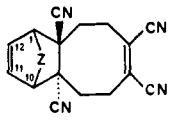
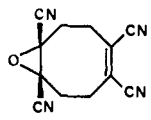
where $\theta = 2.303RT$ kcal/mol. These rate constants are considerably (*e.g.*, 4×10^3 times at 100°) lower than those found for solution isomerization of 1,4-dicyanobicyclo[2.2.0]hexane,[12] the structurally most similar model compound.

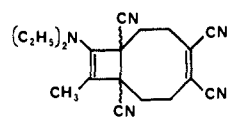
The chemical reactivity of **2c** was briefly investigated. **2c** undergoes reactions at the (*E*) double bond with cyclopentadiene or furan in acetonitrile at 20° with quantitative formation of adducts **5** (mp 259–260°) and



5 Z = CH_2
6 Z = O



7



8

6 (mp 188–189°), respectively, with trans-fused cyclooctene rings (nmr).[7] The solid-state thermolysis (105°, vacuum) of **6** is of interest insofar as only pure **2c** is formed. The absence of (*Z,Z*)-isomer **3c**, thermodynamically more stable by at least 9 kcal/mol,[13] excludes any stepwise cleavage of single bonds during the retro-Diels–Alder reaction of **6** and is, in our opinion, a striking demonstration of the concertedness of this reaction.

When solutions of **2c** are exposed to air at room temperature, epoxide **7** (mp 195–196°)[7] forms spontaneously. More convenient is oxidation of **2c** with hydrogen peroxide or *m*-chloroperbenzoic acid giving **7** in 95% yield. The inversion of configuration on one of the (*E*) double bond carbons during the oxidation was established by X-ray analysis of **7**.[14]

Treatment of **2c** in acetonitrile at −10° with 1-diethylamino-1-propyne gave **8** (mp 165–166°; ir(KBr) ν 2231 (sat. CN), 2219 (unsat. CN), 1675 cm^{-1} (C=C in cyclobutanoneenamine[15]))[7] in 62% yield. Its stereochemistry is presently unknown.

Why can the tricyclooctane **1c** isomerize exclusively to (*Z,E*)-cycloocta-1,5-diene **2c** while tricyclooctanes **1a** and **1b** apparently isomerize directly to (*Z,Z*)-cycloocta-1,5-dienes **3a** and **3b**? One reason may be that the dissociation energy of the first endocyclic single bond to be opened in **1c** is decreased by some 14.6 kcal/mol[12] because of the two bridgehead α-cyano groups. As a consequence, the difference between the activation energy for formation of the (*Z,E*) isomer and the activation energy for consecutive (*Z,E*) → (*Z,Z*) isomerization[16] may be considerably higher in the case of **1c** than the corresponding difference in the case of **1a** or even **1b**.[17] It is also not unreasonable to assume intermediate formation of **2a** and **2b** in the latter two cases followed by rapid geometric isomerization to **3a** and **3b** under reported[3,4] reaction conditions.[18,19]

The performance of the isomerization of **1c** as a solid-state reaction may be another reason for its remarkable stereoselectivity. If the first step, **1c** → **2c**, required only minimal molecular motions in the crystal[21] while the second step, **2c** → **3c**, involved extensive displacements in the lattice, the first step should be considerably kinetically preferred.

Acknowledgment. We are indebted to Dr. H.-D. Martin and Dr. J. Watthey for helpful comments on the manuscript.

Supplementary Material Available. A listing of structure factor amplitudes, fractional atomic coordinates, and thermal parameters will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-5007.

(12) D. Belluš and G. Rist, *Helv. Chim. Acta*, **57**, 194 (1974).
(13) R. B. Turner and W. R. Meador, *J. Amer. Chem. Soc.*, **79**, 4133 (1957).
(14) Crystals of **7** are: monoclinic; $P2_1$; $a = 6.684(2)$, $b = 10.391(3)$, $c = 8.355(2)$ Å; $\beta = 105.34(5)°$; $V = 559.6$ Å^3; $\rho_{calcd} = 1.33$ g cm^{-3} for $Z = 2$. Least-squares refinement of positional and anisotropic thermal parameters for all non-hydrogen atoms on 938 independent reflections ($I \geq 2\sigma(I)$) converged at $R = 0.094$. A disorder in the crystal packing does not allow further refinement. However, the cis fusion of the oxirane ring in **7** is unequivocally established. See paragraph at end of paper regarding additional supplementary material.
(15) J. Ficini and A.-M. Touzin, *Bull. Chem. Soc. Fr.*, 2386 (1972).
(16) J. A. Berson, P. B. Dervan, and J. A. Jenkins, *J. Amer. Chem. Soc.*, **94**, 7598 (1972).
(17) Radical stabilization energy of the α-carbomethoxy group is about 4–4.5 kcal/mol relative to a hydrogen atom: (a) E. N. Cain and R. K. Solly, *J. Amer. Chem. Soc.*, **95**, 4791 (1973); (b) H.-D. Martin and M. Hekman, *Chimia*, **28**, 12 (1974).
(18) Indeed, our preliminary experiments conducted in the molten state at lower temperature (105° rather than 140° reported in ref 4) show that **1b** isomerizes to a mixture of **2b** (60%) and **3b** (28%). **2b** can be isolated in pure form and gives Diels–Alder reactions similar to **2c**.
(19) The influence of the 1,4-substituents on the rates of cycloreversion in bicyclo[2.2.0]hexanes has been interpreted[17a,20c,e] in terms of formation of 1,4-biradical-like intermediates.[20] If, however, the cleavage of such a 1,4-biradical to a 1,5-diene were rate determining (as the thermal inversion of bicyclo[2.2.0]-*exo*-2,3,5,6-d_4-hexane appears to indicate[20b]), the direct comparison of molecules (*e.g.*, **1a–c**) with different substituents on *both* cleaving single bonds might be of limited value.
(20) (a) L. A. Paquette and J. A. Schwartz, *J. Amer. Chem. Soc.*, **92**, 3215 (1970); (b) M. J. Goldstein and M. S. Benzon, *ibid.*, **94**, 5119 (1972); (c) E. N. Cain and R. K. Solly, *ibid.*, **95**, 7884 (1973); (d) A. Sinnema, F. van Rantvijk, A. J. DeKoning, A. M. van Vijk, and H. van Bekkum, *J. Chem. Soc., Chem. Commun.*, 364 (1973); (e) E. N. Cain and R. K. Solly, *ibid.*, 148 (1974).
(21) The torsional flexibility of the tricyclo[4.2.0.0^{2,5}]octane carbon skeleton (see ref 22 for **1a**) may preorientate, to some extent, the endocyclic single bonds for the ($\sigma 2_s + \sigma 2_a$) process.
(22) B. Andersen and L. Fernholt, *Acta Chem. Scand.*, 24, 445 (1970).

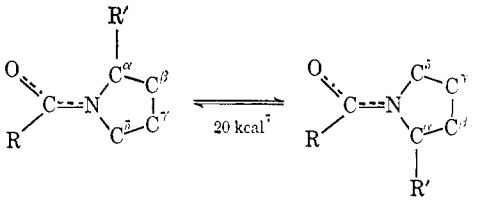
Daniel Belluš,* Hans-Christian Mez
Greti Rihs, Hanspeter Sauter
Central Research Laboratories, Ciba-Geigy AG
4002 Basel, Switzerland
Received March 19, 1974

Carbon-13 Chemical Shifts of Amides and Imino Acid Residues. Effects of the Carbonyl Substituent and Syn–Anti Geometries

Sir:

Two well-separated ^{13}C resonances[1–5] have been reported for each C^β and C^γ ring carbon in peptides containing L-prolyl and hydroxy-L-prolyl (pyrrolidine) residues and have been assigned to the trans (I) and cis (II) isomers of the X–Pro[6] and X–Hyp peptide

(1) W. A. Thomas and M. K. Williams, *J. Chem. Soc., Chem. Commun.*, 994 (1972).
(2) K. Wüthrich, A. Tun-Kyi, and R. Schwyzer, *FEBS (Fed. Eur. Biochem. Soc.) Lett.*, **25**, 104 (1972).
(3) D. E. Dorman and F. A. Bovey, *J. Org. Chem.*, **38**, 2379 (1973), and references therein.
(4) I. C. P. Smith, R. Deslauries, H. Saito, R. Walter, C. Garrigou-Lagrange, H. McGregor, and D. Sarantakis, *Ann. N. Y. Acad. Sci.*, **222**, 157 (1973).
(5) D. A. Torchia and J. R. Lyerla, Jr., *Biopolymers*, **13**, 97 (1974).
(6) Abbreviations: Pro = L-prolyl, Hyp = hydroxy-L-prolyl, X = any amino acid residue, Gly = glycyl, Ala = L-alanyl, Val = L-valyl, Sar = sarcosyl = *N*-methylglycyl.



trans I cis II

bonds. These assignments are based, in part, on evidence, obtained from acyclic model amides,[8-10] which indicates that the chemical shift of a carbon syn to the carbonyl oxygen (*e.g.*, C^γ in II) is upfield of the chemical shift of the given carbon when it is anti to the oxygen (*e.g.*, C^γ in I). We define this chemical shift difference as $\Delta C^i = \tau_{syn} - \tau_{anti}$, where i is the given carbon (α, β, γ, δ) and τ_{syn} and τ_{anti} are the chemical shifts of the carbon in the respective isomers.[11] Although the acyclic amides have been used as models for the peptides, it is not yet certain that the chemical shift differences ΔC^i in the amides and peptides have a common origin. Indeed, the surprising result that the values of ΔC^α and ΔC^δ are smaller than ΔC^β and ΔC^γ in the pyrrolidine containing peptides[1-5]—despite the fact that the C^α and C^δ carbons are closer to the peptide bond—cannot readily be explained by the available acyclic amide data.

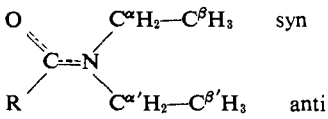
In order to elucidate the factors which influence pyrrolidine chemical shifts, ΔC^i values were determined (relative to external CS_2)[12] for a series of *N,N'*-diethylamides and related compounds containing imino acid residues, using a 15.08-MHz pulsed spectrometer. The data presented herein provide strong evidence (a) that the carbonyl substituent, R, greatly affects ΔC^α in amides and ΔC^α and ΔC^δ in imino acid residues and (b) that for a given substituent the ΔC^i values for acyclic amides and pyrrolidine-containing peptides are consistent and are determined primarily by chemical shift differences arising from syn *vs.* anti geometries.

Spectra of the *N,N'*-diethylamides were obtained to determine the effect of R upon ΔC^i in the absence of the pyrrolidine ring. The results (Table I) reveal a threefold reduction in the ΔC^α values (differences between syn and anti methylene carbons) when R is varied from H (diethylformamide) to alkyl (Me, Et, Pr), as well as a second threefold reduction in ΔC^α when R is changed from alkyl to NH_2CH_2–(glycine diethylamide). Similar decreases in ΔC^α are observed for an analogous series of compounds containing the acyclic imino acid sarcosine (Table II). Significantly, the substituent which produces the smallest value of ΔC^α in the amides—and the smallest ΔC^α and ΔC^δ values in the sarcosyl compounds—is R = NH_2CH_2–. The comparable, small values of ΔC^α and ΔC^δ, observed for Gly-*N*-Me-L-Ala attest to the generality of this result.

The large influence of the carbonyl substituent on the ΔC^α and ΔC^δ values, found in the acyclic amides and peptides, persists when the C^α and C^δ atoms are incorporated into pyrrolidine rings as in X-Pro and X-Hyp peptides. Reductions of 1.6–2.8 ppm occur in the values of ΔC^α and ΔC^δ when a glycyl moiety replaces acetyl as the predecessor of the imino acid (Table III).[13]

For a given substituent, ΔC^β is *ca.* twice as large in the ring compounds as in the acyclic compounds. This

Table I. Influence of Carbonyl Substituents (R) on Syn and Anti Chemical Shift Differences[a] in *N,N'*-Diethylalkylamides[b,c]



R	ΔC^α	ΔC^β
H–	5.7	1.9
CH_3–	2.9	0.8
CH_3CH_2–	2.1	1.1
$CH_3CH_2CH_2$–	2.3	1.1
NH_2CH_2–	0.7[d]	0.8[d]

[a] In ppm. [b] Aqueous solution, concentration = 50–100 mg/ml, temperature = 30°. [c] ΔC^α = chemical shift of $C^\alpha H_2$ (syn) minus chemical shift of $C^\alpha H_2$ (anti). ΔC^β is defined similarly. All ΔC^i are positive since the syn carbons are assumed to be the more shielded. [d] Value independent of pH over the range 2–11.

Table II. Influence of Carbonyl Substituents (R) on Syn and Anti ^{13}C Chemical Shift Differences in Sarcosine (*N*-methylglycine) and *N*-methylalanine Peptides[a,b]

Peptide	R	ΔC^α	ΔC^δ[c]	ΔC^β
N-formyl-Sar[d]	H–	5.0[e]	4.9	
N-acetyl-Sar[d]	CH_3–	2.5	2.7	
Gly-Sar	NH_2CH_2–	⩽0.7[e]	⩽0.5[e]	
Gly-*N*-Me-L-Ala	NH_2CH_2–	⩽0.7[e]	⩽0.5[e]	1.0[f]

[a] Aqueous solution, concentration = 50–100 mg/ml, temperature = 30°. [b] In the trans conformation of the peptide bond, the C^α and its substituents are syn to the carbonyl oxygen, and the *N*-methyl carbon (C^δ) and its substituents are anti. The situation is reversed for the cis isomer. In each case $\Delta C^i = \tau_{syn} - \tau_{anti}$. [c] ΔC^δ = difference in the *N*-methyl carbon chemical shifts. [d] Chemical shifts from ref 3. [e] Only one peak resolved (width greater than other resolved peaks). The value reported represents the maximum ΔC magnitude, sign undetermined. [f] ΔC^β is positive since C^β is assumed to be more shielded when it is syn to the carbonyl oxygen.

Table III. Influence of Carbonyl Substituents (R) on Syn and Anti ^{13}C Chemical Shift Differences in Proline and Hydroxyproline Peptides[a,b]

Peptide	R	ΔC^α	ΔC^δ	ΔC^β	ΔC^γ
N-formyl-L-Pro[c]	H–	2.7	3.0	1.3	1.4
N-acetyl-L-Pro[c]	CH_3–	1.9	1.7	1.6	1.8
Gly-L-Pro[c]	NH_2CH_2–	−0.3	−0.6	2.0	1.9
t-Boc-Gly-L-Pro[d]	*t*-Boc-NH_2CH_2–	0.3	−0.5	2.3	2.5
Ala-L-Pro[e,f]	NH_2CHY–	0.0	−0.6	2.2	2.5
Val-L-Pro[e,g]	NH_2CHY–	0.0	−0.6	2.5	2.5
N-acetyl-L-Hyp[d]	CH_3–	2.3	1.8	1.6	1.4
t-Boc-Gly-L-Hyp[d]	*t*-Boc-NH_2CH_2–	0.5	−0.4	2.5	1.8

[a] In aqueous solution, concentration = 50–100 mg/ml. [b] ΔC^i values are defined in Table II, footnote *b*. [c] Assignments from ref 3. [d] Assignments from ref 5. [e] Assignments from ref 1. [f] Y = CH_3. [g] Y = $(CH_3)_2CH_2$–.

(7) W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970).
(8) W. McFarlane, *Chem. Commun.*, 418 (1970).
(9) G. C. Levy and G. L. Nelson, *J. Amer. Chem. Soc.*, **94**, 4897 (1972).
(10) D. E. Dorman and F. A. Bovey, *J. Org. Chem.*, **38**, 1719 (1973).
(11) For imino acids ΔC^i is given by $\tau_{trans} - \tau_{cis}$ for $i = \alpha$ or β and by $\tau_{cis} - \tau_{trans}$ for $i = \gamma$ or δ.
(12) On the TMS chemical shift scale, the signs of the ΔC^i values are opposite to those given here.
(13) The isomer populations are unequal in the compounds containing imino acid residues. The assignments in Tables II and III—based on the assumption that $\tau_{syn} > \tau_{anti}$—are consistent, in all cases, with a trans assignment of the predominant isomer.

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.

(16) NRC–NAS Postdoctoral Research Associate.

D. A. Torchia,* J. R. Lyerla, Jr.[16]
Polymers Division, National Bureau of Standards
Washington, D. C. 20234

C. M. Deber*
Department of Biological Chemistry, Harvard Medical School
Boston, Massachusetts 02115

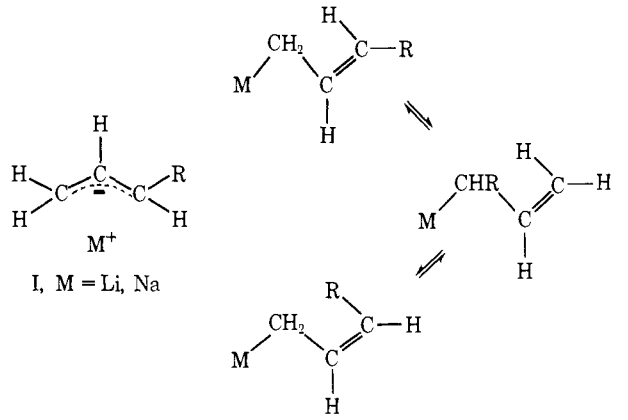
Received April 12, 1974

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.*, neopentyl-

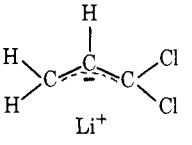


I, M = Li, Na

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

allyllithium[3]) results in C=O addition reactions in which products from both termini of the reagent are obtained even with unhindered ketones.

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



III

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.

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

(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.