Structure, configuration, conformation and quantification of the push–pull effect of 2-alkylidene-4-thiazolidinones and 2-alkylidene-4,5-fused bicyclic thiazolidine derivatives

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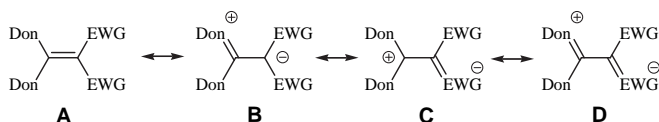
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ABSTRACT

Structures of a series of push–pull 2-alkylidene-4-thiazolidinones and 2-alkylidene-4,5-fused bicyclic thiazolidine derivatives were optimized at the B3LYP/6-31G(d) level of theory in the gas phase and discussed with respect to configurational and conformational stability. Employing the GIAO method, ^{13}C NMR chemical shifts of the C-2, C-2′, C-4 and C-5 atoms were calculated at the same level of theory in the gas phase and with inclusion of solvent, and compared with experimental data. Push–pull effect of all compounds was quantified by means of the quotient π_*/π, length of the partial double bond, ^{13}C NMR chemical shift difference ($\Delta\delta_{C=C}$) and ^{1}H NMR chemical shifts of olefinic protons. The effect of bromine on donating and accepting ability of other substituents of the push–pull C=C double bond is discussed, too.

1. Introduction

Push–pull alkenes are substituted olefins containing one or two electron-donating groups (Don) at one end of the double bond and one or two electron-withdrawing groups (EWG) at the other end (**A** in Scheme 1). Electronic interactions between the donor and acceptor groups via the C=C double bond substantially reduce its π-bond order, thus increasing π-bond orders of the C–Don and C–EWG bonds (**B–D**). This push–pull effect highly influences dynamic behaviour and chemical reactivity of this class of compounds.
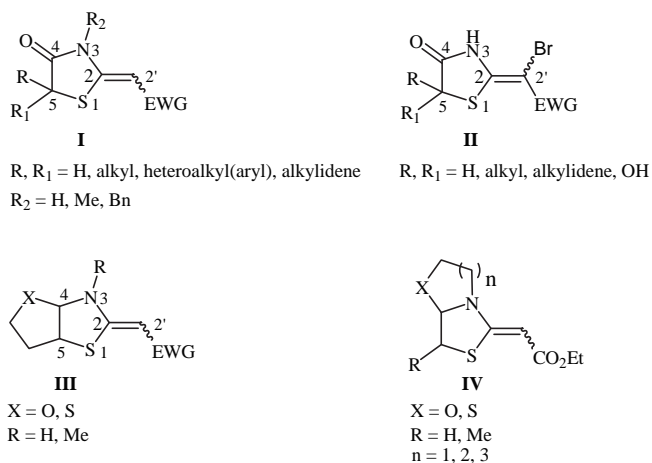
Scheme 1.

The barrier to rotation ($\Delta G^{\neq}$) about this partial double bond, readily determined by dynamic NMR spectroscopy (DNMR) or theoretically calculated, can be employed as a measure of push–pull effect.[1] Another parameter for predicting the push–pull character is the ^{13}C NMR chemical shift difference ($\Delta\delta_{C=C}$) of the two carbons of the double bond,[1b,d,2] which is increased due to bond polarization (**B–D**). This parameter is especially useful in cases when $\Delta G^{\neq}$ cannot be determined either because it lies outside the boundaries of the NMR time scale,[1a,2a] or because the double bond is part of a ring.[2b,c] However, chemical shifts are highly influenced by the type of substituents and $\Delta\delta_{C=C}$ as a measure of the push–pull effect is limited to alkenes with very similar substitution pattern, i.e., when structural changes do not take place directly at the double bond.[1b] Beside $\Delta G^{\neq}$ and $\Delta\delta_{C=C}$, bond length of the C=C partial double bond, experimentally available by X-ray analysis, can be used to describe the push–pull effect,[1d,3] but the most general parameter for quantifying the donor–acceptor character in push–pull alkenes proved to be the quotient of the occupation numbers of π_* and π orbitals of the C=C double bond, available from ab initio MO calculations combined with a NBO analysis.[1d,2h,3,4] Since electron-donating substituents release their electrons into the π_* orbital and electron-withdrawing groups attract π-electron density from the corresponding π orbital, the quotient π_*/π is a very sensitive measure of the push–pull effect

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and much broader than the bond length, which can be influenced by steric hindrance or hydrogen bonding.[1d] It also needs a stronger polarization for a discernible effect.[4]

Over the last decade, a number of thiazolidine derivatives **I** and **II**, belonging to the class of push−pull alkenes, were synthesized in our laboratory (Scheme 2).[5] These compounds are of interest as precursors of various heterocyclic compounds, such as 1,2-dithiols,[6] 1,3-thiazines,[7] substituted and unsubstituted pyridinium salts containing 4-oxothiazolidine moiety,[8] or condensed thiazolidines **III**[5e,9] and **IV**.[10] The introduction of a hetero-substituent at the C-5 position of the *N*-unsubstituted thiazolidine ring was possible via the novel, nucleophile induced double bond/C-5 ring bromine migration of vinyl bromides **II**.[11] In addition, synthetic and naturally occurring thiazolidines attract attention as they show antitumour, antibiotic, antimicotic, diuretic, antiinflamatory and antiproteolytic activity.[12]

R, R₁ = H, alkyl, heteroalkyl(aryl), alkylidene
R₂ = H, Me, Bn

R, R₁ = H, alkyl, alkylidene, OH

III
X = O, S
R = H, Me

IV
X = O, S
R = H, Me
n = 1, 2, 3

Scheme 2.

The aim of the present paper is to report push−pull 2-alkylidene-4-thiazolidinones **I** and **II**, and fused thiazolidines **III** (X=O) with respect to their push−pull effect, configurational and conformational stability, as they greatly affect their dynamic[5a,13] and chemical behaviours.[6−10]

2. Results and discussion

2.1. Calculation of ¹³C chemical shifts of thiazolidine derivatives 1−19

The experimental ¹³C NMR chemical shifts of C-2, C-2′, C-4 and C-5 of compounds **1**−**19** (Scheme 3) are presented in Table S1 in Supplementary data (all spectral data for thiazolidines **1b**,[5f] **2b**,[5f] **2d**,[5f] **2h**,[6b] **3a**−**e**,[5a,c] **4**−**7**,[14] **8**,[5d] **9f**,[14] **10**[6b], **11**,[6b] **12**,[9] **14**−**16**,[14] **17a**[11b] and **19b**−**e**[9] have already been published).

The ¹³C chemical shifts of compounds **1**−**19** were calculated using the GIAO method[15] at the B3LYP/6-31G(d) level of theory and they are presented in Table S2 in Supplementary data. The basis for these calculations were the structures optimized at the same level of theory, in the gas phase. The best agreement between experimental and calculated values was obtained for the saturated carbons C-4 in **19**, C-5 in **1**−**7**, **9**−**17**, and olefinic C-2′ of **1**−**13** and **19** (Fig. 1). Due to the relativistic effects,[16] the calculated chemical shifts for carbons bearing a bromine (C-5 in **9f** and C-2′ in **14**−**18**) were overestimated by 10−20 ppm, but their trend is in excellent agreement with the trend of the experimental values (Fig. 1). The calculated chemical shifts for unsaturated carbons C-2 in all **1**−**19** and C-5 in **8** and **18** were in bad agreement with the

experimental values (correlation coefficients being R^2=0.68 and 0.55, respectively) and almost no correlation was obtained for the ring carbonyl carbon atoms. As expected for these highly polar push−pull compounds, the inclusion of the solvent in the calculations (DMSO and CHCl₃, as specified in Tables S3 and S4, Supplementary data) greatly improved the correlation between the calculated and experimental chemical shifts for olefinic C-2 atoms in **1**−**18** and olefinic C-5 atoms in **8** and **18** (Fig. 2). In addition to solvent inclusion, the calculation of the C-2 chemical shifts of bicyclic derivatives **19** and the carbonyl carbon chemical shifts was better described with 6-31+G(d,p) basis set as shown in Fig. 3. The use of the triple split basis set gave slightly better results only for carbonyl carbon in the gas-phase calculations, while all other chemical shifts were overestimated, more so when solvent effects were considered. The influence of solvent and basis set on the calculated ¹³C NMR chemical shifts of the test compounds **14a**-*E* and **19c** is presented in Table S3 and calculated ¹³C NMR chemical shifts of the selected compounds considering solvent effects using 6-31G(d) and 6-31+G(d,p) basis is presented in Table S4 in Supplementary data.
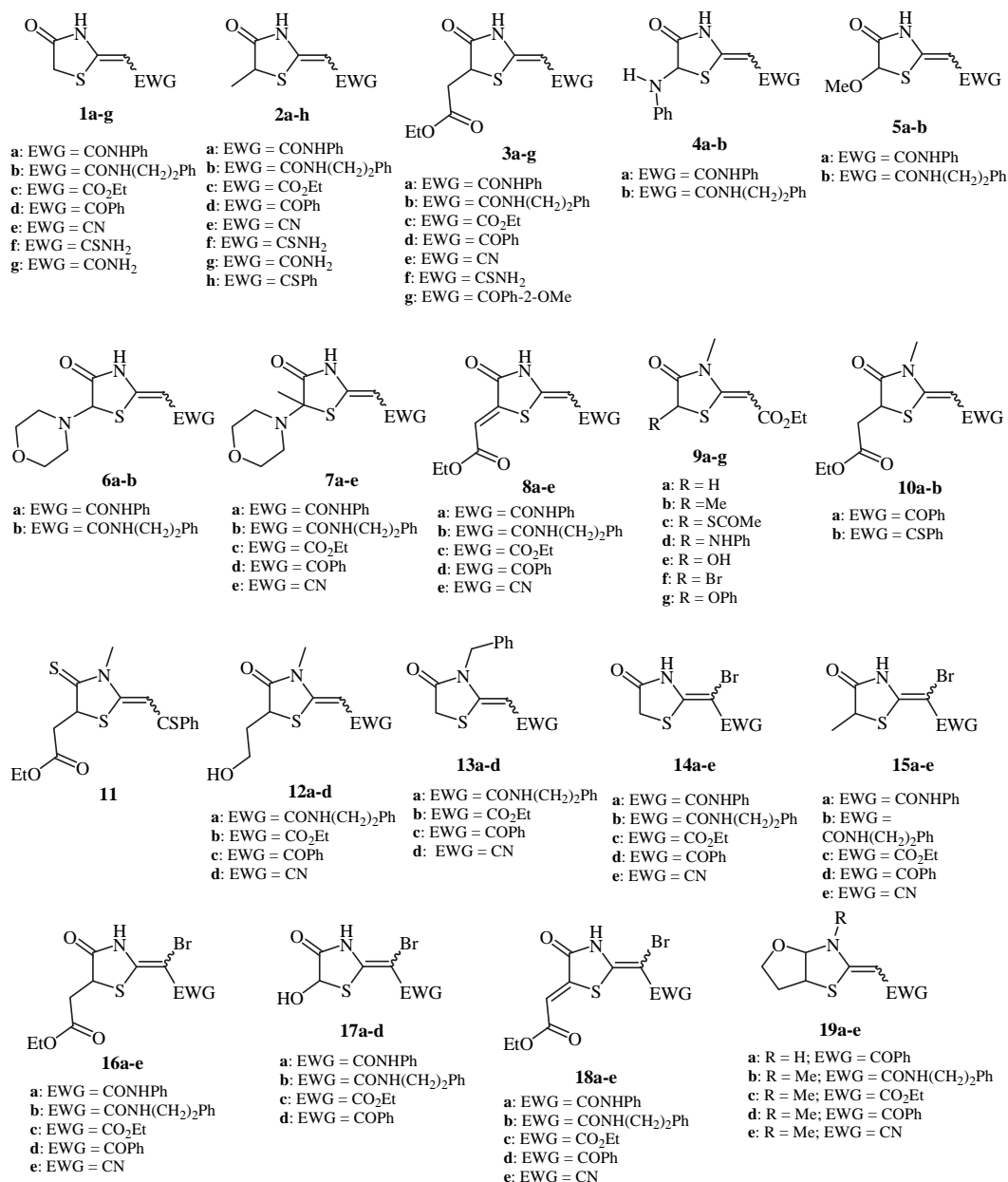
Though inclusion of solvent in the calculations strongly increases the accuracy of the calculated chemical shifts of slightly positively charged olefinic carbons (C-5 in **8** and **18**, and C-2 in all **1**−**19**) and partially positively charged carbonyl carbon atoms. Structures are negligibly different only as obtained from the gas-phase computation. This result, together with the very good correlations of experimental and calculated values for the other carbon atoms indicated that useful structures already in the gas phase were obtained. For this reason, only these gas-phase obtained structures were basis of further conclusions and the NBO analysis.

2.2. Structural peculiarities of thiazolidine derivatives 1−19

Energies of the most stable conformations of *Z* and *E* isomers of **1**−**18** are presented in Table S5 and energies of the four possible diastereomers of bicyclic compounds **19** in Table S6 in Supplementary data. As expected, in the highly conjugated systems **1**−**18** the thiazolidinone ring is flat and is in plane with the EWG for both *Z* and *E* isomers of **1**−**8** and **14**−**18** (the absolute values of S−C=C−C, N−C=C−C and C=C−C=O(S) torsional angles range from 0 to 4°). The coplanarity with the electron-withdrawing group is still found in the *Z* isomers of **9**−**13**, whereas in their *E* counterparts the strong steric interactions with the ring nitrogen substituent contribute to significant deviations from planarity, the sum of dihedral angles τ_2 (N−C=C−C) and τ_3 (C=C−C=O) ranging from 14° for the CO₂Et to 52° for CSPh (Table 1).

In the case of bicyclic derivatives **19**, the cis fusion with the almost planar thiazolidine ring is energetically more favoured than the trans fusion. In the latter case a severe angle strain of the planar ring forces it to adopt a nonplanar conformation with no optimal conjugation between the donor and acceptor part, thus raising its energy from 15 to 18 kcal/mol (see Table S6 in Supplementary data and Fig. 4). In these compounds, too, the electron-withdrawing group is in plane with the thiazolidine ring (the absolute values of τ_1, τ_2 and τ_3 range from 0 to 2°).

In all compounds the *s-cis* conformation (**a** and **c** in Scheme 4) is energetically preferred over *s-trans* in both *Z* and *E* isomers (Table 2). Clearly, it is hydrogen bonding stabilization of the *E* isomers (*Z* in the case of vinyl bromides), which is responsible for the greater preference of the *s-cis* conformation. In the optimized geometries of *Z* isomers (*E* for vinyl bromides) the distance between the ring sulfur atom and sulfur/oxygen of the (thio)carbonyl group of EWG is 3.04−3.1 Å/2.6−2.8 Å, which is substantially less than the sum of van der Waals radii (3.6 Å and 3.32 Å, respectively). This short distance indicates the existence of polar 1,5-type S···S and S···O interactions, which stabilize the *s-cis* conformation. The same is the case for

1a-g

a: EWG = CONHPh
b: EWG = CONH(CH₂)₂Ph
c: EWG = CO₂Et
d: EWG = COPh
e: EWG = CN
f: EWG = CSNH₂
g: EWG = CONH₂

2a-h

a: EWG = CONHPh
b: EWG = CONH(CH₂)₂Ph
c: EWG = CO₂Et
d: EWG = COPh
e: EWG = CN
f: EWG = CSNH₂
g: EWG = CONH₂
h: EWG = CSPh

3a-g

a: EWG = CONHPh
b: EWG = CONH(CH₂)₂Ph
c: EWG = CO₂Et
d: EWG = COPh
e: EWG = CN
f: EWG = CSNH₂
g: EWG = COPh-2-OMe

4a-b

a: EWG = CONHPh
b: EWG = CONH(CH₂)₂Ph

5a-b

a: EWG = CONHPh
b: EWG = CONH(CH₂)₂Ph

6a-b

a: EWG = CONHPh
b: EWG = CONH(CH₂)₂Ph

7a-e

a: EWG = CONHPh
b: EWG = CONH(CH₂)₂Ph
c: EWG = CO₂Et
d: EWG = COPh
e: EWG = CN

8a-e

a: EWG = CONHPh
b: EWG = CONH(CH₂)₂Ph
c: EWG = CO₂Et
d: EWG = COPh
e: EWG = CN

9a-g

a: R = H
b: R = Me
c: R = SCOMe
d: R = NHPh
e: R = OH
f: R = Br
g: R = OPh

10a-b

a: EWG = COPh
b: EWG = CSPh

11

12a-d

a: EWG = CONH(CH₂)₂Ph
b: EWG = CO₂Et
c: EWG = COPh
d: EWG = CN

13a-d

a: EWG = CONH(CH₂)₂Ph
b: EWG = CO₂Et
c: EWG = COPh
d: EWG = CN

14a-e

a: EWG = CONHPh
b: EWG = CONH(CH₂)₂Ph
c: EWG = CO₂Et
d: EWG = COPh
e: EWG = CN

15a-e

a: EWG = CONHPh
b: EWG = CONH(CH₂)₂Ph
c: EWG = CO₂Et
d: EWG = COPh
e: EWG = CN

16a-e

a: EWG = CONHPh
b: EWG = CONH(CH₂)₂Ph
c: EWG = CO₂Et
d: EWG = COPh
e: EWG = CN

17a-d

a: EWG = CONHPh
b: EWG = CONH(CH₂)₂Ph
c: EWG = CO₂Et
d: EWG = COPh

18a-e

a: EWG = CONHPh
b: EWG = CONH(CH₂)₂Ph
c: EWG = CO₂Et
d: EWG = COPh
e: EWG = CN

19a-e

a: R = H; EWG = COPh
b: R = Me; EWG = CONH(CH₂)₂Ph
c: R = Me; EWG = CO₂Et
d: R = Me; EWG = COPh
e: R = Me; EWG = CN

Scheme 3.

5-ethoxycarbonylmethylidene substituent in compounds **8** and **18** (Scheme 3).

The higher energy of hydrogen bonding stabilization compared to the non-bonded S···O/S···S polar interactions is clearly seen in the lower energy of hydrogen bonded isomers (the difference in energy between the two isomers amounts 2.3–6 kcal/mol, Table S5). The large steric strain between the *N*-substituent and cis-oriented acceptor group strongly favours the *Z* isomers of **9**–**13**, the energy difference now being 5.9–8.7 kcal/mol (the smallest values of 1.4–1.8 kcal/mol were found for the linear cyano group).

2.3. Push–pull effect in thiazolidine derivatives 1–19

2.3.1. Bond lengths and occupation quotient π*/π as a measure of the push–pull effect. As already mentioned, the quotient $\pi*/\pi$ proved to be a very useful parameter for quantifying the push-pull effect in substituted alkenes.[1d,4] As the occupation numbers of various

molecular orbitals are readily assessed from the Natural Bond Orbital (NBO) Population Analysis, all the compounds were further studied by NBO method. The occupation numbers of lone pair orbitals of donors (LP N and LP S), π and $\pi*$ orbitals of the C=C double bond of **1**–**18** and of the most stable isomers of **19** are presented in Table S7 in the Supplementary data, together with the quotient of the occupation numbers $\pi*/\pi$ and length of the corresponding C=C double bond.

2.3.1.1. The push–pull effect in the thiazolidinone derivatives **1**–**13** *and bicyclic compounds* **19**. The two push–pull parameters, occupation quotients $\pi*/\pi$ and bond lengths of thiazolidinones **1**–**13** and fused thiazolidines **19** are correlated and fine linear dependence was obtained, as depicted in Fig. 5. The existence of two lines in Fig. 5 arises from the steric interactions present in the *E* isomers of **9**–**13** (with the exception of nitriles **12d** and **13d**). Changes in the push–pull effect on $\pi*/\pi$ and the corresponding
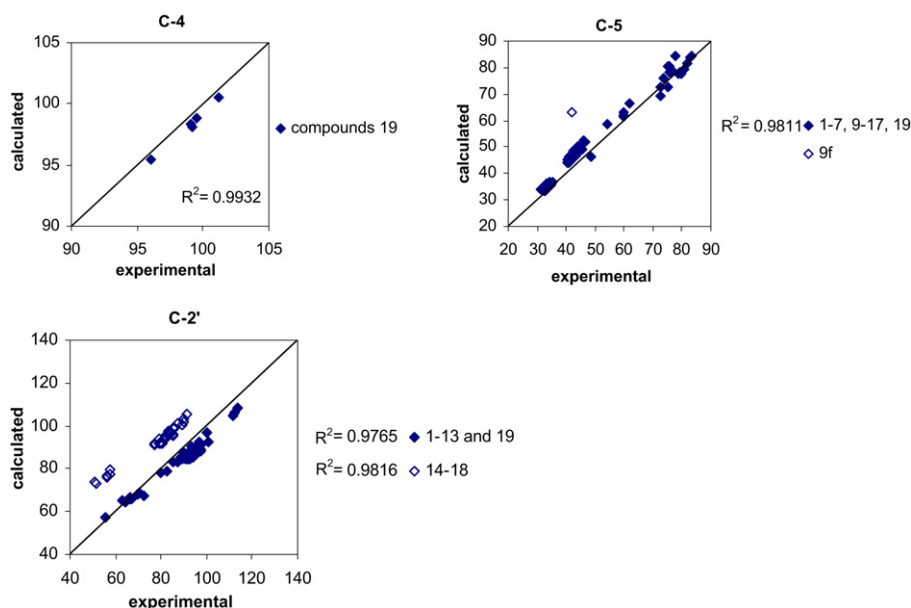
Fig. 1. Correlation of experimental and theoretically calculated ^{13}C NMR chemical shifts of thiazolidines **1**–**19**, at the B3LYP/6-31G(d) level of theory, in the gas phase.
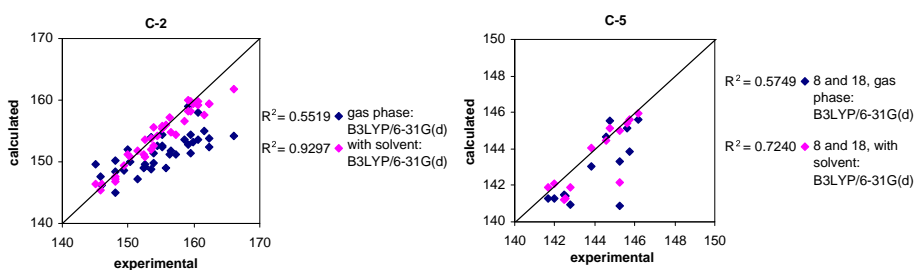

Fig. 2. The influence of solvent on the correlation between experimental and calculated olefinic C-2 and C-5 chemical shifts of a representative number of compounds.
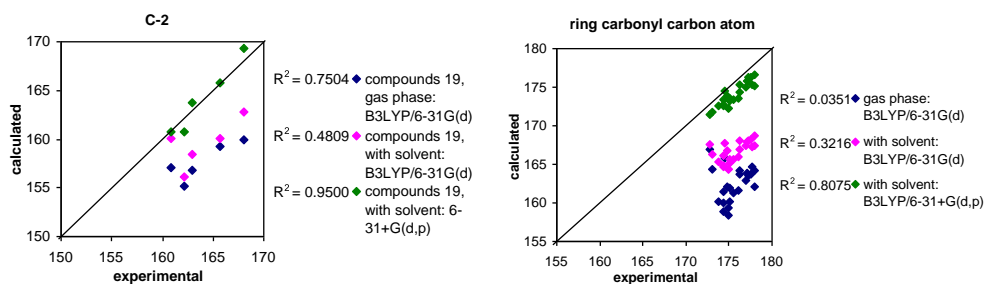

Fig. 3. The influence of solvent and basis set on the correlation between experimental and calculated ^{13}C chemical shifts of the C-2 carbon atoms of compounds **19** and ring carbonyl carbon of a representative number of compounds.

bond length are identical (same slopes of the two correlations), but the bond length, due to repulsive steric interactions of the cis positioned *N*-R and EWG, lengthened additionally by ca. 0.01 Å.

In general, the accepting ability of the electron-withdrawing substituents decreases in the following order: CSPh> CSNH$_2$>COPh>CN>CONHPh>CO$_2$Et>CONH$_2$>CONH(CH$_2$)$_2$Ph. The order of CN and CONHPh is reversed in *E* isomers, obviously because of hydrogen bonding enhancement of electron-withdrawing capability of the amide group.

Though bond lengths are affected additionally by steric effects of EWG, the quotient $\pi*/\pi$ appears as very sensitive indicator of the donor–acceptor interactions useful for predicting electronic and steric effects, hydrogen bonding, non-bonded interactions and even remote effects such as structural changes at the N-3, C-4 and C-5

positions of the heterocyclic ring. Thus, the following sequence of electron-withdrawing power was obtained for the *N*-substituted *E* isomers of **10**, **12** and **13**: CSPh>CN>COPh>CO$_2$Et>CONH (CH$_2$)$_2$Ph and the difference in the push–pull effect of *Z* and *E* isomers linearly correlates with the difference of the twists of the two isomers, as is shown in Fig. 6.

The enhancement of the push–pull effect by hydrogen bond formation between C=O(S) and ring NH is evident in the higher values of the quotient $\pi*/\pi$ for all hydrogen bonded structures compared to the related isomer (for example, $\pi*/\pi$ is 0.1617 for **1a**-*Z* and 0.1629 for **1a**-*E*). It is corroborated by the rather small difference in $\pi*/\pi$ (0–0.0007) in the case of cyano-substituted alkenes **1e**–**3e**, **7e** and **8e**. In addition, very similar values of $\pi*/\pi$ for both isomers of thioamides **1f**–**3f** (0.1743 and 0.1737 for **1f**, 0.1744 and
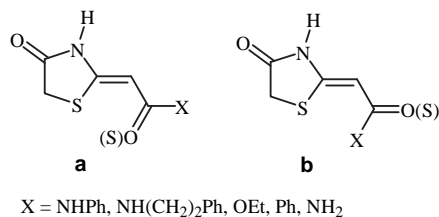
Table 1
Absolute values of torsional angles (τ) in Z and E isomers of N-substituted compounds **9–13**

Compound	Z isomer; τ (°)			E isomer; τ (°)		
	τ_1 S–C=C–C			τ_2 N–C=C–C		
	τ_3 C=C–C=O(S)			τ_3 C=C–C=O(S)		
	τ_1	τ_3	$\tau_1+\tau_3$	τ_2	τ_3	$\tau_2+\tau_3$
9a	0.01	0.01	0.01	12.31	13.20	25.52
9b	0.02	0.51	0.53	12.14	13.26	25.41
9c	0.25	0.38	0.64	10.60	13.49	24.09
9d	0.56	1.26	1.82	12.78	13.48	26.26
9e	0.77	0.18	0.95	12.13	13.12	25.26
9f	0.12	2.24	2.36	9.24	13.11	22.35
9g	0.62	1.35	1.97	12.75	13.41	26.16
10a	0.90	1.56	2.46	18.04	19.92	37.96
10b	0.34	2.99	3.33	24.35	27.82	52.17
11	0.20	3.14	3.34	24.22	26.47	50.69
12a	0.09	0.11	0.20	12.51	21.54	34.05
12b	0.06	0.13	0.18	12.28	13.07	25.35
12c	0.32	1.41	1.73	18.05	19.60	37.65
12d	0.21		0.21	0.10		0.10
13a	0.20	2.22	2.43	7.78	12.67	20.44[a]
13b	0.48	0.15	0.63	7.81	6.92	14.72[a]
13c	0.81	3.38	4.19	13.29	17.13	30.42[a]
13d	1.04		1.04	2.75		2.75

[a] Due to calculation of a *single conformation* the deviations from planarity are lower for *N*-Bn derivatives compared to *N*-Me, which is contrary to what one would actually expect.

Fig. 4. The cis and trans configurations of **19c**-Z.

Fig. 5. Correlation of bond lengths in Å and occupation quotient $\pi*/\pi$ of the C=C double bond in thiazolidinones **1–13** and fused thiazolidines **19**.

Fig. 6. Correlation of the amount of twisting of EWG and occupation quotient $\pi*/\pi$ of the C=C double bond in *N*-substituted compounds **10**, **12** and **13**. The Y axes represent the difference between the sum of τ_1 and τ_2, presented in Table 1.

X = NHPh, NH(CH$_2$)$_2$Ph, OEt, Ph, NH$_2$

Scheme 4.

Table 2
Relative energies of the *s-cis* and *s-trans* conformations of the Z and E isomers of compounds **1a-c**, **1d-g** and **2h**

Compound	Z isomer		E isomer	
	E (kcal/mol) *s-cis*	E (kcal/mol) *s-trans*	E (kcal/mol) *s-cis*	E (kcal/mol) *s-trans*
1a	0	7.14	0	10.55
1b	0	5.40	0	9.25
1c	0	2.57	0	3.79
1d	0	8.71	0	10.87
1f	0	2.95	0	6.99
1g	0	4.93	0	8.35
2h	0	5.47	0	7.23

0.1744 for **2f**, and 0.1736 and 0.1739 for **3f**, Z and E isomers, respectively) are indicative of similarly strong influence (compared with H-bonding) of the S···S interactions on accepting ability of CSNH$_2$ group. In the absence of steric interactions, the introduction of a Me group at the ring nitrogen increases the push–pull effect, e.g., $\pi*/\pi$=0.1617 for **9a**-Z but 0.1582 for **1c**-Z, whereas Bn substituent at the same position has a negligible effect. As expected,
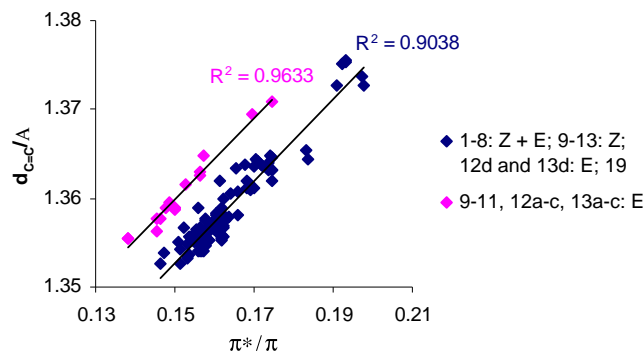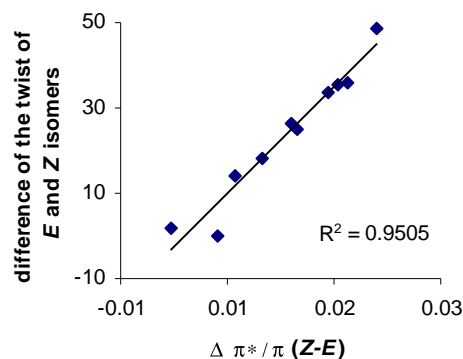
the substitution of the ring C=O for C=S diminishes ring nitrogen pushing effect, thus decreasing the push–pull effect of **11**-E ($\pi*/\pi$=0.1696) in comparison to **10b**-E ($\pi*/\pi$=0.1744). In **11**-Z, however, the diminished nitrogen pushing effect is compensated by sulfur electrons (the difference of the occupation numbers of sulfur lone pair orbitals between **10b**-E and **11**-E is 0.0096, but between **10b**-Z and **11**-Z 0.0147), so that the value of the quotient $\pi*/\pi$ is almost the same as in **10b**-Z. Whereas the 5-Me group slightly enhances and 5-CH$_2$CO$_2$Et substituent slightly decreases donor–acceptor interactions (for example, $\pi*/\pi$=0.1617 for **1a**-Z, 0.1619 for **2a**-Z and 0.1613 for **3a**-Z), the effect of heteroatoms bonded to the C-5 position of the ring is more discernible. Thus, the introduction of methoxy, morpholino and anilino group decreases the push–pull effect in the order OMe>morpholino>NHPh ($\pi*/\pi$=0.1617 for **1a**-Z, 0.1583 for **4a**-Z, 0.1577 for **6a**-Z and 0.1560 for **5a**-Z), as is also the case for OH in the bromo derivatives ($\pi*/\pi$=0.1901 for **14a**-E and 0.1837 for **17a**-E) and for PhO, Br, OH, NHPh and SCOMe groups ($\pi*/\pi$=0.1617 for **9a**-Z, 0.1537 for **9g**-Z, 0.1540 for **9f**-Z, 0.1542 for **9e**-Z, 0.1579 for **9d**-Z and 0.1603 for **9c**-Z). The values of $\pi*/\pi$ get also smaller with the introduction of another exocyclic C=C double bond at the C-5 of the ring, e.g., $\pi*/\pi$=0.1613

for **3a**-*Z* and 0.1514 for **8a**-*Z*, indicating weaker push−pull effect of the C-2 double bond, obviously due to the weaker donor capacity of sulfur, which now shares electrons with two double bonds.

An inspection of the occupation numbers of lone pair orbitals of the two donor atoms (LP N and LP S) reveals that each atom is the better donor when it is *syn* to EWG (for example, LP N=1.6458 for **1a**-*Z* and 1.6089 for **1a**-*E*, LP S=1.8114 for **1a**-*Z* and 1.8385 for **1a**-*E*). As can be supposed, nitrogen electrons are shared between the ring C=O and exocyclic C=C double bond. More electron density goes to the C=O, as was estimated from the energies of stabilization of C=O and C=C bonds by the lone pair of nitrogen, obtained from the NBO analysis. As a consequence, changes of the occupancy of lone pair orbitals with the push−pull effect are high for sulfur, but pretty constant for nitrogen in *Z* isomers (Fig. 7). In *E* isomers, where nitrogen becomes the better donor, the changes are more evident, though those for sulfur are still larger (Fig. 7). Finally, in the absence of C=O group in the fused derivatives **19**, the occupancy of nitrogen lone pair orbitals is changed much more with the push−pull effect, whereas the values for sulfur are rather constant (Fig. 7).

between bromides **14**−**16** and **18** and parent thiazolidinones **1**−**3** and **8** are presented in Table S8 and differences between the occupation numbers of π* of acceptor CN and CHO groups in Table S9 in Supplementary data.
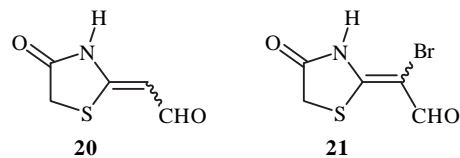
Scheme 5.

The following can be seen: (i) the occupation numbers of π orbitals of the C=C double bond are slightly higher in bromo compounds; (ii) the occupation numbers of π* orbitals of the C=C double bond are much higher in bromo compounds; (iii) the occupation number of π* orbitals of electron-withdrawing CN and CHO groups are lower in bromo derivatives; (iv) the occupancies of
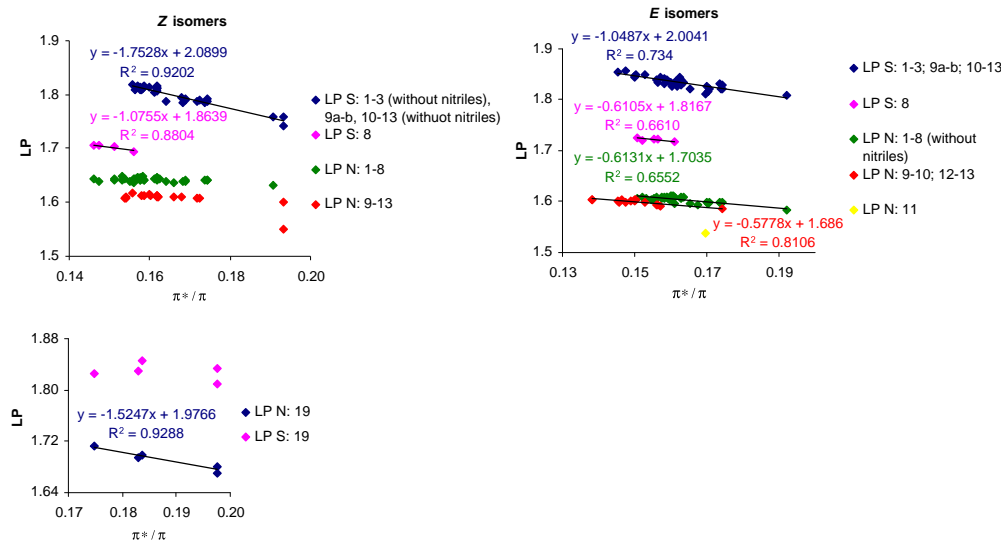

Fig. 7. Changes of the occupation number of lone pair orbitals of sulfur (LP S) and nitrogen (LP N) donors in *Z* and *E* isomers of compounds **1**−**13** and in compounds **19**. The sulfur lone pairs of 5-heterosubstituted derivatives **4**−**7** and **9c**−**g** were not taken into account due to additional influence of heteroatom on them. The sulfur lone pairs of *Z* nitriles and the nitrogen lone pairs of *E* nitriles are excluded, too, since their occupation values are somewhat higher than expected.

*2.3.1.2. The push−pull effect in the thiazolidinone bromides **14**−**18**. The special effect of bromine on the push−pull character.* The values of both parameters, π*/π and bond length, are higher in bromides with respect to the parent thiazolidinones, but the situation here is more complex since a third donor (Br) is connected to the double bond. Thus, the introduction of bromine into the C=C double bond can: (i) enhance push−pull effect, (ii) enhance donor efficiency of sulfur and/or nitrogen, or/and (iii) enrich π* orbital of the C=C double bond with electrons. Now, a comparison of the occupation numbers of all the orbitals involved in the conjugation with the C=C double bond should be made. The occupation numbers of π* orbitals of acceptor amide, ester and benzoyl substituents are difficult to compare due to resonances of the groups themselves. To eliminate this resonance effect on the occupation number of π* orbitals of acceptor C=O groups additional compounds **20** and **21** were included in the examination (Scheme 5). The differences in the occupation numbers of π and π* orbitals of the C=C double bond and lone pair orbitals of nitrogen and sulfur (LP N, LP S)

lone pair orbitals of nitrogen are lower in *E* bromides, but slightly higher in *Z* bromides; (v) the occupancies of lone pair orbitals of sulfur are lower in *Z* bromides and slightly lower in *E* bromides, except for the 5-alkylidene compounds **18**, nitriles **14e**−**16e**, **18e** and aldehyde **21** where they are somewhat higher. The values of the occupation numbers of lone pairs of bromine are not presented. They vary in the range of 1.943−1.955, which is higher than the calculated value for ethylenebromide (1.931). This means that electronic interactions of bromine with the C=C double bond are lower in thiazolidinone derivatives compared to ethylenebromide, obviously because of the push−pull effect already present. On the basis of the previous observations it seems as if bromine *decreases acceptor activity*, but *increases donor activity*, more so when it is *syn* to the donor. The steric hindrance between Br and EWG is not the reason for the diminished withdrawing ability, since in the optimized geometries the EWGs are still in plane with the rest of the molecule. Only in compounds containing benzoyl substituent the phenyl ring is now more twisted, but this should actually increase
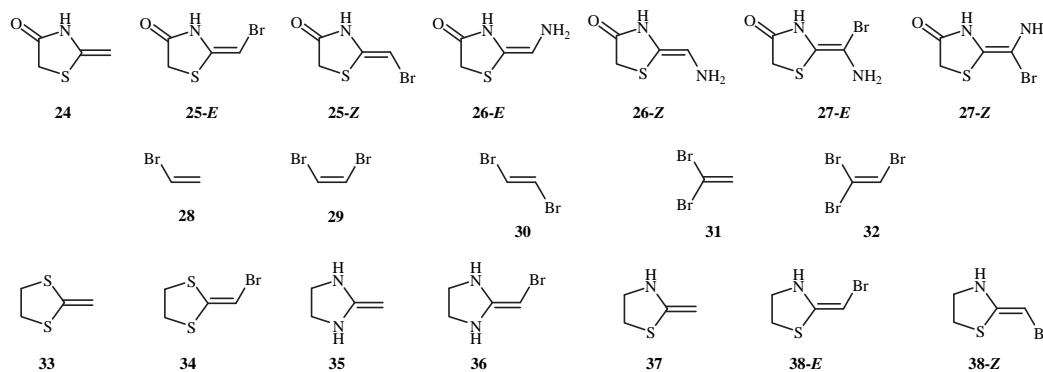
withdrawing of electrons from π orbital of the C=C double bond by the C=O group. The same effect on the electron-withdrawing ability was observed for model compounds **22** and **23**, without donor atoms (Table S10, Supplementary data): the occupation of π orbitals is higher and C=C bond length shorter in all bromides **23**. The bromine here is slightly more involved in the resonance with the C=C double bond than in thiazolidinones (the occupation numbers range from 1.932 to 1.945), but again less than in ethylenebromide (Scheme 6).

a: EWG = CONHPh
b: EWG = CONH(CH$_2$)$_2$Ph
c: EWG = CO$_2$Et
d: EWG = COPh
e: EWG = CN
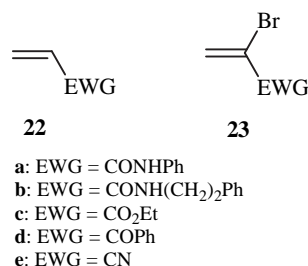
Scheme 6.

As far as the donor atoms are concerned, it is obvious that bromine cis to the sulfur improves its donor action in **14–16** (for example, LP S=1.8385 in **1a**-*E* and 1.8245 in **14a**-*Z*), but it is less clear for 5-alkylidene derivatives **18**, since sulfur electrons could be shifted to both C=C double bonds. Again, energies of stabilization of C=C double bonds by the sulfur electrons revealed that in bromides more electron density goes to the C-2 double bond than in the parent thiazolidinones. The same is true for nitrogen lone pair when it is cis to Br: its conjugation with the C=C double bond is increased and resonance with the ring C=O decreased. The higher occupation numbers of the lone pair orbitals of N in all *Z* bromides indicate weaker donating ability of nitrogen, which is also the case for sulfur in *E* isomers of all cyano-substituted bromides (**14e–18e**) and 5-alkylidene compounds **18a–d**.

In order to learn if this enhancement of electron-donating ability of the *syn* donor can also occur in alkenes with no push–pull effect, model compounds **24–38**[17] were included in the calculations (Scheme 7 and Table 3).

Table 3
Occupation numbers of various molecular orbitals in the model compounds **24–38** obtained by NBO analysis and lengths of the C=C double bonds

Compound	π	π_*	$d_{C=C}$/Å	LP D1	LP D2	LP D3	LP D4
24	1.9766	0.2154	1.3367	1.6561	1.8717		
25-*E*	1.9758	0.2814	1.3382	1.6498	1.8711	1.9473	
25-*Z*	1.9752	0.2872	1.3388	1.6593	1.8574	1.9420	
26-*E*	1.9586	0.2395	1.3419	1.6429	1.8732	1.9544	
26-*Z*	1.9617	0.2827	1.3410	1.6639	1.8910	1.8724	
27-*E*	1.9528	0.2972	1.3418	1.6495	1.8652	1.9574	1.8671
27-*Z*	1.9530	0.3034	1.3436	1.6485	1.8569	1.8904	1.9501
28	1.9973	0.0669	1.3265	1.9314			
29	1.9949	0.1546	1.3292	1.9205	1.9204		
30	1.9948	0.1336	1.3265	1.9313	1.9312		
31	1.9950	0.1319	1.3280	1.9319	1.9316		
32	1.9924	0.2176	1.3329	1.9203	1.9348	1.9193	
33	1.9902	0.1978	1.3380	1.8672	1.8672		
34	1.9864	0.2685	1.3383	1.8513	1.8699	1.9353	
35	1.9791	0.1608	1.3444	1.8387	1.8419		
36	1.9804	0.2683	1.3463	1.8120	1.8472	1.9627	
37	1.9878	0.1924	1.3403	1.8266	1.8765		
38-*E*	1.9869	0.2908	1.3415	1.8021	1.8766	1.9547	
38-*Z*	1.9860	0.2783	1.3416	1.8266	1.8614	1.9504	

lowers the occupation number of the *cis* Br, but increase that of the *trans* Br. If the occupancy of lone pair orbitals of sulfur and nitrogen in bromides **34**, **36** and **38** are compared with those for the parent compounds **33**, **35** and **37** it appears as if all the atoms become better donors when they are *cis* to Br, but slightly weaker in the *trans* position. Thus, on the basis of consideration of the presented model systems together with compounds **14–16** and **18** the following can be concluded: (i) introduction of bromine at the C=C double bond increases the donating ability of a cis donor; (ii) bromine itself is a better donor when it is cis oriented to a weaker donor, which is also the case for the amino group in model compounds **26** and **27**; (iii) the effect on the trans oriented donor is less straightforward: it is much smaller and can go in both directions.

Since the changes of donating abilities of the two donors depend on the C-5 substituent in thiazolidinone vinyl bromides **14–18**, the

Scheme 7.

From the data in Table 3 it can be seen that introduction of bromine at the double bond increases the donation of electrons by nitrogen and sulfur also in the absence of EWG at the C=C double bond (compound **25** compared to **24**) and this even in the presence of the third donor (amino group in compounds **26** and **27**). More electrons are released into the C=C double bond in *cis* dibromoethene **29** than in bromoethene **28** and *trans* dibromoethene **30**. If a third Br is added to geminally disubstituted dibromoethene **31** it

push–pull effect of the C=C double bond can be compared only within a series of the same C-5 substitution, as is shown in Fig. 8. The slopes are identical. The values of C^5–C(sp^3) substitution (**14–16**) fall on one line, the 5–OH substituted compounds **17** on another one and finally the values of **18** (C^5=C substitution) on a third line. In this direction same bond lengths are related to reduced π_*/π quotients (i.e., reduced push, pull polarization of the exocyclic C=C double bond). This is comprehensible as C^5–C(sp^3)

substitution in **14**–**16** does not influence the push, pull properties of the thiazolidinone moiety but C^5–OH and C^2=C reduce this push, pull polarization by interaction with especially the donor atom sulfur, adjacent to the C^5–substituent unit, the C^5=C double bond more by conjugation than C^5–OH. The cyano derivatives **14e**–**16e** and **18e** would form additional two lines because the changes still vary in those compounds. The steric hindrance with the voluminous Br can affect bond lengths, as well.
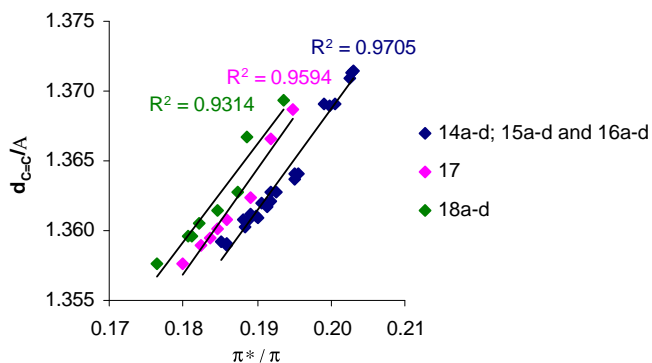
Fig. 8. Correlation of bond lengths in Å and occupation quotient $\pi*/\pi$ of the C=C double bond in vinyl bromides **14**–**18**.

The electron-withdrawing power is now in the order: $COPh > CO_2Et > CN > CONHPh > CONH(CH_2)_2Ph$ and both nitrogen and sulfur are again better donors if they are *syn* to EWG, except in the case of EWG=C≡N. Then, releasing of electrons into the C=C double bond is higher in *anti* position with EWG.

In these systems with higher electron density in the C=C double bond, the bond length is only influenced by the π bond order because EWG changes the bonding π-orbital of the C=C double bond only. Correlation of the C=C double bond length and occupation numbers of π orbitals of bromides **14**–**18** and model compounds **24**–**27** is shown in Fig. 9.
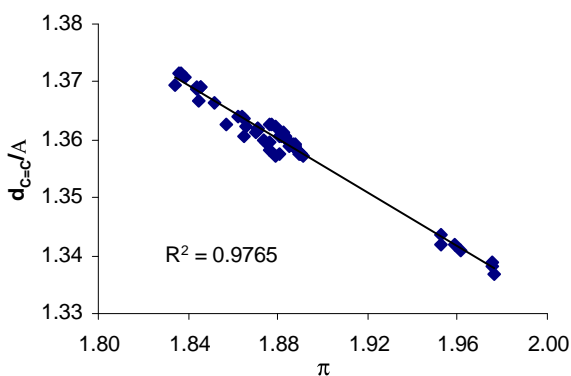

Fig. 9. Correlation of bond lengths in Å and occupation numbers of π orbitals of the C=C double bond in vinyl bromides **14**–**18** and model compounds **24**–**27**.

2.3.2. NMR parameters for quantifying the push–pull effect in thiazolidine compounds.

2.3.2.1. ^{13}C NMR chemical shift differences ($\Delta\delta_{C(2)=C(2')}$) as a measure of push–pull effect. The chemical shift difference of the two carbons of the double bond in push–pull alkenes becomes larger as the push–pull effect raises, because of the strengthened deshielding of the carbon at the donor side (C-2 in the case of the studied thiazolidine derivatives) and increased shielding of the carbon at the acceptor side (C-2' in thiazolidine derivatives; cf. **B** and **C** in Scheme 1). However, due to the strong influences of substituents on the chemical shifts, this parameter is applicable only when substituent changes do not take place directly at the double bond. This proved to be the case

for the studied thiazolidine compounds **1**–**13**, **19** with the same EWG and the bromo compounds **14**–**18**, respectively, and $\Delta\delta_{C(2)=C(2')}$ should be a good estimate of the push–pull effect in the two groups of compounds having the same acceptor, but vary in the substitution at the N-3, C-4 and C-5 position of the ring. The calculated chemical shift differences are well correlated to the quotient $\pi*/\pi$, as presented in Fig. 10 for compounds containing CO_2Et as the electron-withdrawing group. Because of the additional heavy atom effect[16] of Br on chemical shifts of the C-2' in bromides **14**–**18**, the correlation for these compounds lies on another regression line, but of same slope, in the diagram. The correlations for compounds with EWG=CONHPh, CONH$(CH_2)_2$Ph, COPh, CN are shown in Supplementary data as Fig. S1.
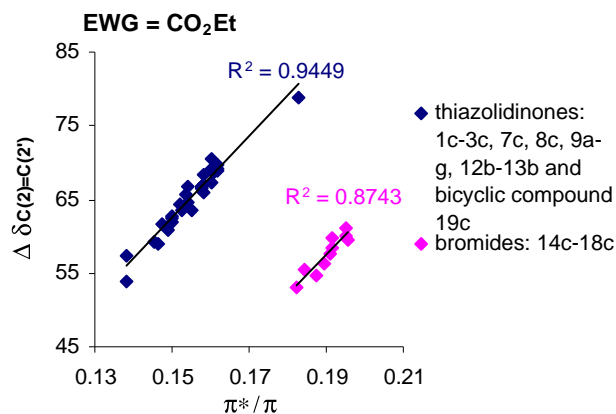

Fig. 10. Correlation of the calculated chemical shift differences $\Delta\delta_{C(2)=C(2')}$ of the two carbons of the double bond and occupation quotient $\pi*/\pi$ of the C=C double bond for all compounds with EWG=CO_2Et.

2.3.2.2. Olefinic ^1H NMR Chemical shifts as a measure of the push–pull character. It could be anticipated that in the push–pull systems with the trisubstituted C=C double bond the olefinic ^1H NMR chemical shifts are affected by the strength of the push–pull effect. If the proton is at the donor side it should become less shielded with increasing push–pull effect and the one at the acceptor side more shielded. Proton chemical shifts, being highly solvent dependent, were not calculated and experimental values only were correlated with the occupation quotient $\pi*/\pi$. Fig. 11 represents the correlation for compounds with EWG=CO_2Et. Since proton chemical shifts are more sensitive to environmental effects, this correlation is slightly worse than the aforementioned correlation of $\Delta\delta_{C(2)=C(2')}$. Nevertheless it could be used as a rough parameter for describing the push–pull effect. Correlations of similar quality for compounds having EWG=CONHPh, CONH$(CH_2)_2$Ph, COPh, CN were obtained and are presented in Fig. S2 in Supplementary data.
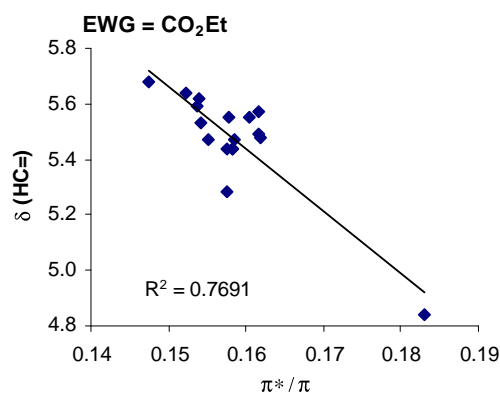

Fig. 11. Correlation of experimental olefinic ^1H NMR chemical shifts and occupation quotient $\pi*/\pi$ of all compounds with EWG=CO_2Et.

3. Conclusions

Structures of a series of push−pull 2-alkylidene-4-thiazolidi-nones **1**−**18** (80 compounds) and 2-alkylidene-4,5-fused bicyclic thiazolidine derivatives **19** (5 compounds) were optimized as both *Z* and *E* isomers at the B3LYP/6-31G(d) level of theory, in the gas phase. The 4-thiazolidinone ring was shown to be flat and in plane with the electron-withdrawing group at the other end of the C═C double bond. Deviations from planarity were found only in *N*-substituted compounds with cis-oriented ring nitrogen substituent to the electron-withdrawing group. For the bicyclic compounds **19** cis fusion was found to be energetically more favoured than trans fusion. In all compounds *s-cis* arrangement around the α,β-unsaturated (thio)carbonyl fragment was pre-ferred, since it is stabilized either by hydrogen bonding or by 1, 5-type polar S···S/S···O interactions. Higher hydrogen bonding stabilization energy is reflected in the 2.3−6 kcal/mol lower energy of hydrogen bonded structures with respect to the cor-responding isomers stabilized by non-bonded S···S/S···O interactions.

^{13}C NMR chemical shifts for C-2, C-2′, C-4 and C-5 atoms were calculated at the same level of theory in the gas phase and com-pared to experimental values. Very good agreement was obtained for saturated C-4 and C-5 atoms, and for double bonded C-2′ atoms. In the corresponding vinyl bromides **14**−**18** calculated values were overestimated due to the heavy atom effect of Br but the slope is the same and the correlation excellent. Calculations of chemical shifts of slightly positive olefinic C-2 of **1**−**18** and C-5 in **8** and **18** required inclusion of solvent, as could be expected for these highly polar push−pull compounds. In addition to solvent inclusion, for good agreement of experimental and calculated chemical shifts of C-2 in **19** and ring carbonyl carbon in **1**−**18** the 6-31+G(d,p) basis set was required.

The push−pull effect of all compounds was quantified by means of the quotient of the occupation numbers of $\pi*$ and π orbitals of the partial C═C double bond ($\pi*/\pi$), bond length, difference of the calculated chemical shifts of the two carbons constituting the double bond ($\Delta\delta_{C═C}$) and experimental ^{1}H NMR chemical shifts of olefinic protons of the trisubstituted double bond. Due to the strong influences of substituents on chemical shifts, both NMR parameters were confined to compounds with the same electron-withdrawing group, but with varying sub-stitutions at the N-3, C-4 and C-5 positions of the heterocyclic ring. Bond length, as a measure of push−pull effect, was influ-enced by steric interactions, but the quotient $\pi*/\pi$ proved to be a general and excellent indicator of the donor−acceptor inter-actions in these molecules.

The examination of the occupation numbers of lone pair orbitals of donor atoms in push−pull 2-alkylidene-4-thiazolidinone derivatives and in model compounds lacking an EWG revealed that introduction of bromine into the C═C double bond enhances donor efficiency of the cis donor, whereas its own donating ability is higher when it is cis oriented to a weaker donor atom. The effect on the donating power of the trans donor is less straightforward and much smaller. Owing to the existing push−pull effect, Br is a weaker donor in all vinyl bro-mides **14**−**18** compared to bromoethene. In the case of these electron-enriched vinyl bromides **14**−**18** and model compounds **24**−**27** C═C double bond length was more influenced by the occupation of π orbital.

4. Experimental

4.1. General

Synthesis of compounds **1b**,[5f] **2b**,[5f] **2d**,[5f] **2h**,[6b] **3a**−**e**,[5a,5c] **4**−**7**,[14] **8**,[5d] **9f**,[14] **10**,[6b] **11**,[6b] **12**,[9] **14**−**16**,[14] **17**,[11b] **18**,[11b] **19a**[5e] and **19b**−**e**[9]

have already been published. Compounds **1a**, **1c**−**g**, **2a**, **2c**, **2e**−**g** and **3f**−**g** were prepared by the base catalyzed reaction of α-mercapto esters and α-substituted nitriles according to the published procedure.[5c] The synthesis of compounds **9a**−**e**, **9g** and **13** will be published soon.

The NMR spectra were recorded on a Varian Gemini 2000 spectrometer (^{1}H at 200 MHz, ^{13}C at 50.3 MHz) in DMSO-d_6 or CDCl$_3$. Chemical shifts are reported in parts per million (ppm) on the δ scale from TMS as an internal standard.

Ab Initio MO Calculations and the Natural Bond Orbital (NBO) Population Analysis[18] were performed using *Gaussian 03*.[19] Geom-etry optimizations were performed at the B3LYP level of theory[20] using 6-31G(d) basis set,[21] in the gas phase. The solvent effects (DMSO and CHCl$_3$, ε=46.7 and 4.9, respectively) were included in the calculations by the SCRF theory using IEFPCM model[22] and geome-tries of the selected compounds were optimized at the B3LYP level of theory using different basis sets. Chemical shieldings were calcu-lated using the GIAO method[15] at the B3LYP level of theory using the 6-31G(d) basis set for gas-phase calculations and different basis sets for calculations including solvent effects. Chemical shifts were obtained by the difference of the calculated shielding values to that of TMS (calculated at the same level of theory). All calculations were carried out on LINUX clusters.

Supplementary data

Supplementary data contain absolute energies and atomic coordinates of compounds **1**−**38**, experimental and calculated ^{13}C NMR chemical shifts of C-2, C-2′, C-4 and C-5 of compounds **1**−**19**, in the gas phase and considering the influence of solvent and basis set on the calculated ^{13}C NMR chemical shifts of the test com-pounds **14a**-*E* and **19c**, calculated ^{13}C NMR chemical shifts of the selected compounds with inclusion of the solvent, the occupation numbers of various orbitals in compounds **1**−**19** and model com-pounds **22** and **23**, and differences in the quotient $\pi*/\pi$ and occu-pation numbers of various orbitals between bromides and parent thiazolidines. Correlation of $\Delta\delta_{C(2)═C(2')}$ and occupation quotient $\pi*/\pi$, and correlation of experimental olefinic ^{1}H NMR chemical shifts and occupation quotient $\pi*/\pi$ of compounds having EWG=CONHPh, CONH(CH$_2$)$_2$Ph, COPh and CN are also presented. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.09.040.

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17. It should be noted that all thiazolidine and imidazolidine derivatives presented in Scheme 7 would actually exist as imino tautomers due to the absence of EWG at the other side of the C=C double bond, which otherwise stabilizes the enamino form. Here, they are included only as enamino tautomers for comparison with the studied compounds.
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