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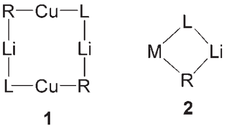
Organocopper Reagents

Structural Studies on a Lithium Organo-Amidocuprate in the Solid State and in Solution**

Robert P. Davies,* Stefan Hornauer, and Peter B. Hitchcock

Lithium organo-amidocuprates are an important class of organocopper reagents with applications in carbon–carbon bond formation.[1] They differ from homocuprates, $[R_2CuLi]$, by replacement of one of the reactive organic groups (R) with a nontransferable amido group (L). Although heterocuprates, including amidocuprates, were originally developed to cut wastage of the reactive R group, they have also attracted much attention for applications in enantioselective synthesis when the nontransferable ligand L is chiral.[2,3] Crucial to the optimization of these species for high yields and enantiomeric excesses is a thorough understanding of their structures and mechanisms of reaction. However, despite these implications and in contrast to the large body of work on lithium homocuprates,[1] there have been very few studies on the coordination chemistry of lithium amidocuprates. Early work by Dieter and Rossiter led to the assumption that these species adopt a dimeric aggregate **1** (Scheme 1) in both their resting and reactive states.[4–6] More recently, Davidsson and co-workers confirmed, using NMR spectroscopy, the existence of such a dimer for the heterocuprate with R = *n*Bu and L = (*R*)-*N*-methyl-1-phenyl-2-(1-pyrrolidinyl)ethanamine.[7] However, monomeric aggregates such as **2** (Scheme 1, M = Cu) have also been suggested to play a role in the reaction of heterocuprates with enones, particularly in polar solvents.[8] Calculations by Yamanaka and Nakamura have shown the importance of the *trans* effect and strong Li–L bonds for the nontransferability of the heteroatom groups in these reagents.[9] In addition, studies on related lithium heterobimetallic species have recently revealed monomeric structures analogous to **2** for M = ZnL,[10a] MgL,[10a] MnR,[10b] and AlR_2,[10c] although as far as we are aware there are currently no examples of these metals forming dimeric aggregates similar to **1**.



Scheme 1. Structural models for lithium organo-amidocuprates (R = organic group; L = amido group).

Reaction of CuMes (Mes = 2,4,6-trimethylphenyl) with $LiN(CH_2Ph)_2$ in toluene gave the organo-amidocuprate of stoichiometry $[CuLiMes\{N(CH_2Ph)_2\}]$ (we have previously demonstrated how the mesityl group can act as a model for the reactive R group in organocuprates, wherein its lack of β-hydrogen atoms results in increased thermal stability and ease of handling[11]). Crystals of **3** were obtained from this reaction solution and were characterized using X-ray diffraction studies (Figure 1).[12] This study constitutes the first solid-state structure of a hetero-amidocuprate.

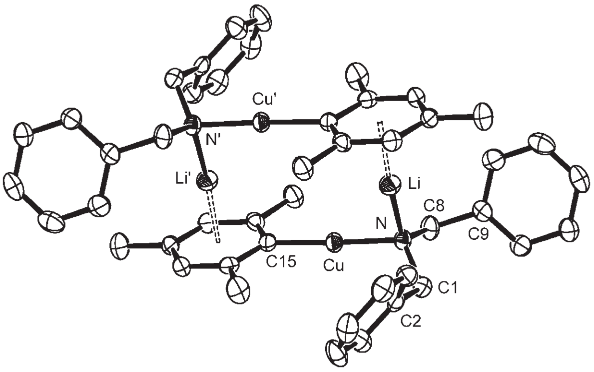


Figure 1. The molecular structure of the C_i-symmetric complex **3**; thermal ellipsoids are set at 50%; hydrogen atoms are omitted for clarity.

The structure of **3** is consistent with previous predictions for lithium hetero-amidocuprates (**1**, Scheme 1); it is dimeric and contains two $[RCuL]^-$ cuprate units lying antiparallel, or head-to-tail, to one another. The molecule is located on an inversion center, with both cuprates adopting a nearly linear conformation (C15-Cu-N = 175.3(2) Å). The Cu–C bond lengths (1.913(5) Å) are shorter than in the related homocuprate $[Cu_2Li_2Mes_4]$ (1.925(2) Å, 1.936(2) Å),[11] but comparable to those reported for the $[CuMes_2]^-$ anion (1.915(9) Å).[13] The Cu–N bond in **3** (1.921(4) Å) is significantly longer than the Cu–N bonds observed in the homobis(amido)cuprates $[Cu\{N(SiMePh_2)_2\}_2]^-$ (mean 1.88 Å)[14] and $[\{Li(dme)Cu(NHMes)(NHPh)\}_2]$ (mean 1.855 Å; dme = dimethoxyethane).[15] The Li^+ ions in **3** are coordinated to both an amido nitrogen atom (Li–N 1.969(10) Å) and a mesityl aryl ring (Li–C in the range 2.334(10) to 2.445(10) Å; mean 2.386 Å). Similar η^6 coordination of Li^+ ions has been reported in the homocuprate $[Cu_2Li_2Mes_4]$.[11]

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[*] Dr. R. P. Davies, S. Hornauer
Department of Chemistry
Imperial College London, South Kensington
London, SW7 2AZ (UK)
Fax: (+44) 870-1300438
E-mail: r.davies@imperial.ac.uk
Dr. P. B. Hitchcock
School of Chemistry
University of Sussex
Brighton, BN1 9QJ (UK)

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Although the solid-state structure of **3** provides some valuable insights into the bonding within organo-amidocuprates, virtually all cuprate addition reactions are carried out in solution, and hence elucidation of the solution structures is crucial to understanding the reaction mechanisms and selectivity of these reagents. ^{7}Li NMR spectroscopic studies on a [D$_8$]toluene solution of **3** revealed no less than five main lithium environments (corresponding to signals A–E in Figure 2), indicative of at least a partial break up of the dimeric form **3** and the presence of Schlenk-type equilibrium. Cyroscopic relative molecular mass (RMM) measurements on **3** in benzene (0.19 M solution) gave an association value of $n = 1.8$ for $[\mathrm{CuLiMes\{N(CH_2Ph)_2\}}]_n$, suggesting a predominance of dimeric aggregates.

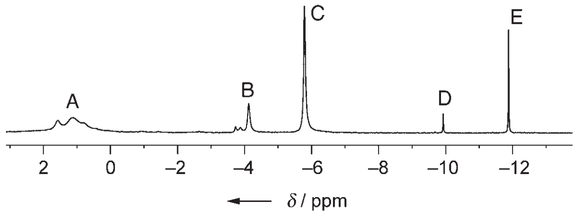


Figure 2. ^{7}Li NMR spectrum of **3** in [D$_8$]toluene (298 K). See text for peak assignments.

Assignment of the solution species, as represented by the different lithium environments in Figure 2, has been aided by the use of modified pulse field gradient (PFG) inverse-detected ^{1}H–^{7}Li HOESY NMR spectroscopy (Figure 3).[16]

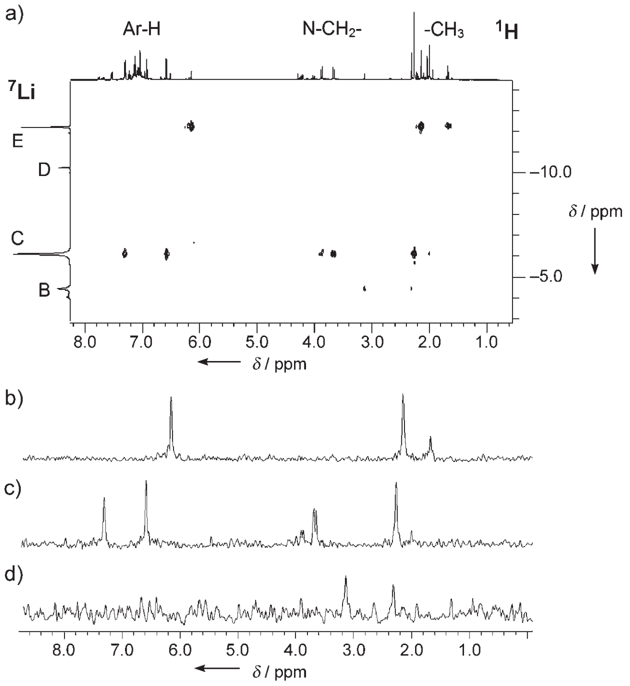
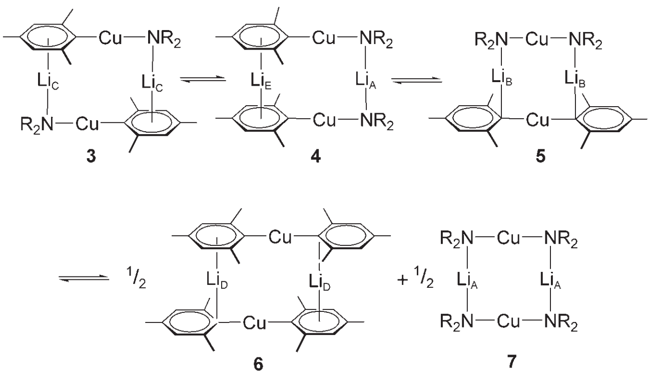


Figure 3. a) Modified PFG inverse-detected ^{1}H–^{7}Li HOESY NMR spectrum of $[\mathrm{Cu_2Li_2Mes_2\{N(CH_2Ph)_2\}_2}]$ in [D$_8$]toluene. b)–d) Individual slices through the ^{7}Li NMR chemical shifts at $\delta = -11.88$ ppm (b), $\delta = -5.79$ ppm (c), and $\delta = -4.13$ ppm (d).

The largest peak in the ^{7}Li NMR spectrum, signal C ($\delta = -5.79$ ppm), shows strong NOE cross-peaks with mesityl CH$_3$, dibenzylamido CH$_2$, and aromatic ArH protons. Consequently, Li$_\mathrm{C}$ must lie in close proximity to both mesityl and amido groups, and can therefore be assigned as the head-to-tail dimer **3** (Scheme 2), which is analogous to the solid-state structure. This assignment also fits with its high upfield shift of $\delta = -5.79$ ppm, which is symptomatic of a lithium cation sitting directly above one aromatic ring.[17,18]



Scheme 2. Predicted Schlenk equilibrium for the lithium hetero-amidocuprate $[\mathrm{Cu_2Li_2Mes_2(NR_2)_2}]$ in toluene ($\mathrm{R = CH_2Ph}$).

Although no NOE cross-peaks are observable for peak D owing to its weak signal, its chemical shift of $\delta = -9.93$ ppm is almost identical to that previously reported for the η^1,η^6 bis(mesityl)-coordinated Li centers in $[\mathrm{Cu_2Li_2Mes_4}]$ ($\delta = -9.99$ ppm).[11] Hence, Li$_\mathrm{D}$ can be assigned as arising from this homocuprate (**6**, Scheme 2). Peak E is at an even higher upfield shift ($\delta = -11.88$ ppm), suggestive of a Li center sandwiched in an η^6,η^6 mode between two mesityl groups, and hence being subjected to the full magnetic anisotropic effect of both aromatic rings. In addition, peak E exhibits NOE cross-peaks solely to mesityl CH$_3$ and aromatic protons. In our view, the most probable assignment for Li$_\mathrm{E}$ is therefore the head-to-head dimer **4**. The other lithium center in **4** can be accounted for by the peaks at signal A ($\delta = +1.11$ ppm), as these fall within the correct range expected for a bis(amido)-coordinated Li center.[18] Signal A, in fact, consists of several broad overlapping peaks and may also comprise the bis(amido)-coordinated Li centers in the homo-bis(amido)cuprate **7**, which would be expected to form concurrently with **6**. The lack of any observable NOE cross-peaks for the signals at A can be attributed to the Li$^+$ ions being located in between two quadrupolar N nuclei.

Peak B lies at $\delta = -4.06$ ppm and is therefore in the correct region for a Li$^+$ ion coordinated to the π system of one aromatic ring. This signal possesses weak NOE cross-peaks with amido methylene protons and *ortho*-CH$_3$ mesityl protons. We tentatively assign this peak to the mixed homocuprate species **5**, in which, because of geometric restraints, the Li$^+$ ions are η^1-coordinated to the mesityl group and hence more downfield than the η^6-coordinated Li centers in **3**. Although an alternative assignment would perhaps be a monomeric species similar to **2**, this possibility can be discounted since the upfield shift of $\delta = -4.06$ ppm suggests Li_B is located at least partially above the aromatic ring, which is not possible in the monomer owing to steric requirements. Unlabelled minor peaks in the ^7Li NMR spectrum (which can be seen in the ranges $\delta = +0.5$ to $+1.5$ ppm and $\delta = -3.0$ to -4.0 ppm) are speculatively assigned as $[Cu_2Li_2\{N(CH_2Ph)_2\}_3Mes]$, $[Cu_2Li_2\{N(CH_2Ph)_2\}Mes_3]$, and monomeric species. It is worthwhile to note that no peaks were observed for the lithium species $[Li\{N(CH_2Ph)_2\}]_n$[19] in either the ^1H or ^7Li NMR spectra, signifying that **3** does not disassemble back into its monometallic precursors.

Inspection of the ^1H–^7Li HOESY NMR spectrum (Figure 3c) allows the assignment of the dibenzylamido CH_2 protons in **3** as two doublets at $\delta = 3.67$ and 3.88 ppm; their inequivalence presumably is due to the geometric constraints posed by the dimeric structure. Comparison of the integrals of these signals with the other methylene proton signals in the ^1H NMR spectrum reveals the head-to-tail dimer **3** to be the dominant species in solution, accounting for 64% of the amido groups (298 K, 0.22 M in $[D_8]$toluene). Variable-temperature NMR studies show this ratio to remain approximately constant in the temperature range 298 to 166 K. Variable-concentration studies reveal the amount of **3** present to fall with increasing dilution to 51% for a 0.02 M $[D_8]$toluene solution. This decrease may be due to dissociation of the dimer to give monomeric species as suggested by the cryoscopic RMM studies (see above).

Density functional calculations (B3LYP) were performed on the model system $[Cu_2Li_2Me_2(NH_2)_2]$ to further investigate the relative thermodynamic stabilities of the different lithium hetero-amidocuprate structural isomers. The lowest energy of all the optimized structural isomers (Figure 4) is the head-to-tail dimer **I**. This result is in agreement with our solid-state and solution structural studies on $[Cu_2Li_2Mes_2\{N(CH_2Ph)_2\}_2]$, for which this isomer was shown to be the dominant species. The head-to-head dimer **II** is $+0.744$ kcal mol^{-1} higher in energy, and the mixed homodimer **III** is $+1.763$ kcal mol^{-1} higher in energy. The optimized homodimers (**IV** and **V**) and mixed homo- and heterodimers (**VI** and **VII**) were also confirmed to be higher in energy than **I** (Figure 4). The lowest-energy optimized monomeric structure (Figure S8 in the Supporting Information) was calculated to be considerably higher in energy than **I** ($+61.27$ kcal mol^{-1} for two monomeric units), making the formation of monomeric species seem unlikely. However, it is possible that any $[CuLiMes\{N(CH_2Ph)_2\}]$ monomeric complex would contain additional stabilization from Li···HC interactions, similar to those previously reported for $[Li\{N(CH_2Ph)_2\}]_n$,[19,20] thus making its formation more favorable than that for the calculated $[CuLiMe(NH_2)]$ model system.

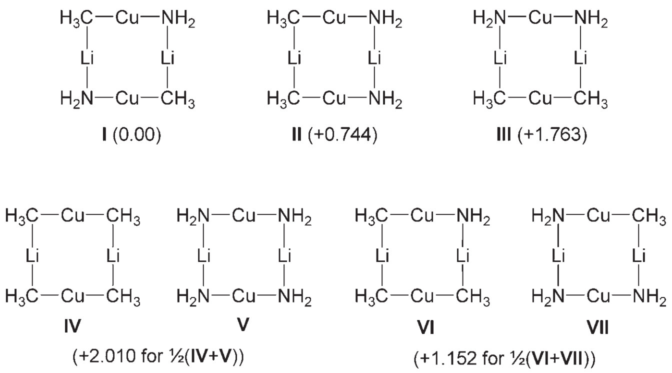


Figure 4. Schematic diagram of the optimized structural isomers of $[Cu_2Li_2Me_2(NH_2)_2]$ at the B3LYP/631AS level (energies relative to I in kcal mol^{-1}; see the Supporting Information for full details).

In summary, the first solid-state structure of an organo-amidocuprate has been presented and shown to form a head-to-tail dimeric aggregate consistent with previous theories. In addition, DFT calculations have been carried out, which predict this head-to-tail dimer to be favored over other possible structural isomers for a simple model system. However, NMR studies on $[Cu_2Li_2Mes_2\{N(CH_2Ph)_2\}_2]$ have shown a mixture of structural isomers to be present in toluene solution as a result of Schlenk equilibrium, and these structural isomers have been identified with the aid of modified PFG inverse-detected ^1H–^7Li HOESY NMR spectroscopy. To our knowledge, this is the first time such structural isomers have been identified in solution. The presence of more than one isomer in solution is potentially significant for the mechanism of hetero-amidocuprate addition reactions, and is of particular relevance to asymmetric addition reactions involving chiral hetero-amidocuprate reagents where high enantiomeric excesses are sought.

Experimental Section

All reactions were carried out in a protective nitrogen atmosphere.

3: *s*BuLi in hexanes (1.3 M, 1.53 mL, 2 mmol) was added to a solution of dibenzylamine (340 mg, 2 mmol) in toluene (5 mL) at 0 °C. The solution was allowed to warm to room temperature and stirred for 1 h to give a light-red precipitate. A solution of CuMes (365 mg, 2 mmol) in toluene (5 mL) was added dropwise to give a clear red solution, which was filtered through celite and concentrated under vacuum to approximately 2 mL. Storage at 4 °C for two days yielded colorless crystals suitable for X-ray analysis (431 mg, 56%); m.p. 89 °C (decomp).

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[12] Crystal data for **3**: $C_{46}H_{50}Cu_2Li_2N_2$, $M_r = 771.84$, triclinic, space group $P\bar{1}$ (no. 2), $a = 9.0311(4)$, $b = 10.8223(4)$, $c = 11.4544(6)$ Å, $\alpha = 77.951(3)$, $\beta = 71.413(2)$, $\gamma = 70.608(3)°$, $V = 994.28(8)$ Å^3, $Z = 1$, $\rho_{\text{calcd}} = 1.29\ \text{g cm}^{-3}$, $\mu(\text{Mo}_{K\alpha}) = 1.10\ \text{mm}^{-1}$, $T = 173(2)$ K; 3885 independent measured reflections, $R_1 = 0.061$, $wR_2 = 0.177$, 3214 independent observed reflections $[|F_o| > 4\sigma(|F_o|)$, $2\theta_{\max} = 52°]$, 237 parameters. CCDC-637881 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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