difference in ΔC^β values is attributed to chemical shift averaging in the acyclic systems, which arises from the wider range of spatial positions available to the rotating C^β methyl carbon.

Tables I-III show that ΔC^β and ΔC^γ in each cyclic and acyclic compound containing Gly are greater than ΔC^α and ΔC^δ. This result is apparently general for R = NH_2CHY–, since Gly-Pro, Ala-Pro, Val-Pro, and *t*-Boc-Gly-Pro have essentially equal ΔC^i values (Table III), and shows that the polypeptide ΔC^i values are in accord with chemical shift differences arising from syn and anti geometries, provided that the influence of the carbonyl substituent (-NHCHY-) is considered.[14] Hence, the model systems studied here provide a firm empirical basis for assigning Pro and Hyp resonances to cis and trans isomers on the basis of their ΔC^i values.[15]

(14) These results also show that differences in ring conformations need not be hypothesized to account for the pyrrolidine ΔC^i values. Indeed, the small variation ($\lesssim 0.4$ ppm) of the trans and of the cis Pro C^γ chemical shift in a wide range of linear and cyclic peptides[3] (in which a variety of Pro ring conformations must certainly occur) is strong evidence that the pyrrolidine ring conformation has but a small influence on the C^γ chemical shift. A similar conclusion (for all the ring carbons) has resulted from a comparative analysis of ΔC^i values in a variety of X-Pro and X-Hyp compounds.[5]

(15) Although the assignment of pyrrolidine resonances on the basis of ΔC^i values should proceed with caution in cases where unusual peptide geometry (*e.g.*, diketopiperzines) may perturb chemical shifts, Dorman and Bovey[3] have shown that even in such unfavorable circumstances, the Pro C^γ shift is well correlated with the type of peptide isomer present.

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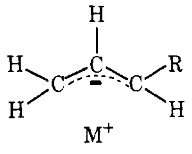
Addition of *gem*-Dichloroallyllithium to Aldehydes and Ketones. Unprecedented Ambident Character of an Allylic Metal Reagent Governed by Substrate Electronic Factors

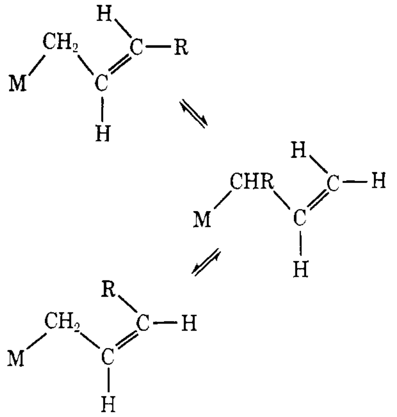
Sir:

We have reported recently concerning the synthesis of *gem*-dichloroallyllithium and its coupling reactions with metallic and metalloidal halides.[1] In our continuing investigations we have studied the reactions of *gem*-dichloroallyllithium with aldehydes and ketones and have found unprecedented ambident behavior that is governed by electronic, not steric, factors in the substrate and reagent.

In known C=O addition reactions of substituted allylmetallics I and II, *e.g.*, with R = Me or Et, the new C—C bond is formed at the -CHR end of the reagent except in those cases where the >C=O bond becomes sterically encumbered by branched alkyl group substitution.[2] Then, depending on the degree of steric hindrance, either a mixture of >C(OH)CH_2CH=CHR and >C(OH)CHRCH=CH_2 products is obtained or the new C-C bond is formed exclusively at the CH_2 terminus of the reagent. The introduction of bulky substituents into the allylmetal reagent (*e.g.*, neopentylallyllithium[3]) results in C=O addition reactions in which products from both termini of the reagent are obtained even with unhindered ketones.

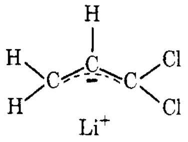


I, M = Li, Na



II, M = MgX, Mg/2, ZnX, Zn/2

In general, however, C=O addition reactions are controlled by electronic as well as by steric factors. In potentially ambident nucleophiles of types I and II, the electronic properties of the two possible reacting termini are not greatly different, and thus one observes product distributions caused primarily by the operation of steric factors. In *gem*-dichloroallyllithium (III), we have a potentially ambident nucleophile whose two reacting termini differ substantially in terms of both steric and electronic properties. It therefore was of considerable interest to study its addition to the C=O bond of aldehydes and ketones in order to see which effect would be of greater importance.



III

The reaction of *gem*-dichloroallyllithium with benzaldehyde is described below to illustrate the procedures used. *n*-Butyllithium (38.3 mmol in 15 ml of hexane) was added dropwise with stirring under nitrogen to 38.1 mmol of $Ph_3PbCH_2CH{=}CCl_2$[1] in 300 ml of dry THF at −90°. The resulting light amber solution was stirred at −90° for 20 min and subsequently 4.5 ml (*ca.* 45 mmol) of benzaldehyde was added dropwise with continued cooling to −90°. During the addition the reagent solution color was discharged. After 5 min of further stirring, the reaction mixture was hydrolyzed by rapid addition of 50 ml of 1 *N* HCl and then was allowed to warm to room temperature. Extraction with diethyl ether and water gave an organic layer which was dried and concentrated under reduced pressure. An nmr spectrum of the residue (before any heating) showed that only $PhCH(OH)CH_2CH{=}CCl_2$ was present.[4] Vacuum distillation of the reaction mixture

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(1) D. Seyferth, G. J. Murphy, and R. A. Woodruff, *J. Organometal. Chem.*, **66**, C29 (1974).

(2) G. Courtois and L. Miginiac, *J. Organometal. Chem.*, **69**, 1 (1974).

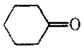
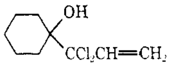
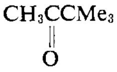
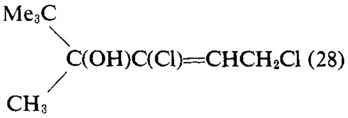
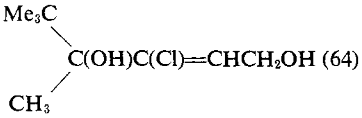
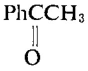
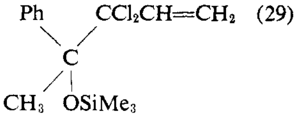
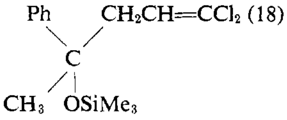
(3) W. H. Glaze, J. E. Hanicak, M. L. Moore, and J. Chaudhuri, *J. Organometal. Chem.*, **44**, 39, 49 (1972); W. H. Glaze, D. J. Berry, and D. P. Duncan, *J. Organometal. Chem.*, **52**, 233 (1973).

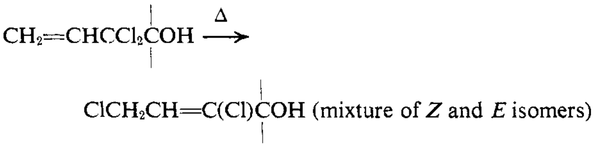
(4) The two types of addition are easily distinguished from one another on the basis of the proton nmr spectra. Thus $PhCH(OH)CH_2CH{=}CCl_2$ had an nmr spectrum (in CCl_4) which showed the CH_2 protons as two doublets at δ 2.40 (J_1 = 6.5 Hz, J_2 = 7.0 Hz) and the vinyl proton as a triplet (J_1 = 6.5 Hz) at 5.75 ppm. In contrast, the acetone-derived product, $Me_2CH(OH)CCl_2CH{=}CH_2$, showed its vinyl protons as an ABC multiplet (3d of d) at δ 5.25–6.60 ppm.

gave 8.10 g (97%) of this alcohol, bp 88–90°, $n^{25}\mathrm{D}$ 1.5578.

The results of this study to date are summarized in Table I. All products listed have been fully characterized spectroscopically and with satisfactory (±0.3%) combustion analyses. The alcohols derived from CH_2-end addition of the reagent were thermally stable, but those formed by reaction at the CCl_2 terminus were not. Most, when heated above 120°, isomerized *via* allylic chloride migration (eq 1). In the case of pinacolone, the initial product, $Me_3C(Me)C(OH)CCl_2CH{=}CH_2$, underwent such isomerization at room temperature and one of the allylic chlorides formed was hydrolyzed during the aqueous work-up.

Table I. Reactions of *gem*-Dichloroallyllithium with Carbonyl Compounds

Carbonyl compound	Products (% yield)	% attack *via* CCl_2 terminus	% attack *via* CH_2 terminus
$(CH_3)_2C{=}O$	$(CH_3)_2C(OH)CCl_2CH{=}CH_2$ (90)	100	
	 (81%)	100	
 $CH_3C(=O)CMe_3$	 $Me_3C(CH_3)C(OH)C(Cl){=}CHCH_2Cl$ (28)  $Me_3C(CH_3)C(OH)C(Cl){=}CHCH_2OH$ (64)	100	
$C_2H_5CH{=}O$	$C_2H_5CH(OH)CCl_2CH{=}CH_2$ (69) $C_2H_5CH(OH)CH_2CH{=}CCl_2$ (28)	71	29
 $PhC(=O)CH_3$	 $Ph(CH_3)C(OSiMe_3)CCl_2CH{=}CH_2$ (29)  $Ph(CH_3)C(OSiMe_3)CH_2CH{=}CCl_2$ (18)	62	38
$PhCH{=}O$	$PhCH(OH)CH_2CH{=}CCl_2$ (97)		100
$Ph_2C{=}O$	$Ph_2C(OH)CH_2CH{=}CCl_2$ (91)		100
$(CF_3)_2C{=}O$	$(CF_3)_2C(OH)CH_2CH{=}CCl_2$ (90)		100



$$\mathrm{CH_2{=}CHCCl_2\overset{|}{\underset{|}{C}}OH \xrightarrow{\Delta} ClCH_2CH{=}C(Cl)\overset{|}{\underset{|}{C}}OH}\ \text{(mixture of } Z \text{ and } E \text{ isomers)} \quad (1)$$

In our initial reactions of $Li(CCl_2CHCH_2)$ with acetophenone, hydrolysis of the reaction mixtures invariably gave the product alcohol mixture in less than 50% yield and large amounts of unconverted acetophenone were recovered, even when the lithium reagent was used in excess. When such a reaction mixture was treated with trimethylchlorosilane instead of aqueous HCl, the expected silyl ethers were formed in 47% yield (Table I), in the same ratio as that observed for the alcohols in reaction mixtures which had been hydrolyzed. In addition, 1-phenyl-1-trimethylsiloxyethylene was formed in 43% yield, which indicates that 43% of the lithium reagent reacted with the ketone to form the lithium enolate.

Examination of Table I shows that electronic factors, not steric factors, must determine whether the new C–C bond is formed *via* the CCl_2 or the CH_2 terminus of the lithium reagent. The reaction with pinacolone, which gives none of the alcohol derived from addition *via* the CH_2 end of the reagent, as well as the reaction with hexafluoroacetone speak strongly in favor of this. In the absence of detailed knowledge concerning the mechanism of these addition reactions (simple nucleophilic addition of the allyl anion to the C=O group or an electron transfer process), it is premature to speculate concerning the significance of the results given in Table I. *If* the nucleophilic addition mechanism is assumed, it is possible to view these reactions in terms of the HSAB approach,[5] in which the CCl_2 terminus of the *gem*-dichloroallyl anion is the "soft" end and the CH_2 terminus the "hard" end. The changing double bond character of the C=O group (greater with alkyl substituents, *i.e.*, "softer," less, *i.e.*, more polarized, $C^{\delta+}–O^{\delta-}$, and "harder" with electronegative substituents) would then determine which $[CCl_2CHCH_2]^-$ terminus reacts.

Although it has been established that allylic magnesium and zinc reagents can add reversibly to carbonyl compounds, this has not yet been demonstrated for allylic lithium compounds.[2] In the present instance, reversible addition of the dichloroallyl anion to the C=O bond followed by formation of the thermodynamically more stable alcohol might merit serious consideration. This possibility has yet to be explored thoroughly, but preliminary results of experiments in which reaction mixtures were allowed to warm to room temperature and stirred for more than 1 hr before hydrolysis showed that acetone and benzaldehyde still exhibit the same exclusive and opposite preference for the CCl_2 and CH_2 end of the anion, respectively. A further experiment with acetophenone established that the product distribution observed after immediate low temperature hydrolysis is unchanged if the reaction mixture is warmed to room temperature and stirred for 1 hr before work-up.

Our studies of this interesting system are continuing. It will be of special interest to see if electron-releasing and withdrawing substituents in substituted acetophenones can influence the relative proportions of CH_2- and CCl_2-ended attack at the C=O bond. Also, if it is experimentally feasible, nmr investigation of *gem*-dichloroallyllithium in solution also may be useful in helping understand the nature of the reagent, although the limited thermal stability of $Li(CCl_2CHCH_2)^1$ may limit the effectiveness of such studies.

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