Direct Insight into the Ion Pair Equilibria of Lithium Organocuprates by ^{1}H,^{6}Li HOESY Experiments

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Received January 26, 2000

An equilibrium between a monomeric solvent-separated ion pair (SSIP) and a contact ion pair (CIP) is observed directly for a representative lithium diorganocuprate, $Me_2CuLi{\cdot}LiCN$, in THF, using the ^{1}H,^{6}Li HOESY technique. Interestingly, crystal structures of related systems are also of the SSIP and the CIP type, whereby the latter shows a dimer as the fundamental structural element and the structure type depends on the Li^+ solvating capability of the solvent. In crystal structures of CIPs the shortest lithium−α-carbon distances are around 220 pm, which should lead to a strong dipolar interaction. Indeed, for the salt-free Me_2CuLi in Et_2O a strong cross-peak between lithium and the CH_3 groups of the cuprate is seen in the ^{1}H,^{6}Li HOESY spectrum, indicating that the main species in solution is a CIP. In contrast, the crystal structures of SSIPs show that the distance between lithium and the organic moiety of the cuprate is too long to lead to any dipolar interaction (shortest lithium−α-carbon distances longer than 530 pm). This is confirmed by the ^{1}H,^{6}Li HOESY spectra of MeCu(CN)Li and t-$Bu_2CuLi{\cdot}LiCN$ in THF. However, deviating from the pure SSIP structures, a weak dipolar interaction between lithium and the CH_3 groups could be observed for $Me_2CuLi{\cdot}LiCN$ and Me_2CuLi in THF, which was attributed to a direct dipolar interaction. The magnitude of this dipolar interaction was used to identify an equilibrium between the SSIP and the CIP of $Me_2CuLi{\cdot}LiCN$ in THF. At 213 K the dominant species in THF is the SSIP with some contributions of the CIP. As expected, this equilibrium could be shifted at lower temperatures toward the SSIP. It is demonstrated that the ^{1}H,^{6}Li HOESY technique can be used to get direct insight into the structural features of lithium diorganocuprates in solution, which is of great significance for their reactivity.

Introduction

Lithium organocuprates are some of the most widely used reagents for carbon−carbon bond forming reactions in synthetic organic chemistry.[1] They have been increasingly used for regio- and stereoselective syntheses.[2] Recently, the long scientific discussion about “higher order” or lower order cuprates has converged to the conclusion that reagents prepared from 2 equiv of RLi and 1 equiv of CuCN exist as cyano-Gilman reagents, $R_2CuLi{\cdot}LiCN$, and not as “higher order” cuprates.[3] Several experimental techniques such as NMR,[4] IR,[5] and EXAFS,[6] as well as theoretical calculations,[7] indicated that $R{-}Cu{-}R^-$ exists as a nearly linear unit in solution. This feature was also found in several X-ray crystal structures of cuprates in which the $R{-}Cu{-}R^-$ unit is shown to exist in different arrangements such as dimers,[8] monomeric solvent-separated ion pair type structures,[8e,9] and polymeric chains.[10,9c] Most of the

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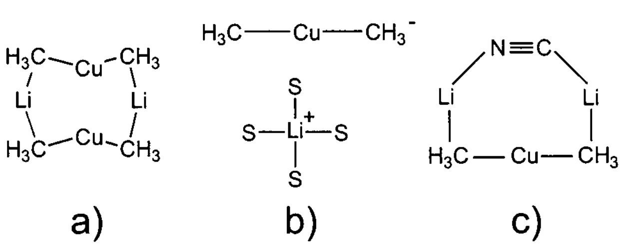
10.1021/om000068n CCC: $19.00
Publication on Web 06/23/2000

Chart 1. Proposed Structures of Lithium Diorganocuprates: (a) Homodimer; (b) SSIP; (c) Heterodimer



NMR investigations carried out so far dealt with the question of “higher” or lower order cuprate structures. However, very little is known about the structural details of R_2CuLi in solution, and more precisely, about the influence of *solvent* or *salt effects* on its structure. An in-depth study is lacking even for the simplest case, namely salt-free Me_2CuLi (**1**).

From colligative measurements in Et_2O (diethyl ether) an association value of around 1.8 was found for **1**.[11] This suggested the formation of the dimer (**1**)$_2$ in Et_2O, which was also supported by theoretical investigations[7e−g] and crystal structures of related systems crystallized from Et_2O or DMS (dimethyl sulfide).[8] Thus, the dimeric structure (**1**)$_2$ is expected for **1** in weakly Li^+ coordinating solvents such as Et_2O and DMS (see Chart 1a). The structural information available for **1** in THF (tetrahydrofuran), a much better Li^+ coordinating solvent, does not provide a clear picture. From ebullioscopic measurements an association number of 1.8 is reported.[11b] However, the only crystal structure of a related lithium diorganocuprate available from pure THF, $[Li(THF)_4][Cu\{C(SiMe_3)_3\}_2]$,[9a] reveals that the Li^+ is coordinated by four THF molecules and completely separated from the anion just as shown in the monomeric solvent-separated ion pair type structure of $Me_2Cu^-Li^+{\cdot}4S$ (see Chart 1b). Moreover, the two X-ray structures available for **1,** crystallized from DME (1,2-dimethoxyethane)[8e] and 12-crown-4,[9b] respectively, are also of the solvent-separated ion pair type. Interestingly, there has been no detailed NMR investigation of **1** either in THF or in Et_2O. In the only relevant report, Mobley et al.[4g] mentioned the existence of a dipolar interaction between the protons of the methyl groups and lithium. Therefore, the question of whether **1** exists in THF as a dimer of the CIP type (**1**)$_2$ or as a monomer of the SSIP type such as $Me_2Cu^-Li^+{\cdot}4S$ is not yet solved.

In connection with the influence of salts (LiX) on the structure of R_2CuLi in solution many investigations of lithium diorganocuprates of the type $R_2CuLi{\cdot}LiX$ (R = alkyl, aryl; X = Cl, Br, I, CN) have been performed, especially in the context of the discussion of lower or “higher” order cuprates. The cryoscopic investigations of **1**·LiCN and **1**·LiI indicated the presence of monomeric units in THF.[12] Most of the theoretical calculations proposed a model in which LiCN or LiHal is incorporated into a seven-membered (or six-membered, respectively) hetero-dimer ring[13] (see Chart 1c). A recent NMR study of ^{15}N-labeled $Bu_2CuLi{\cdot}LiCN$[14] and an infrared study of the CN stretching vibration[5] of **1**·LiCN also seem to support the seven-membered LiCN-bridged structure in THF. In a combined NMR and theoretical study, Bertz et al. suggested an equilibrium between a homo- and a heterodimer for **1**·LiI, with the latter lying primarily on the side of the homodimer.[15] Interestingly, the crystal structures available to date for Li cuprates crystallized in the presence of LiX do not show the existence of a heterodimer.[10] In summary, the SSIP of **1**·LiX in THF is assumed to exist as a $RCuR^-$ anion and a $LiXLi^+$ cation unit, while the nature of the CIP, if present, is not known.

In this study we show, by means of ^{1}H,^{6}Li HOESY experiments, that it is possible to detect SSIPs and CIPs of organocuprates in solution. It is shown that the presence of SSIPs does not lead to any detectable dipolar interactions between the organic group of a linear cuprate and lithium, whereas CIPs give rise to organic group−lithium cross-peaks in the ^{1}H,^{6}Li HOESY spectra. Since the magnitude of the dipolar interaction is proportional to an averaged H−Li distance in solution, it can be correlated to the amount of SSIPs and CIPs in an equilibrium in a certain environment. Thus, direct evidence is given for the existence of an equilibrium between a CIP and a SSIP in THF by the temperature dependence in the case of **1**·LiCN. The main species of **1** in Et_2O is found to be the CIP, which is proposed to have a dimeric structure.

Experimental Section

NMR Measurements. All NMR spectra were recorded by means of a Bruker AMX 500 spectrometer equipped with a 5 mm broad-band triple resonance gradient probe. The experimental frequencies were 500.13 and 73.7 MHz for ^{1}H and ^{6}Li, respectively. The proton spectra were referenced to external TMS and the ^{6}Li spectra to a 1 M solution of LiCl in water (δ 0) at 273 K. Typical ^{1}H and ^{6}Li 90° pulses were 14 and 18 μs, respectively. All the measurements, unless noted otherwise, were carried out at 213 K. The temperature was controlled by a Bruker BVT 2000 unit. The ^{1}H,^{6}Li HOESY experiments were performed using a standard pulse sequence[16] combined with an additional ^{6}Li filter and pulsed field gradients to suppress spectral artifacts.[17] The other experimental parameters are as follows: spectral window of 6 ppm ($f_2 = {}^6$Li) and 9 ppm ($f_1 = {}^1$H); 1024 points in the f_2 dimension, 128 increments and 8 scans for each increment, mixing time of 1.7 s, and 6 s relaxation delay. The typical experimental time was about 2.5 h. The data were processed with the software package X-WINNMR (Bruker) after apodization with a sine bell weighting in f_1 and exponential multiplication with a line broadening of

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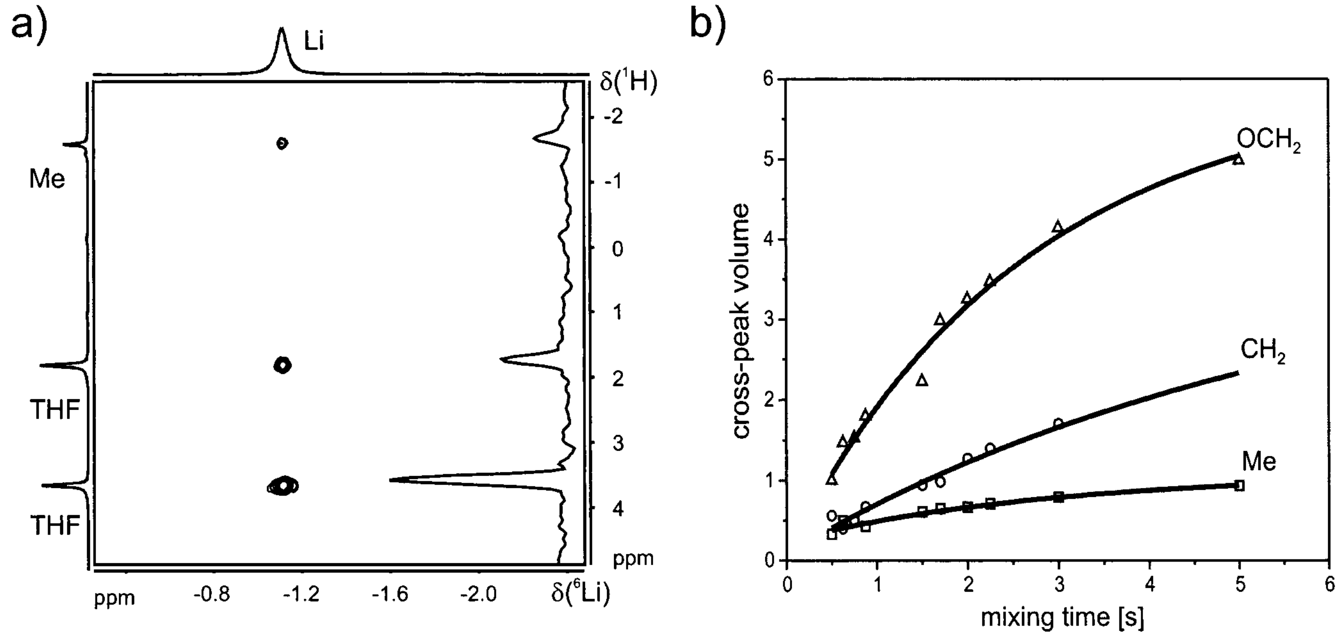

Figure 1. ^{1}H,^{6}Li HOESY data of $Me_2CuLi·LiCN$ in THF at −213 K: (a) ^{1}H,^{6}Li HOESY spectrum at a mixing time of 1.7 s; (b) build-up curves from 2D ^{1}H,^{6}Li HOESY spectra.

2 Hz in f_2. Quadrature detection in the indirect dimension was achieved with TPPI.[18]

^{6}Li-enriched samples were used for the NMR measurements at a concentration of 0.67 M in a solvent mixture containing 80% deuterated and 20% protonated THF or Et_2O, respectively. The concentrations of the samples used were precisely adjusted by comparing the integral of the proton spectra obtained with a single 90° pulse.

Sample Preparation. **1**·LiCN was prepared by reacting CuCN with ^{6}Li-enriched MeLi in dry THF or Et_2O at 233 K under an argon atmosphere. The solvent from the above solution was evaporated at 273 K under vacuum until a clear oil remained in the flask which was redissolved in THF-d_8 or Et_2O-d_{10} and transferred into a NMR tube at 195 K. **1** was prepared by the 2-cyclohexenone method described by Bertz et al.[15] CuI was reacted with commercial MeLi in dry Et_2O at 233 K to get $Me_2CuLi·LiI$, which was reacted with 2-cyclohexenone at 195 K without isolation. The reaction mixture was centrifuged at 195 K to isolate a yellow solid of MeCu, which was suspended in dry THF or Et_2O and reacted with ^{6}Li-enriched MeLi at 233 K to get **1**. MeCu(CN)Li (**2**) was prepared in a way similar to that for **1**·LiCN, except that 1 equiv of ^{6}Li-enriched MeLi was used. The reaction of dry CuCN and 2 equiv of *t*-Bu^{6}Li in THF at 195 K yielded *t*-$Bu_2CuLi·LiCN$ (**3**·LiCN). The solutions for NMR studies were prepared as described for the sample **1**·LiCN. The samples were kept at 195 K and were found to be stable at this temperature for many weeks.

Results and Discussion

The ^{1}H,^{6}Li HOESY experiment[19,20] is one of the most powerful NMR techniques available for the structural elucidation of organolithium compounds, as it directly gives the through-space information about the distance between protons and lithium. In most of the reports it is used to obtain qualitative information.[20] Quantitative data can be obtained in principle as well, since the magnitudes of the NOEs are inversely proportional to the sixth power of the distance.[21] Due to this dependency the intensities of the cross-peaks in a HOESY spectrum decrease rapidly with increasing proton−lithium distance, leading to an upper limit for detectable interactions of 400−500 pm.[20g,21] Therefore, in SSIPs of lithium diorganocuprates dipolar interaction should not be observable between the organic groups at copper and lithium, as the average proton−lithium distance expected from SSIP type X-ray crystal structures is more than 500 pm.[9,10] In contrast, the dimeric lithium-diorganocuprate contact ion pairs, crystallized from less solvating agents, show an average α-C−Li distance of less than 250 pm.[8] This should lead to an observable NOE in the latter case. Hence, the existence of an NOE between lithium and the protons of the organocuprate moiety should give an indication of the nature of the species in solution.

The presence of a dipolar interaction between lithium and the protons of **1**·LiCN in THF (20% THF, 80% THF-d_8) can be clearly seen in the 2D ^{1}H,^{6}Li HOESY spectrum shown in Figure 1a. Only one lithium signal is seen in the indirect dimension, indicating the presence of either one species or a fast equilibrium in the NMR time scale in solution. Two of the cross-peaks are between the methylene protons of THF and lithium, while the third one is due to the cuprate moiety (CH_3

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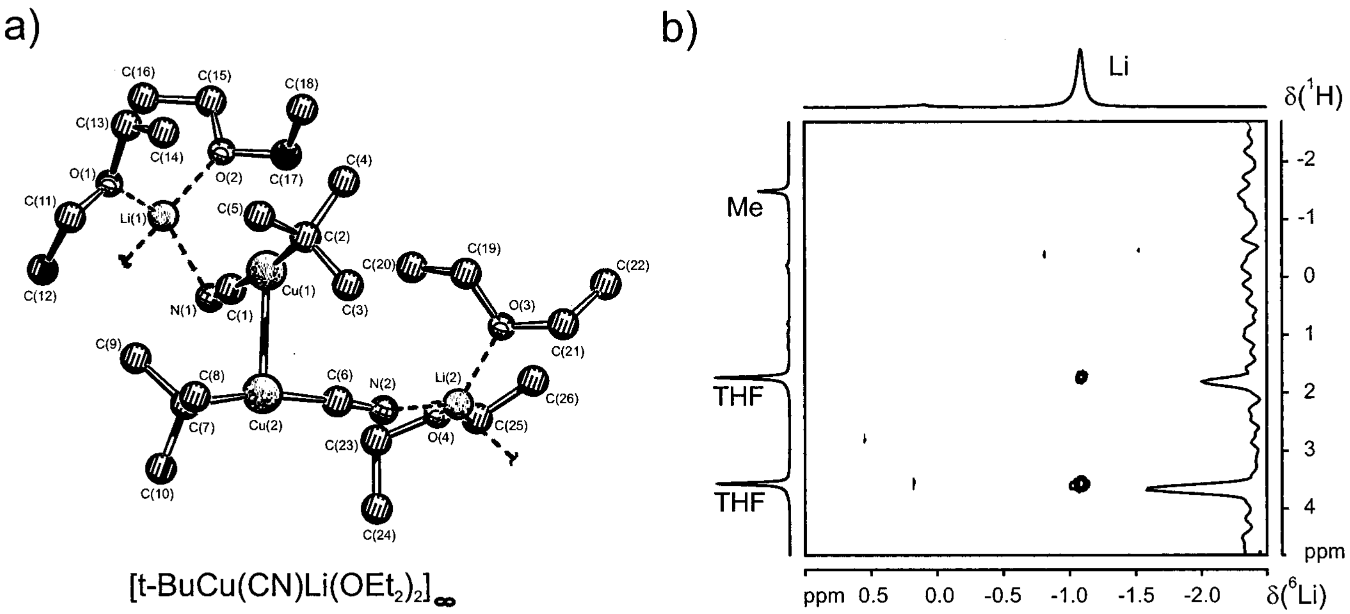


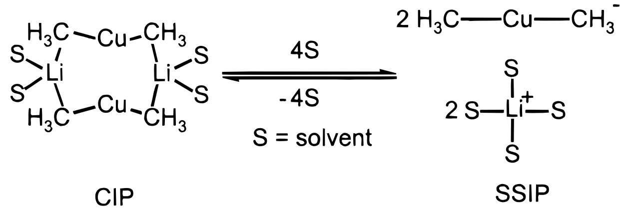
Figure 2. Comparison of the X-ray crystal structure of *t*-BuCu(CN)Li(OEt$_2$)$_2$ (a) and the ^{1}H,^{6}Li HOESY spectrum of MeCu(CN)Li in THF at 213 K (b).

groups). The origin of the cross-peaks between the protons of the solvent and lithium can undoubtedly be attributed to the excellent Li$^+$ solvating capability of THF. Since the solvent system used for the measurements is an 80:20 mixture of deuterated and protonated solvent, only 20% of the solvent contributes to the observed proton−lithium interactions. Therefore, the dominance of solvent−lithium dipolar interactions in this THF mixture is underestimated to a great extent in the ^{1}H,^{6}Li HOESY spectrum shown.

The third cross-peak indicates the presence of a weak CH_3−^{6}Li dipolar interaction. In that situation with a strong solvent−lithium and a weak CH_3−lithium interaction, the possibility of a relayed transfer has to be excluded in our system for arriving at more meaningful quantitative information. In the extreme narrowing limit, a three-spin system with one short and one long distance can give rise to a relayed transfer of the NOE.[21c] In the presence of both direct and relayed transfer an induction period during the initial part of the NOE buildup is observed. In this situation the magnitude of the NOE cannot be correlated to a real distance in solution. The buildup curves presented in Figure 1b do not show any induction period for the CH_3−lithium cross-peak. Moreover, it was also checked that under identical conditions the NOE buildup obtained in only deuterated THF does not differ significantly from the one in Figure 1b (data not shown). These clearly indicate that the observed CH_3−lithium cross-peak arises only from a direct dipolar interaction and hence can be used for quantification.

To address the question of the minimum distance that leads to a detectable dipolar interaction between the organic group of a linear lithium organocuprate and lithium, the ^{1}H,^{6}Li HOESY of a heterocuprate with a known X-ray crystal structure was studied. From the X-ray structure of [*t*-BuCu(CN)Li(OEt$_2$)$_2$]$_\infty$ it is known that lithium is bonded to the nitrogen of the cyanide group[10b] (see Figure 2a). In this structure, the nearest distance between lithium and the CH$_3$ carbon of the *t*-Bu groups is around 540 pm. This is more than the normally detectable distance by NOE measurements. Considering a similar structure for the CIP of MeCu(CN)Li (**2**) in THF, there should be no detectable dipolar interaction between the CH_3 groups and Li, even in the presence of an equilibrium between the CIP and the corresponding SSIP. This is evident from Figure 2b, which shows that the CH_3−^{6}Li cross-peak is missing in the ^{1}H,^{6}Li HOESY spectrum of **2** in THF. Therefore, we conclude that distances in the range of 500 pm cannot be detected in lithium organocuprates under the experimental conditions used here.

Scheme 1. Model of the CIP−SSIP Equilibrium in Me$_2$CuLi·LiCN



In contrast to the chain structures as found for heterocuprates such as [*t*-BuCu(CN)Li(OEt$_2$)$_2$]$_\infty$, crystallized from solvents with poor solvation qualities of Li$^+$ like Et$_2$O, the X-ray crystallographic data available for systems related to **1**·LiCN, crystallized from good solvating agents such as THF, show the existence of solvent-separated ion pair type structures with H−Li distances larger than 500 pm.[9,10b] Likewise NMR investigations of Ph$_2$CuLi showed the preference for a monomeric structure in strongly coordinating solvents such as THF.[4c,f] In contrast, it was concluded that Me$_2$CuLi (**1**) in Et$_2$O[11a] and Ph$_2$CuLi in DMS exist as dimers.[4c,f,22] Thus, the question arises whether the weak CH_3−^{6}Li cross-peak in the ^{1}H,^{6}Li HOESY spectrum of **1**·LiCN in THF (see Figure 1a) is due to a weak dipolar interaction in a SSIP or to a small amount of CIP which is in equilibrium with the SSIP (see Scheme 1).

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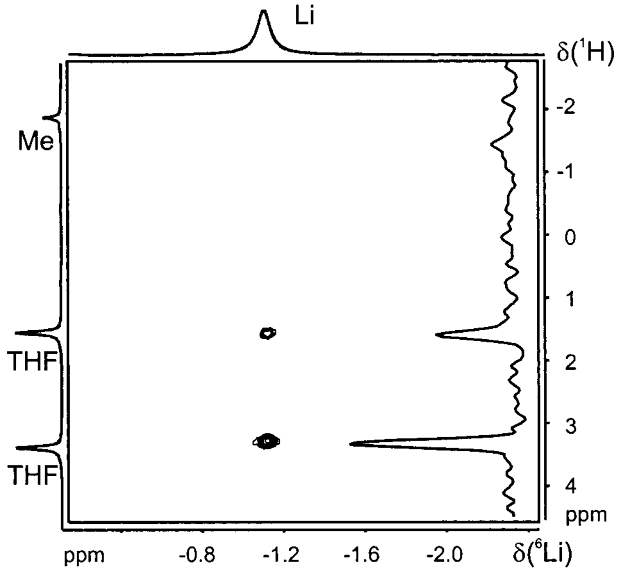

Figure 3. ^{1}H,^{6}Li HOESY spectrum of $Me_2CuLi \cdot LiCN$ in THF at 173 K.

It is well-known that the SSIP−CIP equilibrium shifts toward the SSIP at lower temperatures.[23] Assuming that the dipolar interaction results exclusively from the CIP, a shift in the equilibrium toward the SSIP should result in a reduction of the cross-peak intensity between the CH_3 groups and lithium. ^{1}H,^{6}Li HOESY experiments of **1**·LiCN at different temperatures (238−163 K) clearly showed a decrease in the CH_3−^{6}Li cross-peak intensity with decreasing temperature. It completely vanished at 163 K (Figure 3). Similar observations were also made for fluorenyllithium in THF by Hoffman et al.[23b] However, the observed decrease in NOE could also come from a decrease in the maximum NOE enhancement near the crossover point of the NOE curve.[21b,24] To exclude that, correlation times of **1**·LiCN at different temperatures were estimated from ^{13}C T_1 measurements and were found to be in the range $(3.8-17) \times 10^{-12}$ s. These values are still in the extreme narrowing limit for the ^{1}H−^{6}Li NOE, and therefore, the NOE magnitude is not affected appreciably. Hence, the observed decrease in the CH_3−^{6}Li cross-peak intensity is clearly attributed to the shift in the equilibrium toward the SSIP at lower temperatures, which results in a longer average distance between the CH_3 groups and lithium. Therefore, we can conclude that at 213 K **1**·LiCN exists largely as a SSIP with only a minor contribution of the CIP.

SSIP type crystals of lithium dimethylcuprate and other organocuprates can be obtained in the presence of good chelating agents such as crown ethers and PMDETA (pentamethyldiethylenetriamine).[9b,10b] In pure THF, to get SSIP type crystals, the electrostatic attraction between the organocuprate and lithium has to be reduced by modifying the organic moiety, e.g. by introducing bulky organic substituents. Thus, it should be possible to shift the equilibrium also in solution either by the addition of chelating agents or by changing the organic moiety. We observed that the CH_3−^{6}Li cross-peak intensity of **1**·LiCN in THF could be reduced only to a limited extent even by adding 3 equiv of TMEDA, tetramethylethylenediamine (data not shown). The effect of larger organic substituents on the equilibrium was studied by ^{1}H,^{6}Li HOESY using *t*-$Bu_2CuLi \cdot LiCN$ (**3**·LiCN) in THF. The crystal structure of [*t*-Bu_2CuLi_2(CN)(THF)(pmdeta)] (Figure 4a) has recently been published by Boche et al.[10b] showing SSIP-type crystals in the presence of THF and PMDETA. In the ^{1}H,^{6}Li HOESY spectrum of **3**·LiCN even in THF alone no cross-peak between the CH_3 groups of the *t*-Bu groups and lithium could be observed (see Figure 4b), in agreement with the absence of a detectable contribution from a SSIP. The absence of a dipolar interaction between the organic moiety and lithium in the ^{1}H,^{6}Li HOESY spectra of **2** and **3**·LiCN and the disappearance of the cross-peak in the spectra of **1**·LiCN at lower temperatures (Figure 3) show also that under the conditions mentioned SSIPs of linear cuprates do not contribute to a detectable ^{1}H−^{6}Li dipolar interaction.

In contrast, weakly coordinating solvents such as Et_2O and DMS should shift the equilibrium more toward the CIP, which would be in agreement with the assumption that Me_2CuLi (**1**) is a dimer in Et_2O and DMS, respectively.[8e,11a] Structures of the CIP type with a dimer as the essential structural feature were also found in the X-ray crystal structure investigations of some lithium diorganocuprates crystallized from solvents such as DMS and Et_2O.[8d,e] Therefore, we expect the CIP to be a dimer in Et_2O with a short CH_3−^{6}Li distance leading to a strong dipolar interaction. A comparison of the ^{1}H,^{6}Li HOESY spectra of **1** in THF and Et_2O, respectively, is shown in Figure 5. The HOESY spectrum of **1** in THF is similar to that of **1**·LiCN in THF (Figure 1a) except for a small decrease of the CH_3−^{6}Li cross-peak intensity in **1**·LiCN arising from the *salt effect* of LiCN. The influence of the salt LiX as compared to that of the solvent is discussed elsewhere.[8e] In contrast to THF, where the SSIPs are the dominant species, the reverse is found to be the situation in Et_2O. Here, the most intense cross-peak is the one between the CH_3 groups and lithium (see Figure 5b). This confirms that a dimeric CIP type structure with short CH_3−Li distances is much more favored in Et_2O than in THF.

In conclusion, we established by ^{1}H,^{6}Li HOESY investigations that lithium diorganocuprates exist in ethereal solvents as an equilibrium between a dimeric CIP species and a monomeric SSIP, depending on the solvent properties and the temperature. A small influence of salt is also observed. The dipolar interaction detected between the organic moiety and lithium in the ^{1}H,^{6}Li HOESY spectra results exclusively from the dimeric CIP species. SSIPs of linear cuprates do not contribute to a measurable extent to the ^{1}H,^{6}Li HOESY cross-peaks under the experimental conditions detailed above. The determination of the SSIP−CIP equilibrium is of special interest because it is directly related to the reactivity.[8e]

Summary

Different representative structural motifs of lithium diorganocuprates (**1**−**3**) were investigated by NMR

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[23] (a) Hogen-Esch, T. E.; Smid, J. *J. Am. Chem. Soc.* **1966**, *88*, 318. (b) Hoffman, D.; Bauer, W.; Schleyer, P. v. R. *J. Chem. Soc., Chem. Commun.* **1990**, 208.

[24] Pochapsky, T. C.; Wang, A.-P.; Stone, P. M. *J. Am. Chem. Soc.* **1993**, *115*, 1108.

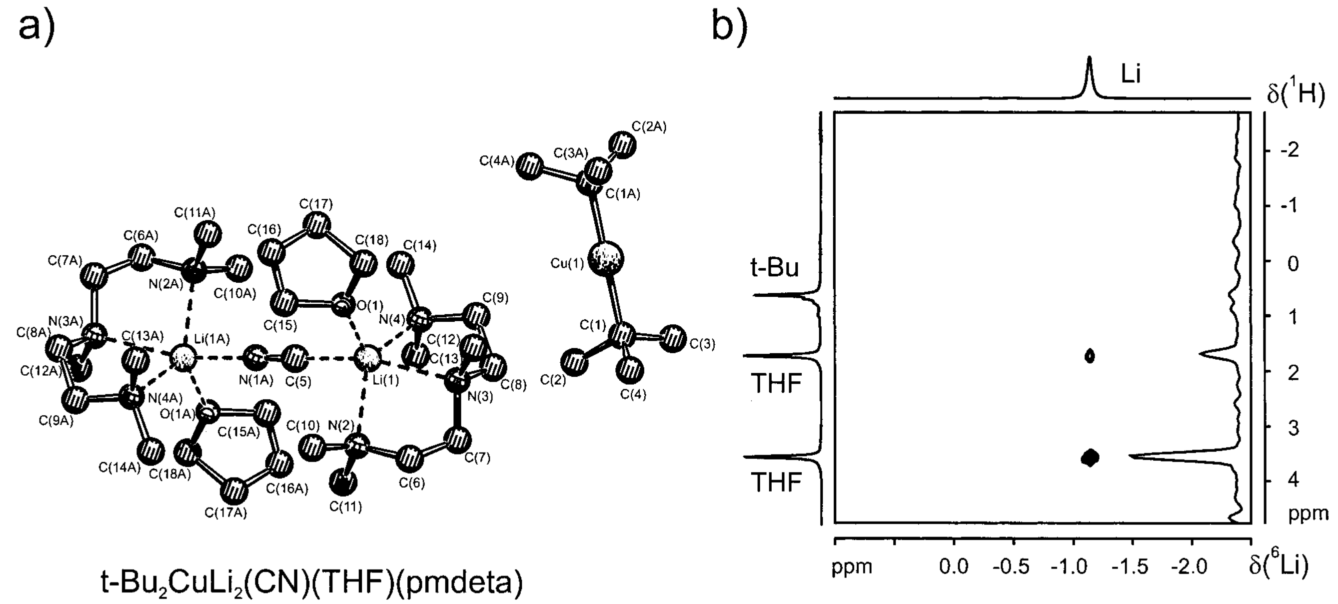

Figure 4. Comparison of the X-ray crystal structure of *t*-Bu$_2$CuLi·LiCN crystallized from a mixture of THF and PMDETA (a) and the ^{1}H,^{6}Li HOESY spectrum of *t*-Bu$_2$CuLi·LiCN in THF at 213 K (b).

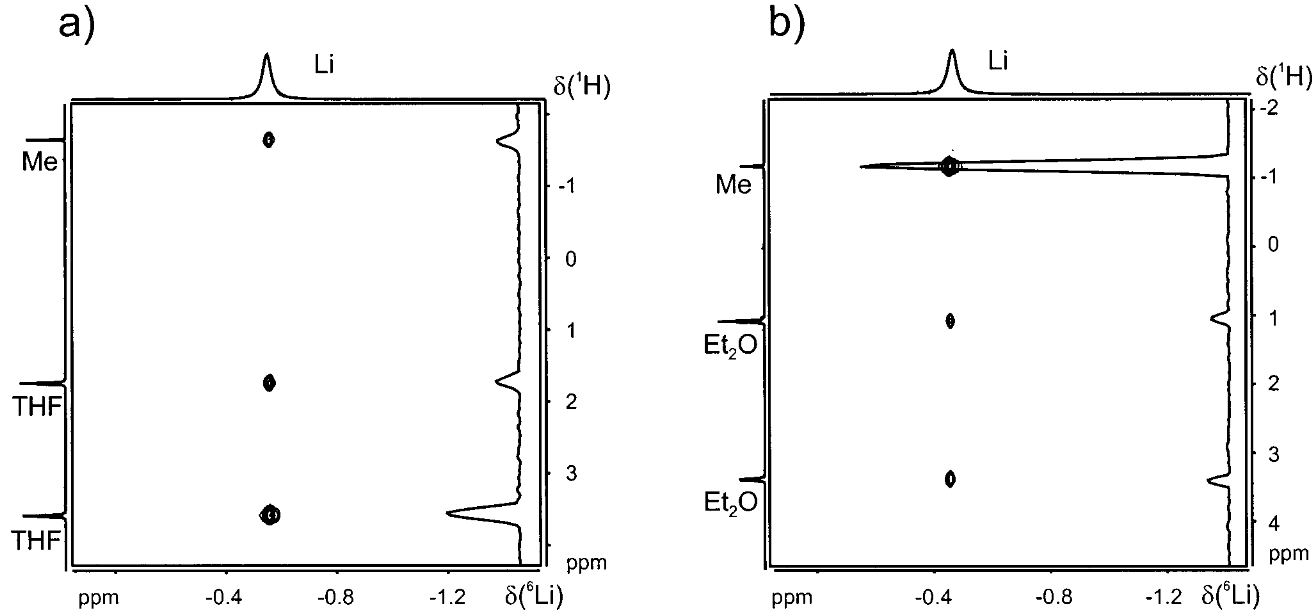

Figure 5. ^{1}H,^{6}Li HOESY spectra of Me$_2$CuLi in (a) THF and (b) Et$_2$O.

spectroscopy using the ^{1}H,^{6}Li HOESY technique. Monomeric solvent-separated ion pairs (SSIPs) of linear homocuprates and cyano-heterocuprates do not show detectable dipolar interactions between the organic moiety and lithium. This is underscored by comparing the ^{1}H,^{6}Li HOESY spectra of MeCuCNLi (**2**) and *t*-Bu$_2$CuLi·LiCN (**3**·LiCN) in THF with X-ray crystallographic data of closely related systems, which are of the SSIP type. In contrast, dimeric contact ion pairs of lithium cuprates in Et$_2$O show ^{1}H,^{6}Li HOESY cross-peaks between the organic groups of the cuprate and lithium. They can clearly be attributed to direct dipolar interactions, as shown for Me$_2$CuLi·LiCN (**1**·LiCN) in THF. The different systems studied showed a strongly solvent dependent equilibrium between SSIPs and CIPs. In contrast, in the corresponding X-ray crystal structures only one component was observed. In Et$_2$O the main species is a CIP with a dimeric structure, whereas in THF the monomeric SSIP is dominant. By means of **1**·LiCN it was shown that the temperature dependence of the SSIP–CIP equilibrium, which is shifted toward the SSIP at lower temperatures, could be followed from the change in the magnitude of the dipolar interaction. It is concluded that ^{1}H,^{6}Li HOESY experiments can be used as a technique to monitor the position of the SSIP–CIP equilibrium of lithium organocuprates in solution, which is important for the reactivity of lithium organocuprates.

Acknowledgment. We gratefully acknowledge financial support from the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich 260) and the Fonds der Chemischen Industrie.

OM000068N