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EFFECT OF LITHIUM COMPLEXATION BY 12-CROWN-4 ON THE REGIOSELECTIVITY OF THE ATTACK OF *GEM*-DICHLOROALLYL-LITHIUM ON SOME CARBONYL COMPOUNDS

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Abstract

Substituted benzaldehydes and acetophenone preferentially attack the γ position of *gem*-dichloro allyl anion, but show a significantly increased α-selectivity if 12-crown-4 is present. This behaviour is discussed on the basis of theoretical computations.

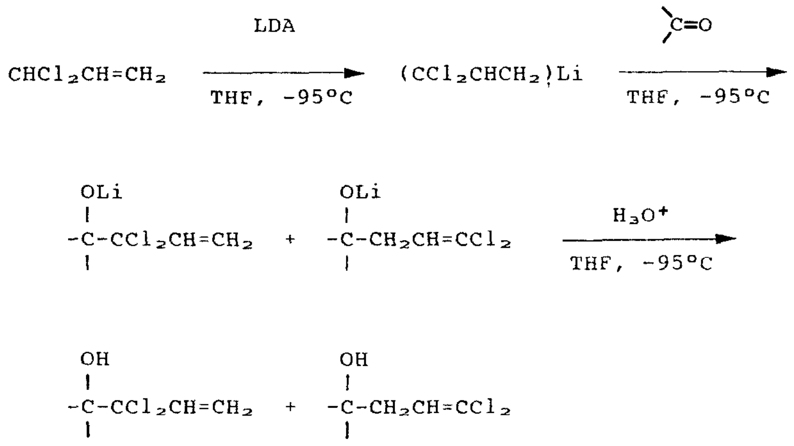
Introduction

Gem-dichloroallyl-lithium was prepared by Seyferth and coworkers[1] exploiting the reaction of *n*-butyllithium with $Ph_3PbCH_2CH=CCl_2$; its reactions with metallic and metalloidal halides,[1] and with aldehydes and ketones[2] were also reported. The ambident behaviour of *gem*-dichloroallyl-lithium found in these studies was explained in terms of electronic factors, interpreting the α *vs.* γ regioselectivity on the basis of the HSAB theory,[3] and excluding an important role of steric factors.

The behaviour of closely related systems has also been studied. In particular Seyferth and coworkers discussed in a subsequent paper[4] the complete α regioselectivity observed in the addition reactions of several carbonyl compounds to *gem*-difluoroallyl-lithium. A rationalization of this finding was offered stressing the role of the lithium counter-ion, and arguing that it should preferentially engage the CH_2 terminus, thus preventing an electrophilic attack on the γ position. Mauzé and coworkers, on the other hand, have deeply investigated the reaction of chloroallyl-lithium and *gem*-chloro(methyl)allyl-lithium with different electrophiles.[5]

Different complexing agents have been reported to affect the degree of interaction of several organic anionic species with their counterion.[6] This effect is for instance illustrated by the UV spectra of some fluorenyl salts in solvents where they predominantly exist as contact ion pairs (the addition of increasing quantities of polyglycol dimethyl ethers is shown to favour the formation of separated ion pairs);[6b] similarly, in the case of lithium carbanions derived from methyl benzyl sulfoxide and benzyl phenyl thioether, an increase in conductivity is detected upon the addition of [2.2.2] cryptand, indicating the formation of free ions.[7]

The aim of the present paper is to study the effect of 12-crown-4 on the regiochemical outcome of the reaction reported in the Scheme.



$$CHCl_2CH{=}CH_2 \xrightarrow[\text{THF, }-95^\circ C]{\text{LDA}} (CCl_2CHCH_2)Li \xrightarrow[\text{THF, }-95^\circ C]{>C{=}O}$$

$$\overset{\displaystyle OLi}{-\overset{|}{\underset{|}{C}}-}CCl_2CH{=}CH_2 + \overset{\displaystyle OLi}{-\overset{|}{\underset{|}{C}}-}CH_2CH{=}CCl_2 \xrightarrow[\text{THF, }-95^\circ C]{H_3O^+}$$

$$\overset{\displaystyle OH}{-\overset{|}{\underset{|}{C}}-}CCl_2CH{=}CH_2 + \overset{\displaystyle OH}{-\overset{|}{\underset{|}{C}}-}CH_2CH{=}CCl_2$$

Scheme

An interpretation of these results is also offered in terms of computed structural and electronic features of the lithiated and free anions.

Experimental procedure

All the reactions of *gem*-dichloroallyl-lithium were carried out under argon atmosphere in a flame-dried glassware. THF was distilled from sodium benzophenone ketyl immediately prior to the reaction. Lithium diisopropylamide (LDA), 10% suspension in hexane, was purchased from Aldrich. 3,3-Dichloropropene and 12-crown-4 were stored over molecular sieves. ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer R-24B 60 MHz high resolution spectrometer using TMS as internal standard. The reaction vessel consisted of a 200 ml Schlenk bottle capped with a rubber septum, equipped with a teflon covered stirring bar and connected to an argon line. The apparatus was kept at low temperatures by placing it in a Dewar flask filled with acetone cooled to the freezing point (-95 °C) with liquid nitrogen.

The reactions have been carried out according to an *in situ* procedure,[8] by adding dropwise with a syringe within 1 min, under vigorous stirring, an equimolar mixture of 3,3-dichloropropene and carbonyl compound (dissolved in 1.0 ml of anhydrous THF) to a LDA solution in THF at -95 °C. When 12-crown-4 was present, it was placed first into the cooled reaction flask. The reaction mixture was then stirred for 2 h at -95 °C. After hydrolysis (HCl 0.5N, 15 ml) at that temperature the reaction mixture was allowed to reach room temperature, the organic layer was separated and the aqueous phase extracted twice with diethyl ether. The combined organic phases were washed with water and dried with anhydrous sodium sulphate. The solvent was eliminated under reduced pressure and the crude reaction product was analysed by ^1H NMR spectroscopy, in order to establish the reaction conversion and the $\alpha:\gamma$ ratio. All the reaction mixtures showed ^1H NMR spectra consistent with the assigned structure, the only by-products being the reduction product of the carbonyl compounds.

Theoretical method

The computations reported in the text have been done using the *ab initio* program system GAUSSIAN82.[9] Stable structures corresponding to energy minima have been determined by completely optimizing the geometrical parameters using gradient methods.[10] These optimizations were carried out at the RHF level of theory, using the STO-3G* basis set;[11a,b] the energies of the stable structures and the data reported in Table 3 were recomputed using the 3-21+G(*) basis set.[11c]

Results and discussion

The results of the reaction of *gem*-dichloroallyl-lithium with the tested carbonyl compounds, both in the absence and in the presence of 12-crown-4, are reported in Table 1 and 2 respectively.

Table 1. Observed Regioselectivity in the Absence of 12-Crown-4[a]

Carbonyl Compound	% Conversion[b]	% Yield[c]	$\alpha:\gamma$ Ratio[d]
PhCHO	91	78	7:93
p-$CF_3C_6H_4CHO$	94	73	0:100
p-$CH_3OC_6H_4CHO$	88	88	23:77
$PhCOCH_3$	34[e]	28	50:50

a: Carbonyl compound, 2.5 mmol.; 3,3-Dichloropropene, 2.5 mmol.; LDA, 2.75 mmol.; THF 25.0 ml; T= -95°C.
b: by ^1H NMR, comparing the integration area of the aldehydic proton with that of the olefinic portion of the spectrum, unless indicated otherwise.
c: established from the weight of the collected product on the basis of the conversion.
d: by ^1H NMR on the crude reaction product.
e: by ^1H NMR by comparing the integration area of the $PhCOCH_3$ singlet with that of the corresponding group in the products.

In the absence of 12-crown-4 some preference for the γ attack can be noted; comparable results were obtained and discussed by other authors[2,5] when studying similar reactions. The presence of the complexing agent changes significantly the reaction outcome, with a sharp increase in α selectivity. The role of 12-crown-4 could be twofold: (i) deaggregation of the oligomers (possibly dimers[12]) present in the THF solution; (ii) weakening[13] of the ionic[14] C-Li bond. This action would lead toward a situation describable in terms of lithiated monomers, or even of solvent separated ion pairs; in this case the allylic part of the system would approximate the features of a free anion.

Table 2. Observed Regioselectivity in the Presence of 12-Crown-4[a]

Carbonyl Compound	% Conversion[b]	% Yield[c]	$\alpha:\gamma$ Ratio[d]	12-Crown-4[e]
PhCHO	90	78	61:39	1.5
PhCHO	89	77	73:27	2.0
p-$CF_3C_6H_4CHO$	77	54	59:41	3.0
p-$CF_3C_6H_4CHO$	78	62	47:53	2.0
p-$CF_3C_6H_4CHO$	70	54	39:61	1.0
p-$CH_3OC_6H_4CHO$	95	86	100:0	1.0
$PhCOCH_3$	30[f]	20	100:0	1.0

a: Carbonyl compound, 2.5 mmol.; 3,3-Dichloropropene, 2.5 mmol.; LDA, 2.75 mmol.; THF 25.0 ml; T= -95 °C.
b: by ^{1}H NMR, comparing the integration area of the aldehydic proton with that of the olefinic portion of the spectrum, unless indicated otherwise.
c: established from the weight of the collected product on the basis of the conversion.
d: by ^{1}H NMR on the crude reaction product.
e: equiv. with respect to 3,3-dichloropropene.
f: by ^{1}H NMR by comparing the integration area of the $PhCOCH_3$ singlet with that of the corresponding group in the product.

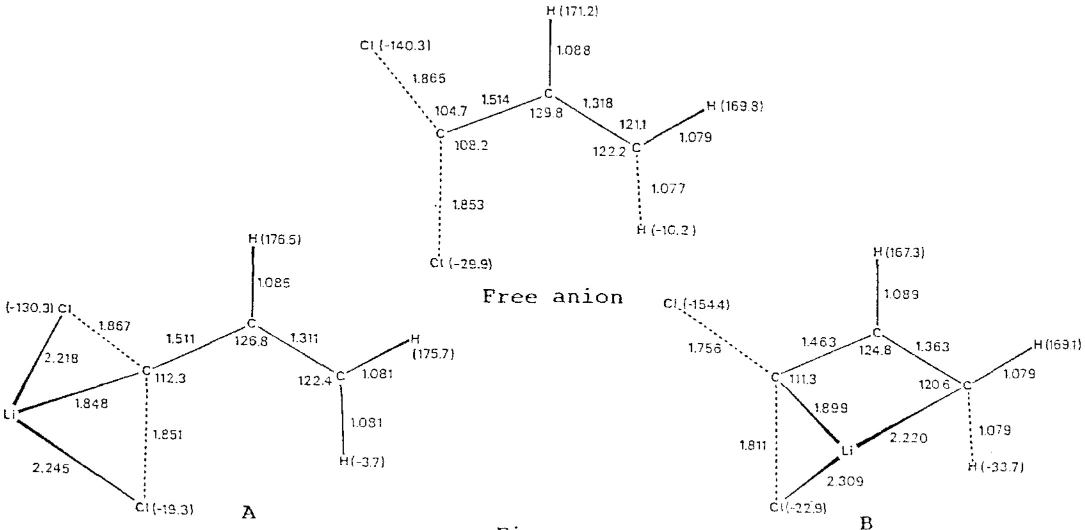
Theoretical computations have been therefore performed both on the free anion and on several lithiated species, in order to provide a description of the situations just discussed. The results show that the free dichloro allyl anion can exist in several different conformational arrangements, of which those having a pyramidalized α carbon are the more stable. This is in contrast with the computed structure of the parent allyl anion, which is planar with a delocalized π system,[15] but reflects the findings of a previous study of the similar *gem*-difluoro anions.[16] The structure of the free *gem*-dichloroallyl anion shows C_α-C_β and C_β-C_γ bond lengths which approximate the typical values of single and double carbon-carbon bonds respectively (Figure).[17] The structural features are consistent both with the charge distribution, which could influence the behaviour of a *harder* electrophile, and with the polarization of the highest occupied molecular orbital (HOMO), to which a *softer* electrophile could be sensitive (Table 3). The electric charge is localized on the CCl_2 group and the $CHCH_2$ group has a polarized double bond. The HOMO is significantly polarized toward the α carbon.

Table 3. Group Charges[a] (Q) and Polarization of the HOMO[b] (P)

Species:	Free Anion	Structure A	Structure B
$Q(CCl_2)$	0.65	0.38	-0.10
$Q(CH_2)$	0.40	0.01	0.23
$P(C_\alpha)$	0.66	0.62	0.51
$P(C_\gamma)$	0.18	0.13	0.18

a: Computed as the sum of the net Mulliken atomic charges, for the atoms belonging to the group.
b: Computed as the sum of the squared HOMO coefficients on C_α and C_γ.

The lithium counter-ion has been found to be associated with the anion preferentially in correspondence to the structures A and B shown below.



Figure

These two structures are of comparable stability. Structure A has a pyramidal α carbon, and two CC bond lengths approximating the typical values of a single and a double CC bond (as in the free anion). The electron distribution is polarized toward the α carbon; the HOMO is polarized in the same way (Table 3). Structure B presents a different situation in that the lithium counter-ion is interacting with both α and γ carbon atoms: this structure, where lithium occupies an almost central position, is closer to that of allyllithium.[18] The electron distribution is slightly polarized toward the γ terminal, while the HOMO polarization favours again the α position (Table 3).

The position assumed by the lithium counter-ion is important because it can interact with the carbonyl oxygen in the transition structure[19] thus favouring an attack onto the closest carbon atom. This factor and the structural features of monomers A and B do not appear to lead to a sharp preference for one of the two positions of attack. The direct interaction of Li with the carbonyl oxygen in Structure A clearly favours an α attack; on the contrary in Structure B the Li position does not appear to be able to discriminate between the two possible attacks. In a similar way the electron distribution is polarized in opposite directions in the two structures. As a consequence of the experimental and theoretical data, a possible rationalization of the clearcut preference for the α attack in the presence of 12-crown-4 is that the crown ether partially cleaves the C-Li bond, leading toward a solvent separated ion pair where the allylic moiety approximates the free anion in geometrical and electronic structure, rather than simply lowering the degree of aggregation; this in turn would imply a less direct role of the lithium cation in affecting the regiochemistry through the geometry of the transition structure.

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