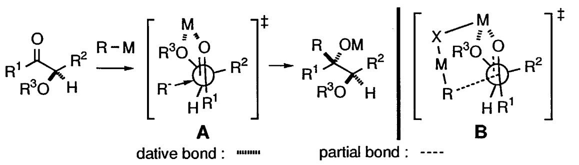
# Open Dimer Participation in Chelation Controlled Addition of Methyllithium Dimer to *α*- and *β*-Alkoxy Aldehydes

Seiji Mori, Byeang Hyean Kim,† Masaharu Nakamura, and Eiichi Nakamura*
*Department of Chemistry, The University of Tokyo, Bunkyo-ku, Tokyo 113*

(Received July 23, 1997; CL-970576)

The chelation controlled additions of a MeLi dimer to alkoxy carbonyl compounds occur through an open dimer cluster, in which only one lithium atom participates in the chelate formation and the other acts as an anchor of the methyl nucleophile to be delivered to the carbonyl group. Solvation of a lithium atom with a water molecule does not change much the structure of the transition state.

Chelation controlled carbonyl addition reaction is the classical method of stereocontrol.[1] Although a variety of qualitative discussions have been made on the basis of schematic stereochemical analyses of the transition states (cf. **A**), little has been known for the details of the structures of the intermediates and transition states of the reaction. We report in this communication the results of quantum mechanical calculations on the addition of MeLi dimer to α- and β-alkoxy carbonyl compounds. The present studies elucidated for the first time the importance of an open cluster (cf. **B**)[2] in the chelation controlled carbonyl addition of bimetallic organometallic species, and will provide a basis for the construction of rational models for carbonyl addition of aggregated organometallics. Together with the parallel studies[3] on the monomeric species, the present studies showed that the chelation controlled addition to β-alkoxy carbonyl compound (β-chelation) may proceed through two stereochemically distinct pathways of similar energies, while that to α-alkoxy one (α-chelation) through a single pathway.[4] As has been found experimentally,[5] dimeric MeLi was found to be a highly reactive species and the transition state of the addition reaction is earlier than those of monomeric $Me_2Mg$ and monomeric MeLi.[6]



The model reactions were constructed on the bases of our previous studies on a solvated and unsolvated MeLi cyclic dimer to formaldehyde and acetaldehyde.[2a] α-Chelation control was studied first for the reaction with methoxyacetaldehyde (Figure 1). We found that four-centered dimeric MeLi forms a complex (**αCPcl**)[7] with retention of its cyclic structure as well as an open complex (**αCPop**) by opening its methyl-bridged structure. The latter goes to the product (**αPD**) via a transition structure (TS) involving an open dimeric structure (**αTS**). Alternative possibilities of chelate complexes **C** and **D**, wherein both lithium atoms are engaged in chelate formation, were found not to be stationary points and to isomerize to **αCPcl**. Analysis of intermediates on the intrinsic reaction coordinate (IRC)[8] near **αTS** indicated that **αCPop** goes directly to **αPD**. It is most notable that, in this "open dimer pathway," only one ($Li^1$) of the two lithium atoms is engaged in chelation and another ($Li^2$) acts as an anchor of the nucleophilic $C^1H_3$ group.[9] We could not locate a TS, which directly connects the closed complex **αCPcl** and the product.

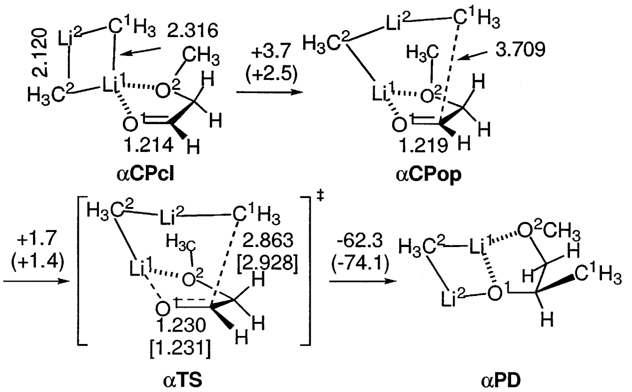
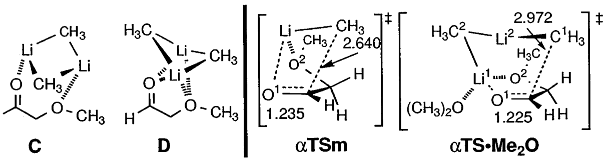


**Figure 1.** Complexes, TS, and product in the addition of $(MeLi)_2$ to methoxyacetaldehyde. Bond lengths in Å are at the HF/3-21G level. Energy changes in kcal $mol^{-1}$ are at the MP2/6-31+G(d)//HF/3-21G level in brackets are at the HF/3-21G level. Total energy of **αCPcl** at the MP2/6-31+G(d)//HF/3-21G level is -361.976226 hartree. The geometry obtained by the self-consistent reaction field method ( in bracket, $\varepsilon_0$=4.34 of ether, 20 °C) suggests that the effect of solvent polarity is small.

In **αCPcl**, the $C^1$–$Li^1$ bond is elongated and then cleaved to generate the open dimer chelate **αCPop**, wherein the $C^1$–$Li^2$–$C^2$ bond becomes nearly linear (166°). The forming C–C bond (2.863 Å) in **αTS** is very long (much longer than that in **αTSm** for MeLi monomer, 2.640 Å, or in TS in the $Me_2Mg$ reaction,[3] which is 2.512 Å), and the activation energy from **αCPcl** to **αTS** is very small (5.4 kcal $mol^{-1}$). Being an earlier and more flexible TS (due to the presence of the $C^2H_3$-$Li^2$ bridge) than the α-chelation TS of the $Me_2Mg$-monomer reaction,[3] the dimer TS (**αTS**) ought to be less sensitive to nearby steric hindrance. It is notable that such structural features of the TS remains unchanged even when $Li^1$ is solvated with a water molecule[2a] as seen in the TS solvated with $Me_2O$ (**αTS•Me$_2$O** with the even longer forming C–C bond length of 2.972 Å).



The reaction pathway of β-chelation controlled reaction was examined next for the addition of MeLi dimer to 3-methoxypropanal. (Figure 2). As in the α-chelation reaction, we could locate a chelation complex of the closed dimer **βCPcl** and two isomeric TSs (**βTSb** and **βTSc**) involving an open dimeric

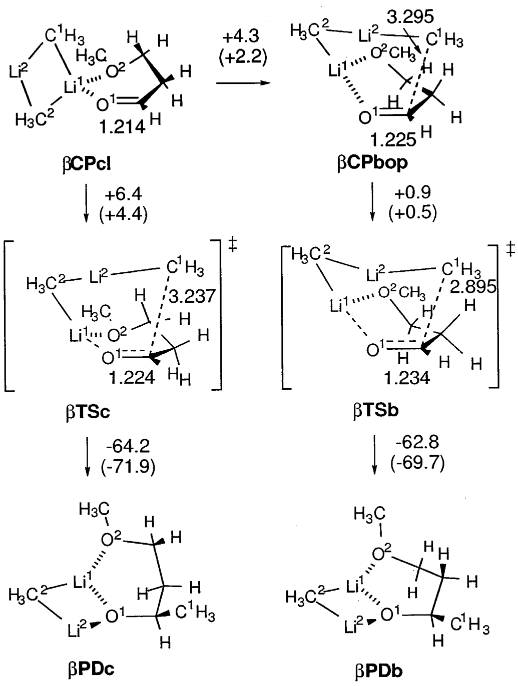
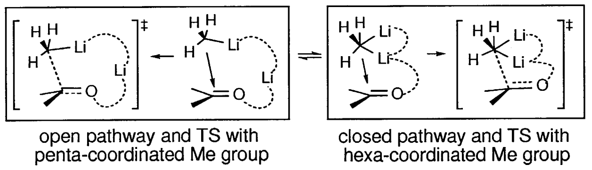


**Figure 2.** Complexes, TSs, and products in the addition of (MeLi)$_2$ to 3-methoxypropanal. Total energy of **βCPcl** at the MP2/6-31+G(d)//HF/3-21G level is -401.150503 hartree.

structure. In **βTSb**, the chelate structure formed by the aldehyde substrate and Li$^1$ is in a boat form, and in **βTSc** it is in a twist chair form. The boat TS (**βTSb**) was more stable than the chair one (**βTSc**) by 1.3 kcal mol$^{-1}$. Similar energetic trend favoring a (stereochemically ill-defined) boat TS was also found in the Me$_2$Mg addition to the same substrate. Following the path along the IRC from **βTSb** revealed the presence of an open boat complex intermediate **βCPbop**, whereas the same procedure for **βTSc** led directly to **βCPcl**.[10] As in the α-chelate reaction, chelation was found to be retained throughout the reaction pathway from the closed complexes to the products, and the TSs of the β-chelate reactions are very early.

In summary, in the α- and β-chelation controlled additions, alkoxy aldehydes coordinate to a single lithium atom (Li$^1$) of the MeLi dimer. The C$^2$H$_3$-Li$^2$ group acts as an anchor for the delivery of the nucleophilic methyl group realizing a push-pull action in the nucleophilic addition. This anchor group may be replaceable by certain other groups as lithium halide and the product alkoxide. A general scheme **B** will be applicable to other organometallic species such as Grignard reagents and organozinc compounds.[11] The calculated energetics and structures are consistent with the low selectivities experimentally encountered for alkyllithium reagents.[12,13,14]

We could not locate a pathway directly connecting the closed complexes and the TSs of the reaction. This is due to the difficulty of a penta-coordinated bridging alkyl group to participate in nucleophilic addition (see below). We therefore propose that opening of a cyclic cluster structure is an essential part of the nucleophilic chemistry of alkyllithium clusters as was recently discussed in organocuprate reactions.[15] Although the crystal structures of organolithium aggregates often reveal closed structures[5] such as **αCPcl** giving us an impression that the reactive species in solution may also be closed aggregates, the present studies suggest that the reality may well be different and more complex.[16]



This work was supported by Grant-in-Aid for Scientific Research on Priority Areas (No. 283, "Innovative Synthetic Reactions") from Monbusho. We thank the Institute for Molecular Science, Japan for computational time. S.M. thanks JSPS for a predoctoral fellowship. B.H.K. thanks Korea Science and Engineering Foundation (KORSEF) fellowship for the visiting scholarship.

## References and Notes

† On leave from Department of Chemistry, Center for Biofunctional Molecules, Pohang University of Science and Technology, Pohang 790-784, Korea.

1 D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959). For pertinent recent references, see ref 3. For the case of olefinic substrates, see: M. Arai, T. Kawasuji, and E. Nakamura, *J. Org. Chem.*, **58**, 5121 (1993).

2 a) M. Nakamura, E. Nakamura, N. Koga, and K. Morokuma, *J. Am. Chem. Soc.*, **115**, 11016 (1993). b) M. Nakamura, E. Nakamura, N. Koga, and K. Morokuma, *J. Chem. Soc., Faraday Trans.*, **90**, 1789 (1994). c) S. Harder, J. H. van Lenthe, N. J. R. van Eikema Hommes, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **116**, 2508 (1994).

3 S. Mori, M. Nakamura, E. Nakamura, N. Koga, and K. Morokuma, *J. Am. Chem. Soc.*, **117**, 5055 (1995).

4 V. S. Safont, V. Moliner, M. Oliva, R. Castillo, J. Andrés, F. González, and M. Carda, *J. Org. Chem.*, **61**, 3467 (1996).

5 J. F. McGarrity, C. A. Ogle, Z. Brich, and H.-R. Loosli, *J. Am. Chem. Soc.*, **107**, 1810 (1985). For crystal structures of BuLi dimer, see: M. A. Nichols and P. G. Williard, *J. Am. Chem. Soc.*, **115**, 1568 (1993). N. D. R. Barnett, R. E. Mulvey, W. Clegg, and P. A. O'Neil, *J. Am. Chem. Soc.*, **115**, 1573 (1993). T. Kottke and D. Stalke, *Angew. Chem., Int. Ed. Engl.*, **32**, 580 (1993).

6 The calculations were performed with Gaussian 94 program (M. J. Frisch, *et al.* Gaussian Inc. 1995). Geometry optimization was performed without symmetry constraints at the HF/3-21G level, and TSs were characterized by normal coordinate analysis. The energies were obtained at the MP2/6-31+G(d) level for the HF/3-21G structures. We have confirmed for the MeLi addition to formaldehyde, that the HF/3-21G structures reproduce well the MP2/6-31+G(d) geometries for TS, while *the HF/6-31+G(d) geometry does not.* The reasons for this fortuitously good performance of the HF/3-21G method is unclear at this time.

7 For the energetics of such complexation reaction, see ref 3.

8 C. Gonzalez and H. B. Schlegel, *J. Phys. Chem.*, **94**, 5523 (1990).

9 In αTS, the C=O$^1$-Li$^1$-O$^2$ dihedral angle of 20.7° and the C=O$^1$-Li$^1$ angle of 110.4° show that chelating Li$^1$ atom favors the planar coordination scheme (*n*-coordination). Note, however, that ideal *n*-coordination cannot be achieved in αTSm due to structural constraints.

10 This difference, however, is of little consequence in light of the Curtin-Hammett principle, since **βCPbop** is almost a shoulder on the potential surface near **βTSb**.

11 Cf. E. C. Ashby and J. T. Laemmle, *J. Org. Chem.*, **40**, 1469 (1975). M. Yamakawa and R. Noyori, *J. Am. Chem. Soc.* **117**, 6327 (1995).

12 Note however that the experimental results are generally much perturbed by participation of the lithium alkoxide products.

13 Cf. α-chelation: W. C. Still and J. H. McDonald III, *Tetrahedron Lett.*, **21**, 1031 (1980).

14 Cf. β-chelation: T. J. Leitereg and D. J. Cram, *J. Am. Chem. Soc.*, **90**, 4011 (1968).

15 E. Nakamura, S. Mori, M. Nakamura, and K. Morokuma, *J. Am. Chem. Soc.*, **119**, 4887 (1997). E. Nakamura, S. Mori, and K. Morokuma, *J. Am. Chem. Soc.*, **119**, 4900 (1997).

16 Cartesian coordinates of optimized stationary points are available upon request to the corresponding author.