

Further Insights into the Chemistry of Acyllithium Compounds $R_2NC(O)Li$: Characterization of an Amide (R_2NLi) Adduct ($R_2NCHNR_2(OLi)$) to a Formamide ($R_2NC(O)H$)

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Studies of the reaction of lithium morpholide with *N,N*-dibutylformamide and 1-formylpiperidine, respectively, indicate that in the complex equilibria resulting from these compounds the mixed diamino lithium alkoxides derived from morpholine and the corresponding amide (*N,N*-dibutylformamide or 1-formylpiperidine) are formed first. These intermediates then collapse to the lithium morpholide carbamoyl anion which reacts with morpholine to finally give the lithium dimorpholinemethoxide, which was detected by ¹³C NMR as well as independently synthesized.

Introduction

Studies of the aggregation states of lithium dialkylamides in the solid state¹ and in solution^{2–4} as well as the formation of homo- and mixed-solvated species with ethers⁵ and alkyl amines,^{4,6} are the subject of intense research activity at present. Besides the fundamental significance, the association phenomena have important consequences in synthetic organic chemistry.^{1c,6–8} We have recently described the solid-state structure of a 1:1 lithium amide–amine mixed aggregate, [piperidine–lithiumpiperidide]₄, which was the first mixed tetramer described.⁹ The formation of this aggregate had been predicted from the results observed in the reaction of lithium pentamethylene amide with carbon monoxide in THF solution.¹⁰ The carbonylation of lithium dialkylamides is a synthetically useful reaction that has been thoroughly investigated,^{1c,7,10} in addition to the effect

of metal catalysts^{11,12} and carbonylation in the presence of radical scavengers.¹³ The resulting carbamoyl intermediates, $R^1R^2NC(O)Li$, however, are very reactive acyl “anions” which usually lead to complex systems; this is essentially the reason why synthetic chemists have switched to “umpolung” or to acyllithium equivalents instead. The likely equilibrium between lithium dialkylamides and the corresponding dialkylformamides is a key step in the mechanism of carbonylation since it could explain the striking dependence on the reaction conditions, including the effects of “free” amine and the lithium amide nature.^{7,10a} We provide an NMR study of the equilibrium between formamide/lithium amide pairs, which together with the results of trapping reactions shed some more light on the complexity of the case. The procedure developed was successfully applied for the preparation of disubstituted formamides, which have been used lately as reagents in the industrial preparation of 2-halo-5-substituted pyridines,¹⁴ trihalobenzaldehydes,¹⁵ carbamates and ureas,¹⁶ intermediates for heterocyclic compounds with known clinical activity,¹⁷ and electrically conducting polymers.¹⁸ More-

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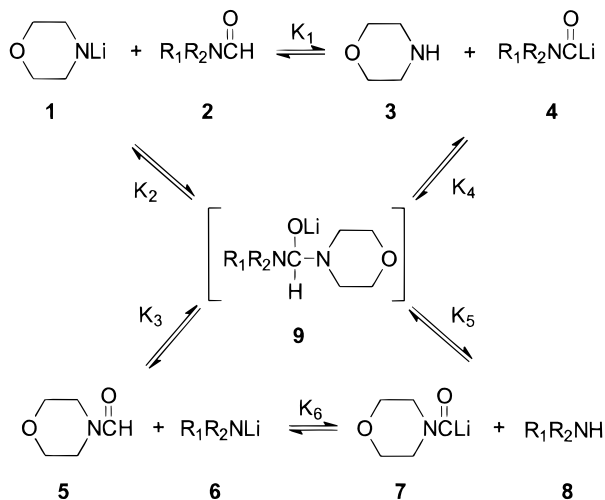
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Table 1. Reaction of Lithium Morpholide, 1, with Disubstituted Formamides^a

	2	3	5	8
<i>N,N</i> -dibutylformamide	0.31	1.0	0.62	0.60
1-formylpiperidine	0.49	1.0	0.49	0.45

^aAmounts of products (in mmoles) determined by GC after hydrolysis. Initial concentrations of both reactants: 0.7 M. A 0.9 mmol amount of each reactant was initially present in the mixture.²⁰ In the reaction mixture, each product was accompanied by its lithium derivative, the amounts given in mmoles corresponds to the total amount in each case, i.e. (2 + 4), (3 + 1), (5 + 7), and (8 + 6).

Scheme 1. Equilibrium Reactions between Lithium Morpholide and Disubstituted Formamides

over, formamides were recently found to have antimicrobial activity.¹⁹

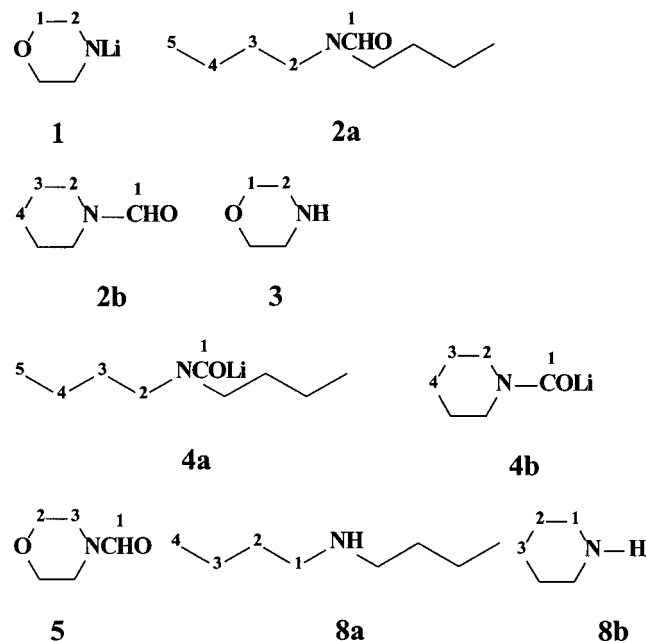
Results and Discussion

The reaction of lithium morpholide (1) with *N,N*-dibutylformamide (2a) and 1-formylpiperidine (2b), respectively, was studied in THF at room temperature using 0.7 M solutions of the reactants. The reaction was initiated by mixing 1.3 mL of lithium morpholide, 1 (0.9 mmol), with an equimolar amount of the corresponding neat formamide and was allowed to react for 15 min before quenching with MeOH/HCl. The amounts of products determined by GC after hydrolysis are listed in Table 1. It is important to notice that while being prepared, 1 precipitates as an (amine, lithium amide)_n aggregate⁴ (as similarly reported for lithium piperidide).^{4,9} Therefore, 0.9 mmol of morpholine was also present in the mixture. In the carbonylations of acyclic lithium dialkylamides, intentional addition of amine as a proton donor was used to lead the reaction toward the desired product.^{10a}

The observed formation of the morpholine-derived formamide 5 from 2a as well as 2b indicates the presence of an interesting series of equilibria among different species, which can be represented as shown

in Scheme 1. Similar equilibria have been postulated for the reaction of *N,N*-dialkylformamide dimethyl acetals with secondary amines,²⁰ which have been reported to occur with the exchange of the CH(OMe)₂ unit.

The equilibrium composition of the different reaction mixtures in THF was studied by ¹³C NMR. A comparison of the NMR shifts with those of the individual species 1–5 and 8 in the same solvent is given in Table 2. The assignments correspond to the carbons as



numbered below. In the case of the disubstituted alkylamides both alkyl groups are not equivalent, which leads to two signals for each type of carbon.

Recently, we have shown that due to the high acidity of morpholine, the equilibrium K_1 (Scheme 1) is far on the left side.²¹ Therefore, 3 and 4 are minor components, and consequently, the equilibria involving K_1 and K_4 are not significant. In the hydrolyses (with MeOH/HCl up to pH \approx 7), the amides and carbamoyl "anions" present in solution are converted into the corresponding amines and formamides. Therefore, what is being represented in Table 1 as morpholine is the total amount of morpholine, 3, and lithium morpholide, 1. This is similarly true for the rest of the products (5 + 7, 2 + 4 and 8 + 6), which are in equilibrium with their corresponding organolithium species. Transfer of the formyl group is assumed to occur via nucleophilic addition of lithium morpholide 1 to the corresponding formamide 2 to give intermediate 9, which then collapses to 2, 3, 5, and 8. We have previously suggested that an intermediate similar to 9 is formed in the reaction of lithium amides with CO.^{4,10}

The ¹³C NMR spectrum of the reaction mixture of lithium morpholide with *N,N*-dibutylformamide, 1 + 2a (see Figure 1a), shows a set of signals in which those due to the carbons of dibutylamine, 8a, are clearly recognized, together with three other peaks which are marked A–C in the spectrum. These signals, A–C, are

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Table 2. ^{13}C NMR Shifts of the Individual Species^a

compd	C ₁	C ₂ ^b	C ₃	C ₄	C ₅
1	71.38	53.80			
2a	161.98	41.60/46.74	29.93/31.27	19.98/20.54	13.57/13.73
2b	160.31	40.28/46.34	25.83/27.04	25.13/25.61	
3	68.36 ^c	47.23			
5	160.72	66.63/67.55 ^c	40.68/45.80		
8a	50.03	32.73	20.84	14.00	
8b	47.65	27.45	25.88 ^c		
9a ^d	104.4	71.8	43.5	42.6	32.2 ^e
9b ^d	108.1	71.8	43.5	41.3	27.6 ^f
10 ^d	108.1(106.2)	71.8 (72.0)	43.5 (52.6)		

^a δ_{C} /ppm; THF-C₆D₆ (5:1). ^b Shifts separated by slashes correspond to the *cis* and *trans* conformers. ^c Under one of the signals corresponding to THF. ^d Calculated shifts. Values in parentheses correspond to the dilithiated (R₂CLi(OLi)) compound. Signals corresponding to C₁, C₂, and C₃ of **9** and **10** are marked A, B, and C, respectively, in the figures. ^e Additional signals: C₆, 20.8 and C₇, 13.7. ^f Signal for C₆, 26.2.

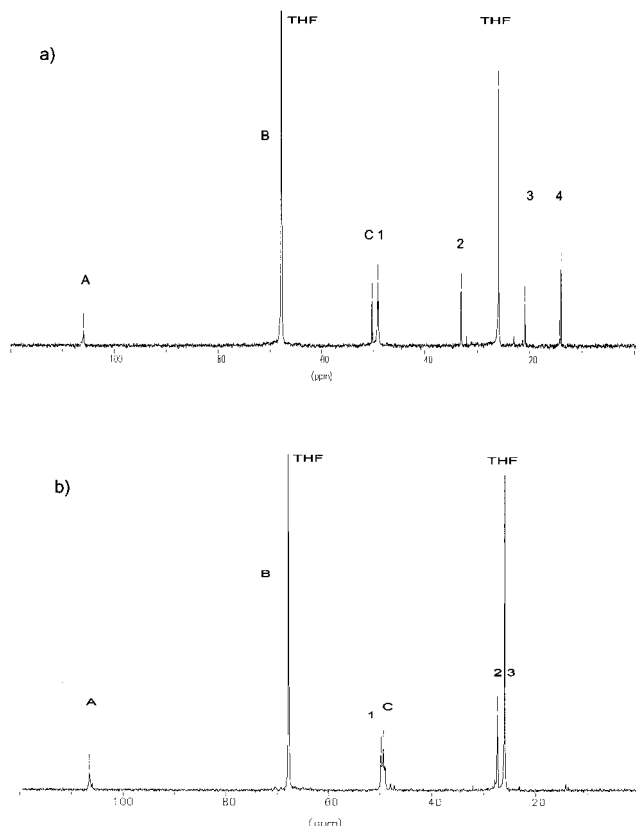


Figure 1. ^{13}C NMR spectra in THF-C₆D₆ (5:1) of the reaction mixtures of lithium morpholide, **1**, with *N,N*-dibutylformamide, **2a**; the signals numbered 1–4 correspond to the carbons in compound **8a**; 1-formylpiperidine, **2b**; the signals numbered 1–3 correspond to the carbons in compound **8b**. The signals marked A–C in Figures 1a and b correspond to C₁–C₃ in compound **10**.

also seen in the NMR spectrum of a mixture of **1** + **2b** (see Figure 1b), in addition to the peaks due to piperidine, **8b**. The spectrum of **1** + **5** shows the signals for morpholine, **3**, morpholine carboxaldehyde, **5**, and again the signals marked A–C (see Figure 2).

The signals corresponding to the mixture of **1** + **2a** at around 106 ppm are broad (A in Figure 1a); the same is true for the equivalent signals observed in the mixture of **1** + **2b** (see Figure 1b) and also for those of **1** + **5** (Figure 2). This probably results from the interconversion of different aggregated species. Although Li⁷ quadrupole relaxation is known to produce broadening of the signals,²² in these compounds Li is most likely closer to oxygen than to any other atom and

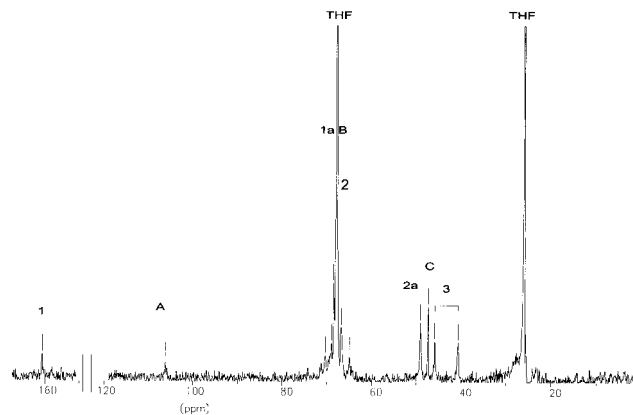


Figure 2. ^{13}C NMR spectrum of the reaction mixture of lithium morpholide, **1**, with 1-formylmorpholine, **5**, in THF-C₆D₆ (5:1). The signals numbered 1–3 correspond to the carbons in compound **5**, those numbered 1a and 2a to the carbons of **3**, and the signals marked A–C to C₁–C₃ in compound **10**.

thus not coupled to ^{13}C .²³ In the case of the *N,N*-tetramethyldiaminoalkoxide, we have shown by ab-initio calculations that the bond lengths of both Li atoms to oxygen (172 and 174 ppm) are shorter than those to carbon (196 and 230 ppm, respectively).²⁴

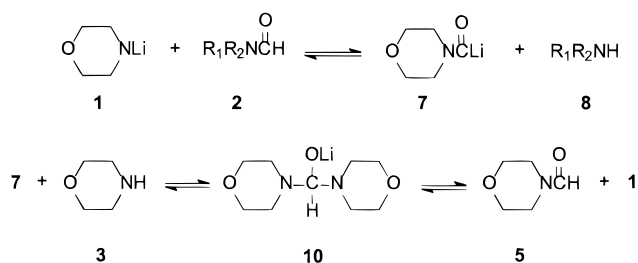
The similarity of the signals A–C in the three spectra suggested the presence of a common intermediate. Therefore, efforts were made to accumulate further evidence for their descent. When the ^{13}C NMR spectrum of the reaction mixture of **1** + **2a** is measured below room temperature, the signals at 49.06 and 105.93 ppm decreased in size as the temperature is lowered and finally disappear at –50 °C. Under these conditions, the formation of a precipitate is observed, indicating that the above-mentioned signals are due to a compound which crystallizes on cooling. Exactly the same behavior is observed in the case of the mixture of **1** + **5**.

These observations suggested that the set of signals A–C, detected in the mixtures of **1** + **2** and **1** + **5**, are due to the adduct **10**, formed by further reaction of **7** with morpholine which is present in the reaction mixture (see Scheme 2). Calculation of the ^{13}C NMR

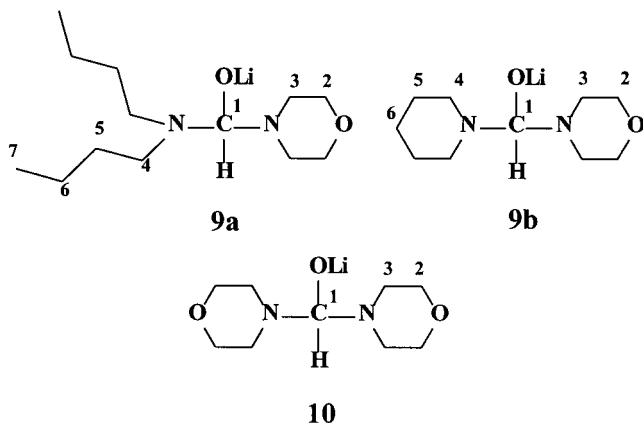
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Scheme 2. Formation of Intermediate **10**

shifts of **9** and **10** by means of commercial software²⁵ are in reasonable agreement with the experimental results (see values in Table 2). Although calculated



shifts for the corresponding dilithiated compound agree even better, the stoichiometry of the reaction (two morpholine units per lithium) is in better agreement with the presence of compound **10**. Correspondingly, only traces of carbonyldi-*N,N*-morpholine are produced on oxidation of the reaction mixture (lithium morpholide/*N,N*-dibutylformamide) with oxygen, indicating that the dilithiated compound, which should be oxidized very easily as observed in other cases,⁷ is not present.

In principle, the mixed intermediate **9** could also be present in the reaction mixtures of **1** + **2**. The absence of any signal for C_4 (around 40–45 ppm), however, suggests that **9** is not there in any significant amounts. In order to prove that the signals A–C indeed correspond to the common intermediate **10**, **10** was independently synthesized as described in the Experimental Section. Its ^{13}C NMR spectrum in THF solution is shown in Figure 3. The set of signals A–C is clearly observed as the only signals present in the spectrum. The hydrogen-coupled ^{13}C NMR spectrum of **10** was also determined, and it showed a doublet for the signal at 105.85 ppm, corresponding to carbon A. This constitutes additional evidence that **10** has the monolithiated structure as discussed before.

Since the signal at 49.01 ppm in Figure 1b which was assigned to C_1 of piperidine (**8b**) is shifted by 2.8 ppm with respect to the value of pure **8b** (see Table 2), some complexation between **8b** and **10** was thought to be responsible for that shift, which is experimentally confirmed: the ^{13}C NMR spectrum of **10** plus pure **8b** (in a 1:0.2 mol ratio) showed the signal of C_1 at 49.79 ppm.

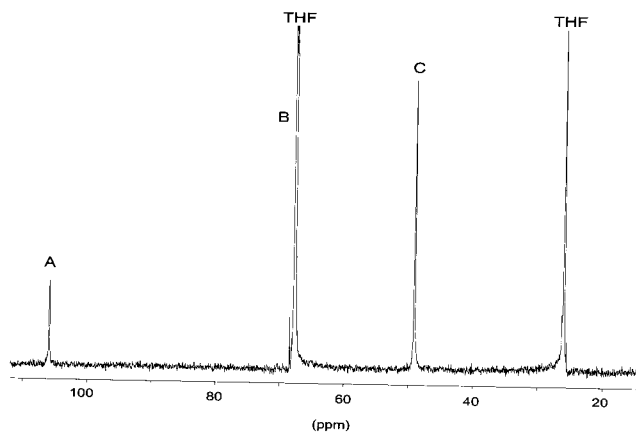


Figure 3. ^{13}C NMR spectrum of compound **10** in THF– C_6D_6 (5:1). The signals marked A–C correspond to C_1 – C_3 in compound **10**.

In conclusion, it is shown by protonation reactions and NMR investigations that the equilibria involving lithium morpholide (**1**) and *N,N*-dibutylformamide (**2a**) or 1-formylpiperidine (**2b**) are first shifted toward the formation of the carbamoyl “anion” **7** and the amine **8** (*N,N*-dibutylamine or piperidine). The “anion” **7** then reacts with morpholine (**3**), which is always present in an equimolar amount to **1**, to give compound **10**, probably via the equilibria shown in Scheme 2. To the best of our knowledge, an adduct like **10**, which can be considered as an adduct of an amide $R_2NC(O)H$ with $R_2N\text{Li}$ —related adducts have been proposed in reactions of amides and esters with metalated nucleophiles—has not been characterized before.²⁶

The equilibria are shifted toward the formation of **1** and **5** (in preference to **3** + **7**) due to the high acidity of morpholine.²¹ In the presence of water, **10** decomposes giving rise to the results shown in Table 1, which does not reflect the real equilibria occurring in the reaction mixture: this emphasizes the significance of the ^{13}C NMR investigations to get more insight in the products formed from Li amides and *N,N*-dialkylamides in THF, as well as in the carbonylation of lithium amides. One should, however, also mention that neither the present nor previous studies uncovered the NMR spectrum of a carbamoyllithium compound.

As shown before, the presence of amine as a proton source in the reaction medium can be purposely used in the carbonylations to tune up the reaction toward the synthesis of the desired product in satisfactory to good yields.^{4,10a,12} *In situ* proton transfer to the very reactive carbamoyl intermediate as soon as it is formed to give an adduct like **10** prevents its further reaction and the formation of more complex products.

Experimental Section

General Comments. All reactions involving organolithium reagents were carried out by using standard techniques for the manipulation of air- and water-sensitive compounds.²⁷ Distilled THF was refluxed over sodium benzophenone ketyl until a dark blue solution was obtained and then distilled immediately before use under dry oxygen-free nitrogen. Com-

(25) ChemWindow 3, Version 3.0.0.C13. The ^{13}C NMR module was developed by Dr Ernő Pretsch of the Department of Organic Chemistry, ETH, Zurich, Switzerland.

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mercial dialkylamines were left over sodium strings for several days, refluxed and distilled over sodium, and then kept under nitrogen in sealed ampoules, which were opened immediately prior to use. *n*-Butyllithium,^{1c} lithium amides,⁷ and *N,N*-dialkylformamides¹⁰ were prepared as previously described.

¹³C NMR Measurements. ¹³C NMR spectra of THF solutions of all the involved amines, formamides, and lithium amides were recorded. In all cases, shifts were determined with respect to the central signal corresponding to deuterated benzene ($\delta = 128.00$ ppm). The spectra of the lithium amide/formamide mixtures were determined as follows: 0.5 mL of a 0.7 M lithium morpholide (**1**) solution were syringed into a nitrogen-filled NMR tube capped with a septum. An equimolar amount of the corresponding formamide was syringed into the tube at room temperature and shaken manually (in all cases some heating of the solution was observed). To this mixture 100 μ L of benzene-*d*₆ was added to achieve deuterium lock, and after 15 min, 1000–2000 scans of proton-decoupled ¹³C

spectra were accumulated. Low-temperature spectra were recorded in the same way except that the NMR probe was cooled down by means of a cold nitrogen gas stream.

Synthesis of Compound 10. 1-Formylmorpholine (1.4 mmol, 0.14 mL) (**5**) was added to 2 mL of a 0.7 M lithium morpholide THF solution at room temperature. Most of the THF was then distilled under reduced pressure, and after a couple of hours at -20 °C white crystals appeared. The remaining solvent was syringed, and the precipitate was dried under vacuum for 2 h.

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