Note

Downfield chemical shifts at α -protons and carbons of β -propiothiolactones

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Received 13 August 1999; revised 4 February 2000; accepted 7 February 2000

ABSTRACT: Both the α -protons and carbons of β -propiothiolactones exhibit atypical downfield chemical shifts. The α -protons of β -propiothiolactones with no heteroatom at the α -position appear at 3.53–5.35 ppm, whereas the α -carbons appear at 56.9–86.2 ppm. The major cause of the unexpected deshielding effect was rationalized by assuming a through-space interaction between the occupied orbital of the α -carbon and the vacant orbital of sulfur. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ¹H NMR; ¹³C NMR; 2-D INADEQUATE; β -propiothiolactones; deshielding effect; throughspace interaction

INTRODUCTION

As part of a research program directed at the efficient preparation of captopril, the first angiotensin-converting enzyme-inhibiting antihypertensive,¹ we recently became interested in the synthesis of β -propiothiolactone **1** (Scheme 1).



Scheme 1. Structure of 1 and captopril.

Comparable yields of **1** have been obtained according to procedures outlined in the literature.² Its ¹³C NMR spectrum shows a surprising downfield shift (65.7 ppm) for the α -carbon. In comparison with other structurally related heterocyclic four-membered ring compounds (Scheme 2),³ this chemical shift is unusually large. In contrast, the α -carbons to the carbonyl group of β -lactone and β -lactam are relatively shielded compared with that of cyclobutanone.



Scheme 2. ¹³C chemical shifts (ppm) of related four-membered rings.

Contract/grant sponsor: Development Fund for Industrial Basic Technology.

A literature survey revealed only five papers which reported on the ¹³C chemical shifts of β -propiothiolactones having no heteroatom at the α -position (Scheme 3).⁴ Moreover, the assignments of the chemical shifts for the α -carbons are not consistent with each other. The anomalous deshielding effect at the α -carbons in certain four-membered rings was reported several years ago and explained as an inherent property of the carbon orbitals that contribute to the paramagnetic shielding, $\sigma^{p.5}$ However, there has been no study that has particularly focused on β -propiothiolactones.



Scheme 3. ¹³C NMR chemical shifts (ppm) of β -propiothiolactones reported in the literature.

It was therefore considered necessary to establish the structure of **1** unambiguously and then examine NMR spectral properties of the related β -propiothiolactones. Here we report a systematic study of the chemical shifts of several β -propiothiolactones and propose an origin for the atypical deshielding effect at their α -carbons.

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RESULTS AND DISCUSSION

First, the structure of **1** was confirmed by both spectral and chemical means. A 2-D INADEQUATE experiment together with the DEPT and proton non-decoupling spectra established that the tertiary carbon was connected to the other three carbons. The IR spectrum and the exact mass data indicated a four-membered ring structure.

The ring-opening reactions of **1** in acidic aqueous solution or with benzylamine gave back the starting mercapto acid or its *N*-benzylamide, respectively. A product identical with **1** was also produced by treatment of 4-methyl-1,2-dithiolan-3-one, obtained via an independent route,⁶ with triphenylphosphine, as shown in Scheme 4.



Scheme 4. Structural correlation studies.

Various β -propiothiolactones were then synthesized to identify their spectral characteristics. The substituted β propiothiolactones were prepared using various adaptations of methods reported in the literature (Scheme 5). As a result, β -propiothiolactones **3–7** and **14** were prepared by the cyclization of the corresponding 3-mercapto acids in 17–42% yield, while **2** and **8–13** were obtained by the substitution reactions of **6** or **1** with the corresponding electrophiles in 30–55% yield. All β -propiothiolactones prepared in the present study showed satisfactory spectroscopic (NMR, Mass, IR) data.



Scheme 5. Structure of the β -propiothiolactones prepared in the present study.

The spectral data for the β -propiothiolactones are summarized in Table 1. These data clearly exhibit a downfield resonance trend for the α -protons and carbons. All of the ¹H chemical shifts at the α -position of β -propiothiolactones are larger than 3.5 ppm, and the α protons of **6** are deshielded further by ca 1 ppm than those of cyclobutanone. Mono- and disubstituted α -carbons show chemical shifts larger than 65 and 72 ppm, respectively. The largest ¹³C chemical shift is observed with **13** that has two deshielding substituents. In view of these results, the ¹³C chemical shifts reported by earlier workers^{4b,c} should be interchanged between the α - and β -carbons. Indeed, β , β -dimethyl- β -propiothiolactone (**14**) prepared by us has chemical shifts of 67.3 and 40.7 ppm for its α - and β -carbon, respectively, which was supported by an *ab initio* calculation (see Scheme 3 and below).

The unexpected deshielding at the α -protons and α carbons of β -propiothiolactones might be rationalized by two main factors. One is the less efficient overlap between the C=O π and S 3p orbitals, resulting in a stronger deshielding effect by the carbonyl group. The other involves a through-space interaction between the occupied orbital of the α -carbon and the vacant orbital of sulfur. For example, a fairly extensive overlap between the back lobe of the α -C bonding orbital and the empty S d orbital can be assumed to be due to the almost planar tetragonal geometry of the β -propiothiolactone rings (we thank a referee for suggesting the back-lobe overlap mechanism as an alternative to our rationale of the through-space interaction between the occupied pseudo- π -orbital of α -CH₂ and the vacant orbital of S⁷).

An ab initio calculation of the isotropic shielding constants (σ) was carried out to test the latter proposition using the individual gauge atoms in molecules (IGAIM) method⁸ with the HF/6-31++G** basis set implemented in Gaussian 94 (Revision A.1) program (Gaussian, Pittsburgh, PA, USA) (Table 2). The geometries used for the IGAIM calculations were fully optimized at the B3LYP/6-31++ G^{**} level in order to consider the electroncorrelation effect. In fact, a significant difference in the shielding constants (σ) of a saturated system is observed in the contribution from the direction perpendicular to the molecular plane of thietane (σ_{zz}). The difference becomes much larger in the unsaturated system, thiolactone. The nearly planar geometry of β -propiothiolactone makes the orbitals overlap more effectively, resulting in a greater deshielding effect.

In conclusion, a unique deshielding effect has been observed at the α -protons and carbons of β -propiothiolactones that can be mainly attributed to the through-space interaction between the occupied orbital of the α -carbon and the vacant orbital of sulfur.

EXPERIMENTAL

NMR measurements

All the NMR spectra in CDCl₃ were recorded on a JEOL JNM-LA 300 or 400 spectrometer. In all cases, a 5 mm o.d. tube was used at room temperature. All proton and carbon spectra, except for the 2-D INADEQUATE spectrum, were recorded at 300.40 and 75.45 MHz, respectively. The chemical shifts were referenced from TMS at 0.00 ppm for the ¹H spectra and from the central solvent peak at 77.0 ppm for the ¹³C spectra.

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	R^{+}_{3}														
	Atom	1	2	3	4	5	6	7	8	9	10	11	12	13	14
¹ H	H-3	4.25	5.02	4.16	4.47	5.35	4.02	3.53 4.11							3.71
	H-4	2.67 3.18	3.19 3.50	2.75 3.13	2.81 3.03	3.20 3.46	3.05	3.74	2.83	2.70 2.89	2.62 3.00	2.84 3.62	2.79	3.38 4.04	
	H-1′	1.37	,	1.81	3.02 3.13			1.68 ^a		1.37	1.41	1.70			
	H-1″								1.39	1.71	2.70 3.13		2.73 3.19		1.81 ^a
	H-2' H-2" CO ₂ Me		3.81	1.01						1.01		3.81		3.78	
	Ph				7.18 ~7.35	7.29 ~7.42					7.16 ~7.34		7.18 ~7.34	7.34 ~7.45	
¹³ C	C-2	195.0	184.9	195.1	194.4	192.5	191.1	190.2	199.0	199.0	198.7	190.0	198.4	187.5	189.7
	C-3	65.7	72.3	71.8	70.7	74.3	56.9	62.6	72.1	76.3	75.7	78.8	79.6	86.2	67.3
	C-4	23.8	18.0	21.4	21.4	23.7	15.0	27.9	31.2	28.6	28.0	26.9	24.0	27.5	40.7
	C-I'	15.8		24.0	36.3			23.5ª	22.5	21.5	22.5	20.8	41.0		21 68
	$C - 1^{\prime\prime}$			10.2					23.5	29.5	42.1		41.9		31.6"
	C-2″			10.2						84					
	CO ₂ Me		53.0 165.2							011		53.1 168.6		53.6 167.5	
	Ph			~	126.8 ~136.6 ~	126.6 ~135.4					126.9 ~135.8		127.0 ~135.5	125.5 ~135.5	

Table 1. ¹H NMR and ¹³C NMR data for the β -propiothiolactones in CDCl₃ (δ , ppm)

^a 4-CH₃.

Table 2. Calculated values of components for isotropic shielding constants (σ) and chemical shifts (δ) for the four-membered rings



Comp	ound	$(\sigma + \sigma)/2$	σ /2	otheo	eexp		
Х	Y	$(\sigma_{xx} + \sigma_{yy})/3$ (ppm)	(ppm)	(ppm) ^a	(ppm) ^b		
CH_2	H_2	125.5	53.6	24.3	22.4		
NH	H_2	125.7	53.4	24.3	19.0		
0	H_2	126.4	52.5	24.5	22.9		
S	H_2	126.9	47.8	28.7	28.1		
CH_2	0	116.9	39.4	47.1	47.8		
NH	0	120.1	42.2	41.1	38.3		
0	0	121.5	41.5	40.4	39.1		
S	Ο	119.5	30.0	53.9	56.9°		

^a $\delta^{\text{theo}} = 203.4$ (estimated value of σ^{TMS}) – σ , [$\sigma = (\sigma_{xx} + \sigma_{yy} + \sigma_{zz})/3$]. ^b Literature value³.

^c This work.

The ¹H NMR spectra were taken with a spectral width of 6 kHz and a 30° pulse angle, 32K data points and a repetition time of 1.5 s. For the ¹³C NMR spectra, a spectral width of 22.7 kHz, a pulse angle of 37.5° , 32K data points and a repetition time of 1.0 s were used.

The 2-D INADEQUATE experiment was recorded on a JEOL JNM-LA 400 spectrometer operating at 100.40 MHz (500 mg ml⁻¹ solution). The spectral widths were 20 and 40 kHz in the F_2 and F_1 dimensions, respectively. The matrix used 2K × 128 data points, and 16 scans were accumulated for each increment. The repetition time was 37.4 s and the ¹³C–¹³C coupling constant was set to 50 Hz.

Materials

Preparation of β -propiothiolactones by the cyclization reactions. To a magnetically stirred solution of substituted acrylic acid (10 mmol) in THF (15 ml) was added dropwise thiolacetic acid (13 mmol) in THF (15 ml), and the reaction mixture was heated at 50 °C for 18 h. The solvent and excess thiolacetic acid were evaporated, then dry-column flash chromatography of the residue with *n*-hexane and EtOAc afforded substituted *S*-acetyl-3-thiopropionic acid.

To a stirred solution of substituted *S*-acetyl-3-thiopropionic acid (5 mmol) in water (10 ml) was added concentrated H₂SO₄ (50 mg, 0.5 mmol), and the reaction mixture was heated under reflux for 5 h. The resulting mixture was extracted with CH₂Cl₂ (3 × 20 ml) and the combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to give crude substituted 3-mercaptopropionic acid. To a magnetically stirred solution of the crude substituted 3-mercaptopropionic acid and triethylamine (5.5 mmol) in diethyl ether (10 ml) at 5 °C was added dropwise methyl chloroformate (5.5 mmol) in diethyl ether (10 ml). After the dropping was complete, the reaction mixture was warmed to room temperature and the stirring continued for 3 h. The resulting mixture was washed with 0.5 M HCl and the separated organic layer was dried (MgSO₄), filtered and concentrated. Dry-column flash chromatography with *n*-hexane and EtOAc afforded β -propiothiolactone.

Preparation of *β***-propiothiolactones by the substitution reactions.** To a magnetically stirred solution of lithium bis(trimethylsilyl)amide (LHMDS) (4.0 ml of a 1.0 м solution in THF, 4.0 mmol) in THF at -78 °C in an acetone–dry-ice bath was added *β*-propiothiolactone (3.0 mmol) in THF (5.0 ml). After stirring for 30 min, an electrophile (5.0 mmol) (MeI, EtI, BnBr or ClCO₂Me) in THF (5.0 ml) at -78 °C was added dropwise via a syringe over 2 min. The reaction mixture was stirred at the same temperature for 1 h and then allowed to warm to 0 °C. After addition of saturated aqueous NH₄Cl solution, the resulting mixture was extracted with diethyl ether (2 × 10 ml). The combined organic layers were dried (MgSO₄), filtered, and concentrated. Dry-column flash chromatography with *n*-hexane and EtOAc afforded *α*-substituted *β*propiothiolactone.

Acknowledgments

This work was financially supported by the Development Fund for Industrial Basic Technology, administered by the Ministry of Trade, Industry and Energy (MOTIE, '95–'97) of Korea. We are also grateful to Ms Jong Ok Park for the 2-D INADEQUATE spectrum.

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