Available online at www.sciencedirect.com
ScienceDirect
Journal of Molecular Structure 800 (2006) 85–92
Journal of MOLECULAR STRUCTURE
www.elsevier.com/locate/molstruc

^{1}H NMR Dynamic study of thermal Z/E isomerization of 5-substituted 2-alkylidene-4-oxothiazolidine derivatives: Barriers to rotation about C=C bond

R. Marković [a,b,*], M. Baranac [a,b], N. Juranić [c], S. Macura [c], I. Cekić [d], D. Minić [d]

[a] Faculty of Chemistry, University of Belgrade, Studentski trg 16, P.O. Box 158, 11001 Belgrade, Serbia and Montenegro
[b] Center for Chemistry ICTM, P. O. Box 815, 11000 Belgrade, Serbia and Montenegro
[c] Department of Biochemistry and Molecular Biology, Mayo Graduate School, Mayo Clinic and Mayo Foundation, Rochester, MN 55905, USA
[d] Faculty of Physical Chemistry, University of Belgrade, Studentski trg 12-16, 11001 Belgrade, Serbia and Montenegro

Received 23 February 2006; received in revised form 21 March 2006; accepted 25 March 2006
Available online 11 May 2006

Abstract

The rotational barriers between the configurational isomers of two structurally related push–pull 4-oxothiazolidines, differing in the number of exocyclic C=C bonds, have been determined by dynamic ^{1}H NMR spectroscopy. The equilibrium mixture of (5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (**1a**) in $CDCl_3$ at room temperature to 333 K consists of the *E*- and *Z*-isomers which are separated by an energy barrier $\Delta G^{\#}$ 98.5 kJ/mol (at 298 K). The variable-temperature ^{1}H NMR data for the isomerization of ethyl (5-ethoxycarbonylmethylidene-4-oxothiazolidin-2-ylidene)ethanoate (**2b**) in DMSO-d_6, possessing the two exocyclic C=C bonds at the C(2)- and C(5)-positions, indicate that the rotational barrier $\Delta G^{\#}$ separating the (2*E*,5*Z*)-**2b** and (2*Z*,5*Z*)-**2b** isomers is 100.2 kJ/mol (at 298 K). In a polar solvent-dependent equilibrium the major (2*Z*,5*Z*)-form (>90%) is stabilized by the intermolecular resonance-assisted hydrogen bonding and strong 1,5-type S···O interactions within the S–C=C–C=O entity. The ^{13}C NMR $\Delta\delta_{C(2)C(2')}$ values, ranging from 58 to 69 ppm in **1a–d** and 49-58 ppm in **2a–d**, correlate with the degree of the push-pull character of the exocyclic C(2)=C(2′) bond, which increases with the electron withdrawing ability of the substituents at the vinylic C(2′) position in the following order: COPh ∼ COEt > CONHPh > $CONHCH_2CH_2Ph$. The decrease of the $\Delta\delta_{C(2)C(2')}$ values in **2a–d** has been discussed for the first time in terms of an estimation of the electron donor capacity of the –S– fragment on the polarization of the C=C bonds.
© 2006 Elsevier B.V. All rights reserved.

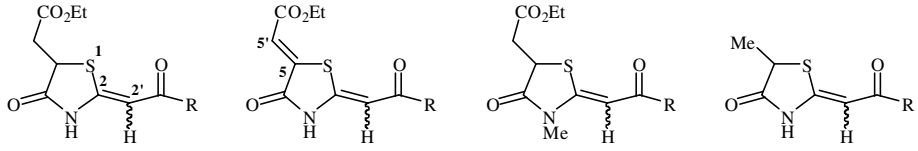
Keywords: 4-Oxothiazolidines; *Z*/*E*-isomerization; Rotational barrier; ^{1}H NMR spectroscopy

1. Introduction

Since the concept of push–pull alkenes was reviewed by Sandström [1], the physicochemical properties and chemical reactivity of numerous functionalized compounds of that type have been extensively studied [2–7]. 5-Substituted 4-oxothiazolidines **1** and **2** with one and two exocyclic double bonds attached to thiazolidine ring, respectively, exemplify typical push-pull compounds which can exist in different configurational and conformational forms. Stereodefined 4-oxothiazolidines **1** and **4**, synthesized according to procedures reported by us [8,9], attracted our attention due to their potential biological activity [10,11]. In addition, they exhibit interesting chemical properties related, for example, to regiospecific bromination-rearrangement process of selected 4-oxothiazolidines **1** [12] and pyridine-assisted bromine transfer from the C=C bond to the C(5) position, followed by the formation of the pyridinium salts via nucleophilic substitution [13].

* Corresponding author. Tel.: +381 11 3282 111x741; fax: +381 11 636 061.
E-mail address: markovic@helix.chem.bg.ac.yu (R. Marković).

0022-2860/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.molstruc.2006.03.075



1a-d **2a-d** **3a-d** **4a-d**

a: R = Ph; **b:** R = OEt; **c:** R = NHPh; **d:** R = $NHCH_2CH_2Ph$;

They also represent an excellent model for investigation of the effects of weak noncovalent interactions on structure–reactivity relationship in solution and in the solid state [14–20]. The equilibrated mixtures of structurally related 4-oxothiazolidines **1a**–**d** consist of the intramolecularly H-bonded (*E*)-isomer and intermolecularly H-bonded (*Z*)-isomer in varying proportions which depend on the solvent polarity [21,22]. The upfield chemical shift of the NH proton of the (*Z*)-**1a** isomer, observed during the *Z*/*E* process in $CDCl_3$ as a function of temperature increase, is explained in terms of a decrease of intermolecular H-bonding, resulting in a greater amount of a free or unassociated *Z*-isomer [23,24]. During the course of the *Z*/*E* isomerization of (*Z*)-**1a** in nonpolar $CDCl_3$ an equilibrated mixture is formed, enriched in the *E*-isomer (*Z*/*E* ratio $\sim$ 10/90 at room temperature). Additionally, temperature-dependent chemical shift differences expressed as $\Delta\delta/\Delta T$ coefficients serve as a parameter for distinction between the intermolecularly hydrogen-bonded (*Z*)-**1a** isomer and free NH groups in derivative **1a**. In principle, the variable-temperature NMR data of that type provide information regarding the hydrogen bonding patterns (inter- vs intra-) in our model system and also in related amides and peptides [23–26]. In light of these results, we wish to report here (i) detailed NMR spectroscopic investigation of the stereodynamic behavior of 4-oxothiazolidines **1** and **2** associated with the kinetics of the configurational isomerization of the stereodefined (*Z*)-**1a** in $CDCl_3$ and (2*E*,5*Z*)-**2b** in DMSO-d_6 and (ii) determination of the energy barriers separating the configurational isomers of substrates **1a** and **2b**. In order to obtain additional structural information regarding the push-pull nature of the 4-oxothiazolidine derivatives, the IR data for selected compounds **1**–**4** were also analyzed in terms of vibrational interactions between the electron-donor(s), electron-acceptor and intervening exocyclic C=C bond.

2. Experimental

The NMR spectra for characterization were obtained using a Varian Gemini 2000 instrument (^1H at 200 MHz, ^{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. Variable-temperature ^1H NMR measurements in the temperature range 273–343 K were carried out on a Bruker AC-300 spectrometer using $CDCl_3$ as a solvent which was dried over activated molecular sieves (4 Å) for one day. In the case of deuterated DMSO, the solvent was distilled from CaH_2 prior to use. The concentrations of $CDCl_3$ solutions were 0.011 or 0.016 M in the case of (*Z*)-**1a** and 0.010 M for (2*E*,5*Z*)-**2b** in DMSO, unless otherwise indicated. The variable temperature was computer controlled employing the BVT 2000 unit. The internal temperature was calibrated with methanol and ethylene glycol using the Bruker Batman program. Caution was taken to increase the temperature slowly when using $CDCl_3$, especially at 333 K to avoid solvent evaporation. The sample was equilibrated at the given temperature and a 128-scan spectrum was recorded with 0.5 Hz per point digital resolution. All chemical shifts were referenced to the solvent residual signal. Typical parameters were: acquisition time 1.892 s, spectral width 7997.6 Hz with 256 repetitions and 32 k data points. 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 1725× spectrophotometer and are reported as wave numbers (cm^{-1}). Samples for IR spectral measurements were prepared as KBr disks. 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 Å, 12–26, ICN Biomedicals). Elemental analyses were performed at the microanalysis laboratory at the Faculty of Chemistry, University of Belgrade.

The structural assignments of all isolated products were made on the basis of spectroscopic data (IR, ^1H and ^{13}C NMR, MS, UV) and elemental analysis [8,9]. For the configurational isomers of derivatives **1a** and **2b**, used in the variable-temperature (VT) ^1H NMR experiments, the following ^1H NMR data are pertinent to the discussion.

*2.1. (Z)-(5-Ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (**1a**)*

^1H NMR ($CDCl_3$): δ 1.26 (t, 3H, CH_3, $J = 7.2$ Hz), 3.00 (dd, 1H, $C\underline{H}_AH_BCH_XS$, $J_{AB} = 17.5$ Hz, $J_{AX} = 8.2$ Hz), 3.15 (dd, 1H, $CH_A\underline{H}_BCH_XS$, $J_{AB} = 17.5$ Hz, $J_{BX} = 4.3$ Hz), 4.19 (q, 2H, CH_2O,$J = 7.2$ Hz), 4.22 (dd, 1H, CH_XS, $J_{AX} = 8.2$ Hz, $J_{BX} = 4.3$ Hz), 6.85 (s, 1H, =CH), 7.39–7.53 (m, 3H, *m*- and *p*-Ph), 7.88–7.93 (m, 2H, *o*-Ph), 8.88 (s, 1H, NH).

2.2. (E)-(5-Ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (**1a**)

^{1}H NMR ($CDCl_3$): δ 1.29 (t, 3H, CH_3, $J = 7.2$ Hz), 2.91 (dd, 1H, $C\underline{H}_AH_BCH_XS$, $J_{AB} = 17.6$ Hz, $J_{AX} = 10.1$ Hz), 3.28 dd, 1H, $CH_A\underline{H}_BCH_XS$, $J_{AB} = 17.6$ Hz, $J_{BX} = 3.7$ Hz), 4.22 (q, 2H, CH_2O, $J = 7.2$ Hz), 4.29 (dd, 1H, CH_XS, $J_{AX} = 10.1$ Hz, $J_{BX} = 3.7$ Hz), 6.32 (s, 1H, = CH), 7.41–7.59 (m, 3H, *m*- and *p*-Ph), 7.88–7.93 (m, 2H, *o*-Ph), 12.06 (s, 1H, NH). Anal. Calcd for $C_{15}H_{15}NO_4S$: C, 59.00; H, 4.95; N, 4.59; S, 10.50. Found: C, 58.76; H, 5.02; N, 4.68; S, 10.54.

2.3. (2E,5Z)-Ethyl (5-ethoxycarbonylmethylidene-4-oxothiazolidin-2-ylidene)ethanoate (**2b**)

^{1}H NMR ($CDCl_3$): 1.30 (t, 3H, CH_3, $J = 7.1$ Hz), 1.35 (t, 3H, CH_3, $J = 7.1$ Hz), 4.22 (q, 2H, CH_2O, $J = 7.1$ Hz), 4.31 (q, 2H, CH_2O, $J = 7.1$ Hz), 5.35 [s, 1H, = CH (C2)], 6.88 [s, 1H, = CH (C5)], 10.82 (s, 1H, NH).

2.4. (2Z,5Z)-Ethyl (5-ethoxycarbonylmethylidene-4-oxothiazolidin-2-ylidene)ethanoate (**2b**)

^{1}H NMR ($CDCl_3$): 1.32 (t, 3H, CH_3, $J = 7.0$ Hz), 1.35 (s, 3H, CH_3, $J = 7.0$ Hz), 4.25 (q, 2H, CH_2O, $J = 7.0$ Hz), 4.32 (q, 2H, CH_2O, $J = 7.0$ Hz), 5.83 [s, 1H, = CH (C2)], 6.80 [s, 1H, = CH (C5)], 10.54 (s, 1H, NH). Anal. Calcd for $C_{11}H_{13}NO_5S$: C, 48.73; H, 4.79; N, 5.16. Found: C, 48.61; H, 4.84; N, 5.27.

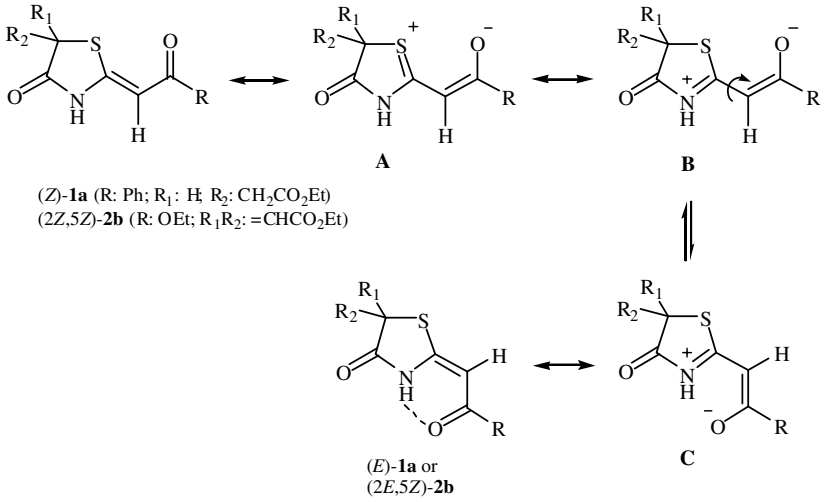
3. Results and discussion

3.1. Stereodynamic behavior of push-pull thiazolidine derivatives **1a** and **2b**

The configurational isomerization of the stereodefined (*Z*)-**1a** in nonpolar $CDCl_3$ and (2*E*,5*Z*)-**2b** in DMSO-d_6 is characteristic process for push-pull alkenes [1,27,28]. It is based on a lowering of the rotational barrier of the C=C bond at the C(2)-position as a consequence of the electronic n,π-interactions between the two electron-donors (-NH and -S-) and one electron-acceptor (the COPh group for **1a** and CO_2Et for **2b**) through the π-conjugated bond (Scheme 1).

We have recently shown that the *push-pull effect*, i.e., the extent of the donor-acceptor interactions, has in combination with other electronic and steric effects, decisive influence on the chemical properties and reactivity of these heterocyclic compounds [12,20]. The ground-state structure of push–pull thiazolidines can be represented as a combination of the neutral resonance forms **1a** and **2b** and charge-separated dipolar resonance forms **A**–**C**. The push-pull character of thiazolidines **1** and **2**, explained in terms of the resonance structures, reflects the extended delocalization in the molecule [15,27]. In this sense the ^{13}C chemical shift difference ($\Delta\delta_{C2,\ C2'}$) between the two olefinic carbons provides an assessment of the degree of n,π-conjugation encompassing the N—C=C—C=O and S—C=C—C=O entities of derivatives **1a**–**d** and **2a**–**d** (Table 1) [29].

In all thiazolidines **1a**–**d** and **2a**–**d** the high field ^{13}C chemical shifts (88.9–97.3 ppm) for the acceptor-substituted C(2′) atoms, and low field shifts (145.0–161.6 ppm) for the donor-substituted C(2) atoms are typical [9]. The ^{13}C NMR $\Delta\delta_{C(2)C(2')}$ values, ranging from 57.6 to 68.9 ppm in **1a**–**d** and 48.5 to 58.0 ppm in **2a**–**d**, indicate that the degree of the push-pull character of the exocyclic C(2)=C(2′) bond increases with the electron accepting ability of the substituents at the vinylic C(2′) position in the following order: COPh ~ COEt > CONHPh > $CONHCH_2CH_2Ph$. The larger numerical values of $\Delta\delta_{C2,C2'}$ in **1a**–**d**, relative to the corresponding $\Delta\delta_{C2,C2'}$ values in **2a**–**d**, correlate with a decrease of the charge polarization of the C(2)=C(2′) bond of the push–pull thiazolidines **2a**–**d** [4,30]. A drop of the $\Delta\delta_{C2,C2'}$ values in compounds **2** for ~ 5–10 ppm reflects the influence of the C(5)=C(5′) bond in thiazolidines **2** on the lowering of the push-pull



Scheme 1.

Table 1
^{13}C NMR Chemical shifts (σ in ppm) of olefinic carbon atoms in **1a–d** and **2a–d**[a]

Entry	Compound[b]	Solvent	C-2	C-2′	$\Delta\delta_{C2,C2'}$	C-5	C-5′	$\Delta\delta_{C5,\ C5'}$
1	(*Z*)-**1a**	DMSO-d_6	161.6	94.9	66.7			
2	(*E*)-**1a**	$CDCl_3$	158.4	94.5	63.9			
3	(*Z*)-**1b**	$CDCl_3$	154.8	91.6	63.2			
4	(*E*)-**1b**	$CDCl_3$	154.4	89.0	65.4			
5	(*Z*)-**1b**	DMSO-d_6	157.8	88.9	68.9			
6	(*Z*)-**1c**	DMSO-d_6	153.5	93.3	60.2			
7	(*Z*)-**1d**	DMSO-d_6	150.8	93.2	57.6			
8	(*E*)-**1d**	$CDCl_3$	150.8	91.1	59.7			
9	(2*E*,5*Z*)-**2a**	$CDCl_3$	153.5	97.0	56.5	139.5	117.3	22.2
10	(2*Z*,5*Z*)-**2b**	$CDCl_3$	150.7	95.3	55.4	142.5	116.7	25.8
11	(2*E*,5*Z*)-**2b**	$CDCl_3$	150.6	92.6	58.0	140.2	116.2	24.0
12	(2*Z*,5*Z*)-**2c**	DMSO-d_6	148.0	97.3	50.7	145.2	113.6	31.6
13	(2*E*,5*Z*)-**2c**	DMSO-d_6	148.0	96.7	51.3	145.3	114.0	31.3
14	(2*Z*,5*Z*)-**2d**	DMSO-d_6	145.8	97.2	48.6	145.8	113.0	32.8
15	(2*E*,5*Z*)-**2d**	DMSO-d_6	145.0	96.5	48.5	145.0	113.7	31.3

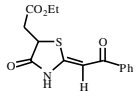
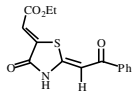
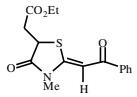
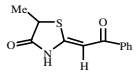
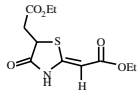
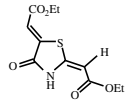
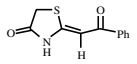
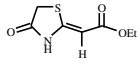
[a] Relative to the solvent residual signal.
[b] See structures **1a–d** and **2a–d** for the numbering of carbon atoms.

effect of the C(2)=C(2′) bond. The push-pull character of the C(5)=C(5′) bond, with just one donor and one acceptor, is significantly reduced in comparison to the C(2)=C(2′) bond, as demonstrated by $\Delta\delta_{C5,C5'}$ values, ranging from 22.2 to 32.8 ppm (Table 1, entries 9–15). In addition, the donor capacity of the —S— fragment in the thiazolidine series **2** – in contrast to series **1** – is being now dissipated between the two exocyclic C=C bonds. Accordingly, the decrease of the $\Delta\delta_{C2,C2'}$ values of ~5–10 ppm in derivatives **2** with respect to these of the counterparts **1** must be roughly equal to the half of the total donor capacity of the sulfur atom. For example, the calculated $\Delta\delta_{C2,C2'}$ values in $CDCl_3$ for the isomers (*E*)-**1b** and (2*E*,5*Z*)-**2b** with identical acceptor, the CO_2Et group, attached to the C=C bonds at the C(2) and C(5) positions, are 65.4 and 58.0 ppm, respectively (Table 1, entries 4 and 11). The two compounds show characteristic drop in $\Delta\delta_{C2,C2'}$ values of 7.4 ppm and for the (*Z*)-**1b**/(2*Z*,5*Z*)-**2b** pair the difference in $CDCl_3$ is 7.8 ppm (Table 1, entries 3 and 10). The data in Table 1 exemplify also larger $\Delta\delta_{C2,C2'}$ values in polar DMSO, which amount to 9.5 ppm for the derivative pair (*Z*)-**1c**/(2*Z*,5*Z*)-**2c** (see entries 6 and 12) and 9 ppm for the pair (*Z*)-**1d**/(2*Z*,5*Z*)-**2d** (entries 7 and 14). These data indicate that the electron-releasing power of the thioether moiety in the cyclic systems enhances the π-electron polarization, expressed through the $\Delta\delta_{C,C}$ parameter, by approximately 15–19 ppm. The lower polarization of the (*Z*)-C(5)=C(5′) bond in thiazolidines **2**, combined with the unfavorable steric and dipole-dipole interactions of the *E*-configurated C(5)-double bond, makes the 5*Z*-configuration fixed and not prone to the *Z*/*E* isomerization [9]. Recently, the reliable method of quantification of the push–pull effect in an extensive series of substituted alkenes, based on the quotient of the occupation numbers of π bonding and π^* antibonding orbitals of the C=C bond, instead of the $\Delta\delta_{C,C}$ parameter, has been reported [31,32].

Valuable information regarding the presence of various functionalities in 4-oxothiazolidine derivatives, and their push–pull character based on interactions between the electron-donor(s), electron-acceptor and intervening exocyclic C=C bond, were obtained by an analysis of the IR spectra of **1–4** (Table 2) recorded in the solid state. As a comparison, the principal frequencies of the IR spectra of 5-unsubstituted 4-oxothiazolidines (*Z*)-**5** and (*Z*)-**6**, previously reported by Taylor [33], are given (entries 7 and 8). All compounds **1–6** containing the five-membered lactam ring as a common skeletal fragment show weak to moderate NH band at 3165–3240 cm^{-1} and C=O stretching absorption band in the region of 1729–1689 cm^{-1}. Thanks to its relatively constant position, high intensity and relative freedom from interfering bands, CO_{ring} band is one of the most typical in the IR spectra of heterocycles **1–6**. Within the given range, the position of this band depends primarily on conjugation effect and nature of the neighboring lactam substituent (hydrogen or methyl group). Thus, the CO band of the parent compound (*Z*)-**1a**, which appears at 1729 cm^{-1}, is shifted in (2*E*,5*Z*)-**2a** to lower frequency (1689 cm^{-1}) due to the conjugation of the ring carbonyl with exocyclic C=C bond at the C-5 position (Table 2, entries 1 and 2). As indicated in Table 2, strong CO_{ring} band of *N*-methyl-substituted 4-oxothiazolidine (*Z*)-**3a** at 1706 cm^{-1} is 23 cm^{-1} below that of the thiazolidine derivative (*Z*)-**1a**. The lower frequency of CO_{ring} upon the replacement of NH by NMe correlates nicely with inductive effect of methyl group. It should be noted that the CO_{ring} frequency in (*Z*)-**1b** is lower than that of the 5-unsubstituted analogue (*Z*)-**6** (Table 2, entries 5 and 8). A decrease of the CO_{ring} frequency for about 14 cm^{-1} can be rationalized by hydrogen bonding effect.

This is proved by the X-ray analysis of the (*Z*)-**1b** isomer, which shows that the molecular packing is controlled by intermolecular hydrogen bonds between the NH group and the C-4 carbonyl of an adjacent molecule [20]. The existence of particularly favorable 1,5-type S···O interactions within the S—C=C—C=O subunit in (*Z*)-**1b** nicely correlates with the shorthening of the nonbonded distance

Table 2
Principal bands in the IR spectra of 2-alkylidene-4-oxothiazolidine derivatives **1**–**6** (KBr pellet)

Entry	Compound	ν(N—H)	ν(C2=C2′)[a]	ν(C=O)$_{ring}$	ν(C=O)$_{exo}$	ν(C=O)$_{ester}$
1	 (*Z*)-**1a**	3239	1515	1729	1618	1729
2	 (2*Z*,5*Z*)-**2a**	3165	1536	1689	1641	1689
3	 (*Z*)-**3a**	–	1515	1706	1627	1731
4	 (*Z*)-**4a**	3254	1522	1708	1627	–
5	 (*Z*)-**1b**	3184	1604	1710	1690	1726
6	 (2*E*,5*Z*)-**2b**	3256	1606	1696	1686	1696
7	 (*Z*)-**5**	3210	1504	1728	1618	–
8	 (*Z*)-**6**	3240	1568	1724	1665	–

[a] The enamine band arising from vibrational couplings of the C=C, C—N and N—H bonds.

S···O (2.873 Å) with respect to the sum of the van der Waals radii (3.22 Å).

The strong-intensity band in the IR spectra of **1a**, **1b** and **3a** (Table 2, entries 1, 5 and 3, respectively), with the maximum at 1729 cm^1 for **1a**, is assigned to the carbonyl fragment of the ethoxycarbonylmethyl group at the C-5 position. The lower frequency peak of this band in **2a**, appearing at 1689 cm^{-1},indicates again the conjugation effect due to the presence of the exocyclic C=C group at the C-5 position. The IR spectra of 4-oxothiazolidine derivatives **1–6** show also a third medium strong peak within the 1618–1690 cm^{-1} region, which is assigned to the exocyclic CO group. It should be emphasized that the band overlapping of the CO_{ring} and CO_{exo} modes at 1729 and 1689 cm^{-1} is observed in compounds (*Z*)-**1a** and (2*Z*, 5*Z*)-**2a**, respectively. The very strong and broad enamine band [3,33,34], resulting from an asymmetric combination of the exocyclic C=C and C—N stretching motions, with a contribution of the in-plane N—H bending mode in case of the (*Z*)-**1a**, (2*Z*, 5*Z*)-**2a** and (*Z*)-**4a** and (*Z*)-**5** isomers, is centered at about 1515 cm^{-1} in the IR spectra of all 4-oxothiazolidines with the COPh group at C-2′ atom (Table 2, entries 1, 2, 4 and 7). In the case of compounds (*Z*)-**1b**, (2*E*,5*Z*)-**2b** and (*Z*)-**6** (Table 2, entries 5, 6 and 8), containing the ethoxycarbonyl group at the same position, this band is shifted to higher frequency.

The stereodynamic behavior associated with the isomerization rate of (*Z*)-**1a** to (*E*)-**1a** at different temperatures in $CDCl_3$ was followed by progressive disappearance of the singlet at δ 6.85 ppm assigned to the olefinic proton of (*Z*)-**1a** and simultaneous appearance of the signal at δ 6.32 ppm for the (*E*)-isomer (Table 3, entries 1 and 2).

In Fig. 1a typical resonances in the 6–9 ppm range in a set consisting of 25 ^{1}H NMR spectra are shown [21], when the *Z*/*E* process of **1a** was monitored at 328 K at regular time intervals (15 min). In Fig. 1b plots are shown, correlating the decrease of the (*Z*)-**1a** isomer with the

^{1}H NMR measurable time-dependent Z/E process conducted at different temperatures.

Fig. 2 depicts series of partial ^{1}H NMR spectra of isomers (2*E*,5*Z*)-**2b** and (2*Z*,5*Z*)-**2b** (only the resonances of the olefinic protons are shown; see Table 3, entries 3 and 4) recorded in DMSO-d_6 during the 2*E*,5*Z*/2*Z*,5*Z*-isomerization process at 298 K (part A) and 328 K (part B).

The ratios of the (2*E*,5*Z*)-**2b** versus (2*Z*,5*Z*)-**2b** isomers were calculated by the integration of the signals at δ 5.63 and 5.69 ppm, corresponding to the C(2′)-vinylic protons of the (2*E*,5*Z*)-**2b** and (2*Z*,5*Z*)-**2b** isomers, respectively. The kinetics of the isomerization at different temperatures can be also studied by the determination of the configurational ratio via integration of the C(5′)-H signals at δ 6.68 ppm [the (2*E*,5*Z*)-**2b** isomer] and 6.59 ppm [the (2*Z*,5*Z*)-**2b** isomer]. In Fig. 3, the decrease of the concentration of (2*E*,5*Z*)-**2b** is plotted as a function of time of the 2*E*,5*Z*/2*Z*,5*Z*-process at three different temperatures. The experimental values for $t_{1/2}$, defined as the time required to reach the 50:50 ratio of isomers are 10.5 h at room temperature and less than 10 min at 328 K.

Table 3
Selected ^{1}H NMR chemical shifts (σ in ppm) of compounds **1a** and **2b**,[a] monitored in the isomerization study

Entry	Compound	Solvent	H-2′	H-5′
1	(*Z*)-**1a**	$CDCl_3$	6.85	
2	(*E*)-**1a**	$CDCl_3$	6.32	
3	(2*Z*,5Z)-**2b**	DMSO-d_6	5.69	6.59
4	(2*E*,5*Z*)-**2b**	DMSO-d_6	5.63	6.68

[a] Relative to TMS as an internal standard.

3.2. Kinetic and thermodynamic aspects of the configurational isomerization

The mechanism of the (*Z*)-**1a** ⇆ (*E*)-**1a** isomerization in $CDCl_3$ and (2*E*,5*Z*)-**2b** ⇆ (2*Z*,5*Z*)-**2b** isomerization in DMSO-d_6 is:

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} A^* \xrightarrow{k_2} B$$

where A and B are concentrations of the configurational isomers and A^* is the concentration of the activated complex. Based on the steady state approximation and assuming that $k_{-1}<k_1$ reaction is further approximated to first order reaction. The rate constant, k, is determined as the slope of the best straight line fitted through the first ten points, when $\ln[A/A_o]$ is plotted against time (t). The slope of the Arrhenius plot (Fig. 4) gives the energy of activation and the intercept at $1/T = 0$ gives the frequency factor A (Table 4).

Thermodynamic and activation parameters calculated from the Eyring equation by substituting $\Delta G_0^{\neq} = \Delta H_0^{\neq} - T\Delta S_0^{\neq}$ are listed in Table 5.

As data indicate the barrier for rotation around the exocyclic C(2)=C(2′) bond separating the (*Z*)-**1a** and (*E*)-**1a** isomers in $CDCl_3$ is 98.52 kJ/mol. With respect to **1a**,

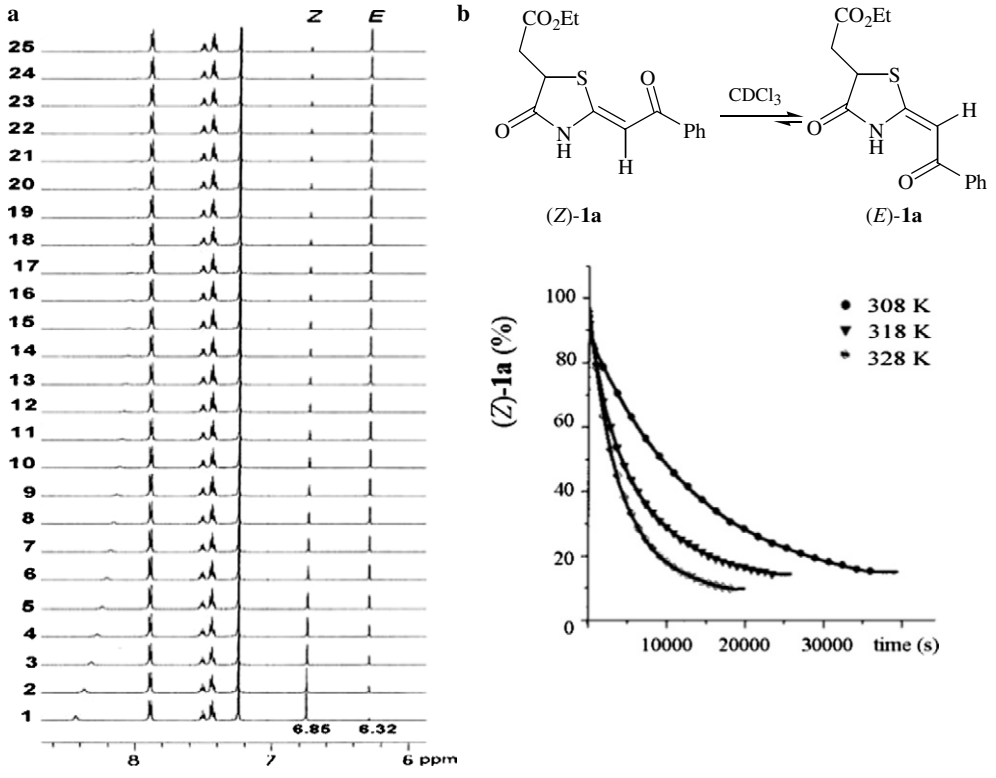


Fig. 1. (a) Partial ^{1}H NMR spectra of (*Z*)-**1a** and (*E*)-**1a** in $CDCl_3$ at 328 K. Olefinic signals at σ 6.85 and 6.32 ppm ascribed to the starting (*Z*)-**1a** isomer and (*E*)-**1a** isomer, respectively. (b) Plots of the (*Z*)-**1a** concentration in $CDCl_3$ against time at temperatures indicated.

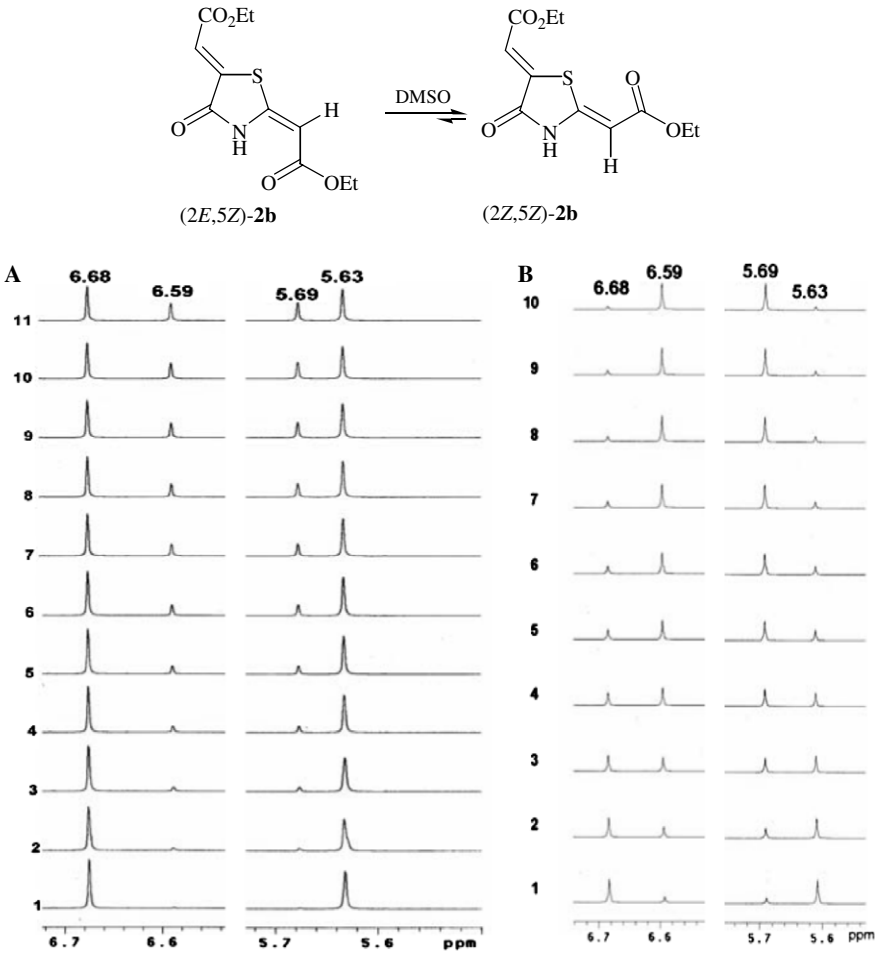


Fig. 2. Spectral evidence for the presence of the starting (2*E*,5*Z*)-**2b** isomer, based on the observation of the olefinic signals at σ 5.63 and 6.68 ppm, and (2*Z*,5*Z*)-**2b** isomer (olefinic signals at σ 5.69 and 6.59 ppm) in DMSO-d_6 at room temperature; 30 min interval (A) and 328 K; 5 min interval (B).

slightly larger value of the rotational barrier has been determined in the case of thiazolidine derivative **2b** for the isomerization 2*E*,5*Z*/2*Z*,5*Z*-process in DMSO-d_6. Compounds **1a** and **2b** have similar rotational barriers in spite of the decreased push-pull nature of the C(2)=C(2′) bond in **2b**, as evidenced by the lower $\Delta\delta_{C2,C2'}$ value relative to that of **1b**. This fact can be interpreted on the basis of the isomerization 2*E*,5*Z*/2*Z*,5*Z*-process occurring via the polarized transition state which is increasingly stabilized by the solvation in the polar solvent [28]. It follows that the ability of the polar solvent molecules in terms of the transition state lowering in the case of **2b**

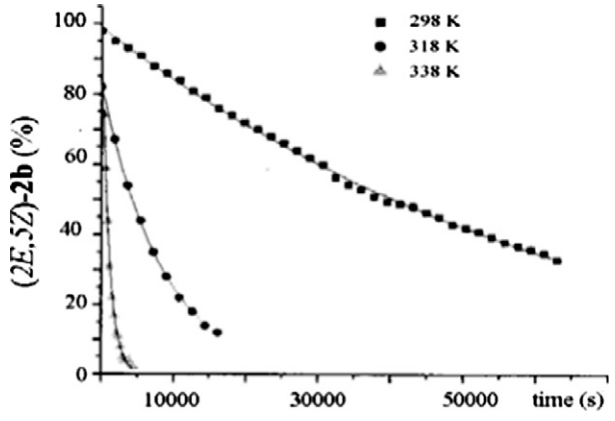


Fig. 3. Change of concentration of (2*E*,5*Z*)-**2b** with time at given temperatures.

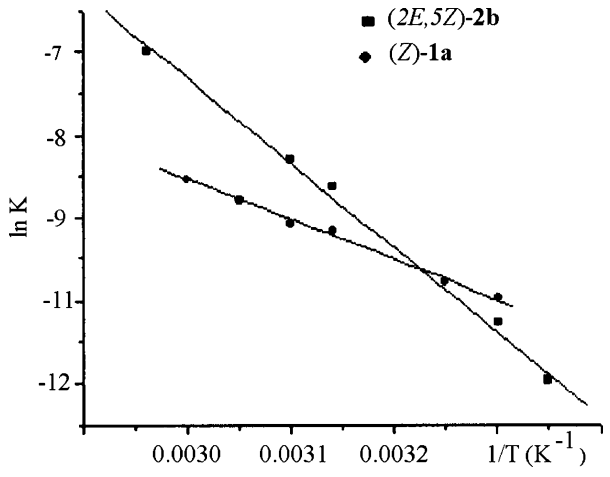


Fig. 4. Arrhenius plots of kinetic data for the interconversion around the C=C bonds in **1a** and**2b**.

Table 4
Energy of activation for **1a** and **2b**

	(*Z*)-**1a**	(2*E*,5*Z*)-**2b**
Ea kJ/mol	41.8 ± 1.6	83.3 ± 1.6
As^{-1}	$1.0 \cdot 10^3$	$7.5 \cdot 10^9$

Table 5
Activation parameters for rotation around C(2)=C(2′) bond in 4-oxothiazolidines **1a** and **2b**

Compound	T [K]	$\Delta G_0^{\neq}$ [kJ mol-1]	$\Delta H_0^{\neq}$ [kJ mol^{-1}]	$\Delta S_0^{\neq}$ [J $K^{-1}mol^{-1}$]
1a	298	98.5	39.3	−198.7
2b	298	100.2	80.9	−64.7

counterbalances the opposing effect of the C(5)=C(5′) bond. The negative activation entropy for the rotation in thiazolidine derivative **2b** (−64.70 J/mol,K) is also attributed to a higher degree of order in the dipolar transition state which is more strongly solvated in comparison to the ground state.

Acknowledgement

Partial financial support by the Ministry of Science, Technology and Development of the Republic of Serbia, Grant No. 1709 (to R.M.), is acknowledged.

References

[1] J. Sandström, Top. Stereochem. 14 (1983) 83.
[2] F. Meyers, S.R. Marder, B.M. Pierce, J.L. Brédas, J. Am. Chem. Soc. 116 (1994) 10703.
[3] J.L. Chiara, A. Gómez-Sánchez, J. Bellanato, J. Chem. Soc. Perkin Trans. 2 (1998) 1797.
[4] E. Kleinpeter, A. Koch, M. Heydenreich, S.K. Chatterjee, W.-D. Rudorf, J. Mol. Struct. 356 (1995) 25.
[5] S. Rajappa, Tetrahedron 55 (1999) 7065.
[6] Z.-H. Xu, Y.-F. Jie, M.-X. Wang, Z.-T. Huang, Synthesis (2002) 523.
[7] O. Ceder, U. Stenhede, K.-I. Dahlquist, J.M. Waisvisz, M.G. van der Hoeven, Acta Chem. Scand. 27 (1973) 1914.
[8] R. Marković, M. Baranac, Heterocycles 48 (1998) 893.
[9] R. Marković, Z. Džambaski, M. Baranac, Tetrahedron 57 (2001) 5833.
[10] T. Kato, T. Ozaki, K. Tamura, Y. Suzuki, M. Akima, N. Ohi, J. Med. Chem. 42 (1999) 3134.
[11] I.O. Edafiogho, C.N. Hinko, H. Chang, J.A. Moore, D. Mulzac, J.M. Nicholson, K.R. Scott, J. Med. Chem. 35 (1992) 2798.
[12] R. Marković, M. Baranac, Z. Džambaski, Heterocycles 63 (2004) 851.
[13] R. Marković, J.G. Pavlovich, M. Baranac, Phosphorus Sulfur Silicon 180 (2005) 1411.
[14] H. Kessler, Angew. Chem. Int. Ed. Engl. 21 (1982) 512.
[15] J.-C. Zhuo, Magn. Reson. Chem. 35 (1997) 311.
[16] J.-M. Lehn, Angew. Chem. Int. Ed. Engl. 29 (1990) 1304.
[17] G.P. Dado, J.M. Desper, S.H. Gelman, J. Am. Chem. Soc. 112 (1990) 8630.
[18] P. Gilli, V. Bertolasi, V. Ferretti, G. Gilli, J. Am. Chem. Soc. 122 (2000) 10405.
[19] J.G. Ángyán, R.A. Poirier, Á. Kucsman, I.G. Csizmadia, J. Am. Chem. Soc. 109 (1987) 2237.
[20] R. Marković, M. Baranac, S. Jovetić, Tetrahedron Lett. 44 (2003) 7087.
[21] R. Marković, A. Shirazi, M. Baranac, Z. Džambaski, D. Minić, J. Phys. Org. Chem. 17 (2004) 118.
[22] P.J. Taylor, Spectrochim. Acta 26A (1970) 153.
[23] E.S. Stevens, N. Sugawara, G.M. Bonora, C. Toniolo, J. Am. Chem. Soc. 102 (1980) 7048.
[24] B.W. Gung, J.A. MacKay, D. Zou, J. Org. Chem. 64 (1999) 700.
[25] J.M. Winningham, D.Y. Sogah, J. Am. Chem. Soc. 116 (1994) 11173.
[26] P.L. Wash, E. Maverick, J. Chiefari, D.A. Lightner, J. Am. Chem. Soc. 119 (1997) 3802.
[27] H.-O. Kalinowski, H. Kessler, Top. Stereochem. 7 (1973) 295.
[28] E. Kleinpeter, S. Klod, W.-D. Rudorf, J. Org. Chem. 69 (2004) 4317.
[29] G. Fischer, W.D. Rudorf, E. Kleinpeter, Magn. Reson. Chem. 29 (1991) 212.
[30] J.L. Mueller, M.S. Gibson, J.S. Hartman, Can. J. Chem. 74 (1996) 1329.
[31] E. Kleinpeter, A. Schulenburg, Tetrahedron Lett. 46 (2005) 5995.
[32] E. Kleinpeter, J. Serb. Chem. Soc. 71 (2006) 1.
[33] P.J. Taylor, Spectrochim. Acta 26A (1970) 165.
[34] D.L. Ostercamp, P.J. Taylor, J. Chem. Soc. Perkin Trans. II II (1985) 1021.