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Organocuprate Conjugate Addition: The Square-Planar "Cu^{III}" Intermediate

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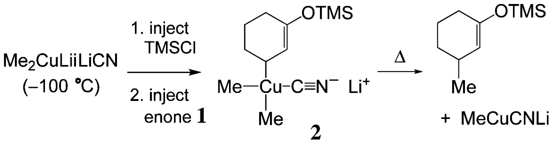
Conjugate addition of organocopper reagents to α-enones is both a classic and a contemporary reaction in organic synthesis. Discovered in 1941[1] and examined further in the 1950s[2] and 1960s,[3] it has been the subject of many studies since. Mechanistically, the reaction has remained an enigma. Early investigators proposed a so-called "Cu^{III} intermediate"[4] as mediator of the key carbon−carbon bond forming step, reductive elimination, an historically popular view that is still in vogue. Likewise, S_N2, S_N2', and vinyl substitution reactions of organocopper reagents have been proposed to operate by way of such a species.[5] In only two instances has a tetracoordinate square-planar copper intermediate been invoked (both S_N2 substitution).[6] The current view of conjugate addition is that preliminary π-complexes[7,8] are rapidly transformed to the Cu^{III} intermediate, which in turn leads directly to enolate product. While such a species has been reproduced virtually in computational investigations,[9] it has nevertheless eluded detection in the laboratory for more than three decades. Ten years ago, we predicted that with the appropriate substituents the tetracoordinate, square-planar intermediate in cuprate conjugate addition could be observed and structurally characterized.[9] This projection has now been realized.[10]

In 2002, the Bertz−Ogle team applied low-temperature rapid-injection NMR (RI-NMR) to observe cuprate π-complexes from 2-cyclohexenone **1** and to measure their rate of formation.[8] In an elegant study employing TMSCN multiple ^{13}C labels, they have now observed and characterized a subsequent species and proposed that it is the elusive product-forming intermediate **2**.[10] The study has produced ^{1}H and ^{13}C NMR chemical shift data and a series of characteristic coupling constants. In order to link spectroscopic observables and structure, both constitution and conformation, we have examined a series of structural variations for the proposed intermediate, calculated all relevant NMR quantities for the low-energy forms, and related the predictions to the measured quantities. We conclude that the species observed by RI-NMR is indeed a tetracoordinate, square-planar copper complex.



The present investigation was initiated by recognizing that **2** embodies considerable structural freedom. The cyano group can be either *cis* or *trans* to the ring methine carbon, while the cyclohexene ring can exist in two nonequivalent half-chair forms positioning the copper moiety in either a pseudoequatorial or a pseudoaxial position. Additionally, the Cu−methine bond can rotate to direct the Cu−CN bond *syn* or *anti* to the methine hydrogen (Figure 1). Given these degrees of freedom, there are six possible geometries for the complex (see Supporting Information). The distal $OSi(CH_3)_3$ group was replaced with OCH_3 to make the calculations tractable, and they were optimized by a density functional theory (DFT) protocol employing an effective core potential for the copper atom (i.e., B3LYP/6-31G*/LANL2DZ[11]).

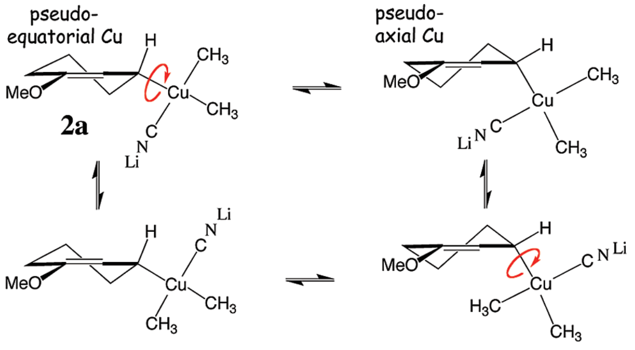


Figure 1. Potential conformations for OCH_3 models of **2**.

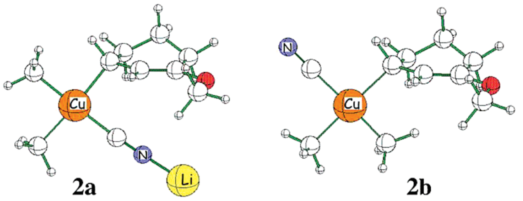


Figure 2. Low-energy DFT conformations of lithiated **2a** and anion **2b**.

The optimizations were repeated for the same molecular geometries at the same level of theory with and without a lithium cation coordinated to the cyano nitrogen. In both series, the lowest energy forms present the square-planar copper unit as equatorial and the cyanide group as *cis* to the methine carbon. The major difference is the orientation of the Cu−CN bond: the neutral lithiated form (**2a**) directing CN *anti* to the pseudoaxial hydrogen, the anion (**2b**) directing it *syn*, as shown in Figure 2. Zero-point energy correction and PCM/THF solvation studies yield similar results. Examination of the C═C−OMe torsion angle indicates planarity is preferred. (See the Supporting Information for molecular geometries and relative solvation energies.) The lowest energy structures were selected for chemical shift and coupling constant calculations. To ensure that the OMe models do not compromise the results, the geometry of lithiated **2a** with $OSi(CH_3)_3$ instead of OCH_3 was optimized with B3LYP/6-31G*/LANL2DZ and likewise subjected to NMR parameter prediction.

Chemical shifts were calculated for the optimized geometries using the GIAO method and a more elaborate DFT model (B3LYP/6-311+G*/Cu: pCVDZ/SDD//B3LYP/6-31G*/LANL2DZ).[12] The ^{1}H and ^{13}C shift predictions versus TMS are compared with experiment for both the lithiated and unlithiated square-planar intermediate in Figure 3 to show that the empirically assigned proton and carbon chemical shifts are reproduced with reasonable fidelity. The calculated ^{13}C shifts for the anion seem to match experiment slightly better, particularly at the cyano carbon, suggesting either a solvent-separated ion pair or rapid cation−anion exchange.

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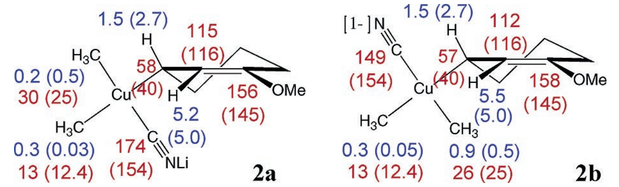

Figure 3. Calculated ^{1}H (blue) and ^{13}C (red) chemical shifts for lithiated **2a** and unlithiated **2b** relative to TMS and compared with experimental values (parentheses); B3LYP/6-311+G*/Cu: pCVDZ/SDD// method.

Table 1. Two Bond C−C Coupling Constants ^2J (Hz) around Square-Planar Copper for Lithiated Species **2a** and Anion **2b**[a−c]

		OCH$_3$				OSi(CH$_3$)$_3$	
		Li$^+$ salt **2a**		Anion **2b**		Li$^+$ salt	
coupling[c]	exptl[a]	DZ[c]	TZ[c]	DZ[c]	TZ[c]	DZ[c]	TZ[c]
t-C−CN	35.4	36.4	34.5	44.0	41.8	36.9	35.1
t-C−C$_r$	38.1	46.1	45.9	52.2	51.7	45.7	45.4
c-C−C	2.9	−3.4	−5.6	−4.4	−6.4	−3.2	−5.4
c-C−CN	5.4	−6.1	−8.1	−6.4	−8.5	−5.9	−8.1
c-C$_r$−CN	ND[d]	0.01	−0.7	−1.7	−2.0	0.0	−0.6
c-C$_r$−C	ND[d]	2.5	1.5	1.9	0.9	2.4	1.3

[a] Experimental values.[10] [b] The ^2J values sum all four Ramsey terms; see text for basis set. [c] DZ = pCVDZ;[13] TZ = pVTZ;[14] *t* = *trans*, *c* = *cis*, r = *ring*. [d] Not determined owing to low S/N at the unlabeled ring C.

Two-bond ^{13}C−^{13}C coupling constants were computed with two recently described methods. Namely, the coupled carbons were treated with the aug-cc-pCVDZ-sd[13] and aug-cc-pVTZ[14] basis sets in the B3LYP framework, the ^2J values obtained being the sum of the four Ramsey terms[15] (FC (with tight s-type functions), SD, DSO, and PSO). All other atoms were accommodated with the B3LYP/6-311+G*/SDD model. The coupling constants in Table 1 are in good to excellent agreement with experimentally assigned couplings with respect to both absolute and relative magnitudes. Carbons *trans* across copper are characterized by the large values falling between 30 and 60 Hz, whereas *cis* couplings are well below 10 Hz. This observation agrees nicely with a 2.0 kcal/mol relative energy calculated for the *trans*- versus *cis*-CN isomer of **2a**, both energy and *J*-coupling results ruling out the *trans* relationship. Furthermore, the *trans* methyl−cyano coupling is predicted to be slightly smaller than the *trans* methyl−ring C coupling, while the relative magnitudes of the corresponding *cis* values are reversed, both in agreement with observation. The two *cis* couplings that are not observed are predicted to be smallest ($<$0.3 Hz). Finally, lithiated OSi(CH$_3$)$_3$ provides a nearly identical set of ^2J values, confirming that OCH$_3$ substitution is a suitable structural model. The present data are insufficient to definitively determine the extent of lithiation for **2**; however, the calculated coupling constants are compatible with the presence of lithiated **2a** as a substantial mole fraction of a rapidly exchanging system of anions and cations.

The claim that the copper surround is square-planar is based on precedent[16] and on the B3LYP/6-31G*/LANL2DZ optimizations described above. However, tetracoordinate copper readily adopts tetrahedral geometries.[17] To examine this possibility, we have calculated δ and ^2J values for the analogue of **2a** with copper bond angles constrained at 109.5° (i.e., $\mathbf{2a^T}$). For the latter, the average difference $\Delta\delta$(exptl − calcd) is 16 versus 9 ppm for **2a**, while aug-cc-pVTZ ^2J values differ from experiment (Table 1) by 20−200 Hz. The results for $\mathbf{2a^T}$ are inconsistent with observation and incompatible with tetrahedral copper as the observed species.

The experimental conditions employed by Bertz and Ogle for cuprate conjugate addition have achieved observation of the essential tetravalent copper intermediate (**2a** or **2b** or a mixture) at −100 °C using $Me_2CuLi{\bullet}LiCN$.[10] While early predictions envisioned a square-planar trialkylcopper complex stabilized in the fourth position by a solvent molecule,[9] the present work achieves it with a cyanide group. Above −80 °C, however, reductive elimination leads to product.[10]

Is it possible that ligands other than cyanide might promote even greater stability for the square-planar copper structure? We have examined this question by optimizing the geometries of the following series with the same model used for isomers of **2**: $[(CH_3)_3CuX]^{1-}$, X = CH$_3$, CN, F, Cl, Br, I. Relative stabilities were assessed by means of isodesmic reactions.[18] While cyanide stabilizes the complex relative to halide ions by 1−5 kcal/mol, a methyl group is predicted to favor the complex relative to cyanide by ca. 20 kcal/mol. As a result, we foresee the observation of tetraalkyl square-planar copper complexes at much higher temperatures than −80 °C. It is conceivable that the appropriate substituents will permit room-temperature isolation.

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Supporting Information Available: Computational results and complete ref 11. This material is available free of charge via the Internet at http://pubs.acs.org.

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