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QUANTUM CHEMICAL STUDY OF THE ACIDITY OF 3,4-DIHYDRO-2*H*-THIOPYRAN-1,1-DIOXIDES

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Abstract. *We conducted quantum chemical modelling by REVPBE0 3,4-dihydro-2H-thiopyran-1,1-dioxide,3,4,6-triphenyl-3,4-dihydro-2H-thiopyran-1,1-dioxide and their anions. The authors calculated the Gibbs free energies for the reaction of their interaction with hydroxide anion as a base. We have found a difference in the acidic properties of the protons of the 2H-thiopyran rings and the positions of the reaction centres in the subsequent reactions involving the formed anions.*

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Introduction

Compounds containing thiopyran fraction are of interest as promising biologically active substances [1]. Nevertheless, they are poorly studied organic compounds due to the preparative complexity of their preparation and further functionalisation [1, 2]. Therefore, the comprehensive development of thiopyranes chemistry is an urgent task.

It is known [3] that double bond migration of 3,4-dihydro-2*H*-thiopyran-1,1-dioxide can occur in the presence of bases (Fig. 1).

In the presence of aqueous NaOH solution for 24 h, the authors [3] observed isomerisation of 1 to 2 with a conversion of 67%. It is also noted the formation of isomers 1 and 2 in the equilibrium mixture in the ratio of 5:95 occurred on exposure to a weaker base DBU (6 eq.) for 7 days.

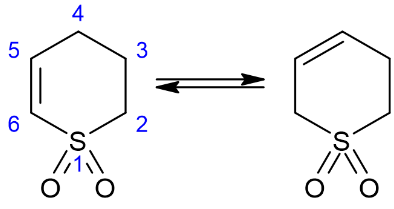

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Fig. 1. General scheme of double bond migration in the ring of 3,4-dihydro-2*H*-thiopyran-1,1-dioxide

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The present paper deals with the problem of the thiopyran ring acidity using unsubstituted 3,4-dihydro-2*H*-thiopyran-1,1-dioxide and trisubstituted 3,4,6-triphenyl-3,4-dihydro-2*H*-thiopyran-1,1-dioxide as examples.

It is necessary to determine the possibility of the different anions formation of 3,4-dihydro-2*H*-thiopyran-1,1-dioxides not only to analyse the possible migration of the double bond, but also to study the reactions involving the probable anions. We have made such an assessment using quantum-chemical calculations.

Quantum chemical studies of the synthesis of substituted 3,4-dihydro-2*H*-thiopyrans [4, 5], synthetic precursors of 3,4-dihydro-2*H*-thiopyran-1,1-dioxides, were previously conducted

Main body

We calculated all quantum-chemical parameters using the Orca software, version 5.0.3 [6-8] using the electron density functional method REVPBE0 (updated PBE0 method) [9, 10] with the Grimme dispersion correction D4 [11, 12] in the valence-splitting triple-exponential 3ζ basis with polarisation functions Def2-TZVPPD [13-15]. The approximations of Coulomb interactions and exchange HF-integrals by the RIJCOSX method [16] in the additional Def2/J [14] and Def2-TZVPPPD/C [17, 18] bases in the calculations were used. The polarisable continuum model C-PCM, solvent - DMFA [19] was used in calculations that take solvation into account.

We calculated all theoretically possible anions of 3,4-dihydro-2*H*-thiopyran-1,1-dioxide and 3,4,6-triphenyl-3,4-dihydro-2*H*-thiopyran-1,1-dioxide to determine the acidity of different positions of the thiopyran ring. We calculated the Gibbs free energy change for the reaction of their interaction with hydroxide anion as base. Table 1 presents the results. The Gibbs energy change was calculated for a temperature of 293K.

Table 1. Gibbs free energy of deprotonation of 3,4-dihydro-2*H*-thiopyran-1,1-dioxide and 3,4,6-triphenyl-3,4-dihydro-2*H*-thiopyran-1,1-dioxide by hydroxide anion (REVPBE0/def2-TZVPPD method, C-PCM(DMF), $T = 293$ K). The numbering of atoms is according to the scheme of Fig. 1.

Deprotonation position in the thiopyran ring	ΔG, kcal/mol	
	3,4-dihydro-2*H*-thiopyran-1,1-dioxide	3,4,6-triphenyl-3,4-dihydro-2*H*-thiopyran-1,1-dioxide
2	7.580	1.713
3	26.220	8.951
4	-7.578	-23.056
5	15.694	13.754
6	3.584	–

According our research, deprotonation of the **C4** atom is the most energetically favourable for both compounds. The ease of deprotonation is related to the stability of the formed anion, which is largely determined by the electron density distribution. At detachment of a proton from the **C4** atom, the formed anion is resonance-stabilised due to interaction with electrons of the **C6** atom (Fig. 2).

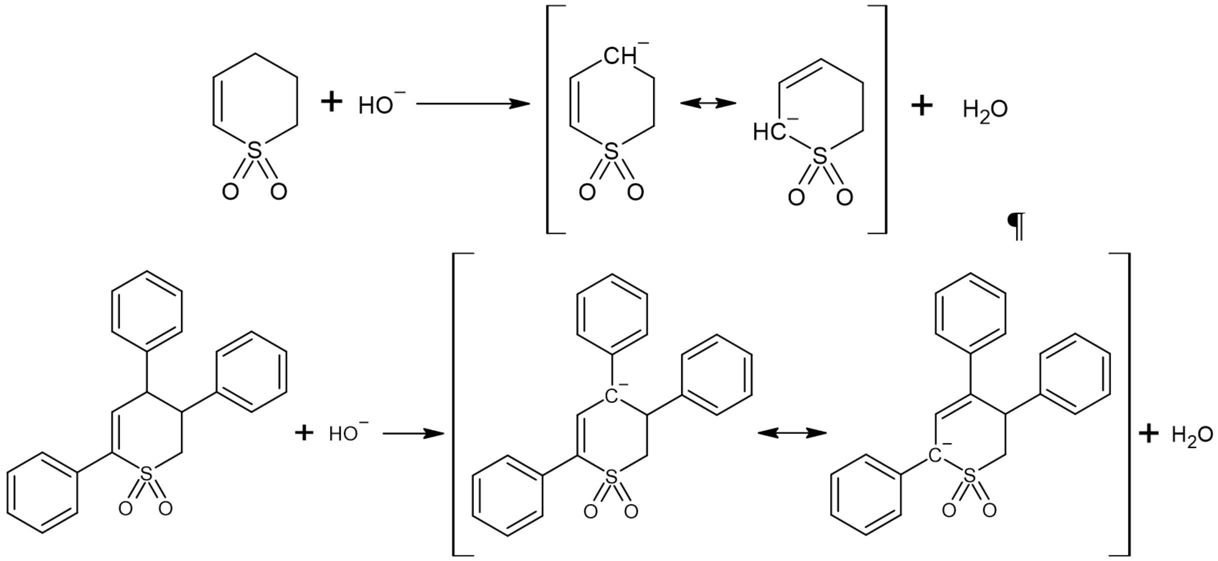

Fig. 2. Scheme of anion formation upon deprotonation of **C4** 3,4-dihydro-2*H*-thiopyran-1,1-dioxide and 3,4,6-triphenyl-3,4-dihydro-2H-thiopyran-1,1-dioxide atoms

These same atoms host the bulk of the highest occupied molecular orbital (HOMO), as can be seen in Fig. 3. The localisation of the HOMO also demonstrates the active reaction centres of the anion - atoms **C4** and **C6**.

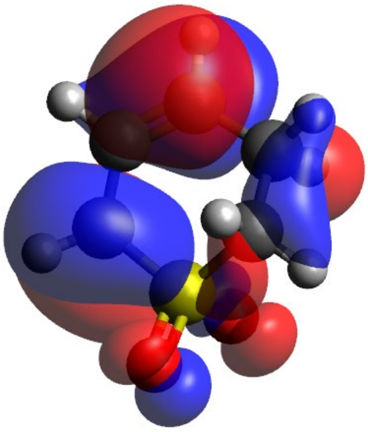

Fig. 3. Distribution of HOMO in the anion of 3,4-dihydro-2*H*-thiopyran-1,1-dioxide (C4 deprotonated)

Comparing the Gibbs energies of deprotonation of C4 2H-thiopyran-1,1-dioxide (-7.578 kcal/mol) and 3,4,6-triphenyl-3,4-dihydro-2H-thiopyran-1,1-dioxide (-23.056 kcal/mol), it is possible to conclude that 3,4,6-triphenyl-3,4-dihydro-2H-thiopyran-1,1-dioxide has more acidic properties. The distribution of HOMO in the resulting anion, shown in Fig. 4 provides an explanation for this fact. The phenyl fragments at the 4 and 6 positions participate in the electron density distribution and stabilize the anion.

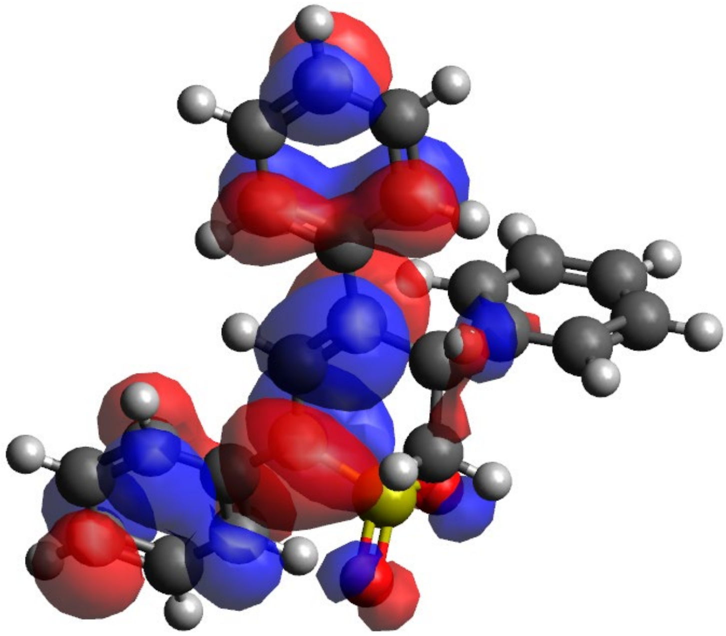

Fig. 4. Distribution of HOMO in the anion of 3,4,6-triphenyl-3,4-dihydro-2*H*-thiopyran-1,1-dioxide (C4 deprotonated)

Predicting the reactivity of the formed anions in subsequent chemical reactions, it is expected to be higher for the 3,4-dihydro-2H-thiopyran-1,1-dioxide anion, due to the greater localization of the HOMO on the carbons of the 2H-thiopyran ring and the smaller influence of the steric factor. The **C4** and **C6** atoms can act as reaction centres in subsequent reactions involving these anions, since it is on them that the major part of the anion's HOMO is localised.

Moreover, there is a minor participation of the sulfone group in the distribution of HOMO, which is consistent with the calculated low acidity of the **C2** atom.

Conclusions and recommendations

As a result of quantum-chemical Gibbs free energy calculations, it was found that in 3,4-dihydro-2*H*-thiopyran-1,1-dioxide and 3,4,6-triphenyl-3,4-dihydro-2*H*-thiopyran-1,1-dioxide, the strongest acidic properties are exhibited by the proton at the carbon in the **4** position of the thiopyran ring. Phenyl fragments in the **4** and **6** positions of 3,4,6-triphenyl-3,4-dihydro-2*H*-thiopyran-1,1-dioxide participate in the electron density distribution of the anion, thereby enhancing the acidic properties of this compound. Therefore, the localization of HOMO in anions allows us to assume that C4 and C6 atoms will act as reaction centres in subsequent reactions involving these anions.

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