

Communications

Evidence for a Lithium Amidocuprate/Cyclohexenone Complex in Solution

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Summary: A monomeric copper π -complex between a lithium amidocuprate and cyclohexenone has been observed. The data obtained from NMR and IR spectroscopy investigations in diethyl ether show that this complex is the dominant species. The origin of enantioselectivity in the amidocuprate alkylation is to be found in the different coordination capability of the two lithium cations in the lithium amidocuprate dimer.

The copper-mediated 1,4-alkylations of α,β -unsaturated ketones are of undisputable use in synthetic organic chemistry. Therefore, it is not surprising to find that a large variety of chiral ligands have been developed to facilitate the enantioselective 1,4-alkylation reaction.^{1–5} More surprising is the scarce knowledge about the detailed mechanism^{6–13} of these 1,4-alkylation reactions. The cyanocuprate system has received much attention,^{14,15} but the knowledge about the lithium amidocuprate system is rather underdeveloped. In a previous investigation of chiral lithium amidocuprates,¹⁶ based on a chiral ligand, (*R*)-*N*-methyl-1-phenyl-2-(1-pyrrolidiny) ethanamine¹⁷ (**1**), in diethyl ether (DEE), formation of a reagent (**2**) exhibiting the conventional

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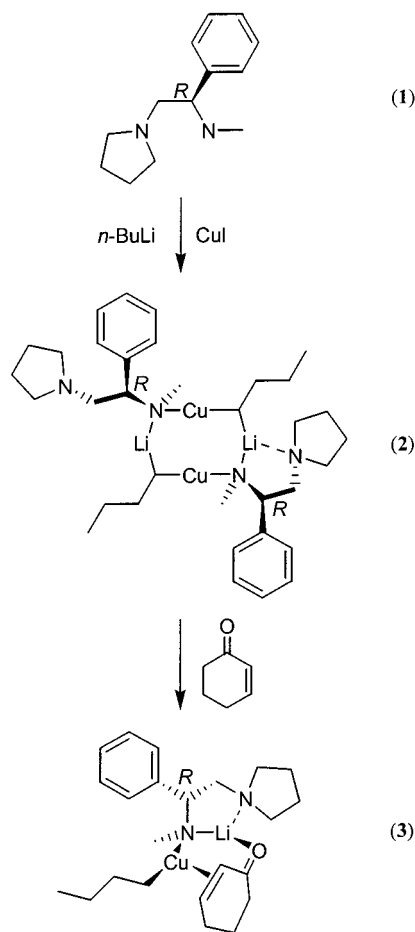
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Scheme 1



dimeric structure (see Scheme 1) was observed.^{18,19} The study clearly showed that the amidocuprate dimer

(18) The presence of two ⁶Li NMR signals but only one set of ¹³C NMR signals gives us reason to believe that the cuprate complex is a dimer. In a previous publication,¹⁶ where a ¹⁵N-labeled ligand was used, no ⁶Li–¹⁵N coupling information could be seen in the ⁶Li NMR signal from LiI. This fact indicates that LiI is not a part of the dimer. This is in accordance with a recent publication where it was shown, using a newly developed pulse sequence, that LiX (X = I, CN) is not a part of the dimer.¹⁹

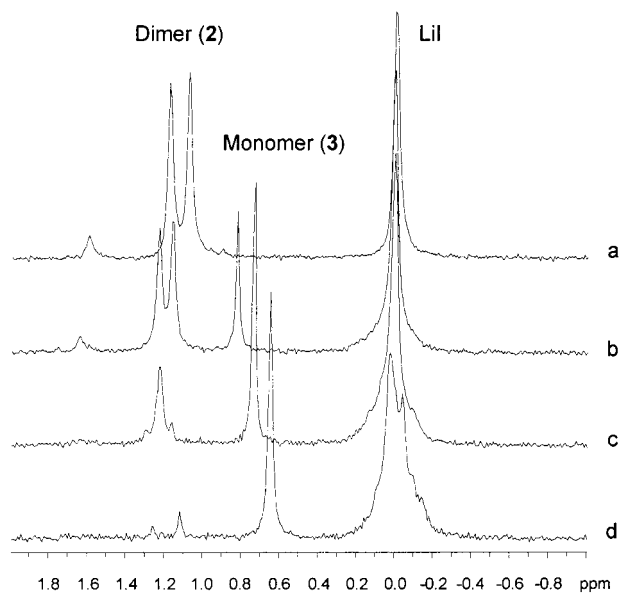


Figure 1. Titration of **2** with cyclohexenone, showing the ^6Li NMR spectra with (a) 0.00 equiv of enone, (b) 0.28 equiv of enone, (c) 0.57 equiv of enone, and (d) 0.85 equiv of enone. All equivalents are relative to copper.

exhibits two nonequivalent lithium cations, which showed large differences in coordinative ability toward tetrahydrofuran (THF). When the DEE solution was titrated with THF, a monomeric amidocuprate species also formed in low concentration. In this work we wanted to investigate the effect of adding a substrate such as cyclohexenone to the dimeric amidocuprate reagent. In our experimental preparation²⁰ we tried to match, as close as possible, a common synthetic application procedure.

Addition of cyclohexenone to the amidocuprate reaction mixture results in ^1H and ^6Li NMR (Figure 1) spectra very similar to those observed when the amidocuprate was titrated with THF.²¹ For example, the ^1H NMR signals from the diastereotopic α -protons in the butyl group appear at approximately the same upfield shift regardless if THF or cyclohexenone is added.²¹ This is a strong indication that a monomeric complex like **3** is formed according to Scheme 1. When 0.57 equiv (with respect to complexed *n*-BuCu) of

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(20) An NMR tube was charged sequentially with CuI (76.3 mg, 0.40 mmol) and DEE-*d*₁₀ (600 mL) in a Mecaplex GB-80 glovebox. Chiral ligand **1** (80.8 mg, 0.40 mmol) was added to the NMR tube. The NMR tube was cooled in dry ice/acetone, and *n*-Bu⁶Li (neat) was added. The addition of *n*-Bu⁶Li was followed by NMR until **2** equiv was added. The cuprate sample was titrated with a DEE-*d*₁₀ solution of cyclohexenone (100 μL in 200 μL DEE-*d*₁₀) until no more cuprate dimer could be detected. All glassware and syringes used for the NMR studies were dried at 50 °C in a vacuum oven before being transferred into a glovebox. The NMR spectra were recorded on a Varian Unity 500 spectrometer using a 5 mm ^1H , ^{13}C , ^6Li , ^{15}N quadruple resonance probe head custom built by Nalorac. ^1H NMR signals were referenced to TMS via the ^1H residue signal in the solvent used. ^6Li NMR signals were referenced to the ^6LiI (0 ppm) formed along with the complex.

(21) ^1H NMR shifts for the diastereotopic α -protons in the butyl group from the monomer obtained in THF are 0.06 and -0.03 ppm, respectively, and with an integral ratio of 1:1. In the case where cyclohexenone was added to the cuprate the α -protons appeared at -0.20 and -0.30 ppm, respectively, with an integral ratio of 1:1. The shift of the ^6Li NMR signal from the monomer obtained in THF was 0.35 ppm. Similarly the shift of the ^6Li NMR signal from the monomer obtained with cyclohexenone was 0.65 ppm. The difference in the ^6Li NMR shifts is probably due to the difference in the solvation of the Li cation.

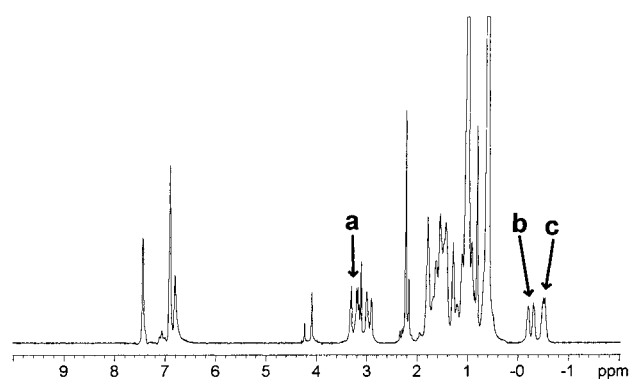


Figure 2. ^1H NMR spectrum of the amidocuprate with 0.57 equiv of cyclohexenone added. The signals labeled a originates from the former vinylic protons. The BuCu α -protons in the monomer arise at -0.20 and -0.30 ppm, respectively, (b) and (c) and the BuCu α -protons in the dimer arise at -0.50 ppm (c).

cyclohexenone is added, the integral ratio between the BuCu α -protons in the monomer and the corresponding protons in the dimer is virtually 1:1. Furthermore, a new set of ^{13}C NMR signals appears (Supporting Information). This also indicates the presence of a monomeric cyclohexenone complex. The low ^1H NMR chemical shifts, at -0.20 and -0.30 ppm, respectively (Figure 2), originating from these two diastereotopic α -protons show that the butyl group is σ -bonded to copper in **3**. This was also verified by a TOCSY ^1H NMR experiment, which clearly showed correlations only among the proton signals within the butyl group and not further on to the enone (see Supporting Information).

What is the coordination mode of the substrate in this monomeric amidocuprate/cyclohexenone complex? The chemical shifts of the ^1H NMR signals from the vinylic protons in cyclohexenone were shifted upfield from 6.00 and 6.98 ppm to 3.40 and 3.55 ppm, respectively, upon complexation as in **3**. These shifts are in the typical range for alkene/enone copper π -complexes.²² It is thus likely that cyclohexenone is π -coordinated in **3** as drawn in Scheme 1. Consequently, the copper atom in this monomeric complex exhibits a carbon σ -bond and an alkene π -bond simultaneously. To our knowledge only two such complexes have been structurally characterized in the solid state,^{23b,24} and neither of them are based on cuprate reagents. Attempts were made to record the IR absorption²⁵ from the C=C double bond vibrations in the π -complex, and when cyclohexenone was added to an amidocuprate solution, indications of weak absorption bands in the 1500–1600 cm^{-1} range appeared, which are in accord with earlier IR spectroscopic investigations of copper π -complexes.²³ The most obvious feature in the IR spectra is otherwise the

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broadening and disappearance of the C=O vibration at 1636 cm^{-1} and the appearance of a new absorption band at 1223 cm^{-1} when cyclohexenone is added to the lithium amidocuprate solution. Consequently, cyclohexenone is also (apart from the π -coordination) coordinated via the carbonyl oxygen, presumably to lithium.

The origin of the enantioselectivity can be found in the different availability for coordination to the lithium cations as shown in a previous paper.¹⁶ We believe that the enantioselectivity is determined by the selective coordination of cyclohexenone to one of the Li cations in the amidocuprate dimer and the subsequent orienta-

tion of cyclohexenone by the chiral surrounding. One of the Li cations is strongly bonded to the pyrrolidine nitrogen and thus cannot coordinate the substrate as readily as the other Li cation, which is more available for solvent and substrate coordination. A striking feature about the addition of cyclohexenone is that there is no formation of intermediate complexes. The formation of the amidocuprate/substrate complex (**3**) is clearly independent of the cyclohexenone concentration.²⁶ The absence of ^1H NMR signals from noncoordinated cyclohexenone indicates that the substrate is strongly coordinated in the copper π -complex. Assuming that the monomeric copper π -complex is stereochemically rigid,²⁷ the enantioselectivity has to be determined when the substrate binds to the dimeric reagent and splits it into a monomer.

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Supporting Information Available: ^1H - ^1H -TOCSY NMR spectrum showing that the spin system of the butyl group is separated from cyclohexenone. ^1H , ^6Li , and ^{13}C NMR showing signals from both the dimer and the monomer. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(25) A reaction flask cooled in dry ice/acetone was charged with CuI (0.11 g, 0.58 mmol), dry DEE (5 mL), and amine (0.124 g, 0.61 mmol). Reference spectra were recorded prior to each addition. To the reaction mixture, *n*-BuLi (1.4 mL, 2.5 M, 3.5 mmol) was added and the temperature was raised in order to form the cuprate complex. The reaction mixture was stirred for an additional 30 min. Cyclohexenone was added, and the reaction was monitored by recording spectra every minute for an initial period of 30 min. Then spectra were recorded every second minute for 30 min and finally every 10th min for 180 min. IR measurements were performed on an ASI ReacIR 1000 using a DiComp probe. All spectra were recorded using 128 scans.

(26) This should be compared to THF, of which it is required a significant amount in order to dissociate the dimer into a monomer.

(27) The absence of any dynamics in the ^1H NMR spectrum at $-50\text{ }^\circ\text{C}$ is seen from the narrow line widths of the ^1H NMR signals from the vinylic protons in the cyclohexenone complex. The low temperature used in synthetic applications should also prevent racemization of the copper π -complex.