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Influence of Tetrahydrofuran on Reactivity, Aggregation, and Aggregate Structure of Dimethylcuprates in Diethyl Ether

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Abstract: The comprehension of factors influencing the reactivity of organocuprates is still far from enabling a rational control of their reactions. Especially the degree of aggregation and structures of organocuprates are the focus of discussion about the factors affecting their reactivity. Therefore, this study combines kinetic measurements and NMR investigations to elucidate the influence of disaggregation via addition of tetrahydrofuran (THF) on the reactivity and aggregate structure of Gilman cuprates. As model systems, $\mathrm{Me_2CuLi\cdot LiI}$ (**1**·LiI) and $\mathrm{Me_2CuLi\cdot LiCN}$ (**1**·LiCN) in diethyl ether (DEE) were chosen; as model reaction, the 1,4-addition to 4,4-dimethylcyclohex-2-enone. The kinetic data show for **1**·LiI a pronounced acceleration effect upon addition of distinct amounts of THF, whereas the reactivity of **1**·LiCN continuously decreases with the addition of THF. Series of NMR diffusion measurements as well as ^{1}H−^{7}Li heteronuclear Overhauser effect (HOE), and ^{1}H−^{1}H nuclear Overhauser effect (NOE) spectra show different structural influences of THF on **1**·LiI and **1**·LiCN. For **1**·LiI, small salt units are separated from the cuprate aggregate by THF. In contrast to this, THF disaggregates the oligomeric structures of **1**·LiCN, while the core structures remain intact with salt attached. Thus, the reactivity of **1**·LiI seems to be fine-tuned through distinct amounts of salt or THF, whereas the decreasing reactivity of **1**·LiCN correlates with the disaggregation of oligomers via THF. Thus, for synthetic chemists with reactivity problems in specific reactions of iododialkylcuprates, the addition of small amounts of THF might be useful to enhance the reactivity. In addition to these structure−reactivity studies, the CN$^-$ group is shown to be directly attached to the cuprate moiety via a combination of ^{1}H−^{13}C HOE- and ^{1}H−^{1}H NOEs. This represents the first direct experimental evidence in solution for the position of the CN$^-$ group relative to the cuprate moiety in cyano-Gilman cuprates.

1. Introduction

The systematic control of chemical reactions via the comprehension of structure−reactivity and structure−selectivity correlations is still a long-term objective for many chemical reactions. Especially for organometallic reagents forming complex aggregates as reactive species, the comprehension of the factors influencing their reactivity and selectivity is still in its infancy. A famous example is the group of lithium organocuprate reagents. There, despite their wide application in carbon−carbon bond-forming reactions and intensive theoretical and structural investigations, the structures of the reactive species are not yet fully determined.[1−3] During the first long-standing scientific discussion about structure−reactivity correlations of organocuprates, different reactivities of cyano- and iodocuprates were explained by different monomeric structures for a long time. However, in the end the "lower order" alkylcuprates were finalized.[1,4,5] Then different degrees of aggregation depending on the kind of solvent and salt[6,7] were observed and the core structure of the aggregates was identified to be a homodimer in DEE.[8] This put the aggregation, previously indicated by ^{15}N NMR,[9] mass spectroscopy studies,[10] crystal structures,[6,11] colligative measurements,[12−14] and extended X-ray absorption fine structure (EXAFS) studies[15] into the focus of interest as a possible explanation for different reactivities[16] despite similar

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core structures. A first aggregation reactivity study comparing very different degrees of aggregation in DEE and THF identified contact ion pairs as reactive species.[6] Then we found different degrees of aggregation for the contact ion pairs in DEE, depending on steric hindrance and the kind of salts.[17] A comparison with kinetic data derived by Bertz et al.[16] suggested an increase of reactivity through disaggregation by THF down to the dimeric contact ion pair. However, such more refined aggregation reactivity correlations lack direct comparability of structural and kinetic data, which up to now have always been performed under different experimental conditions. Additionally, the influence of small amounts of THF on the aggregation and the aggregation structure of organocuprates is unknown.[3,7,17,18]

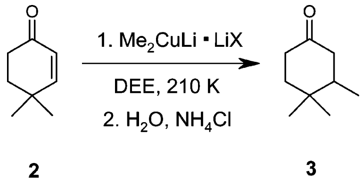
As a second important point concerning organocuprates, the core structure of the salt-containing dimethylcuprates in the reactive species again came up as a subject in the discussion during recent years. In the known X-ray structures of lithium dialkylcuprates crystallized from salt-containing solutions[6,11] and in our NMR investigations of the pure reagents in solution,[8] only homodimeric structures were found. Also, a recent study about the control of electron transfer versus alkylation pathway in the reaction of the Gilman reagent $Me_2CuLi{\cdot}LiI$ (**1**·LiI) shows that the lithium halide is not differentially involved in the competition between these two reaction types.[19] In contrast, numerous theoretical calculations proposed heterodimeric core structures[20−22] of the Gilman reagents **1**·LiX (X = I, CN) and a recent theoretical publication suggested besides the involvement of heterodimeric structures even the contribution of "higher order" Lipshutz cuprates in the transition state of the addition reaction of **1**·LiCN to acetylene.[23] The main problem in the discussion mentioned above is the lack of experimental evidence about the position of the salt unit (LiI or LiCN) relative to the organocuprate moiety in solution. The only information experimentally available in solution is the coordination of the salt by Li^+, confirmed by previous ^{15}N NMR[9] and IR spectroscopic[24] studies. The crystal structures,[25−27] highly valuable in other respects, showing different positioning possibilities of the salt in organocuprates, are less meaningful for the aggregate structure in solution, since significant differences of the aggregate structures in the solid state and in solution were found.[6,17]

In this study experimental results for both subjects are presented, concerning the correlation between disaggregation via THF and reactivity of Gilman cuprates as well as regarding the position of the salt units in solution. Thus, for the first time kinetic studies and NMR structural investigations were performed under identical experimental conditions, which are standard conditions for synthetic procedures. The results show that addition of THF has a different influence not only on reactivity and disaggregation but also on the aggregate structure of **1**·LiCN and **1**·LiI. Thus, for the first time different reactivities of Gilman cuprates can be directly correlated to different aggregate structures. Additionally, a direct dipolar interaction with the CN^- moiety in aggregates of **1**·LiCN is presented. In principle, with NMR spectroscopy the structures of transition states cannot be detected, but the investigation of the real existing structures of reagents and intermediates is an essential prerequisite to choose the ideal starting structures for theoretical calculations.

2. Results and Discussion

2.1. Kinetic Data. The kinetic studies were carried out as described previously.[28] As model system we selected the 1,4-addition of the Gilman cuprates **1**·LiX (X = I, CN) to 4,4-dimethylcyclohex-2-enone (**2**) in DEE at 210 K (Scheme 1). The reaction mixture contained equimolar concentrations of the reactants in the range of 0.025−0.1 M, as well as variable amounts of THF and tetradecane as internal standard. The progress of the reaction was determined by removing aliquots at specific time intervals, which were hydrolyzed and analyzed by gas chromatography. The substrate concentration showed an exponential decrease against the reaction time (see Figure S1 in Supporting Information for an example), and the measured values were fitted by use of the exponential function $c = c_0 \exp(-kt)$.[28] The resulting first-order rate constants k typically showed errors within 10% of the value of k.

Scheme 1. 1,4-Addition of the Gilman Cuprates **1**·LiX (X = I, CN) to 4,4-Dimethylcyclohex-2-enone (**2**) in DEE at 210 K Used as Representative Model Reaction in the Kinetic Studies



2 **3**

X = I, CN

In accordance with the "traditional" solvent effects in the conjugate cuprate addition,[6] we observed a continuous decrease of the reaction rate for the 1,4-addition of the cyano-Gilman cuprate **1**·LiCN to enone **2**,[1] as shown exemplarily in Figure 1. This behavior proved to be independent of the concentration of the reactants within the range examined here (see above and Figure S2 in Supporting Information). In striking contrast to this, the corresponding 1,4-addition of the copper iodide-derived Gilman cuprate **1**·LiI to the standard enone **2** showed a pronounced acceleration effect. At 0.1 M concentration of the reactants, addition of just 0.25 equiv of THF caused a 2.5-fold rate acceleration, and even in the presence of 1.0 equiv of THF the reaction was slightly faster than in pure DEE (Figure 2). This effect is in agreement with the observations of Bertz et al.;[16] however, they could not quantify the acceleration. We also observed a strong dependence of the acceleration effect on the concentration of the reactants: at 0.05 M, only a slight rate increase (ca. 1.5-fold) was observed with the maximum at 1.0

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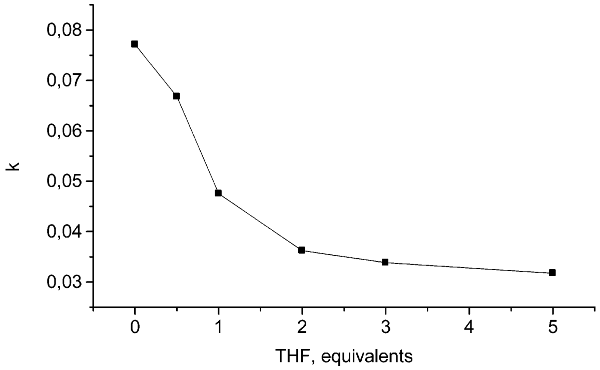

Figure 1. Rate constants of the 1,4-addition of **1**·LiCN (0.025 M) to **2** (0.025 M) at 210 K in pure DEE and in solvent mixtures of DEE and different equivalents of THF.

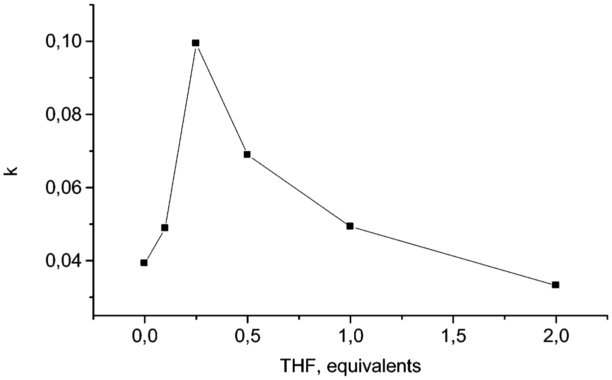

Figure 2. Rate constants of the 1,4-addition of **1**·LiI (0.2 M) to **2** (0.1 M) at 210 K in pure DEE and in solvent mixtures of DEE and different equivalents of THF.

equiv of added THF. However, it is noticeable that the reaction rate of **1**·LiCN without any THF is remarkably higher than for the corresponding **1**·LiI, which is contrary to the observations of Bertz et al.[16]

From these kinetic data a recommendation for syntheses with dialkylcuprates can be derived. For syntheses with cyanocuprates it is not advisable to add THF. However, if the reactivity of iodocuprates is too low in a specific reaction, the addition of up to 1 equiv of THF or the use of cyanocuprates is worthwhile trying.

2.2. Diffusion Studies. To investigate whether the described decrease of the reaction rate for **1**·LiCN or the acceleration effect for **1**·LiI upon addition of THF is correlated with a change in the degree of aggregation of these organocuprates in solution, pulsed field gradient (PFG) NMR diffusion experiments were performed. In DEE as solvent, series of diffusion coefficients of **1**·LiI, **1**·LiCN, and THF were measured with increasing amounts of THF up to 4 equiv (see Figure 4). In addition to one of the conditions used in the kinetic experiments (0.1 M, 210 K), an identical series of diffusion coefficients was determined at 239 K, the temperature used in previous structural studies.[8,17] Diffusion studies at concentrations lower than 0.1 M could not be performed because of the too low signal-to-noise ratio in the convection compensated diffusion experiments. From the diffusion coefficients obtained and the aggregation models shown in Figure 3, the degree of aggregation of the investigated dimethylcuprates was calculated as described previously.[17] In the following, the homodimeric core structure of **1**·LiX with no salt attached is denominated as homodimer and the salt-containing aggregate is denoted as dimer with salt.

In Figure 4a the results of the diffusion measurements for **1**·LiI are presented. Lower diffusion coefficients of **1**·LiI and of THF at 210 K compared to 239 K indicate higher aggregates at lower temperatures. Furthermore, at both temperatures, the diffusion coefficients of THF ($D_{\mathrm{THF}} = 1.15-1.45 \times 10^{-9}$ m^2/s) are remarkably reduced in comparison to that of THF in pure DEE ($D_{\mathrm{THF}} = 2.16 \times 10^{9}$ m^2/s) but much higher than those of **1**·LiI. This indicates that THF is partially attached to the organocuprate aggregates. The diffusion coefficient ($D = 0.74 \times 10^{9}$ m^2/ s) of **1**·LiI in pure DEE at 210 K correlates to 1.3 times a homodimer or a dimer with one LiI attached. Surprisingly, the addition of up to 4 equiv of THF does not lead to an increase of the diffusion coefficients beyond the error range. This indicates that the average hydrodynamic radius of the organocuprate aggregates is not significantly affected by these amounts of THF in the case of **1**·LiI. However, small changes in the aggregation structure cannot be detected by these PFG NMR diffusion experiments, since the scattering of the diffusion coefficient values due to the low concentration induces an error of ±5%.

The corresponding results for **1**·LiCN are given in Figure 4b. Similar diffusion coefficients of the cuprate at 210 and 239 K show a lower temperature dependence of aggregation for **1**·LiCN than **1**·LiI. Again the diffusion coefficients of THF [$D_{\mathrm{THF}} = (0.89-1.52) \times 10^{-9}$ m^2/s] are between the value of free THF and those of the cuprate, indicating a partial binding of THF to the organocuprate aggregates. As expected from previous studies,[17] the diffusion coefficient ($D = 0.52 \times 10^{9}$ m^2/s) of **1**·LiCN in pure DEE indicates higher oligomeric aggregates of 2−2.5 dimers with salt at 210 K. In contrast to **1**·LiI, a clear disaggregation is observed for **1**·LiCN with increasing amounts of THF indicated by rising diffusion coefficients. By addition of 4 equiv of THF, a disaggregation to a dimer with one salt attached is calculated for the diffusion coefficient $D = 0.8 \times 10^{-9}$ m^2/s at 210 K. For the diffusion coefficients of THF, a similar trend with rising values is observed upon addition of different equivalents of THF. This indicates that the averaged

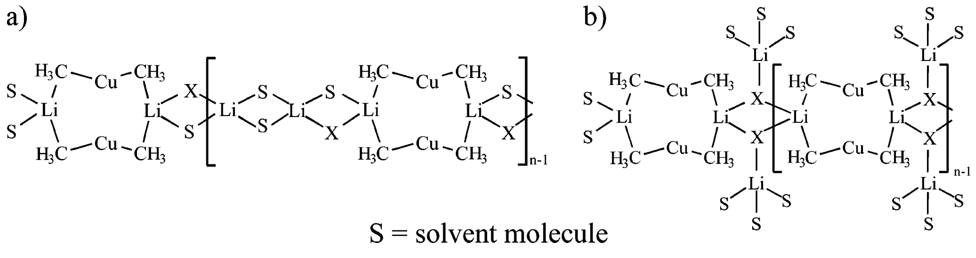

Figure 3. Structure models of salt-containing cuprate aggregates containing homodimeric core structures and salt units connecting the core structures with (a) four and (b) six solvent molecules per homodimer.

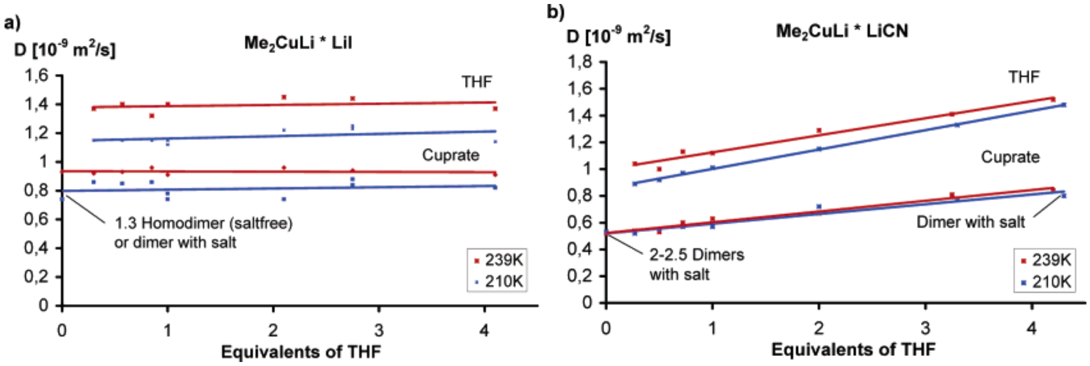

Figure 4. Diffusion coefficients of **1**·LiI and THF (a) and of **1**·LiCN and THF (b) in pure DEE and solvent mixtures of DEE with different equivalents of THF at 239 and 210 K.

hydrodynamic radii of the complexes containing THF decrease with increasing amounts of THF.

These studies for the first time allow us to directly compare the reactivity and aggregation of organocuprates at identical experimental conditions. In the case of **1**·LiCN, the decline in the reaction rates with increasing amounts of THF seems to be directly correlated to a disaggregation of the oligomeric structures of **1**·LiCN. However, in the case of **1**·LiI the surprising maxima in reactivity upon addition of 0.25−1 equiv of THF are not reflected in the diffusion coefficients of this system.

2.3. ^{1}H−^{7}Li HOE and ^{1}H−^{1}H NOE Studies with Different Equivalents of THF. Since the observed enhancements in the reaction rates of **1**·LiI are not caused by an obvious change of aggregation, it was investigated whether small structural changes induced by the addition of THF can be detected. Therefore, ^{1}H−^{7}Li heteronuclear Overhauser effect spectroscopy (HOESY) and ^{1}H−^{1}H nuclear Overhauser effect spectroscopy (NOESY) experiments of **1**·LiX (X = I, CN) in mixtures of DEE with 1, 2, and 4 equiv of THF were recorded at 0.1 M concentration and 210 K. In Figure 5, exemplary ^{1}H−^{7}Li HOESY spectra of **1**·LiI (a) and **1**·LiCN (c) in a mixture of DEE with 4 equiv of THF are shown. Additionally, bar charts of the HOE cross-peak volume integrals between the lithium signal and the protons of DEE (CH_2 DEE/CH_3 DEE) and THF (CH_2 THF/CH_2O THF) of **1**·LiI (b) and **1**·LiCN (d) at different equivalents of THF are given in Figure 5. There, the volume integrals are displayed relative to the volume integrals of the cross-peak between lithium and the methyl groups of the cuprates in each spectrum.[29]

In the case of **1**·LiI, the volume integral of the cross-peaks of THF increases in a superproportional manner upon the addition of THF, while the DEE cross-signal volume integrals remain constant or increase only slightly. This trend indicates that DEE is not replaced by THF, but additional coordination sites are generated by increasing the amount of THF.

In the case of **1**·LiCN, the volume integral of the cross-peaks of THF increases proportionally to the added equivalents of THF, while the cross-peak volume integral of DEE dramatically decreases. This indicates a replacement of DEE by the addition of THF at a similar number of coordination sites.

To prove these hypotheses, ^{1}H−^{1}H NOESY spectra were recorded to investigate the closeness of THF to the cuprate aggregates. The bar charts of the cross-peak volume integrals between the methyl group of the cuprates and the two different CH_2 groups of THF are shown in Figure 6. In the respective ^{1}H−^{1}H NOESY spectra the volume integrals were calibrated in relation to the cross-peak volume integral between the two chemically nonequivalent CH_2 groups of THF. Therefore, the volume integrals shown in the bar charts of Figure 6 are directly related to the actual amount of THF.

In the case of **1**·LiI, the relative ^{1}H−^{1}H NOE cross-peak volume integrals between the cuprate and THF decrease upon the addition of THF. Based on our calibration relative to the internal THF signal, this indicates a reduced fraction of THF being bound to the cuprate aggregates with increasing equivalents of THF. Further to this, change of the ^{1}H−^{1}H NOE volume integrals is confirmation of the structural modification caused by the addition of THF, indicated previously by the ^{1}H−^{7}Li HOE results. In contrast to that, the ^{1}H−^{1}H NOE volume integrals of **1**·LiCN show similar integrals at increasing amounts of THF. This mirrors a similar fraction of THF being bound to the cuprate at different equivalents of THF. Again, the constancy of the ^{1}H−^{1}H NOE volume integrals corroborates the results from the ^{1}H−^{7}Li HOE measurements. It confirms that, in the case of **1**·LiCN, the core structure of the aggregates is not affected by increasing amounts of THF.

From these results we can build up a new model of salt-containing organocuprates **1**·LiX (X = I, CN) in mixtures of DEE and THF (Figure 7). The kind of salt seems to influence the disaggregation behavior induced by the addition of THF. In the case of **1**·LiI, the diffusion studies show no obvious disaggregation by THF. However, the more sensitive ^{1}H−^{7}Li HOE and ^{1}H−^{1}H NOE studies show a structural change upon the addition of THF. The coordination sites on lithium are increased and simultaneously THF is not only bound to the organocuprate. These facts suggest a separation of small salt units from the homodimeric core structure not observed by the less sensitive diffusion measurements. This means, at larger amounts of THF, the THF is bound not only to lithium inside the homodimeric cuprate but also to additional lithium species separated from the cuprate. Previously published structural suggestions for these additional lithium species are solvent-separated ion pairs,[6] Li−I−Li^{+} moieties,[25,30] and dimeric $(LiI)_2$ clusters.[30] Additionally, this model complies with the observation that LiI itself is very well soluble in DEE and THF. Since there was recently a revival of heterodimeric structures in the

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[29] The absolute integral of the reference cross-peak remains constant for **1**·LiI at different amounts of THF within experimental error. In the spectra of **1**·LiCN the absolute volume integral of the reference cross-peak increases according to the general signal-to-noise improvement of all signals in the spectra of **1**·LiCN caused by disaggregation.

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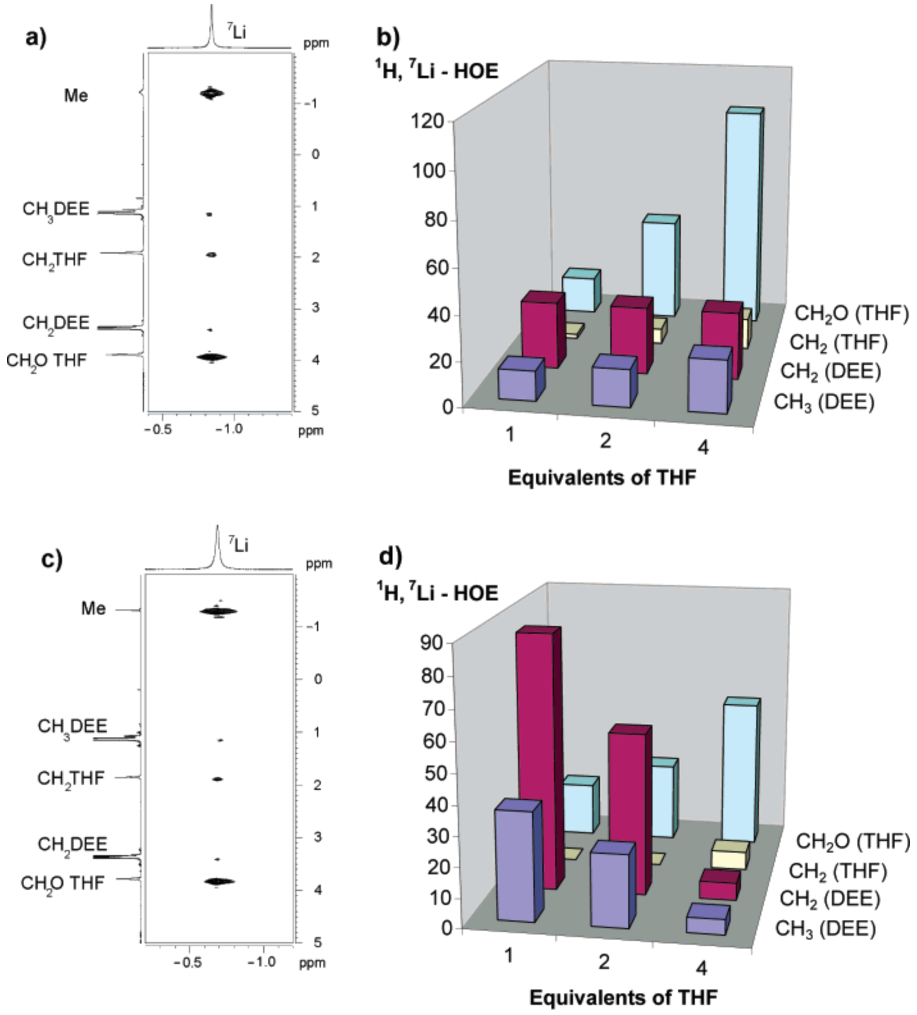

Figure 5. Representative for a series of spectra in different solvent mixtures, the ^{1}H−^{7}Li HOESY spectra of **1**·LiI (a) and **1**·LiCN (c) are shown in DEE with 4 equiv of THF at 210 K. For mixtures of DEE and 1, 2, and 4 equiv of THF, the volume integrals of the ^{1}H−^{7}Li HOE cross-peaks between lithium and the protons of DEE and THF are summarized as bar charts for **1**·LiI (b) and **1**·LiCN (d).

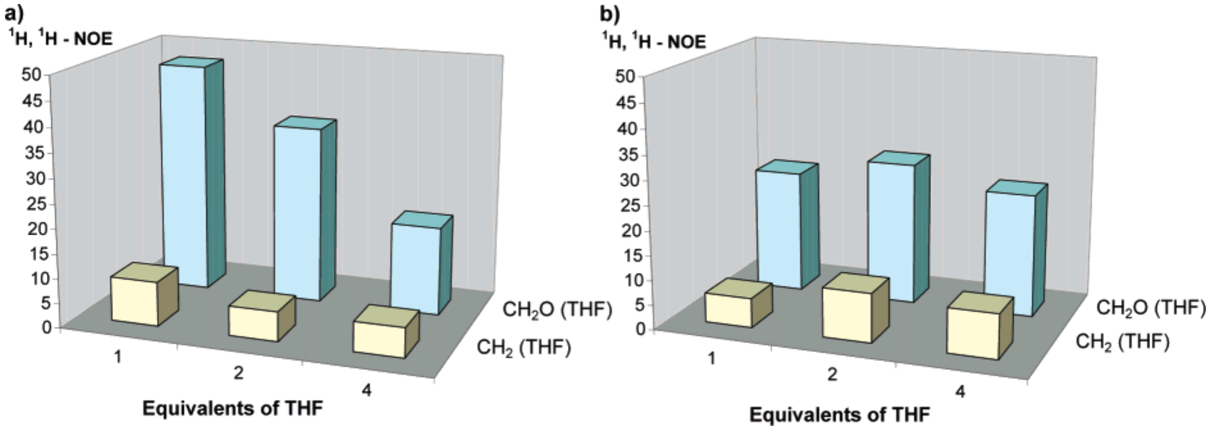

Figure 6. Bar charts summarizing the ^{1}H−^{1}H NOE volume integrals of the cross-peaks between the methyl group of the cuprate and the two different CH$_2$ groups of THF for **1**·LiI (a) and **1**·LiCN (b) in mixtures of DEE and 1, 2, and 4 equiv of THF.

discussion of the intermediate structures of organocuprates upon addition to enones,[23,31,32] we also tried to interpret our data in terms of heterodimeric structures. However, considering heterodimeric oligomers, a separation of Li moieties would lead to a severe reduction of the ^{1}H−^{7}Li HOE cross-peaks between the Li moieties and the methyl groups of the cuprates as well as to a significant reduction of the hydrodynamic radius, that is, a considerable increase in the diffusion coefficient. Both factors are not supported by the experimental data.

In the case of **1**·LiCN, a clear disaggregation of the oligomeric chains in combined homodimer/salt aggregates can be observed

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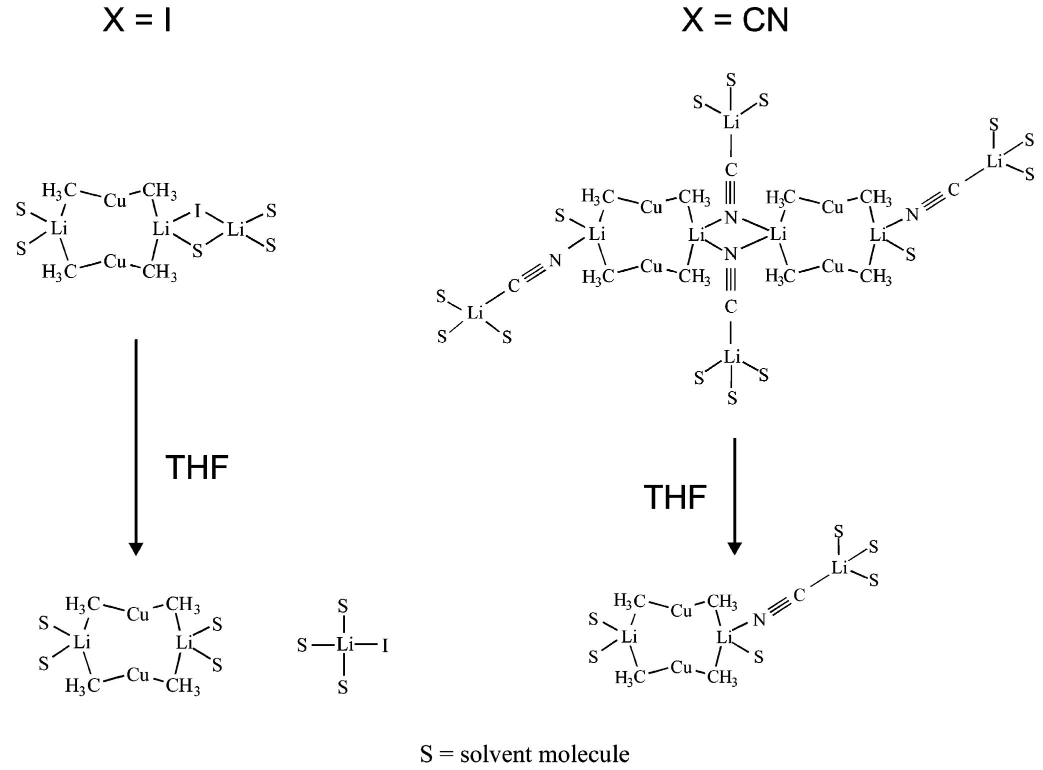

Figure 7. Postulated aggregate structures of **1**·LiI and **1**·LiCN at 0.1 M concentration in pure DEE and their change through addition of 4 equiv of THF derived from combined results of diffusion, NOE, and HOE studies.

by the addition of THF, but this does not significantly induce either additional coordination sites or a structural change in the aggregation structure (see Figure 7). The continuity of the combined organocuprates' salt aggregation structure by disaggregation is also congruent with the fact that LiCN is poorly soluble in DEE or/and THF.[33]

Now the kinetic data can be compared with the NMR studies again. In the case of **1**·LiI, a distinct amount of salt and/or THF attached to the homodimeric core structure seems to enhance the reactivity. The reason for this could be that an optimal tuning of the Lewis acidity of the solvated Li^+ cations is reached. For **1**·LiCN the higher Lewis basicity of THF, compared to DEE, induces a disaggregation of the oligomeric species and a decrease of the Lewis acidity of the Li^+ cations, and both effects are correlated with a significant decrease in the reactivity. Interestingly, the combined HOE/NOE studies show that for **1**·LiCN the disaggregation is not accompanied by a separation of the salt unit from the core structure, but the combined cuprate and salt unit persists. Thus, the presented kinetic and NMR spectroscopic data point out that for cyanocuprates the short oligomeric structures and the Lewis acidity of the lithium cations, induced by the oligomeric structure, affect the reactivity more than the presence of the cyanides alone. An estimation of the contribution of each factor to the reactivity of the cuprate may be possible with the aid of high-level quantum chemical calculations of the complete oligomeric cuprate clusters.

2.4. $^1H-^{13}C$ HOE and $^1H-^1H$ NOE Studies Concerning the Position of CN^-. Our results again raise the central question in the long-standing discussion about the special reactivity of LiCN-containing diorganocuprates, namely, the question about the position and role of CN^- in the structures and reactive intermediates of lithium diorganocuprates in solution. In contrast to the large number of theoretical studies regarding this subject,[21,23,34] from experimental studies up to now only indirect evidence was given for the position of CN^- in the different cuprate species in solution (for details see Introduction). With a special sample preparation and the utilization of ^{13}C-labeled LiCN salt, it was now possible for the first time to detect a direct $^1H-^{13}C$ HOE to the CN^- moiety in organocuprate aggregates.

Due to the extremely low signal-to-noise ratio of the ^{13}C signal of CN^- in samples of **1**·$Li^{13}CN$ with a 0.1 M concentration, a sample of **1**·$Li^{13}CN$ in DEE with a 3-fold higher concentration (0.3 M) was prepared. Thereby 12 equiv of THF was used to adjust a degree of aggregation comparable to the studies discussed above. The diffusion coefficient ($D = 0.83 \times 10^{-9}$ m^2/s) of the resulting cuprate aggregate at 239 K indicates an aggregation equivalent to a dimer with one salt attached. Under these experimental conditions the usually fast exchange of solvent molecules between a position bound to the cuprate aggregate and the solvent bulk is slowed on the NMR time scale. Thus, for the first time we observed the THF signals being split into two sets of signals, one set with small line widths for the bulk THF molecules (THF) and one set with broad line widths for the THF molecules attached to the organocuprate aggregates (THF*) (Figure S3 in Supporting Information). Via the cross-peaks between the methyl group of the cuprate and the two different CH_2 groups of THF* in the $^1H-^1H$ NOESY spectrum, THF* can be unambiguously assigned to be bound to the cuprate aggregate (Figure S4 in Supporting Information).

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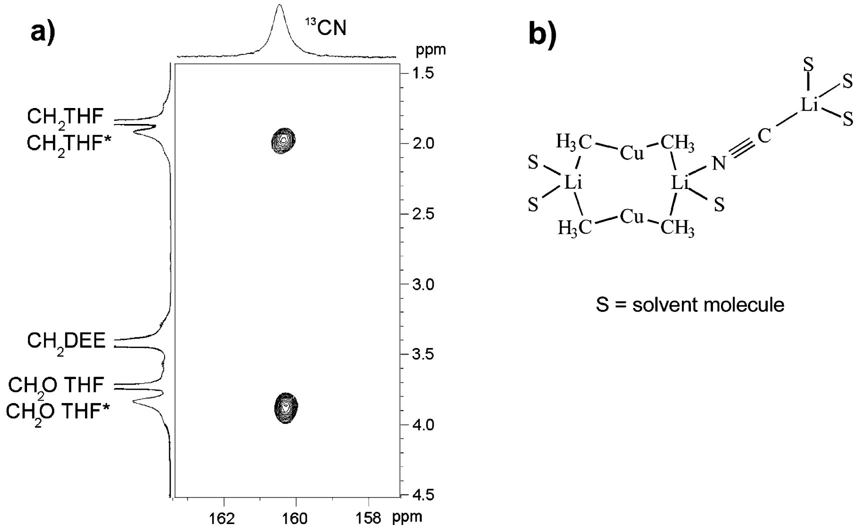

Figure 8. (a) ^{1}H−^{13}C HOESY spectrum of **1**·LiCN (0.3 M) with 12 equiv of THF at 239 K. Two sets of signals are observed for THF in the solvent bulk (THF) and THF bound to the cuprate aggregate (THF*). (b) Model structure for **1**·LiCN derived from combined results of diffusion, NOE, and HOE studies.

In the respective ^{1}H−^{13}C HOESY spectrum (Figure 8a), for the first time cross-peaks to the ^{13}CN$^-$ group are observed, namely, cross-peaks between the ^{13}CN$^-$ group and both THF* signals in considerable signal-to-noise ratios. A cross-peak between the methyl group of **1**·Li^{13}CN and the ^{13}CN$^-$ moiety could not be detected despite an extensive experimental effort of varying the parameters in a number of test spectra.

In Figure 8b a structure model is depicted based on the combined results of the diffusion measurements and ^{1}H−^{13}C HOESY and ^{1}H−H NOESY spectra. The diffusion coefficient indicates a dimer with one salt attached. The ^{1}H−^{1}H NOESY spectrum shows a direct contact between the cuprate and THF*. The strong contact in the ^{1}H−^{13}C HOESY spectrum between THF* and the CN$^-$ in conjunction with the absence of a cross-peak between the CN$^-$ group and the methyl group of the cuprate suggest the shown orientation of the CN$^-$. Although this agrees with models from infrared spectroscopy,[24] the shown orientation cannot be postulated as fixed due to the relatively small isomerization barrier in LiCN[35] and known crystal structures.[36] Thus, for the first time it is experimentally shown that in **1**·LiCN the CN$^-$ group is attached to the cuprate aggregate even at a low degree of aggregation. The not detectable ^{1}H−^{13}C HOE contact between the CN$^-$ group and the methyl groups suggests that the carbon of the CN$^-$ group is aligned away from the cuprate units.

3. Conclusion

Kinetic measurements and NMR investigations performed under identical experimental conditions, which are standard conditions of synthetic protocols, allow us for the first time to correlate directly the structure of LiI- or LiCN-containing Gilman cuprates in DEE with their reactivity in the 1,4-addition to an enone. To confirm or to invalidate previous hypotheses about aggregation/reactivity correlations in these reactions, the influence of different equivalents of THF on the reactivity and aggregation structure was investigated. Surprisingly, different influences of THF on the reactivity as well as on the aggregate structure are found for **1**·LiI and **1**·LiCN. For **1**·LiI, the addition of 0.25−1.0 equiv of THF led to a pronounced acceleration effect. In contrast, the reaction rate of **1**·LiCN, being remarkably higher in pure DEE, significantly decreases upon addition of THF. The parallel NMR investigations show that, in **1**·LiI starting from a dimer with salt attached, small salt units are separated through the addition of THF. Thus, the reactivity of **1**·LiI seems to show a fine-tuning through distinct amounts of salt or THF influencing the Lewis acidity of the Li$^+$ cations. In striking contrast, **1**·LiCN starting from a short oligomeric structure is disaggregated to dimers through THF without structural change in its core structure; that is, the LiCN remains attached. This is additionally confirmed via ^{1}H−^{13}C HOE contacts to the CN$^-$ group, the first direct experimental evidence for the position of the CN$^-$ group in small aggregates of dialkylcuprates in solution. Thus, the decrease of reactivity of **1**·LiCN shows a direct correlation with the disaggregation of its oligomeric structure, indicating simultaneously a decreasing Lewis acidity of the Li$^+$ cations.

In the long-standing scientific discussion about the special reactivity of LiCN-containing organocuprates, the role of LiCN for the reactivity was controversially discussed. Recently Nakamura and Yoshikai[23] again proposed a special contribution of LiCN to the transition state. Since our NMR studies show that LiCN remains directly attached to the homodimeric cuprates through all kinds of aggregation, a contribution of the LiCN cannot be excluded. However, our work shows that disaggregation of short oligomers significantly decreases the reactivity of cyanocuprates despite the permanent presence of cyanides in the structures. This indicates that the oligomeric structure of cyano dialkylcuprates and/or the Lewis acidity of Li$^+$ gained by this oligomeric structure influence the reactivity of LiCN-containing cuprates rather than the presence of single LiCN units alone.

For synthetic chemists with reactivity problems in specific reactions of iodo- and cyanodialkylcuprates, a recommendation can be derived from the presented data. Whereas for cyanocuprates the addition of THF is unfavorable, in the case of iodocuprates it is worthwhile to try the addition of small amounts of THF to enhance the reactivity.

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4. Experimental Section

Sample Preparation. All samples were prepared by a method described by John et al.[6] The ratio of DEE-d_{10}/DEE, the equivalents of THF, and the concentration of the samples were adjusted by comparing the integrals of the proton spectra obtained by a single 90° pulse as well as the values gained from the synthesis. The mixture of DEE-d_{10}/DEE is denoted as pure DEE solvent throughout this paper.

Internal Viscosity Reference. The viscosity value of nondeuterated DEE at 239 and 210 K was obtained by nonlinear fitting to literature data in the temperature range of 173−298 K.[37] The viscosity value of the mixed solvent (DEE-d_{10}/DEE) used in this study was defined to be 1.1 times of the value of the nondeuterated DEE at the same temperature.[38,39]

Since we noticed a strong dependence of the viscosity on the concentration, the temperature, and the kind of cuprates, a trace (2−3 drops) of benzene (C_6H_6) was used as an internal reference.[40] To check influences of the added amounts of THF on the viscosity, diffusion measurements of a sample with the internal viscosity reference and THF (0.2 M) in DEE-d_{10} were performed. The respective diffusion coefficients showed no influence of these amounts of THF on the viscosity. By a comparison of the diffusion coefficients of the reference measured in pure DEE-d_{10} and in the cuprate sample, the viscosity correction factors for the cuprate samples were determined.

Theoretical Diffusion Coefficients. As described in our previous publication,[17] the theoretical diffusion coefficients were calculated from hard-sphere increments[41] and the Stokes−Einstein theory[42] modified by a shape factor.[43]

NMR Data Collection and Processing. The NMR spectra were recorded on a Bruker DRX500 spectrometer equipped with a 5 mm broadband triple-resonance Z-gradient probe (maximum gradient strength 53.5 G/cm). All diffusion measurements were performed with a convection-suppressing pulse program[44] in pseudo-2D mode and processed with Bruker software package t1/t2. For each experiment, 16 dummy scans and 16 actual scans were used, with a relaxation delay of 3 s and a diffusion delay of 30 ms. The shape of the gradients was sinusoidal, with a length of 2 ms, and the strength was varied in 10 increments (5−95%) of the gradient ramp created by Bruker software DOSY. The diffusion coefficients were determined by using the Bruker software package t1/t2 to fit the measured decline of intensity. The obtained diffusion coefficients are the average results of 2−3 repetitions of each measurement.

For the $^1H-^7Li$ HOESY and the $^1H-^{13}C$ HOESY measurements, the standard Bruker pulse program[45] was used. $^1H-^7Li$ HOESY was carried out with 16 number of scans, TD(F2) = 8k, TD(F1) = 256, 3 s of relaxation delay for acquisition, and a mixing time of 1.3 s. The data were processed with SI(F2) = 2k and SI(F1) = 256. For the $^1H-^{13}C$ HOESY measurements, 256 scans, TD(F2) = 16k, TD(F1) = 170, 2 s of relaxation delay, and a mixing time of 900 ms were applied. The processing parameters were SI(F2) = 4k and SI(F1) = 128.

The $^1H-^1H$ NOESY measurements were also carried out with the standard Bruker pulse program[46] using 16 scans, TD(F2) = 16k, TD(F1) = 512, 5 s of relaxation delay for acquisition, and a mixing time of 800 ms. Here the data were processed with SI(F2) = 4k and SI(F2) = 512. The temperatures for all measurements were calibrated with the Bruker methanol sample and the AU program *calctemp* and were controlled by a Bruker BVT 3000 temperature unit.

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Supporting Information Available: Comparison between calculated and experimental diffusion coefficients, additional kinetic curves, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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