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Association and Dissociation of Lithium Cyanocuprates in Ethereal Solvents

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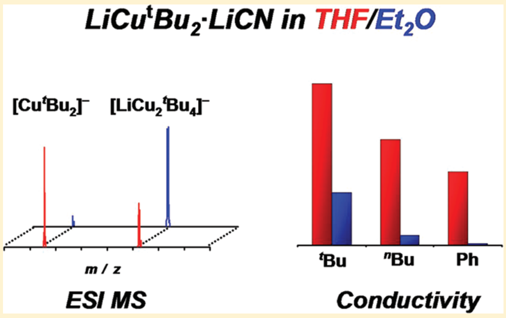
Supporting Information



ABSTRACT: We use a combination of electrospray ionization mass spectrometry and electrical conductivity measurements to probe the ions present in ethereal solutions of lithium cyanocuprates. Electrospray ionization mass spectrometry shows that solutions of $LiCuR_2{\cdot}LiCN$ and $Li_{0.8}CuR_{0.8}(CN)$ (R = Me, Et, ^{n}Bu, ^{s}Bu, ^{t}Bu, and Ph) in diethyl ether contain $Li_{n-1}Cu_nR_{2n}{}^-$ and $Li_{n-1}Cu_nR_n(CN)_n{}^-$ anions, respectively. Analogous species are also observed for solutions of $LiCu^tBu_2{\cdot}LiCN$ and $Li_{0.8}Cu^tBu_{0.8}(CN)$ in 2-methyltetrahydrofuran, cyclopentyl methyl ether, and methyl *tert*-butyl ether and were previously found for solutions of lithium cyanocuprates in tetrahydrofuran. Although the change of solvent thus does not lead to the formation of any major new cuprate anions, it has a strong effect on the association/dissociation equilibria. As directly confirmed by the conductivity experiments, contact ion pairs strongly predominate in solutions of lithium cyanocuprates in diethyl ether, whereas the more polar tetrahydrofuran gives rise to larger amounts of solvent-separated ion pairs; a particularly high dissociation tendency is observed for the $LiCu^tBu_2{\cdot}LiCN$ reagent. Temperature-variant conductivity measurements of $LiCuPh_2{\cdot}LiCN$ solutions in tetrahydrofuran do not show a significant temperature dependence of the association/dissociation equilibria for this system. The present findings largely support the results of previous NMR spectroscopic studies and help to explain how the solvent affects the reactivity of lithium cyanocuprates.

1. INTRODUCTION

Lithium organocuprates have long been known as valuable reagents in organic synthesis.[1] The great potential of these reagents comes at the price of an enormous complexity, however, which has made mechanistic studies difficult and slowed down the optimization of reagents and synthetic protocols.[2] Key progress in the elucidation of the structure and reactivity of lithium organocuprates has been only achieved since the role of association and dissociation equilibria of these reagents has been focused on. A first breakthrough came with theoretical calculations by Nakamura and co-workers.[3] These calculations pointed to the crucial importance of Li^+ centers in the organocuprate reagents for activating Michael-type acceptors in 1,4 addition reactions. As the Li^+ centers are only present in associated contact ion pairs, but not in dissociated solvent-separated ion pairs, only the former should be effective in Michael-type additions. This conclusion explained the previously observed detrimental effect of crown ethers on the reactivity of lithium organocuprates,[4] as these strongly coordinating compounds break up contact ion pairs. A second breakthrough then came with the finding of Gschwind and collaborators that the association/dissociation equilibria of homoleptic lithium organocuprates are largely determined by solvation. Using $^1H,^6Li$ HOESY NMR spectroscopy, these authors showed for $LiCuR_2$ model systems (R = Me and $(Me_3Si)CH_2$) that the coupling between the Li^+ counterion and the α protons of the organyl substituent strongly depends on the polarity of the solvent.[5] In the less polar diethyl ether, they observed a strong coupling, which indicated a small distance between the Li^+ counterion and the organyl substituent and thus pointed to the presence of a contact ion pair. In contrast, such a coupling was almost completely absent in the more polar tetrahydrofuran (THF), suggesting a shift of the association/dissociation equilibrium toward solvent-separated ion pairs (eq 1). In line with this rationalization, the structures of $LiCuR_2$ crystals grown from diethyl ether correspond to homodimeric contact ion pairs, whereas $LiCuR_2$ crystallized from solvents of higher affinity to Li^+ contain solvent-separated ions.[5b] Notably, the inferred solvent dependence of the association/dissociation equilibria also permitted a straightforward interpretation of reactivity data of lithium organocuprates previously obtained by Bertz et al.[2j,6]

$$(LiCuR_2)_2(solv) \rightleftharpoons 2Li^+(solv) + 2CuR_2{}^- \qquad (1)$$

Despite the progress made so far, important aspects of the association/dissociation equilibria of lithium organocuprates await clarification. In particular, it remains to be shown whether the observed solvent dependence of the equilibrium really is a general phenomenon seen for a larger series of lithium organocuprates and for other solvents in addition to THF and Et_2O. Moreover, only very little is known about the association/dissociation equilibria of related heteroleptic cuprates, such as

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LiCuR(CN). Here, we address these questions by a combination of electrospray ionization (ESI) mass spectrometry and conductivity measurements. ESI mass spectrometry[7] selectively probes the charged components of the solutions under investigation and gives unambiguous stoichiometric information. Therefore, it is increasingly employed for analyzing organometallic reagents and intermediates.[8] Following up on pioneering work by Lipshutz et al.,[9] we have recently shown that ESI mass spectrometry is a useful method for providing qualitative insight into the structural motifs and aggregation states of the ionic components of lithium cyanocuprates in THF.[10] We now extend these studies to solutions of lithium cyanocuprates in Et_2O and, for selected cases, also probe solutions in 2-methyltetrahydrofuran (MeTHF), cyclopentyl methyl ether (CPME), and methyl *tert*-butyl ether (MTBE). However, a caveat with respect to the use of ESI mass spectrometry is that the ESI process disturbs the system in a not easily predictable way. In the course of the ESI process, the solution forms charged nanodroplets, from which the analyte ions are then ejected into the gas phase and become amenable to mass spectrometric detection.[11] As the analyte concentration in the nanodroplets is higher than in solution[12] and also the effective temperature may change,[13] association/dissociation equilibria are likely to be shifted. Although these shifts should not prevent qualitative insight[14] and the comparison of different systems, they do not permit absolute quantitation. As an independent and well-established method, we, therefore, employ electrical conductivity measurements as well. Like ESI mass spectrometry, these measurements selectively probe the ionic components of solutions. While they can provide valuable quantitative information, they afford only limited qualitative insight. Thus, ESI mass spectrometry and conductivity measurements complement each other very well[15] and promise to improve our understanding of the association/dissociation equilibria of lithium cyanocuprates in different ethereal solvents.

2. EXPERIMENTAL SECTION

2.1. Sample Preparation. Standard Schlenk techniques were employed for handling air- and moisture-sensitive substances throughout. THF and Et_2O were distilled from sodium/benzophenone; MeTHF, CPME, and MTBE were dried over a molecular sieve (4 Å). CuCN was dried by repeated heating under vacuum at 350 °C. Solutions of organolithium compounds RLi were used as purchased: MeLi (1.49 M) in Et_2O, EtLi (0.42 M) in benzene/cyclohexane (90/10), ^{n}BuLi (2.37 M) in hexane, ^{s}BuLi (1.58 M) in cyclohexane, ^{t}BuLi (1.88 M) in pentane, and PhLi (1.74 M) in Bu_2O. The exact concentrations were determined by titration of 1,3-diphenyl-2-propanone tosylhydrazone.[16]

Solutions of $CuCN/(RLi)_n$ were prepared by treating suspensions of CuCN in the solvent of choice (THF, Et_2O, MeTHF, CPME, or MTBE) with RLi under argon at −78 °C. After stirring at this temperature for 1 h, the CuCN completely dissolved for $CuCN/(RLi)_n$ (n = 1 or 2), forming LiCuR(CN) and $LiCuR_2 \cdot LiCN$, respectively. In the case of the sample solutions prepared for ESI mass spectrometric analysis, the smaller volumes necessarily increase the likelihood of small errors in the measured reagent quantities. As we have shown previously for solutions in THF, such errors can be particularly detrimental to the analysis of LiCuR(CN). To avoid an excess of RLi in the probed samples, we, therefore, added only 0.8 equiv of LiR. The resulting solutions of nominal $Li_{0.8}CuR_{0.8}(CN)$ composition are supposed to contain LiCuR(CN) because the excess CuCN does not dissolve, as could also be directly seen from the presence of a solid residue.

2.2. ESI Mass Spectrometry. Organocuprate solutions of $c \approx 25$ mM were continuously administered into the ESI source of an HCT quadrupole ion trap mass spectrometer (Bruker Daltonik) by a pump-driven gastight syringe (1 mL h^{-1}). As the organocuprate solutions in Et_2O proved to be even more susceptible to hydrolysis than those in THF, particular care was taken to exclude moisture from the inlet line connecting the syringe with the ESI source. To this end, the inlet line was flushed with dry THF for ≥1 h before introducing the sample solution. Whereas the macroscopic stabilities of solutions of $LiCuR_2 \cdot LiCN$ held in the syringe at room temperature were fairly high, decomposition of solutions of $Li_{0.8}CuR_{0.8}(CN)$ was fast (≤5 min) and produced black or greenish precipitates, which then could lead to clogging of the inlet line. To avoid this problem, solutions of $Li_{0.8}CuR_{0.8}(CN)$ were analyzed as quickly as possible.

The ESI source was operated with N_2 as a sheath and drying gas (0.7 bar backing pressure and 5 L min^{-1} flow rate, respectively) at an ESI voltage of 3 kV. To minimize decomposition reactions during the ESI process, we applied mild conditions identical to those reported previously (60 °C drying gas temperature and low potential differences along the path of the ions).[10,15] The helium-filled quadrupole ion trap (estimated pressure $p(\mathrm{He}) \approx 2$ mTorr) was operated at a trap drive of 20. While this rather low value leads to a bias toward the detection of ions with low m/z ratios, it avoids unwanted fragmentation of the labile organocuprate ions in the quadrupole ion trap. For deliberate fragmentation, the mass-selected ions (isolation widths ≤ 2 amu) were subjected to excitation voltages with amplitudes of V_{exc} and allowed to collide with the He gas.

2.3. Conductivity Measurements. Electrical conductivity measurements were performed with a SevenMulti instrument (Mettler Toledo) and a stainless steel electrode cell (InLab741, Mettler Toledo, $\kappa_{\mathrm{cell}} = 0.1$ cm^{-1}) calibrated against a 0.1 M solution of aqueous KCl at 298 K. In a first set of experiments, the conductivity of solutions of $CuCN/(RLi)_n$ (n = 1 or 2; R = ^{n}Bu, ^{t}Bu, and Ph) in THF or Et_2O, respectively, was measured at 258 K. To this end, we monitored the conductivity after the successive addition of 1 and 2 equiv of LiR to a suspension of CuCN. Iodometric titration[17] of aliquots of the resulting solutions showed that we were able to suppress hydrolysis quite successfully (measured concentrations of $c(\mathrm{LiCuR(CN)}) = 97 \pm 2$ mM and $c(\mathrm{LiCuR_2 \cdot LiCN}) = 91 \pm 4$ mM compared to nominal concentrations of c = 104 mM; for more diluted solutions of $LiCuPh_2 \cdot LiCN$, we measured c = 47 and 21 mM for nominal concentrations of c = 52 and 26 mM). In a second set of experiments, we measured the conductivity of LiCuPh(CN) and $LiCuPh_2 \cdot LiCN$ in THF at various temperatures. Besides probing separate sample solutions at different (fixed) temperatures, we also recorded how increasing the temperature in increments of 5 K (starting at 233 K) changed the conductivity of a single sample solution. Iodometric titrations performed at the beginning and end of the measurements again showed only very little hydrolysis (measured concentrations $c \geq 100$ mM compared to nominal concentrations of c = 107 mM).

3. RESULTS

3.1. ESI Mass Spectrometry. *$LiCuR_2 \cdot LiCN$ Solutions.* The negative ion mode ESI mass spectra of solutions of $LiCuR_2 \cdot LiCN$ (R = Me, Et, ^{n}Bu, ^{s}Bu, ^{t}Bu, and Ph) in Et_2O are dominated by complexes of the homologous series $Li_{n-1}Cu_nR_{2n}^-$, n = 1−3 (Figure 1 and Figures S1−S5 in the Supporting Information). These species are identical to those observed in our previous investigation of solutions of $LiCuR_2 \cdot LiCN$ in THF and, as expected, also show the same fragmentation behavior (for a detailed discussion of the gas-phase fragmentation of mass-selected cuprate anions, see refs 10 and 18). Interestingly, however, the distributions obtained for the Et_2O solutions are systematically shifted to higher aggregation states compared with

Table 1. Organocuprate Anions Observed upon ESI of Et_2O Solutions of $LiCuR_2 \cdot LiCN$ in High [++], Medium [+], and Low/Negligible [−] Relative Abundance[a,10]

	n	R = Me	Et	^{n}Bu	^{s}Bu	^{t}Bu	Ph
$Li_{n-1}Cu_nR_{2n}^-$	1	− (−)	− (−)	− (+)	− (++)	+ (++)	+ (++)
	2	++ (++)	− (−)	− (−)	− (−)	++ (+)	− (−)
	3	++ (++)	++ (++)	++ (++)	++ (++)	− (−)	++ (++)

[a] For comparison, the relative abundances measured for the analogous solutions in THF are given in parentheses.

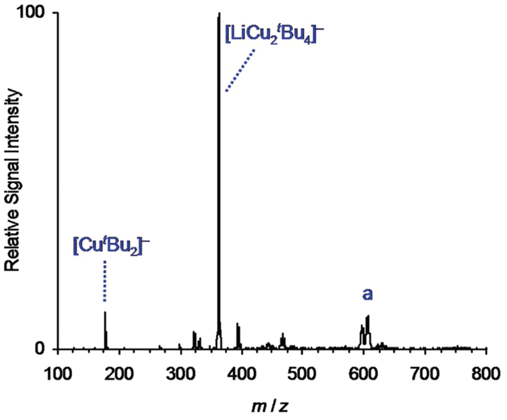


Figure 1. Negative ion mode ESI mass spectrum of a 25 mM solution of $LiCu^tBu_2 \cdot LiCN$ in Et_2O. The ion "a" (m/z 605/607/609) corresponds to $Li_3Cu_4{}^tBu_4(CN)_4{}^-$, which presumably results from partial hydrolysis.

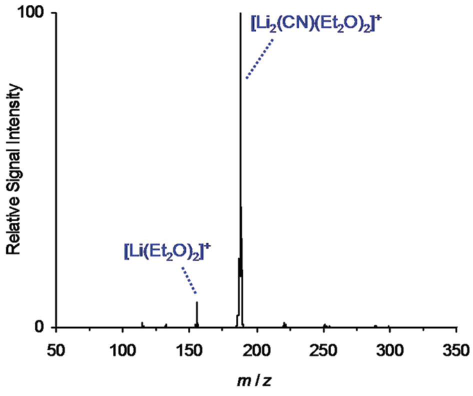


Figure 2. Positive ion mode ESI mass spectrum of a 25 mM solution of $LiCu^tBu_2 \cdot LiCN$ in Et_2O.

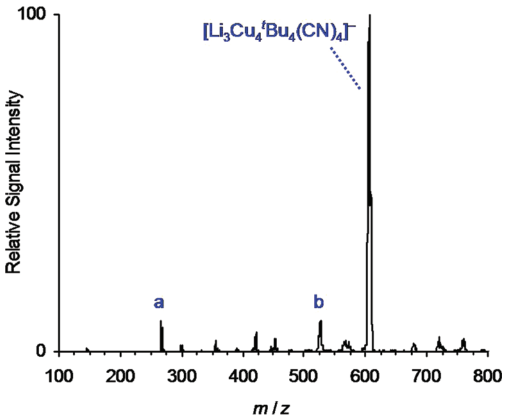


Figure 3. Negative ion mode ESI mass spectrum of a 25 mM solution of $Li_{0.8}Cu^tBu_{0.8}(CN)$ in Et_2O: a = $Cu_2{}^tBu_2(CN)^-$, b = $Li_3Cu_4{}^tBu_2(OH)_2(CN)_4{}^-$.

their THF counterparts (Table 1). Also note that the absolute ESI signal intensities are considerably lower in the case of the Et_2O solutions. For R = ^{t}Bu, we also probed the effect of other ethereal solvents and again found $Li_{n-1}Cu_nR_{2n}^-$ anions, n = 1 and 2 (Figures S6−S8, Supporting Information). While the fraction of the dimeric complex $LiCu_2R_4^-$ is relatively small for MeTHF solutions, this ion apparently prevails in CPME and MTBE.

Turning to the positive ion mode ESI mass spectra of solutions of $LiCuR_2 \cdot LiCN$ in Et_2O, we observe $Li(Et_2O)_2{}^+$ and $Li_2(CN)(Et_2O)_2{}^+$ as main species (Figure 2 and Figures S9−S13, Supporting Information). With the exception of R = Et, $Li_2(CN)(Et_2O)_2{}^+$ predominates in all cases, thus resembling the situation in THF. For the latter solvent, however, we also detected the complexes $Li(THF)_3{}^+$ and $Li_2(CN)(THF)_3{}^+$, whereas ions with n = 3 solvent molecules attached are largely missing in the mass spectra recorded for Et_2O solutions. For solutions of $LiCuPh_2 \cdot LiCN$ in Et_2O, we also observe the incorporation of Bu_2O in the ions $Li_2(CN)(Et_2O)_{2-n}(Bu_2O)_n{}^+$ (n = 1 and 2) (Figure S13, Supporting Information), although the fraction of Bu_2O in solution (stemming from the preparation of the reagent; see the Experimental Section) is lower than that of Et_2O by a factor of 60. While none of these cations contain a Cu center, we do find small amounts of $Li_2CuR_2(Et_2O)_2{}^+$ for R = Me. The ESI mass spectra measured for solutions of $LiCu^tBu_2 \cdot LiCN$ in MeTHF, CPME, and MTBE are similar to those obtained for Et_2O and THF solutions in that $Li(solv)_n{}^+$ and $Li_2(CN)(solv)_n{}^+$ are the predominant cations observed (Figures S14−S16, Supporting Information).

Solutions of $Li_{0.8}CuR_{0.8}(CN)$. As detailed in the Experimental Section, samples of a nominal composition of $Li_{0.8}CuR_{0.8}(CN)$ contain LiCuR(CN) in the solution phase because the excess CuCN does not dissolve. In line with this assessment, we have previously shown that solutions of $Li_nCuR_n(CN)$ in THF (n = 0.5, 0.8, and 1.0) yield very similar ESI mass spectra. Negative ion mode ESI of solutions of $Li_{0.8}CuR_{0.8}(CN)$ in Et_2O affords a multitude of different organocuprate anions (Figure 3 and Figures S17−S21, Supporting Information), most of which are already known from our previous analysis of the corresponding THF solutions.[10] A first set of ions belongs to the homologous series $Li_{n-1}Cu_nR_n(CN)_n{}^-$. Ions of this series or the corresponding partially hydrolyzed species $Li_{n-1}Cu_nR_{n-1}(OH)(CN)_n{}^-$ are observed in all cases (Table 2; the partial hydrolysis most likely occurs in ion−molecule reactions with background water present in the ion trap. See the Addition/Correction in ref 10). Compared to the situation in THF, the change to Et_2O as the solvent does not seem to result in a clear shift in the aggregation states. A second set of prominent ions comprises $Li_{n-1}Cu_nR_{2n}^-$ complexes, which do not show the expected stoichiometry but instead are typical of $LiCuR_2 \cdot LiCN$ solutions (see above). As we have discussed previously,[10] species such as $LiCuR_2$ might possibly form from LiCuR(CN) in Schlenk-type equilibria (along with $LiCu(CN)_2$). The remaining anions observed for solutions of $Li_{0.8}CuR_{0.8}(CN)$ in Et_2O exhibit intermediate stoichiometries and are of limited abundance only. For $Li_{0.8}Cu^tBu_{0.8}(CN)$ in MeTHF, CPME, and MTBE, we also find

Table 2. Organocuprate Anions Observed upon ESI of Et_2O Solutions of $Li_{0.8}CuR_{0.8}(CN)$ in High [++], Medium [+], and Low/Negligible [−] Relative Abundance[a,10]

	n	R = Me	Et	^{n}Bu	^{s}Bu	^{t}Bu	Ph
$Li_{n-1}Cu_nR_n(CN)_n^-$	2	++ (++)	+ (++)	+ (+)	− (+)	− (−)	++ (++)
	3	− (+)	− (+)	− (+)	− (−)	− (+)	++ (+)
	4	+ (++)	+ (+)	− (−)	− (−)	++ (+)	− (−)
	5	− (+)	− (−)	− (−)	− (−)	− (−)	− (−)
$Li_{n-1}Cu_nR_{n-1}(OH)(CN)_n^-$	3	− (−)	− (−)	− (+)	− (+)	− (−)	− (−)
	4	− (−)	+ (−)	− (+)	++ (++)	− (−)	− (−)
$Li_{n-1}Cu_nR_{2n}^-$	1	− (−)	− (−)	− (−)	− (+)	− (++)	++ (+)
	2	− (−)	− (−)	− (−)	− (−)	− (+)	− (−)
	3	++ (+)	++ (+)	++ (++)	+ (++)	− (−)	++ (−)
$Cu_2R_2(CN)^-$		− (−)	− (+)	− (−)	− (−)	− (−)	− (−)
$Cu_3R_4^-$		− (−)	− (−)	+ (−)	− (−)	− (−)	− (−)
$LiCu_4R_6^-$		− (−)	− (−)	− (−)	− (−)	− (−)	+ (−)

[a] For comparison, the relative abundances measured for the analogous solutions in THF are given in parentheses.

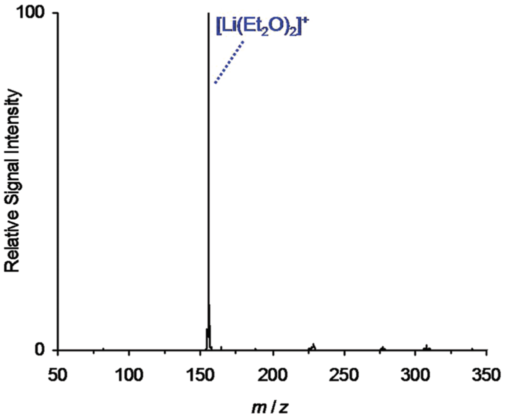


Figure 4. Positive ion mode ESI mass spectrum of a 25 mM solution of $Li_{0.8}Cu^tBu_{0.8}(CN)$ in Et_2O.

$Li_{n-1}Cu_nR_n(CN)_n^-$ and $Li_{n-1}Cu_nR_{2n}^-$ complexes as the predominating anions (Figures S22−S24, Supporting Information).

The positive ion mode ESI mass spectra obtained for solutions of $Li_{0.8}CuR_{0.8}(CN)$ in Et_2O in all cases show $Li(Et_2O)_2^+$ as the main peak (Figure 4 and Figures S25−S29, Supporting Information). Very similarly, the corresponding THF solutions also afforded solvated Li^+ ions as the predominant species.[10] Less abundant cations observed for the Et_2O solutions are $Li_2(CN)(Et_2O)_2^+$ and $Li_2CuR(CN)(Et_2O)_2^+$. Solutions of $Li_{0.8}Cu^tBu_{0.8}(CN)$ in MeTHF also yield $Li(solv)_n^+$ ions as main species ($n = 2$ and 3), whereas $Li_2(CN)(solv)_2^+$ prevails for CPME and MTBE (Figures S30−S32, Supporting Information).

3.2. Electrical Conductivity Measurements. *$LiCuR_2 \cdot LiCN$ Solutions.* Solutions of $LiCuR_2 \cdot LiCN$ in THF display significant electrical conductivities (Table 3). The determined molar conductivities show a clear dependence on the nature of the R substituent: $\Lambda(LiCu^tBu_2 \cdot LiCN) > \Lambda(LiCu^nBu_2 \cdot LiCN) > \Lambda(LiCuPh_2 \cdot LiCN)$. The conductivities of $LiCuR_2 \cdot LiCN$ in Et_2O are much smaller, but exhibit a very similar trend.

For $LiCuPh_2 \cdot LiCN$ in THF, we also investigated the concentration and temperature dependence. At lower concentrations, the molar conductivity increases (Figure S33, Supporting Information). A rise in temperature also increases the conductivity (Figure 5). This behavior is expected because higher temperatures lower the viscosity of the solvent, thus resulting in enhanced ion mobilities. Taking into account Walden's rule, which assumes that the product of the molar conductivity Λ of a given electrolyte and the viscosity of the solvent η is constant,[19] we attempt to fit the measured conductivities on the basis of the known temperature dependence of η(THF).[20] The obtained fit is reasonably good (Figure 5), suggesting that the observed temperature dependence of the molar conductivity indeed can be rationalized by the change in the viscosity of the solvent.

Table 3. Molar Electrical Conductivities Determined for Solutions of $LiCuR_2 \cdot LiCN$ ($c = 91 \pm 4$ mM) and $LiCuR(CN)$ ($c = 97 \pm 2$ mM) in THF and Et_2O at 258 K (Activity Coefficients Are Neglected)

	molar conductivity $\Lambda(LiCuR_2 \cdot LiCN)/(S\ cm^2\ mol^{-1})$		molar conductivity $\Lambda(LiCuR(CN))/(S\ cm^2\ mol^{-1})$	
R	THF	Et_2O	THF	Et_2O
^{n}Bu	13 ± 1	1.00 ± 0.02	0.3 ± 0.1	0.008 ± 0.005
^{t}Bu	19 ± 1	6.2 ± 0.1	4.0 ± 0.5	0.7 ± 0.1
Ph	8.2 ± 0.3	0.20 ± 0.05	0.42 ± 0.04	0.20 ± 0.05

LiCuR(CN) Solutions. The molar conductivities of solutions of LiCuR(CN) in THF are significantly smaller than those of the corresponding $LiCuR_2 \cdot LiCN$ solutions (Table 3). Again, a strong dependence on the nature of the R substituent is noticeable: $\Lambda(LiCu^tBu(CN)) \gg \Lambda(LiCuPh(CN)) > \Lambda(LiCu^nBu(CN))$. The conductivities in Et_2O are even lower (also lower than the conductivities measured for Et_2O solutions of $LiCuR_2 \cdot LiCN$) but show a similar trend. For LiCuPh(CN) in THF, we observe a temperature dependence that, like in the case of its $LiCuPh_2 \cdot LiCN$ counterpart, is reproduced by a simple fit that only considers the effect of the changed solvent viscosity (Figure S34, Supporting Information).

4. DISCUSSION

4.1. Equilibria Operative. We rationalize the detection of $Li_{n-1}Cu_nR_{2n}^-$ anions in $LiCuR_2 \cdot LiCN$ solutions by the operation of association/dissociation equilibria, as depicted in Scheme 1. The proposed scenario essentially corresponds to the equilibrium already suggested by Gschwind and collaborators[5] (eq 1) but, in

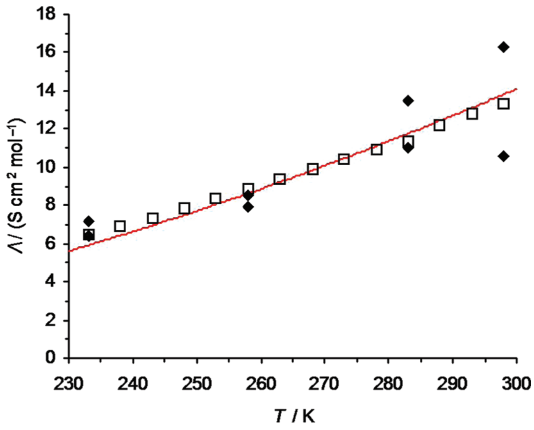


Figure 5. Molar electrical conductivity of a solution of $\mathrm{LiCuPh_2 \cdot LiCN}$ in THF (c = 98 mM; activity coefficients are neglected) as a function of temperature. The open symbols represent data points collected during a single conductivity measurement, in which the temperature was raised continuously from 233 to 298 K in 5 K increments. The filled symbols represent data points collected independently for different samples at fixed temperatures. The red line corresponds to a fit that only takes into account the effect of the temperature dependence of the solvent viscosity.

addition, also accounts for the formation of higher ionic aggregates. While ESI mass spectrometry cannot detect the neutral homodimers $\mathrm{Li_2Cu_2R_4}$, the presence of these species in ethereal solutions of $\mathrm{LiCuR_2 \cdot LiCN}$ has been proven by NMR spectroscopy, X-ray scattering, and ebullioscopic methods.[5,21]

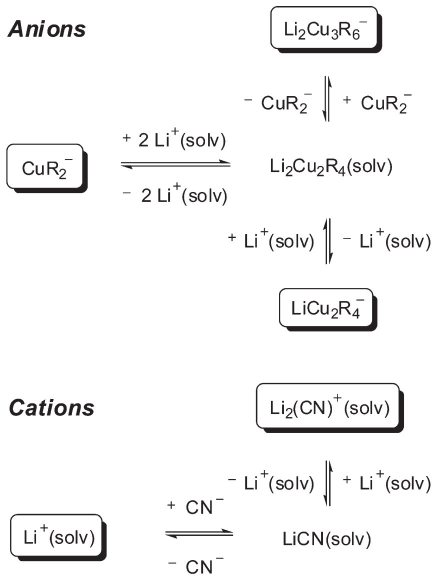
For LiCuR(CN) solutions, the situation is less clear because the aggregation state of the neutral, undissociated component [LiCuR(CN)] is not known precisely. Nonetheless, the experimental findings point to the operation of association/dissociation equilibria, such as eq 2. Here, the incorporation of $\mathrm{CN^-}$ in the cuprate anions explains why simple, cyanide-free $\mathrm{Li^+(solv)}$ cations prevail, in contrast to the case of $\mathrm{LiCuR_2 \cdot LiCN}$. Association of $\mathrm{Li^+}$ with neutral [LiCuR(CN)] rationalizes the formation of $\mathrm{Li_2CuR(CN)^+(solv)}$ cations, eq 3.

$$n[\mathrm{LiCuR(CN)}] \rightleftharpoons \mathrm{Li^+(solv)} + \mathrm{Li}_{n-1}\mathrm{Cu}_n\mathrm{R}_n(\mathrm{CN})_n^- \qquad (2)$$

$$\mathrm{Li^+(solv)} + [\mathrm{LiCuR(CN)}] \rightleftharpoons \mathrm{Li_2CuR(CN)^+(solv)} \qquad (3)$$

A comparison between the $\mathrm{Li}_{n-1}\mathrm{Cu}_n\mathrm{R}_{2n}^-$ anions characteristic of $\mathrm{LiCuR_2 \cdot LiCN}$ solutions and the $\mathrm{Li}_{n-1}\mathrm{Cu}_n\mathrm{R}_n(\mathrm{CN})_n^-$ observed for LiCuR(CN) solutions suggests that the latter reagents favor higher aggregation/association states, thus reducing the concentration of free ions. The relatively lower electrical conductivities measured for solutions of LiCuR(CN) fully corroborate this interpretation. Also note that the higher dissociation tendency of $\mathrm{LiCuR_2 \cdot LiCN}$ helps to rationalize why already small amounts of this species present in solutions of LiCuR(CN) can result in appreciable concentrations of $\mathrm{Li}_{n-1}\mathrm{Cu}_n\mathrm{R}_{2n}^-$ anions and their detection by ESI mass spectrometry. As discussed previously,[10] the lower dissociation tendencies of the LiCuR(CN) reagents presumably result from the incorporation of the cyanide in the cuprate species. $\mathrm{CN^-}$ can not only bridge different Cu centers but, owing to its ambident nature, at the same time, also bind to a $\mathrm{Li^+}$ cation with high affinity, thus causing the buildup of larger aggregates.

Scheme 1. Association/Dissociation Equilibria Proposed To Be Operative in Ethereal Solutions of $\mathrm{LiCuR_2 \cdot LiCN}$[a]



[a] The highlighted species have been observed by ESI mass spectrometry.

4.2. Effect of the Solvent. The ESI mass spectrometric experiments show that the transition from THF to $\mathrm{Et_2O}$ or other ethereal solvents does not lead to the formation of new ionic species in significant quantities. Instead, it results in a shift in the association/dissociation equilibria for the $\mathrm{LiCuR_2 \cdot LiCN}$ reagents. We first analyze whether the observed shift reflects the situation in solution or whether it might mirror a different behavior during the ESI process. THF and $\mathrm{Et_2O}$ not only differ in their polarity but also in their boiling point (Table 4). Whereas the higher polarity of THF is likely to favor dissociation in solution, the lower boiling point of $\mathrm{Et_2O}$ should facilitate desolvation during the ESI process and thus could also explain the higher propensity to association observed for this solvent. However, the results obtained for $\mathrm{LiCu^tBu_2 \cdot LiCN}$ in MeTHF, CPME, and MTBE clearly show that the solvent polarity is the decisive factor (Table 4). It is obvious that the Lewis-basic ethereal solvents do not interact with both cations and anions in a similar way but that they bind to the $\mathrm{Li}_n(\mathrm{CN})_{n-1}^+$ cations (n = 1 and 2) much more strongly than to the cuprate anions. As a consequence, we do not detect any microsolvated cuprate anions by ESI mass spectrometry, whereas we exclusively find $\mathrm{Li}_n(\mathrm{CN})_{n-1}(\mathrm{solv})_x^+$ cations, x = 2 and 3. Note that the number of bound solvent molecules observed for the gaseous ions presumably does not correspond to the first solvation shell in solution but rather reflects the relative interaction energies (too weakly bound molecules will be lost upon energetic collisions during the ESI process). The higher number of $\mathrm{Li^+}$-bound THF and MeTHF molecules ($x \geq 2$) correlates very well with the higher macroscopic polarity of these solvents and their effect of shifting the equilibria toward dissociated ions.

The conductivity data provide independent and unambiguous evidence that THF favors the dissociation of $\mathrm{LiCuR_2 \cdot LiCN}$ in comparison to $\mathrm{Et_2O}$. For the LiCuR(CN) reagents, the trend is much weaker. In line with this observation, the ESI mass spectra measured for solutions of LiCuR(CN) in THF, on the one hand, and $\mathrm{Et_2O}$, on the other, do not display notable differences.

4.3. Effect of the Organyl Substituent. Although all of the $\mathrm{LiCuR_2 \cdot LiCN}$ reagents sampled, as well as their LiCuR(CN) counterparts, behave quite similarly, some differences are discernible.

Table 4. Properties of Ethereal Solvents Sampled and Aggregation Tendencies of $Li_{n-1}Cu_n{}^tBu_{2n}^-$ Anions in These Solvents As Determined by ESI Mass Spectrometry of Solutions of $LiCu^tBu_2 \cdot LiCN$

solvent	relative permittivity ε (298 K)	boiling point (K)	$I(LiCu_2{}^tBu_4^-)/I(Cu^tBu_2^-)$
THF	7.42[a]	338[a]	<1
MeTHF	6.97[a]	353[b]	<1
CPME	4.76[b]	379[b]	>1
Et_2O	4.24[a]	308[a]	>1
MTBE	2.60[b]	328[b]	>1

[a] Reference 22. [b] Reference 23.

As the conductivity measurements clearly show, the ^{t}Bu substituent favors dissociation and the formation of solvent-separated ion pairs more than the ^{n}Bu and Ph groups. In full accordance with this observation, ESI mass spectrometry finds ^{t}Bu to be the only substituent for which the aggregation state of the $Li_{n-1}Cu_nR_{2n}^-$ anions is limited to $n \leq 2$. We ascribe the lower aggregation tendency of the ^{t}Bu-containing cuprates to the higher steric demands of this substituent, which apparently prevents the association of >2 $Cu^tBu_2^-$ monomers. The conductivity data moreover suggest that the ^{n}Bu-bearing homoleptic cuprates give somewhat higher fractions of dissociated ions than their Ph-containing analogs. This finding seems to be at odds with the ESI mass spectrometric results, which point to a slightly higher aggregation tendency for the ^{n}Bu-bearing cuprates. This discrepancy may possibly arise from the different temperatures in both experiments (258 K for the conductivity measurements and approximately 298 K for the ESI mass spectrometric studies). However, it could also be the case that the deviating behavior observed by ESI mass spectrometry is due to a (though rather small) perturbation of the system caused by the very ESI process.

The recorded molar conductivities Λ also comprise information on the absolute fractions of dissociated ions. For calculating the degree of dissociation α according to eq 4, the limiting molar conductivity Λ_0 must be known.

$$\alpha = \Lambda/\Lambda_0 \qquad (4)$$

Although Λ_0 could be derived by the extrapolation of experimental data to $c = 0$, the very steep slope and the increased susceptibility to inevitable hydrolysis reactions at lowest concentrations render such an approach unreliable. For a rough estimation, we instead approximate the limiting molar conductivities of the lithium cuprates by known values of other electrolytes in THF. At 298 K, the limiting molar conductivities of many diverse 1:1 electrolytes in THF all fall into the range of $75 < \Lambda_0(298\ K) < 135\ S\ cm^2\ mol^{-1}$,[20,24] which converts into $\Lambda_0(258\ K) = 65 \pm 20\ S\ cm^2\ mol^{-1}$ on the basis of Walden's rule.[19] If, simplistically, we apply this value to the lithium cuprates, we obtain effective degrees of dissociation of $0.09 \leq \alpha(THF) \leq 0.44$ and $0.002 \leq \alpha(Et_2O) \leq 0.14$ for solutions of $LiCuR_2 \cdot LiCN$ at concentrations of $c \approx 100$ mM at 258 K.[25] These estimates indicate that, even in the more polar THF, the lithium cuprates are far from being completely dissociated. This assessment is also consistent with the ESI mass spectrometric experiments, which show abundant $Li_{n-1}Cu_nR_{2n}^-$ aggregates in all cases examined.

4.4. Effect of the Temperature. From the temperature dependence of the $^1H,^6Li$ HOESY coupling observed for solutions of $LiCu(CH_2(Me_3Si))_2$ in THF, John et al. concluded that the association/dissociation equilibrium of this reagent is strongly affected by temperature.[5b] According to the authors, the formation of the solvent-separated ion pairs is enthalpically favored, but entropically disfavored, because the enhanced solvation of the free Li^+ cations results in the loss of degrees of freedom.[5b] For the $LiCuPh_2 \cdot LiCN$/THF system, our present measurements show only a modest increase of the conductivity as a function of temperature. The observed increase can be fully explained by the effect of the reduced viscosity and thus excludes a pronounced temperature effect on the association/dissociation equilibrium. This result does not directly disagree with the conclusions of John et al., because the cuprate reagents probed in both studies are different.

4.5. Comparison of Analytical Methods. Beyond providing insight specific to the lithium cuprate reagents examined, the present investigation, in conjunction with previous work, also permits a comparison of different experimental methods used for the analysis of ionic species in solution. NMR spectroscopy, electrical conductivity measurements, and ESI mass spectrometry all agree that the association/dissociation equilibria of lithium cyanocuprates are largely governed by the nature of the solvent and, in particular, its Li^+ affinity. While NMR spectroscopy and conductometry constitute well-established techniques and thus are expected to give the same results, the consistency of the ESI mass spectrometric findings deserves some further comments. As mentioned above, the mass spectrometrically detectable ions do not originate directly from the sampled solution, but from the intermediately formed nanodroplets. The good agreement between the results obtained by ESI mass spectrometry and by conventional analytical methods indicates that the relative position of the association/dissociation equilibria is largely preserved in the nanodroplets. Note that the ESI mass spectrometric experiments are sensitive to the nature of the solvent even if the observed ions do not contain any solvent molecules, as the example of the $Li_{n-1}Cu_nR_{2n}^-$ complexes demonstrates. The observed solvent-dependent shift in the aggregation state of these ions rationalizes at the microscopic level what the conductivity measurements find macroscopically. The consistency between the ESI mass spectrometric and conductometric results is not limited to the effect of the solvent but also extends to the observation of a particularly high dissociation tendency of the $LiCu^tBu_2 \cdot LiCN$ reagent. In contrast, a comparison of the data for $LiCu^nBu_2 \cdot LiCN$ and $LiCuPh_2 \cdot LiCN$ possibly points to some smaller deviations between the two methods and thus seems to suggest that their overall agreement is not absolutely perfect. Nevertheless, the present results demonstrate the suitability of ESI mass spectrometry to probe the speciation of cuprate ions in solution and to provide qualitatively correct insight into their association/dissociation behavior. This assessment is in line with the conclusions of several other recent studies that investigated the performance of ESI mass spectrometry.[14,15]

5. CONCLUSIONS

We have used a combination of ESI mass spectrometry and electrical conductivity measurements to probe the speciation of $LiCuR_2 \cdot LiCN$ and $LiCuR(CN)$ reagents in ethereal solvents. ESI mass spectrometry shows that the transition from THF to Et_2O does not give rise to the formation of any major new ions for the $LiCuR_2 \cdot LiCN$ systems but that $Li_{n-1}Cu_nR_{2n}^-$ anions are present in both solvents. However, the change to Et$_2$O, that is, the less polar solvent, causes a shift of the equilibria toward higher aggregation states. In the case of the LiCuR(CN) reagents, we consistently find Li$_{n-1}$Cu$_n$R$_n$(CN)$_n^-$ anions. The relatively high aggregation states of these complexes presumably arise from the presence of cyanide ions that adopt bridging binding modes. Additional experiments on solutions of LiCu^{t}Bu$_2$·LiCN and LiCu^{t}Bu(CN) in MeTHF, MTBE, and CPME as well as conductivity measurements confirm that the polarity of the solvent and its Li$^+$ affinity control the association/dissociation behavior of lithium cyanocuprates. Thus, our findings agree with the results from previous NMR spectroscopic studies and demonstrate the generality of the relation between solvent polarity and association tendency for ethereal solutions of lithium cyanocuprates.[5] This dependence also bears practical importance because only the associated contact ion pairs of lithium cuprates are supposed to undergo efficient Michael-type addition reactions.[3,5]

Besides the solvent, the nature of the organyl substituent also influences the association/dissociation equilibria. As the example of LiCu^{t}Bu$_2$·LiCN shows, increased steric hindrance results in higher degrees of dissociation, whose absolute values can be estimated on the basis of the measured molar conductivities. For the case of LiCuPh$_2$·LiCN in THF, we have also investigated the temperature dependence of the molar conductivity. The modest increase observed at higher temperatures can be simply explained by the effect of the lowered solvent viscosity. In contrast to the conclusions drawn by John et al. for LiCu(CH$_2$(Me$_3$Si))$_2$ in THF, we thus do not find any evidence of a significant temperature dependence of the association/dissociation equilibria of lithium cyanocuprates.

In a broader context, the present work adds to a growing number of studies that demonstrate the suitability of ESI mass spectrometry for probing ion speciation in solution.[14,15] Although the ESI process most likely will shift association equilibria relative to the situation in solution, qualitative trends in ion speciation seem to be remarkably robust. Until this finding has been further validated, however, the most reliable approach remains the combination of ESI mass spectrometry with other, well-established analytical methods, such as electrical conductivity measurements or NMR spectroscopy.[15,26,27]

ASSOCIATED CONTENT

Supporting Information. Additional negative and positive ion mode ESI mass spectra and figures showing the concentration and temperature dependence of the molar conductivity of lithium cyanocuprate solutions. This material is available free of charge via the Internet at http://pubs.acs.org.

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