Determination of the Degree of Aggregation of Organocopper Compounds by Cryoscopy in Tetrahydrofuran**

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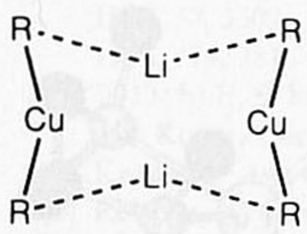
Organocopper compounds belong to a class of frequently used organometallic reagents in organic synthesis, because they are readily accessible and exhibit high reactivities and selectivities for the formation of C–C bonds. This bond formation occurs by (stoichiometric or catalytic) substitution, addition, or carbocupration reactions.[1] In contrast to the overwhelming number of preparative applications, however, little is known about the reaction mechanisms[2] or structures of the organocopper species involved.[3] Whereas monoorganocopper compounds are usually aggregates to some degree, polyorganocuprates mostly exist as discrete species in the solid state, and dimeric complexes of type **1** are frequently observed.[3]



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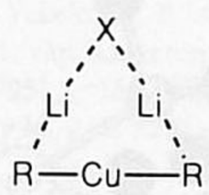

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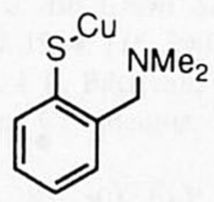

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For the preparative application of these reagents, information on the solution structure is highly relevant but currently scarce. Spectroscopic investigations by NMR spectroscopy have revealed the existence of equilibria between a number of different organocopper species in solution.[4] The aggregation behavior of these cuprates has only been examined for lithium dimethylcuprate (Me_2CuLi). This compound has been shown to exist as a dimer (probably also of type **1**) by ebullioscopy and vapor pressure measurements in ethereal solvents.[5] The structures of cyanocuprates of the stoichiometry $R_2Cu(CN)Li_2$ (from two equivalents of RLi and one equivalent of CuCN), which were introduced by Lipshutz fifteen years ago,[1b–d] are particularly controversial. The high reactivity of these reagents was initially explained by the assumption that the cyanide ion was bound to the Cu center as a third carbon substituent to form a "higher order" cyanocuprate ($[R_2Cu(CN)]^{2-} + 2\ Li^+$). The structures of cyanocuprates in the solid state are still unknown, and investigations by NMR spectroscopy provided contradictory conclusions about the nature of the complexes in solution.[6] It was later shown by EXAFS and XANES spectrocopy that most of the Cu atoms (more than 90%) in cuprates formed from two equivalents of MeLi or *n*BuLi and one equivalent of CuCN do not contain a coordinated cyanide ligand.[7] Ab initio calculations for $[Me_2Cu(CN)Li_2]$ have also pointed to species **2** (R = Me, X = CN) as the most stable structure, that is, one without a Cu–CN bond but instead containing a lithium-coordinated cyanide ion.[7c, 8] One possible explanation for the discrepancy between the structural and reactivity studies is that the thermodynamically most stable complex is not the kinetically most reactive one. The work detailed above only helps to underline the necessity of gathering further information about the structures of organocopper compounds in solution. To this end, the examination of the aggregation behavior of cuprate reagents in tetrahydrofuran (THF) by cryoscopy should provide some insight into this important area of organometallic chemistry. The conditions used here to examine the copper species are very similar to those used in the preparative application of the reagents. Investigations of this kind have been carried out successfully with a number of organolithium compounds[9] but not with organocopper complexes.

After the determination of the cryoscopic constant E_k of THF for the apparatus (see Experimental), the degrees of aggregation n[10] of several organolithium reagents used in this work were determined. These values are in good agreement with those found in the literature (Table 1); thus for MeLi values for n between 3.89 and 4.20 were observed (in ref. [9a] 4.37) whereas monomeric *t*BuLi gave values of 1.15–1.20 (in ref. [9b] 1.1). In a similar way, phenyllithium was shown to exist not as single species in THF but rather as a 2:1 mixture of dimer and monomer, as reported previously.[9a] These results firmly establish the validity of our experimental protocol to be used in the organocopper case.

Table 1. Cryoscopic investigation of organocopper and organolithium compounds in THF.

Substrate	c_{nom} [mmolal]	$n = c_{nom}/c_{exp}z$
$[MeLi]_n$	90.9–150.9	3.89–4.20 [9a]
$[tBuLi]_n$	78.1–151.5	1.15–1.20 [9b]
$[PhLi]_n$	27.4–88.2	1.63 [9a]
$[Me_2Cu(I)Li_2]_n$	45.5–75.5	0.95–1.03
$[MeCu(CN)Li]_n$	27.0–113.0	[a]
$[tBuCu(CN)Li]_n$	70.4	1.05
$[PhCu(CN)Li]_n$	88.2	2.00
$[Me_2Cu(CN)Li_2]_n$	35.2–72.9	1.08–1.19
$[tBu_2Cu(CN)Li_2]_n$	46.0–75.7	0.74–0.76 [b]
$[Ph_2Cu(CN)Li_2]_n$	25.5	1.18
$[tBu(iPr_2N)Cu(CN)Li_2]_n$	51.3	0.97 [c]
3	13.7–41.1	0.95–1.06

[a] The degree of aggregation could not be determined because some of the cuprate precipitated prior to crystallization of the solvent. [b] See text. [c] After taking into account the formation of 1 equiv $(CH_3)_3CH$ from the reaction of *t*BuLi with iPr_2NH.

The Gilman cuprate $[Me_2CuLi]_n$ (+ LiI) was formed by the addition of 0.5 equivalents of CuI to a cold MeLi solution. The degree of aggregation determined by cryoscopy gave a value of $n = 0.95–1.03$ when taking into account that two molecules of MeLi are bound in the cuprate (i.e., $z = 2$[10]). This neutral species exists as a monomer in THF, and the LiI formed during its preparation is bound to this complex, which therefore has the stoichiometry $[Me_2Cu(I)Li_2]$. This finding is in agreement with the experimental observation that the chemical reactivity of Gilman cuprates depends on the presence of a lithium salt.[11] In contrast to our experiment, the salt-free cuprate was used in the earlier determination of the aggregation state of Me_2CuLi,[5] and this exists as a dimer in solution. The related Gilman cuprate tBu_2CuLi could not be examined here, because its low

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thermal stability results in considerable decomposition during the preparation of this reagent. Similarly, the aggregation state of the "lower order" cyanocuprate $[MeCu(CN)Li]_n$ (prepared by the addition of one equivalent of CuCN) could not be measured because of the inherent low solubility of this complex in cold THF. For the analogous reagents $[RCu(CN)Li]_n$, however, values of $n = 1.05$ and $n = 2.00$ were determined for R = *t*Bu and Ph, respectively. This indicates that these cyanocuprates exist as discrete monomeric and dimeric species in THF solution. In accordance with previous studies[1b–d, 6] the cyanide is probably bound to these aggregates, because free LiCN would precipitate during cooling due to its known low solubility in cold THF. The formation of a precipitate was not observed with these reagents under the conditions used.

The degree of aggregation was also found to depend on the nature of the R group for the "higher order" cyanocuprates $R_2Cu(CN)Li_2$ (formed from 1.0 equiv of RLi and 0.5 equiv of CuCN). Values of $n = 1.08–1.19$ and 1.18 were measured for R = Me and Ph, respectively, indicating that these cuprates are monomers in THF. In contrast, values of n between 0.74–0.76 were determined when R = *t*Bu. The degree of aggregation of $n \approx 0.75$ for $[tBu_2Cu(CN)Li_2]_n$ ($z = 2$) corresponds to a $c_{nom}/c_{exp} \approx 1.5$ (with regard to the *t*BuLi used). This result suggests an equilibrium between a "higher order" and a "lower order" cyanocuprate in solution according to Equation (a).

$$[R_2Cu(CN)Li_2]_n \overset{K}{\rightleftharpoons} [RCu(CN)Li]_o + [RLi]_p \qquad (a)$$

Both species [*t*BuCu(CN)Li] and *t*BuLi[9b] are known to be monomeric in THF (Table 1). Therefore, assuming that the cuprate $[tBu_2Cu(CN)Li_2]_n$ also exists as a monomer, a value of $c_{nom}/c_{exp} = 1.5$ is calculated with an equilibrium constant K of 0.5. Unfortunately, our attempts to show the presence of the "lower order" species [*t*BuCu(CN)Li] in a $[D_8]$THF solution of the "higher order" cuprate by low temperature ^{13}C NMR spectroscopy were unsuccessful. Only one cyanide resonance for $[tBu_2Cu(CN)Li_2]$ was observed in the ^{13}C NMR spectrum at $\delta \approx 160$, whereas cyanide signals at $\delta \approx 150$ are typical for [RCu(CN)Li].[6, 12] Thus, if an equilibrium according to Equation (a) does exist, a rapid exchange on the NMR time scale between two copper species must take place.[13]

Finally, the aggregation behavior of two other organocopper compounds in THF was examined. These were the amidocuprate $[tBu(iPr_2N)Cu(CN)Li_2]_n$ and the copper arenethiolate **3**. Amidocuprates obtained by the formal replacement of one carbon group of a homo- or cyanocuprate by a chiral amide ligand are particularly interesting for applications in enantioselective Michael additions.[1, 14] Therefore, as a model of these reagents, the cuprate formed from one equivalent each of *t*BuLi, iPr_2NLi, and CuCN were examined. The complex is present as a monomeric species in THF ($n = 0.97$) and there is no evidence of an equilibrium according to Equation (a). The copper arenethiolate **3** is an important catalyst for both Michael additions and S_N2' substitution reactions.[1, 2h, 15] It also exists mostly as a monomer in THF ($n = 0.95–1.06$). The free coordination sites at the copper center are probably occupied by THF molecules (Cu-S-Cu bridges are formed in the absence of this donor, and **3** exists as a trimeric aggregate in the solid state and in nonpolar solvents[3, 16]).

To summarize the results of this study, cryoscopy is an excellent method for the determination of the aggregation behavior of organocopper reagents in THF solution. The "lower order" cyanocuprates of the stoichiometry RCu(CN)Li formed from one equivalent each of RLi and CuCN have been shown to exist as discrete monomeric (R = *t*Bu) or dimeric (R = Ph) species. The latter might possess a structure of type **1** with alternating Ph and CN bridges. In a similar way, we have shown for the first time that the Gilman cuprate $[Me_2Cu(I)Li_2]_n$ is present in THF solution as a monomer with coordinated iodide (in contrast to the salt-free cuprate), and the same is true for the cyanocuprates $[R_2Cu(CN)Li_2]$ (R = Me, Ph) and the amidocuprate $[tBu(iPr_2N)Cu(CN)Li_2]$.

Cryoscopic measurements cannot be used to determine whether the ligand X = I or CN associated with the reagents of the stoichiometry $R_2Cu(X)Li_2$ is coordinated to Cu[1b–d, 6b, e] or Li.[6a, c, 7, 8] Also, this method provides information about the thermodynamically most stable complex only, which may differ from a kinetically active species that is involved in the reactions of these compounds. The solid-state structure of a neutral aggregate related to the cuprates $[R_2Cu(X)Li_2]$ was reported recently. The copper complex $[\{C_6H_4(CH_2N(Me)CH_2CH_2NMe_2)\text{-}2\}_2\text{-}Cu_3Br]$ contains a Cu-Br-Cu bridge (Figure 1).[3, 16] By analogy, the organocopper compounds found in this work to be monomeric might adopt a similar structure of type **2** with a Li-X-Li bridge in the thermodynamically most stable form. This structure is therefore a reasonable alternative to the well-known dimeric structures of type **1**.

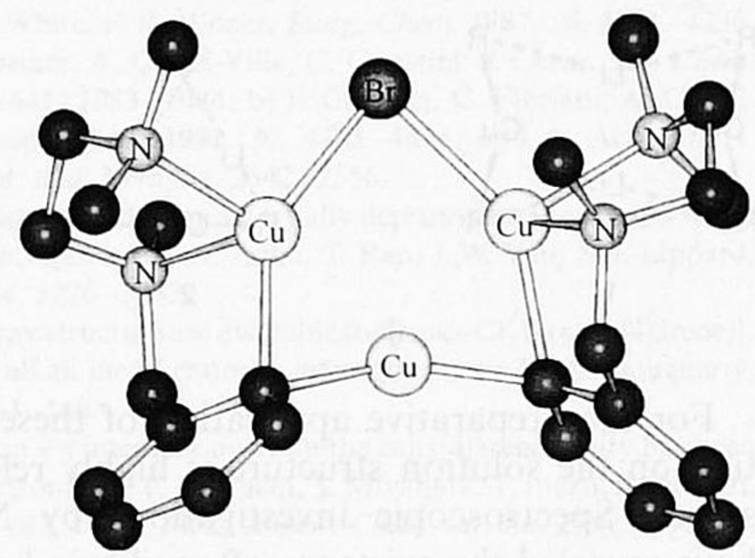

Figure 1. Solid-state structure of $[\{C_6H_4(CH_2N(Me)CH_2CH_2NMe_2)\text{-}2\}_2Cu_3Br]$ [3,16] (hydrogen atoms were omitted for clarity).

Experimental

The cryoscopic measurements were conducted under nitrogen in a double-walled Schlenk flask. The temperature was determined with a F25 precision thermometer provided with a glass-mantled Pt-100 sensor (±0.005 K), or with an S2541 thermolyzer and a metal-mantled Pt-100 sensor (±0.01 K). THF (23.7–28.3 g) was weighed into the flask and cooled by immersion into liquid nitrogen. By application of vacuum or a stream of gaseous nitrogen to the outer part of the double-walled flask, the cooling rate was controlled to about 10 K min^{-1} down to 150 K and to 1.2–1.5 K down to the freezing point. The cooling curve was recorded with a RE-511 recorder.

For the calibration, naphthalene was added in the form of weighed tablets, and the freezing point of the solutions thus obtained was determined. Repetition of this procedure with different amounts of naphthalene gave the following cryoscopic constants: $E_k = 5.187$ K kg mol^{-1} for the F25 precision thermometer and $E_k = 2.245$ K kg mol^{-1} for the S2541-thermolyzer (ref. [9a]: $E_k = 1.874$ K kg mol^{-1}) [17].

Solid MeLi and *t*BuLi were obtained by removal of the solvent from commercially available solution in diethyl ether or pentane, respectively. Phenyllithium was prepared according to a published procedure [9a]. The addition of the organolithium reagents as weighed tablets took place under a nitrogen atmosphere to the precooled apparatus (170–210 K). After dissolution, the freezing point was determined (three repetitions), and care was taken to observe whether the organolithium compound remained in solution completely prior to its crystallization. The same procedure was applied to copper arenethiolate **3**.

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The cuprates were formed by addition of weighed tablets of CuI or CuCN to the precooled (170–210 K) solutions of the organolithium reagents. After complete dissolution of the copper salt (occasionally with slight warming), the freezing point was determined as above. In the case of the amidocuprate [tBu(iPr$_2$N)Cu(CN)Li$_2$], one equivalent of diisopropylamine was added prior to CuCN.

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[10] Equations used: $\Delta T = E_k c_{exp}$; $n = c_{nom}/c_{exp} z$ (ΔT: measured freezing point depression; c_{exp}: experimental concentration of RLi; c_{nom}: nominal concentration of RLi; z: number of molecules RLi bound per formula unit).

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[12] Cyanide resonances in the ^{13}C NMR spectra (THF, −80 °C): [tBuCuCNLi]: $\delta = 149.6$; [tBu$_2$Cu(CN)Li$_2$]: $\delta = 159.9$.

[13] The observation of a rather broad cyanide resonance in the ^{13}C NMR spectra at −80 °C for the "higher order" cuprates [R$_2$Cu(CN)Li$_2$] supports the idea that a dynamic process is indeed operating. In contrast, sharp signals are detected for the corresponding "lower order" cuprates [RCu(CN)Li]. For a further discussion of the spectroscopic properties of cyanocuprates, see H. Huang, K. Alvarez, Q. Lui, T. M. Barnhart, J. P. Snyder, J. E. Penner-Hahn, *J. Am. Chem. Soc.* **1996**, *118*, 8808–8816.

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[17] The dependence of the cryoscopic constants on the thermometer may be attributed to different heat conductabilities and immersion depths of the sensors used.

Total Synthesis of (−)-Epothilone B: An Extension of the Suzuki Coupling Method and Insights into Structure–Activity Relationships of the Epothilones**

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Recently, synthetic studies directed to epothilone A (**3**)[1, 2] culminated in its first total synthesis.[3–5] Our synthesis passed through the *Z*-desoxy compound (**4**), which underwent highly stereoselective epoxidation with 2,2-dimethyldioxirane, under carefully defined conditions, to yield the desired β-epoxide. The same myxobacterium of the genus *Sorangium* that produces **3** also produces epothilone B (**1**). The latter is significantly more potent than **3** both in antifungal screens and in cytotoxicity assays in some cell lines.[6, 7] Clearly then, there was a strong rationale for preparing epothilone B (**1**).

Our interim goal structure was desoxyepothilone B (**2**) or a suitable derivative thereof. With access to such a compound, we could investigate the regio- and stereoselectivity of the epoxidation of the C12–C13 double bond. Not the least interesting issue in the project was the synthesis of *Z*-trisubstituted olefinic precursors of **2** with high margins of stereoselection. In our synthetic route to epothilone A[3] we had employed a palladium-mediated B-alkyl Suzuki coupling[8, 9] of the *Z*-vinyl iodide **5** with borane **7** derived from hydroboration of compound **6** with 9-BBN (Scheme 1).

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