

Reaction Pathway of the Conjugate Addition of Lithium Organocuprate Clusters to Acrolein

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Received December 6, 1996[⊗]

Abstract: The reaction pathway of transfer of a methyl group of a cuprate cluster (Me₂CuLi)₂ to acrolein (conjugate addition of the methyl group) has been studied with the hybrid density functional B3LYP method. All intermediates and transition structures (TSs) on the potential surface of the reaction as well as the structures on the intrinsic reaction coordinate near the C–C bond forming stage of the reaction have been determined. In addition to two previously proposed species, a lithium/carbonyl coordination complex (CPLi) and a copper/olefin complex retaining a closed cuprate structure (CPCI), a new copper/olefin complex with an open cuprate structure (CPOP) was characterized and proven to be an intermediate directly leading to the conjugate addition product (PD) via a TS of C–C bond formation (TS). The overall pathway of the reaction can be viewed, in one way, as C–C bond formation via reductive elimination of a Cu(III) species and, in another, as a 1,4-addition of MeLi assisted by copper. The present studies revealed that the large cluster framework of (Me₂CuLi)₂ allows intricate cooperation of two lithium atoms and a copper atom. A small cluster such as Me₂CuLi cannot achieve such cooperative action of different metal atoms as smoothly as larger clusters such as (Me₂CuLi)₂ and Me₂CuLi·LiCl. Mechanistic relationships between conjugate addition, carbocupration, and alkylation reactions of cuprate are discussed. A close similarity has been found between the conjugate addition and the carbocupration of acetylene for the cooperative action of metal and the involvement of a Cu(III) species.

Conjugate addition of organocuprate reagents to α,β -unsaturated carbonyl and related compounds (hereafter called enones) has long attracted the great interest of chemists because of its synthetic importance and its obscure mechanism.¹ As early as in the 1960s, House noted that the reactive species is a Gilman reagent (R₂CuLi) and suggested that the role of the Cu(I) atom is to transfer an electron to the carbonyl substrate.² However, attempts to physically detect evidence for single electron transfer failed³ and the experimental evidence once considered to be proof of a single electron transfer process did not necessarily receive support from later studies,⁴ though the reaction with highly electrophilic olefinic acceptor (e.g., 1,1-dicyanoolefins) appears to involve an electron transfer mechanism.⁵ Among various mechanistic possibilities, the conjugate addition to sterically unbiased, moderately electrophilic α,β -unsaturated carbonyl compounds is now considered to proceed through a process involving a redox process involving Cu(I)/Cu(III) interconversion (vide infra). Rate-retardation effects of an enone β -substituent, which was revealed by kinetic studies,⁶ has been

considered to support such an organometallic mechanism rather than an electron transfer mechanism.

Ample experimental evidence indicated that cuprates in solution exist largely as a dimer (R₂CuLi)₂, which is hence often invoked as the reactive species in conjugate addition. Dimeric cuprate was identified as a major species in ethereal solution by physical measurement⁷ and characterized in crystals, for instance, as a solvated cluster **A** (R = Ph, Me₃SiCH₂) having one ether molecule on each lithium atom as shown in Scheme 1.⁸ Recent theoretical calculations indicated that the cyclic dimer **A** (R = Me, S = H₂O) is much more stable than the monomer Me₂CuLi which has an open structure (see the preceding article⁹),¹⁰ and this is consistent with the aggregation state determined by experiments.^{7,11} The kinetic results were consistent with the participation of the dimer (R₂CuLi)₂/enone complex in the C–C bond forming process of conjugate addition.⁶ Thus, a complex between cuprate and the enone substrate forms reversibly and affords the conjugate addition product. Participation of a 1:1 complex in the C–C bond forming stage was also proposed in kinetic studies of S_N2 alkylation reactions.¹² These kinetic studies indicated that the kinetic expression does not change upon addition of LiI, though the overall rate of the reaction was affected by its presence.⁶

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[⊗] Abstract published in *Advance ACS Abstracts*, May 1, 1997.

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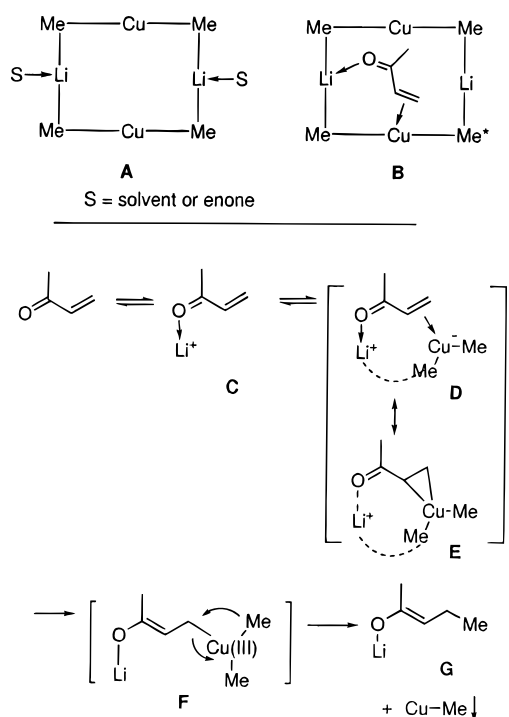
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Scheme 1



The recent NMR studies have succeeded in identifying what may well be the kinetically observed cuprate/enone complex.^{13,14} Namely, relatively unreactive α,β -unsaturated ketones, esters, and nitriles were found to form a complex(es), which was schematically depicted as a general structure **B** based either on intuition or on calculations with extend-Hückel and PRDDO methods.^{13b,15} In addition, the remarkable recent observation¹⁴ of large two-bond $^{13}\text{C}/^{13}\text{C}$ spin coupling between the β -carbon of an α,β -unsaturated nitrile and a methyl group on the copper atom (Me^*) indicated not only the $\text{C}(\beta)\text{--Cu--Me}^*$ connectivity but also the presence of a nonexchanging bond between $\text{C}(\beta)$ and Cu. The $^{13}\text{C}/^{13}\text{C}$ spin coupling studies also indicated that the $\text{C}(\alpha)\text{--C}(\beta)$ double bond in **B** is significantly weakened. Therefore, the cuprate/enone complex **B** might be better depicted as the cupriocyclopropane **E** (i.e., a donation/back-donation complex¹⁶) in Scheme 1.

Coordination of a lithium atom (or atoms) with the carbonyl group has been implicated by NMR studies (e.g., the general structure **C** or **A**, $\text{S} = \text{enone}$).¹⁷ When the lithium atom is removed from a lithium cuprate by solvation with crown ether, conjugate addition does not take place.¹⁸ The X-ray structure of a Me_2CuLi /crown ether complex contains free, linear Me--Cu--Me^- and solvent separated Li^+ .¹⁹ Thus, in contrast to the

robust Me--Cu bonding, the bonds between a pentacoordinated methyl group and a dicoordinated lithium atom in **A** are much weaker and susceptible to cleavage by coordination of a Lewis base to the lithium atom. The weakness of such bonds is also known for the oligomeric alkyl lithium clusters in ethereal solution.²⁰

The reaction pathway after the formation of a cuprate/substrate complex still remains open to debate. It has long been considered that a Cu(III) intermediate^{21,22} **F** forms as an intermediate and undergoes reductive elimination to give lithium enolate **E**. MeCu often precipitates in the absence of a suitable solvating ligand.²³ Recent quantum mechanical studies on monomeric noncluster model reactions offered support to the intermediacy of $\text{R}_3\text{Cu(III)}$ species, which rapidly decomposes to give reductive elimination products, R--R and RCu(I) .²⁴

The body of the previous information thus suggests that cuprate conjugate addition takes place in two stages: formation of a cupriocyclopropane-type complex (**D/E**) due to donation/back-donation interaction between cuprate and enone,^{6,13,14,16,17,25} followed by bond reorganization (**D/E** \rightarrow **F** \rightarrow **G**) involving C--C bond formation, O--Li bond formation, C=C bond migration, and generation of discrete MeCu . In spite of the prevailing view favoring the participation of $(\text{Me}_2\text{CuLi})_2$ in the reaction, it is not clearly understood either how the dimeric cluster takes part in the crucial C--C bond forming step, or how essential the dimer structure could be in the conjugate addition pathway. In the density functional studies described below, we have determined all intermediates and transition structures (TSs) on the potential surface of the reaction pathway of transfer of a methyl group of a cuprate cluster $(\text{Me}_2\text{CuLi})_2$ to acrolein (conjugate addition) by full structure optimization. The intrinsic reaction coordinate (IRC) analysis was performed in the stage of the crucial C--C bond formation to obtain information on the nature of this important process. The work indicates that the cluster structure allows intricate cooperative action of two lithium atoms and a copper atom. Although the work largely focuses on the gas-phase addition of $(\text{Me}_2\text{CuLi})_2$ to acrolein, some considerations have been given to $(\text{Me}_2\text{CuLi})_2$ solvated by explicit solvent molecules and to the smaller clusters, $\text{Me}_2\text{CuLi--LiCl}$ and Me_2CuLi . Taken together with carbocupration studies on acetylene, the present work demonstrates the important roles of the cluster structure and cooperation of different metals therein.

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Models and Computational Methods

The model substrate chosen is acrolein, which is the smallest α,β -unsaturated carbonyl compound and participates as an acceptor in conjugate addition reactions.²⁶ As to the cuprate model, we primarily studied the cuprate dimer **RT1**,¹⁰ which is commonly assumed to be the reactive species.⁶ Monomeric cluster $\text{Me}_2\text{CuLi}\cdot\text{LiX}$ is often involved in the “higher order cuprate” controversy ($\text{X} = \text{CN}$)^{27,28} and a model for enone/ $\text{Me}_2\text{CuLi}\cdot\text{MeLi}$ complex has been reported previously.¹⁵ Recent molecular weight measurement indicated that $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ exists in this stoichiometry in THF.²⁹ Therefore, we also examined $\text{Me}_2\text{CuLi}\cdot\text{LiCl}$ to compare its behavior with that of dimer. A minimal cluster formulation, Me_2CuLi ,¹⁰ has been employed routinely to represent reagent stoichiometry. In order to shed light to the effect of cluster size, we also studied its behavior to be compared with that of the higher clusters, whereas this minimal cluster is generally not believed to be the reactive species of cuprate reactions. The preceding article describes discussions on noncluster species, MeCu and Me_2Cu^- , which are experimentally known not to be the reactive species in cuprate reactions.

Studies on the transition structures of cuprate reactions mandate the use of a theoretical method which takes dynamical electron correlation effects into accounts. The work described in the previous article⁹ led to the following generalization. The B3LYP/631A method gives qualitatively the same structures as those obtained at the MP2(FC) level of theory³⁰ and B3LYP energies are rather close to the CCSD(T) values. In addition, relativistic effects as to the copper atom were found to be very small. Therefore, in the present work, geometry optimization was performed (without symmetry assumption) by the B3LYP hybrid functional³¹ with the basis set denoted as B3LYP/631A, which consists of the Ahlrichs all-electron SVP basis set³² for Cu and 6-31G(d)³³ for the rest. Normal coordinate analysis

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(performed for all TSs) and natural charges³⁴ are calculated at the same level unless noted otherwise. Unless otherwise noted, the energies discussed in the text were obtained at the B3LYP/631A level. In the intrinsic reaction coordinate (IRC) analysis,³⁵ we used the B3LYP method using Ahlrichs SVP for Cu and 3-21G for others (B3LYP/321A). As in the previous paper,⁹ the B3LYP/321A structures (obtained for most of the stationary points in the $(\text{Me}_2\text{CuLi})_2$ reaction) were found to show reasonable agreement with the B3LYP/631A structures (data not shown; a tendency was found with the 321A basis set to overestimate oxygen-lithium interactions³⁶). For complexes and TS of C–C bond formation at the B3LYP/321A geometry, the RB3LYP/321A wave functions were found to be stable with respect to becoming UB3LYP functions.³⁷ The Boys localization for occupied Kohn–Sham molecular orbitals was performed for the B3LYP/631A TS structures for C–C bond formation.³⁸ ¹³C NMR chemical shifts were calculated by the gauge invariant atomic orbitals (GIAO)-B3LYP/631A method,^{39,40} which reproduces the experimental data for **RT** and acrolein with a 3–12 ppm error. Chemical shift values are given with reference to Me_4Si (isotropic part of the shielding tensor = 189.7 ppm). The GIAO ¹³C chemical shift of –11.6 ppm for $(\text{Me}_2\text{CuLi})_2$ agrees reasonably well with the experimental values of –9.25 ppm as well as with the LORG values ranging between –10.8 and –13.6 ppm.¹¹

Results

Pathways for Reaction of $(\text{Me}_2\text{CuLi})_2$ with Acrolein. The pathway for the carbocupration of acetylene in the preceding article⁹ revealed the mechanistic significance of electron donation from a copper atom to the substrate. On the basis of this knowledge and the previous experimental evidence for cuprate/enone complexes,^{6,13,16,17} we started to explore the mechanistic possibilities of a conjugate addition reaction with special focus on search for the C–C bond forming pathway.

Events in the conjugate addition reaction revealed by the present studies are summarized in Scheme 2. All stationary points shown here between **RT1** + **RT2** and **PD** have been structurally correlated either by the IRC reaction path following method (near the C–C bond forming TS, **TS**) or the usual structure optimization procedure, and therefore the pathway shown in Scheme 2 presents the entire reaction pathway of transfer of one methyl group of $(\text{Me}_2\text{CuLi})_2$ to acrolein in the gas phase as studied at the B3LYP theoretical level. Figure 1a shows the energetics obtained at the B3LYP/631A//B3LYP/631A (as well as the MP2/631A//B3LYP/631A level). The energy profiles obtained by the two methods commonly point out an extremely important character of the reaction in that there exist two high energy barriers: The first (**TSiso1**) represents

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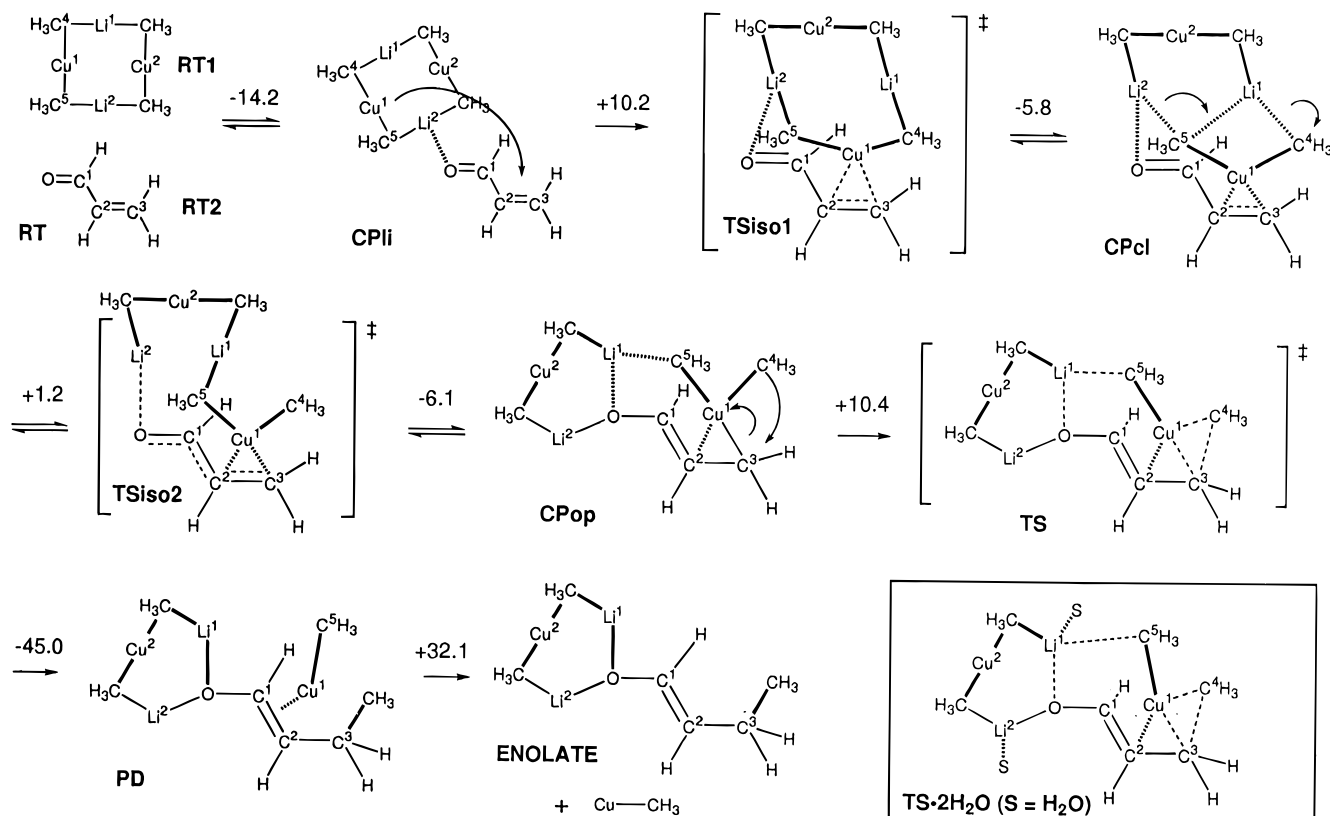
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Scheme 2^a

^a The reaction pathway of the conjugate addition of $(\text{Me}_2\text{CuLi})_2$ to acrolein. See Figure 2 for 3D representations. Approximate stereochemistry is implied by the use of bold lines. Dative bonds are depicted by thick dotted line and forming/cleaving forming bonds by broken line. Note, however, that this distinction could be oversimplified and may be misleading. The energy changes in kcal/mol at the B3LYP/631A//B3LYP/631A are given above the arrows. For the summary of energetics, see Figure 1. Inset: TS solvated with two solvent molecules ($\text{S} = \text{H}_2\text{O}$).

the process of olefin/copper π -bond formation (face-selection process) and the second (TS) the process of C–C bond formation. In light of the studies in the previous article, the 10.4 kcal/mol B3LYP activation energy of the C–C bond formation (CPop to TS) may be too small, the 24.4 kcal/mol MP2 energy barrier too large and the “real” activation energy may be in between.^{24b} Figure 2 shows the changes of energies (a), geometric parameters (b and c), and natural charges (d) for representative structures on stationary points and various intermediate structures obtained by the IRC analysis in the vicinity of the C–C bond forming step at the B3LYP/321A level.

First, we have studied the previously proposed lithium–carbonyl complex and the “closed” copper–olefin complex.^{13b} The lithium complex CPlI is a complex formed by coordination of acrolein (RT2) to a lithium atom of the dimer RT1 (Scheme 2). Turning the dimer structure in CPlI around the Li^2 –oxygen bond makes Cu^1 approach the olefin (note that the olefinic face is selected at this stage) and generates CPlI via a TS of isomerization, TSiso1, with an activation energy of 10.2 kcal/mol. These two types of complexes have been discussed in the literature.^{13,14}

We have also located a new copper π -complex CPop, which has not previously been considered. This complex has its cluster “opened”⁴¹ so that it can interact with acrolein through three-

point binding. It is in equilibrium with the close complex CPlI via a TS of structural isomerization TSiso2, which lies only 1.2 kcal/mol above CPlI. It is important to note that, in CPop, the carbonyl group is doubly activated by the two lithium atoms, one nearly on the carbonyl plane and another on the carbonyl π -face. Most importantly, we found that CPop smoothly follows the intrinsic reaction pathway via TS (note that this C–C bond forming process is totally independent of the face selection process) with a 10.4 kcal/mol activation energy to reach the product complex PD. On the other hand, we could not locate a pathway directly connecting CPlI with PD (without going through CPop), because such a process necessarily made the already pentacoordinated C4 group to take an apparently unfavorable hexacoordinated geometry in the TS. As shown in Figure 2b, the forming C^3 – C^4 bond shrinks monotonously as the reaction proceeds from CPop to PD. This product is a copper complexed lithium enolate and may be responsible for the difference in behavior between a pure lithium enolate and an equivalent enolate species generated by conjugate addition reaction. Dissociation of PD into MeCu and ENOLATE (a mixed cluster of Me_2CuLi and a lithium enolate of butanal) is energetically disfavored by 32.1 kcal/mol in gas phase. In experiments,^{42,43} MeCu often precipitates as polymeric material. For more soluble organocopper reagents, the species corresponding to PD may remain in solution as such. ENOLATE is potentially capable of undergo further conjugate addition by itself (see the results for $\text{Me}_2\text{CuLi}\cdot\text{LiCl}$ below) or after cluster reorganization regenerating RT1. Differentiation of these pathways is, however, out of the scope of the present studies.

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(43) House, H. O.; Wilkins, J. M.; *J. Org. Chem.* **1978**, *43*, 2443–2454. Cf.: Klein, J.; Levene, R. *J. Chem. Soc., Perkin II* **1973**, 1971–1978.

(41) Cf.: (a) Bernstein, M. P.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 789–790. (b) Willard, P. G.; Liu, Q.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 3380–3381. (c) Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1993**, *115*, 11016–11017. Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Chem. Soc., Faraday Trans.*, **1994**, *90*, 1789–1798. (d) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327–6335.

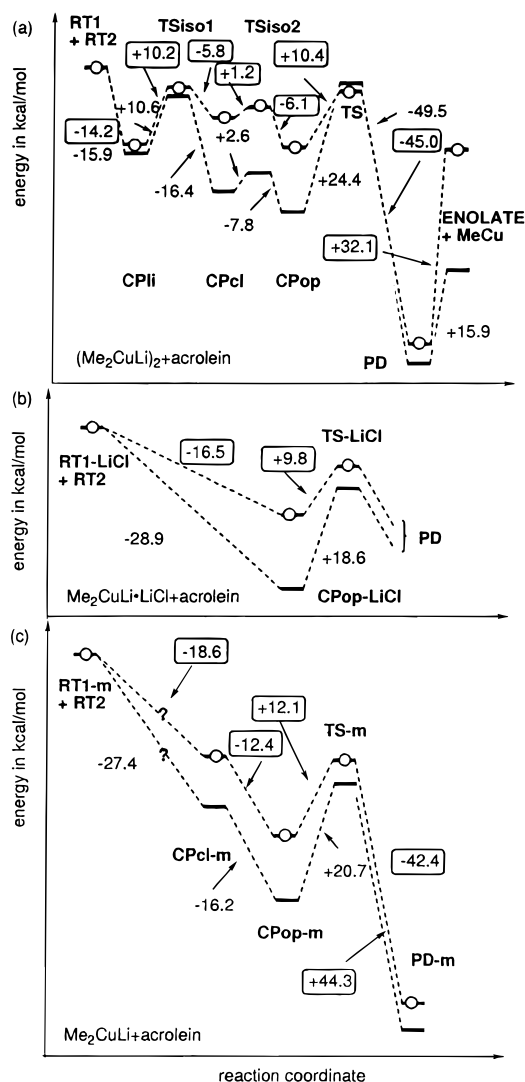


Figure 1. Energetics of conjugate addition. Values in boxes are at the B3LYP/631A//B3LYP/631A level, and values without boxes are at the MP2/631A//B3LYP/631A level.

The data in Figure 2c,d (B3LYP/321A//B3LYP/321A) reveal that two independent events take place in the conjugate addition reaction. The first event takes place during conversion from **RT** to **CPop**, wherein the electron density at C^3H_2 and carbonyl oxygen increases, and that at Cu^I decreases because of back-donation from Cu^I to acrolein. The negative charge on the oxygen atom has increased to $-0.86e$ during conversion from **RT** to **CPop**, and it remains virtually unchanged till **PD** ($-0.89e$). This charge profile is reflected in the structure (Figure 2c): the enolate geometry (long C^1-O and short C^1-C^2) in **PD** is already found in **CPop**.

The second event takes place during the reaction near **TS**. The magnitude of the charge decrease of the nucleophilic C^4H_3 group ($+0.16e$) is matched by the charge increase at Cu^I ($-0.15e$), and the tetracoordinated $Cu(III)$ geometry in **CPop** changes to the $Cu(I)$ geometry in **PD** (vide infra). A similar electron flow was also observed in the acetylene carbocupration reaction.⁹

In summary, we have located various intermediates and TSs on the B3LYP/631A potential surface of the gas-phase reaction that smoothly connects the lithium complex **CPli** to the product **PD**. In the first step of the reaction, electron donation from the copper atom to acrolein generates a $Cu(III)$ state, which goes back to a $Cu(I)$ state in the second stage of the reaction. As described later, solvation of the two lithium atoms in **TS** with

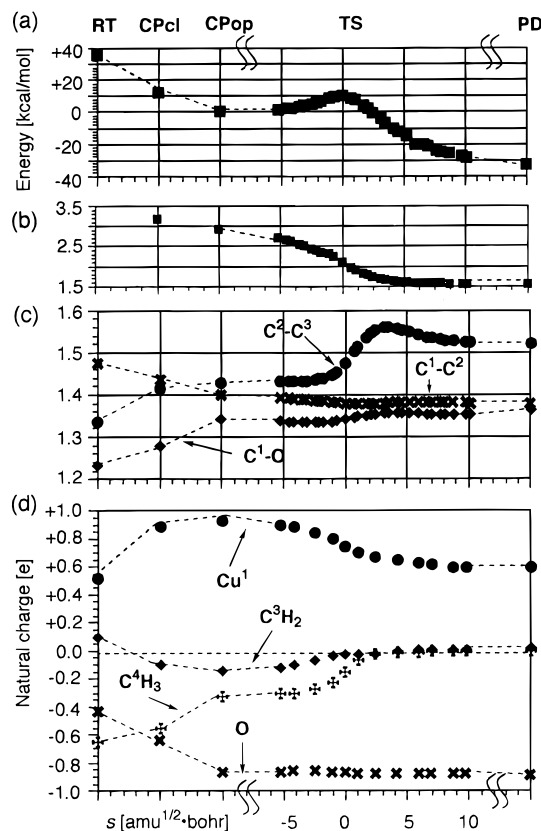


Figure 2. Representative stationary points and representative points on IRC near TS (B3LYP/321A). Changes of (a) energy changes [kcal/mol], (b) C^3-C^4 bond length [Å], (c) bond lengths: x, C^1-C^2 ; •, C^1-C^3 ; cross, C^1-O [Å], (d) natural charge of various atoms and groups along the reaction coordinate: •, Cu^I ; x, O; cross, C^4H_3 ; square, C^3H_2 .

explicit solvent molecules was found not to change the structure of **TS** to a significant degree.

Details of the Intermediates and Transition States Involved. In the following paragraphs are given the details of each stationary point mentioned above (Figure 3). The complex **CPli** simply consists of the cuprate dimer and acrolein as connected by a Li–oxygen bond. As was reported for the solvated dimer **A** ($S = H_2O$),^{10,11} the Li^2-C^5 and Li^1-C^4 bonds are slightly elongated (3.4–6.4%). The lithium coordination to carbonyl oxygen occurs in the carbonyl plane, and the acrolein bond lengths remain virtually unchanged ($<1\%$). In the conversion of **CPli** to **CPcl** via **TSiso1**, the Li^2 atom moves from the carbonyl plane (nonbonding) to the plane perpendicular to it (π -coordination).

The complex **CPcl** is a two-point binding complex, wherein the dimer and acrolein are bound together through Cu^I and Li^2 (front view in Figure 3). The Li^2 atom coordinates to the π -orbital of the carbonyl group. It is a consequence of the copper π -coordination to the olefinic bond and the maintenance of acrolein conjugation. The $C^4-Cu^I-C^5$ cuprate moiety has undergone major geometrical changes. It is now bent and the Cu^I atom is tightly bound to the olefin. Thus, the four $Cu-C$ bonds on Cu^I are of nearly equal length (2.025–2.089 Å), and the Cu^I atom has a near square planar geometry (top view of Figure 3)—a geometry conforming to the d^8 $Cu(III)$ formalism.^{21,22} These structural changes accompany electron donation from copper to acrolein (cf. Cu^I and C^3H_2 , in Figure 2d). The olefinic bond (1.410 Å) is elongated half way from acrolein (**RT2**, 1.338 Å) to the product (**PD**, 1.515 Å), which is consistent with the results of the reported ^{13}C NMR spin coupling data.¹⁴

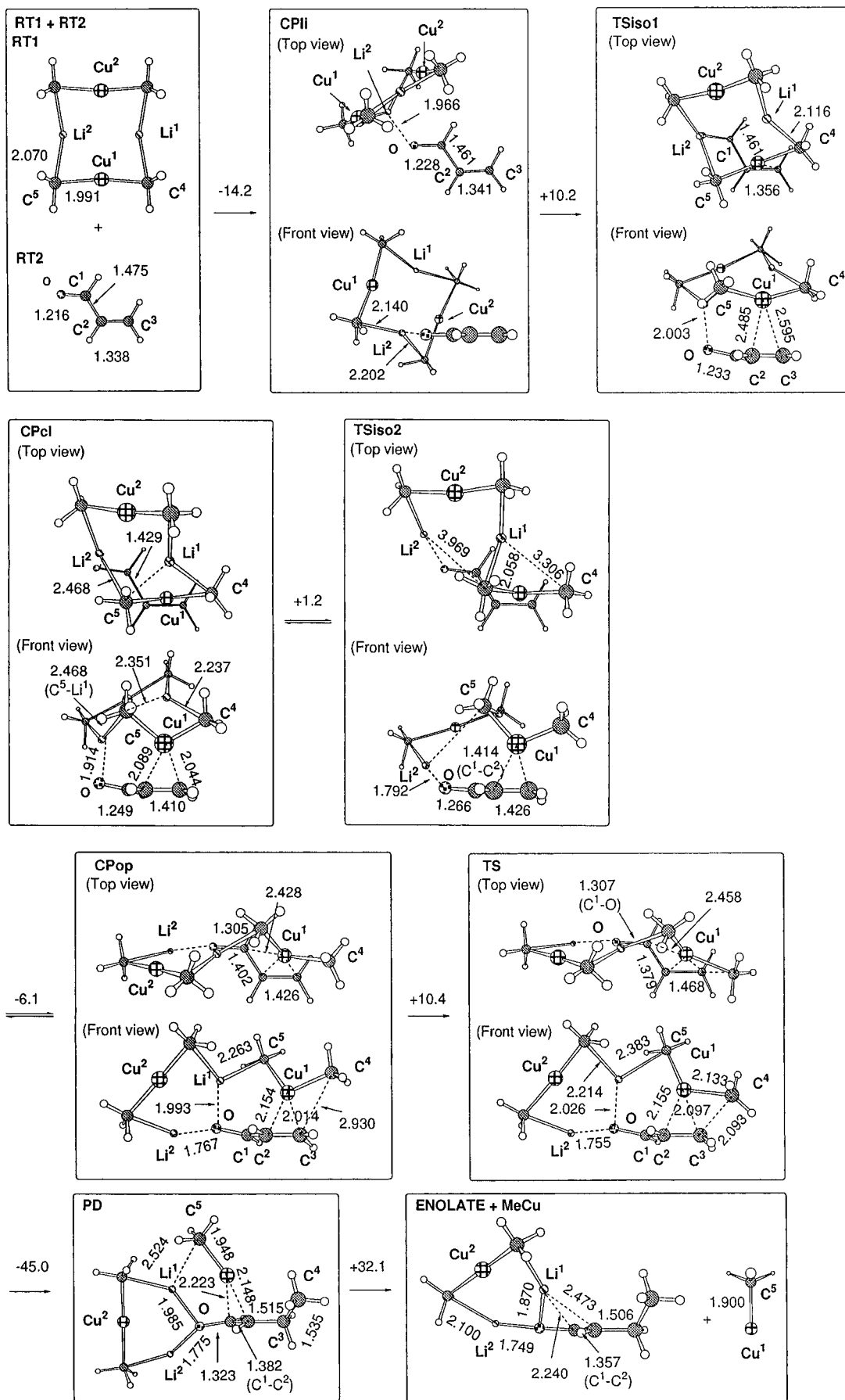


Figure 3. Reactants, intermediates, and transition states in the conjugate addition of $(\text{Me}_2\text{CuLi})_2$ to acrolein. Bond lengths are in Å at the B3LYP/631A level. The energies above the arrows are at the B3LYP/631A/B3LYP/631A level are in parentheses. Values of imaginary frequencies of **TSiso1**, **TSiso2**, and **TS** are $140.9i$, $39.9i$, and $338.5i$ cm^{-1} , respectively. Total energies of **RT1** and **RT2** at the B3LYP/631A/B3LYP/631A level are -3455.47672 and -191.91197 hartrees, respectively.

Careful analysis of the cluster moiety of **CPcl** (see the top view in Figure 3) reveals that the dimer structure in **CPcl** represents an intermediate stage in the conversion of the fully closed structure in **CPli** to the completely opened one in **CPop**. Thus, both the C⁴–Li¹ (2.237 Å) and the C⁵–Li² bonds (2.468 Å) are elongated (14.5% and 19.2% longer than in **RT1**, 2.070 Å), while the Li¹–C⁵ bond is much shortened (2.351 Å; 4.148 Å in **RT1**). As a result, the Li¹ atom now bridges the C⁴ and C⁵ methyl groups, and Li² is held close to the oxygen atom (1.914 Å). This structural change occurs in parallel with the decrease and increase of negative charge on the C⁴ methyl group and the carbonyl oxygen, respectively (cf. Figure 2d). The above structural features relate **CPcl** to **CPop** in its atom connectivity.

In line with the above analysis, we could locate a low energy TS connecting **CPcl** to **CPop**. This TS of closed/open isomerization (**TSiso2**) lies 1.2 kcal/mol above **CPcl**. Both the C⁴–Li¹ and the C⁵–Li² bonds are being cleaved, and the Li¹ atom is now bound to the C⁵ methyl group. The Li² atom, which was π -complexed with the carbonyl group in **CPcl**, is moving onto the carbonyl plane.

In **CPop**, the Li¹ atom is now fully bonded to the C⁵ methyl group, from which the Li² atom is totally detached. This bond reorganization makes the C⁴ methyl group free from lithium coordination. It must be also noted that such a cluster reorganization process involving cleavage of the bonds between a dicoordinated lithium atom and a pentacoordinated alkyl group is experimentally known to be a very facile process in solution as found for alkyllithium clusters.^{41c} Our theoretical results indicate that this reorganization is easy even in the absence of solvation.

The cupriocyclopropane structure in **CPop** is similar to that in **CPcl** except that the Cu¹ cuprate moiety is slightly tilted toward C³ (see the top view). The carbonyl moiety has undergone a major change to become a MeCu–complexed lithium enolate (as shown in Figure 2c). The oxygen–C¹ (1.305 Å) is longer than acrolein (**RT2**) by 7.3% (8.8% in **PD**), and the C¹–C² (1.402 Å) bond is shorter by 5.0% (6.3%). The Li²–oxygen bond of 1.767 Å is a fully formed bond (cf. **PD**, 1.775 Å). Li² is also attached to the oxygen atom and the Li¹–C⁵ bond is lengthened (2.263 Å). The charge change shown in Figure 2d agrees well with these structural changes, and the acrolein moiety (mainly the carbonyl oxygen) has accepted significant negative charge, making Cu¹ the most positively charged among the points on the reaction pathway. The structure of **CPop** now resembles the TS of C–C bond formation, **TS**.

The IRC analysis indicated that the TS of C–C bond formation (**TS**) smoothly connects **CPop** and **PD**. The activation energy from **CPop** to **TS** is 10.4 kcal/mol. The structural change in the course of the conversion of **CPop** to **PD** via **TS** is straightforward as seen from Figure 3. The major event is the C³–C⁴ bond formation, which pushes the C⁴ methyl group against the acrolein C³–terminal (see also Figure 2b). The C⁵–Li¹ bond, which was already quite weak in **CPop**, is further weakened to make the C⁴–Cu¹–C⁵ moiety almost separated from the remainder of the cluster. This TS consists of one molecule of the dimer and acrolein and is consistent with the experimental kinetics (i.e., first order to both cuprate and acrolein concentrations).⁶

The localized molecular orbital **LMO1** of **TS** (occupied Kohn–Sham LMOs, Figure 4) shown on the C²–C³–C⁴ dissection corresponds to the C–C bond formation between C³ and C⁴. **LMO2** on the C²–C³–Cu¹ plane indicates that a copper 3d orbital is responsible in the Cu¹–C³ bond. Notably,

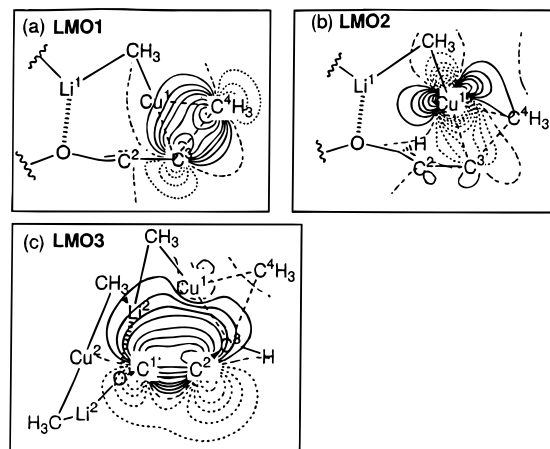


Figure 4. Contour plots of localized Kohn–Sham MOs (B3LYP/631A) of **TS**: (a) **LMO1** on the C²–C³–C⁴ plane, (b) **LMO2** on the C²–C³–Cu¹ plane, and (c) **LMO3** on the C¹–C²–Cu¹ plane. Contour levels in e·au^{−3} are from −0.30 to +0.30 at intervals of 0.05. Positive contours are solid, negative are dotted, and nodal lines are long dashes.

LMO3, shown on the C¹–C²–Cu¹ plane, indicates that the forming enolate π -orbital acts as a donor ligand to the Cu¹(III) atom. This electronic property is reflected structurally in the π -allylcopper-type geometry for Cu¹(C³C²C¹) moiety^{17,25,44} with the Cu¹–C distances of 2.093–2.458 Å.

The product **PD** is a lithium enolate of butanal, complexed simultaneously with MeCu(I) and with a MeCu/MeLi cluster. MeCu(I) is weakly bound to the enolate double bond (C¹–Cu¹ = 2.223 Å and C²–Cu¹ = 2.148 Å) which precipitates in a polymeric state. In the gas phase, the dissociated pair of the lithium enolate (**ENOLATE**) and **MeCu** is energetically disfavored by 32.1 kcal/mol (cf. Figure 1).

The Solvent Effects. The solvation effects were investigated (B3LYP/321A) for the important C–C bond formation stage of the reaction (Figure 5). One water molecule was put on each of the two lithium atoms of **TS** (Figure 3), as such a solvation state was found in the known crystal structure of the dimer **A**.⁸ Notably, the gross structure of the solvated **TS** (**TS·2H₂O**), particularly, for the geometry of atoms directly bonded to the acrolein moiety, is very similar to the unsolvated one in Figure 3. The major differences reside in the bonds connecting the two lithium atoms to the Me–Cu²–Me moiety and the length of the Li²–C⁵ bond, which is now virtually broken. The energy of the solvated **TS** relative to solvated reactant⁴⁵ remained virtually unchanged as compared to the unsolvated cluster (Me₂CuLi)₂, i.e., it decreased only by 0.1 kcal/mol at the B3LYP/321A/B3LYP/321A level.⁴⁶

Reactions of Me₂CuLi–LiCl and Me₂CuLi with Acrolein. From what was observed in the dimer calculations in this and the preceding article, the second cuprate molecule in the dimeric cluster seems essentially nonfunctional. We therefore also

(44) Gais, H.-J.; Müller, H.; Bund, J.; Scommoda, M.; Brandt, J.; Raabe, G. *J. Am. Chem. Soc.* **1995**, *117*, 2453–2466. Persson, E. S. M.; van Klaveren, M.; Grove, D. M.; Bäckvall, J.-E.; van Koten, G. *Chem. Eur. J.* **1995**, *1*, 351–359, references cited therein.

(45) The solvated dimer shown in Figure 4 is an isomer of the previously reported solvated one (refs 10 and 11). The present isomer is 0.7 kcal/mol more stable than the previous at the B3LYP/321A/B3LYP/321A level.

(46) Most of the stationary points in this and the preceding article (ref 9) were investigated both at the B3LYP/631A and B3LYP/321A levels (only some representative data shown in Table 1 in the preceding article). The geometries were very similar to each other, allowing qualitative comparison of structural data at different levels. The qualitative energy profiles were also the same for both levels of theory, though there were considerable difference in the absolute magnitude of energies (relative to reactants). This difference is likely due to the deficiency of the 321A basis set in evaluating lithium–oxygen and copper–olefin interactions.

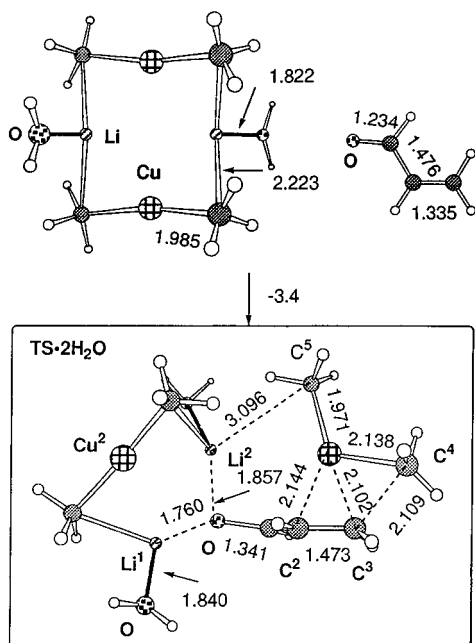


Figure 5. Reactants and TS in the $[\text{Me}_2\text{CuLi}(\text{H}_2\text{O})_2]_2$ addition to acrolein. Bond lengths are in Å at the B3LYP/321A level. The energy changes at the B3LYP/631A/B3LYP/321A level are shown on the arrows. Total energies of solvated reactant and acrolein at the B3LYP/631A/B3LYP/321A level are -3608.34614 and -191.91127 hartrees, respectively.

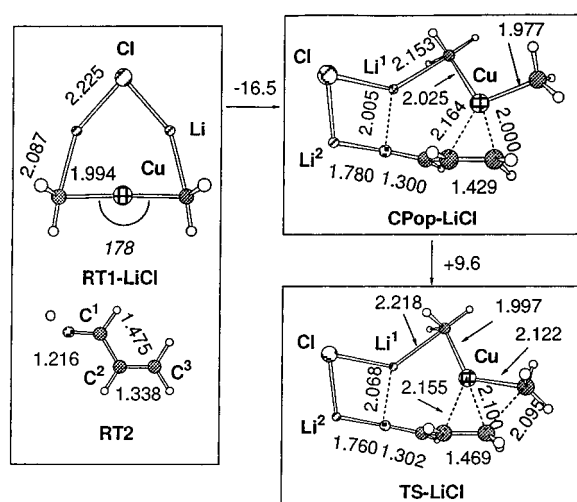


Figure 6. Reactants, open complex, and TS in the conjugate addition of $\text{Me}_2\text{CuLi}\cdot\text{LiCl}$ to acrolein. Bond lengths are in Å at the B3LYP/631A level. The energies near arrows are at the B3LYP/631A/B3LYP/631A level are in parentheses. The value of imaginary frequency of **TS-LiCl** is $334.0i\text{ cm}^{-1}$. Total energy of **RT1-LiCl** is -2195.57684 hartree at the B3LYP/631A/B3LYP/631A level.

examined the monomeric cluster $\text{Me}_2\text{CuLi}\cdot\text{LiCl}$ (**RT1-LiCl**) to see if it also reacts smoothly with acrolein. As shown in Figure 6, the structures of the open complex (**CPop-LiCl**) and the open TS (**TS-LiCl**) were found to be virtually identical to those for the dimer, except for the difference in the “bridging” LiCl moiety. The activation energy (Figure 1b) turned out to be essentially the same (9.8 kcal/mol) as that of the dimer (10.4 kcal/mol).

For further comparison of the cluster structures, we examined stationary points for the minimum cluster Me_2CuLi (energies in Figure 1c and structures in Figure 7; **CPcl-m** was previously examined.)^{10,24b,47} Unlike the dimer cluster, the minimum energy structure of this monomeric cluster has been found to be an open form **RT1-m**,¹⁰ since the cluster size is too small to

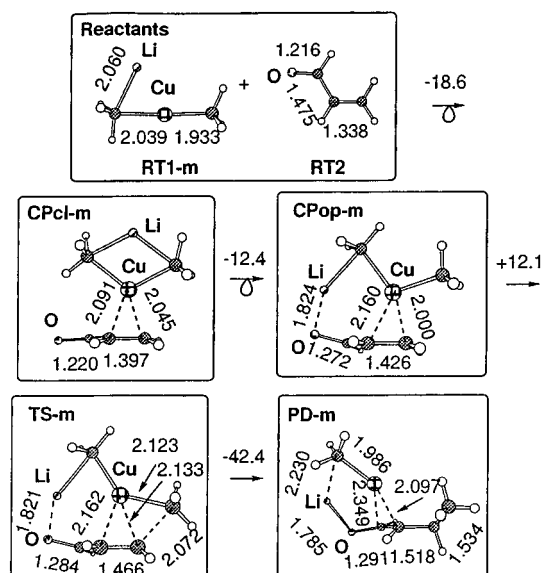


Figure 7. Structures of representative stationary points in the conjugate addition of Me_2CuLi to acrolein. Bond lengths are in Å at the B3LYP/631A level. The energy changes on the arrows are at the B3LYP/631A/B3LYP/631A level are in parentheses. The value of imaginary frequency of **TS-m** is $356.5i\text{ cm}^{-1}$. Energies of **RT1-m** and **RT2** are -1727.68718 and -191.91197 hartrees at the B3LYP/631A/B3LYP/631A level, respectively.

accommodate the linear $\text{Me}-\text{Cu}-\text{Me}$ structure found in the dimer (hence Me_2CuLi is less stable than its dimer). Upon complexation with acrolein, the cluster closes to form **CPcl-m**. This process results in large energy gain due to the formation of the charge-stabilized four-centered structure as well as to the copper-olefin complexation. In contrast to the situation in the larger and more flexible clusters, the carbonyl group in **CPcl-m** does not interact with the lithium atom, as it is placed far away from the carbonyl oxygen because of structural rigidity of the four-centered cluster. We also located an open complex **CPop-m** and the TS of C-C bond formation **TS-m**. In light of the “open” nature of **RT1-m**, the open complex may be directly accessible from **RT1-m** rather than via **CPcl-m**. (There also may exist a $\text{Li}/\text{carbonyl}$ complex like **CPLi**, but we did not look for this as it is unlikely to be directly related to the reaction. There also should be a transition state like **TSiso2** between **CPcl-m** and **CPop-m**, which we did not search since **CPop-m** seems to be accessible directly from **RT1-m**.) The activation energy of 12.1 kcal/mol from **CPop-m** to **TS-m** is comparable to those obtained for higher clusters. The stationary points for Me_2CuLi may be viewed as the “core structure” in each of the corresponding stationary points in the reaction of $(\text{Me}_2\text{CuLi})_2$ and $\text{Me}_2\text{CuLi}\cdot\text{LiCl}$. The product structure is a mixed cluster of a lithium enolate and MeCu . We would conclude that once **RT1-m** forms in a significant quantity in solution, it would have an equal chance to undergo conjugate addition to acrolein.

¹³C NMR Chemical Shifts. Experimental ^{13}C NMR chemical shift values provided valuable experimental data points, to which our calculations can be compared. Among recent ^{13}C NMR studies, the complex formation between 10-methyl- $\Delta^{1,9}$ -2-octalone and $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ (Figure 8a) presents a case closest to the present one.¹⁷ Although the present computational power does not allow high-precision calculations of this molecule itself, we considered that the difference of the chemical shift values between the complexes and the starting enone will provide a useful standard reference, with which one can compare the data calculated for acrolein.

(47) Dorigo, A. E.; Morokuma, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1884–1886.

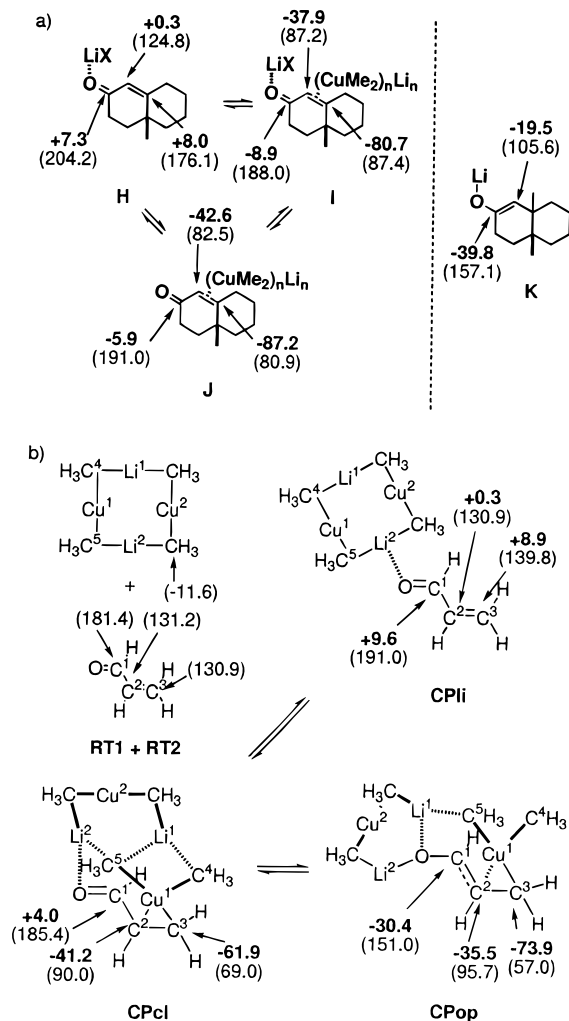


Figure 8. Experimental (a) and calculated (b) ¹³C NMR data in ppm: raw chemical shift data are in parentheses, and the shift changes relative to the starting carbonyl compound in bold. (a) Representative experimental data for the enone/cuprate complexes in the conjugate addition of Me₂CuLi·LiI to 10-methyl-Δ^{1,9}-2-octalone (ref 17). (b) The calculated (GIAO-B3LYP/631A) ¹³C NMR chemical shift values (parentheses) and the shift changes (bold) relative to acrolein. See Figure 2 for 3D representation of the structures.

Experimentally, a few types of species (each consists of few signals due to structural isomers) formed (Figure 8a) and decreased as the conjugate addition proceeded. **H**, **I**, and **J** are examples of intermediate species assigned to the observed signals.¹⁷ One immediately finds agreement of the data calculated for the lithium complex **CPlI** (Figure 8b) with the experimental signal ascribed to a lithium/carbonyl complex **H** (the nature of the X group has not been specified).⁴⁸ For copper complexes **I** and **J**, olefinic carbons undergo significant upfield shift, while the carbonyl carbon remains relatively unchanged. The observed shifts of the olefinic carbons for **I** and **J** can be qualitatively accounted for by either **CPcI** or **CPop**. On the other hand, the carbonyl group in **CPcI** maintains its carbonyl character, making the carbonyl carbon signal shifted only by +4.0 ppm, while the carbonyl group in **CPop** assumes much of an enolate character, making the carbonyl carbon signal shifted by as much as -30.4 ppm. The observed carbonyl carbon shifts for **I** (-5.9 ppm) and **J** (-8.9 ppm) falls between those of **CPcI** and **CPop**; a **CPcI/CPop** equilibrium ratio of ca. 2:1 would explain the experimental feature. This interpretation

(48) Experiments did not tell if this is a cuprate/enone complex or simply a lithium halide/enone complex.

of the NMR chemical shift data is, however, not consistent with the energetics we have obtained above. Namely, **CPcI** is less stable than **CPop** by 4.9 kcal/mol, and the barrier for conversion of **CPcI** to **CPop** is only 1.2 kcal/mol at **TSiso2**. Thus, one would expect that **CPop** is dominant in equilibrium. Further studies are hence required for the more definite assignment of the experimental NMR shift data for species **I** and **J**.⁴⁹ However, at the present stage we can conclude that a lithium/carbonyl complex such as **CPlI** is a species responsible for the spectra assigned to **H** and a copper complex such as **CPcI** or/and **CPop** for **I** and **J**.

Discussion

The above results represent the first computational simulation of the reaction pathway of large polymetallic cuprate clusters with an unsaturated carbonyl compound. The energy profile and structures shown in Figure 1 and Scheme 2 are consistent with the basic idea of the cuprate reaction mechanism based on the experimental observations. The present work demonstrated firstly that there is a rational pathway for a dimer to undergo conjugate addition and, secondly, that lithium and copper atoms cooperate to facilitate the reaction. A series of complexes exist in equilibrium with each other before the TS of irreversible C–C bond formation is reached. This agrees with the conventional mechanistic sketch discussed in Scheme 1. Theory supported the formation of cuprate/enone complexes previously proposed (**A** and **B**) and suggested a new three-point binding “open” complex **CPop**. We also noted that these complexes will readily interconvert with each other and go to the product only through **CPop**. Interestingly, the energy profile in Figure 1a clearly shows that the olefinic face selection and the C–C bond formation take place as separate steps and may be independently affected by reaction conditions.

Charge transfer from the cluster to acrolein through a copper atom characterizes the present reaction pathway, which hence possesses some similarity to the electron-transfer mechanism speculated in earlier mechanistic studies.^{3,4,50} Olefinic bond isomerization was observed during conjugate addition of Me₂CuLi to a *cis*-enone having bulky substituents, and such double bond rotation has often been taken as a sign of single electron transfer mechanism of conjugate addition.⁵¹ The present results studied offer a certain alternative interpretation of the observed bond rotation. Thus, recognizing that the process between the reactants and **CPop** is reversible and that the enolate moiety in the intermediate **CPop** is acting as a donor ligand to the Cu(III) center, one can speculate that coordination of a strong ligand to the Cu(III) center in **CPop** may loosen the enolate/Cu bonding (i.e., generation of a discrete intermediate such as **F**) and result in double bond isomerization (after reversion to the starting material).

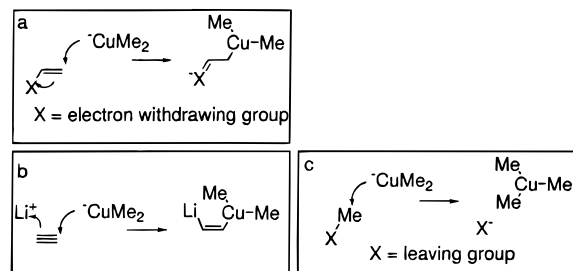
We found close similarity in the structure and energies of stationary points in the reaction of the dimer and Me₂CuLi·LiCl

(49) There are several possible explanations for this discrepancy. The experiment is for complex enone systems, while calculations are for acrolein. The present NMR chemical shift calculation at the B3LYP/631A level at the B3LYP/631A optimized geometries may not be accurate enough. One may also require a better optimized geometries with polarization functions (ref 40 and see, also: Schindler, M.; Kutzelnigg, W. *J. Am. Chem. Soc.* **1983**, *105*, 1360–1370.) and a better basis set at triple- ζ plus polarization level (ref 40 and Sieber, S.; von Ragué Schleyer, P. Gauss, J. *J. Am. Chem. Soc.* **1993**, *115*, 6987–6988; reference cited therein.). One may also speculate a solvent effect. **CPcI** (with a weak lithium/carbonyl π -coordination) will receive more solvent molecules on the two lithium atoms than those in **CPop**, in which Li¹ is already heavily coordinated and consequently that **CPcI** may become more stable in solution than **CPop**.

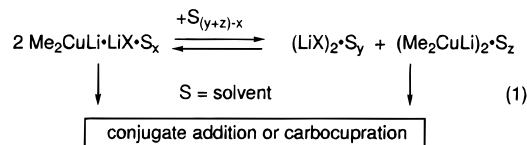
(50) We found little biradical character in the complexes and the TSs as shown by the lack of RB3LYP-UB3LYP instability (vide supra).

(51) House, H. O.; Weeks, P. D. *J. Am. Chem. Soc.* **1975**, *97*, 2770–2777.

Scheme 3



species. This observation indicates that as long as the cluster has a reasonable size and can accommodate the linear Me–Cu–Me arrangement (as in the dimer), it exists as a thermodynamically stable species and provides a framework for smooth electron-flow. In light of the predominance of $(\text{Me}_2\text{CuLi})_2$ in ethereal solution, dimer participation is certainly not an unreasonable possibility.^{6,7} On the other hand, given the comparable activation energy of the $\text{Me}_2\text{CuLi}\cdot\text{LiCl}$, we can also consider that $\text{Me}_2\text{CuLi}\cdot\text{LiX}$ may be a reactive species under the conditions where it exists in high concentration.²⁹ The predominance of $(\text{Me}_2\text{CuLi})_2$ in an ether solution of $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ has been attributed to the equilibrium (eq 1),¹¹ which favors the right side owing to the high stability of a LiI cyclic dimer (or oligomer). Under such conditions, the dimer will be a reactive species. If the equilibrium is shifted to the left side as for $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ in THF,²⁹ $\text{Me}_2\text{CuLi}\cdot\text{LiX}$ may act as a reactive species. The same possibility also exists in the carbocupration reaction, where $\text{Me}_2\text{CuLi}\cdot\text{LiCl}$ was calculated to exhibit almost the same reactivity as $(\text{Me}_2\text{CuLi})_2$.⁹ If monomeric Me_2CuLi existed in solution,¹¹ it could undergo C–C bond formation reaction with activation energy comparable to the larger clusters.



The products of conjugate addition and carbometalation reactions⁹ are much different from each other (the latter covalently retains the copper atom in the product, while the former only very loosely), and their similarity has not been well appreciated thus far. However, the present theoretical analyses revealed that they share a common important character, as shown in the simplified picture in Scheme 3. In both reactions, a cuprate moiety donates electrons to one (electrophilic) end of the olefin (or acetylene) through the filled d -orbital, and the donated electrons flow into an electron sink attached to the other end of the C–C bond. The electron sink in the conjugate addition is the internal carbonyl group (Scheme 3a), and, in the acetylene carbocupration, it is the lithium atom in the cluster (Scheme 3b). Similar electron flow (Scheme 3c) has been considered for cuprate alkylations with MeX (X = halogen, tosyloxy).¹² The transient Cu(III) species then undergo reductive elimination to form a C–C bond. The TS of the reductive elimination of Me_3Cu was recently reported²⁴ and shows remarkable similarity to those obtained for carbocupration and conjugate addition. As illustrated in Figure 9, all three TSs have a near square planar, tetra-coordinated geometry with a shrinking C–C bond shown by a double-headed arrow. The geometry difference as to the fourth ligand (a dotted line) may be the consequence of the difference of intra- and intermolecular coordination.

As in the carbocupration reaction, the present mechanism of conjugate addition can also be viewed as a “trap-and-bite”

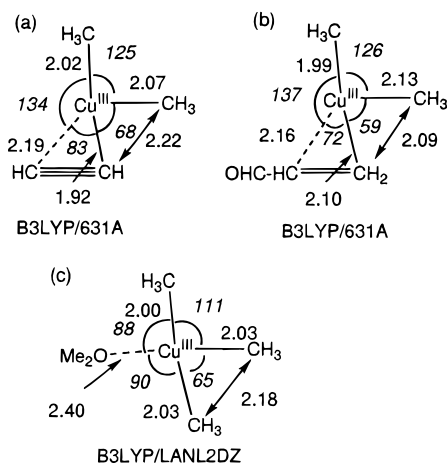
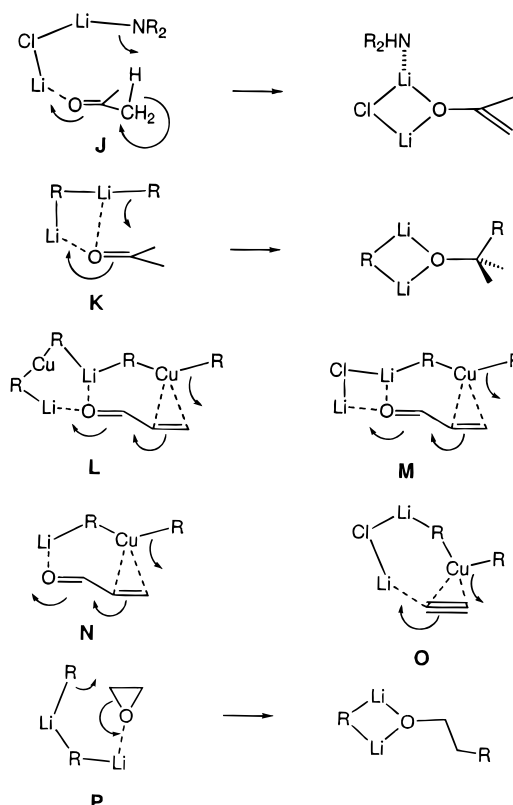


Figure 9. The transition structures of C–C bond formation in (a) $(\text{Me}_2\text{CuLi})_2$ addition to acetylene, (b) conjugate addition of $(\text{Me}_2\text{CuLi})_2$ to acrolein, and (c) reductive elimination from $\text{Me}_3\text{Cu}(\text{Me}_2\text{O})$ reported (ref 24b). Bond distances in Å are shown in plain, and angles in deg are in italic.

Scheme 4



process in that the cluster first traps the substrate by opening the cluster to tightly bind the substrate with the copper atom and subsequently undergo C–C bond formation. In a sense, the conjugate addition reaction is a 1,4-addition of MeLi assisted by copper, as the acetylene carbocupration involves a copper-assisted 1,2-addition of MeLi .

The process of a cluster opening pathway⁵² for reaction of nucleophiles and bases is not unique to organocup reactions (Scheme 4). Recent experimental and theoretical studies suggested that the “open” forms of organolithium clusters play important roles in other reactions.^{20,41,52,53} The crystallographic studies of lithium amide bases^{41b} suggested the kinetic impor-

(52) Cf.: Jackmann, L. M.; Rakiewicz, E. F. *J. Am. Chem. Soc.* **1991**, *113*, 1202–1210.

tance of an "open dimer", such as **J**.^{41a} The TSs of conjugate addition (**L**, **M**, and **N**) reveal open dimer structures, which tightly hold the carbonyl substrate. In the addition of MeLi dimer to acetaldehyde, an open dimer TS (**K**) gives the product with very low activation barrier.^{41c} One can view the conjugate addition reaction (**L**, **M**, and **N**) as a stretched form of **K**, which is the TS of (RLi)₂ addition to a carbonyl compounds.^{41c} One can also note similar "open cluster structures" in the TS of carbocupration (**O**)⁹ and in the epoxide alkylation with MeLi dimer (**P**).⁵⁴ An apparent merit of such an open pathway resides in the realization of the push-pull mechanism by allowing a coordination-free nucleophile to attack an electronic center which is activated by an intramolecular electrophilic metal.

Conclusion

In this and the preceding papers,⁹ we have examined the reaction pathways of cluster cuprate reagents in two of the most important reactions characteristic of organocuprate chemistry, carbocupration, and conjugate addition. The essence of cuprate addition resides in the electron donation from the electron-rich cuprate anion to the substrate, which generates a transient Cu(III) species. Electron donation processes do not occur with the simple MeCu reagent. Electrophilic assistance by the lithium atom plays an essential role. The rate retardation effects of polar and strongly coordinating agents (which generate a naked R₂Cu⁻) on conjugate addition, acylation, and carbocupration^{9,18} indicated experimentally that the presence of a solvent-separated lithium ion (and perhaps also a larger alkali metal ion like sodium cation)⁵⁵ in solution is not sufficient for the cuprate reactions and that the lithium atom must be incorporated in the cluster. As has been demonstrated theoretically in the series of structural rearrangements in conjugate addition (Scheme 2), the two Lewis acidic lithium atoms in the cluster cooperatively assist the electron-transfer process. The cluster opening is triggered by electron transfer from the cuprate moiety to the substrate. Active role of lithium atoms was also found in the carbocupration of acetylene.⁹ The cations in the cuprate cluster therefore play important roles in the C-C forming stage of the reaction.

As the cationic metal is incorporated in the cluster structure, its identity will also influence various other steps of the reaction pathway, e.g., the equilibrium concentrations of the cluster species, which will affect the overall rate of the conjugate addition and carbocupration reactions. Solvation effects may not significantly affect the C-C bond forming stage of the

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(54) Harder, S.; van Lenthe, J. H.; van Eikema Hommes, N. J. R.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1994**, *116*, 2508–2514.

(55) Bertz, S. H.; Gibson, C. P.; Dabbagh, G. *Organometallics* **1988**, *7*, 227–232.

carbocupration reaction and the conjugate addition, but it will have a significant impact on the energies and the pathway before and after this stage. Finally, we expect that the "open" cluster model and the presence of two discrete rate limiting steps in the conjugate addition will generate new concepts for designing asymmetric conjugate additions, which has thus far been based largely on closed cluster models.⁵⁶ The present studies will also serve as the first step toward elucidation of the dramatic rate accelerating effects of Lewis acidic additives such as Me₃SiCl, in which we have had a long standing interest.^{26,57}

In light of the extensive theoretical studies, we can draw the following conclusions as to the viability of theoretical methods in the analysis of bond forming/breaking processes in organo-copper chemistry. First, the MP2 and B3LYP methods give chemically sensible structures and energies, while the calculations on the HF levels are totally unreliable. Relativistic effects do not appear to exert large influence on the chemistry of cuprates. In light of its high cost performance, good structures, and reasonable energies, the B3LYP method would be the method of choice at the present time.

Acknowledgment. We thank Prof. B. H. Lipshutz for helpful comments. Financial support from the Ministry of Education, Science, Sports and Culture, Japan to E.N. and from the National Science Foundation to K.M. is gratefully acknowledged. We thank the generous allotment of computer time from the Institute for Molecular Science, Japan. S.M. thanks JSPS for a predoctoral fellowship.

Supporting Information Available: Structures of the **CPLi**, **TSiso1**, **CPcl**, **CPop**, **TSiso2**, **TS**, **PD**, **ENOLATE**, **CP-LiCl**, **TS-LiCl**, **CPcl-m**, **CPop-m**, **TS-m**, and **PD-m** and **TS·2H₂O** (14 pages). See any current masthead page for ordering and Internet access instructions.

JA964209H

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