. M.; KhanBauer, I. M. *J. Comput. Chem.* **1995**, *16*, 1067–1080. (d) Bauer, W. *J. Am. Chem. Soc.* **1996**, *118*, 5450–5455. (e) Pratt, L. M. *Mini-Rev. Org. Chem.* **2004**, *1*, 209–217. (f) Pratt, L. M.; Fujiwara, S.-i.; Kambe, N. *Tetrahedron* **2009**, *65*, 1017–1025.

(32) (a) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563–1572. (b) Eisenstein, O.; Schlegel, H. B.; Kayser, M. M. *J. Org. Chem.* **1982**, *47*, 2886–2891. (c) Menger, F. M. *Tetrahedron* **1983**, *39*, 1013–1040. (d) Liotta, C. L.; Burgess, E. M.; Eberhardt, W. H. *J. Am. Chem. Soc.* **1984**, *106*, 4849–4852.

TABLE 4. Main Geometrical Parameters Describing the Tetrameric and Hexameric Complexes [(Me—C≡C—Li)$_n$(Me$_2$NLi)$_m$]−HCHO at the Steady and TS[b]

Entry				Steady state				Transition state			
	n	m		α	β	γ	d(Å)	α	β	γ	d(Å)
1	4	0		117.5	3.1	8.6	2.02	96.7	87.7	7.3	1.96
2	3	1		119.6	4.5	14.2	2.02	98.3	104.4	0.3	1.87
3	3	1		109.6	7.1	36.8^a	2.01	94.6	40.8	44.8^a	2.03
4	6	0		119.8	3.9	13.3	2.03	110.2	58.6	34.6	1.85
5	5	1		103.4	4.8	15.3	2.02	105.7	78.5	18.9	1.85

[a] For the docking on the *N*-side, the angle *γ* is the dihedral C^{1}OLiN instead of C^{1}OLiC^2. [b] The angles α, *β*, and *γ* and distance *d* are defined in Figure 6.



-514.830165 (+12.3)

-514.828327 (+13.4)

-514.829404 (+12.8)

-514.849724 (0.0)

FIGURE 9. Optimized heterogeneous tetramer [(MeCH≡CLi)$_3$(Me$_2$NLi)] (absolute energies are in au and relative ones in kcal·mol^{-1}).

above for the dimers. These values increase slightly with the aggregation state of the acetylide. In all cases, the N−C bond formation is expected to be favored both on kinetic and thermodynamic grounds.

Study of the Homogeneous and Heterogeneous Tetramers and Hexamers of Propynyllithium. Tetramers and hexamers are very important aggregates, found in ethereal solution, in particular THF, for the tetramers and in apolar solvents,

TABLE 5. **Energy (kcal·mol^{-1}) of Interaction between Tetrameric or Hexameric $[(Me{-}C{\equiv}C{-}Li)_n(Me_2NLi)_m]$ and HCHO before, during, and after the Condensation Reaction**

entry	system	docking	activation	condensation
1	homo tetramer	−13.5	+2.8	−39.0
2	hetero tetramer C	−12.6	+3.3	−40.6
3	hetero tetramer N	−11.6	+2.6	−51.0
4	homo hexamer	−11.0	+6.4	−44.8
5	hetero hexamer C	−16.5	+6.0	−44.5

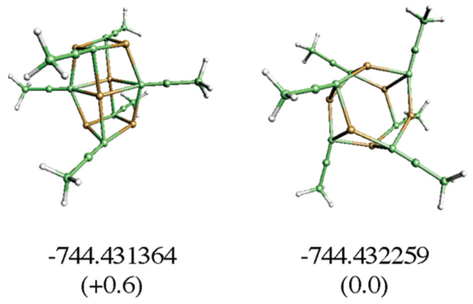


FIGURE 10. Optimized homogeneous hexamers $(MeCH{\equiv}CLi)_6$ (absolute energies are in au and relative ones in kcal·mol^{-1}).

such as toluene, for the hexamers.[26,33] The tetramer can adopt three main arrangements: planar, ladder, or cubic. For each, the relative orientations of the lateral acetylenic chains can vary, leading to a large number of conformers almost isoenergetic. Since it would be both fastidious and useless to describe all of them, we have restricted this study to the more stable ones.

Let us first discuss the case of the homogeneous tetramer $(MeCH{\equiv}CLi)_4$. The fully optimized arrangements are displayed in Figure 8 (note that the quasilinear $C{\equiv}C{-}Li$ geometry is conserved in the three cases). The cubic form, of which the T_d conformer is preferred by > 16 kcal·mol^{-1}, will be the sole to be considered below.

The geometrical parameters characterizing the docking complex of formaldehyde on this cubic aggregate and the following TS are displayed in Table 4 (entry 1). For the sake of space saving, the graphical representations of the various phases of the reaction are given in the Supporting Information (entry 1 of Table S3). The process follows once again the same global pathway, the rotation of the aldehyde being the key event to reach the TS. Comparison of the data (in particular β) with those for the dimer (Table 1, entry 3) and trimer (entry 5) complexes suggests that for both the trimer and tetramer, the TS of the condensation is noticeably less early than for the dimer (β = 94.4° and 87.7° vs. 58.1°, respectively). The data obtained for another conformer of the cubic tetramer (lying 0.4 kcal·mol^{-1} above the previous one) are presented in entry 2 of Table S3 (Supporting Information). The associated figures are sufficiently similar to justify the restriction of this study to the more stable conformer.

Let us now consider the heterogeneous tetramer $[(MeCH{\equiv}CLi)_3(Me_2NLi)]$. Four local minima have to be compared here since the ladder arrangement now has two isomers (Figure 9). Nevertheless, the cubic form remains preferred by > 11 kcal·mol^{-1} and the difference between its various conformers is < 0.2 kcal·mol^{-1} (Table S4 of the Supporting Information). Therefore, only the more stable conformer of this latter cubic isomer will be considered for the condensation reaction.

Formaldehyde can approach this heterogeneous tetramer in many ways. Let us first consider the acetylide condensation (C−C bond formation). The cubic arrangement has three different types of lithium nuclei. One of those is surrounded by three acetylide units and can be considered, in first approximation, as very similar to the homogeneous tetramer described above; it will therefore not be considered here. The two remaining lithium nuclei have two acetylides and one amide in their neighborhood, but their orientation with respect to the amide is different. However, the flexibility of the acetylenic lateral chains upon docking of HCHO is likely to render the difference between these sites meaningless. A few significant cases are displayed in Table S5 (Supporting Information) and the associated figures show that there are indeed very small differences. The entry 2 of Table 4 indicates that the geometrical parameters governing the condensation are similar to those applying to the case of the homogeneous cubic tetramer (entry 1). Comparing entries 1 and 2 of Table 5 shows that the same comment applies to the energies involved in the process.

When it comes to the C−N bond formation, the geometry corresponds to a very early TS, with a remarkably low (≈40°) β angle and a long Li−O distance (d > 2.0 Å) at the TS. This observation is valid at all levels of aggregation (compare data in Tables 1 and 4). Energywise, the C−N condensation energy is significantly larger than that for the C−C bonding (compare entries 2 and 3 of Table 5), as noted before for the heterogeneous dimer and trimer (see entries 4, 10, and 11 of Table 3). Actually, the docking and condensation energies are relatively insensitive to the aggregation state of the alkynyllithium.

The homogeneous hexamer was next on the list. Only two "realistic" conformers have been considered (obtained by stacking three cyclic dimers, double cube, or two cyclic trimers, prismatic, of propynyllithium). The energies associated to the optimized structures, displayed in Figure 10, show that the prismatic form (in which the acetylenic chains adopt a gearwheel arrangement) is preferred by ~0.6 kcal·mol^{-1}. We have thus restricted the following study to this conformer. In addition, a heterogeneous hexamer has been generated from this homogeneous structure by replacing one acetylide unit with a Me_2NLi one.

When reacted with formaldehyde, the hexamers follow the usual sequence (Table S6, Supporting Information). For both aggregates, the TS for the CC bond formations are relatively early ($\beta \approx 58°$ and 78°, respectively). Curiously, we could not identify any complex prefiguring the CN bond formation for the heterogeneous hexamer. Energywise, these reactions go through TS's higher in energy than for tetramers

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(33) See for instance for tetramers and hexamers: (a) Raghavachari, K.; Sapse, A.-M.; Jain, D. C. *Inorg. Chem.* **1987**, *26*, 2585–2588. (b) Armstrong, D. R.; Barr, D.; Snaith, R.; Clegg, W.; Mulvey, R. E.; Wade, K.; Reed, D. *J. Chem. Soc., Dalton Trans.* **1987**, 1071–1081. (c) Jackman, L. M.; Rakiewicz, E. F.; Benesi, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 4101–4109. (d) Jackman, L. M.; Cizmeciyan, D.; Willard, P. G.; Nichols, M. A. J. *J. Am. Chem. Soc.* **1993**, *115*, 6262–6267. (e) Aubrecht, K. B.; Lucht, B. L.; Collum, D. B. *Organometallics* **1999**, *18*, 2981–2987. (f) Fraenkel, G. In *The chemistry of organolithium compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons: New York, 2006; Vol. 2. (g) Popenova, S.; Mawhinney, R. C.; Schreckenbach, G. *Inorg. Chem.* **2007**, *46*, 3856–3864. (h) Nichols, M. A.; Leposa, C. M.; Hunter, A. D.; Zeller, M. *J. Chem. Crystallogr.* **2007**, *37*, 825–829.

(about twice as high, entries 4 and 5, Table 5) or any other aggregates (compare with data in Table 3). Finally, the docking and condensation energies do not call for particular comments with respect to previous aggregates.

It is difficult to conclude on the effect of aggregation on the geometrical and energetic parameters of the condensation reaction or even to draw general conclusions from the data in Tables 1, 3, 4, and 5 since the overall trends admit, in most cases, exceptions. Nevertheless, one can underline the following: (1) At the level of the docking complexes α is smaller than 120° for monomers and dimers and tends to become ~120° for larger oligomers, at least for the docking on the pro-C side; β and γ are ~0° for all the complexes, the aldehyde and the nucleophile standing more or less in the same plane; the O$-$Li distance d is more or less constant, around 2.0 Å; and the docking energy decreases when going from the monomer to the trimers, then stays more or less stable (except for one hexamer). (2) At the level of the transition states α varies marginally with the aggregation (94.6$-$110.2°), whatever the docking side; β tends to increase with the aggregation (going from 47.5° to 104.4°), with irregular variations for the hexamer; γ is small and does not vary much with the aggregation, the aldehyde and the nucleophile are thus lined up at the TS (this fits well with a Bürgi$-$Dunitz type trajectory in all cases); the O$-$Li distance d does not change very much with respect to that calculated in the docking complexes (however it tends to shorten for larger aggregates (d = 1.85 Å for an hexamer), suggesting that the condensation is not as early as for smaller aggregates); and the activation energies are small and vary little with the aggregation (the hexamer is again an exception, with an activation barrier almost twice as big as that of the dimer for instance; the level of aggregation of mixed aggregates does not seem to exert an important influence on the C/N preference). (3) At the level of the condensation, only the energies have been compared. The data show that this value increases with the aggregation, when a C$-$C or a C$-$N bond is formed. This energy is always larger for the C$-$N bond formation.

Conclusions

This work focuses on the interaction of unsolvated monomers, homogeneous and heterogeneous (with $LiNMe_2$) dimers, trimers, tetramers, and hexamers of sp 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. Overall, the general reaction scheme remains the same whatever the hybridization and the aggregation: the oxygen of the electrophilic carbonyle docks on one of the lithiums belonging to a C$-$Li$-$X$-$Li (X = C or N) parallelogram, a metastable planar complex is formed, then the aldehyde rotates around its C=O axis and exposes the π face of the carbonyle to the nucleophilic attack of C or X. In general, this later rotation is only at its onset when the transition state of the reaction is reached, as expected for an early TS. Finally, the expected condensation product is obtained as a mixed aggregate with the C$-$Li or X$-$Li unreacted moiety.

The main objective of this work being the evaluation of the impact of the hybridization of the nucleophilic carbon on the course of the condensation reaction, we have compared for monomers and dimers the data concerning propynyllithium, vinyllithium, and methyllithium. We conclude that dimeric sp nucleophiles are expected to be more reactive (at least in kinetic conditions), while monomeric sp^3 entities would be the most favored in kinetic and thermodynamic conditions, even if its docking is the least exothermic. Thus, the nucleophilicity order does not necessarily parallel the well-known acidity order (sp > sp^2 > sp^3). This work was also aimed at evaluating the influence of the aggregation. Our data suggest that the initial docking energy, which decreases when going from the monomer to the trimer, then stays stable, is the factor more sensitive to aggregation.

This leaves open the Curtin$-$Hammett question of knowing whether all the oligomers are in rapid equilibrium with their monomer, which acts as the ultimate nucleophile, or if this equilibrium is slow, giving a chance to each oligomer to express its own reactivity. The theoretical evaluation of these equilibrium constants, which are intimately related to the solvent in which they are measured, would require calculations on very large systems and are hardly within reach of current computational methods. However, recent experimental data suggest there is more precise information on these phenomena that could be available from spectroscopy;[18] hence, a solid backing should soon be available to undertake this type of ambitious theoretical exploration.

Acknowledgment. All computations have been carried out at the Centre de Ressources Informatiques de Haute-Normandie (CRIHAN, St Etienne-du-Vouvray). The Région de Haute Normandie is acknowledged for his support through the CRUNCh interregional network. The Agence Nationale pour la Recherche funded part of this work through the grant ANR-07-BLAN-0294-01.

Supporting Information Available: Figures and tables giving geometrical characteristics and energy values for several aggregates considered in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.