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THE STEREOCHEMISTRY OF 2,4-DISUBSTITUTED γ-BUTYROLACTONES AND 2,4,6-TRISUBSTITUTED-5,6-DIHYDRO-4H-1, 3-OXAZINES

J. ALTMAN,* H. GILBOA and D. BEN-ISHAI
Department of Chemistry Israel Institute of Technology, Haifa, Israel

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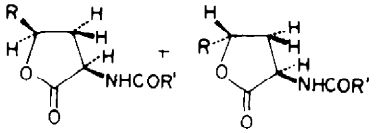
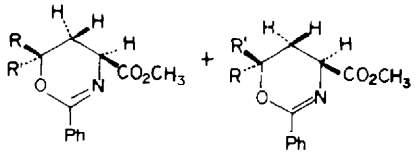
Abstract—2,4-Disubstituted butyrolactones and 2,4,6-trisubstituted-5,6-dihydro-4H-1,3-oxazines show similar features in their ^1H and ^{13}C-NMR spectra. Two geminal ring hydrogens of *cis*-isomers give rise to a complex ABXY spectra when the substituent is alkyl or aryl. In spectra of *trans* isomers these patterns are degenerated. When R is OMe(in **4**) or OCOMe (in **6**) the difference in chemical shifts of geminal protons and vicinal coupling constants cannot be used for diagnosis. In ^{13}C spectra ring carbons C-2 and C-3 in lactones and C-4 and C-5 in oxazine of *trans* isomers show a small but consistent shift to higher fields.

In the course of a study on the amidoalkylations of olefins and active methylene compounds we have obtained three types of related compounds: open chain unsaturated α-acylaminoacids, α-acylamino-γ-butyrolacontes **1–4** and substituted 5,6-dihydro-4H-1,3-oxazines **5–7**.[1,2] The 4,6-disubstituted oxazines, produced by a 4+2 polar cycloaddition reaction,[3] and the 2,4-disubstituted lactones were obtained as mixtures of *cis-trans* isomers.



cis *trans*

1 R = CH_3; R′ = Ph
2 R = Ph; R′ = Ph
3 R = Ph; R′ = OCH_2Ph
4 R = CH_3O; R′ = Ph

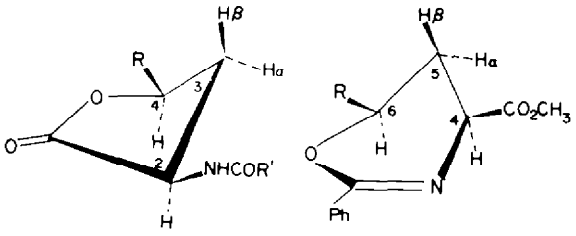


cis *trans*

5 R = Ph; R′ = H
6 R = $OCOCH_3$; R′ = H
7 R = R′ = CH_3

The stereochemistry of different γ-butyrolactones has been studied by several workers using ^1H NMR spectroscopy,[4–6] ^{13}C-NMR[7–9] as well as a chemical approach.[7] 1,3-Oxazine system was extensively investigated by Schmidt and Hoffmann[3] and Giordano and Abis.[10] We would like to emphasize some of the common features of 2,4-disubstituted butyrolactones and 2,4,6-trisubstituted-5,6-dihydro-4H-1,3-oxazines prepared in our laboratory.

In order to determine the *cis* or *trans* configurations of cyclic compounds using ^1H NMR spectral data, the vicinal coupling constants of the ring protons are usually a good structural indication. There is another striking feature in the ^1H NMR spectra of lactones **1,2,3** and oxazine **5** having a Me or Ph substitutent. The difference in the chemical shifts of two geminal protons 3α, 3β in *cis* lactons and 5α, 5β in *cis* oxazine is of the order of 0.4–0.9 ppm whereas in *trans* configuration it is very small (Tables 1 and 2). This difference in *cis* configuration is due to the different magnetic environment of the two geminal hydrogens; the one "sees" at its side two vicinal hydrogens, the other is in the vicinity of two substituents. The *cis* isomers give rise to a complex ABXY type pattern. The vicinal coupling constants 2,3β and 3β,4 in thesese lactones and 4,5β and 5β,4 in oxazine **5** are characteristic of *quasi*-axial interactions indicating that at room temperature these compounds generally adopt only one of two possible conformations. The 1,3 interactions of substituents (positions 2 and 4 in *cis* lactones **1**, **2**, **3** and **4** and **6** in *cis* oxazine **5**) are minimized being in the more stable *quasi*-equatorial positions. These findings are consistent with the results of X-ray studies indicating that the conformation of γ-butyrolactone is an envelope[7,11] and 2,4,6-trisubstituted-5,6-dihydro-4H-1,3-oxazine is in the "half boat" conformation[12] (or "sofa" conformation).



When the substituent is OCH_3 group (in **4** *cis*) a difference of 0.5 ppm in Δδ of the two geminal hydrogens 3α, 3β is observed but there is no longer a significant difference in the vicinal J coupling constants, and the assignment of *quasi*-equatorial and *quasi*-axial interactions is no longer possible.

In the *cis* oxazine **6** (R = $OCOCH_3$) the chemical shifts of the two geminal hydrogens are equal, and vicinal

Table 1. Chemical shifts and vicinal coupling patterns in the ^1H NMR spectra of 2,4-disubstituted-γ-butyrolactones (1–4)

Compd.	Solv.	δ (ppm)						J/Hz			
		NH	H-2	H-3α	H-3β	H-4	NH_2	J2,3α	J2,3β	J3α,4	J3β,4
1 cis[a]	$CDCl_3$+TFA[b,e]		5.09	2.92	2.05	4.73		9	12.6	6	11.5
1 trans[a]	$CDCl_3$+TFA[b,e]		4.98	2.98	2.98	5.01		9.5	9	5	4.5
2 cis	$CDCl_3$+TFA+D_2O[b]		5.12	3.17	2.37	5.54		8	12.5	5	11
	$CDCl_3$[c]	7.2	5.08	3.28	2.33	5.55	6.5	8	12.5	5	11
2 trans	$CDCl_3$+TFA+D_2O[b]		4.83	2.80	2.80	5.83		9.5	9.5	7	5
	$CDCl_3$[c]	7.2	4.82	2.80	2.80	5.77	6	9.5	9.5	7	5
3 cis	$CDCl_3$+Et_3N+D_2O[b]		4.60	3.02	2.21	5.35		8	12.5	5	11
	$CDCl_3$[c]	5.7	4.60	3.02	2.21	5.35	6	8	12.5	5	11
3 trans	$CDCl_3$+TFA+D_2O[b]		4.48	2.69	2.62	5.73		10	9.5	6	5.5
	$CDCl_3$[c]	5.9	4.46	2.63	2.55	5.70	7	10	9.5	6	5.5
4 cis	Acetone d_6+D_2O[b]		4.95	2.90	2.42	5.45		8	9	4.5	6
	CD_3CN[c]	7.6[d]	4.95	2.90	2.42	5 45	6	8	9	4.5	6
4 trans	CD_3OD+AcOH[b]		4.82	2.56	2.40	5.65		9	9.5	2	5
	CD_3CN[c]	7.5[d]	4.68	2.56	2.40	5.64	5	9	9.5	2	5

a - Spectra taken on WH-270 Bruker FT Spectrometer. b - Computed as a 4-spin system using Nicolet NMR CAL program. c - Computed as 5-spin system (ring protons and NH). d - NH chemical shift overlaps aromatic absorption. e - Decoupled spectrum with methyl irradiation.

Table 2. Chemical shifts and vicinal coupling constants in the ^{1}H NMR spectra of some 5,6-dihydro-4H-1,3-oxazines (**5–7**)

Compd	Solv	δ (ppm)				J/Hz			
		H-4	H-5α	H-5β	H-6	J4,5α	J4,5β	J5α,6	J5β,6
5 cis*	$CDCl_3$	4.56	2.43	2.05	5.34	4	12	3	11
5 trans*	$CDCl_3$	4.46	2.46	2.18	5.52	4	6	4	9
6 cis*	CCl_4	4.35	2.32	2.32	6.46	7	6	4.5	4.5
6 trans*	CCl_4	4.35	2.16	2.16	6.53	9	8.5	2	2.5
7**	$CDCl_3$	4.32	2.12	1.96		5	11.5		

* - computed as a 4-spin system using Nicolet NMR CAL program.

** - computed as a 3-spin system

coupling constants in both isomers are of the same order (Table 2). Schmidt[13] also noted that two geminal hydrogens and vicinal hydrogens in 5-acetoxy-2-phenyl-5,6-dihydro-4H-1,3 oxazine gave rise to AB_2 type spectrum whereas 2,6-diphenyl oxazines gave ABC type pattern. It may be because of the acetal nature of the acetoxy group and its smaller steric requirements that the difference in chemical shifts of the two geminal hydrogens in the *cis* isomer vanishes and the contribution of the conformation with two substituents in the axial position is more pronounced. The assignments of configuration in this case is based on chemical behavior of those isomers.

When 6-acetoxyoxazines were submitted to BF_3–Et_2O action at room temperature only one isomer isomerized, whereas the other was unchanged. The one which withstood epimerisation is probable the more stable *cis* isomer. The isomerization in this case may be due to the cleavage of the C-O bond of the acetate substituent. **5**-*cis* and **5**-*trans* do not equilibrate with one another under the same conditions.

In the oxazine **5** (R = Ph) H-6 of the *trans* isomer resonates at a lower field δ 5.52 ppm than H-6 of *cis* isomer: δ 5.32 ppm. In all examples of lactones the H-4 hydrogen of *trans* isomer also resonates at a lower field than H-4 of *cis* isomers. The difference in δ is in the range 0.2–0.4 ppm. In **6** (R = $OCOCH_3$) H-6 of one isomer resonates at 6.46 ppm whereas the other at 6.53 ppm. By analogy with the previous cases, the *cis* configuration may be assigned to the one having H-6 resonance at higher field.

A very cautious analogy may be made with some unsaturated acetylated carbohydrates.[14] In tetraacetates of 2,3-didehydro-3-deoxyderivatives of hexoses, *quasi* axial acetoxy group is assigned to α and to β anomers in half chair conformations. C(1) protons on compounds having *quasi*-axial ester group at C (4) resonate at slightly lower fields δ 6.44 ppm than those on compounds with quasi-equatorial C(4) groups δ 6.35 ppm.

A characteristic feature of *trans* isomers of lactones and oxazine in ^{1}H NMR spectrum is a very small difference in the chemical shifts of 3α, 3β and 5α 5β geminal hydrogens. In the *trans* lactones (**1**, **2**, **3**) the AB part of the ABXY system degenerated to four lines. Such degeneration is due to the similar magnetic environment of the hydrogens; each one sees in its vicinity one substituent and one vicinal hydrogen. J coupling constants of vicinal hydrogens are of the same magnitude, probably due to equal contributions of two possible conformers in which pseudo axial equatorial positions are interchanged.

^{13}C NMR spectra of 2,4-disubstituted butyrolactones are less sensitive than ^{1}H NMR spectroscopy to configurational differences (Table 3). Ollis *et al.*[7] have already pointed out this feature in the case of 2,4-diphenyl-γ-butyrolactone. However, a small but consistent shift to higher field was observed for C-2 (1.3 to 3.3 ppm) and for C-3 (~2 ppm) of *trans* lactones **1**, **2** and **3** (Table 3). Also the carbon atoms of the ring C-4, C-5 and C-6 of the *trans* isomer in oxazine **5** resonate at slightly higher field (Table 4).

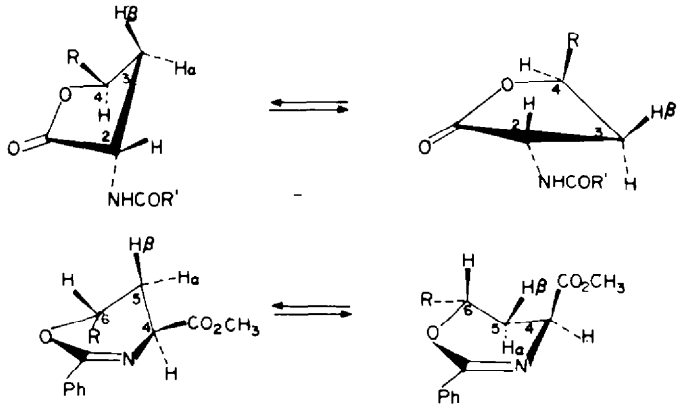


Table 3. ^{13}C NMR spectra of 2,4-disubstituted and 2,4,4'-trisubstituted γ-butyrolactones (1–3)

Compd	δ (ppm)							
	Carbon number of ring					Other		
	C-1	C-2	C-3	C-4	CO	OCH_2	CH_3	CH_3
1 cis*	175.8	51.5	37.2	75.7	169.1		20.4	
1 trans*	176.8	50.2	34.9	77.9	170.6		20.9	
2 cis *	176.4	51.8	37.5	80.5	170.0			
2 trans*	177.6	50.0	35.6	81.0	170.6			
3 cis**	180.0	60.2	44.1	90.7	201.3	77.6		
3 trans**	179.9	56.9	42.1	90.1	201.3	77.7		

* - 10% Trifluoroacetic acid in deuteriochloroform were used as a solvent.

** - Deuteriochloroform was used as solvent.

Table 4. ^{13}C NMR sectra of 4-carboxymethyl-2,6-diphenyl and 4-carboxymethyl-6,6-dimethyl-2-phenyl-5,6-dihydro-4H-1,3-oxazines (in $CDCl_3$)

Compd	δ (ppm)							
	Carbon number of ring					Other		
	C-2	C-4	C-5	C-6	CO	OCH_3	CH_3	CH_3
5 cis	156.9	56.5	32.5	74.9	172.6	52.3		
5 trans	157.1	54.2	31.2	73.9	172.9	52.3		
7	156.2	54.2	35.2	74.6	173.1	52.2	29.2	26.1

EXPERIMENTAL

^1H NMR spectra were recorded on a varian T.60 spectrometer. The compound 3 was measured on Bruker WH-270 FT Spectrometer with TMS as internal standard. ^{13}C NMR spectra were recorded on a Bruker WP-60 FT NMR Spectrometer with $CDCl_3$ as "lock" and TMS as internal standard. Theoretical ^1H NMR spectra were calculated with a BNC 12 computer by using the Nicolet NMR CAL program. Most of the spectra were run in $CDCl_3$. To simplify spectra, by elimination of the interaction NH-H-2, D_2O and trifluoroacetic acid were added or D_2O and triethylamine. Lactones 4 were measured in deuterated acetonitrile. As the acetal system is sensitive to strong acid the exchange of the NH proton was made in the case of 4-*cis*, in deuterated acetone and D_2O and in the case 4-*trans* with deuterated methanol and acetic acid.

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