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Hydrogen bonding in push-pull 5-substituted-2-alkylidene-4-oxothiazolidines: ^{1}H-NMR spectroscopic study

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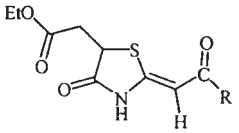
Abstract: Application of dynamic ^{1}H-NMR spectroscopy added to the understanding of the hydrogen bonds existing in the structurally related 5-substituted-2-alkylidene-4-oxothiazolidines in polar and apolar solvents. The equilibrated mixtures of these typical push-pull alkenes in $CDCl_3$ consist of the intramolecularly H-bonded (*E*)-isomer and intermolecularly H-bonded (*Z*)-isomer in varying proportions which depend on the solvent polarity. For the representative of the series, (*Z*)-2-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone, a concentration effect on the degree of intermolecular hydrogen bonding in apolar $CDCl_3$ has been studied.

Keywords: push-pull alkenes, hydrogen bonding, ^{1}H-NMR spectroscopy.

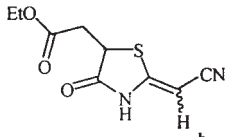
INTRODUCTION

In previous papers[1,2] we reported the regioselective preparation of the stereodefined 5-substituted thiazolidinone derivatives **1**–**5** which represent a class of push-pull alkenes.These compounds and new derivatives thereof[3,4] have attracted our attention due to (i) their possible biological activity[5,6] and (ii) utility as organic intermediates for the synthesis of push-pull polyenes[7] whose potential application in electronic and optical devices is promising.[8]



(*Z*)-**1**-**4**[a]

(*Z*)-**1** (R = Ph)
(*Z*)-**2** (R = NHPh)
(*Z*)-**3** (R = $NHCH_2CH_2Ph$)
(*Z*)-**4** (R = OEt)



(*Z*)-**5** and (*E*)-**5**[b]

[a] Isolated exclusively as the (*Z*)-isomers in ethanol as a solvent.
[b] Isolated as a *Z*/*E* mixture.

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We also found that the equilibrated mixtures of thiazolidinone derivatives in various solvents, enriched in one of the two configurational isomers, revert in the solid state upon the solvent evaporation almost completely to the more stable (*Z*)-isomer.[9] While the different *Z*/*E* proportions in the above examples are apparent result of the different solvent polarity as found for other push-pull alkenes,[10] the origin and the degree of favoring the (*Z*)- or (*E*)-isomer are compatible with the type of hydrogen bonding.[11] In this paper we now describe ^{1}H-NMR spectroscopic study as a method to distinguish between the intramolecular and intermolecular hydrogen bonding in (Z)-2-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (**1**), being an example of the thiazolidinone series. Furthermore, important aspect of this study emphasizes the concentration effect of the (*Z*)-**1** isomer on the extent of intermolecular hydrogen bonding in apolar solvent.

RESULTS AND DISCUSSION

Thiazolidinone derivatives **1**–**5**, possessing the exocyclic C=C bond inserted between the two electon-donor substituents (–NH–, –S–) and one electron-acceptor, *i.e.*, COR (derivatives **1**–**4**), or CN (derivative **5**) as a common structural unit, are susceptible to the extended n,π-conjugation.[12,13] The π-bond character of C=C bond is therefore drastically reduced, enabling *Z*/*E* isomerization to occur, with the population of (*Z*)- and (*E*)-isomers being dependent on (i) the medium polarity[2] and (ii) the nature of the substituents.[11]

Starting with the pure (*Z*)-isomer of the model substrate **1**, the *Z*/*E* process in lipophilic $CDCl_3$ was monitored at 25 ºC during the 15 hour-period in regular time intervals (60 minutes) by ^{1}H-NMR spectroscopy (300 MHz) *via* integration of the characteristic signals of both isomers (Fig. 1). The relevant ^{1}H-NMR data for thiazolidinones (*Z*)-**1** and (*E*)-**1** and other derivatives **2**–**4** are given in Table I. As illustrated in Fig. 1 the isomerization of (*Z*)-**1** isomer to its (*E*)-counterpart was followed by progressive disappearance of a singlet at δ 6.85 and simultaneous growth of the signal at δ 6.32, ascribed to the (*E*)-isomer. The olefinic proton of the (*Z*)-**1** isomer resonates at considerably lower field due to the deshielding effect of the *syn*-lactam nitrogen, relative to the *E*-analog having this proton in *syn* postion to less electronegative sulfur atom. Thus, proper configurational assignment, based on the consideration of this effect, magnetic anisotropy and mesomeric effects as well, was possible, not only for the whole series **1**–**5**, but for numerous derivatives thereof.[4]

Another diagnostic signal of the (*Z*)-**1** is that of the lactam proton which appears at δ 8.88. The ^{1}H-NMR spectrum of (*Z*)-**1** recorded almost immediately upon its dissolution in $CDCl_3$ (designated as the 0 time in Fig. 1) contains, as expected, nearly a perfect set of signals belonging due to the sole isomer.

However, small signals in this spectrum at δ 6.32 and 12.06 were ascribed respectively, to the olefinic and lactam protons of the (*E*)-**1** isomer. The presence of (*E*)-**1** isomer, regardless of its low abundance (< 5 %), indicates that the *Z*/*E* isomerization begins in time just needed to prepare sample and record its spectrum. The enhanced and clear splitting of signals of the diastereotopic CH_2 protons at C(5'), in addition to the signals mentioned above, was already noticed in the spectrum 1.

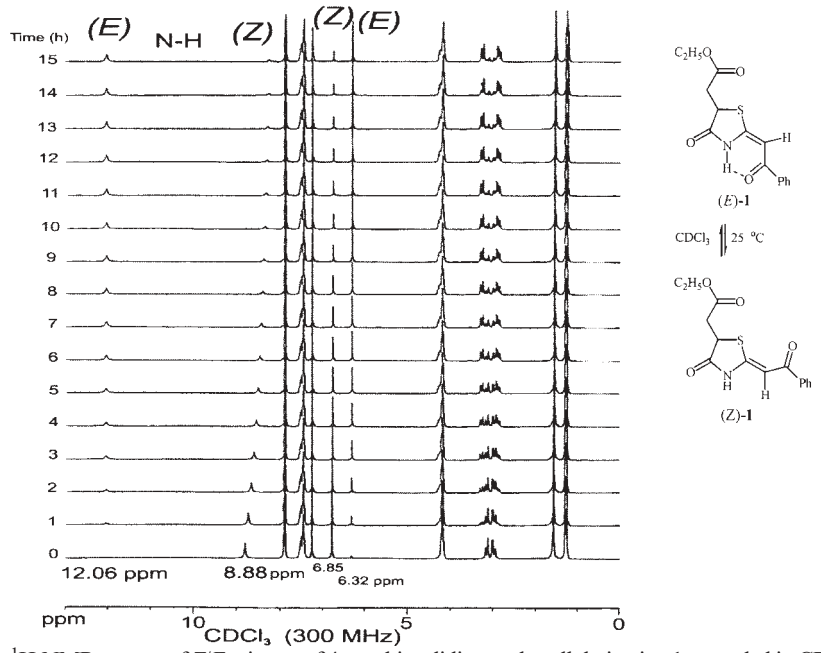


Fig. 1. ^{1}H-NMR spectra of *Z*/*E* mixture of 4-oxothiazolidine push-pull derivative **1**, recorded in $CDCl_3$ at room temperature, in regular 1 hour-time intervals.

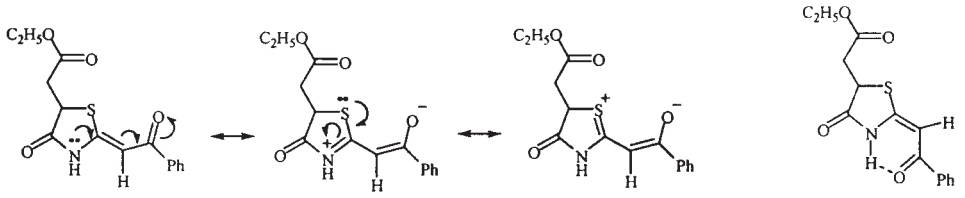
TABLE I. Selected ^{1}H-NMR chemical shifts of configurational isomers **1**–**5**

Isomer	R	Solvent	Vinyl H	Lactam H	*Z*/*E* ratio
(*Z*)-**1**	Ph	DMSO-d_6	6.78	11.93	100/0
(*Z*)-**2**	NHPh	DMSO-d_6	5.79	11.57	100/0
(*Z*)-**3**	$NHCH_2CH_2Ph$	DMSO-d_6	5.55	11.30	94.6[a]
(*E*)-**3**	$NHCH_2CH_2Ph$	DMSO-d_6	5.15	11.49	
(*Z*)-**3**	$NHCH_2CH_2Ph$	$CDCl_3$	5.54	9.44	22/78[a]
(*E*)-**3**	$NHCH_2CH_2Ph$	$CDCl_3$	4.90	11.43	
(*Z*)-**4**	OEt	$CDCl_3$	5.59	9.35[b]	> 99
(*Z*)-**4**	OEt	$CDCl_3$	5.59	8.70[b]	43/57[a]
(*Z*)-**4**	OEt	$CDCl_3$	5.59	8.28[b]	10/90[a]
(*E*)-**4**	OEt	$CDCl_3$	5.12	10.63	
(*Z*)-**5**		DMSO-d_6	4.93	12.06	
(*E*)-**5**		DMSO-d_6	4.87	12.06	

[a] Determined for the equilibrated *Z*/*E* mixture.

[b] A decrease of the extent of intermolecular hydrogen bonding in (*Z*)-**4**, which depends on concentration decrease, moves this proton upfield.

This is consistent with the dynamic behavior of the model substrate **1**, *i.e.*, the presence of both isomers.[2,6] Furthermore, that reflects the progressive decrease of the *Z*/*E* ratio



I **II** **III** **IV**

with time, which converged after 15 h to the ratio of 13/87. The ^{1}H-NMR chemical shifts for the lactam proton at 12.06 ppm and 8.88 ppm assigned to (*E*)-**1** and (*Z*)-**1** isomer respectively, provide evidence of hydrogen bonding. In the case of the (*E*)-**1** isomer prevailing contribution of the neutral structure, depicted as **IV**, to the ground state should be expected in apolar $CDCl_3$.[10]

Structure of that type is stabilized by intramolecular H-bonding.[13] Extensive n, π delocalization in the starting (*Z*)-**1** isomer can be described in terms of the neutral structure **I** and charge-separated dipolar resonance forms **II** and **III**. Polar solvents (EtOH, DMSO, acetone) enhance sulfur or nitrogen participation in the ground-state polarization, making the forms **II** and **III** particularly dominant. In fact, they increase the stability of the *Z*-configurated structure **1** *via* intermolecular H-bonding and strong electrostatic interactions, respectively.[14,15] Consistent with this, the stereospecific formation of the thiazolidinone derivative (*Z*)-**1** in ethanol is understandable and also the fact that the ^{1}H-NMR spectrum of (*Z*)-**1** in DMSO-d_6 does not change with time. However, strong intermolecular H-bonding, present in the original (*Z*)-isomer in solid state and polar solvents is suppressed in nonpolar solvent, inducing the isomerization around the double bond and formation of the intramolecularly H-bonded *E*-isomer. The *Z*/*E* mixture becomes progressively enriched in more stable *E*-isomer (Table II) during the course of relatively slow isomerization process (≈ 15 h). Accordingly, two sets of signals observed in the ^{1}H-NMR spectrum in $CDCl_3$ are compatible with the presence of both configurational isomers.

TABLE II. ^{1}H-NMR chemical shifts (ppm) of the NH proton in the (*Z*)-**1** isomer in $CDCl_3$ in function of concentration[a]

	(*E*)-**1** (%)	(*Z*)-**1** (%)	δNH_o	δNH_x	Chem. shift diff. ($\Delta\delta = \delta NH_o - \delta NH_x$)
Spectrum 0	4.49	95.51	8.880		
Spectrum 1	17.94	82.06		8.802	0.0783
Spectrum 2	29.88	70.12		8.729	0.1514
Spectrum 3	38.27	61.73		8.671	0.2088
Spectrum 4	44.12	55.88		8.619	0.2610
Spectrum 5	49.39	50.61		8.577	0.3028
Spectrum 6	55.03	44.97		8.535	0.3445
Spectrum 7	59.64	40.36		8.504	0.3758
Spectrum 8	64.96	35.04		8.473	0.4072

TABLE II. Continued

	(*E*)-**1** (%)	(*Z*)-**1** (%)	δNH_o	δNH_x	Chem. shift diff. ($\Delta\delta = \delta NH_o - \delta NH_x$)
Spectrum 9	69.26	30.74		8.447	0.4333
Spectrum 10	73.66	26.34		8.421	0.4594
Spectrum 11	77.66	22.34		8.400	0.4802
Spectrum 12	81.75	18.25		8.379	0.5011
Spectrum 13	83.50	16.50		8.379	0.5220
Spectrum 14	86.42	13.58		8.337	0.5429
Spectrum 15	87.10	12.90		8.327	0.5533

[a]δNH_o value spectrum 0 (recorded immediately upon dissolution);
δNH_x values from spectra 1 to 15 recorded in 1 h intervals (Fig. 1).

At this point attention should be drawn to the experimental fact that the addition of trifluoroacetic acid to a chloroform solution of the structurally similar (*Z*)-**4** isomer initiates an immediate *Z*/*E* isomerization, giving rise to a mixture in a 29/71 ratio of the *Z*- and *E*-isomers. As the ratio remains pretty much the same after 75 min, it is likely that the isomer equilibration under these conditions is instantaneous, or in other words equally fast as the isomerization itself. That is the reason why $CDCl_3$, used for the ^{1}H-NMR spectroscopy, was passed through the neutral alumina to neutralize eventually the traces of DCl.

Obviously, the key factor which determines the *Z*/*E* ratio in $CDCl_3$ is the strength of the hydrogen-bonding interactions. The high chemical shift of the lactam NH proton in the (*E*)-**1** isomer (δ 12.06), involved in the intramolecular NH· - -O=C bond formation, indicates strong deshielding effect of C=O group. The unchanged position of this signal and its growth, being quantitatively proportional to the simultaneous concentration increase of the (*E*)-isomer are in agreement with the internal hydrogen bonding.[16] Following this reasoning, the intramolecular hydrogen bonding in the major (*E*)-**1** isomer is stronger than the intermolecular hydrogen bonding in the (*Z*)-**1**, as evidenced by the appearance of the lactam NH proton at higher field (δ 8.88).

Contrary to the strong ionic-type intermolecular hydrogen bonds formed between the solvents such as DMSO or ethanol and (*Z*)-**1** isomer (dominant structures **II** and **III**), the solute-solvent electrostatic interactions are negligible in $CDCl_3$.[4,14] That reflects the difference in the NH chemical shift of the (*Z*)-**1** isomer in DMSO (δ 11.93) relative to $CDCl_3$ (δ 8.88). As a result, apolar solvents will weaken the intermolecular hydrogen bond as it is formed by neutral donor and acceptor groups, *i.e.*, N–H and O=C. The data in Table II (taken from Fig. 1) indicate a progressive upfield direction of chemical shift of the NH proton with decreasing concentration of the (*Z*)-**1** isomer. This is attributed to the decrease in degree of intermolecular hydrogen bonding with decreasing concentration. Accordingly, the ^{1}H-NMR chemical shift values show that the decrease in the formation of intermolecular hydrogen bonds, accompanying a decrease in concentration of the (*Z*)-**1** isomer, results in a shielding of the hydrogen-bonded NH proton. Finally, as depicted in Fig. 2, there is a good linear relationship between the chemical shifts of the lactam hydrogen in (*Z*)-**1** isomer and its concentration.

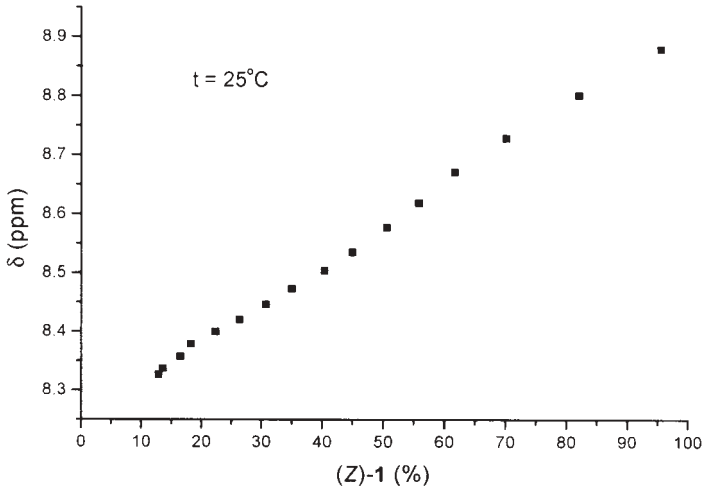


Fig. 2. Plot of the NH chemical shift difference versus concentration of (*Z*)-**1** at room temperature (data taken from Table II).

Investigation of the temperature effect on rates of double bond isomerisation in push-pull thiazolidinone derivatives **1**–**5** in order to derive thermodynamic parameters, such as the entropy of activation $\Delta S^{\neq}$, the enthalpy of activation $\Delta H^{\neq}$ and activation energy of *Z*/*E* process, is in progress.

EXPERIMENTAL

*General procedure for the preparation of push-pull 4-oxothiazolidine derivatives **1**–**5***[2]

To a stirred suspension of activated β-oxonitrile (3 mmol), prepared by standard procedure, and diethyl 2-mercaptosuccinic acid ester (≈ 1 % molar excess) in 5–10 ml of absolute ethanol, a catalytic amount of K_2CO_3 was added. The mixture was brought to reflux and reaction mixture was stirred for 3–7.5 h. The reaction mixture was cooled down to rt and separated solid was filtered, washed with ethanol and recrystallized from 96 % ethanol to provide the final product in 42–70 % yield. The structural assignments of all isolated products **1**–**5** were made on the basis of spectroscopic data (IR, ^{1}H- and ^{13}C-NMR, MS, UV) and elemental analysis. Melting points were determined on a Micro-Heiztisch Boetius PHMK apparatus and Büchi apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer 1725X and are reported as wave numbers (cm^{-1}). Samples for IR spectral measurements were prepared as KBr disks. The NMR spectra were obtained using a Varian Gemini 2000 instrument and Bruker AMX-300 (^{1}H at 200 MHz and 300 MHz and ^{13}C at 50.3 MHz). Chemical shifts are reported in parts per million (ppm) on the δ scale from TMS as an internal standard in the solvents specified. Low-resolution mass spectra were recorded using a Finnigan MAT 8230 BE spectrometer. Isobutane was used as the ionizing gas for the chemical ionization (CI) mass spectra. The UV spectra were measured on a Beckman DU-50 spectrophotometer. Analytical thin-layer chromatography (TLC) was carried out on Kieselgel G nach Stahl, and the spots were visualized by iodine. Column chromatography was carried out on SiO_2 (silica gel 60 A, 12-26, ICN biomedicals). Elemental analyses were performed at the microanalysis laboratory at the Department of Chemistry, University of Belgrade.

ИЗВОД

ВОДОНИЧНА ВЕЗА У PUSH-PULL 5-СУПСТИТУИСАНИМ 2-АЛКИЛИДЕН-4-ОКСОТИАЗОЛИДИНИМА: ^{1}H-NMR СПЕКТРОСКОПСКО ПРОУЧАВАЊЕ

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Применом динамичке ^{1}H-NMR спектроскопије дошло се до бољег разумевања о врсти водоничних веза које постоје у структурно сличним 5-супституисаним 2-алкилиден-4-оксотиазолидинима у поларним и аполарним растварачима. Уравнотежене смесе ових типичних push-pull алкена у $CDCl_3$ садрже (*E*)-изомер везан интрамолекулском водоничном везом као и интермолекулски водоничном везом везан (*Z*)-изомер у различитим односима, који зависе од поларности растварача. У случају типичног представника серије, (Z)-2-(5-етоксикарбонилметил-4-оксотиазолидин-2-илиден)-1-фенилетанона, утицај концентрације на степен стварања интермолекулске водоничне везе у аполарном $CDCl_3$ је такође проучаван.

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