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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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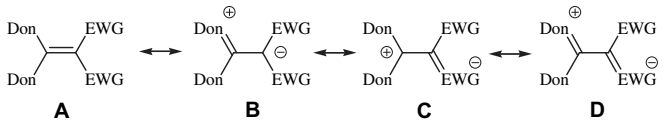
ABSTRACT

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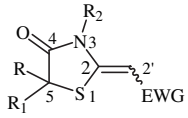
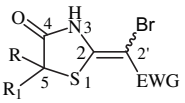
and much broader than the bond length, which can be influenced by steric hindrance or hydrogen bonding.[1d] It also needs a stronger polarization for a discernible effect.[4]

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]



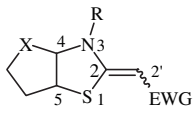
I

R, R_1 = H, alkyl, heteroalkyl(aryl), alkylidene
R_2 = H, Me, Bn



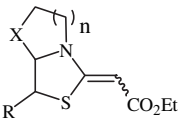
II

R, R_1 = 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 ^{13}C chemical shifts of thiazolidine derivatives 1–19

The experimental ^{13}C 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 ^{13}C 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 **19**, 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 $CHCl_3$, 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 ^{13}C NMR chemical shifts of the test compounds **14a**-*E* and **19c** is presented in Table S3 and calculated ^{13}C 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 CO_2Et 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