Reaction Mechanisms

Mechanism of Remote Conjugate Addition of a Lithium Organocuprate to a Polyconjugated Carbonyl Compound**

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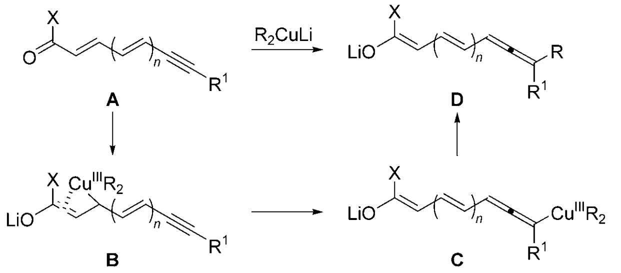
Conjugate addition[1] of a nucleophile to a polyconjugated carbonyl compound is an intriguing reaction as it can potentially result in C–C bond formation at one of the remote carbon atoms. In many cases, however, the regioselectivity may be poor, unpredictable, or condition-dependent, and the origin of the regioselectivity often difficult to determine with certainty.[2,3] The particular combination of a polyenynyl carbonyl compound **A** and a lithium organocuprate is unique in all respects in that the C–C bond formation takes place always at the remote acetylenic carbon atom to give an adduct **D** (Scheme 1).[4,5] Although important pieces of information—NMR spectroscopic identification of the reaction intermediate and the activation energy of the reaction—have been reported,[4b,c] they do not give an answer to the fundamental question as to why the cuprate addition takes place at the acetylene terminal. We report herein a density-functional study on the reaction pathway and the origin of the regioselectivity of this reaction.[6]



Scheme 1. Regioselective conjugate addition of a lithium organocuprate to a polyenynyl carbonyl compound.

What is intriguing is that the low-temperature NMR spectroscopic analysis of the reaction showed the formation of only one species that can be ascribed to a copper/olefin complex structurally best represented by a σ/π-allyl structure such as **B**, but none of what might be more relevant to the formation of the remote addition product (i.e., **C**).[4b,7] This underscores the importance of the copper/lithium aggregate structure of the organocuprate reagent: Thus, initial formation of the complex **B** can be understood as the result of a sequence of coordination of the Lewis acidic lithium atom to the carbonyl group and the copper atom to the nearest C–C unsaturated bond.[7] On the basis of this background information, we examined the reaction of Me_2CuLi and hepta-2,4-dien-6-ynal (and its shorter homologues; see Supporting Information) as a model reaction, starting from a complex **1**. The pathways for the formation of 1,4-, 1,6-, and 1,8-adducts, and the energy diagram are summarized in Scheme 2 and Figure 1, respectively.[8]

The energy diagram immediately suggests that the kinetically and thermodynamically most favorable pathway is the 1,8-addition pathway that involves three organocopper(III) intermediates **1**, **3**, and **5**. Double migration of the copper atom (**1**→**3**→**5**) and reductive elimination of the final intermediate **5** via **TS5** gives the 1,8-adduct; the first copper migration is the rate-determining step. Reductive elimination of **1** and **3** (via **TS1** and **TS3**) can produce the 1,4- and 1,6-adducts **2** and **4**, respectively, but these routes are kinetically unfavorable relative to the copper migration pathways.[9] Remarkably, the reductive elimination of **5** requires a much lower activation energy than that of **1** and **3**. The reaction pathway is discussed in detail below.

The first intermediate **1** has a structure essentially the same as that of the intermediate generally found in a 1,4-conjugate addition of Me_2CuLi to an α,β-unsaturated carbonyl compound,[7] and can undergo reductive elimination via **TS1** to give the 1,4-addition product **2**. The activation energy (18.5 kcal mol^{-1}) is higher than that of simple 1,4-addition to an acrolein or a cyclohexenone ($\approx$12–15 kcal mol^{-1}),[7] since the C–C bond formation disturbs the polyenyne conjugation system present in **1**.[10]

Alternatively, the Me_2Cu moiety in **1** can migrate to the C5–C6 double bond (via **TS2**) to form a new σ/π-allyl–copper(III) intermediate **3**. The migration ($\Delta E^{\neq} = 16.3$ kcal mol^{-1}) is kinetically preferred by 2.2 kcal mol^{-1} over C–C bond formation. **TS2** contains an intrinsically unstable T-shaped triorganocopper(III) geometry (see Supporting Information),[11] but is partially stabilized by the neighboring C5–C6 double bond.

The second intermediate **3** is a σ/π-allyl–copper(III) complex that can either form a C–C bond via **TS3** or undergo further Cu migration to the C7–C8 triple bond via **TS4** to give another copper(III) intermediate **5**. The former process again disturbs the conjugation system, and the latter pathway is overwhelmingly favored by 7.8 kcal mol^{-1}.

The low activation energy of the Cu migration is due to coordination of the terminal acetylene moiety in **TS4** (Figure 2). Intermediate **5** has a distorted square-planar geometry in which the copper atom is much more strongly bonded to the terminal C8 atom (Cu–C8: 2.02 Å) than to the

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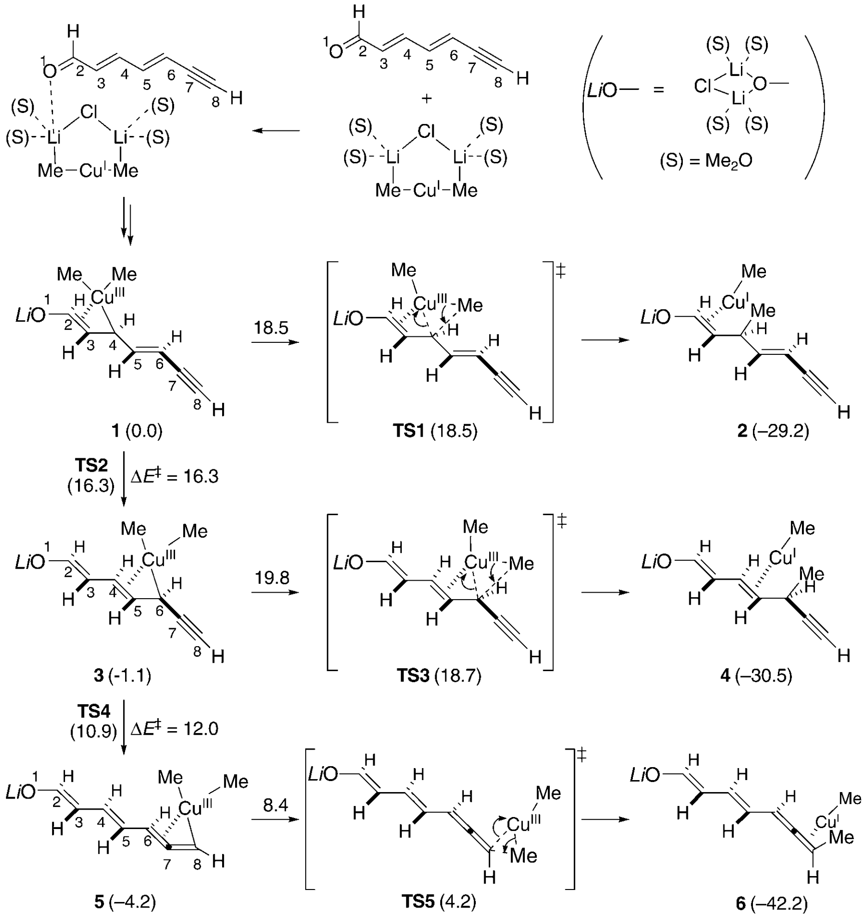

Scheme 2. Reaction pathways and potential energy changes for 1,4-, 1,6-, and 1,8-addition of Me_2CuLi to hepta-2,4-dien-6-ynal. Potential energies (kcal mol^{-1}, calculated at the B3LYP/631SDD//B3LYP/321SDD level) relative to **1** are shown in parentheses. Energy changes are shown together with arrows.

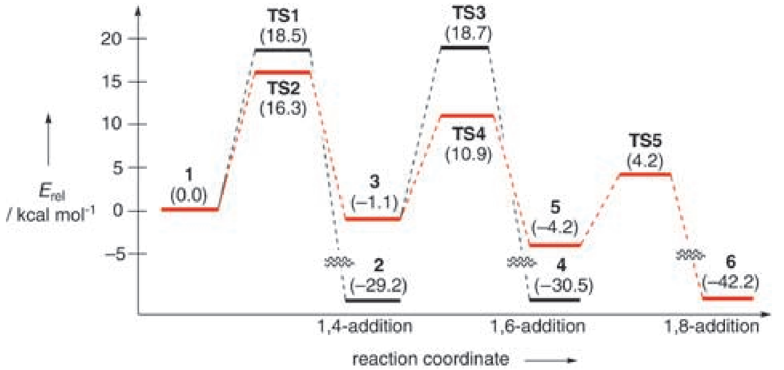

Figure 1. Potential energy profiles for 1,4-, 1,6-, and 1,8-addition pathways (B3LYP/631SDD//B3LYP/321SDD). The energetically most favored 1,8-pathway is shown in red.

C6 atom (Cu–C6: 2.47 Å). This structural feature indicates that the copper atom is σ-bonded to C8 and π-coordinated by the C6–C7 bond, and hence in this case **5** may be called a σ/π-allenyl–copper(III) complex.[10,12] The dissymmetric bonding would be the result of the intrinsic stability of a C(sp^2)–metal bond (relative to a C(sp^3)–metal bond) and the electron-rich dienolate substituent at C6.[10]

The complex **5** undergoes reductive elimination at C8 (via **TS5**) with very low activation energy (8.4 kcal mol^{-1}) owing to the intrinsic linear geometry of the allene: The C6-C7-C8 bond strain (153.9°) is released, and the C6–C7 double bond of **5** is easily detached from the copper(III) center to give a kinetically unstable triorganocopper(III) species,[11] which undergoes rapid reductive elimination (see inset of Figure 2). Furthermore, participation of the allenyl C7–C8 π orbital orthogonal to the Cu–C8 σ bond in C–C bond formation may also contribute to the low activation barrier.[13]

We also studied in some detail the 1,6-addition reaction to the less conjugated analogues pent-2-en-4-ynal and penta-2,4-dienal (see Supporting Information). The former reaction proceeds in essentially the same manner as the 1,8-reaction described above: The 1,6-adduct is formed through a rate-determining Cu migration ($\Delta E^{\ddagger} = 12.2$ kcal mol^{-1}) and quick reductive elimination of the σ/π-allenyl copper(III) intermediate ($\Delta E^{\ddagger} = 8.4$ kcal mol^{-1}). In the latter case, Cu migration takes place with an activation energy of 15.8 kcal mol^{-1} to give a σ/π-allyl–copper(III) intermediate, the reductive elimination of which requires a much higher activation energy (13.3 kcal mol^{-1}) than that of σ/π-allenyl–copper(III) intermediates. Furthermore, theoretical ^{13}C NMR spectroscopic data calculated for the initially formed olefin complex, employing ethyl 6,6-dimethyl-hept-2-en-4-ynoate as a substrate, showed reasonable agreement with experimental findings (see Supporting Information).[4b]

In summary, we proposed a general mechanistic framework for remote conjugate addition of an organocuprate to a polyconjugated Michael acceptor. Interaction between the two reactants initially generates a β-cuprioenolate intermediate, which undergoes sequential copper migration via σ/π-allyl–copper(III) intermediates. The final migration to the acetylene terminal gives a key σ/π-allenyl–copper(III) intermediate, the kinetic instability of which results in rapid C–C bond formation at the terminal carbon atom. C–C bond formation at the internal carbon atoms is disfavored as it disturbs the conjugation system. This mechanism for polyenyne substrates also explains why conjugate addition to polyenyl carbonyl compounds tends to be unpredictable: The copper intermediates formed from a polyene substrate lack such a decisive structural feature as that in **5** and may undergo C–C bond formation at any possible carbon atom, depending on structure and reaction conditions.[2] The present mechanistic framework should apply to remote substitution reactions,[14] and we consider also that rapid 1,3 copper migration similar to that reported herein is responsible for the remarkably high regioselectivity of the multi-

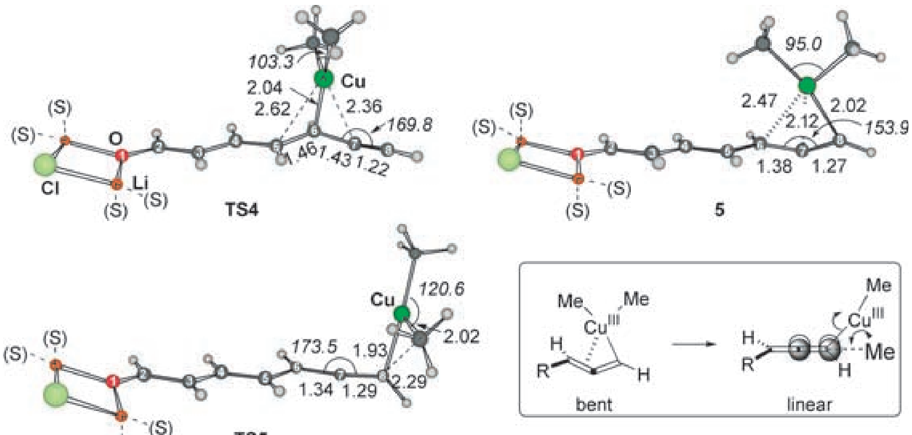

Figure 2. Structures of the copper migration transition state **TS4**, the π-propargyl/allenyl–copper(III) intermediate **5**, and the 1,8-reductive elimination transition state **TS5** (B3LYP/321SDD), and a schematic representation for reductive elimination of a σ/π-allenyl–copper(III). (S) represents a Me_2O molecule coordinated to a Li atom. The values refer to bond lengths (Å) and bond angles (°, italics).

addition of organocopper reagents to [60]- and [70]fullerenes.[15] The relevance of the present mechanism to the dynamic behavior of transition-metal complexes of polyconjugated molecules[16] is worthy of further consideration.[17]

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