JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2004; **17:** 118–123
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.700

Configurational isomerization of push–pull thiazolidinone derivatives controlled by intermolecular and intramolecular RAHB: ^{1}H NMR dynamic investigation of concentration and temperature effects

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Received 10 December 2002; revised 4 July 2003; accepted 18 July 2003

ABSTRACT: ^{1}H NMR spectroscopy was used to investigate hydrogen bonding in the structurally related (*Z*)- and (*E*)-5-substituted-2-alkylidene-4-oxothiazolidines in polar and apolar solvents. The equilibrated mixtures of these typical push–pull alkenes consist of the intramolecularly H-bonded *E*-isomer and intermolecularly H-bonded *Z*-isomer in varying proportions which depend on the solvent polarity. For a representative of the series, (*E*)-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (**1**), the lack of a concentration and temperature dependence of the large chemical NH shift (δ 12.06 ppm) in $CDCl_3$ indicates strong intramolecular resonance-assisted hydrogen-bond formation (RAHB). The upfield chemical shifts of the NH proton of the (*Z*)-**1** isomer as a function of temperature increase and the large ^{1}H NMR $\Delta\delta/\Delta T$ value (-11.82 ppb °C^{-1}, $Z/E = 60:40$, or -10.33 ppb °C^{-1}, $Z/E = 20:80$) in $CDCl_3$ are explained in terms of a decrease in intermolecular H-bonding resulting in a greater amount of free or unassociated *Z*-isomer. Copyright © 2004 John Wiley & Sons, Ltd.
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KEYWORDS: push–pull alkenes; *Z/E* isomerization; hydrogen bonding; temperature effect; ^{1}H NMR spectroscopy

INTRODUCTION

There is ample evidence in the literature regarding the ability of hydrogen bonding to influence structure or intermolecular association of organic compounds in the solid state and in solution.[1–7] Stereodefined (*Z*)-5-substituted thiazolidinones **1**–**4** (Scheme 1) and new derivatives thereof,[8–10] which have attracted our attention owing to their possible biological activity[11,12] and utility as organic intermediates, represent an excellent model to study specific hydrogen bonding interactions in solution. One of the most often employed methods to investigate this type of weak non-covalent interaction, present not only in small molecules but also in nucleic acids, peptides and proteins as well, is NMR spectroscopy.[1,13–18]

We report here the first ^{1}H NMR dynamic study of the concentration and temperature dependence of the lactam proton chemical shift for a representative of the series, (*Z*)-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (**1**),[8] undergoing the well-defined *Z/E* process in apolar $CDCl_3$, to discriminate and determine the degree of intra- and intermolecular hydrogen bonding interactions.

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EXPERIMENTAL

The NMR spectra for characterization were obtained using a Varian Gemini 2000 instrument (^{1}H 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 ^{1}H NMR measurements in the temperature range 273–333 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 1 day. The concentrations of $CDCl_3$ solutions were 0.011 or 0.016 M unless indicated otherwise. The variable temperature was computer controlled employing a 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, especially when approaching 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 signal for residual $CHCl_3$. A one-dimensional NOE experiment was run on a Varian Inova 500 MHz spectrometer. 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 1725X spectrophotometer and are reported as wavenumbers (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 with iodine. Column chromatography was carried out on SiO_2 (silica gel 60 Å, 12–26 μm, ICN Biomedicals). Elemental analyses were performed at the microanalysis laboratory at the Department of Chemistry, University of Belgrade.

Push–pull (*Z*)-5-substituted-4-oxothiazolidines **1–4** listed in Table 1 were obtained according to the following general procedure reported previously.[8] To a stirred suspension of the corresponding β-oxonitrile[19] (3 mmol) (Scheme 1) and diethyl mercaptosuccinate (~1% molar excess) in 5–10 ml of ethanol, a catalytic amount of K_2CO_3 was added. **CAUTION:** *All reactions involving diethyl mercaptosuccinate, owing to the unpleasant odor, should be carried out in a well-ventilated hood.* The mixture was brought to reflux and the reaction mixture was stirred for 3–7.5 h. The reaction mixture was cooled to room temperature and the separated solid was filtered, washed with ethanol and recrystallized from 96% ethanol to provide the final product (*Z*)-**1–4** (Table 1). 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]

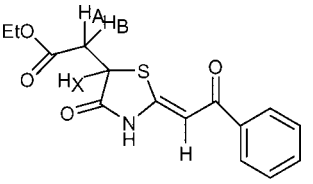
Table 1. Synthesis of (*Z*)-5-substituted-4-oxothiazolidines **1–4**

Entry	Product	R	M.p. (°C)	Yield (%)[a]
1	(*Z*)-**1**	Ph	126–127	52
2	(*Z*)-**2**	NHPh	183–185	24
3	(*Z*)-**3**	$NHCH_2CH_2Ph$	152–153	29
4	(*Z*)-**4**	OEt	106–108	54

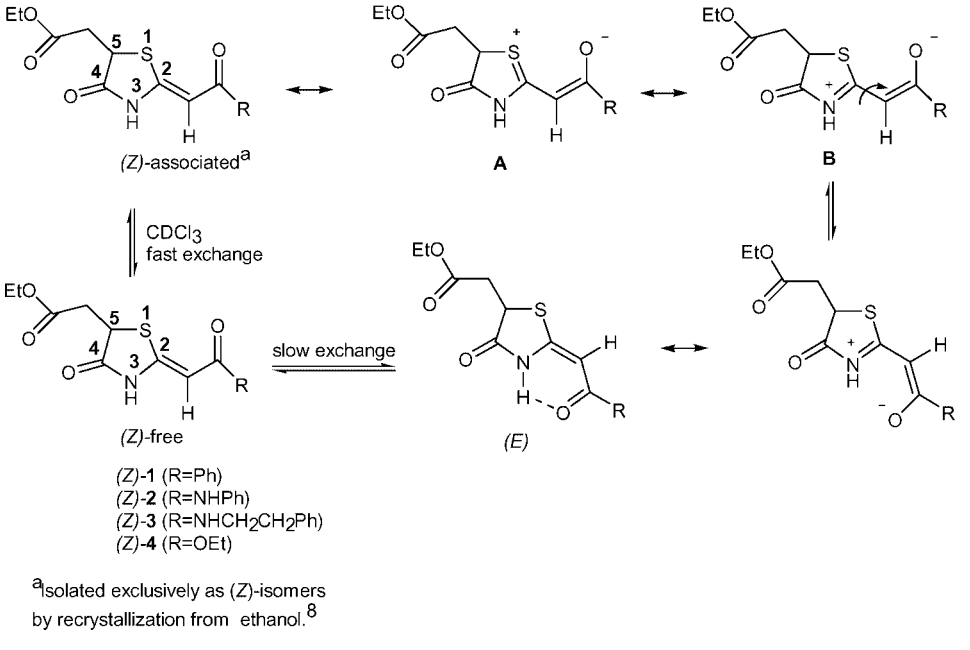
[a] Yields of isolated pure compounds obtained by crystallization; the use of a large molar excess of diethyl mercaptosuccinate relative to the β-oxonitrile derivative (molar ratio β-oxonitrile : mercapto derivative = 1.73 : 1.00) greatly improved the yields of cyclization products to 60–85%.

For configurational isomers of the sample **1** used in the variable-temperature (VT) ^1H NMR experiment, the following ^1H NMR data are pertinent.

*(Z)-(5-Ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone [(Z)-**1**].* ^1H NMR ($CDCl_3$): δ 1.26 (t, 3H, CH_3, *J* 7.2 Hz), 3.00 (dd, 1H, $CH_AH_BCH_XS$, J_{AB}



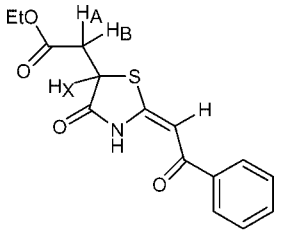
(*Z*)-**1**



Scheme 1

17.5 Hz, J_{AX} 8.2 Hz), 3.15 (dd, 1H, $CH_AH_BCH_XS$, 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). ^{13}C NMR (DMSO-d_6): δ 14.5 (CH_3), 36.4 (CH_2COO), 42.5 (CHS), 61.2 (CH_2O), 94.9 (=CH), 127.5 (*o*-Ph), 129.3 (*m*-Ph), 132.6 (*p*-Ph), 138.7 (C-1 Ph), 161.6 [=C(2)], 170.7 (C4), 176.3 (CO_{ester}), 187.7 (CO_{exo}).

(E)-(5-Ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone [(E)-1]. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, 3H, CH_3, J 7.2 Hz), 2.91 (dd, 1H, $CH_AH_BCH_XS$, J_{AB}



(*E*)-**1**

17.6 Hz, J_{AX} 10.1 Hz), 3.28 (dd, 1H, $CH_AH_BCH_XS$, 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). ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 37.5 (CH_2COO), 42.3 (CHS), 61.7 (CH_2O), 94.5 (=CH), 127.8 (*o*-Ph), 128.6 (*m*-Ph), 132.6 (*p*-Ph), 138.0 (C-1 Ph), 158.4 [=C(2)], 170.1 (C4), 174.6 (CO_{ester}), 188.29 (CO_{exo}).

An analytical sample was obtained by column chromatographic purification of the crude (*Z*)-**1** on silica gel, eluting with a gradient of toluene–ethyl acetate (100 : 0 to 50 : 50, v/v), followed by concentration of the fractions containing the desired compound **1**. 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%.

RESULTS AND DISCUSSION

Starting with the pure (*Z*)-**1** isomer (0.011 M), the *Z/E* process in $CDCl_3$, at 0.011 M concentration, was monitored at 25 °C during a 15 h period at regular time intervals (1 h) by ^{1}H NMR spectroscopy (Fig. 1).

The progressive decrease in the *Z/E* ratio with time, which reached 13 : 87 after 15 h, was based on the observation of the signals assigned to the (*Z*)- and (*E*)-**1** lactam protons which initially appear at δ 8.88 and 12.06 ppm, respectively. The isomerization of (*Z*)-**1** to its counterpart was also followed by the gradual disappearance of the vinylic proton at δ 6.85 ppm and the simultaneous growth of the signal at δ 6.32 ppm. The ^{1}H NMR spectrum of (*Z*)-**1** recorded almost immediately

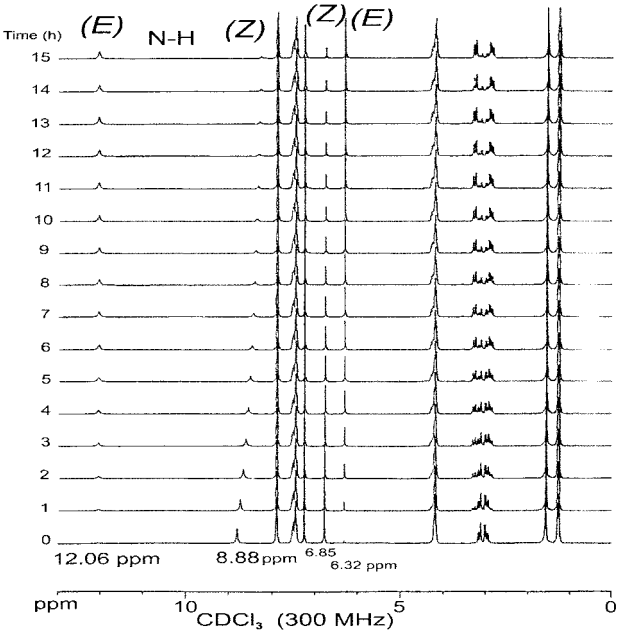


Figure 1. ^{1}H NMR spectra of *Z/E* mixture of derivative **1**, recorded in $CDCl_3$ at room temperature, at regular 1 h intervals

upon its dissolution in $CDCl_3$ (designated as zero time in Fig. 1) contains, as expected, a nearly perfect set of signals belonging to the single isomer.

The olefinic proton of the (*Z*)-**1** isomer resonates at considerably higher frequency owing to the deshielding effect of the *syn*-lactam nitrogen, relative to the *E*-analogue having this proton in a *syn* position to the less electronegative sulfur atom. Proper configurational assignment, based on the consideration of this effect, magnetic anisotropy and mesomeric effects, was possible, not only for the whole series **1**–**4**, but also for numerous derivatives thereof.[9,10] One-dimensional nuclear Overhauser effect (NOE) experiments showed that the irradiation of the singlet at δ 6.85 ppm of the (*Z*)-**1** isomer gave an enhancement of 4.4% to the aromatic region and an enhancement of 1.7% to the lactam proton singlet at δ 8.88 ppm. This is in agreement with the *Z*-configuration as the correct assignment. Subsequently, the NOE experiment was conducted on a solution of the *Z/E* mixture, containing about 85% of the (*E*)-**1** isomer after 24 h. Irradiation of the vinyl singlet at δ 6.32 ppm showed an NOE on the aromatic region, but not on the singlet at δ 12.06 ppm assigned to the lactam proton of the (*E*)-**1** isomer. The configurational isomerization of **1** is an intrinsic structural property, based on electronic n–π interactions of the two electron-donor substituents (—NH—,—S—) and one electron-acceptor, i.e. the COPh substituent, *via* the C=C bond, as found for other push-pull alkenes.[20–27] The key factor controlling the *Z/E* ratio is the strength of inter- and intramolecular hydrogen bonds which depends on, among other factors, the polarity of the medium[28,29] (Table 2).

Table 2. Effects of medium polarity and solute concentration on selected ^{1}H NMR chemical shifts of configurational isomers **1–4**

Entry	Compound	Solvent	=CH	NH(ring)	*Z/E* ratio
1	(*Z*)-**1**	$CDCl_3$ (0.011 M)	6.85	8.88[a]	96 : 4 (after a few minutes)
2	(*Z*)-**1**	$CDCl_3$ (0.050 M)	6.85	9.88[a]	97 : 3 (after a few minutes)
3	(*Z*)-**1**	$CDCl_3$ (0.050 M)	6.85	8.96[a]	11 : 89 (after 10 days)
4	(*Z*)-**1**	DMSO-d_6 (0.011 M)	6.78	11.93	100 : 0
5	(*Z*)-**2**	DMSO-d_6	5.79	11.57	100 : 0
6	(*Z*)-**3**	DMSO-d_6	5.55	11.30	94 : 6[b]
7	(*E*)-**3**	DMSO-d_6	5.15	11.49	
8	(*Z*)-**3**	$CDCl_3$	5.54	9.44	22 : 78[b]
9	(*E*)-**3**	$CDCl_3$	4.90	11.43	
10	(*Z*)-**4**	$CDCl_3$ (0.050 M)	5.59	9.35[a]	96 : 4 (after a few minutes)
11	(*Z*)-**4**	$CDCl_3$ (0.050 M)	5.59	8.70[a]	43 : 57 (after 2 days)
12	(*Z*)-**4**	$CDCl_3$ (0.050 M)	5.59	8.28[a]	10 : 90[b](after 6 days)
13	(*E*)-**4**	$CDCl_3$	5.12	10.63	

[a] An enhancement of intermolecular hydrogen bonding in the (*Z*)-**1** and (*Z*)-**4** isomers, which depends on their initial concentration (entries 1 and 2), or in the *Z/E* mixture (greater *Z/E* ratio; entries 10–12) moves the lactam proton downfield.
[b] Determined for equilibrated *Z/E* mixture.

Polar solvents (EtOH, DMSO, acetone) enhance sulfur or nitrogen participation in the ground-state polarization, favoring the resonance forms **A** and **B** (Scheme 1). In fact, **A** and **B** increase the stability of the *Z*-isomers via intermolecular H-bonding. The configurational stability of *Z*-isomers **1–4** should be also attributed to the strong electrostatic oxygen–sulfur interactions (structure **A**).[10] Ángyán and co-workers[30] have reported that in a large number of sulfur-containing heterocycles, the interactions of non-bonded S and O may influence the physicochemical properties and chemical reactivity of these compounds. Consistent with this, the stereospecific formation of the (Z)-thiazolidinone derivatives **1–4** in ethanol is understandable. In line with the postulated solvent stabilization is also the fact that the ^{1}H NMR spectrum of the *Z*-isomers in DMSO-d_6 does not change with time (Table 2, entries 4 and 5). In the case of the *E*-isomers, the dominant thermodynamic species in a non-polar solvent, e.g. in $CDCl_3$, is the neutral, intramolecularly H-bonded structure. In other words, the intermolecular H-bonding, present in the original *Z*-isomer, is suppressed in a non-polar solvent, inducing the rearrangement around the double bond. As depicted in Scheme 1, a fast exchange process (*Z*-associated $\rightleftharpoons$ Z-free) precedes the rearrangement around the double bond. Worth noting is the experimental fact that the equilibrated mixtures of thiazolidinone derivatives **1–4** in non-polar solvents ($CHCl_3$ or toluene), enriched in the *E*-isomer, revert in the solid state, upon solvent evaporation, almost completely to the configurationally more stable *Z*-isomer. The high chemical shift of the NH proton for (*E*)-**1** (δ 12.06 ppm), the unchanged frequency and the intensity enhancement of its signal, being proportional to the simultaneous concentration increase of the *E*-isomer, are typical of strong intramolecular resonance-assisted $\cdots$HN—C=C—C=O$\cdots$ hydrogen bonding (RAHB).[1,31] Conversely, the effects of a change in concentration of (*Z*)-**1** on the chemical shift of the NH chemical shift were apparent. Thus, the data in Table 3 show a gradual upfield shift of the NH chemical shift of (*Z*)-**1**, from δ 8.88 (*Z/E* ratio 96 : 4) to 8.32 ppm (*Z/E* ratio 13 : 87) with decreasing concentration of (*Z*)-**1** (see also Table 2, footnote a). This case is typical for intermolecular H-bonds. Accordingly, the shielding of the NH proton accompanying the concentration decrease of the (*Z*)-**1** isomer reflects the decrease in the population of the form with intermolecular H-bonds.[13–15, 32–34]

In contrast to the strong ionic-type intermolecular hydrogen bond interactions between the solvent, such as DMSO or ethanol, and (*Z*)-**1**, the solute–solvent interactions are negligible in $CDCl_3$ (see below). Thus, the

Table 3. ^{1}H NMR chemical shifts (ppm) of the NH proton of (*Z*)-**1** in $CDCl_3$ as a function of concentration at room temperature[a]

Time (h)	(*Z*)-**1** (%)	δNH_x	Chemical shift difference ($\Delta\delta = \delta NH_0 - \delta NH_x$)
0[b]	96	8.88	—
1	82	8.80	0.08
2	70	8.73	0.15
3	62	8.67	0.21
4	56	8.62	0.26
5	51	8.58	0.30
6	45	8.54	0.34
7	40	8.50	0.38
8	35	8.47	0.41
9	31	8.45	0.43
10	26	8.42	0.46
11	22	8.40	0.48
12	18	8.38	0.50
13	17	8.38	0.50
14	14	8.34	0.54
15	13	8.33	0.55

[a] δNH_0 value from spectrum 0 at 298 K (recorded immediately upon sample dissolution); selected δNH_x values from spectra 1–15 (Fig. 1).
[b] Low abundance of the (*E*)-**1** isomer (<5%) at time 0 indicates that the *Z/E* isomerization of the *Z*-isomer in $CDCl_3$ begins in time enough to prepare sample and record the spectrum.

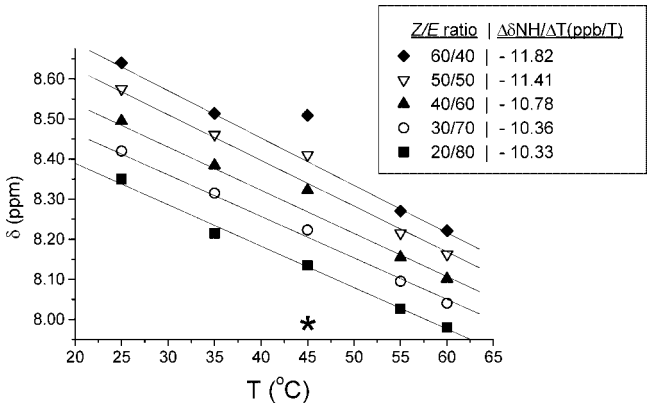


Figure 2. Lactam proton NMR chemical shifts for the (*Z*)-**1** isomer against temperature. *Initial concentration of (*Z*)-**1** in $CDCl_3$: 0.011 M, except at 45 °C when it was 0.016 M

NH resonance of (*Z*)-**1** is shifted downfield by 3.05 ppm in DMSO (δ 11.93 ppm; Table 2, entry 4) relative to δ 8.88 ppm in $CDCl_3$ (entry 1). The chelate-type H-bonding of major (*E*)-**1** isomer is stronger in $CDCl_3$ than intermolecular hydrogen bonding in (*Z*)-**1**. Following this reasoning, an apolar solvent would weaken the intermolecular H-bonds to the benefit of the formation of intramolecular bonds. Short and obviously strong intramolecular RAHB are formed as the configuration of the molecule brings the neutral donor and acceptor groups involved, i.e. N—H and O=C, into close contact.

The signals corresponding to the lactam proton in the (*Z*)-**1** and (*E*)-**1** isomers were used to follow the stereodynamic of push–pull derivative **1**. The temperature dependence of the NH chemical shifts based on the VT ^{1}H NMR technique[1,4,8] permits further discrimination to be made between the inter- and intramolecular hydrogen bonding in model substrate **1** (Fig. 2). A lack of temperature dependence of the NH chemical shift (δ 12.06 ppm), assigned to intramolecularly H-bonded isomer (*E*)-**1** experiencing the same electronic environment, was expected. In the case of the (Z)-**1** isomer, NH chemical shifts in $CDCl_3$ were plotted against temperature over a range of *Z/E* ratios of 60 : 40 to 20 : 80. Large temperature coefficients were observed ($\Delta\delta$NH/$\Delta T = -11.8$ ppb °C^{-1}, *Z/E* = 60 : 40, or -10.3 ppb °C^{-1}, *Z/E* = 20 : 80) in agreement with a solvent-free or unassociated *Z*-isomer. The consistent upfield shift of the lactam proton as a function of temperature increase appears to be due to the disruption of the intermolecular hydrogen bonds, leading to a shielding of the lactam proton. We assume that the large value of the $\Delta\delta/\Delta T$ coefficients reflects the decrease in the solute–solute interaction in $CDCl_3$, rather than relatively weak solute–$CDCl_3$ interactions. This is consistent with the conclusion of Stevens *et al.*[13] that the NH group of linear peptides exposed to $CDCl_3$ has a low value of $\Delta\delta/\Delta T$, implying weak hydrogen bonds in $CDCl_3$.

It is noteworthy that higher values of the NH chemical shifts were obtained for the *Z/E* process of 0.016 M (*Z*)-**1** conducted at 45 °C as indicated by the points off the lines over the whole *Z/E* range. The downfield shift of the NH proton from 0.10 ppm (*Z/E* ratio 60 : 40) to 0.06 ppm (*Z/E* ratio 30 : 70) at 45 °C as a result of a concentration increase from 0.011 to 0.016 M evidently implies the enhancement of intermolecular interactions. The magnitude of these interactions is reflected by the value of the downfield shift that is proportional to the population of the *Z*-isomer in a *Z/E* mixture. This is reasonable since both the (*Z*)-**1** isomer of higher initial concentration and *Z/E* mixtures enriched in this isomer will increase its tendency to form intermolecular self-association (see also Table 2, entries 1–3 and 10–12).

In summary, this VT ^{1}H NMR dynamic spectroscopic study provides clear evidence of an intrinsic interplay between the structural properties of the (*Z*)- and (*E*)-**1** thiazolidinone isomers and concentration and temperature effects on the lactam proton chemical shift. In principle, the competition between (a) the strong intramolecular H-bonds within the (*E*)-**1** isomer formed in the apolar $CDCl_3$ solvent and (b) intermolecular hydrogen bonds in the (*Z*)-**1** isomer is reflected by the unchanged downfield chemical shift of the NH proton and its consistent upfield trend, respectively. The large δ_{NH} values of (*E*)-**1**–**4** in a non-polar solvent, which depend on the strength of the hydrogen bond, indicate that the intramolecular RAHB contribute to the stabilization of the *E*-form. The larger temperature dependence of the NH chemical shift variation for the (*Z*)-**1** isomer, expressed as $\Delta\delta$NH/ΔT, is in agreement with the formation of a greater amount of an unassociated (*Z*)-**1** species for which the lactam proton is shielded in $CDCl_3$. We hope that the push–pull thiazolidinone derivatives **1**–**4**, bearing structural and functional similarities to peptides, may serve as a good system to study and mimic weak non-covalent interactions.

Acknowledgment

This work was supported in part by the Ministry of Science, Republic of Serbia.

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