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The role of complexes in defining organometallic reaction mechanisms

Norma Sbarbati Nudelman

Depto. Quimica Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pab. II, P. 3, Ciudad Universitaria, 1428 Buenos Aires, Argentina.

Abstract: The strategic tool of homo- and hetero-aggregates in the reactions of organometallic compounds involving C-Li, N-Li, C-Sn(IV) and C-Cr(III) is described. In the carbonylation of lithium amides complexation with different agents leads the reactions toward the synthesis of several carbamoyl compounds in good to quantitative yields. *Hetero-aggregates* of cyclic dialkylamides with hydrogen-bond donor persist even in solution giving rise to unusual results, the study of their reactions with dialkylformamides afforded a methodology for the synthesis of the first adduct *amide-lithium amide*.
The study of the reaction of benzaldehyde with Li metal allowed characterization of the species formed on the surface of the Li metal, which can serve as a model for the Fischer-Tropsch reaction. The rate coefficients of the different steps in which each species is involved were determined. The *tandem* reaction of E-cynnamaldehyde with PhLi, followed by nucleophilic addition on the β-carbon affords a useful methodology for the preparation of β-alkyl substituted dihydro-chalcones. Complexation by the dimeric PhLi is the responsible for the unusual mechanism that give rise to stereoselective β-addition.
The inhibiting effect of CO in the reactions of trialkyltins with electrophiles indicates that the first step is an electron transfer. On the other hand, complexing of heterosubstituted alkyl tins with Cu(I) catalysts is an useful substitute of Pd catalysts for the Stille coupling reaction with alkyl halides. The beneficial effect of complexes of Cr(III) for the selective alkyl addition to α,β-unsaturated aldehydes is also discussed.

INTRODUCTION

Organometallic compounds are an exciting, yet complex class of compounds. This complexity is the responsible for specific features in each compound, making it unique for the desired targeted transformation. It is being increasingly recognized that, besides structure, aggregation effects, complexation with non-participating ligands, with solvents and co-solvents, catalysts, and with Lewis bases determine not only the reactivity but, very often, the regio- and stereochemistry of synthetically important reactions.

There are abundant reports on the solid structure of complexes of organoalkali metal compounds, and increasing research on their structures in solution, specially in ethereal solvents. On the other hand the stuctures of other complexes of organometallic compounds have not been so intensively studied.

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Very often, more than one structure can be found in solution; moreover ligands are often flexible, prone to disorder and displacements of several kinds.

The knowledge of the specific reagent structure and that of the different reaction intermediates is dramatically helpful to tune up the reaction to the desired goal. In this paper, some examples are described involving organolithium, organotin and organochromium complexes, where mechanistic studies of the different reaction pathways allow for the prediction of complex structures such as aggregates and mixed complexes with Lewis bases, solvent, ligands, etc., which play a remarkable rol in determining the outset of the reaction.

COMPLEXES INVOLVING N-Li BONDS

The first example to be discussed is the reaction of dialkyllithium amides with CO. The carbonylation of organolithium compounds is a useful method for the synthesis of several highly functionalized compounds as well as for the preparation of synthetic intermediates (1). In particular, the carbonylation of dialkyllithium amides in THF solution, renders three main compounds: formamides, **3,** glyoxylamides, **4**, and tartronamides, **5** (eq. 1) (2).

$$R^1R^2NLi + CO \rightarrow R^1R^2NCOH + R^1R^2NCOCOH + R^1R^2NCOCHOHCONR^1R^2 \quad (1)$$

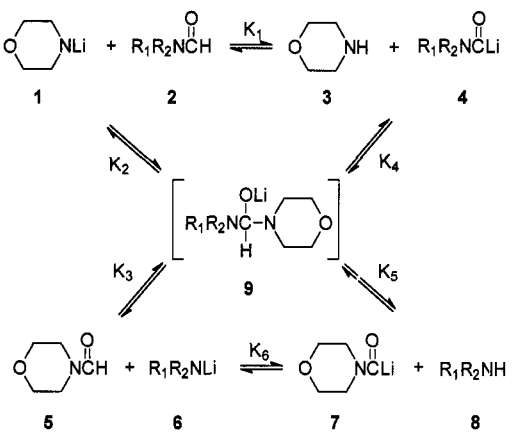
The aggregation states of lithium amides is a subject of intense research at present, (3,4). Our results show that the rate of reaction, as well as the product distribution, are greatly dependent on the state of aggregation of the reactant and by the presence of hydrogen-bonded Lewis bases. By modification of the homo- and mixed-**aggregates** the reaction can be led to the formation of specific products, useful for the synthesis of *fine chemicals*. The effect of different reaction conditions was studied to afford only one of the three products in satisfactory yields. To favor the reaction toward formamide an interesting effect of lithium bromide as a complexing agent was observed: under these conditions, complexation prevents further reaction of the first intermediate and the reaction provides a satisfactory method for the synthesis of the corresponding *formamide* in very good yield (5). On the other hand, running the reaction in the presence of a hydrogen-bond donor (like the free amine) provokes the hydrogen transfer to the second intermediate, giving the *dialkylsubstituted glyoxylamide* in almost quantitative yields (6). The substituted *tartronamides* can be produced under conditions that allow the coupling between the first and second intermediate. Finally, a very useful methodology for the preparation of substituted *ureas* was developed by the oxidative carbonylation of lithium dialkylamides (7).

By the contrary, the reaction of lithium cyclic amides is insensitive to the reaction conditions yielding only the corresponding substituted dicycloalkylformamide, regardless of the presence of complexing additives. Formation of a strong mixed aggregate during the synthesis of the reagent, that remains even in THF solution, was proposed on the basis of the carbonylation results, and the structural characterization of the lithium piperidide (LiN) showed that it was a mixed tetramer containing four units of LiN and four piperidine (HN) molecules: $(LiN)_4.(HN)_4$ (8).

Equilibrium between complexes.- The dramatic role of the complexes in defining the reaction pathways, suggested to us the possible existence of a complex scheme of equilibrium in the reaction mixture. To simulate intermediate states the reaction between lithium morpholide and several dialkylformamides was further studied. 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. GC analysis of the reaction mixtures showed the presence of the corresponding two amines and two formamides as if a simple equilibrium between the four species would had been established (9). Nevertheless, the fact that the morpholine-derived formamide was formed from any of the starting alkylformamides indicates the presence of an interesting series of equilibria among different species, which can be represented as shown by Scheme 1. Although the compounds are written as monomers for the sake of simplicity, all the lithium species involved are aggregated species. In fact, we have recently shown the formation of a mixed aggregate of lithium piperidide-piperidine (8) and the lithium morpholide (LiM) shown in the Scheme 1, is also a 1:1 mixed agreggate:LiM-morpholine.(HM) (see the reactions below).

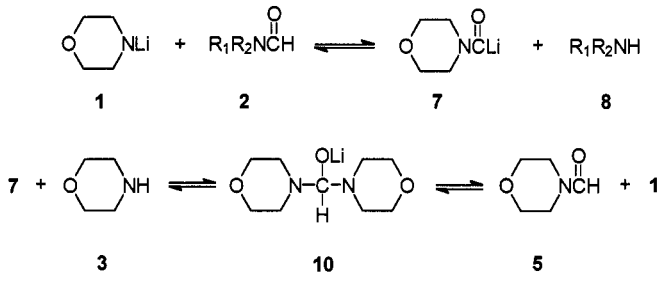
The equilibrium composition of the different reaction mixtures in THF was studied by ^{13}C NMR (7). Recently, we have shown that due to the high acidity of morpholine, the equilibrium K_1 (Scheme 1) is far on the left side. Therefore, **3** and **4** are minor components, and consequently, the equilibrium involving K_1 and K_4 are not significant. Upon hydrolysis, the amides and carbamoyl "anions" present in solution are converted into the corresponding amines and formamides. 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.



Scheme 1

The ^{13}C-NMR spectrum of the reaction mixture of lithium morpholide with N,N-dibutylformamide, **1+2a** 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 labeled A-C in the spectrum. These signals, A-C, are also seen in the NMR spectrum of a mixture of **1+2b**, and of **1+5** in addition to the peaks due to the amines. In these compounds Li is most likely closer to oxygen than to any other atom and thus not coupled to ^{13}C. In the case of the N,N-tetramethyldiaminoalkoxyde 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) (10).

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 descendance, like an adduct **10**, formed by further reaction of **7** with morpholine which is present in the reaction mixture (see Scheme 2).



Scheme 2

Calculation of the ^{13}C NMR shifts of **9** and **10** by means of commercial software are in reasonable agreement with the experimental results. Compound **10** could be synthesized and the ^{13}C NMR showed signals A-C. In conclusion, it is shown by protonation reactions and NMR investigations that the equilibrium involving lithium morpholide (**1**) and N,N-dibutylformamide (**2a**) or 1-formylpiperidine (**2b**) are first shifted towards 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_2NLi has not been characterized before. Related adducts have been proposed as transient likely intermediates in reactions of amides and esters with metalated nucleophiles.

COMPLEXES INVOLVING C-Li BONDS

The Reactions of Benzaldehyde with Li metal :

There is an increasing interest in the study of the mechanisms by which reactions with alkaline and earth-alkali metals occur. The mechanism of formation of Grignard reagents (11) and the very well known Fisher-Tropsch process (12) are just two examples related to the present work. We have recently provided substantial evidence that the first step of the complex mechanism of the solution reaction of phenyllithium with CO is *electron transfer* from PhLi to CO (13). The mechanistic study of the reduction of benzaldehyde by lithium metal shows evidence for a common radical intermediate for both reactions. Benzyl alcohol was the main product, and the rate of formation of this and the other side products, namely: benzoin and benzil, was studied (eq.2).

$$\mathbf{PhCHO + Li \dashrightarrow PhCH_2OH + PhCOCHOH\,Ph + PhCOCOPh} \qquad (2)$$

evidence for a radical intermediate was gathered by esr and be trapping with carbon tetrachloride and with CO. The esr spectra at the end of the reaction was coincident with that of benzil radical, independently prepared. Ingold et alia (14) have recently measured the reaction of benzoyl with CCl_4., in the present case, the presence of the benzoyl radical was proved by running the reaction in the presence of CCl_4. (see eqs. 3-5). Since the main reaction product is benzyl alcohol, the benzoyl chloride initially formed, reacts with the benzyl alcoxide anion giving the benzyl benzoate, while quenching the reaction with acetic anhydride produces de corresponding acetate.

$$\mathbf{PhCO^{\cdot} + CCl_4 \longrightarrow PhCOCl + {}^{\cdot}CCl_3} \qquad (3)$$

$$\mathbf{PhCOCl + PhCH_2O^{-} \longrightarrow PhCO_2\,CH_2Ph + Cl^{-}} \qquad (4)$$

$$\mathbf{PhCH_2O^{-} + (CH_3CO)_2O \longrightarrow CH_3CO_2CH_2Ph} \qquad (5)$$

The kinetics of the reaction at different temperatures shows a sigmoid behaviour which is consistent with surface effects at the onset of the reaction. This is interpreted as an adsorption on the lithium metal surface as the first step. The complete reaction Scheme is shown below, and all the partial rate coefficients for the several steps were determined. The experimental results are clear regarding the influence of the adsorption effects: the strong interaction between the adsorbate and the metal causes the formation of a layer at the metal surface. This causes the presence of reactant species at (or close to) the metal surface in relative amounts higher than the bulk concentration. At the same time, the energetics of the reaction of adsorbed species may be different from those of the dissolved species, and finally there is the problem of forming a blocking layer on the metal surface.

$$\mathbf{PhCHO + Li} \xrightarrow{k_1} \mathbf{PhCHO/Li}$$

$$\mathbf{PhCHO/Li} \xrightarrow{k_2} \mathbf{[(PhCHO)^{\cdot -}, Li^+]}$$

$$\mathbf{PhCHO + (PhCHO)^{\cdot}} \xrightarrow{k_3} \mathbf{PhCH_2O^- + PhCO^{\cdot}}$$

$$\mathbf{2\ PhCO^{\cdot}} \xrightarrow{k_4} \mathbf{PhCOCOPh}$$

$$\mathbf{PhCOCOPh + Li} \xrightarrow{k_5} \mathbf{[(PhCOCOPh)^{\cdot}\ Li^+]}$$

$$\mathbf{(PhCOCOPh)^{\cdot} + PhCHO} \xrightarrow{k_6} \mathbf{PhCOCOHPh^- + PhCO^{\cdot}}$$

$$\mathbf{PhCO^{\cdot} + (PhCHO)^{\cdot -}} \xrightarrow{k_7} \mathbf{PhCOCOHPh^-}$$

$$\mathbf{SH + (PhCHO)^{\cdot}} \xrightarrow{k_8} \mathbf{PhCH_2O^- + S^{\cdot}}$$

Scheme 3

According to the observed results, adsorption of benzaldehyde would seem to be a pre-requisite for rapid electron transfer (as in electrocatalysis) and is probably responsible for the "lag" or induction period. Consistent with this is the fact that the "sigmoid" curve is more pronounced at lower temperatures, with a reduction in the lag as the temperature increases.

The Reaction of Phenyllithium with E-cynnamaldehyde:

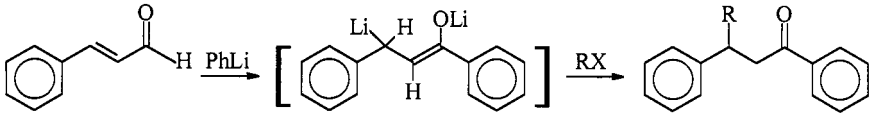
It was usually assumed by synthetic chemists that the "naked" carbanion (the monomer) was more reactive than higher oligomeric states; nevertheless, different complexation effects could lead to a *decrease* in the reactivity of lower aggregates (15). On other cases, the complex-induced proximity effects (CIPE) observed in some conveniently substituted substrates have been successfully used to promote remote directed lithiation, thus providing an expanded synthetic methology for β-substitution (16). In the present case, the aggregation features of the organolithium reagent are conveniently used to promote addition of phenyllithium to *(E)*-cinnamyl aldehyde, **11**, β-lithiation and subsequent electrophilic substitution, thus providing a convenient one-pot one-step methodology for the synthesis of a wide variety of β-alkyl substituted dihydrochalcones, **12** (eq. 6) (17).

A mechanistic study of the addition of phenyllithium to **11**, recently reported (18), showed that the reaction is highly sensitive to the reaction conditions; thus, in THF the *(E)*-1,3-diphenyl-2-propen-1-ol, **12**, is the main product, (yields > 95%) and *(E)*-chalcone, **13**, and *(E)*-1,3-diphenyl-1-propanone, **14**

were found as traces. Nevertheless, by a careful choice of reaction conditions, the product distribution in the reaction mixture can be changed to give a high yield of **14**, the optimum conditions being [PhLi]:[**1**] = 2:1 and 7 h reaction time. Under these conditions a brilliant deep violet solution is formed and **14** is obtained in 97% yield. The precursor of **14** is shown to be a β-lithiated intermediate, since treatment of the reaction mixture with D_2O, gives **14** in 95% yield and 99% d_1

Addition of an electrophile to the reaction mixture, gives the β-substituted dihydrochalcone (eq 6). A wide range of electrophiles have been assayed,. most of these electrophilic substitutions proceed in good yield, giving only one product, the corresponding dihydrochalcone in 77-100% yields.(17) Alkylation can be afforded with alkyl chlorides as well as with bromides; allyl bromide gave a very good yield of product (95%). Benzyl and hindered alkyl bromides, such as *i*-propyl and cyclohexyl, gave also good yields of the β-substituted dihydrochalcone.

No detectable addition to the α-carbon was observed; this fact has received a great deal of interest in



11 **15** **14** (6)

recent years, (18). In light of the different products obtained and the sensitivity to the reaction conditions, a different mechanism is proposed in which the dimer of the reagent is involved is proposed.

Semiempirical theoretical calculations. The optimized geometries and heats of formation for the reactants and intermediates in the reaction of phenyllithium (in excess) with E-cinnamaldehyde, **11**, were calculated by the MNDO and PM3 semiempirical methods.(19) A mechanism is proposed for this unusual reaction in which dimeric phenyllithium is involved; calculations are consistent with that mechanism, and the main transition state of the reaction was located and minimized. Dimerization and solvation energies were calculated as well as heats of formation: a comparison between both semiempirical methods shows that the species are described significantly better by PM3 than by MNDO. Although additional experimental evidence is needed, theoretical calculations on the likely intermediates using dimeric PhLi indicates that **15** is the real transition state for the formation of the precursor of **14** (19).

COMPLEXES INVOLVING C-Sn BONDS

The Reactions of Trialkyltins with Electrophiles. The Complexation Effect of CO

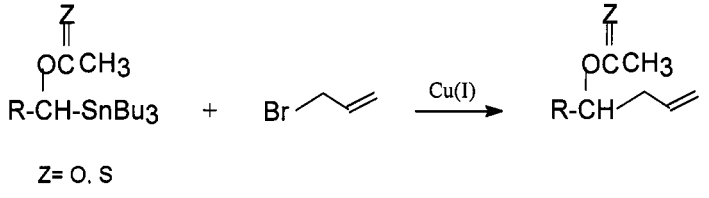
Three basic mechanistic pathways have been proposed for the reaction of alkyl halides with trialkylstannyl alkali-metal compounds: a) a classic S_N2 substitution b) substitution by an electron-transfer (ET)-initiated $S_{RN}1$ process; and c) substitution by halogen-metal exchange. The distribution of products was interpreted as the result of different apportionments between two or three pathways.The present approach is based on the use of carbon monoxide as a good one-electron acceptor, as it has been described in previous studies carried out with phenyllithium (11).

$$Bu_3SnLi + CO \xrightarrow[ET]{k_{CO}} [(Bu_3SnLi)^{+\cdot}, (CO)^{r}] \quad (7)$$

The effects of CO in the reaction of Bu_3SnLi with alkyl halides and aromatic halides in THF at 0°C were examined and a strong inhibition of the reaction was observed. This effect is interpreted as a competition in the first electron transfer step (measured by k_1) in which Bu_3SnLi transfers one electron to the organic bromide, giving a radical cation-radical anion pair. (eq. 7). CO would operate as a good one-electron acceptor competing with the organic halide for the transferred electron. It was observed that for PhBr, in which the radical anion would be more stabilized, the yield of substitution product is higher than for cyclohexyl bromide. The radical ions formed in the first step give the organic free radicals, $R^\bullet$ and $Bu_3Sn^\bullet$ by diffusion out of the solvent cage. $R^\bullet$ reacts with fresh Bu_3SnLi to start the $S_{RN}1$ radical chain. Experiments carried out with radical scavengers confirm the whole reaction scheme (20

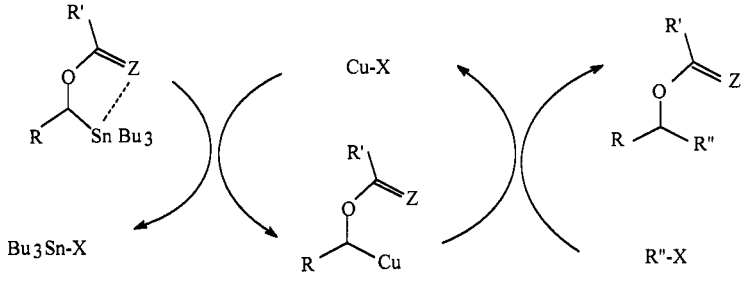
The Reactions of Trialkyltins with Electrophiles. The Complexation Effect of Cu(I)

The effect of Cu(I) catalyst on the coupling of several substituted tributylorganostannanes with allyl halides was studied. Several parameters were examined such as: solvent, temperature, reaction time and concentration of the catalyst. The results show that CuCl could be an effective catalyst and the optimum reaction conditions are: THF, 10 % (mol) of CuCl, 55 °C and 20 hs. of reaction. The presence of an heteroatom (O preferred to S) on the α-C was found to be essential for the reaction to occur under those conditions (eq. 8), (21).



(8)

The effect of Cu(I) as a catalyst in the coupling reactions of organo-tin with electrophiles, could be interpreted as the result of a trasmetalation through an initial complex. The need of an α-heteroatom suggests assistance by the heteroatom Z in the first step of the transmetalation, an oxygen being more effective than a sulfur atom. (Scheme 4)



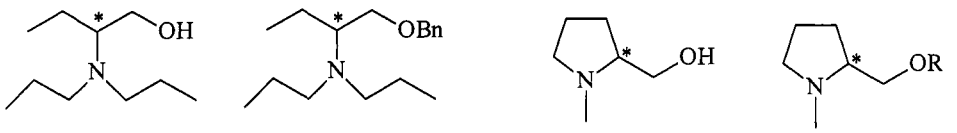
Scheme 4

COMPLEXES INVOLVING C-Cr BONDS

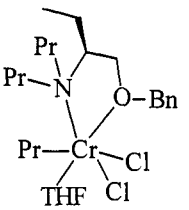
The Reactions of Organochromium (III) complexes with Aldehydes.

Organochromium (III) reagents have the characteristic of selectively adding to aldehydes but normally not to ketones. The reagents $RCrCl_2(THF)_3$,were prepared from $CrCl_3(THF)_3$ and Grignard reagents.

Ketones with a basic group (HO, MeO, Me_2N) in α o β position are alkylated allowing the highly selective alkylation of such ketones in the presence of normal ketones.



The several aminoalcohols and aminoethers shown above, were synthetised as non participant ligands, which could act as chiral ligands inducing enantioselectivity in the final alcohols obtained .



The reaction of monoalkylchromium complexes with prochiral aldehydes in the presence of chiral ligands lead to alcohols with different enantiomeric excess, at the present time we are working on the tune up of this reaction to improve the enantiomeric excess. One of the goals of this work is the synthesis and characterization of a monoalkylchromium (III) – ligand complex, bonded to a chiral aminoalcohol A type compound is shown in which the aminoalcohol is coordinatively bonded to the chromium, generating an asymmetrical complex.

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