the peaks for Me_2CuLi·LiI and Me_2CuLi·LiCN are at 0.03 and −1.03 ppm, respectively. These results are consistent with either our formulation or Lipshutz's, both of which feature a different counterion for Li in the case of the corresponding cuprates prepared from CuI and CuCN. The ^6Li NMR peak for $^6Li^{13}CN$ under the same conditions is at −1.38 ppm, and in the presence of equimolar $LiClO_4$ it is at −0.87 ppm. It is interesting to note that the shifts for R_2CuLi·LiCN are in this range.

The cuprates prepared from CuCN and 1 equiv of RLi have different CN chemical shifts for R = Ph (148.51 ppm) and R = Et (149.11 ppm) or Me (149.33 ppm). Upon addition of Li-complexing agents HMPA and 12-C-4, these chemical shifts move *upfield* to 145.44 and 146.47 or 146.55 ppm, respectively. Increased back-bonding is expected to result in an upfield shift of the CN resonance.[11] These observations are evidence that CN is indeed bonded to Cu in these 1:1 reagents.

In the presence of HMPA and 12-C-4, the corresponding cuprates R_2CuLi·LiI and R_2CuLi·LiCN (R = Ph, Et, Me) have the same spectra (Table I) for the organic groups, to within ±0.01 ppm (digital resolution) for Et and Ph and ±0.05 ppm for Me. Furthermore, the chemical shifts for R in the presence of HMPA and 12-C-4 are only modestly downfield from the values measured without them. For comparison LiCN in THF in the presence of HMPA and 12-C-4 has a chemical shift of 165.2 ppm at −78 °C.

Power and co-workers have reported that mononuclear cuprates can be prepared as $Li(12\text{-}C\text{-}4)_2^+$ salts and characterized by X-ray crystallography.[12] The similarity of our results with and without Li-complexing agents strongly suggests that these cuprates are essentially $[RCuR]^-$ anions or their aggregates (vide infra) in THF solution. The additives may serve to convert aggregates or contact ion pairs to solvent-separated ion pairs,[13,14] or to convert one solvent-separated ion pair into another.

The ^{13}C NMR chemical shifts reported by Hallnemo and Ullenius[15] for Ph_2CuLi·LiI in pyridine-d_5 are close to our values in THF-d_8 (Table I). It is also interesting to note that their values for this reagent in dichloromethane-d_2 are very close to our values measured in dimethyl sulfide (DMS),[16] which are significantly different from those in THF-d_8 or pyridine-d_5. We believe that different species are present in strongly coordinating (THF, pyridine) and weakly coordinating (DMS, dichloromethane) solvents. Power and Olmstead have characterized the crystals grown from DMS solutions of halide-free Ph_2CuLi as dimeric $(Ph_2CuLi)_2$·3DMS.[17] Thus, the ^{13}C NMR chemical shift appears to be useful for elucidating the gross structures of organocuprates, e.g., whether phenyl cuprates are monomeric ($\delta_{ipso} \approx 175$ ppm for 12-C-4 salt) or dimeric ($\delta_{ipso} \approx 162$ ppm in DMS). When HMPA and 12-crown-4 are added to $(Ph_2CuLi)_2$ in DMS, the ^{13}C NMR spectrum changes to that of $Ph_2Cu^-\ Li(12\text{-}C\text{-}4)_2^+$.[18]

$Ph_6Cu_3Li_2^-$ units in crystals grown from THF solutions of Ph_2CuLi·LiI or Ph_2CuLi·LiCN comprise three nearly linear $[PhCuPh]^-$ subunits held together by two Li^+ ions.[17,19] Whether such aggregates are present at equilibrium in our NMR solutions is an open question which does not bear directly upon the question of higher order cuprates. We believe it is significant that neither I nor CN is present in this cluster. If a species with a Cu–CN bond were the "thermodynamic sink", then it should be present in the solid state as well as solution.

The only higher order cuprate that has been confirmed crystallographically is our Ph_3CuLi_2·Ph_2CuLi·4DMS complex,[16] the detailed structure of which was elucidated by Olmstead and Power.[20] The Ph_3Cu^{2-} subunit appears to be held together by three bridging Li cations; therefore, our higher order cuprate is best viewed as $Ph_3CuLi_3^+\ Ph_2Cu^-$. Our NMR study also established that Ph_3CuLi_2 does not exist in ether or THF,[16] presumably because ethereal solvents remove the bridging Li cations and thus destabilize the higher order structure.

In light of the results reported herein, two possibilities are (1) the CN is bonded to Cu in "higher order" cyanocuprates but does not affect the ^{13}C NMR spectra or (2) the CN is not bonded to Cu. We believe the term "higher order" should not be applied to cuprates prepared from CuCN until more positive evidence for such structures is presented.

Acknowledgment. I thank G. Dabbagh for some preliminary spectra and P. Mirau and R. Hoffman for helpful advice. The Et^6Li and PhLi used in this study were prepared by E. Lanfer (Organometallics, Inc.) and H. Hatch (Lithco), respectively. The $^6Li^{13}CN$ was supplied by MSD Isotopes.

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"Higher Order" Cyanocuprates $R_2Cu(CN)Li_2$: Discrete Reagents or "Lower Order" LiCN-Modified Gilman Cuprates?

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In late 1981, an initial disclosure was made that addition of 2 equiv of an organolithium to CuCN leads to "higher order, mixed cyanocuprates".[1] These were written as "$R_2Cu(CN)Li_2$" (**1**), implying a Cu(I) dianionic species containing three covalently bound ligands on copper, one of which is the cyano group.[2] Notwithstanding the now extensive use of higher order (HO) cuprates,[3] reagents that oftentimes afford considerably different chemical outcomes (e.g., in reactivity,[4a] yields,[4b] stability,[4c] etc.) when compared to other commonly used lower order (LO) analogues [e.g., R_2CuLi, $RCu(CN)Li$], the very existence of complexes **1** has recently been challenged.[5] It has been proposed that cuprates prepared from 2RLi and CuCN are simply Gilman-like species containing LiCN, rather than LiX (X = Br, I), somewhere within the cluster and hence should be more accurately represented as R_2CuLi·LiCN. We now describe, using spectroscopic studies, prima facie evidence in support of HO cyanocuprates.

Generation of $Me_2Cu(CN)Li_2$ (**2**) was accomplished in both THF[3] and Me_2S/Et_2O[6] from the usual admixture of 2MeLi (in Et_2O) with CuCN. The low-temperature (−80 °C) ^{13}C NMR

† Proctor & Gamble Predoctoral Fellow, 1989–1990.
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(6) The manner in which the cuprate is formed is critical; the Cu(I) salt must be added to the MeLi in Me_2S. The alternative mode of addition leads to precipitation of lithium salts (i.e., LiBr, LiI). For the first preparation of HO cuprates R_3CuLi_2 in Me_2S, see: Bertz, S. H.; Dabbagh, G. *J. Am. Chem. Soc.* **1988**, *110*, 3668.

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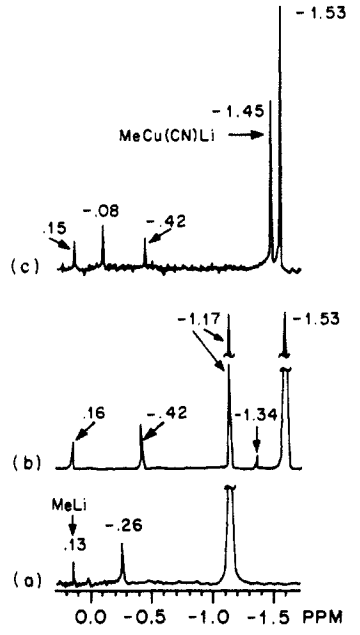


Figure 1. ^1H NMR spectra of (a) $Me_2CuLi{\cdot}LiI$ in Me_2S at −80 °C, (b) $Me_2CuLi{\cdot}LiI$ in Me_2S + HMPA (12%) at −80 °C, and (c) $Me_2CuLi{\cdot}LiI$ in Me_2S containing LiCN/HMPA (1 equiv) at −80 °C.

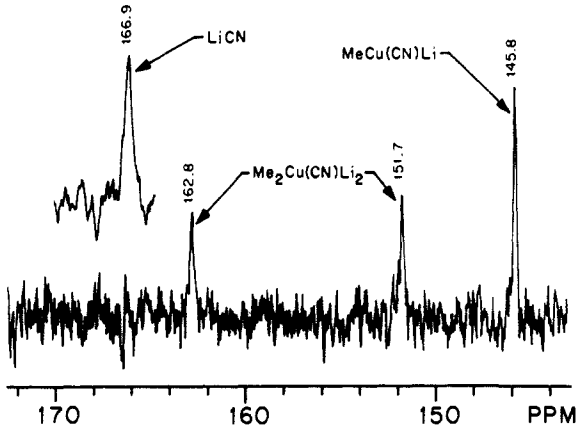


Figure 2. ^{13}C NMR spectrum of $Me_2CuLi{\cdot}LiI$ + LiCN/HMPA (1 equiv) in THF at −40 °C vs LiCN.

spectrum of **2** in THF does indeed appear (δ −10.61) very close to that of $Me_2CuLi{\cdot}LiI$ (**3**, from 2MeLi/Et_2O + CuI, δ −10.72). However, in Me_2S, **2** displays a singlet at δ −8.53, while both **3** and $Me_2CuLi{\cdot}LiBr$ (**4**, from 2MeLi/Et_2O + $CuBr{\cdot}Me_2S$) show a singlet at δ −9.65. Thus, there being a >1 ppm difference in chemical shift between **2** and **3**/**4**, clearly **2** is easily distinguishable from the lower order reagents in this medium.[7]

To demonstrate that the cyano ligand does not come off copper when MeLi is added to MeCu(CN)Li (**5**) but actually *prefers* to be bound to the metal, LiCN (1.0 equiv) in HMPA (12% by volume; 0.75 M) was added to the LO cuprate **3** in Me_2S. The ^1H NMR spectrum revealed the immediate and complete loss of the singlet due to **3** (δ −1.17) with the appearance of two new singlets at δ −1.45 [MeCu(CN)Li][8] and δ −1.53 [due to $Me_2Cu(CN)Li_2$, **2**] (Figure 1), the positions of which are precisely those observed in THF.[9]

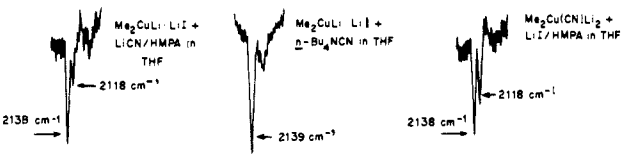
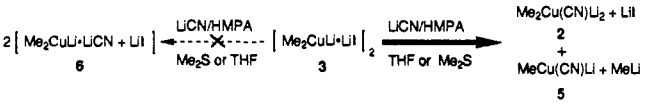


Figure 3. Infrared spectra.

Scheme I



To prove that the peak at δ −1.53 is assignable to **2** and *not* $Me_2CuLi{\cdot}LiCN$ (**6**),[10] a ^{13}C NMR spectrum was taken of $Me_2CuLi{\cdot}LiI$ in THF to which had been added 1 equiv of LiCN/HMPA (Figure 2). The singlet due to LiCN (δ 167) was no longer visible, as three new peaks attributable to HO (δ 163, 152) and LO (i.e., MeCu(CN)Li; δ 146) *cyano*cuprates were observed.[11] The presence of MeCu(CN)Li requires that MeLi·LiI be in solution, and the ^1H NMR spectrum confirms its presence.

To fully corroborate the NMR results above, an IR experiment on $Me_2CuLi{\cdot}LiI$ (**3**) in THF to which had been added LiCN/HMPA was carried out. The spectrum shows the appearance of two CN stretches (2138, 2118 cm^{-1}) characteristic of the HO cuprate **2** (Figure 3). By contrast, codissolution of **3** with an innocuous lithium salt ($LiClO_4$) does not give rise to any IR bands in the 2100–2200-cm^{-1} region.[12] To generalize the affinity of cyanide for Cu(I), Bu_4NCN (in THF, 2057 cm^{-1})[13] was added to **3** in THF, the IR spectrum of which shows the total loss of this salt with concomitant appearance of the *same* two new bands associated with the HO species $Me_2Cu(CN)Li_2$ (**2**). Likewise, the spectrum of **3** + LiCN/HMPA in Me_2S reveals the disappearance of the CN band due to LiCN (2079 cm^{-1}), correlating the above data irrespective of solvent(s). Thus, $Me_2CuLi{\cdot}LiI$ is not equivalent to $Me_2CuLi{\cdot}LiCN$ (**6**) either spectroscopically or in terms of solution behavior[3] (as summarized in Scheme I). In fact, **6** does not exist; a HO cuprate is the thermodynamic sink for a Gilman reagent in the presence of cyanide ion!

In conclusion, there can be little doubt that HO cyanocuprates are bona fide reagents, distinct from LO status as manifested by the data herein. Intuitively, this is the conclusion we knew had to be reached, since several other, even multiply cyano bound cuprates exist, some as yet not fully characterized [e.g., $RCu(CN)_2Li(NBu_4)$],[14] while others have been known for decades (e.g., $K_2Cu(CN)_3$).[15] Arguments negating HO reagents based on ^{13}C NMR chemical shift similarities with LO cuprates in THF are flawed in that spectroscopically significant differences between reagents (e.g., **2** and **3**) cannot be readily detected in this medium alone.[7,11] Changes in aggregation state, from dimers in Me_2S to monomers in THF,[5] do not explain our results. Moreover, speculation that $[RCuR]^-$ is a monomeric, linear complex cannot

(7) (a) The ^1H NMR spectra for **2** vs **3** in either THF (δ −1.53) or Me_2S (δ −1.16, δ −1.17, respectively), however, do not permit differentiation. (b) All comparison spectra were run on a GE GN-500 NMR spectrometer with reagents prepared under carefully controlled, otherwise identical conditions (i.e., at 0.10 M) using low-halide MeLi in Et_2O, used as received from Aldrich following titration.[7c] (c) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

(8) Determined by the appropriate control experiments with independently prepared samples. Peaks downfield of the cuprate signal(s) are due to various aggregation states of MeLi as a function of solvent(s) and additive(s).

(9) Introduction of THF to $Me_2Cu(CN)Li_2$ in Me_2S (δ −1.17) leads to a new signal at δ −1.53, as seen for **2** in THF alone.[2]

(10) The chemical shift in the ^1H NMR spectrum for the methyl group for 2MeLi + CuI + LiCN/HMPA in Me_2S is essentially the same as that for 2MeLi + CuCN in Me_2S containing HMPA.

(11) The chemical shift for the cyano ligand in $Me_2Cu(CN)Li_2$ in THF varies as a function of the percent HMPA present. As HMPA (5–50%) is added, the original peak at ca. δ 157 *gradually* shifts downfield (to δ 164.4), placing it sufficiently close to LiCN to be interpreted as such[5] (although the corresponding IR spectra of each solution in no case show LiCN). This may be the key factor responsible for Bertz's conclusions. The two peaks in Figure 2 assigned to the CN carbon in $Me_2Cu(CN)Li_2$ may be due to the presence of monomeric and dimeric species, the ratio being a function of the amount of HMPA in the medium.

(12) Also, addition of $LiClO_4$ to LiCN in DMF/THF does not alter the position of the cyanide stretch (2180 cm^{-1}) characteristic of LiCN alone.

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possibly account for the multiple NMR signals *always* observed for each ligand in mixed LO reagents in *THF*. In the final analysis, the Bertz contribution[5] admirably brings to light some of the subtleties and potential pitfalls[7a,11] associated with cuprate preparation and study. Indeed, Gilman's reagent alone has many forms.[16] The cuprate prepared from CuCN, however, just happens *not* to be one of them.

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Inactivation of General Acyl-CoA Dehydrogenase by Enantiomerically Pure (Methylenecyclopropyl)acetyl-CoA and Its Implication for This Enzyme-Catalyzed Reaction

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General acyl-CoA dehydrogenase (GAD) is a flavin-dependent (FAD) enzyme that catalyzes the oxidation of a fatty acyl-CoA to the corresponding α,β-enolyl-CoA during the first step of the fatty acid oxidation cycle.[1] When GAD is exposed to (methylenecyclopropyl)acetyl-CoA (MCPA-CoA),[2] a metabolite of hypoglycine A which is the causative agent of the Jamaican vomiting sickness,[3] time-dependent inhibition occurs with concomitant bleaching of the active-site FAD.[4] The molecular course of this inhibition is believed to proceed with an α-proton abstraction, followed by ring fragmentation and then covalent modification of the flavin coenzyme.[4] Although the crucial ring cleavage leading to inactivation has been proposed to be a direct anion-induced process, it may also be envisaged as occurring via a transient α-cyclopropyl radical intermediate.[5] Recently, we have found that this inactivation is nonstereospecific since the partition ratio of the inactivation caused by racemic MCPA-CoA is identical with that obtained from incubation with naturally derived MCPA-CoA.[5] Because the rearrangement of an α-cyclopropyl radical to the straight-chain alkyl radical is an extremely rapid process,[6] such a nonstereospecific inactivation is likely a consequence of a spontaneous ring fragmentation event induced by an α-cyclopropyl radical. However, this result contradicts an existing report in which the authors concluded that because the C_1 epimer of naturally derived MCPA-CoA showed no significant effect on the inactivation of GAD, the inactivation must be stereospecific.[7] In an attempt to resolve this stereochemical discrepancy, we have prepared MCPA-CoA in both enantiomerically pure forms and examined the inactivation of GAD by these compounds. Summarized in this paper are the results of these studies and their implication for the mechanism of the GAD-catalyzed reaction.

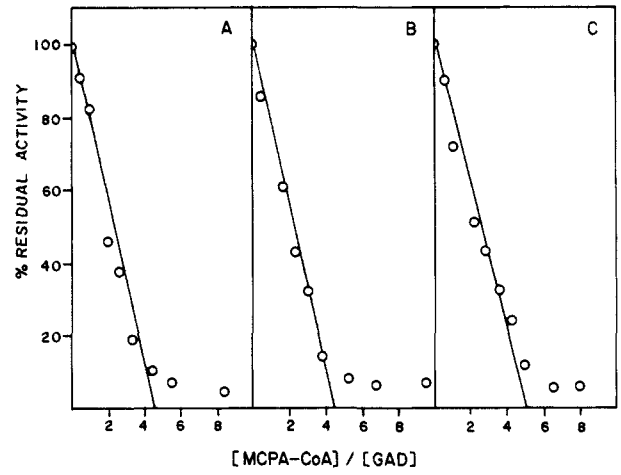
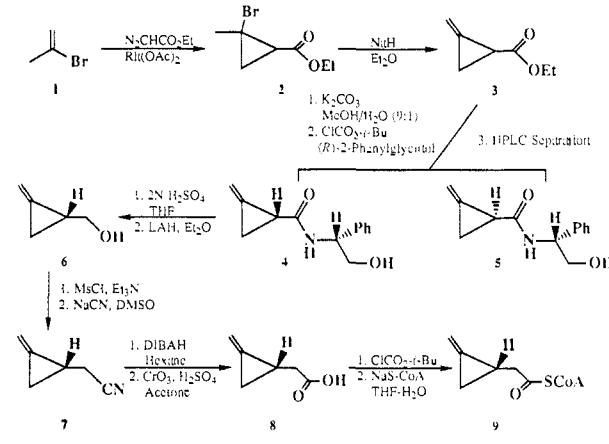


Figure 1. Effect of MCPA-CoA on the catalytic activity of GAD. The purified enzyme (16.8 nmol) in 60 mM potassium phosphate buffer (pH 7.5) was titrated aerobically with successive addition of aliquots of MCPA-CoA. The residual activity was assayed 15 min after each addition according to a procedure of Thorpe.[20] These figures show the percentage of residual activity versus the ratio of MCPA-CoA to enzyme: (A) (*R*)-MCPA-CoA; (B) racemic MCPA-CoA; and (C) (*S*)-MCPA-CoA.

Scheme I



As depicted in Scheme I, the key intermediate, ethyl (methylenecyclopropyl)formate (**3**), was prepared from 2-bromopropene (**1**) and ethyl diazoacetate by a rhodium acetate catalyzed cyclopropanation,[8] followed by a sodium hydride induced elimination (75% yield).[9] Upon hydrolysis and derivatization with (*R*)-2-phenylglycinol, compound **3** was converted to a diastereomeric mixture of amides (**4** and **5**, 72% yield) that are readily separable by flash chromatography (silica gel, 30% EtOAc/hexane).[10] Since the relative elution order of diastereomeric amides of this class by liquid adsorption chromatography has been well established,[10,11]

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