# Theoretical Studies on S_N2-Reaction of MeBr with Me2CuLi·LiCl. Solvent and Cluster Effects on Oxidative Addition/Reductive Elimination Pathway

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Lithium organocuprate reagents ($R_2CuLi$) are unique for their ability to undergo $S_N2$ substitution of an alkyl halide.[1] The reaction takes place with inversion of stereochemistry at the electrophilic center,[2,3] and the reaction rate is first-order both to the cuprate and to the electrophilic substrate.[4] Kinetic isotope effects (KIEs) are consistent with rate-limiting bond breaking involving the electrophilic carbon center.[5]
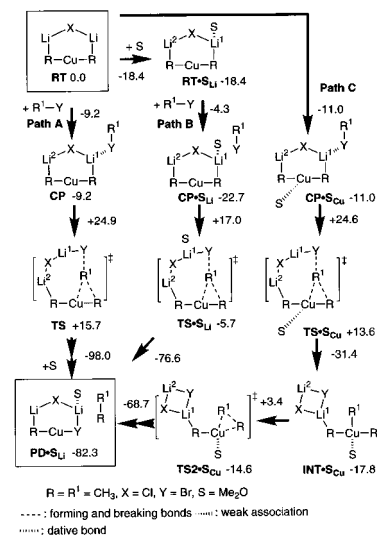
Two mechanistic possibilities have been discussed, a simple $S_N2$ reaction with the R anionic group (eq 1), and the $S_N2$ reaction
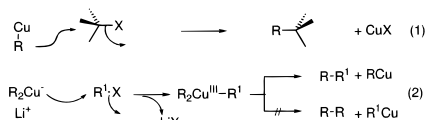


with the Cu atom (i.e., oxidative addition of $R^1X$ to copper) followed by rapid reductive elimination of a trialkylcopper(III) intermediate (eq 2).[6] There has been neither direct experimental evidence to differentiate these pathways nor theoretical analysis on the halide displacement process. A puzzling problem of the second mechanism has been the selective formation of the cross coupling product $RR^1$ without the formation of RR from the Cu(III) intermediate.[7] While lithium organocuprates in solution are aggregated (e.g., $(CH_3)_2CuLi·LiCl$, **RT**, and $[(CH_3)_2CuLi]_2$),[8,9] no discussions on the role of such structures in the alkylation reactions have been made. With the density functional calcula-

## Scheme 1. Substitution Reaction Between Me2CuLi·LiCl and MeBr with and without Me2O[a]



R = $R^1$ = $CH_3$, X = Cl, Y = Br, S = $Me_2O$
----: forming and breaking bonds ···: weak association
······: dative bond

*[a]* The energy changes on each step shown on the arrows are in kcal/mol. The final product mixture in box only suggests one of various possible structures.

tions, we have addressed these unsolved questions in a mechanistic framework incorporating both clusters and solvent coordination.[10]

We examined the $S_N2$ reaction of **RT** and $[(CH_3)_2CuLi]_2$ with $CH_3Br$ in the presence and absence of a coordinating solvent molecule $(CH_3)_2O$ and $(CH_3)_2S$ and found that such cluster species of a reasonable size can equally take part in the alkylation reaction. The **RT**-type species and the dimer are the predominant species in solution,[4,8,9] and their carbon−lithium bonds show fluctional behavior.[11] Such aggregated species will play important roles in the reaction with $\pi$-acceptor electrophiles.[12]

In the unsolvated pathway (path A in Scheme 1), coordination of $CH_3Br$ with the $Li^1$ atom of **RT** generates, with 9.2 kcal/mol (Scheme 1) stabilization energy, a complex (**CP**, Figure 1) in which the $C^2-Li^1$ bond is elongated by 2% and the $C^2-Cu$ bond slightly shortened. Further elongation of the $C^2-Li^1$ bond leads to the transition structure (TS) of C−Br bond cleavage (**TS**) with an activation energy of 24.9 kcal/mol. In **TS**, the $C^1-Br$ bond is elongated by 17% relative to **CP**, and the Br atom is now negatively charged (−0.39). On the other hand, the $C^2-Cu$ cuprate moiety nearly retains its original geometry, the $C^2-Cu$ bond being still short and the $C^2-Cu-C^3$ angle nearly linear.[13] One can identify an "open" cluster structure[12] in **TS**, which is responsible for the push−pull activation of the halide. IRC (intrinsic reaction coordinate) following back from **TS** to the point of $s = -4.81$ amu$^{1/2}$·bohr and subsequent optimization led monotonically downhill to the closed cluster **CP**. IRC following to the forward direction (data not shown) goes through an intermediary (nonstationary) structure similar to **TS2·S_Cu** (vide infra) and smoothly downhill toward ethane and $CH_3Br·LiBr·LiCl$ (**PD·S_Li**).

Effects of solvent coordination were examined next (paths **B** and **C**). Coordination of a molecule of solvent $(CH_3)_2O$ to $Li^1$

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(13) The bromide displacement TS for $[(CH_3)_2CuLi]_2$ is essentially the same as **TS** as to the $C^{2H}_3-Cu-C^{1H}_3-Br-Li$ moiety (details will be discussed in a full paper).
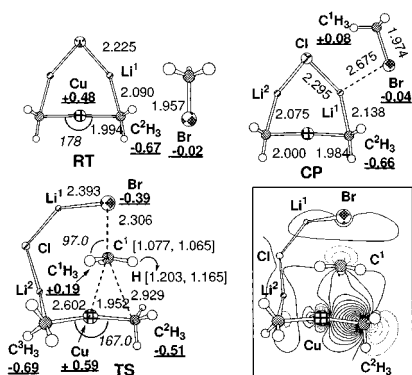
**Figure 1.** B3LYP stationary points in the reaction of $(CH_3)_2CuLi \cdot LiCl$ with $CH_3Br$. Shown are bond lengths in Å, bond angles (in italics) in deg, natural charges (in underlined bold), and the calculated $^2H$ and $^{13}C$ KIEs at $-60$ and $-17$ °C (in brackets). A localized Kohn–Sham orbital in TS is shown in the inset in the $C^1-C^2-Cu$ plane, with the contours from $-0.25$ to $+0.35$ at intervals of $0.025$ in $e \cdot au^{-3}$, with positive and zero contours in solid curves and negative contours in dotted curves. A value of imaginary frequency in **TS** is $218.5i$ cm$^{-1}$.

did not much change the geometries of the complex and the TS (**CP·S$_{Li}$** and **TS·S$_{Li}$**) but lowered the activation energy of the bromide displacement process (path B) by 7.9 kcal/mol.[14] The 17.0 kcal/mol activation energy is a reasonable value for the reaction taking place below ca. 0 °C.

The following experimental primary and secondary KIEs at different temperatures have been determined[5] for the reaction of $(CH_3)_2CuLi \cdot PBu_3$ and $CH_3I$: $1.111 \pm 0.006(-16$ °C) for the $CH_3I/C(^2H)_3I$ pair, and $1.062 \pm 0.003$ ($-17$ °C) for $^{12}CH_3I/$ $^{13}CH_3I$ pair. These values imply linear symmetry (as to the central carbon atom) and loose TS (as to the methyl hydrogen atoms).[15] Theoretical KIEs[16] for the bromide displacement stage were examined for four different systems, **TS** (Figure 1), **TS·S$_{Li}$**, **TS·S$_{Cu}$**, and the TS for $[(CH_3)_2CuLi]_2$.[17] For all cases, the calculated KIE data are in good agreement with the experiments, indicating that the nature of the transition state of the alkylation reaction is well represented by these structures.

While solvent coordination on Cu (path C) has very little effect on the energetics and the structures before the rate-determining C–Br bond cleaving step, it substantially modifies the pathway afterward. Thus, we could not locate any copper-solvated complexes for **RT**, **CP**, and **TS**.[18] Optimization of **CP** and **TS** (in path A) bearing $(CH_3)_2O$ on the Cu atom resulted in the formation of weakly associated structures $(Cu \cdots HCH_2OCH_3,$ ca. 3 Å, $Cu \cdots O =$ ca. 4 Å),[19] **CP·S$_{Cu}$** and **TS·S$_{Cu}$**, respectively. This weak association was little affected by the activation energy ($\Delta E^{\ddagger} = 24.6$ kcal/mol, $\Delta S^{\ddagger} = -3.97$ cal/mol·K).

Stronger solvent coordination to Cu occurs, however, after a negative charge is transferred from the Cu/$C^2H_3$ group to the Br group. Thus, an unstable $(CH_3)_3Cu(III)$ intermediate (**INT·S$_{Cu}$**)[6] was located as a minimum, which gives ethane with an activation energy of only 3.4 kcal/mol via **TS2·S$_{Cu}$**. $(CH_3)_3Cu[(CH_3)_2O]$, lacking the $LiBr \cdot LiCl$ cluster, undergoes reductive elimination

with a much higher activation energy of 8.2 kcal/mol (B3LYP/ 631A).[8] Notably, the KIEs calculated for **TS2·S$_{Cu}$** are far from the experimental data (vide supra), which also indicates that **INT· S$_{Cu}$** is not a kinetically important species.

In **TS**, **TS·S$_{Li}$**, and **TS·S$_{Cu}$**, the stereochemistries at the electrophilic and the nucleophilic carbon centers are inversion and retention, respectively. Since **TS2·S$_{Cu}$** also results in retention at the carbon centers, the same conclusion holds even if **INT· S$_{Cu}$** forms and rapidly decomposes. Note that the group selectivity issue (eq 2) does not arise in paths **A** or **B** or even in path **C** where three methyl carbons are in a different electronic and spatial environment (unless stereomutation takes place with a ≪3.4 kcal/ mol energy barrier).

Putting all the calculations (with and without solvent coordination on one Li center and on the Cu center) together, one can visualize the $S_N2$ reaction of **RT** with $CH_3Br$ in a coordinating solvent as

$$\mathbf{RT \cdot S_{Li} \rightarrow CP \cdot S_{Li} \rightarrow TS \cdot S_{Li} \rightarrow INT \cdot S_{Li} \cdot S_{Cu} \rightarrow}$$
$$\mathbf{TS2 \cdot S_{Li} \cdot S_{Cu} \rightarrow PD \cdot S_{Li} \cdot S_{Cu}}$$

where the notation **S$_{Li}$·S$_{Cu}$** indicates solvation of the two Li atoms and the Cu atom. After **TS·S$_{Li}$**, a positive charge accumulates on the Cu atom, and the solvation at the Cu center becomes thermodynamically favorable.[20] This Cu-center solvation, in addition to that at the Li centers, stabilizes a Cu(III) intermediate **INT·S$_{Li}$·S$_{Cu}$**, which then decomposes to give the products.

The present studies have given the first comprehensive mechanistic pictures on the cuprate substitution reaction. An important function of the open cluster generated from either **RT**, the dimer, or related clusters is to realize a push–pull mechanism with the aid of the Lewis acidic lithium atom.[13] We found experimentally that the free $(CH_3)_2Cu^-$ species, generated by complete de-aggregation of the $(CH_3)_2CuLi \cdot LiI$ reagent, is unreactive,[21] which supports our theoretical model that the lithium cation and the $(CH_3)_2Cu^-$ moiety must be closely associated in the alkylation reaction.[22] In contrast to the reaction with $\pi$-acceptors ($3d_{xz}$ orbital participation),[12] $S_N2$ displacement of the Br atom is effected by the Cu $3d_{z^2}$ orbital which interacts with the C–Br $\sigma^*$ orbital (inset in Figure 1). Finally, one may note that path C, being a typical oxidative addition/reductive elimination reaction involving an organic halide,[20] will serve as a useful model for this important yet mechanistically obscure reaction sequence in the transition metal chemistry.

**Supporting Information Available:** Details of computational methods, geometries of the **CP**, **TS**, **CP·S$_{Li}$**, **TS·S$_{Li}$**, **CP·S$_{Cu}$**, **TS·S$_{Cu}$**, **INT· S$_{Cu}$**, **TS2·S$_{Cu}$**, **PD·S$_{Li}$**, **CP·S$_{Cu}$(ether)**, and **TS•S$_{Cu}$(ether)**, and the TS for bromide displacement in the reaction of $[(CH_3)_2CuLi]_2$ (9 pages, print/ PDF). See any current masthead page for ordering information and Web access instructions.

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(17) $^2H$ and $^{13}C$ KIE values for **TS·S$_{Li}$** at $-17$ °C are 1.179 and 1.068, for **TS·SCu**, 1.157 and 1.067, and for the TS for $[(CH_3)_2CuLi]_2$ are 1.186 and 1.067, respectively.
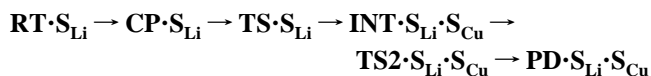
(18) The copper atom in lithium organocuprate does not accept any neutral ligand on copper as confirmed by the lack of such structures in Cambridge Crystallographic Database (version 5.13, 1997). See also: Power, P. P. *Prog. Inorg. Chem.* **1991**, *39*, 75−112.

(19) The effect of the solvent polarity on structures and energetics was also small, as examined for **CP·S$_{Cu}$** and **TS·S$_{Cu}$** with the SCRF method ($\epsilon =$ 4.34 for $Et_2O$.; Wong, M. W.; Wiberg, K. B.; Frisch, M. *J. Chem. Phys.* **1991**, *95*, 8991−8998).

(20) Note that, in an actual solution, **S** in **INT·S$_{Cu}$** and **TS2·S$_{Cu}$** may well be replaced by a halide anion directly attached to the copper atom.

(21) The reaction of $(CH_3)_2CuLi \cdot LiI$ with 1-dodecanyl bromide did not take place (in $Et_2O$, 0 °C → 25 °C) in the presence of 12-crown-4 (see also ref 12a for similar effects in other classes of reactions). We thank A. Hirai for the experiments.

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