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Aggregation Studies of Lithium Dialkylamides. The Role of Aggregates in the Carbonylation Reaction

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^{13}C NMR spectroscopy and isotopic exchange in carbonylation intermediates have been successfully employed to characterize aggregation of lithium dialkylamides in THF solution. It is shown that lithium (3-oxapentamethylene)amide forms a 1:1 mixed aggregate with morpholine. The aggregate remains even in diluted THF solution. Lithium pentamethyleneamide also forms aggregates with piperidine while the less acidic amines do not form mixed aggregates with the corresponding lithium dialkylamide either in the solid state or in THF solution. The product composition in the carbonylation reaction of lithium dialkylamides is highly dependent on their aggregation states, and this phenomenon can be successfully used for synthetic purposes.

Introduction

Recent research affords evidence that lithium dialkylamides exist as aggregates (mainly in the form of cyclic dimers),[1-4] as mixed aggregates (with lithium bromide,[5] or with donor bases[6,7]), and as di- or trisolvated aggregates[8,9] as well as monomeric forms.[10,11] There is a growing recognition that the various aggregation states play a fundamental role as determinants of organolithium selectivity and reactivity,[1-4] but there are still only a few examples in which aggregation and solvation states of organolithiums have been determined in solution. Most of the current understanding of dialkylamide solution structures relies heavily on analogy with solid-state structures[2-4,10,12-14] or with solution structures of related N-lithiated species.[2d,5,15-17] However, a clear definition of the degree of aggregation of the reagent is relevant to reactivity and mechanistic studies, and some direct determinations of lithium dialkylamide solution structures have been achieved.[1,12,18,19]

In the carbonylation of lithium dialkylamides in THF, we have shown that the presence of free amine[20,21] as well as of HMPT[20,22] plays an important role in determining the reaction product composition. The present paper describes some ^{13}C NMR spectroscopic, carbonylation, and isotopic exchange studies. These, together with previous acidity–basicity determinations in THF,[23] contribute to the understanding of the structures of the reagents in solution and suggest structures for the reaction intermediates.

Results

When a lithium dialkylamide is mixed with a secondary amine an equilibrium shown by eq 1 is established:[24]

$$R^1R^2NH + R^3R^4NLi \rightleftharpoons R^1R^2NLi + R^3R^4NH \qquad (1)$$

In the present paper, several amine–lithium amide equilibria, involving the amines morpholine, **1a**, pyrrolidine, **1b**, piperidine, **1c**, dibutylamine, **1d**, diisopropylamine, **1e**, isopropylcyclohexylamine, **1f**, and dicyclohexylamine, **1g**, were studied in THF at room temperature by ^{13}C NMR spectroscopy.

Table I gathers the ^{13}C NMR shifts for the α-carbon of the amines **1** and the corresponding lithium dialkylamides **2** in THF solution. In all cases, the lithium dialkylamide carbon signals are shifted to lower fields, the effect being

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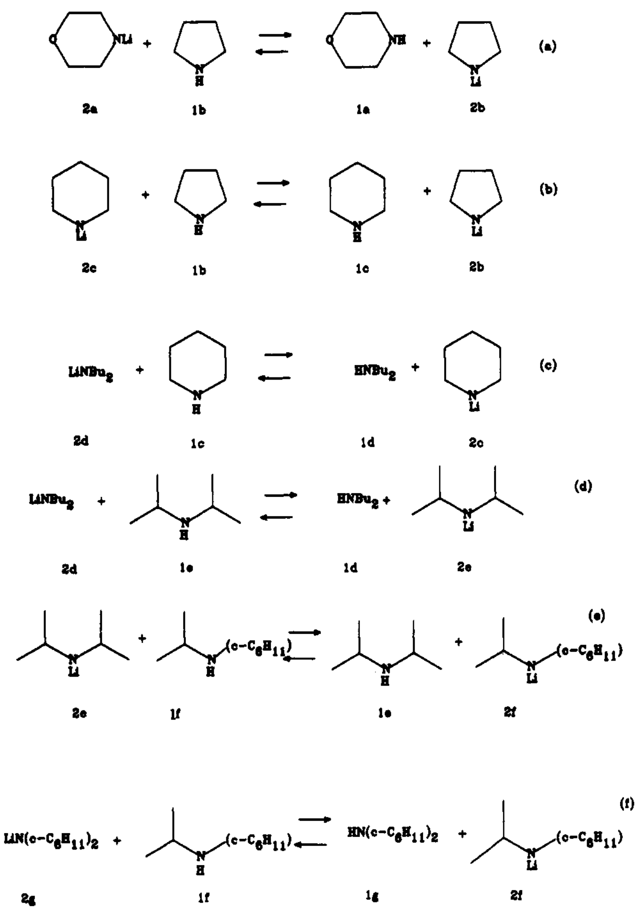


Figure 1. Equilibria of several amine-lithium amide pairs studied by ^{13}C NMR spectroscopy. See the data in Table 1.

Table I. ^{13}CNMR Shifts (ppm) of the α-Carbon of Amines and Lithium Amides in THF. Equilibrium Data for Amine–Lithium Amide Pairs (Figure 1)

system	a	b	c	d	e	f	g
1	48.5	48.7	49.1	51.5	46.8	54.9–46.3	54.5
2	53.5	55.9	55.1	57.5	53.0	63.3–53.1	63.5
(a)	50.9	49.3					
(b)		52.5	50.2				
(c)			53.8	52.8			
(d)				57.5	46.8		
(e)					46.8	54.9–46.3	
					53.0	63.3–53.1	
(f)						63.2–53.2	63.5
						54.9–46.6	54.5

more noticeable for the α-carbon (3–10 ppm). Table I also shows the ^{13}C NMR determinations of the equilibrium position of the exchange reaction depicted in eq 1 for some representative amine–amide pairs. Figure 1 shows the specific equilibria studied. The ^{13}C NMR shifts observed for each pair in Table I allow an estimate of each equilibrium position and show the following relative acidity order:

$$\mathbf{1a} > \mathbf{1b} > \mathbf{1c} > \mathbf{1d} > \mathbf{1e} > \mathbf{1f} > \mathbf{1g}$$

It was found that when the pK_a < 35 the signals for the amine and the amide coalesce and it is not possible to differentiate them. Otherwise, the intensity of each signal is proportional to the relative amount of each reagent in the equilibrium and the pK_a could be determined. (e.g., **1e**, **1f**, **1g**).[23] Mixed aggregation (i.e., $R^1R^2NLi-R^3R^4NLi$) between both lithium amides present in each determination cannot, in principle, be excluded. But, taking into account the relative acidity and basicity order found, the presumable mixed aggregation would not occur to an appreciable extent in the H–Li exchange equilibria shown in Figure 1. The only cases in which both amides are present in observable amounts in the equlibrium are those shown in Figure 1e and f; Table I indicates that the chemical shifts observed in those cases are the same as those determined for the free amines (**1f**, **1g**) and the lithium amides (**2f**, **2g**), respectively. The basicity of the same amines in THF solution was previously determined by measurements of the ion-pair formation between the amine and 2,4-dinitrophenol.[23] The following order holds: **1b** > **1c** > **1d** > **1e** > **1f** > **1g** > **1a**.

Table II. Reaction of Lithium Dialkylamides with Carbon Monoxide at 0 °C. Relative Yields of the Three Main Carbonylation Products

			yield (%) of products		
amide	solvent	[1]:[2]	4	5	6
2d	THF	0.8	15	79	6
	THF	0.2		15	85
	THF–HMPT (1:1)	0.8		100	
2g	THF	0.8	31	57	12
	THF	0.2		10	90
	THF/BrLi	0.8	91	8	1
	THF–HMPT (1:1)	0.8	7	88	5
2f	THF–hexane (5:1)	0.8	66	30	4
	hexane	0.2	12	8	80
	THF–HMPT (1:1)	0.8	8	91	1
2a	THF	*a*	100		
2c	THF	*a*	100		

[a] The yield is independent of the initial free amine content.

It can be observed that **1a** exhibits the greatest acidity but the smallest basicity. This, together with some peculiar behavior in the carbonylation reactions, made us suspect of a special state of aggregation of the lithium (3-oxatetramethylene)amide, **2a**, and of the lithium pentamethyleneamide, **2c**. The other lithium dialkylamides, **2d–g**, most likely exist as dimer aggregates, which form solvates in THF solution (generically named **3**) as previously found for related compounds.[1d]

We have observed that the specific lithium amide behavior against carbon monoxide might provide a useful additional tool for examining the reagent structure in solution. In fact, the carbonylation of lithium amides renders three main products: formamides, **4**, glyoxylamides, **5**, and tartronamides, **6**, depending on the reaction conditions (eq 2).

$$R^1R^2NLi + CO \xrightarrow{H_2O} \underset{\mathbf{4}}{R^1R^2NCOH} + \underset{\mathbf{5}}{R^1R^2NCOCOH} + \underset{\mathbf{6}}{R^1R^2NCOCHOHCONR^1R^2} \quad (2)$$

Table II gathers some interesting effects produced by some complexing agents. First, it can be observed that for the reactions of **2d** and **2g** in THF the [glyoxylamide]:[tartronamide] [**5**]:[**6**], ratio is fully dependent on the [amine]:[lithium amide], [**1**]:[**2**], ratio. The yields of **5** and **6** are competitive depending on the amount of amine present for the reactions of **2d** and **2g** (for more details on the reaction of **2d** see also Figure 1 in ref 20), while the reactions of **2a** and **2c** are insensitive to the presence of free amine. On the other hand, in the reactions of **2d**, **2f**, and **2g** the presence of HMPT improves the conversion to glyoxylamides **5**. Finally, it can be observed in Table II that carrying out the reaction of **2g** in the presence of LiBr affords an excellent yield of *N,N*-dicyclohexylfor-

Table III. ^{13}C NMR Shifts of the α-Carbon of Lithium (3-Oxatetramethylene)amide, 2a, and of Lithium Pentamethyleneamide, 2c, as a Function of the Free Amine Content, [1], in THF[a]

A.	[1a], mmol/mL	0.0	0.15	0.30	0.70	1.5
	δ (ppm)	53.5	51.0	50.2	49.1	48.6
B.	[1c], mmol/mL	0.0	0.70	1.7	4.4	
	δ (ppm)	55.9	53.5	51.8	50.1	

[a] $[1a]_0$ = [BuLi] = 0.33 mmol/mL; $[1c]_0$ = [BuLi] = 1.33 mmol/mL.

mamide, **4g**. On the contrary, addition of LiCl has no noticeable effect on the reaction. No changes in the complete conversion of **2a** and **2c** to the corresponding formamides, **4a** and **4c**, were observed by addition of HMPT or LiBr to the reagent solution prior to carbonylation.

Considering the relative acid-base properties discussed above, and the peculiar behavior of these lithium amides in the carbonylation reactions, formation of (amine$_x$·lithium amide$_y$) solvates was presumed for amides **2a** and **2c**. To examine this assumption the following experiments were carried out.

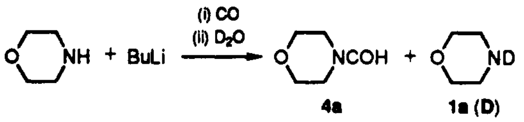
(A) Different amounts of morpholine **1a**, were added to aliquots of standard solution of lithium (3-oxapentamethylene)amide, **2a**, in THF and the ^{13}C NMR spectra determined. It can be observed in Table IIIA that on addition of **1a** the signal shifts to higher fields up to the pure morpholine value.

(B) To avoid the formation of (amine$_x$·lithium amide$_y$) crystals, **2a** was prepared by adding **1a** to a great excess of a solution of butyllithium in THF. The observed shift (δ 56.5 ppm) is higher than the value observed when **2a** is prepared with equimolar amounts of **1a** and butyllithium (δ 53.5 ppm, Table I (**2a**) and Table IIIA).

(C) A similar study was carried out with lithium pentamethyleneamide, **2c**, in THF, and the results are gathered in Table IIIB. Again, a shift to higher fields is observed as the amount of amine is increased up to the value of pure piperidine. "Pure" **2c** prepared with great excess of butyllithium in THF exhibits a lower field α-carbon ^{13}C NMR signal (δ 57.3 ppm) than that shown in Table IIIB or in Table I for **2c**.

(D) To examine the possibility that the higher shift was the result of an amide–butyllithium complex in excess of butyllithium, **2a** was prepared with equimolar amounts of **1a** and BuLi and then worked up as described, but twice the amount of BuLi in THF was added to the **2a**–THF solution immediately before carrying out the ^{13}C NMR determinations. The observed chemical shift was δ 53.5 ppm.

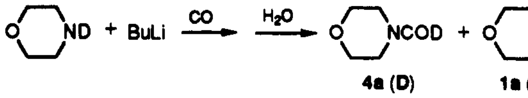
Isotope Exchange Reactions. Isotope exchange is successfully used in this type of compound to confirm structures.[2a,b,19,25–29] In the present study, isotopic exchange in the carbonylation reactions of lithium dialkylamides afforded additional evidence on their aggregation states in solution. Once CO absorption was complete, the reaction mixtures were quenched with heavy water: the results found for lithium (3-oxatetramethylene)amide, **2a**, are shown in eq 3. It can be observed that nondeuterated



(3)

(3-oxatetramethylene)formamide, **4a**, is obtained together with a nearly equimolar amount of deuterated morpholine, **1a(D)**.

On the contrary, the carbonylation of **2a** prepared from deuterated **1a**, yields the results shown in eqs 4 and 5. It



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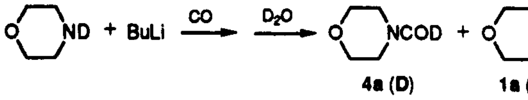


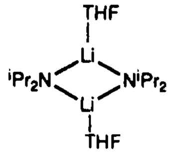
(5)

can be observed that deuterated (3-oxatetramethylene)-formamide, **4a(D)**, is isolated even after hydrolysis with water (eq 4). In this case, an equimolar amount of morpholine, **1a(H)**, is obtained, while treatment with heavy water renders deuterated morpholine, **1a(D)** (eq 5).

For lithium pentamethyleneamide, **2c**, the carbonylation results may be resumed as follows: (a) A mixture of pentamethyleneformamide, **4c**, and piperidine, **1c** (**1c** in excess) is obtained after hydrolysis. (b) Treatment of the reaction mixture with D_2O gives deuterated piperidine, **1c(D)**, plus a mixture of pentamethyleneformamide, **4c**, and deuterated pentamethyleneformamide, **4c(D)**, in a 2:1 ratio. The other lithium dialkylamides shown in Table II, **2d–g**, render *completely deuterated dialkylformamides*, (e.g., dibutylformamide, **4d(D)**), after hydrolysis of the carbonylation reaction mixture with heavy water.

Discussion

Aggregation States. The noncyclic lithium dialkylamides studied in the present work probably exist in the form of solvated dimer aggregates found for other related compounds.[1d] Thus, for the case of lithium diisopropylamide (LDA), **2e**, Seebach[19] reported that it existed as a 5:1 monomer/dimer mixture in THF at −108 °C; this equilibrium seemed to be confirmed by electrochemical results.[18] However, Galiano-Roth and Collum[1c] have recently reported by ^{6}Li and ^{15}N NMR spectroscopic studies that the only observable form of **2e** over a wide range of concentrations in THF solution is an aggregate which is suggested to be the disolvated dimer, **3e**, which



3e

would agree with X-ray analysis of the solid form.[1c] For lithium isopropylcyclohexylamide, **2f**, Collum and coworkers[1d] have proved that **2f** exists as a 1:1 mixture of stereoisomeric dimers *cis*-**3f** and *trans*-**3f** in THF solution. Snaith and co-workers[12] have shown that the complex ladder structure of lithium tetramethyleneamide, **2b**,

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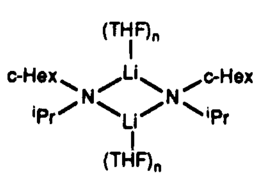
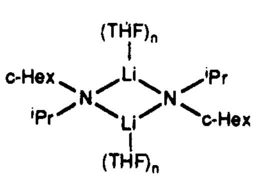


cis-3f



trans-3f

solvated by PMDETA (pentamethyldiethylenetriamine), observed crystallographically, appeared to coexist with a variety of other uncharacterized structural forms in hydrocarbon solutions.

We have recently studied the crystallographic structure of lithium pentamethyleneamide, **2c**, prepared by the same procedure used in the carbonylation reaction[30] (see Experimental Section). It was shown by X-ray diffraction analysis that **2c** forms a 1:1 mixed aggregate with piperidine, **1c**, with four molecules of each reagent forming the aggregate. To our knowledge, this is the first oligomeric 1:1 (amine-Li amide) mixed complex, [(piperidine)$_4$·(lithium pentamethyleneamide)$_4$], described. The only (amine·lithium amide) crystal structure we are aware of is that of the monomeric [Ph(2-Pyr)NLi)·(HN(2-Pyr)Ph)·(HMPA)], although there is an extra HMPA donor ligand.[32] Very recently, the crystal structure of a sodium imide complexed by a nonmetalated ketimine in a 4:2 ratio has been published.[31,32] The solid crystals of the [(piperidine)$_4$·(lithium pentamethyleneamide)$_4$] show the ladder structure previously described by Snaith and co-workers[12] for **2b**.

The results observed in the carbonylation reactions of lithium (3-oxatetramethylene)amide, **2a** (Table II), and of lithium pentamethyleneamide, **2c**, as well as the spectroscopic studies described in the present work, suggest that these amides form mixed aggregates with the corresponding amines even in THF solution. In fact, Figure 2 shows the plot of the ^{13}C NMR shift of the α-carbon of **2a** as a function of the morpholine content assuming that **2a** crystallizes as an (amine$_n$·lithium amide$_n$) aggregate, **7a**; a constant decrease is observed until the value of pure **1a** is reached. The chemical shift for "pure" **2a** (free from morpholine) could be obtained from the plot, by extrapolation to [morpholine] = 0. The extrapolated value coincides with the experimental shift of "pure" **2c** prepared in excess of butyllithium. It appears to us that the high acidity of **1a** and the presence of an oxygen atom contribute to the formation of intraaggregate hydrogen bonds that should remain even in solution since **2a** is scarcely soluble in THF (Figure 2).

Similar results are obtained for **2c**. Figure 3 shows the plot of the ^{13}C NMR shift of the α-carbon of **2c** as a function of the piperidine content, considering that **2c** crystallizes as an (amine$_n$·lithium amide$_n$) aggregate. It can be observed that the same (experimental) value obtained for "pure" **2c** (free from piperidine) results from the plot by extrapolation at [piperidine] = 0. In this case, it is likely that $n = 4$, as it was found in the solid structure.

The carbonylation reactions of **2a** and **2c** are useful to show the existence of amine–lithium amide mixed aggregates and how these affect reactivity. In fact, formation of the several reaction products observed in Table II for the reaction of the other lithium dialkylamides, **2d–2g**, arises from further reaction of the first *carbamoyl* intermediate. The observed yields show that the reactions of the intermediates are highly sensitive to the presence of the several complexing agents. We have previously shown[20] that the precursor for the substituted formamides is the corresponding dialkyl urea dianion, **10**, and not the substituted carbamoyl, as it had been proposed before.[33]

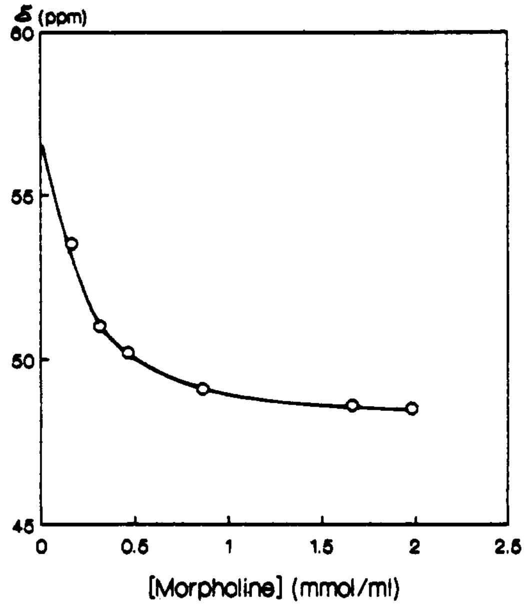


Figure 2. ^{13}C NMR shifts of lithium (3-oxatetramethylene)amide, **2a**, as a function of the morpholine content, **1a**.

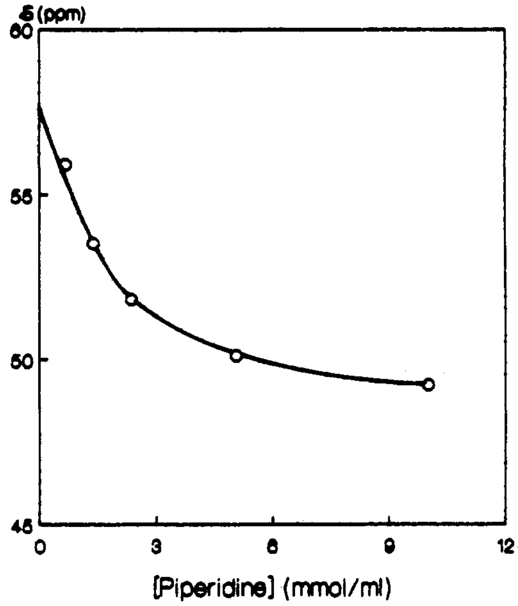


Figure 3. ^{13}C NMR shifts of lithium pentamethyleneamide, **2c**, as a function of the piperidine content, **1c**.

On the contrary, the results observed for the reactions of **2a** and **2c** can be easily explained by the presence of an (amine$_n$·lithium amide$_n$) aggregate, **7**. Proton transfer from morpholine that is present in complex **7a** (for simplification it is assumed $n = 1$), to the carbamoyl moiety in **8a**, gives **9a**, previous to the heavy water quenching

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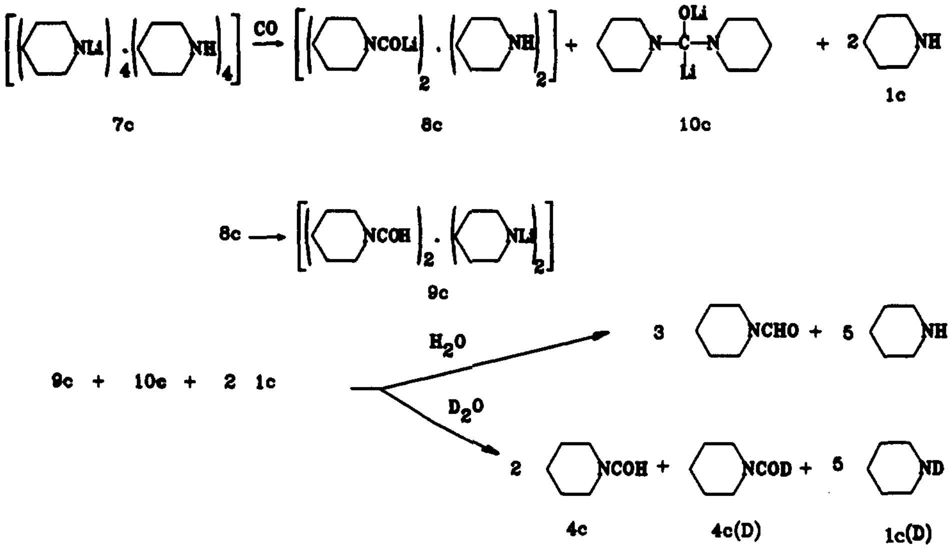
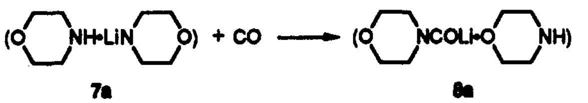
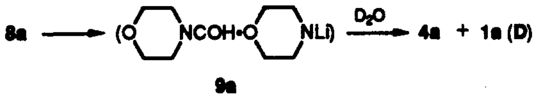
Scheme I



(eqs 6 and 7). Complexation of the resulting lithium (3-oxapentamethylene)amide in aggregate **9a** would prevent its further carbonylation.



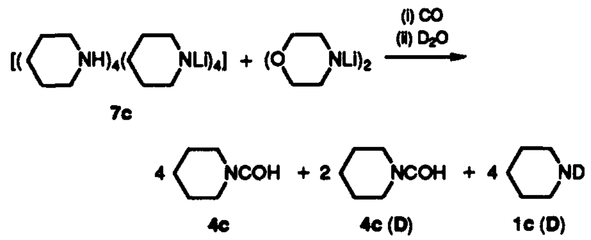
(6)



(7)

Seebach[2a,19] observed a similar phenomenon in the hydrolysis with D_2O of some lithium enolates generated from lithium diisopropylamide. The low deuteration (<20% D) was ascribed to the formation of complexes between the enolates and the amine that favors proton transfer to the lithium enolate before hydrolysis. In the present case, the only proton donor present is **1a**, whereas in the carbonylation of, e.g., lithium dibutylamide, **2d**, hydrolysis with heavy water renders completely deuterated dibutylformamide, **4d(D)**. These results are consistent with the relative "acidity" order mentioned before.

For the case of lithium pentamethyleneamide the assumption of a mixture of: a 1:1 mixed aggegate, **7c**, with a THF solvated lithium pentamethyleneamide dimer, **3c**, as could be suggested by the deuteration results, does not fit the experimental data. If that were the case, hydrolysis after carbonylation should render an excess of the formamide, **4c**, relative to **1c**, as given by eq 8, and not the contrary as it was observed.



(8)

The solid structure of **2c** shows two lithium amides located very close to two piperidine molecules, while the other two lithium amides are not solvated.[30] If a similar structure remains in solution, a reasonable explanation for all the experimental results could be that shown in Scheme I. The piperidine molecules near the lithium amides should quickly transfer a proton to each carbamoyl moiety once they form, giving the complex **9c** and thus preventing further reaction. The other two lithium amides should give the expected intermediate **10c**. The products formed after hydrolysis account for the carbonylation result (a) and for the deuteration result (b) if the workup is carried out with heavy water. Preliminary observations in alternative treatments (oxidation and addition reactions) of the carbonylation mixture before quenching are consistent with Scheme I.

Conclusions. The ^1H and ^{13}C NMR spectroscopic as well as isotopic exchange and complexing effects of different added agents in the carbonylation of lithium dialkylamides demonstrate the presence of different states of aggregation. The results indicate that lithium (3-oxatetramethylene)amide and lithium pentamethyleneamide form (amine$_n$·lithium amide$_n$) aggregates which remain even in THF solution. A strong influence on reactivity and carbonylation reaction products is observed: the shown mixed aggregation leads to the complete conversion of those lithium amides to substituted formamides after carbonylation. The other noncyclic lithium dialkylamides studied show a behavior consistent with previously observed solvated dimer aggregates.

Experimental Section

All reactions involving organolithium reagents were carried out by using standard techniques for the manipulation of air- and water-sensitive compounds.[34] NMR spectra were recorded on a Varian XL-100 spectrometer. Mass spectra were recorded on a Varian Mat CH-7A spectrometer equipped with a Varian Mat Data System 166 computer.

Solvents and Reagents. THF was first passed through a column of alumina, then stirred over sodium hydroxide pellets for several days, and then refluxed over sodium benzophenone ketyl until a dark blue solution was obtained and distilled. It was redistilled from dark blue solutions of benzophenone ketyl under nitrogen immediately prior to use.

Amines. Commercial dialkylamines were left over sodium strings for several days and then refluxed and distilled over sodium immediately prior to use.

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(34) Shriver, D. F. *The Manipulation of Air Sensitive Compounds*; McGraw-Hill: New York, 1969; Chapter 7.

n-Butyllithium. Lithium wire (1.35 g, 193 mmol) was cut in small pieces into a flask containing boiling hexane (80 mL), the flask was capped with a non-air stopper, and kept at 50 °C. Butyl chloride (10 mL, 96 mmol) was syringed in small aliquots into the flask during 3 h and the mixture left to react for 1 h at 50 °C.[35]

Lithium Amides. Cooled (0 °C) *n*-BuLi (2.5 mL, 0.8 M in hexane) was syringed into a tube under nitrogen atmosphere, and the freshly distilled amine (2 mmol) was added. The white lithium amide precipitate was worked up as previously described.[20] For the case of lithium isopropylcyclohexyl- and diisopropylamides, which are soluble in hexane, the solvent was distilled at reduced pressure through a cannula. The resulting syrup was dissolved in THF. To obtain "pure" *amine-free* lithium (3-oxapentamethylene)amide, **2a**, and lithium pentamethyleneamide, **2c**, *n*-BuLi in hexane (5–8 mmol) was syringed into the tube and the solvent vacuum pumped. The resulting syrup was dissolved in THF and the amine (2 mmol) added. After vigorous shaking the resulting solution was used immediately.

Reaction of Lithium Dialkylamide with CO. General procedure: A round-bottomed flask containing a Teflon-coated stirring bar was heated in a vacuum oven at 130–150 °C for at least 30 min and then cooled in a dried nitrogen atmosphere. Ligroin (3–4 mL) was added and heated to boiling until almost complete evaporation occurred. With the remaining ligroin still boiling, the flask was capped with a non-air stopper, and it was left to cool at room temperature and then put into an ice bath with vigorous magnetic stirring. A lithium amide solution (0.5 M) in THF (7–8 mL) containing free amine in a ratio [amine]:[lithium amide] = 0.8 was added by cannula (when necessary the cosolvent and/or the lithium salt was then added), and the stirred solution was exposed to carbon monoxide at ca. 1013 mbar. The bulk of the carbon monoxide was absorbed within the first 3–4 min, and the gas absorption was over in 10–15 min. Once the reaction was completed, H_2O (O_2 free) was added and the remaining carbon monoxide evacuated, and THF (10 mL) and then $NaHCO_3$ (500 mg, 6 mmol) were added; after careful mixing, the organic phase was quantitatively analyzed by GLC.

GLC determinations were carried out on a 5830 Hewlett-Packard or a 2000 Konic gas chromatograph. Operative conditions depended on the sample: for samples derived from **1a** and **1c** a NPGS column and a 70–180 °C temperature program were used, while GLC determinations for samples derived from the other amines were carried out using a OV 101 column and a 70–270 °C temperature program.

^{13}C NMR Determinations. The chemical shifts (C1 of the THF signal as reference) and the intensities (naphthalene as internal standard) of the carbon α to the nitrogen signals were examined. 2 mmol of lithium amide and 1.5 mmol of naphthalene were dissolved in THF (1 mL). 0.4 mL of this solution was syringed into a vacuum-pumped NMR tube capped with a non-air stopper. Benzene-d_6 (0.14 mL) was added and the tube pressure compensated with dried nitrogen.

Deuterolysis. The standard carbonylation procedure was followed, but hydrolysis with D_2O was carried out instead. A 1-mL portion of the solution was syringed into a NMR tube capped with a non-air stopper under nitrogen atmosphere, the THF distilled at reduced pressure, and the resulting solid dissolved with Cl_3CD. The extent of deuteration was determined in each case by comparison with the NMR and GC–MS spectra determined after hydrolysis with water.

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[35] Nudelman, N. S.; Vitale, A. A. *Org. Prep. Proc. Int.* 1981, *13*, 144.