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Rapid-Injection NMR Study of Iodo- and Cyano-Gilman Reagents with 2-Cyclohexenone: Observation of π-Complexes and Their Rates of Formation[1]

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Conjugate additions to α,β-unsaturated carbonyl compounds via organocuprates are among the most important C−C bond-forming reactions available to synthetic chemists.[2] Cuprate−olefin π-complexes appear to be intermediates and have been observed with α,β-unsaturated esters,[3] ketones,[4] and nitriles.[5] With the aid of rapid-injection techniques,[6] we have now been able to observe π-complexes from the prototypical Gilman reagents $Me_2CuLi{\cdot}LiI$ (**1a**) and $Me_2CuLi{\cdot}LiCN$ (**1b**) and the simple (unhindered) α-enone, 2-cyclohexenone **2**, and herein we report on their structures and rates of formation in THF.

Rapid injection proved invaluable for the routine preparation of π-complexes without appreciable enolate formation, since it enabled the addition of **2** to a solution of the cuprate at −100 °C without detectable warming inside the cold NMR probe. Up to 100 ^1H NMR spectra were collected over the first several minutes to obtain rate data, and then further experiments (e.g., COSY, EXSY) were conducted for several hours, since in general the π-complexes were remarkably stable under these conditions. The π-complex vinyl region is shown in Figure 1. In the equilibrium ^1H NMR spectrum from **1a** and **2** at −100 °C (cf. Figure 1a), two sets of peaks corresponding to two π-complexes were observed at 3.80 (d, $J = 7.1$ Hz), 3.31, −0.04 and −1.08 ppm for "complex 1" and 3.68 (d, $J = 7.4$ Hz), 3.23, −0.23 and −1.11 ppm for "complex 2". COSY confirmed the vinyl H assignments. The ^1H NMR spectrum from **1b** and **2** under the same conditions contained relatively broad vinyl peaks at 3.78 and 3.25 ppm (Figure 1c) and two sets of methyl peaks at −0.06 and −1.08 ppm and −0.22 and −1.08 ppm. Coalescence of the vinyl peaks is attributable to rapid chemical exchange between π-complexes.

When an additional 1.0 equiv of LiI (1.3 M in THF-d_8) was added to **1a**, and then **2** was rapid-injected as usual, the ratio of "complex 2" to "complex 1" increased from 0.78 to 1.42 (Figure 1b). On the basis of the effect of LiI and the NMR data, we assign structures **3** and **3·LiI** to "complex 1" and "complex 2", respectively. Analogously, we propose that **3** and **3·LiCN** are the exchanging π-complexes from **1b** and **2**. The methyl group (Me_β) that is bonded only to Cu in **3**, **3·LiI**, or **3·LiCN** has a ^1H NMR chemical shift ca. −0.04 to −0.23 ppm, which is in good agreement with that of CH_3Cu, −0.22 ppm, prepared from MeLi and CuI in dimethyl sulfide, where it has a small but significant solubility.[7] The methyl group (Me_α) that is bonded to one Cu and one Li in these structures has a ^1H NMR shift ca. −1.08 to −1.11 ppm. A good model for this shift is $(Me_2CuLi)_2$ **1c**, which is a contact ion pair (CIP) in ether,[8] with a ^1H NMR shift of −1.10 ppm.[9] In contrast, **1a** in THF-d_8 (δ −1.33 ppm) is predominantly a solvent-separated ion pair (SSIP).[8] NOESY measurements support the methyl assignments, with relatively large cross-relaxation between vinyl H_α and Me_α and between vinyl H_β and Me_β in **3** and also in **3·LiI**.

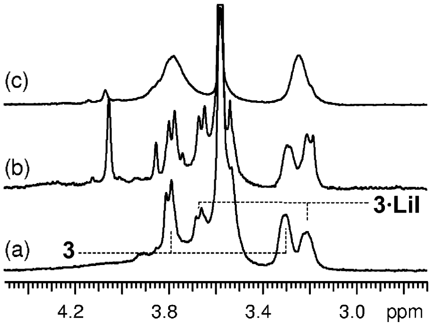
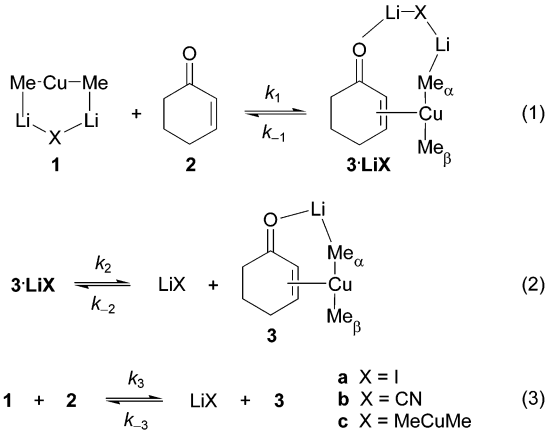


Figure 1. ^1H NMR spectra of the π-complex vinyl region at −100 °C, when **2** (0.5 equiv) is injected into (a) **1a** (0.02 M), (b) **1a** plus added LiI (0.02 M each), or (c) **1b** (0.02 M). The large central peak is residual THF.



The vinyl ^{13}C NMR shifts for **3** were 76.4 ppm (C_α) and 60.6 ppm (C_β).[10] The former is reasonably close to the shift for C_α (δ 82.5 ppm) in the major cuprate-olefin π-complex from 6-methylbicyclo[4.4.0]dec-1-en-3-one;[4] however, the latter is significantly different from the shift for C_β in this complex (δ 80.9 ppm), owing to differences in substitution at the β-position (H vs C). The changes in $\delta(^{13}C)$ upon complex formation are $\Delta C_\alpha = -54.2$ ppm and $\Delta C_\beta = -89.5$ ppm, and the corresponding changes in $\delta(^1H)$ are $\Delta H_\alpha = -2.10$ and $\Delta H_\beta = -3.66$ ppm. Since the resonances for the vinyl H_β/C_β move upfield from those for H_α/C_α, it appears that the polarization of the double bond is reversed upon coordination to the electron-rich Cu. Moreover, the ^1H NMR shifts for both H_α and H_β in the π-complexes are upfield from the vinyl shift (δ 4.05 ppm, Figure 1b) for H_α in the enolate that results from conjugate

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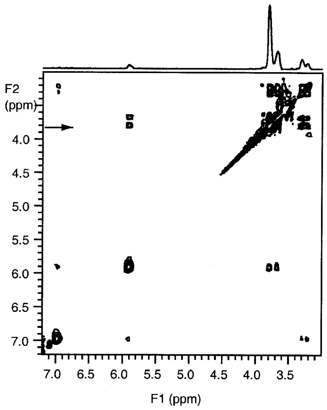

Figure 2. ^{1}H NMR EXSY spectrum ($\tau_{\mathrm{mix}} = 1.0$ s) of the equilibrium mixture of **2**, **3** and **3·LiI** at −100 °C in the double bond region. The arrow indicates where the trace at the top was taken.

addition. We conclude that the π-complexes have substantial enolate character, as predicted by Snyder,[11] and C_β appears to have higher electron density than C_α. This observation explains the anomalous β-silylation of β-aryl-α,β-unsaturated ketones (chlorosilane/$Bu_2CuLi\cdot LiCN$) observed by Amberg and Seebach.[12]

The $[LiILi]^+$ moiety in **3·LiI** is similar to that in cuprate heterodimer **1a**, proposed in 1995,[9] and recently buttressed by an X-ray crystal structure for $Ar_2CuLi\cdot LiBr$.[13] The $[LiCNLi]^+$ unit in **3·LiCN** is also present in the X-ray crystal structures of cyano-Gilman reagents,[14] although in the form of a SSIP, as predicted.[15] At this point, we do not see any evidence for structure **3·LiCuMe$_2$**, which features a $[MeCuMe]^-$ bridge instead of I^- or $[CN]^-$. Nakamura et al.[16] calculated a structure similar to **3·LiCuMe$_2$**, and it is likewise precluded under our conditions. We conjecture that the geometric fit of the bridge determines whether it is held tightly as in **3·LiI** or loosely as in **3·LiCN** (cf. exchange rates)—or not at all (ergo no **3·LiCuMe$_2$**).

In rapid-injection experiments with **1a** and **2**, the ^{1}H NMR peaks for π-complexes **3** and **3·LiI** increased until equilibrium was reached. The differential equations for various kinetic schemes were entered into the computer program MathCad, and the best fit for the measured concentrations as a function of time was determined by systematic variation of the rate constants and iteration until the residual sum of squares (RSS) was minimized. The fits were relatively insensitive to the values of k_2 and k_{-2} (eq 2); therefore, these values were determined more accurately by using exchange spectroscopy (EXSY).[17] A stacked plot of the transformed ^{1}H NMR spectra for a typical rapid-injection experiment is included in the Supporting Information.

An EXSY experiment (Figure 2) revealed cross-peaks for the interconversion of **2** and **3·LiI**, **3** and **3·LiI** (cf. Figure 1, a and b), and **2** and **3**, as well as NOE peaks between adjacent hydrogens. The corresponding one-step exchange equilibria are given in eqs 1−3. The best fit to the experimental results is obtained with $k_3 = k_{-3} = 0$, which means that the one-step process in eq 3 is not involved to a significant degree, and the exchange observed between **2** and **3** is a two-step process, viz. eqs 1 and 2. The significant rate constants are $k_1 = 2.0\ \mathrm{M^{-1}\ s^{-1}}$, $k_{-1} = 0.085\ \mathrm{s^{-1}}$, $k_2 = 0.49\ \mathrm{s^{-1}}$, and $k_{-2} = 28\ \mathrm{M^{-1}\ s^{-1}}$. These rate constants give a good fit for the rapid-injection NMR data points (Figure 3). The rates of exchange for **3** and **3·LiCN** (cf. Figure 1c) were too fast for the EXSY method to measure.

Boche et al. have shown that the conjugate addition reaction of organocuprates proceeds via the CIP, heterodimer $R_2CuLi\cdot LiI$ or homodimer $(R_2CuLi)_2$, even though the SSIP is the predominant species in THF.[8] The identification of **3·LiI** as the initial product from the iodo-Gilman reagent and **2** suggests that heterodimer **1a** is the reactive species as far as conjugate addition in THF is concerned, especially in light of the fact that we do not detect a π-complex (e.g., **3·LiCuMe$_2$**) that would implicate the homodimer, **1c**. Finally, we surmise that the halide-containing complex **3·LiI** is the one that undergoes facile conjugate addition, as the reaction mixture with 2 equiv of LiI contains a significant amount of enolate product (cf. Figure 1b), even at −100 °C.

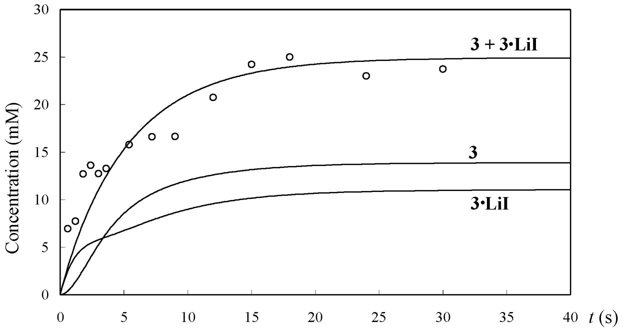

Figure 3. Rapid-injection ^{1}H NMR data points for the reaction of **1a** with **2** at −100 °C, where the curves for the predicted rates of appearance of π-complexes are calculated from the EXSY rate constants.

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Supporting Information Available: Rapid injection ^{1}H NMR stacked plot (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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